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UPDATE ON CHRONIC URTICARIA

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Quality of Life in Patients with Chronic Urticaria or Respiratory Allergy

SF-36 domains	CU (n=21)	Respiratory allergy (n=27)	P value
Physical functioning	85.95±22.73	94.07±8.55	0.046
Physical role	58.33±38.99	81.48±28.24	0.01
Body pain	59.14±30.19	91.77±13.44	0.0001
General health	59.14±16.82	72.18±15.96	0.0043
Vitality	53.33±20.88	48.15±16.53	0.82
Social functioning	64.28±24.77	69.44±20.89	0.21
Emotional role	60.32±38.90	79.01±33.52	0.04
Mental health	59.62±19.79	65.33±16.00	0.13

Baiardini I et al. Allergy 2003; 58: 621-3

SATISFACTION PROFILE (SAT-P)

SAT-P items	CU	Respiratory allergy	P value
Sleep quantity	38.19±26.12	54.55±22.08	0.023
Sleep quality	35.95±23.85	63.85±27.51	0.001
Conduct at eating	43.14±29.17	62.22±26.40	0.025
Resistance to stress	34.95±23.28	54.00±20.27	0.007
Humor	42.14±28.97	61.04±20.40	0.019
Self confidence	54.05±25.19	70.15±22.45	0.019
Type of work	47.87±25.97	65.41±25.85	0.048
Professional role	42.36±32.59	69.45±29.41	0.016
S-P factors			
Sleep/food/hobbies	45.28±32.59	57.77±18.57	0.009

Baiardini I et al. Allergy 2003; 58: 621-3

PREVALENCE OF URTICARIA

	%
For life	8.8
Chronic urticaria	0.6-1.8
Punctual prevalence	0.5-1
Gender	Females 70.3%
Age	35-60 years (peak 20-40 years)
Other studies observed that up to 20 % of the population experiences acute urticaria at some timepoint in their life	

Zuberbier T et al. Clin Exp Dermatol 2010; 35: 869-73
Gaig P et al. J Investig Allergol Clin Immunol. 2004;14(3):214-20

Frequency of Angioedema in selected patients with CSU (Maurer M et al. Allergy 2011; 66: 317-30)

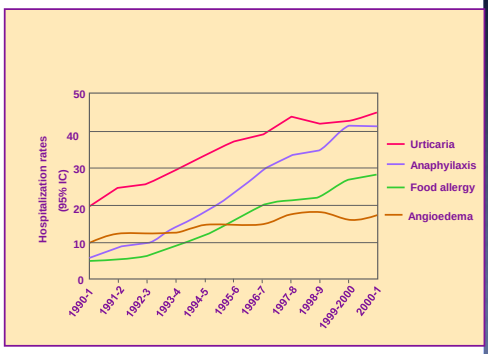
Study	Country	n	Wheals and AE (%)	Wheals alone (%)	AE alone (%)
Champion et al (1969)	UK	554	49	40	11
Juhlin (1981)	Sweden	330	67	29	4
Quaranta et al (1989)	USA	86	53	36	11
Sibbald et al (19910	Canada	254	45	51	4
Kozel et al (2001)	Netherlands	220	54	33	13
Toubi et al (2004)	Israel	139	40	NR	NR
Kulthanan et al (2007)	Thailand	450	34	65	1
Zuberbier et al (2010)	Germany	4093	33	61	6

Prevalence of Chronic Urticaria Subtypes

	%
Chronic spontaneous urticaria	66-93
Physical urticaria	4-33
Cholinergic urticaria	1-7
CU + angioedema	33-67
Urticaria alone	29-65
Angioedema alone	1-13

Maurer M, et al. Allergy 2011; 66: 317-30).

The Prevalence of Urticaria is Increasing



Gupta R et al . Br Med J 2003;327:1142-3.

