



Vascularites Cryoglobulinémiques

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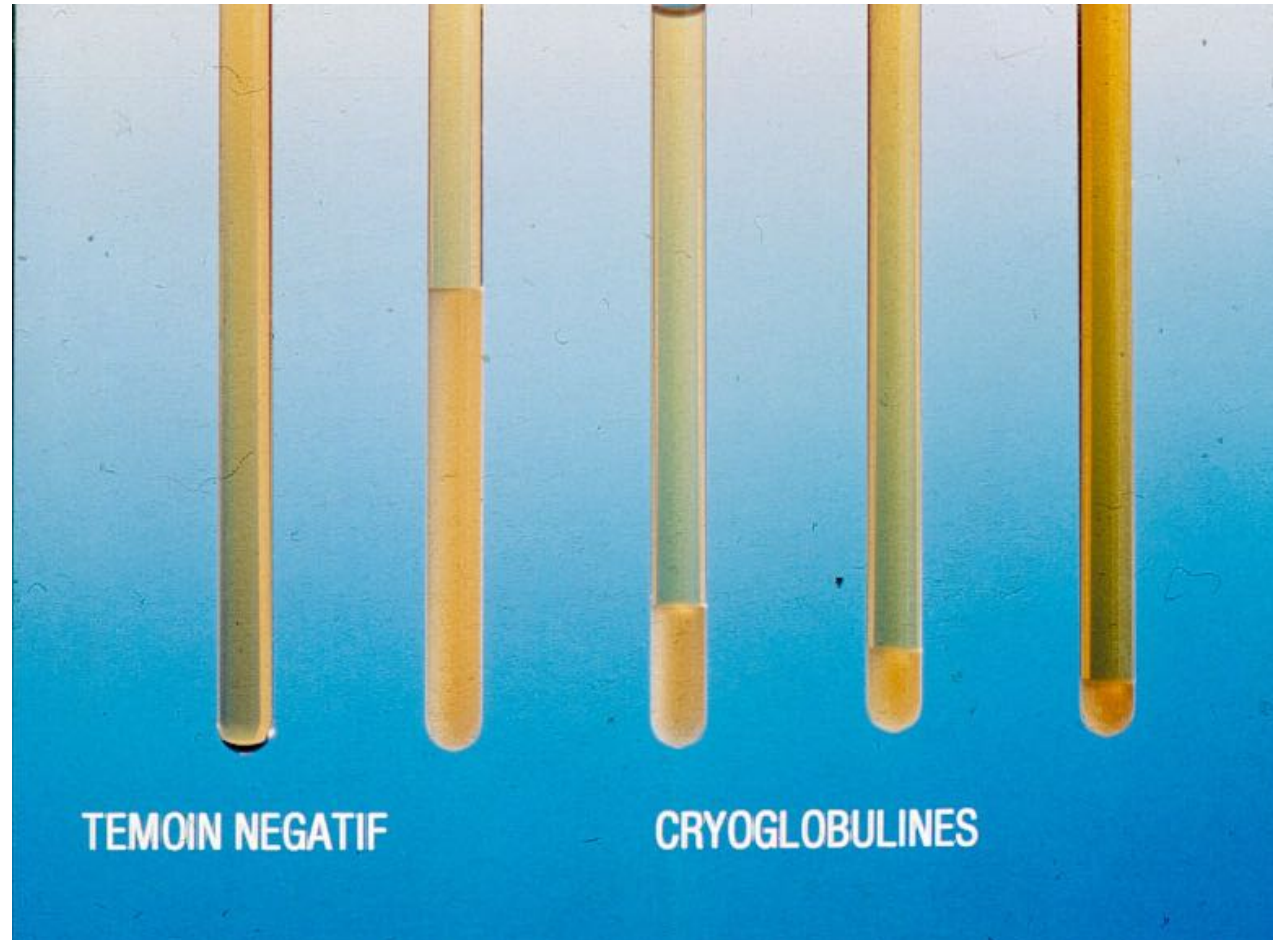
Disclosures

Consulting, research grant and lecturing fees from Abbvie, Amgen, Sanofi, Roche-Chugai, Janssen and Glaxo Smith Kline.

Cryoglobulinemia: Définitions

Cryoglobulinemia

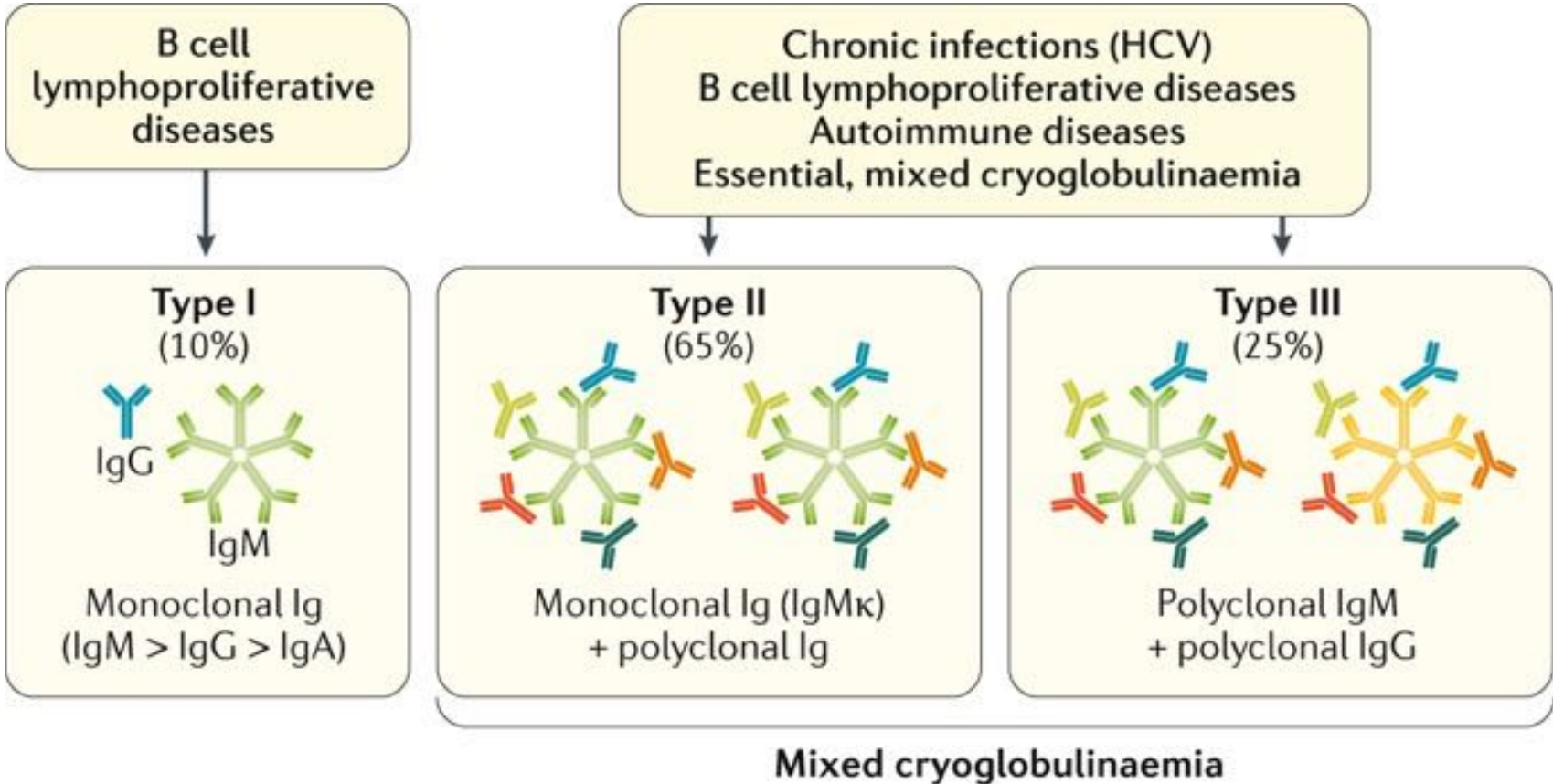
= Immunoglobulins that precipitate at $t^{\circ} < 37^{\circ}\text{C}$
and re-dissolve if the t° rises to $> 37^{\circ}\text{C}$



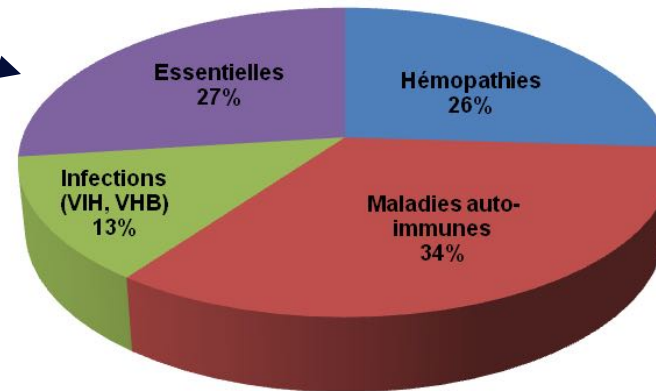
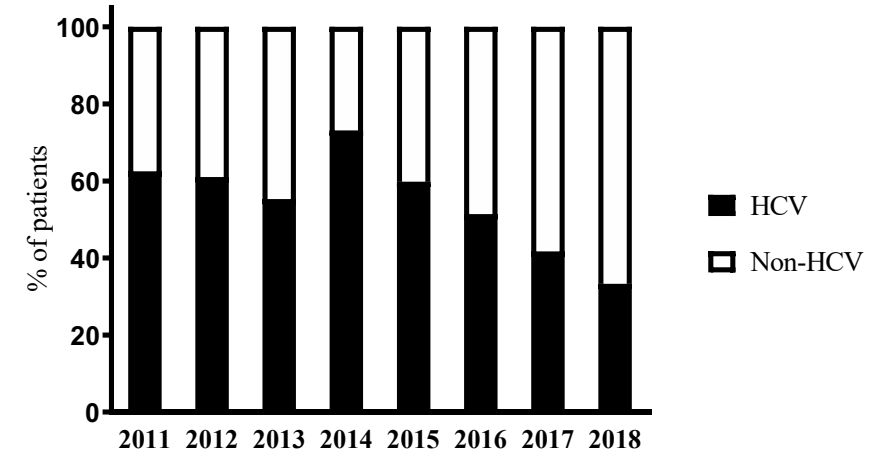
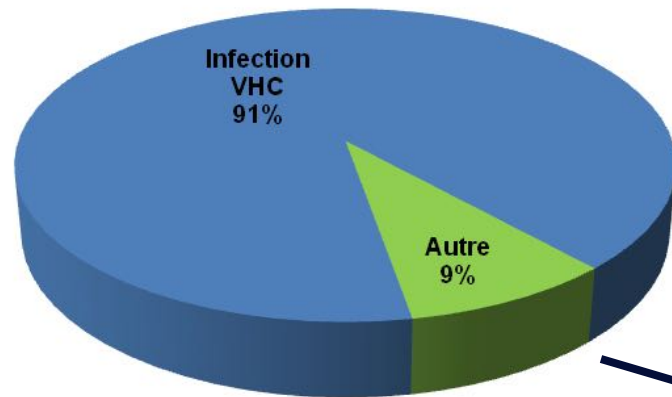
Cryoglobulinemia

- **Variable serum level from 0.05 to 50 g/L:**
 - Difficulties in quantification of cryoglobulins
 - ± Correlation with clinical manifestations/severity
- **Temperature of precipitation between 10 and 37°C**
- **Immunochemical characterization**
 - Electrophoresis after isolation
 - Immunofixation

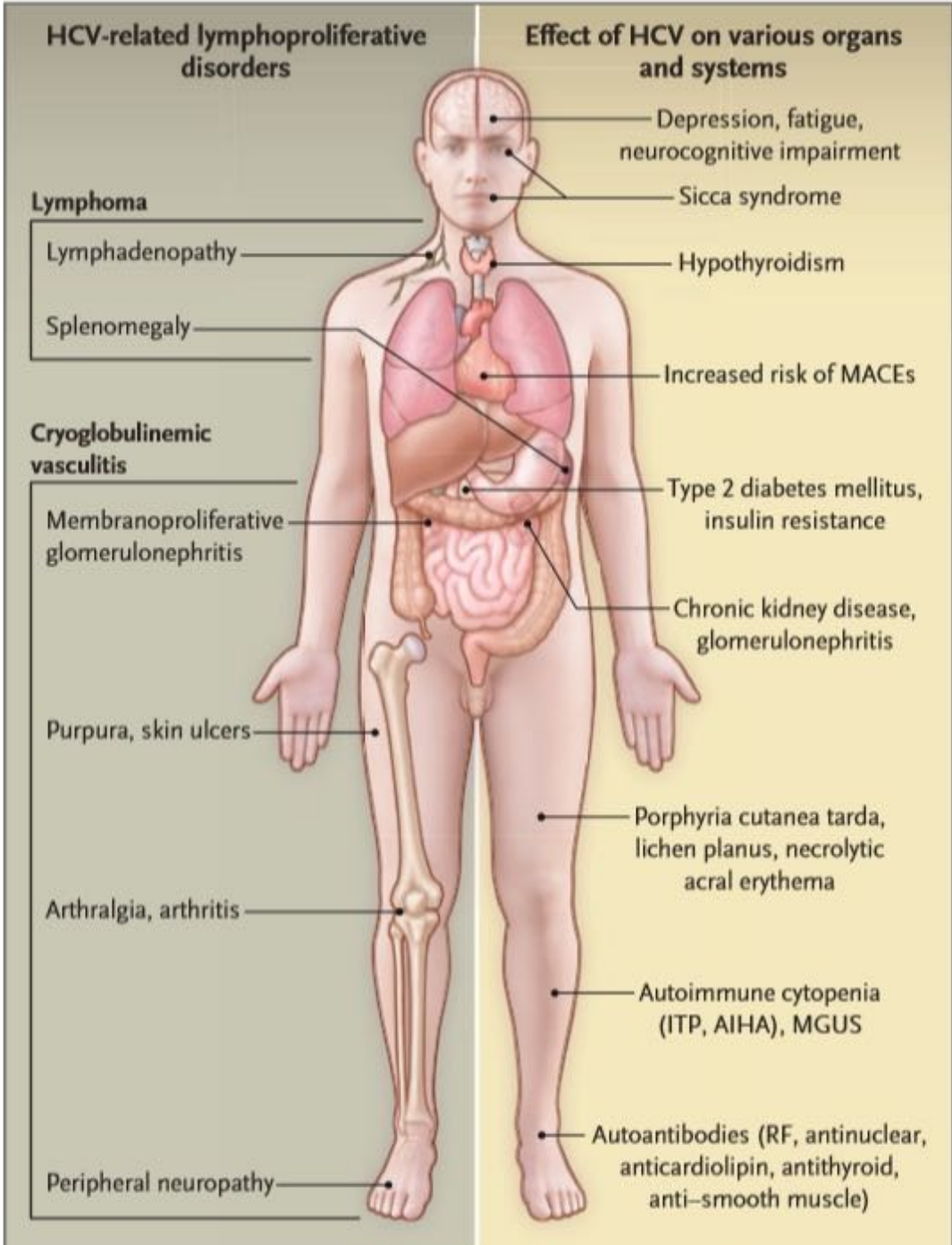
Classification of cryoglobulinaemia based on immune typing



Mixed Cryoglobulinemia and Related Diseases

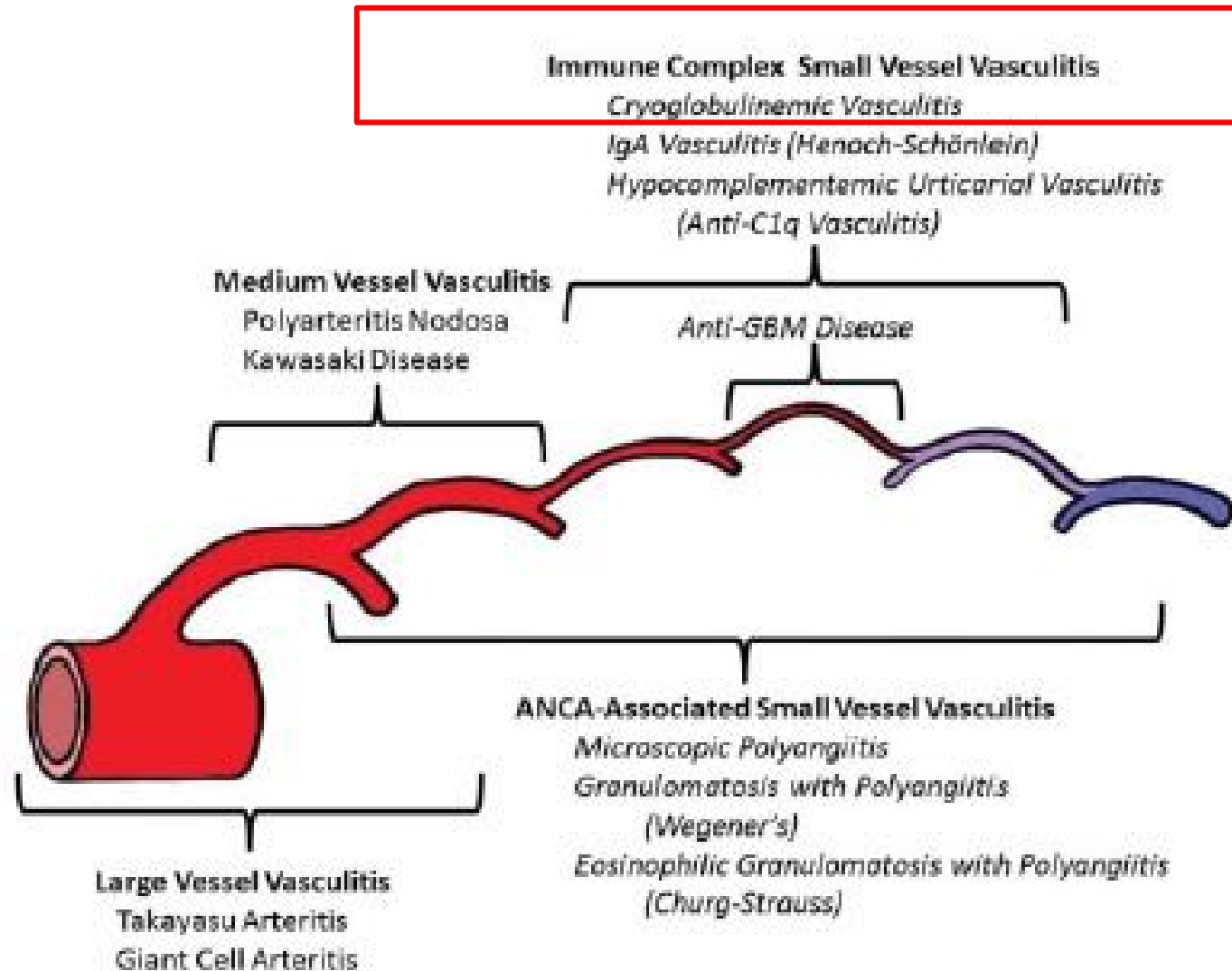


N = 1434 patients



Cryoglobulinemia: Clinical spectrum

Vasculitides classification



Clinical, serological and pathological hallmarks of cryoglobulinaemic vasculitis



Serum MCs alone

- Possible preclinical condition with or without RF and/or low C4
- Careful clinical evaluation of possible underlying infectious (HCV or HBV) autoimmune and/or haematological and/or neoplastic disease
- Monitoring without treatment