CLASSIFICATION OF URTICARIA SUBTYPES BASED ON INDUCING STIMULUS

Types	Subtypes	Definition
Spontaneous	Acute	Spontaneous wheals and/or AE < 6 weeks
	Chronic	Spontaneous wheals and/or AE > 6 semanas
Physical	Contact with cold	Cold objects /air/liquids/wind
	Delayed pressure	Vertical pressure (latency 3-12 hours)
	Contact with heat	Localized heat
	Solar	UV and/or visible light
	Factitia/dermographic	Mechanical forces (begin at 1-5 minutes)
	Vibratory	Vibratory forces
	Aquagenic	Water
Other inducible urticarias	Cholinergic	Increase of body temperature by physical exercise, spicy foods
	Contact	Contact with urticariogenic substance
	Induced by exercise	Physical exercise

Zuberbier T et al. Allergy 2009; 64: 1417-1426

Classification of Chronic Urticaria Subtypes

Chronic Urticaria

Chronic spontaneous urticaria (CSU)	Chronic inducible urticaria
CSU due to known causes (for example, autoimmunity) **CSU due to unknown cause**	**Physical urticarias** • Symptomatic dermographism • Cold urticaria • Delayed pressure urticaria • Solar urticaria • Heat urticaria • Vibratory angioedema **Cholinergic urticaria** **Contact urticaria** **Aquagenic urticaria**

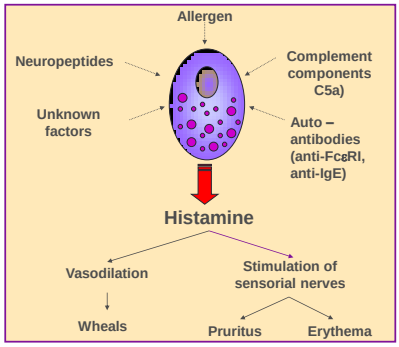
Diseases related to urticaria for historical reasons

- Exercise-induced anaphylaxis/urticaria
- Urticaria pigmentosa (mastocytosis)
- Urticaria vasculitis
- Familial cold urticaria (vasculitis)
- Nonhistaminergic angioedema (e.g. HAE)

Syndromes that can be associated with urticaria/angioedema

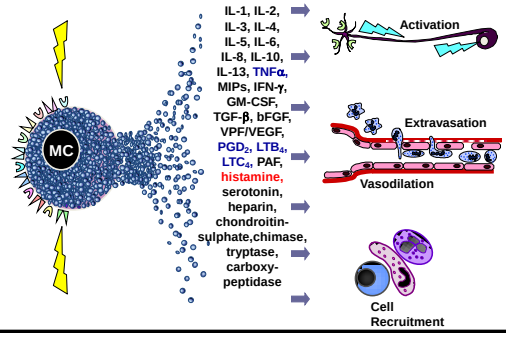
- Muckle-Wells syndrome (Urticaria-deafness-amyloidosis), sensorineural deafness, recurrent urticaria (hives), fever, arthritis
- Schnitzler's syndrome (recurrent non-pruriginous urticaria with monoclonal IgM gammopathy), recurrent fever, arthritis
- Gleich's syndrome (episodic angioedema with eosonophilia), IgM gammopathy, eosinophilia
- Well's syndrome (Eosinophilic cellulitis), granulomatous dermatitis with eosinophilia