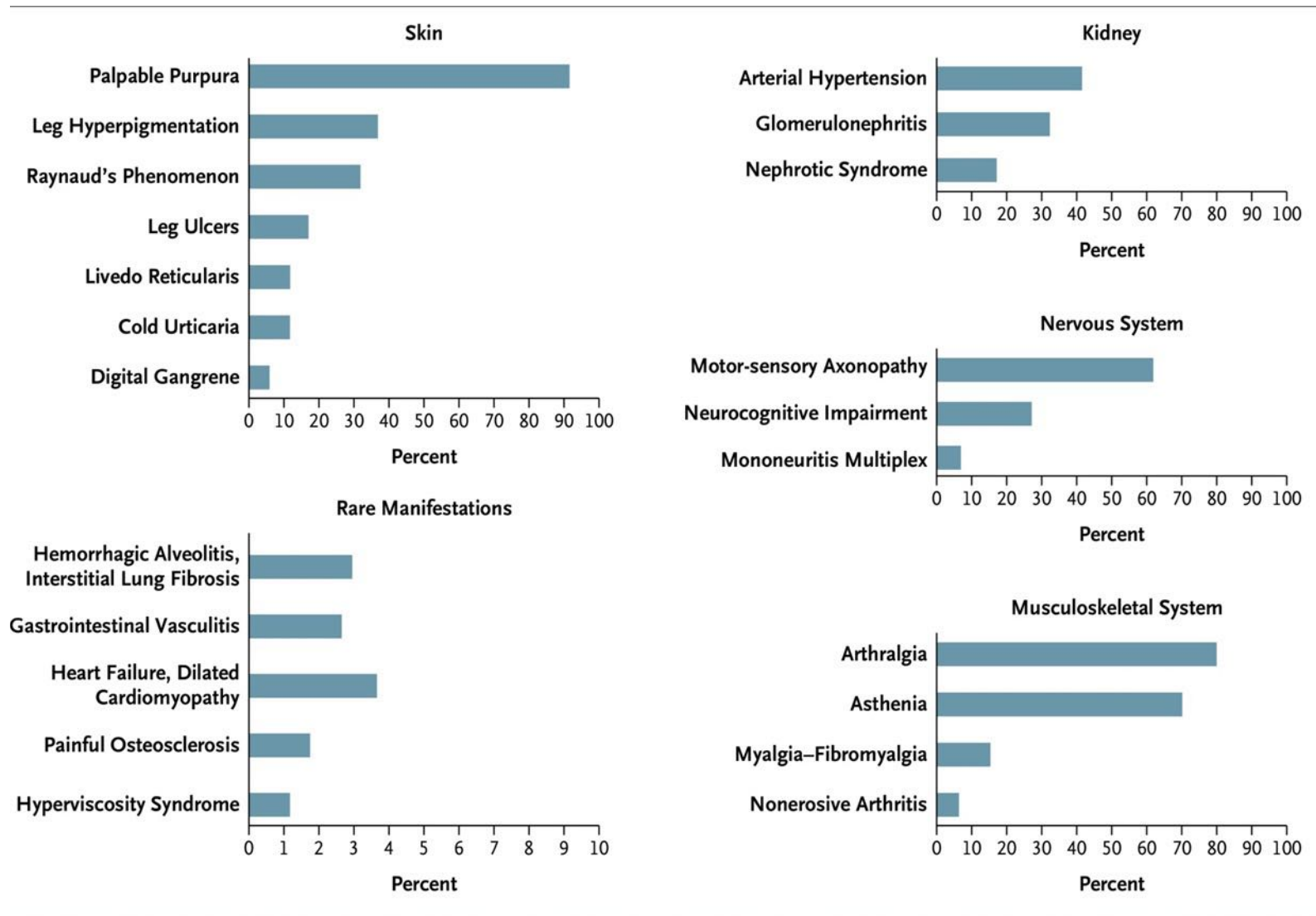
Mixed cryoglobulinaemia vasculitis

Clinical	Serological
<ul style="list-style-type: none"> • Purpura • Weakness • Arthralgias • Liver involvement • Renal involvement • Skin involvement • Peripheral neuropathy 	<ul style="list-style-type: none"> • Mixed cryoglobulins • RF+ • Low C4
	Pathological
	<ul style="list-style-type: none"> • Leukocytoclastic vasculitis • B cell expansion

Clinical symptoms without serum MCs

- Absence of cryoprecipitable IC
- Repeat cryoglobulin detection at different time intervals to confirm the diagnosis of cryoglobulinaemic vasculitis
- Careful clinical evaluation of possible underlying infectious (for example, HCV, HBV) autoimmune and/or haematological and/or neoplastic disease

Main Features of Cryoglobulinemia Vasculitis



Cutaneous Manifestations of Cryoglobulinemia Vasculitis



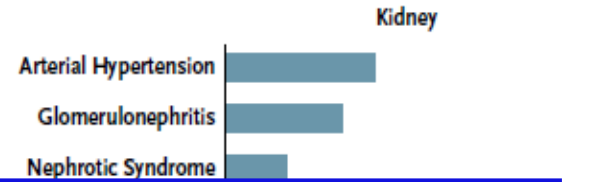
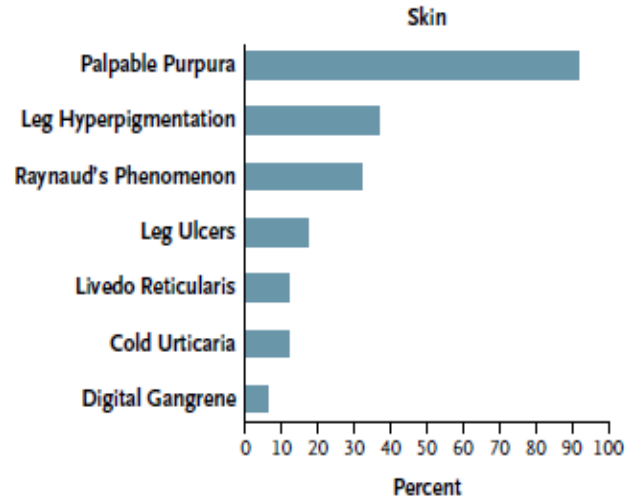
Cutaneous Manifestations of Cryoglobulinemia Vasculitis



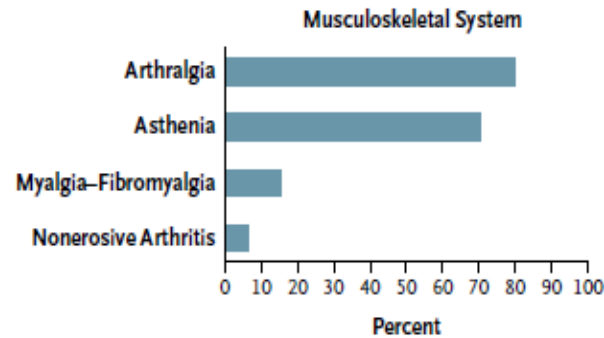
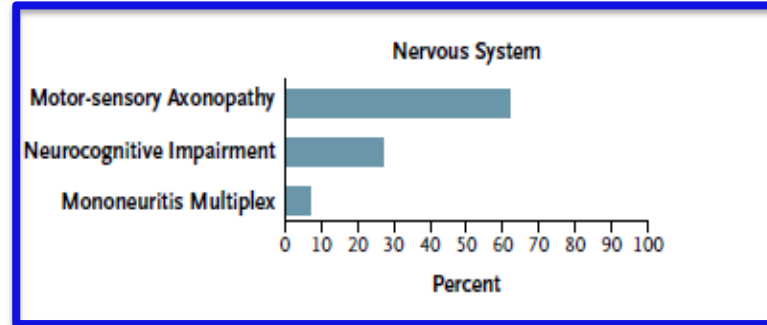




Main Features of Cryoglobulinemia Vasculitis

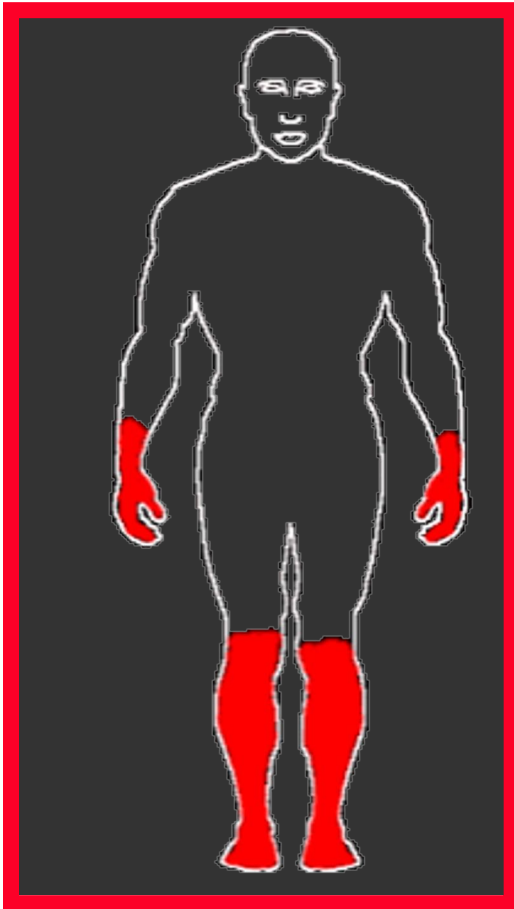


3. NERVE, 65%

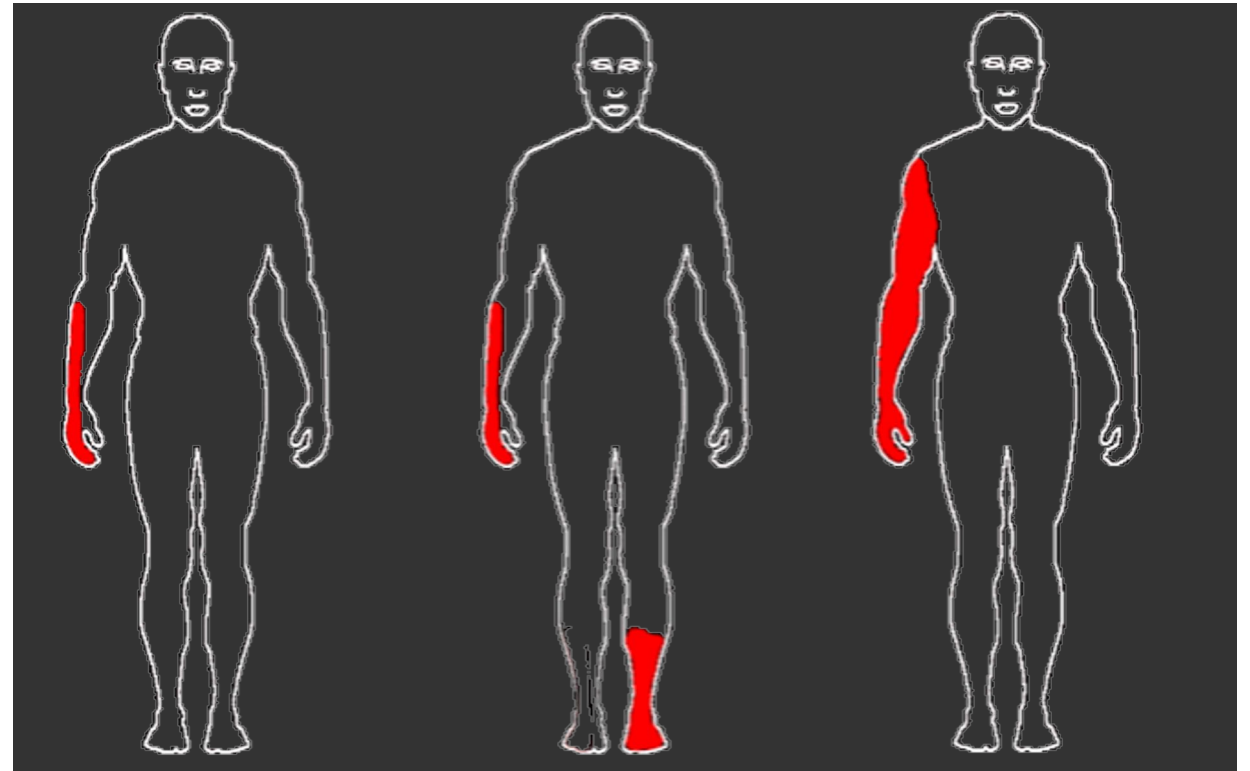


Cryoglobulinemia and Neuropathy

Distal Polyneuropathy 80%

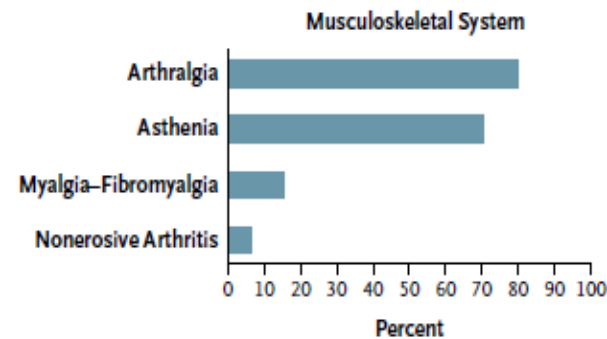
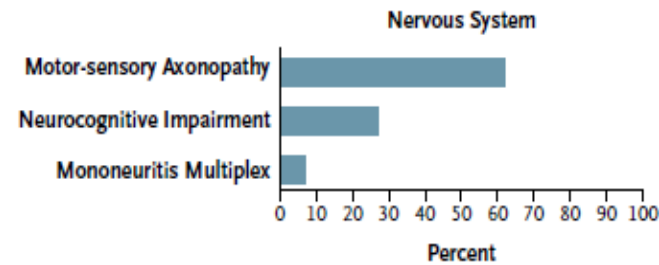
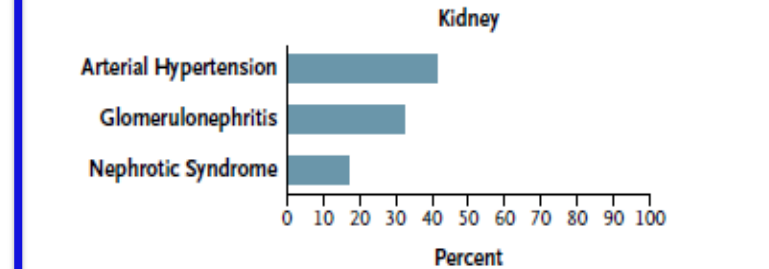
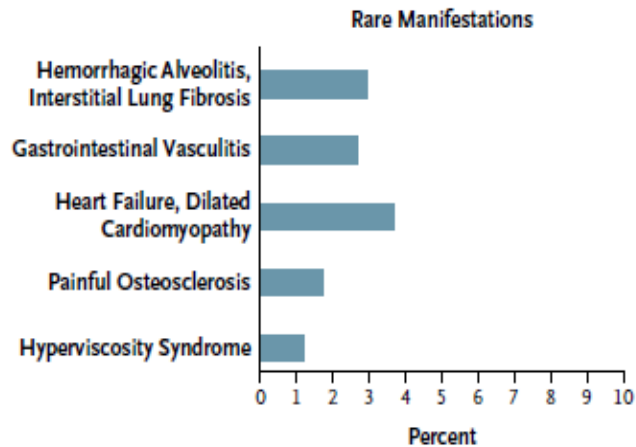
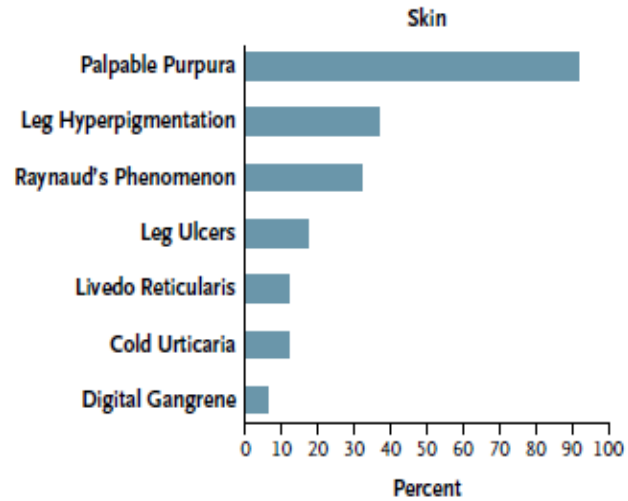


Multiple Mononeuropathy 20%

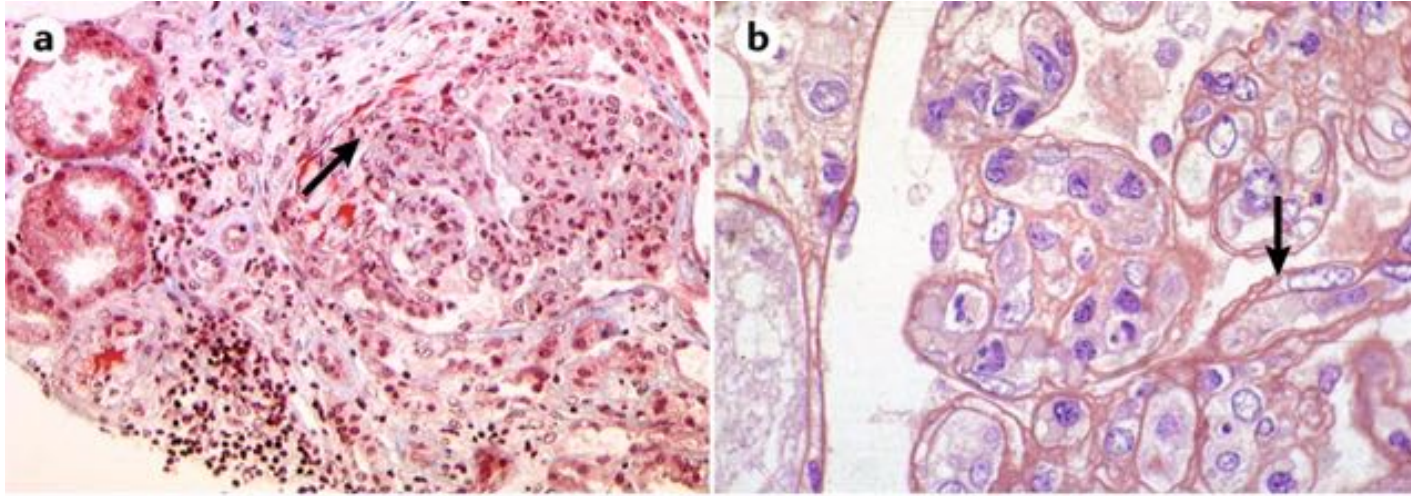


Main Features of Cryoglobulinemia Vasculitis

KIDNEY, 35%

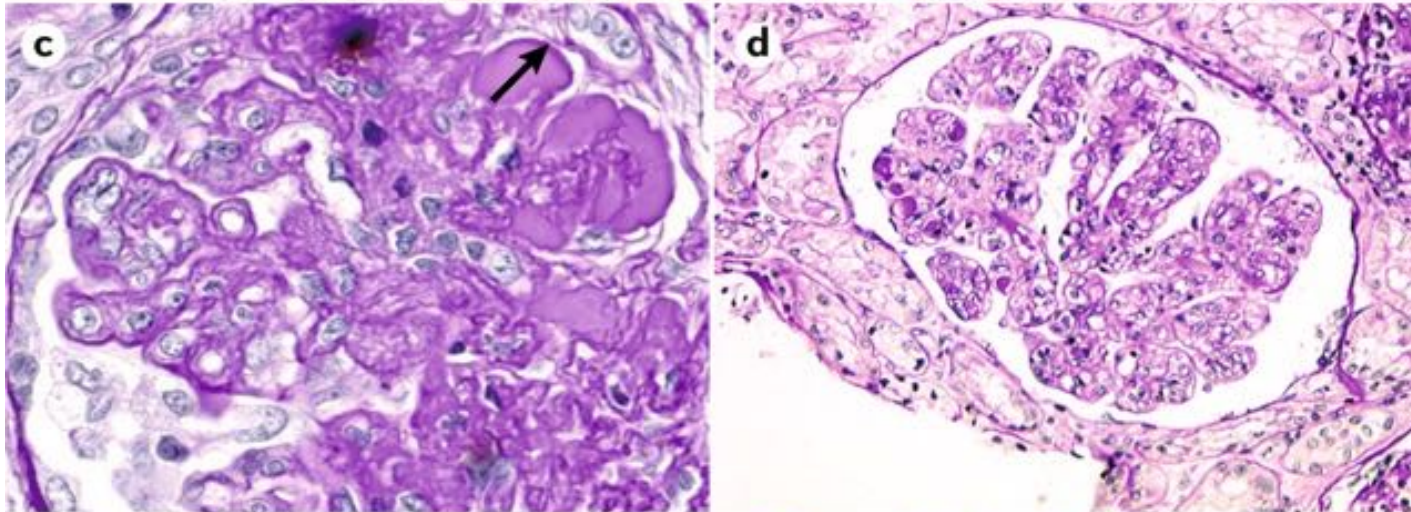


Renal pathology in cryoglobulinaemic vasculitis



a | Extracapillary proliferation in the kidney, with features of fibrinoid necrosis (arrow) and interruption of the capsule.

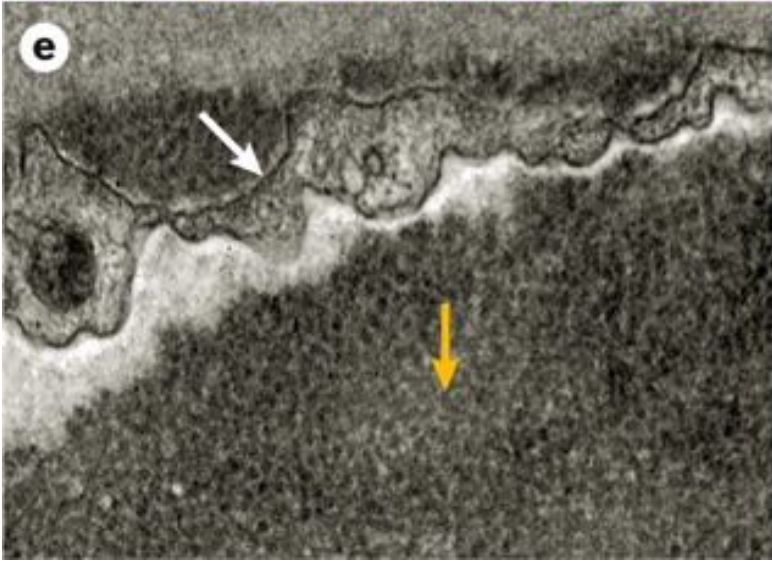
b | Membranoproliferative pattern with **double contour appearance** of the glomerular basement membrane (arrow).



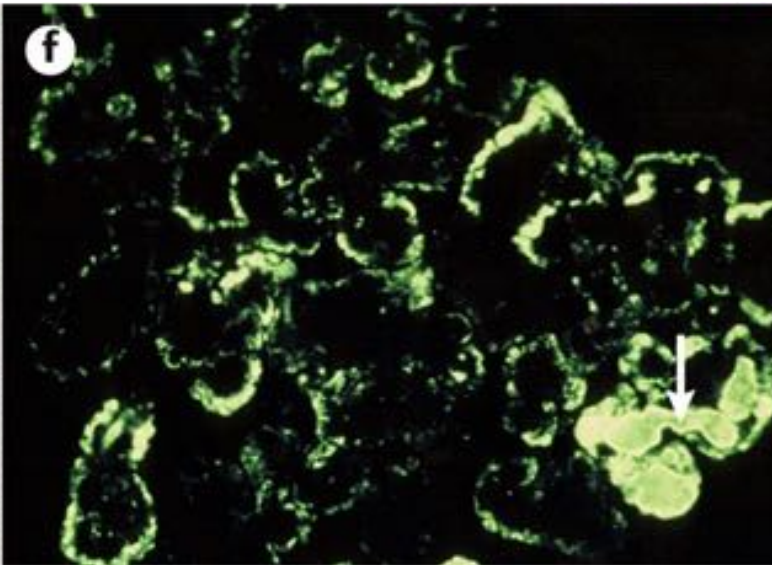
c | Periodic acid–Schiff (PAS)-positive endoluminal pseudothrombi (corresponding to cryoglobulin precipitates) (arrow).

d | PAS stain shows diffuse membranoproliferative glomerulonephritis.

Renal pathology in cryoglobulinaemic vasculitis

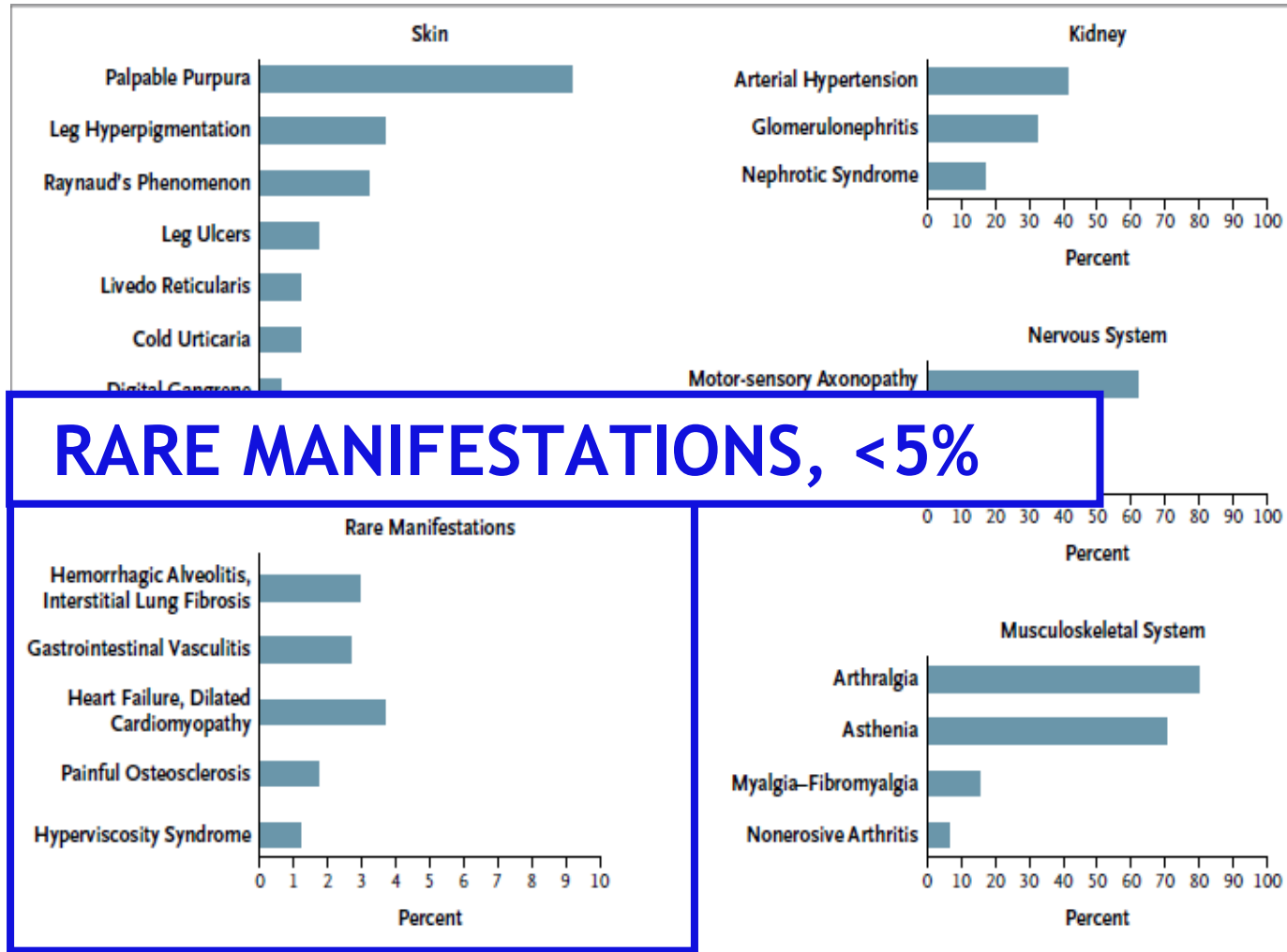


e | Electron microscopy showing **electron-dense deposits** corresponding to **cryoglobulin precipitates** in the subendothelial space (white arrow). Electron-dense material with **structured tubular shape** can also be observed in the capillary lumen (yellow arrow).



f | Immunofluorescence studies showing **immunoglobulin M** with **segmental accumulation** (arrow) corresponding to the **thrombi** observed with light microscopy.

Rare Features of Cryoglobulinemia Vasculitis



Life-Threatening Cryoglobulinemia

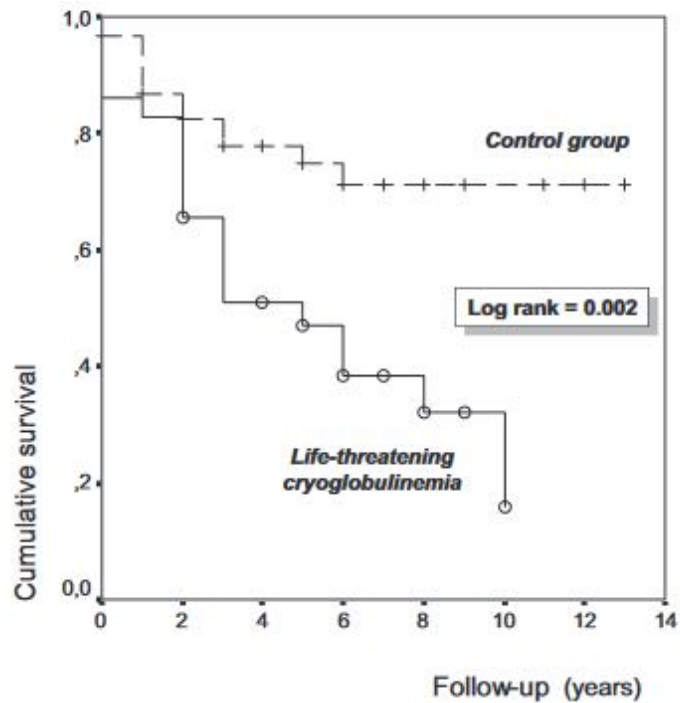


Figure 2 Survival rate of patients with life-threatening cryoglobulinemia in comparison with the control group (log rank significance = 0.0023).

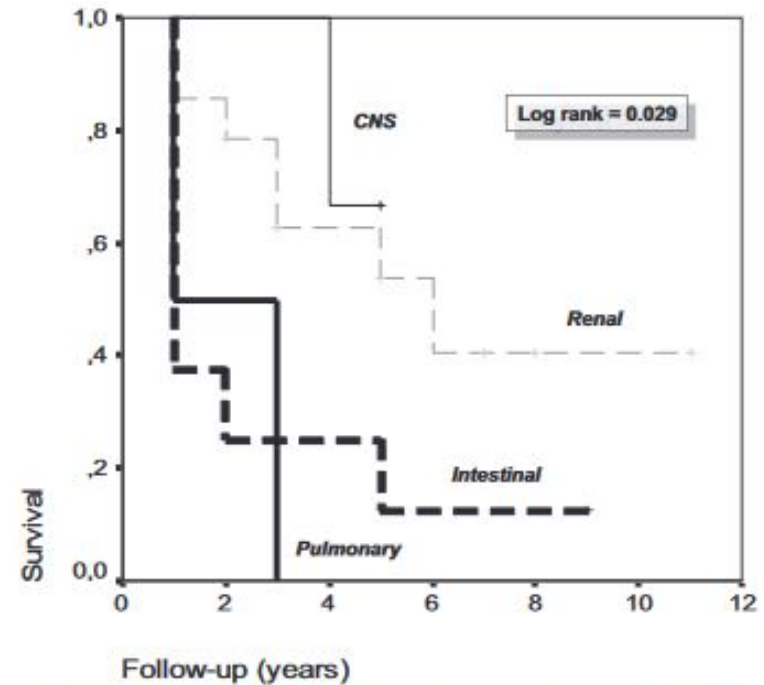


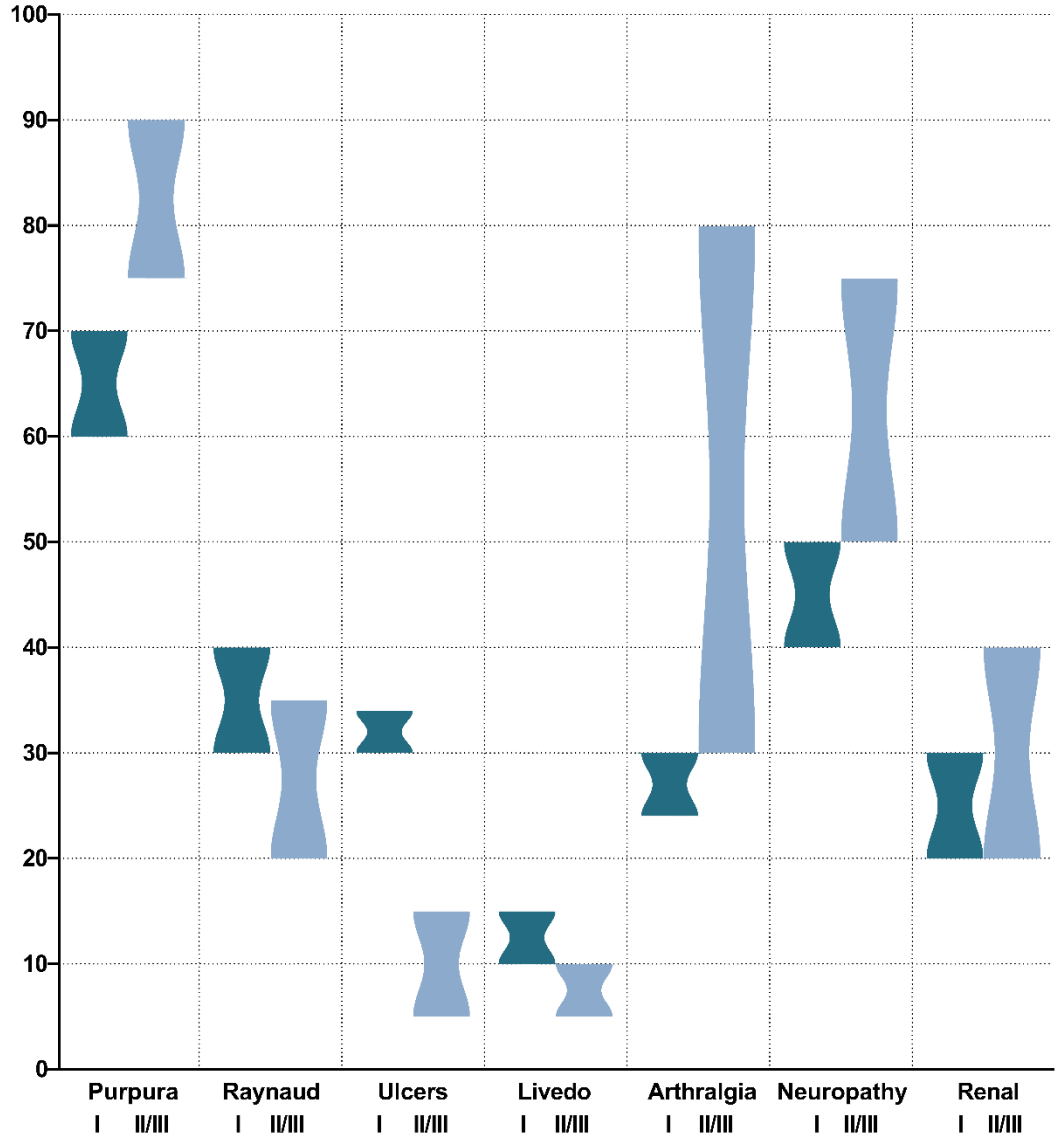
Figure 1 Significant differences in survival curves after the first episode of severe cryoglobulinemia according to the organ involved (log rank significance = 0.029).

Cryoglobulinemia: Monoclonal (type I) vs mixed

Cryoglobulinemia: monoclonal vs mixed

monoclonal (type I)	mixed (type II)
High level (1-30g/l)	Low level ≤ 1 g/l
mIgM or IgG >>> IgA	mIgM κ ++
RF and/or low C4 (40%)	RF and/or low C4 >70%
Vascular obstruction > vasculitis	Vasculitis > vascular obstruction
Cold induced symptoms (Raynaud's, skin necrosis++) and cryovas	CryoVas symptoms
Avoidance of cold++ , warming	Rituximab based therapy
Targeted treatment based on mIgM or IgG	

Frequency of main clinical manifestations of Type I and mixed cryoglobulinemia



Mr B 52 ans

- Depuis hiver 2016 : purpura des pieds associé à des lésions d'allure urticarienne au froid au niveau du tronc, des cuisses et des fesses, qui s'améliorent lors du réchauffement. Par ailleurs, acrosyndrome et rhinite croûteuse depuis environ deux ans.
- Octobre 2017 au Pérou, lésions nécrotiques ulcérées de la face interne des cuisses, de l'oreille droite, des bras.
- Octobre 2018: un seuil thermique estimée $< 10^{\circ}$, réapparition de lésions purpuriques nécrotiques au niveau des mollets, des faces internes des cuisses, associées à des lésions purpurique des fesses.





- Pas d'atteinte rénale, ni de neuropathie.
- MGUS IgG Kappa avec un pic monoclonal IgG Kappa 10 et 15 g/l
- Cryoglobulinémie de type I IgG Kappa à 4,7 g/l initialement. Pas de cryofibrinogène. Pas de facteur rhumatoïde. C4 normal.
- Biopsie des lésions des membres inférieurs objective des thromboses vasculaires multiples. Pas d'argument pour une vascularite. L'immunofluorescence est négative.