Urticaria is Mediated by Histamine

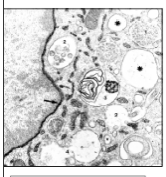


Urticaria – Pathogenesis

Mast cells are the key effector cells for the induction of symptoms of urticaria



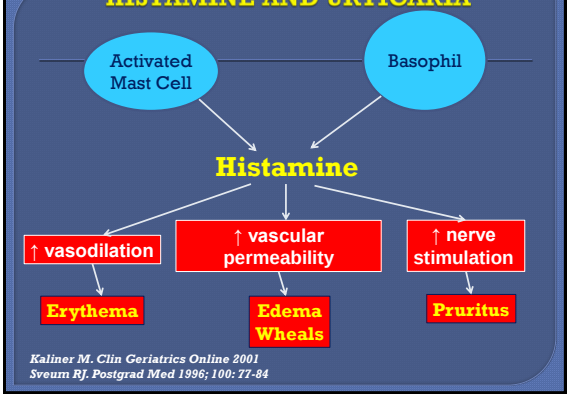
Products of Mast Cell Activation



Mast cell undergoing piecemeal degranulation

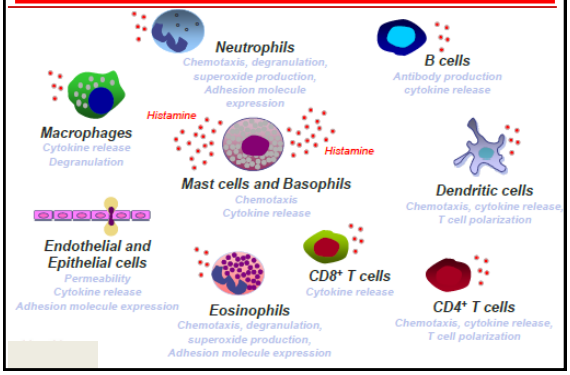
- Preformed Mediators (Minutes): Histamine, Proteases, TNF-α — Early (Edema, Broncho-Constriction, Vasopermeability)
- Newly Formed Eicosanoids (Minutes): Cysteinyl Leukotrienes, LTC4, Prostaglandins, PGD2
- Induced Cytokines/ Chemokines (Hours): IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-11, IL-13, MIP-1α, MIP-1β, MCP-1, TNF-α — Late (Inflammation, Cell Recruitment)

HISTAMINE AND URTICARIA



Kaliner M. Clin Geriatrics Online 2001
Sveum RJ. Postgrad Med 1996; 100: 77-84

Histamine Effects on Immune Cells



Pathogenesis

- Spontaneous
- Nonspecific exogenous factors : exercise, environmental changes, stress
- Psychosomatic factors: anxiety, depression
- Food allergy
- Autoreactivity and autoimmunity
- Immunoglobulin E: efficacy of Omalizumab, abnormal synthesis of IgE ?, IgE vs unknown autoAgs ?

Autoimmunity and autoreactivity

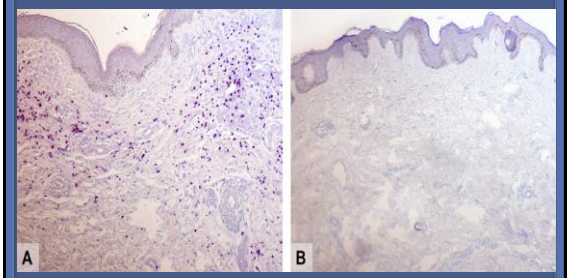
- IgG anti-IgE: 5-10 %
- IgG anti-FcεRIα: 30-40 %
- Complement activation and release of C5a
- Autologous serum or plasma skin test, basophil histamine release test, flow cytometry (CD63, CD203)
- 55 to 60 % CU non autoimmune (idiopathic)
- Vasoactive factors in IgG-depleted sera

SKIN TEST WITH AUTOLOGOUS SERUM AND PLASMA

ADDITIONAL OBSERVATIONS

- Association with Hashimoto's thyroiditis (marker for anti-FcεRI antibodies)
- Increase of CRP and MMP
- Activation of extrinsic coagulation cascade
- Increase of LTC4, cytokines and growth factors
- Increase of intercellular adhesion molecules
- Basophil abnormalities

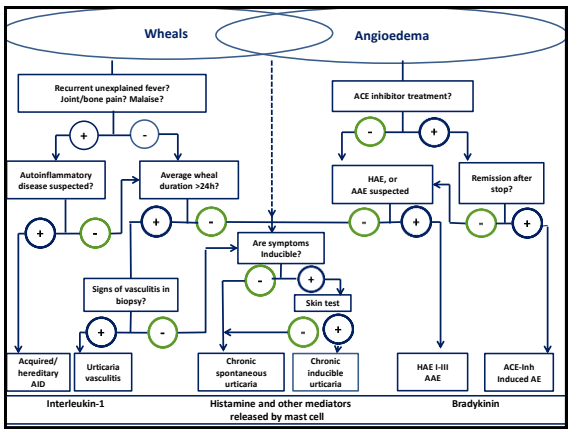
Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria



Asero R et al. J Allergy Clin Immunol 2007; 119: 705-10

Diagnostic Tests Recommended in Urticaria Subtypes

Group	Subgroup	Routine Diagnostic tests	Additional tests
Spontaneous	Acute	None	None
	Chronic	CBC,ESR, CRP, elimination of suspected drugs (NSAIDs)	i) Infectious diseases ii) Type 1 allergy iii) Autoantbodies iv) Thyroid hormones v) Skin tests, physical tests vi) Pseudoallergen-free diet x3w,tryptase vii) ASST,skin biopsy