Echanges plasmatiques
Eviction du froid



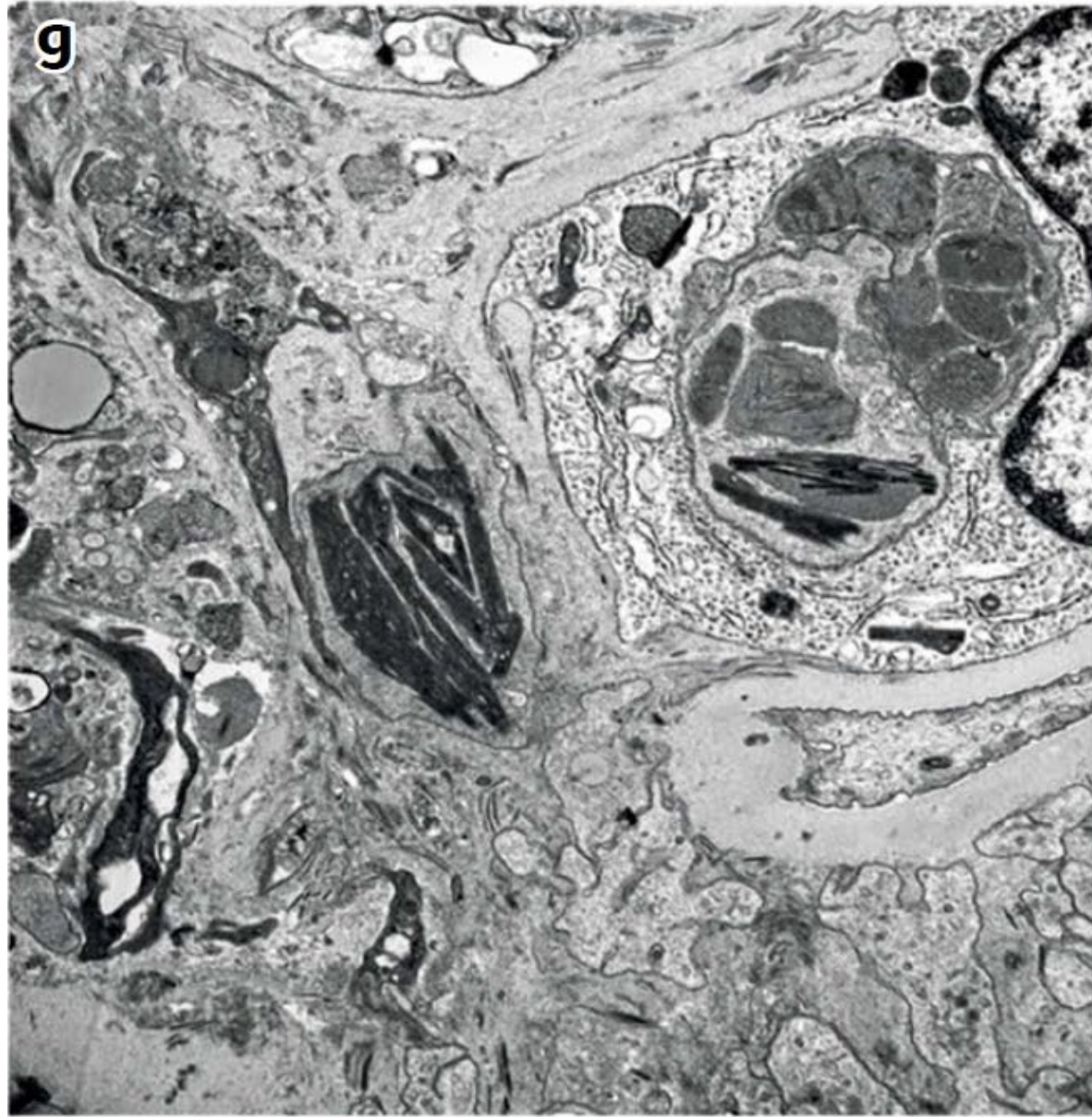


Cryoglobulinemia vs other cryoproteins

61 yrs old patient, mIgG k (« MGUS »)
purpura, renal artery thrombosis

Crystal-cryoglobulin





Phagolysosomes and crystal-cryoglobulins in mesangium

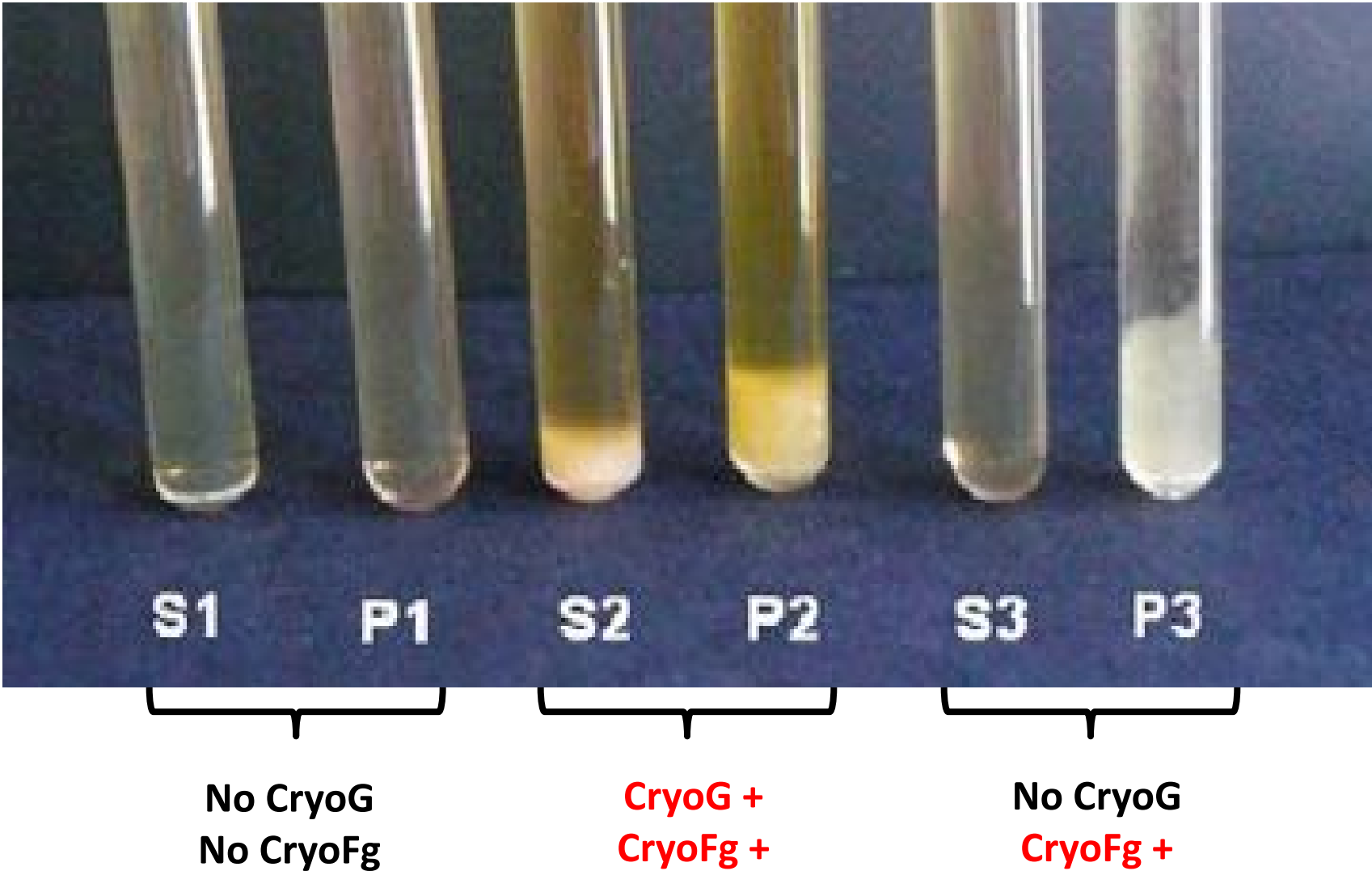
Cryofibrinogenemia



Cryofibrinogenemia vs Cryoglobulinemia

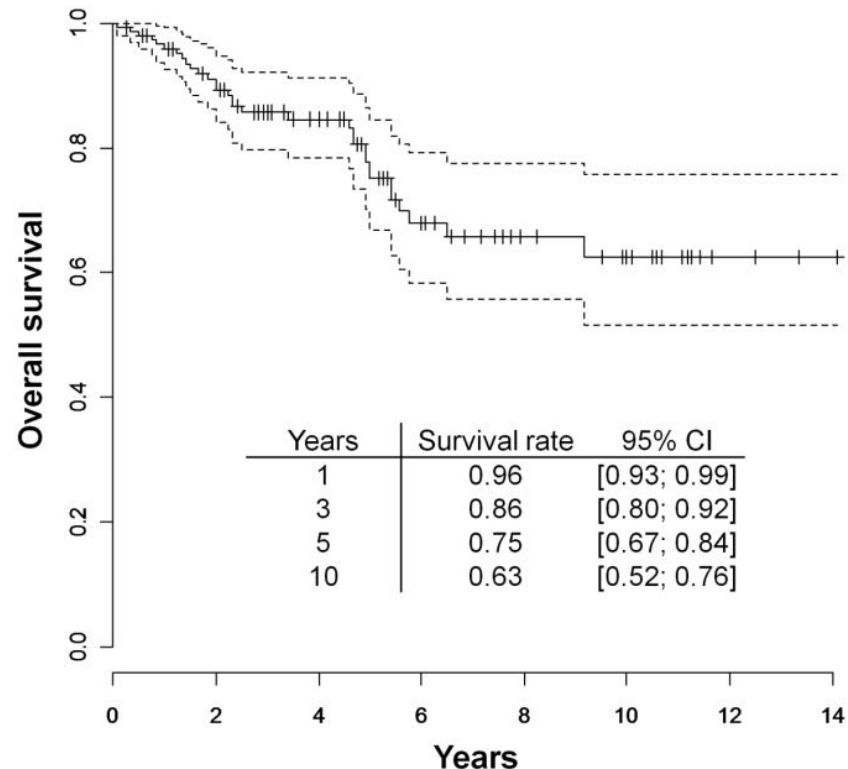
- **Other cause of cold induced skin ulcers and small vessel vasculopathy**
- Mechanical arterial thrombosis by precipitation of cryofibrinogen
- Rare, 10% of cryoproteins
- **Detection in plasma and not in serum**
- Essential or secondary (infections, AID, cancer, hemopathy)
- **Avoidance of cold exposure, fibrinolytics**

Cryofibrinogenemia vs cryoglobulinemia



Cryoglobulinemia: Prognosis

Prognosis of HCV-related mixed cryoglobulinemia vasculitis



Causes of death

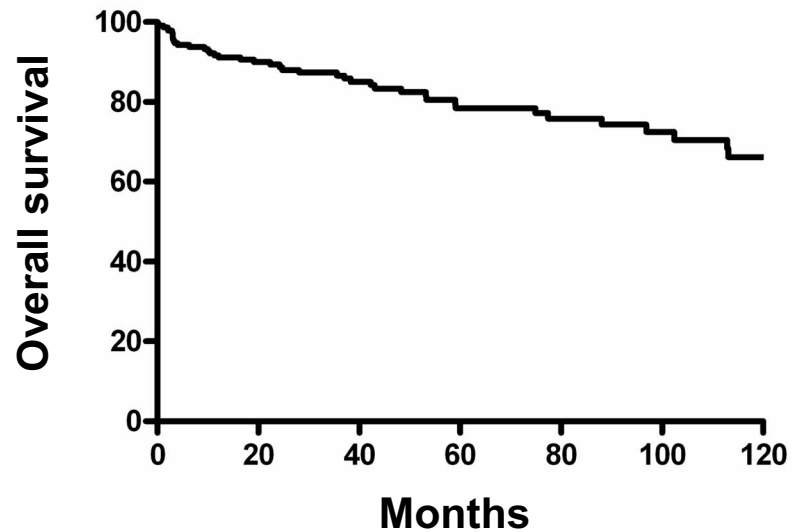
End-stage liver disease
Serious infection

Prognostic factors of survival

Liver fibrosis
Vasculitis severity
Use of immunosuppressants

Antiviral therapy

Overall survival in mixed cryoglobulinemia



Median follow-up (months) 54 (9-77)

Death, n (%) 42 (17%)

VHC-

Survival

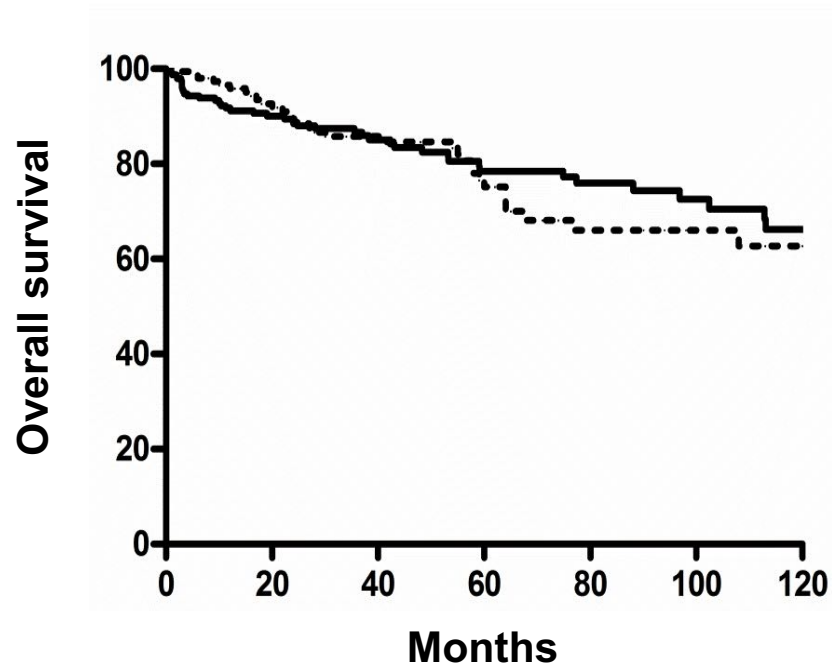
1-year **91 %**

2-year **89 %**

5-year **79 %**

10-year **65%**

Overall survival in mixed cryoglobulinemia



Median follow-up (months) 54 (9-77)

Death, n (%) 42 (17%)

	VHC-	VHC+
--	-------------	-------------

Survival

1-year	91 %	96%
--------	-------------	-----

2-year	89 %	90%
--------	-------------	-----

5-year	79 %	75%
--------	-------------	-----

10-year	65%	63%
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Independent factors associated with survival in CryoVas

	<i>Univariate analysis</i>		<i>Multivariate analysis</i>	
	HR 95% CI	P value	HR 95% CI	P value
Age > 60 years	2.96 (1.5-5.2)	0.0008	1.04 (1.02-1.08)	0.003
Male gender	2.8 (1.7-7.1)	0.0005		
Renal involvement	2.0 (1.1-4.0)	0.026		
GFR < 60 ml/min	5.2 (1.3-22.6)	0.007	5.2 (1.2-22.5)	0.02
Hematuria	1.9 (1.1-4.1)	0.03		
Proteinuria > 1 gr/day	1.8 (0.97-3.8)	0.06		
Gastrointestinal	3.6 (2.7-33.7)	0.0005		

Cryoglobulinemia and Lymphoma

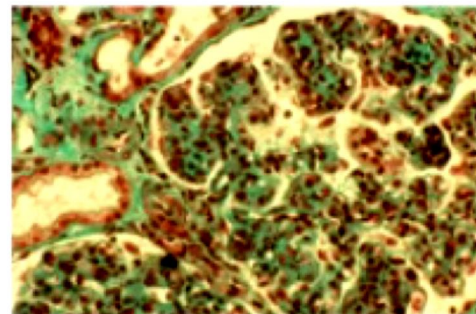
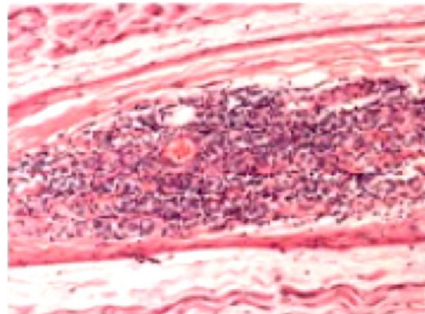
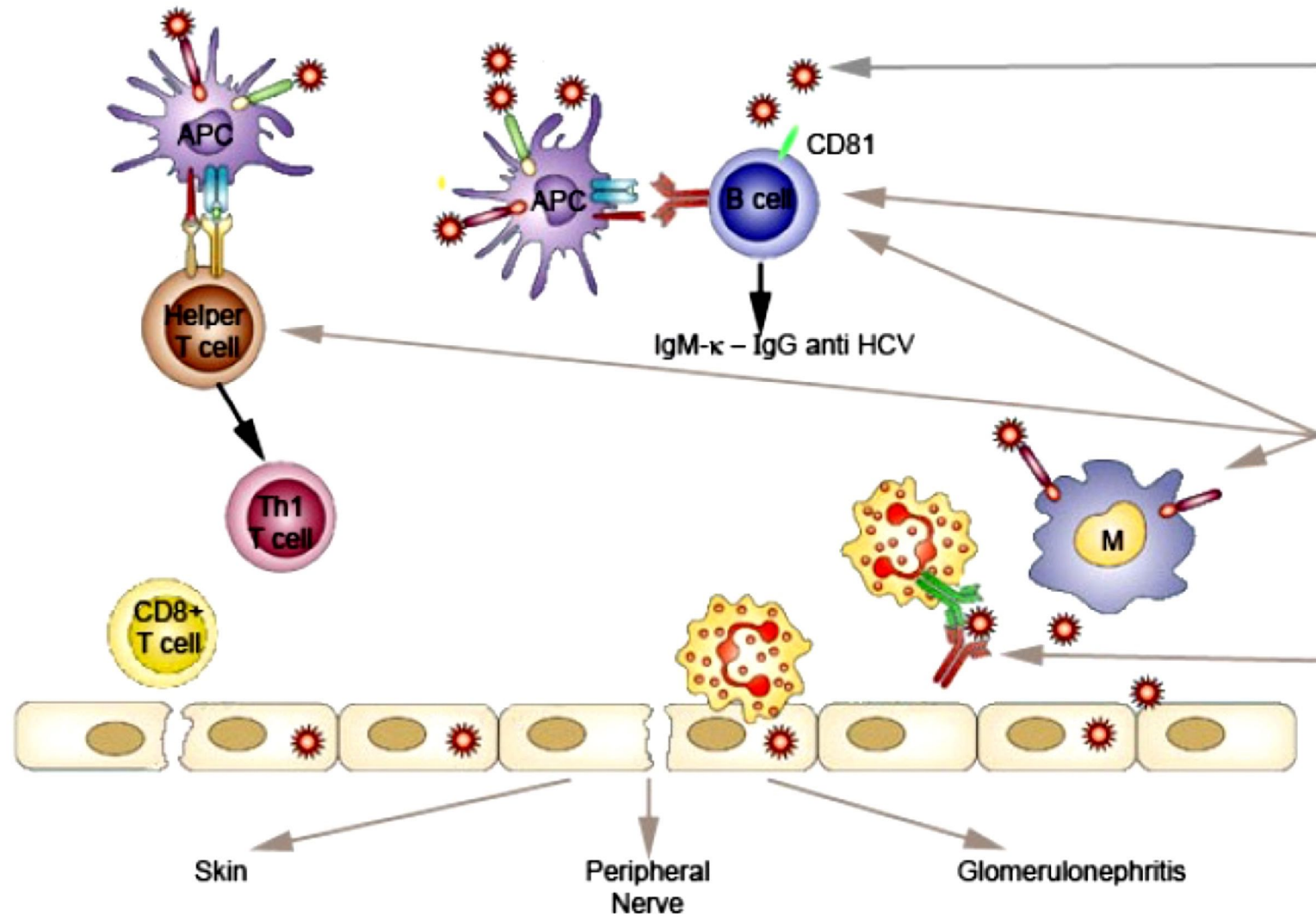
Cryoglobulinemia and B NHL

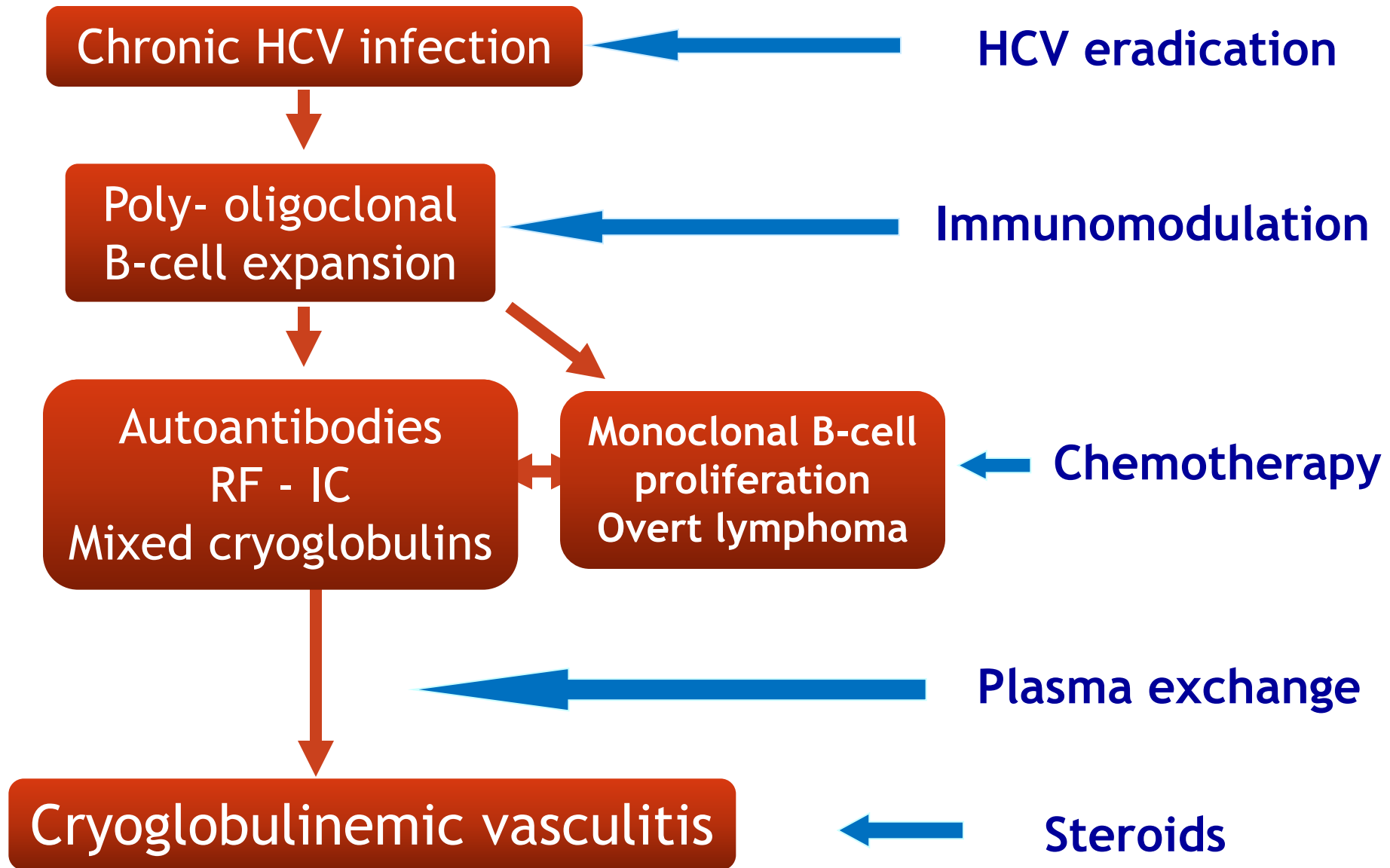
- 5 à 10%
- Mean time of 8.8 years after diagnosis of mixed cryo (Ferri et al 2004)
- More frequent in non HCV cryo (35%) vs HCV cryo (15%) (Saadoun et al 2006)
- Frequently Extra-nodal: salivary glands, liver

Cryoglobulinemia and B NHL

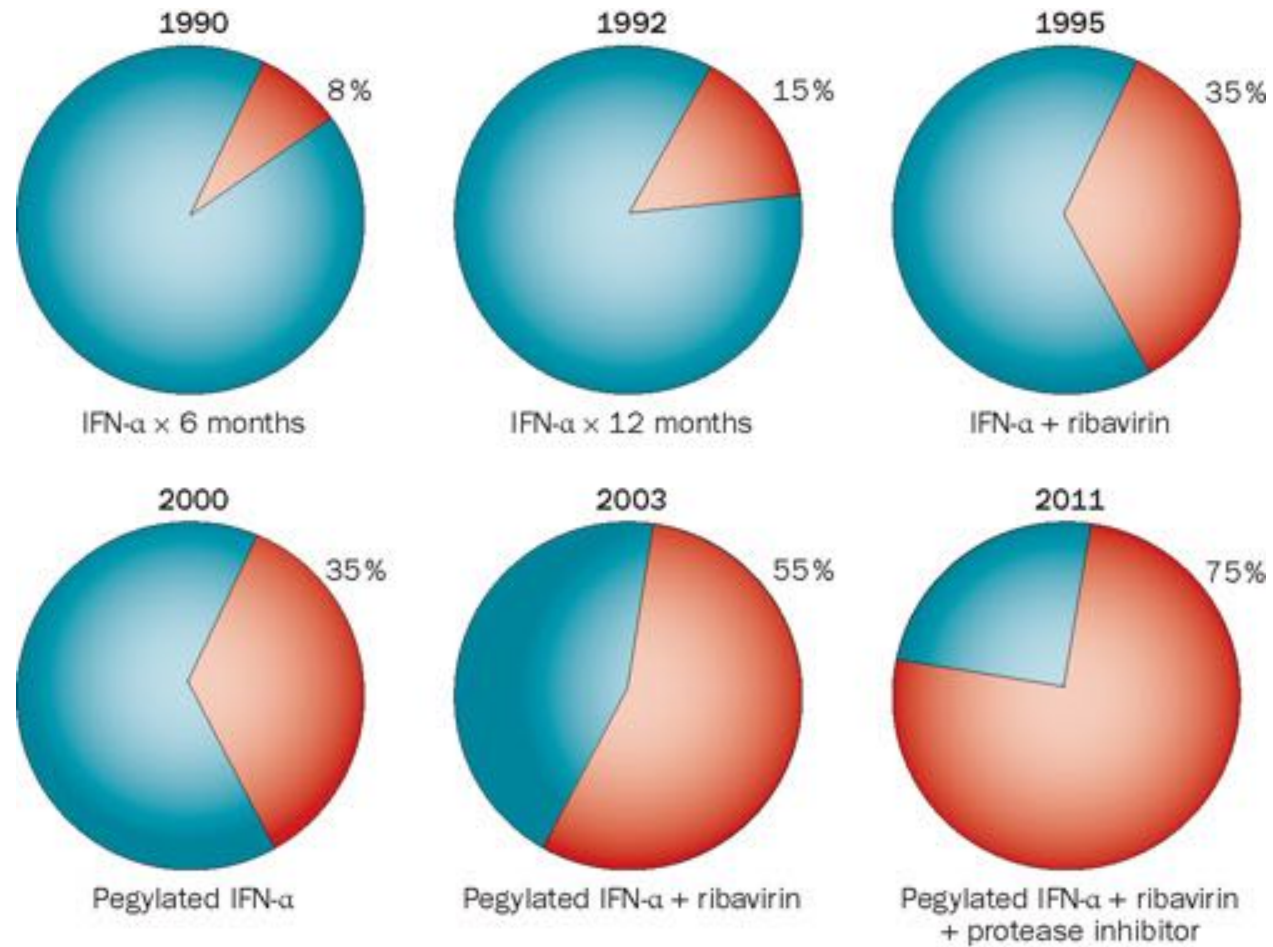
- 5 à 10%
- Mean time of 8.8 years after diagnosis of mixed cryo (Ferri et al., 2004)
- More frequent in non HCV cryo (35%) vs HCV cryo (15%) (Saadoun et al 2006)
- Frequently Extra-nodal: salivary glands, liver
- Histological subtypes :
 - MALT lymphoma ++
- Marginale zone (MZ) (#30%) (including splenic with villous lymphocytes (SLVL))
- Lympho-plasmocytic (# 20%)
 - DLBC : diffuse large B-cell lymphoma (# 30%)

Cryoglobulinemia: Treatment





Correlation between virological and clinical response in Cryovas

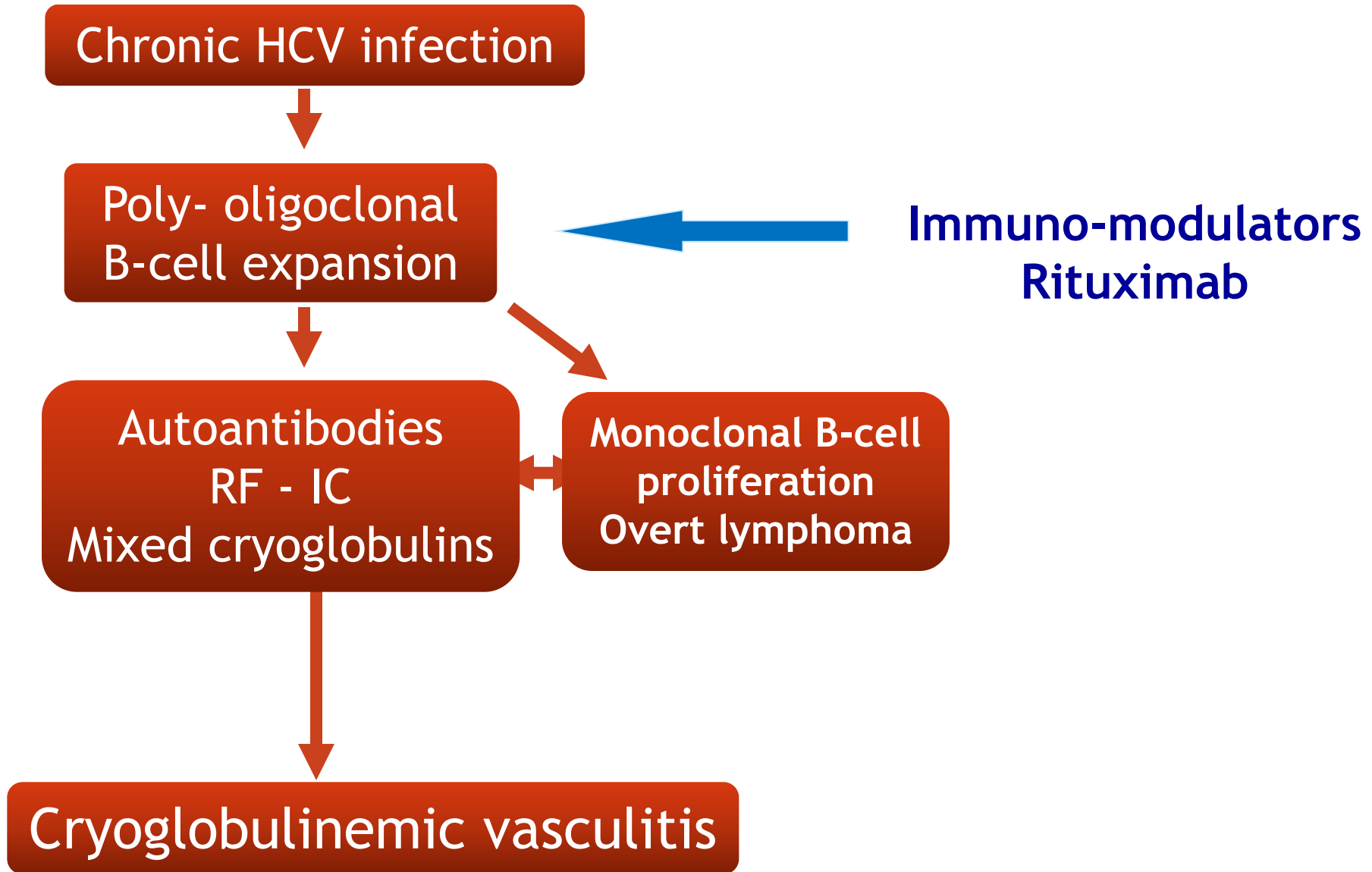


Adapted from Vassilopoulos, D. & Calabrese L. H. (2012) *Nat. Rev. Rheumatol.*

Cryovasc: Anti HCV therapy

	PegIFN-RBV-PI ¹	SOF-RBV ²	SOF-DACLA ³
	N=30	N=24	N=40
Complete clinical response			
At Week 12	46.6%	71%	90.2%
At end of therapy (W24)	66.7%	87.5%	90.2%
Virological response			
At week 12	73.9%	92%	100%
After end of therapy (W36)	66.6%	74%	100%
Clearance of cryoglobulin (W24)	22.2%	41.6%	50%
Serious adverse event	46.6%	8%	0%
Steroids and/or Rituximab	43%	16%	4.8%

1. Saadoun D, et al. Arthritis Rheum 2006; 2. Saadoun D, et al. Ann Rheum Dis 2015; 3. Saadoun D, et al. Gastroenterology 2017 & 2019



A Randomized Controlled Trial of Rituximab Following Failure of Antiviral Therapy for Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis

Michael C. Sneller,¹ Zonghui Hu,¹ and Carol A. Langford²

A Randomized Controlled Trial of Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis

S. De Vita,¹ L. Quartuccio,¹ M. Isola,² C. Mazzaro,³ P. Scaini,⁴ M. Lenzi,⁵ M. Campanini,⁶
C. Naclerio,⁷ A. Tavoni,⁸ M. Pietrogrande,⁹ C. Ferri,¹⁰ M. T. Mascia,¹⁰ P. Masolini,¹
A. Zabotti,¹ M. Maset,¹ D. Roccatello,¹¹ A. L. Zignego,¹² P. Pioltelli,¹³ A. Gabrielli,¹⁴
D. Filippini,¹⁵ O. Perrella,¹⁶ S. Migliaresi,¹⁷ M. Galli,¹⁸ S. Bombardieri,⁸ and G. Monti¹⁹

Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis

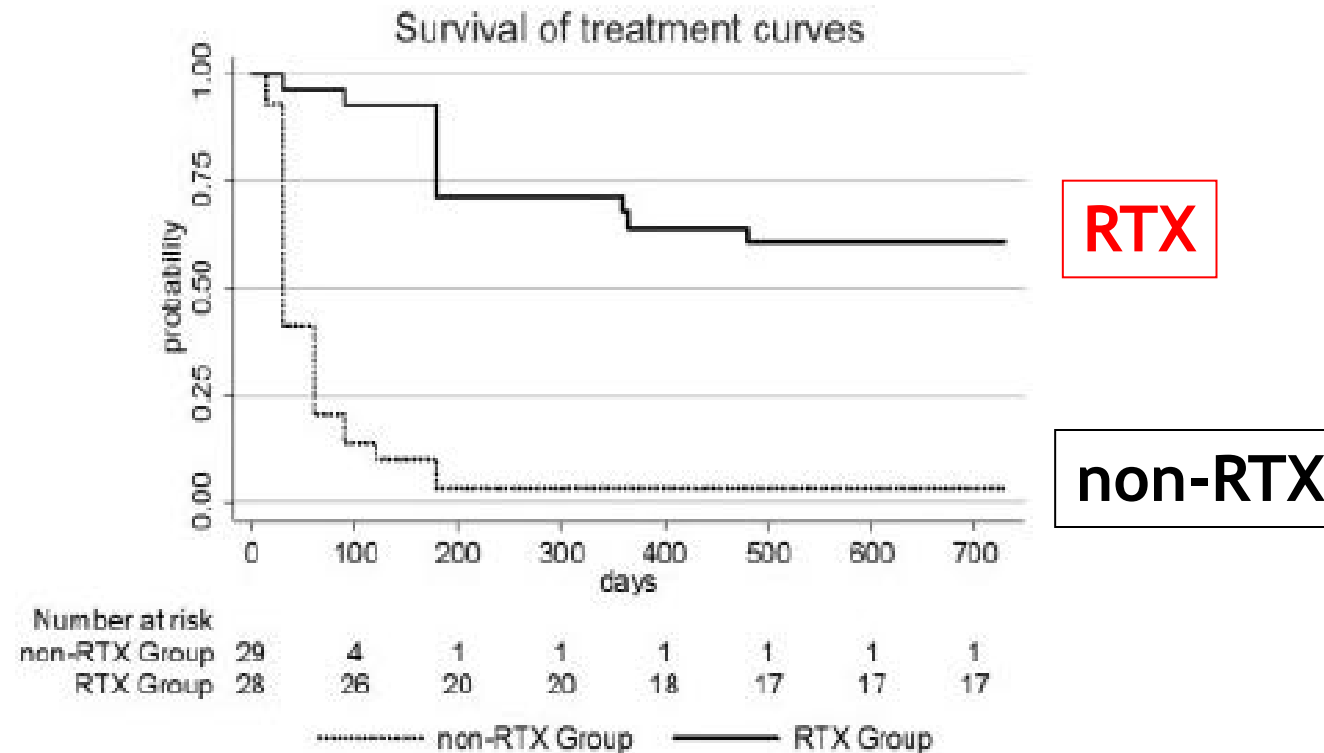
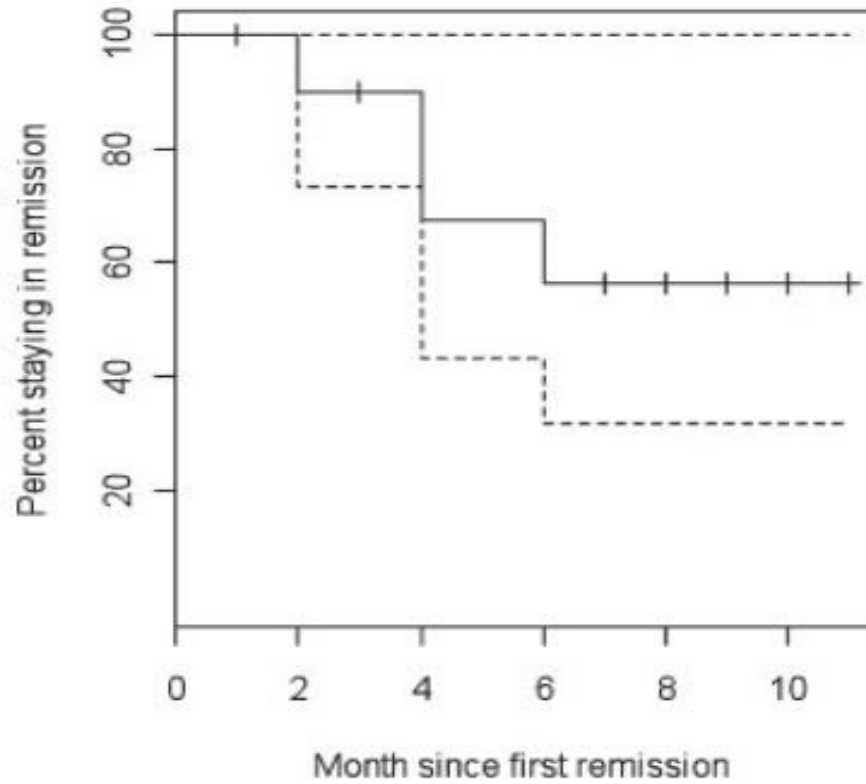


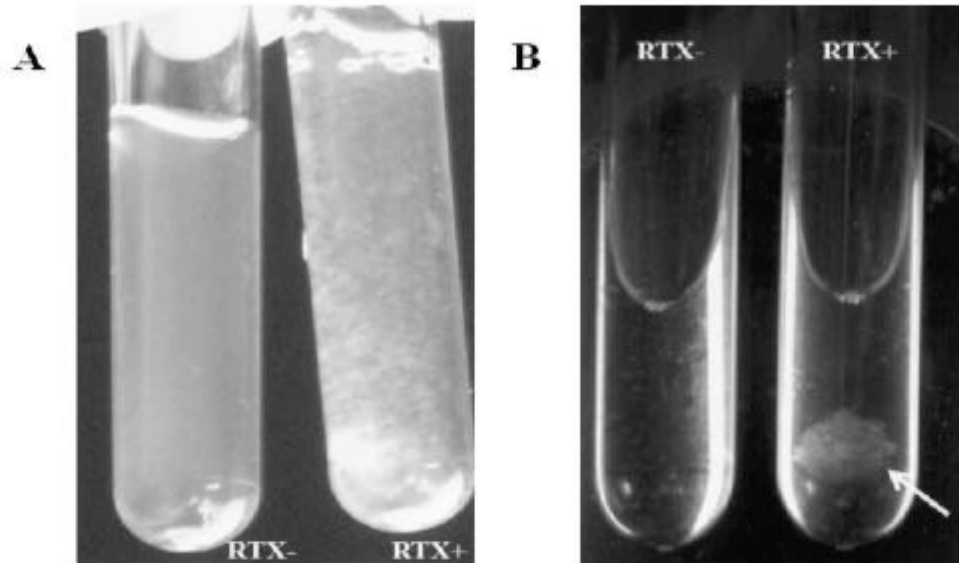
Figure 2. Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.

Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis



No. risk	11	10	9	8	6	6	5	4	3	2	1
No. relapse	0	1	0	2	0	1	0	0	0	0	0

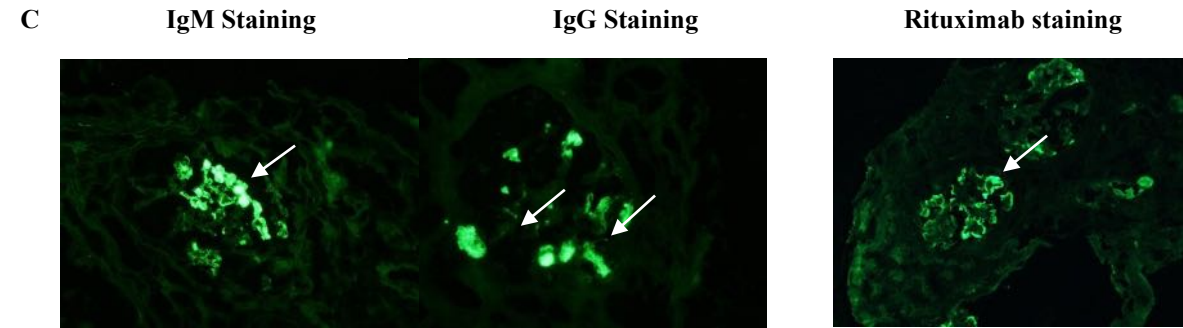
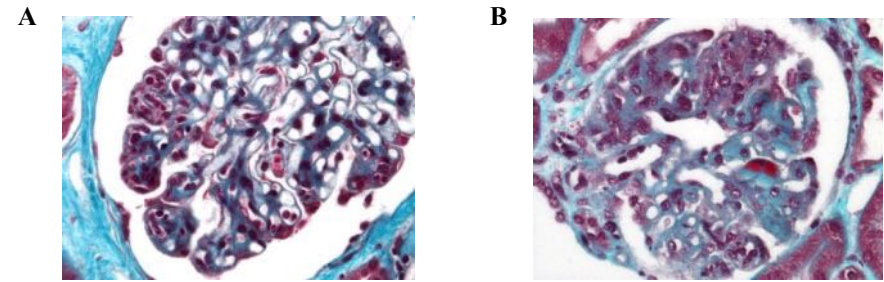
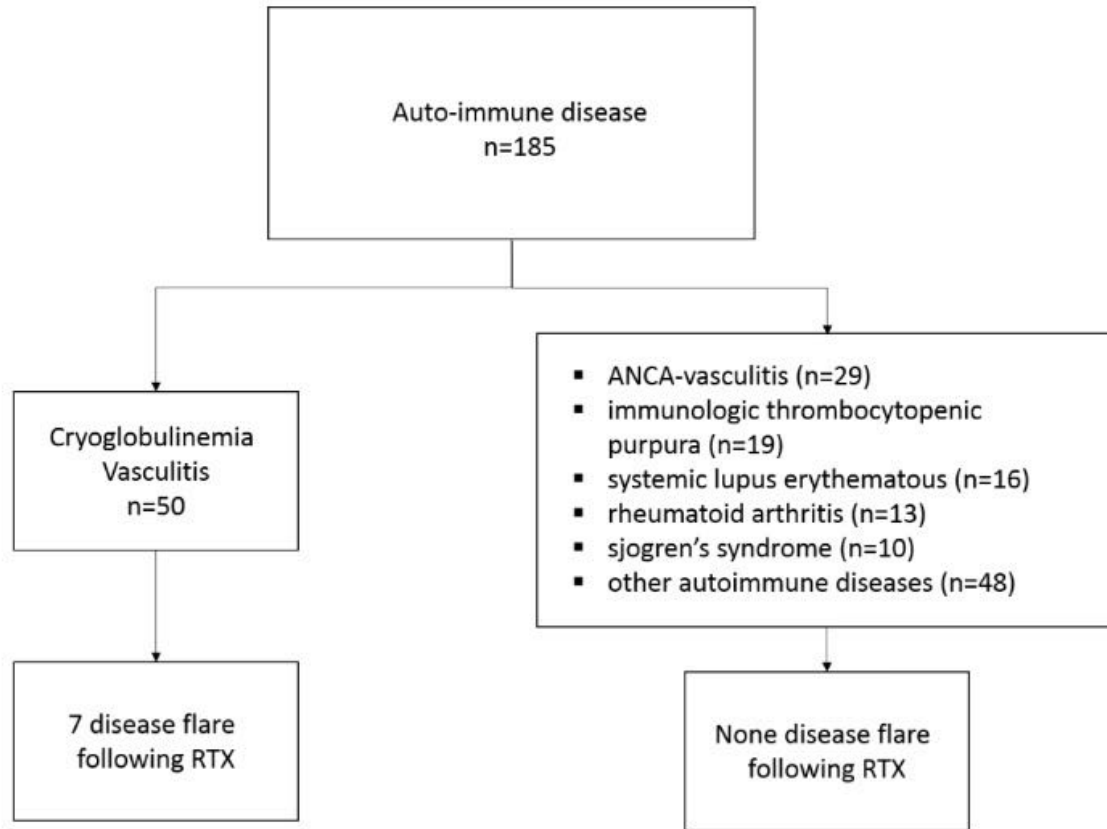
Rituximab May Complex With IgM κ Mixed Cryoglobulin and Induce Severe Systemic Reactions in Patients With Hepatitis C Virus–Induced Vasculitis



Factors associated with flare of Cryovas

- High level of serum cryoglobulin
- NHL associated
- Kidney involvement
- RTX 1g regimen

Rituximab-associated Vasculitis Flare: Incidence, Predictors, and Outcome



Histological findings in patients with vasculitis flare after RTX.