Frequency of identification of the cause in patients selected patients with CU

Study	Country	n	Identification of cause	ASST performed	Autoreactivity included as cause
Small (1982)	Canada	215	11	No	NR
Quaranta (1989)	USA	86	0	No	NR
Humpreys and Hunter (1997)	UK	331	17	No	NR
Giménez-Arnau (2004)	Spain	235	43	92	Si
Kulthanan (2007)	Thailand	407	17	61	No
Ferrer (2009)	Spain	248	15	3	NR

Maurer M et al. Allergy 2011; 66: 317-30

Classification of Hypersensitivity Reactions to ASA and NSAIDs

Reaction time	Clinical picture	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to various hours)	Rhinitis/asthma (AERD)	CR	Asthma/RS/NP	Inhib. COX-1
	Urticaria/AE (AECD)	CR	CSE	Inhib. COX-1
	Urticaria/AE/ anaphylaxis	Induced by multiple NSAIDs	None	Unknown Inhib. COX-1?
	Urticaria/AE/ anaphylaxis	Induced by only one drug	Atopy Food allergy Drug allergy	Specific IgE
Delayed (>24h)	- FDE - Severe bullous reaction - Maculopapular eruption - Neumonitis - Aseptic meningitis - Nephritis - Contact and photocontact dermatitis	Induced by one or multiple drugs	Generally no	T cells Cytotoxic T cells NK cells Other

Kowalski ML et al . Allergy 2011; 66: 818-29

Treatment
Acute spontaneous urticaria

Intervention	Quality of the evidence	Strength of the recommendation
Non sedating anti-H1 antihistamines	Low	Strong
Alternatives		
Prednisolone 40 mg/d x4d	Low	Weak
Prednisolone 50 mg/d x3d	Very low	Weak
Anti-H2 antihistamine x5d	Very low	Weak

Algorithm for the SymptomaticTreatment of Chronic Spontaneous Urticaria

ns H1 Antihistamíne (nsAH)

If symptoms persist after 2 weeks

Increase dose of ns AH (up to 4x)

If symptoms persist after 1-4 weeks

+ LTRA, change nsAH

Exacerbation: systemic corticosteroid (3-7 days)

If symptoms persist after 1-4 weeks

+ H2-Antihistamine, Ciylosporin A, Dapsone, anti-IgE

Exacerbation: systemic corticosteroid (3-7 days)

Zuberbier T et al. Allergy 2009; 64: 1427-1433

Step-therapy for Chronic Urticaria

Other treatments (stanazolol, Theophylline)

Immunosuppressants: calcineurin inhibitors, mycophenolate, cyclophosphamide, or biologics

Anti-inflammatories: hydroxychloroquine, sulfasalazine, colchicine or dapsone

Consider adding leukotriene modifying agent, cyproheptadine or oral albuterol

Maximize H1-antihistamine therapy including H2-antagonist and/or doxepin

Monotherapy with second generation antihistamines

STUDIES ON INCREASED DOSE OF ANTIHISTAMINES IN CSU. (Sánchez-Borges M et al. JIACI, in press)

Author (Year)	Drug	Design	Duration (weeks)	n	Dose (mg)	Improvement with ↑ dose
Zuberbier (1996)	Cetirizine	DB, PC Cholinergic U	3	11	20	Yes
Kameyoshi (2007)	Cetirizine	Open CIU	-	21	20	Yes
Asero (2007)	Cetirizine	Open CIU	2	22	10,30	Insufficient
Finn (1999)	Fexofenadine	DB, PC CIU	4	439	20,60,120,240 BD	Similar with 60,120 and 240
Nelson (2000)	Fexofenadine	DB, PC CIU	4	418	20,60,120,240 BD	Similar with 60,120 and 240
Siebenhaar (2009)	Desloratadine	DB, PC Cold acquired U	1	30	5,20	Yes
Staevska (2010)	Desloratadine Levocetirizine	DB, PC CIU	4	80	5,10,20	Yes
Giménez-Arnau (2007)	Rupatadine	DB, PC CIU	4	533	10,20	No dif between 10 and 20
Dubertret (2007)	Rupatadine	DB, PC CIU	4	277	5,10,20	No dif between 10 and 20
Metz (2010)	Rupatadine	DB, PC Cold acquired U	1	21	20	Yes
Godse (2011)	Ebastine	Open CSU	4	30	10,20	Yes