Figure 1. Incidence and etiologies of RTX-associated flares of autoimmune diseases. RTX: rituximab; ANCA: antineutrophil cytoplasmic antibodies.

Rituximab-associated Vasculitis Flare: Incidence, Predictors, and Outcome

Table 3. Outcome of 7 patients with exacerbation of vasculitis after RTX*.

Patient	Time Between RTX and Exacerbation, days	Symptoms	Histology	Urinary Proteins/Hu	ICU, days	Mechanical Ventilation	Dialysis	CT (dose)	Plasmapheresis, no. courses	IS	Death	Delay Between Flare and Deaths, mos
1	8	Fever, ARI, purpura, GI tract	Proven MPGN after RTX	0.3 g/24 h-Hu	Yes (10)	No	Yes	3 pulses (3 g)	Yes (5)	CYC, RTX, B	Yes	3.6
2	8	Fever*, ARI, cutaneous, pulmonary edema		3 g/l	Yes (10)	No	Yes	Pulses (ND)	Yes (11)	No	No	NA
	5	Fever*, ARI, GI tract*, cutaneous necrosis, hypotension	Ischemic colitis	NA	Yes (15)	Yes	Yes	4 pulses (4 g)	Yes (6)	No	Yes	0.8
3	12	ARI	Worsening renal lesions	1.37 g/24 h-Hu	Yes (7)	No	Yes	3 pulses (3 g)	Yes (5)	No	No	NA
4	13	ARI, purpura	Extremely severe lesions of MPGN	7 g/l-Hu	No	No	No	Pulses (1.5 g)	Yes (3)	No	No	NA
5	2	Cutaneous, GI tract		NA	No	No	No	Pulses (1g)	No	No	No	NA
6	16	ARI, purpura, GI tract*, myocarditis*		0.23 g/l-Hu	No	No	No	Pulses (3 g)	No	No	Yes	3.8
7	4	ARI*, HBP, necrosis		NA -Hu	No	No	No	70 mg	No	No	Yes	3

* New symptoms occurring at relapse. RTX: rituximab; Hu: hematuria; ICU: intensive care unit; IS: immunosuppressant; ARI: acute renal injury; MPGN: membranoproliferative glomerulonephritis; B: bendamustine; GI: gastrointestinal; Cryo: cryoglobulin; CT: corticosteroids; CYC: cyclophosphamide; HBP: hemorrhagic bullous purpura; ND: not determined; NA: not applicable.

Cryoglobulinemia relapses

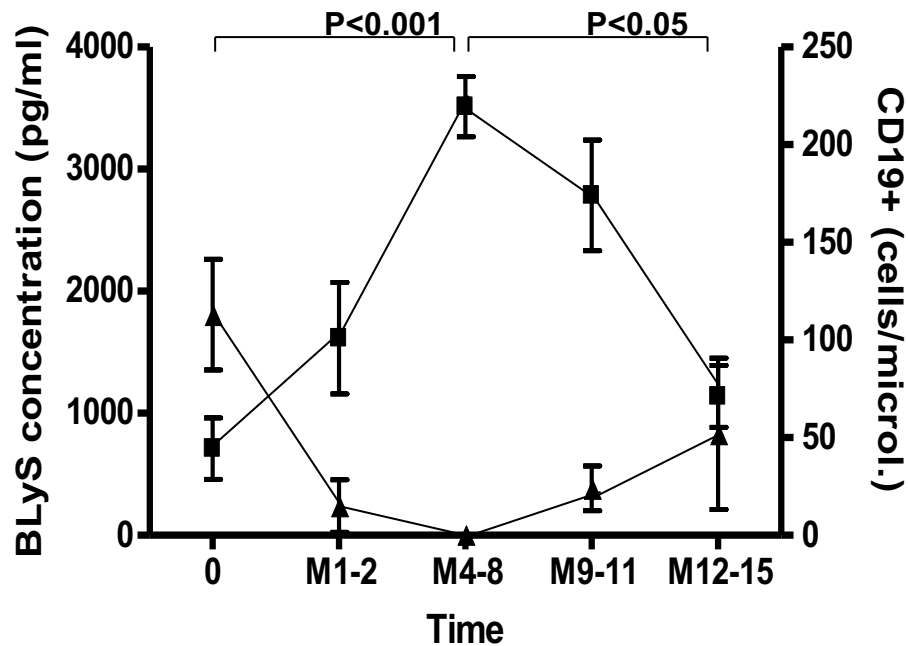
Relapse of Hepatitis C Virus–Associated Mixed Cryoglobulinemia Vasculitis in Patients With Sustained Viral Response

Table 2. Relapse and outcome characteristics of the study patients*

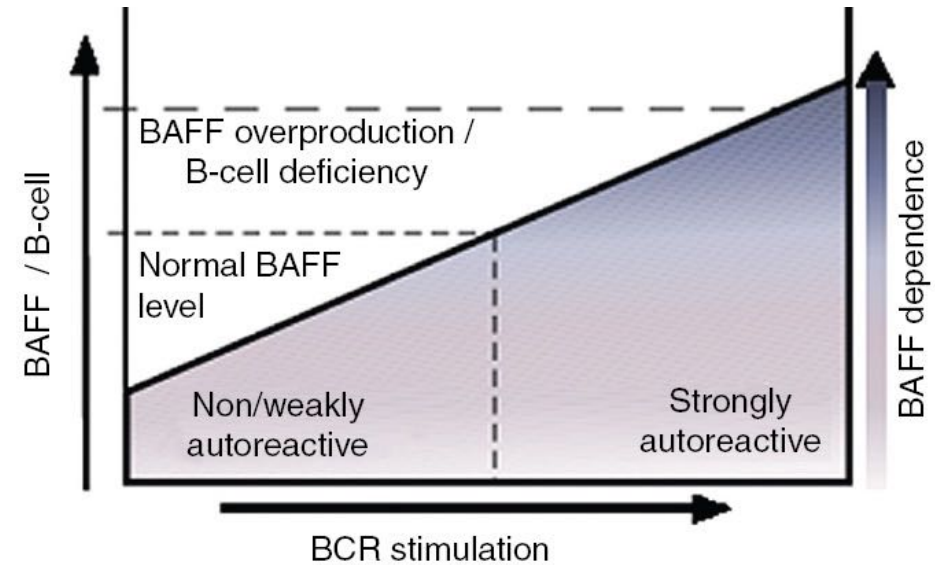
Patient	Relapse after antiviral treatment					Treatment for relapse	1 year after end of antiviral treatment	
	Arthritis/ arthralgia	Purpura	Neuropathy	Nephropathy	NHL		Symptoms	Cryoglobulins
A	+	+	–	–	–	Low-dose steroids	Persistent mild symptoms	Low levels
B	+	+	–	–	–	None	Complete remission	None
C	+	+	–	–	–	Colchicine	Persistent symptoms	Persistent
D	+	–	–	–	–	HCO, NSAIDs	Mild arthralgia	None
E	+	–	+	–	+	Low-dose steroids, HCO	Mild arthralgia	None
F	–	+	–	+	+	Fludarabine, CYC	Complete remission	None
G	–	+	–	–	–	None	Complete remission	None
H	–	+	+	–	+	Chlorambucil, steroids	Died of lymphoma complications	Persistent

* NHL = non-Hodgkin's lymphoma; HCO = hydroxychloroquine; NSAIDs = nonsteroidal antiinflammatory drugs; CYC = cyclophosphamide.

Rituximab treatment is associated with a marked increase in serum BLyS concentration mirroring B-cell depletion



■ BLyS
▲ CD19+



→ But BLyS rich environment may favor auto-reactive clones and counteracts Rituximab treatment

Rituximab plus belimumab in non-infectious refractory cryoglobulinemia vasculitis: A pilot study

Objective: To report the efficacy of rituximab plus belimumab in patients with refractory cryoglobulinemia vasculitis (CV).

Methods: Belimumab was administered intravenously at a dose of 10 mg/kg on days 0, 14, 28 and then every month in association with rituximab in 4 patients with refractory CV. Demographic, clinical and laboratory characteristics, treatment modalities and outcomes were recorded.

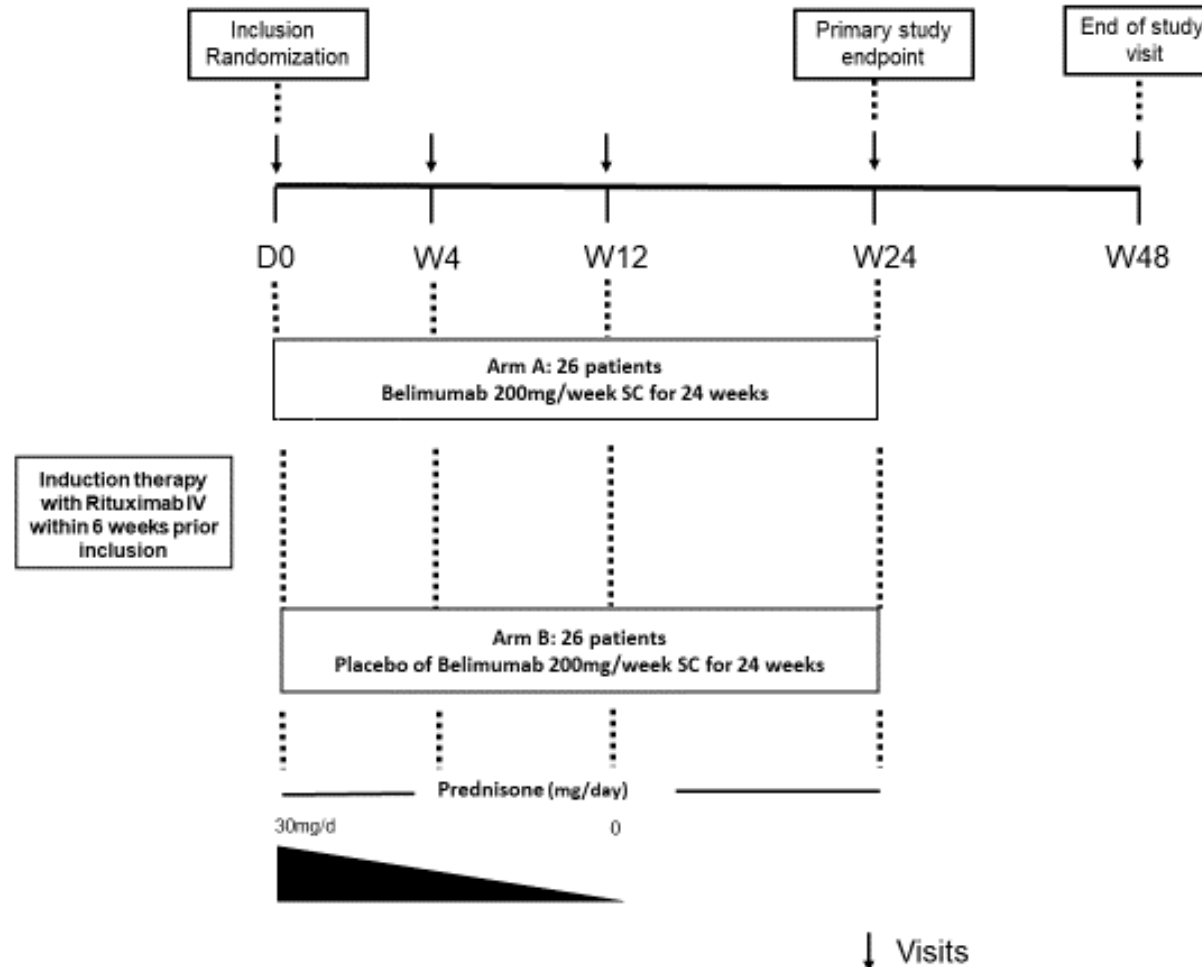
Results: All patients had type II IgM Kappa cryoglobulinemia, which was associated with primary Sjögren syndrome (n = 1), hepatitis C virus infection (n = 1), and essential (n = 2). Main manifestations of CV included purpura (n = 4), arthralgia and peripheral neuropathy (n = 3), and glomerulonephritis and skin ulcers (n = 1). In all cases, CV was refractory and/or relapse following rituximab. Intravenous belimumab infusion along with rituximab resulted in rapid clinical response in the four patients. Osteitis and recurrent urinary tract infections occurred in two patients.

Conclusion: Belimumab along with rituximab showed promising results in refractory patients with CV.

TRIBECA

(Treatment with **R**ituximab plus **B**elimumab in **C**ryoglobulinemia **A**ssociated vasculitis)

Etude multicentrique randomisée, en double aveugle contre placebo évaluant l'efficacité et la tolérance du RTX-Belimumab dans les vascularites cryoglobulinémiques



Therapeutic strategies in mixed cryoglobulinemia

Treatment of underlying diseases
(HCV, NHL..)

Mild disease

(Purpura, arthralgia,
mild neuropathy)



Low dose steroids
Colchicine

Severe disease

(Progressive renal disease,
Mononeuritis multiplex, skin
necrosis)



Rituximab & steroids
±plasmapheresis

Life threatening

(Rapidly progressive GN,
cardiac, digestive vasculitis)



Steroids, plasmapheresis,
Rituximab and/or CYC

Therapeutic strategies in type 1 cryoglobulinemia

Treatment of underlying diseases
(Myeloma, CLL, NHL..)

Monoclonal IgM



Rituximab ± Benda ou CYC
± Plasmapheresis

or CLL/BNHL therapy
Avoid cold exposure++

Monoclonal IgG or IgA

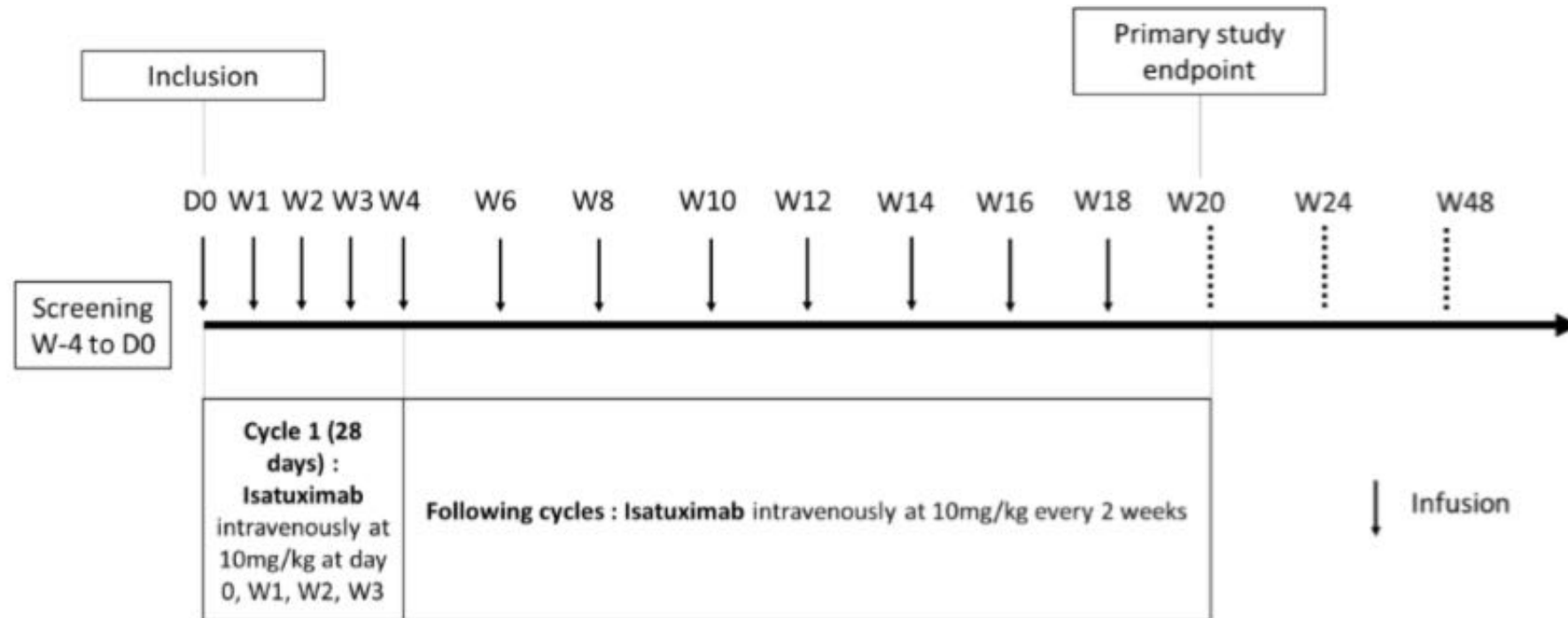


Bortezomib
or IMiDs (Lenalidomide..)
or Anti CD38
± plasmapheresis,
± autologous stem cell transplantation

or CLL/BNHL therapy
Avoid cold exposure++

Isatuximab in type I cryoglobulinemia: A prospective pilot study

ICE STUDY (Isatuximab in type 1 Cryoglobulinemia)





Points clés

- Formes graves: Cardiaques, digestives, rénales et SNC
- Red flag: purpura, ulcérations distales, FR, pic Ig, low C4, VHC+
- Cryo Type 1 vs Cryo mixtes
- RTX based therapy +/- EP

Points clés

Table 2. Findings that should prompt evaluation for cryoglobulinemia

Clinical signs	Laboratory findings	Histopathologic findings
Skin purpura	Unexplained hypocomplementemia (especially low C4)	Leukocytoclastic vasculitis
Livedo reticularis	Unexplained increased RF activity	Membranoproliferative glomerulonephritis
Raynaud's phenomenon	Positive hepatitis C virus	Small vessel hyaline thrombi
Acrocyanosis	Red blood cell urine casts	
Cutaneous ischemia and ulcers	Proteinuria \pm active sediment	
Arthralgia and arthritis		
Peripheral neuropathy		
Cold sensitivity, especially in patients with a monoclonal gammopathy		

Les cryofibrinogénémies



Cryoglobuline ≠ Cryofibrinogène

Autre cause d'ulcères cutanés déclenchés par le froid
(± autres signes ischémiques ± signes généraux)

= thrombose artérielle par cryoprécipitation du fibrinogène

* rare

* cryoprécipité uniquement ds plasma (i.e. nécessite facteurs de la coagulation (thrombine)), pas ds le sérum.

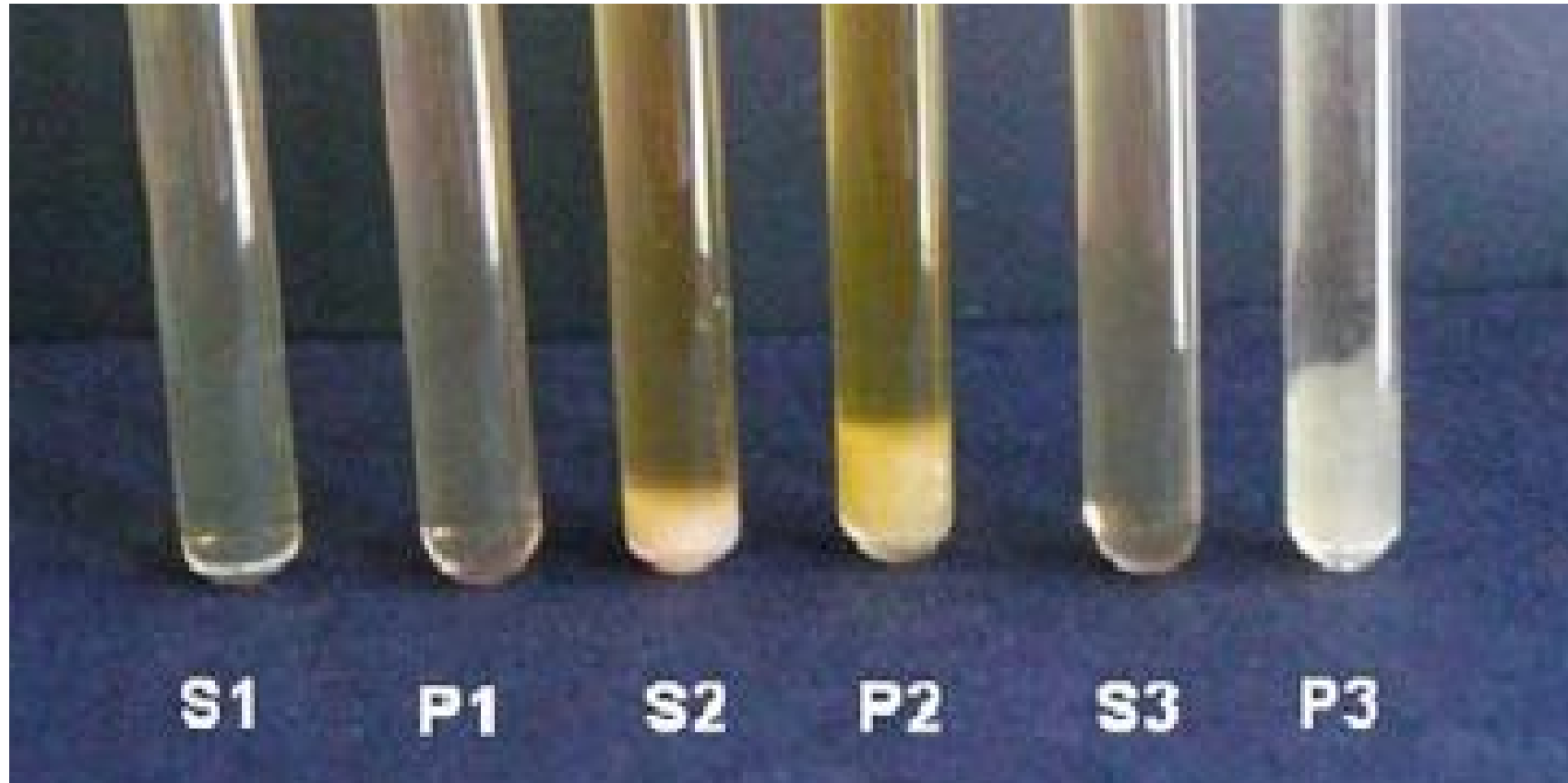
Faux négatif (auto-absorption sur GR), faux positif (héparine)

* physiopathologie mal connue (inhibition fibrinolyse)

* essentiel ou secondaire

(infection, maladies systémiques, malignes, diverses)

Cryofibrinogène: Diagnostic biologique



S1

P1

S2

P2

S3

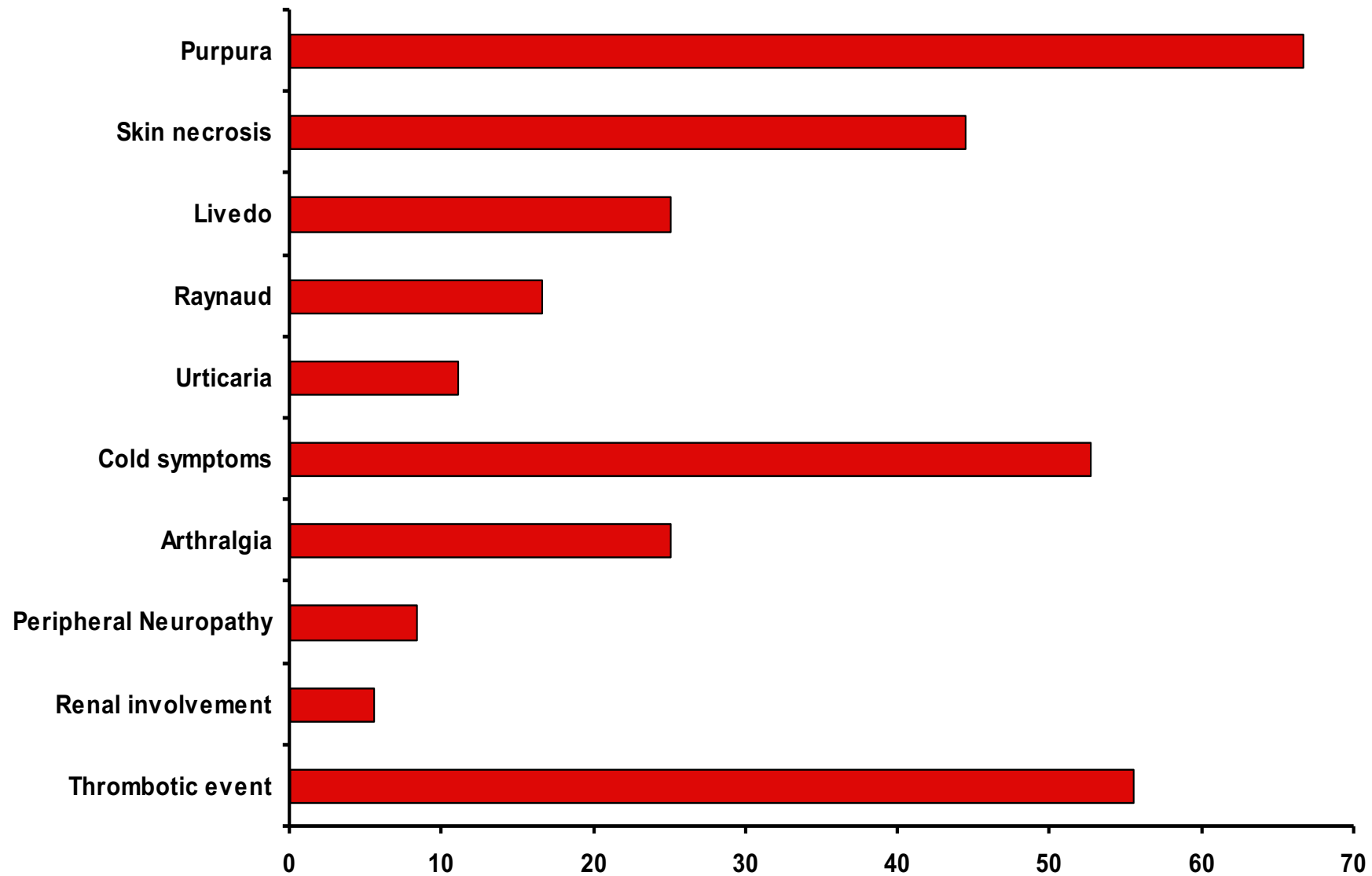
P3

Pas de CryoG
Pas de CryoFg

CryoG +
CryoFg +

Pas de CryoG
CryoFg +

Cryofibrinogenemia: Clinical features (% , n=36)



Diagnostic Criteria for Cryofibrinogenemia

- **Major Criteria**

- Compatible clinical presentation
- Presence of cryofibrinogen in plasma
- Absence of cryoglobulins
- Absence secondary causes of cryofibrinogenemia (infection, neoplasm)

- **Supportive Criteria**

- Elevation of serum α 1-antitrypsin & α 2-macroglobulin
- Angiogram with abrupt occlusion of small to medium sized arteries.
- Typical skin biopsy findings : cryofibrinogen plugging vessels, dermal thrombosis, or dermal necrosis.

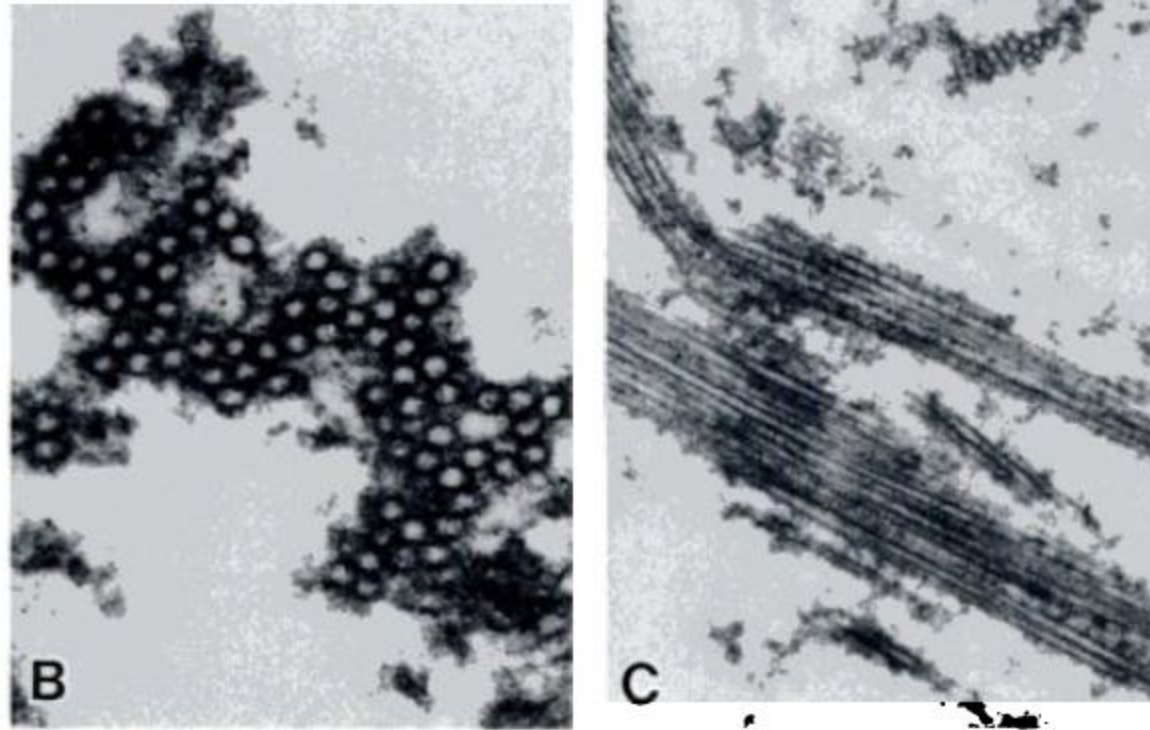
Treatment of Cryofibrinogenemia

- 1. Avoidance of cold-exposure & other environmental triggers of symptoms**
- 2. Cessation of smoking & avoidance of sympathomimetic agents (diet pills, decongestants, caffeine)**
- 3. Anabolic steroid: Stanozolol**
- 4. Fibrinolytic therapy: Actilyse**
- 5. Immunosuppressive and steroids**
- 6. Plasmapheresis**
- 7. Treatment of underlying disease**
- 8. AVK?**

Cryoglobulinemia: Pathogenesis

Characterization of Monoclonal IgG Cryoglobulins: Fine-Structural and Morphological Analysis

By D.N. Podell, C.H. Packman, J. Maniloff, and G.N. Abraham



Transmission electron micrographs of cryogel IgG LON that demonstrate its fibrillar and tubular properties.

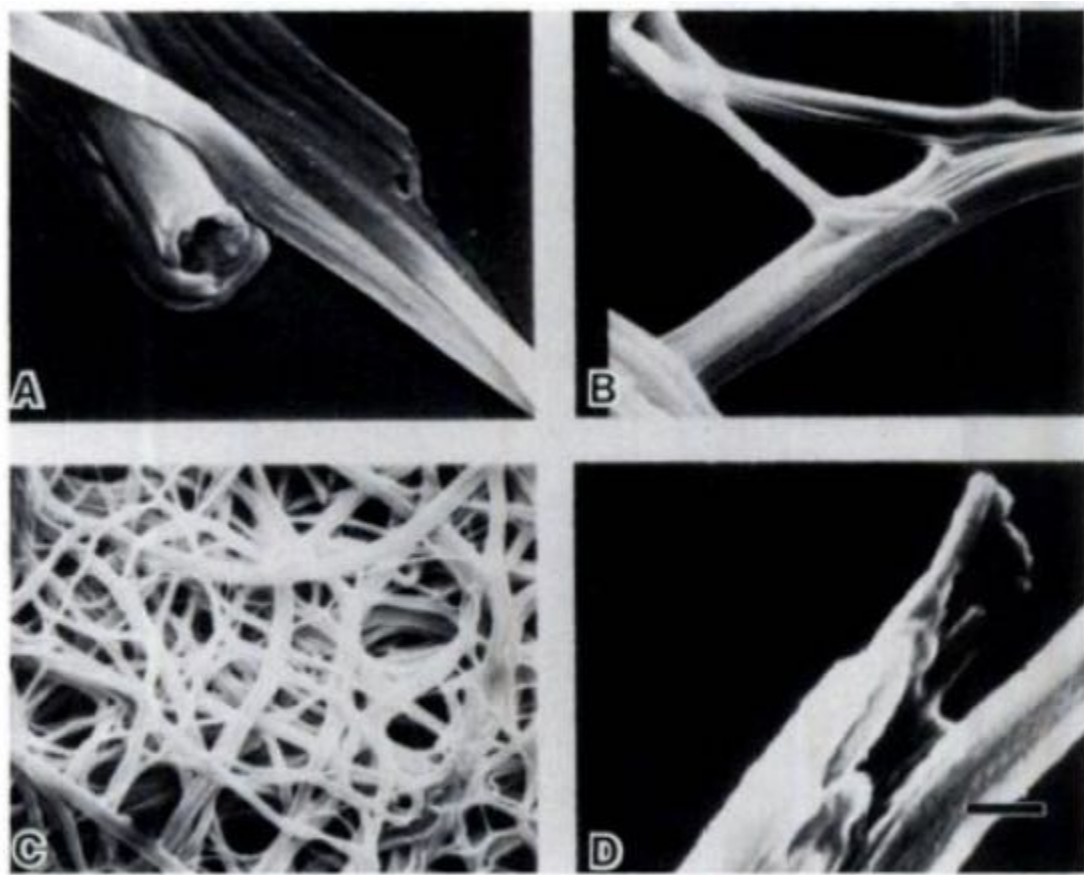
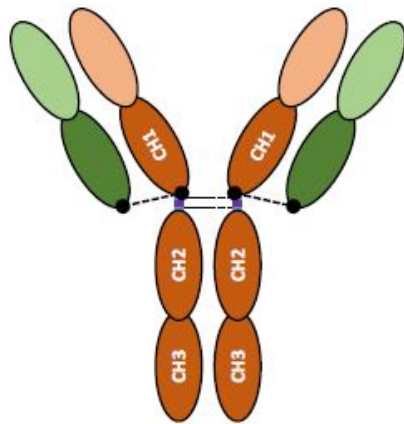
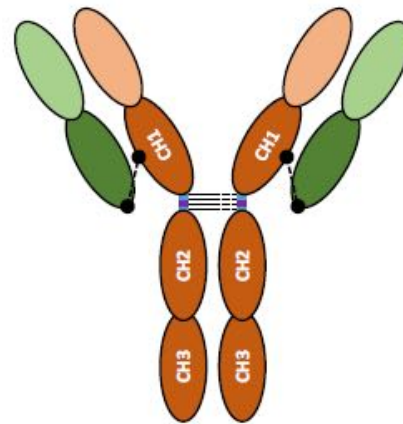


Fig 4. Scanning electron micrographs of IgG WEB crystals. The micrographs demonstrate the ability of the crystals to branch and form nets and their thick tubular structure. Bar A, 1 μ m; B, 1.5 μ m; C, 4 μ m; D, 0.5 μ m.

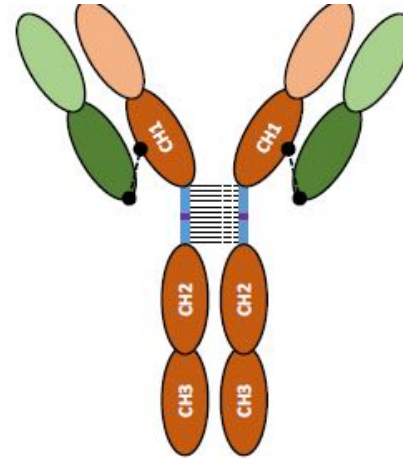
Pathogenicity of human Ig



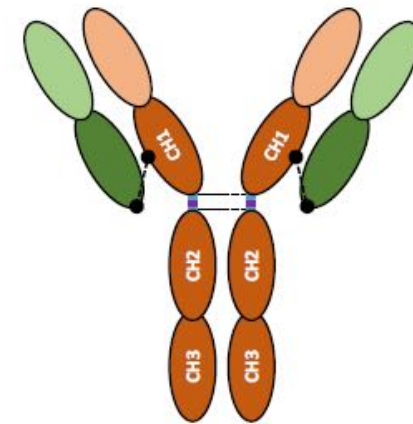
Human IgG1



Human IgG2



Human IgG3

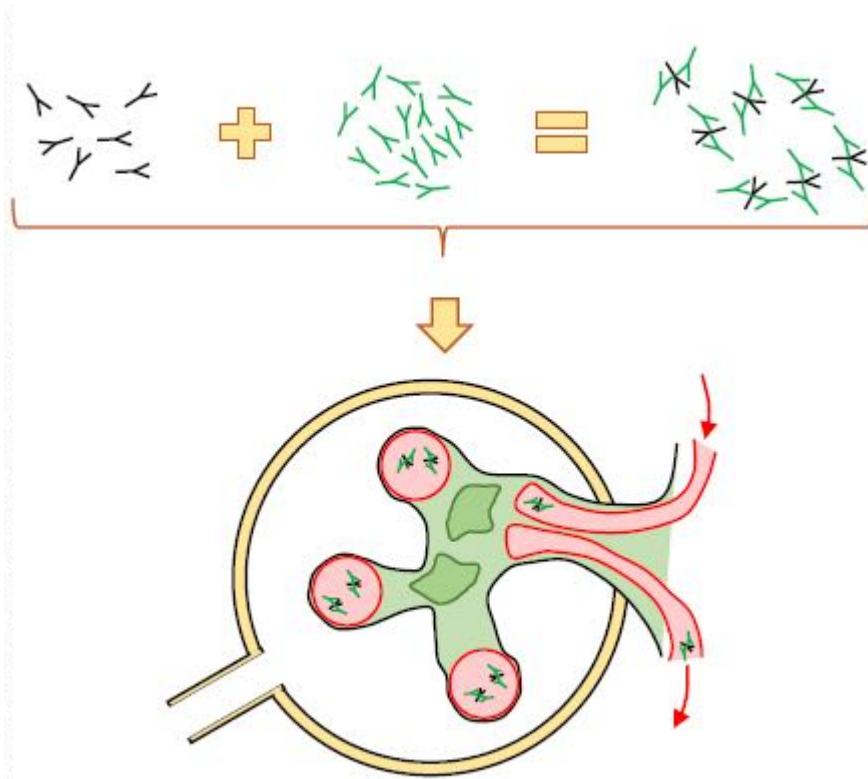


Human IgG4

- Complement activation
 - Affinity for FcR,
 - Crystallisation
- = lower flexibility, IC formation, agregability