Alternative Agents and Level of Evidence

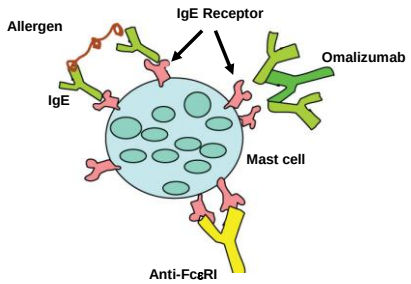
Level of evidence	Alternative agents
Ib	LTRAs, cyclosporin, hydroxychloroquine, androgens, phototherapy, nifedipine, theophylline
IIa	Omalizumab
IIb	Dapsone, mycophenolate, methotrexate, IVIg, anticoagulants
III	Sulfasalazine, cyclophosphamide, gold, plasmapheresis, colchicine
IV	Systemic corticosteroids

Khan DA. Allergy Asthma Proc 2008; 29: 439-46
Morgan M, Khan DA. Ann Allergy Asthma Immunol 2008; 100: 403-12

QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATION FOR USE OF INTERVENTIONS BASED ON GRADE SYSTEM

Drug	Quality of the evidence	Strength of the recommendation
2nd generation antihistamines	High	Strong (+)
1st generation antihistamines	High	Strong (-)
2a generation antihistamines (increased dose)	Moderate	Weak (+)
Anti-H2 +anti-H1 antihistamines	Moderate	Weak (+)
Oral corticosteroids (short course)	Low	Weak (+)
Oral corticosteroids	Very low	Strong (-)
LTRAs + anti-H1	Low	Weak (+)
Antinflammatories (dapsone, sulfasalazine, hydroxychloroquine, colchicine, mofetil mycophenolate)	Low-very low	Weak (+)
Immunosuppressants		
Cyclosporin	Moderate	Weak** (+)
Methotrexate	Very low	Weak (+)
Cyclophosphamide	Very low	Weak (+)
Biologics		
Omalizumab	Moderate	Weak** (+)
IVIg	Low	Weak (+)

(+) recommendation for, (-) recommendation against. *Sánchez-Borges M, et al. WAO Journal 2012; 5:125–147*



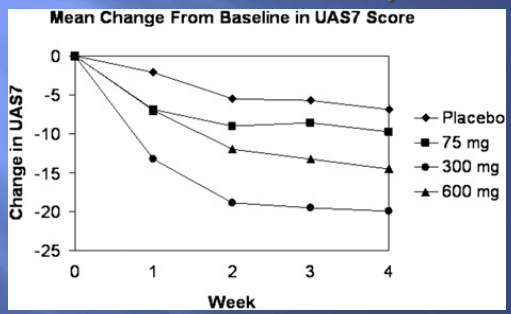
EFFECTS OF OMALIZUMAB IN PATIENTS WITH URTICARIA: UNCONTROLLED STUDIES

Author (year)	Urticaria type	n	No response	Partial response	Complete response
Ivyanskiy (2012)	CIU 12, AIU 6, DPU 1	19	3	5	11
Ferrer (2011)	CSU	9	2	5	2
Groffik (2011)	CSU	9	0	4	5
Sánchez-Machín (2011)	CSU	1	0	0	1
Saavedra (2011)	CSU	1	0	0	1
Krause (2010)	Dermographic U	1	0	0	1
Buller Kotte (2010)	Heat U	1	0	0	1
Binslej-Jensen (2010)	DPU	1	0	0	1
Magerl (2010)	CSU	8	0	1	7
Al-Ahmad (2010)	AIU	3	0	0	3
Kemoli (2010)	CSU	1	0	0	1
Sabroe (2010)	Cholinergic U	1	1	0	0
Waiber (2009)	Solar U	1	0	1	0
Maspero (2009)	AIU	1	0	0	1
Kaplan (2008)	AIU	12	1	4	7
Güzelbey (2008)	Solar U	1	0	0	1
Metz (2008)	Cholinergic U	1	0	0	1
Godse (2008)	CSU	1	0	0	1
Sands (2007)	CAE	3	0	0	3
Spector (2007)	2 AIU, 1 CSU	3	0	0	3
TOTAL		78	7 (8.9%)	20 (25.6%)	51 (65.3%)

EFFECTS OF OMALIZUMAB IN PATIENTS WITH URTICARIA: DOUBLE-BLIND PLACEBO-CONTROLLED STUDIES

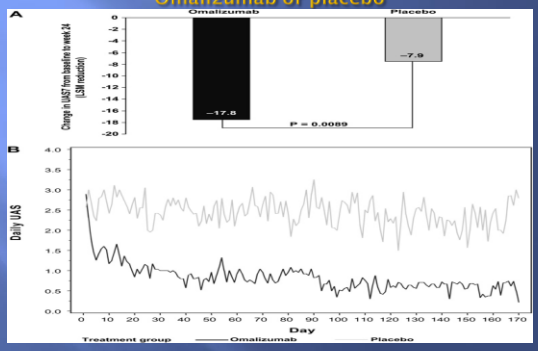
AUTHOR (YEAR)	URTICARIA TYPE	n	RESPONSE (%)
Saini et al (2011)	CSU	90	68.8
Maurer et al (2011)	CU with anti-TPO IgE Abs	49	70.4

Mean change from baseline in UAS7 during treatment with Omalizumab or placebo



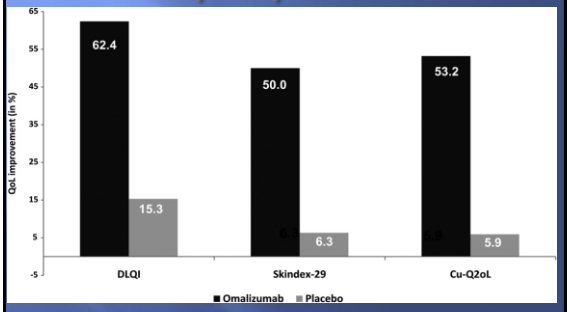
Saini S et al. J Allergy Clin Immunol 2011;128: 567-73

Change in UAS after 24 weeks of treatment with Omalizumab or placebo



Maurer M et al. J Allergy Clin Immunol 2011; 128: 202-9

Percentage improvement in quality of life



Maurer M et al. J Allergy Clin Immunol 2011; 128: 202-9

Omalizumab: Mechanisms of action in Urticaria

1. Anti-IgE: decrease of free IgE, cell-surface IgE, FcεRI numbers *(Beck LA et al. JACI 2004; 114: 527-30)*
2. Eosinophil apoptosis
3. Inhibition of Ag presentation by dendritic cells
4. Downregulation of cytokines: IL-2, IL-4, IL-13, TNF-α *(Iemoli E et al. JIACI 2010; 20:252-4)*
5. Reducion of IL-2 and IL-13(+) T lymphocytes *(Noga O et al. JACI 2006; 139: 122-31)*
6. Increased activity of CD4(+) T cells
7. Decrease of basophil releasability
8. Reduction of B cell activation and homing *(Iemoli E et al. JIACI 2010; 20:252-4)*

PROGNOSIS OF URTICARIA

Type	Comments	References
Acute	In children 20-30 % risk of CU	• Legrain V et al. Pediatr Dermatol 1990; 7: 101-7 • Mortureux P et al. Arch Dermatol 1998; 134: 319-23
Chronic	1/3 resolve in 1-5 years 1/3 partial improvement Spontaneous remission at 1 year 30-50 % 20 % at 5 years Persistence after 5 years 20 % **Prognostic factors:** AE, physical urticaria , + ASST, severe symptoms	• Engstrom J, Neher J. J Family Practice 2011; 60: 168a-168b • Kaplan A. N Engl J Med 1995; 332: 1767-72 • Weller K et al. Hautarzt 2010; 61: 750-7

Duration of CSU in selected patients

Study	Country	n	Resolved in 1 year (%)	Long term course
Juhlin (1981)	**Sweden**	**330**	**20**	**15 % >8 years**
Humphreys y Hunter (1998)	**UK**	**365**	**NR**	**4 % > 15 years**
Kozel et al (2001)	**Netherlands**	**220**	**47**	**NR**
Van der Valk et al (2002)	**Netherlands**	**372**	**NR**	**51 % >10 years**
Toubi et al (2004)	**Israel**	**139**	**25**	**14 % >5 years**
Gaig et al (2004)	**Spain**	**5003**	**80**	**11 % > 5 years**
Kulthanan et al (2007)	**Thailand**	**337**	**35**	**NR**

Maurer M et al. Allergy 2011; 66: 317-30