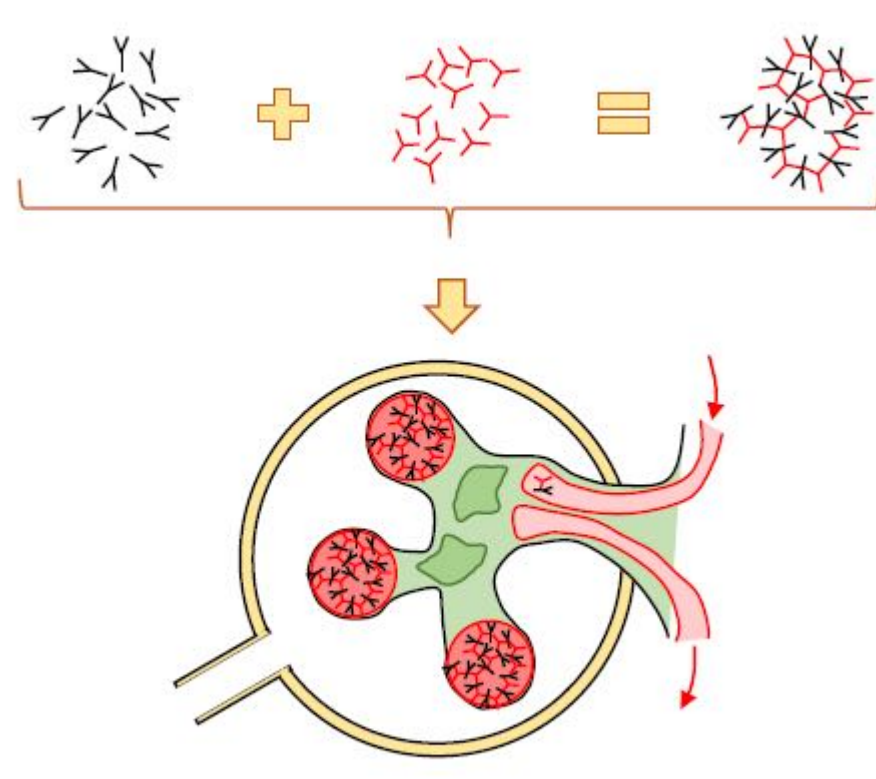
IgG1 protects against renal disease in a mouse model of cryoglobulinaemia

IgG1 protects



Pathogenicity of IgG3

independently of complement and FCyR



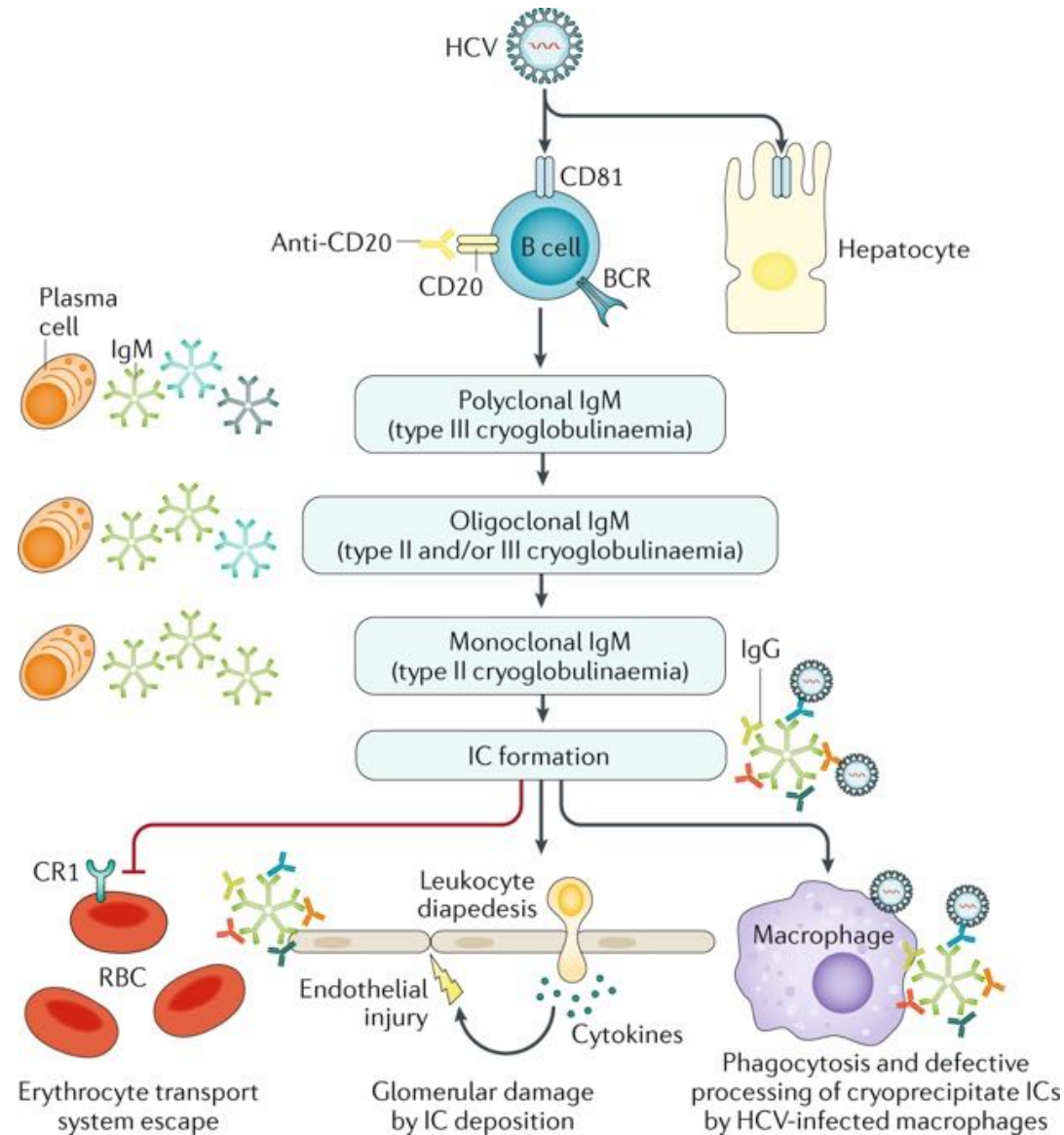
Mice immunized by anti IgD serum

Y Target immunoglobulin

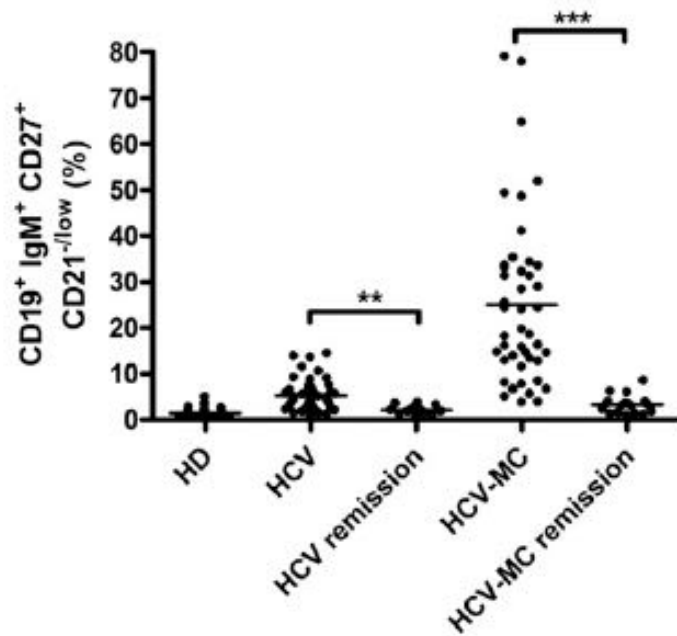
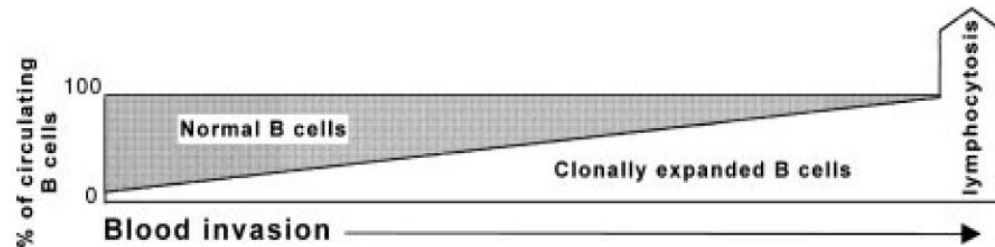
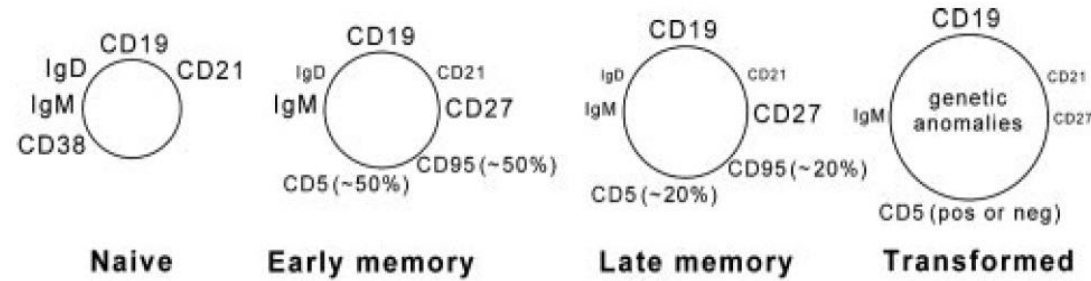
Y Mouse IgG3 with rheumatoid factor activity

Y Mouse IgG1 with rheumatoid factor activity

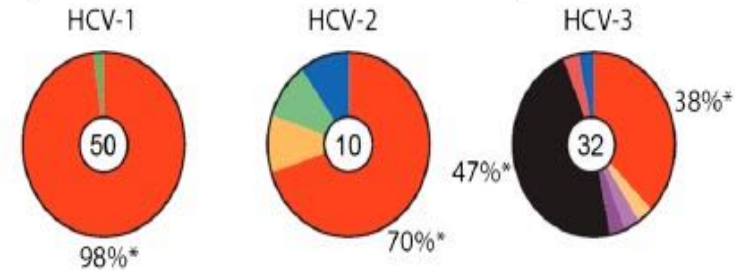
Mechanisms of HCV-related cryoglobulinaemia vasculitis



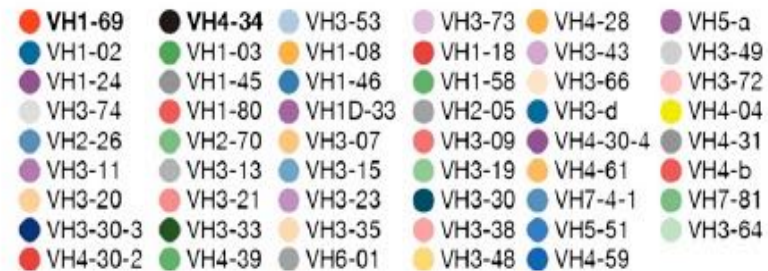
CD21^{low/-} B cells in cryoglobulinemia vasculitis

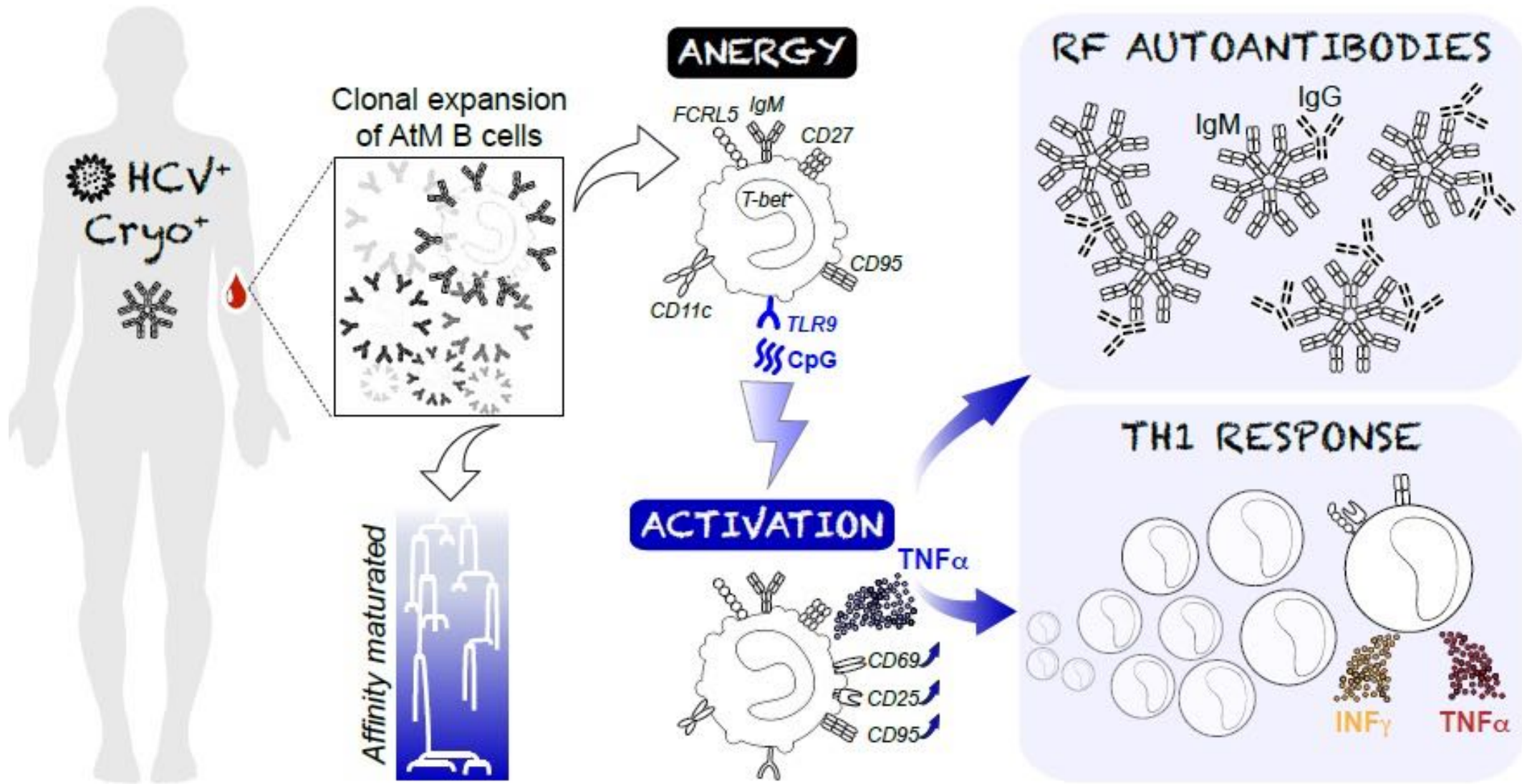


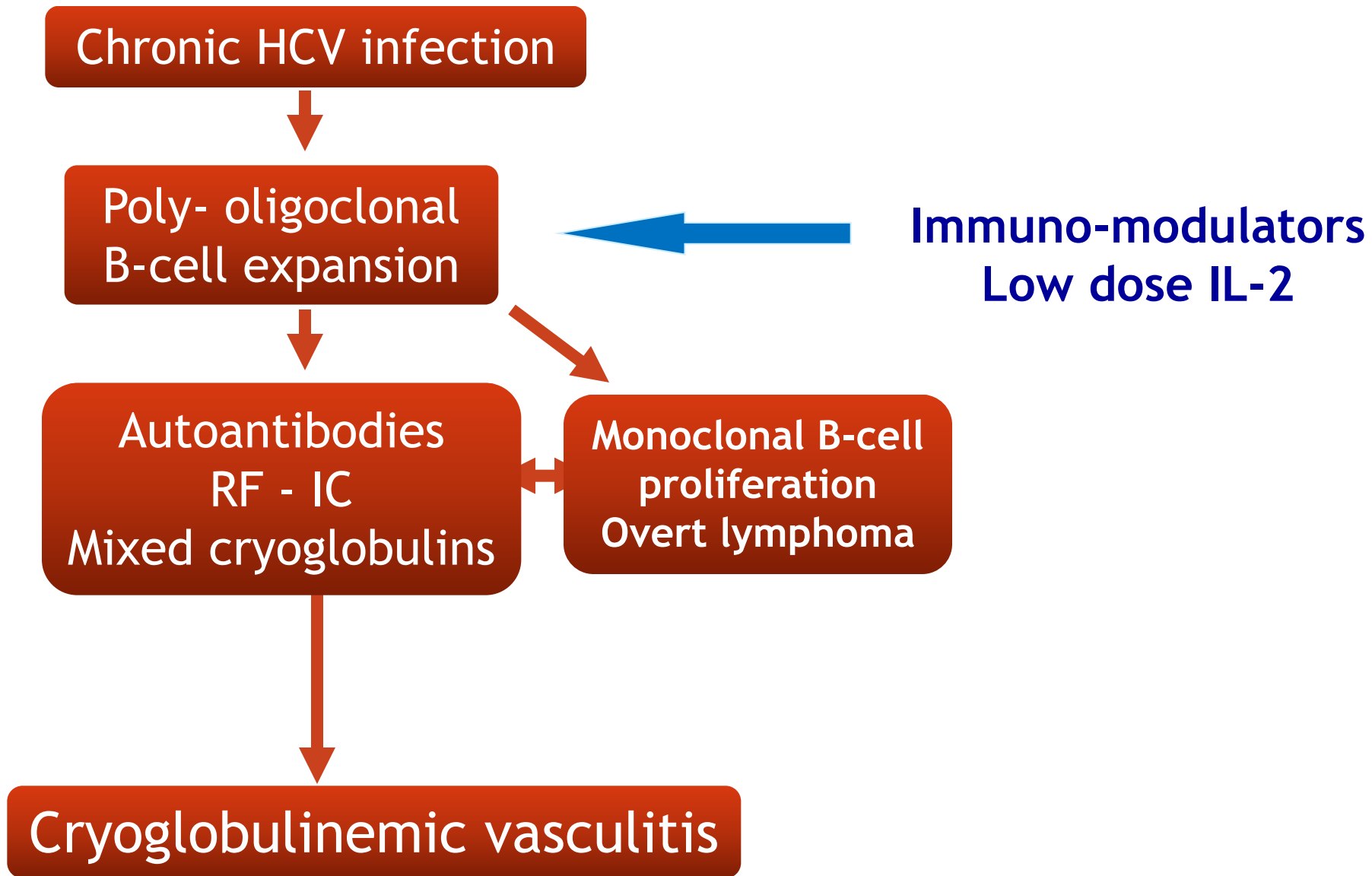
IgM⁺CD27⁺CD21^{low} MZ B cells from HCV-MC patients:



*Single clonal expansions account for these frequencies







ORIGINAL ARTICLE

Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

David Saadoun, M.D., Ph.D., Michelle Rosenzweig, M.D., Ph.D.,
 Florence Joly, Ph.D., Adrien Six, Ph.D., Fabrice Carrat, M.D., Ph.D.,
 Vincent Thibault, Pharm.D., Damien Sene, M.D., Ph.D.,
 Patrice Cacoub, M.D., and David Klatzmann, M.D., Ph.D.

Table 2. Antiinflammatory Effects of Low-Dose Interleukin-2 Revealed through Unsupervised Transcriptome Analyses of Peripheral-Blood Mononuclear Cells.*

Terms and Pathways	Up-Regulated Signature number of signatures	Down-Regulated Signature number of signatures	P Value
Gene Ontology			
Inflammation	0	251	1.30×10^{-40}
Immune response	16	684	3.40×10^{-94}
Lymphocytes	77	555	7.00×10^{-49}
Cell cycle	1701	208	1.50×10^{-138}
Control	226	343	2.50×10^{-1}
KEGG			
Autoimmune diseases or complications of transplantation	0	46	7.60×10^{-9}
Inflammatory infectious diseases	6	242	7.60×10^{-36}
Other diseases	190	211	4.15×10^{-2}

