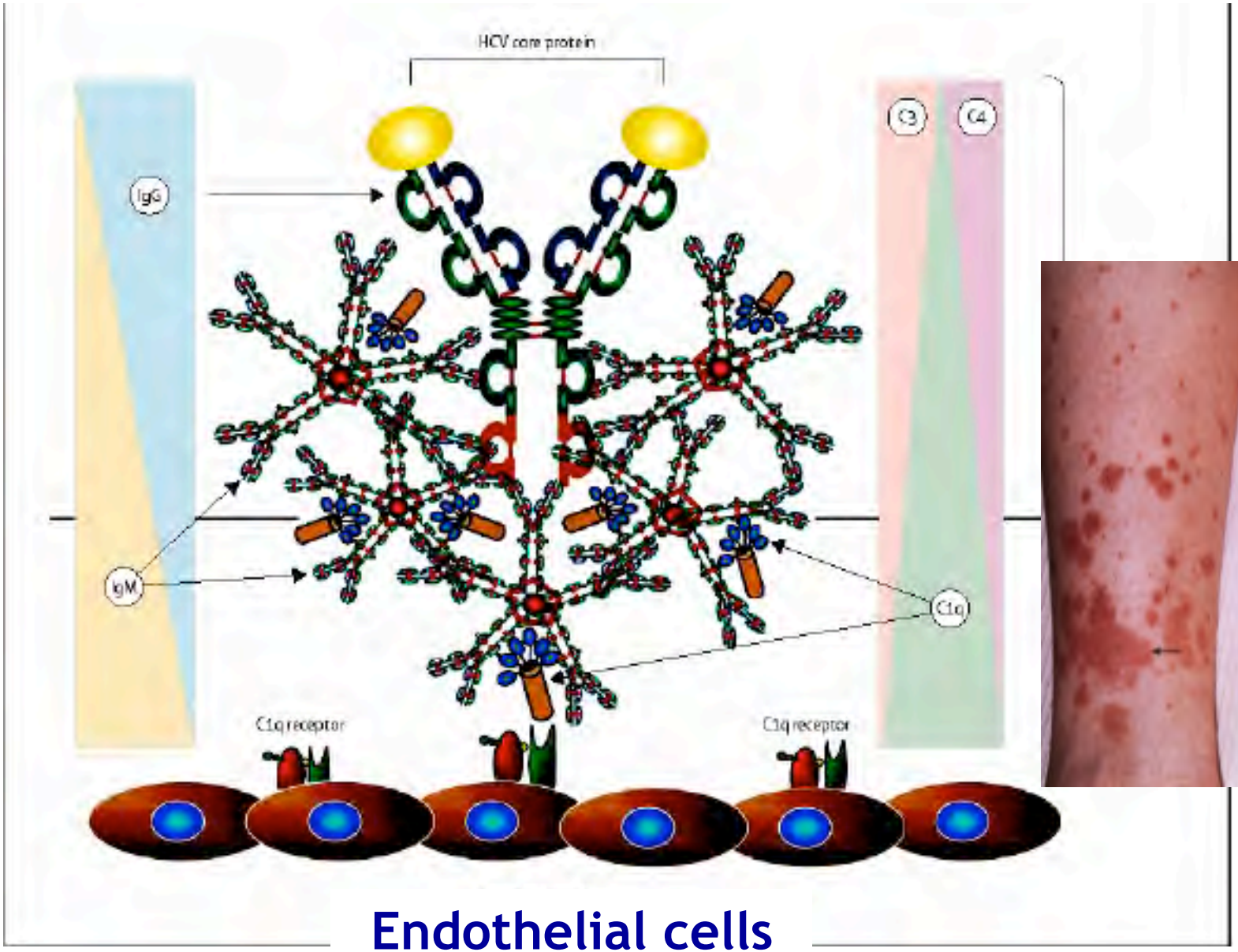
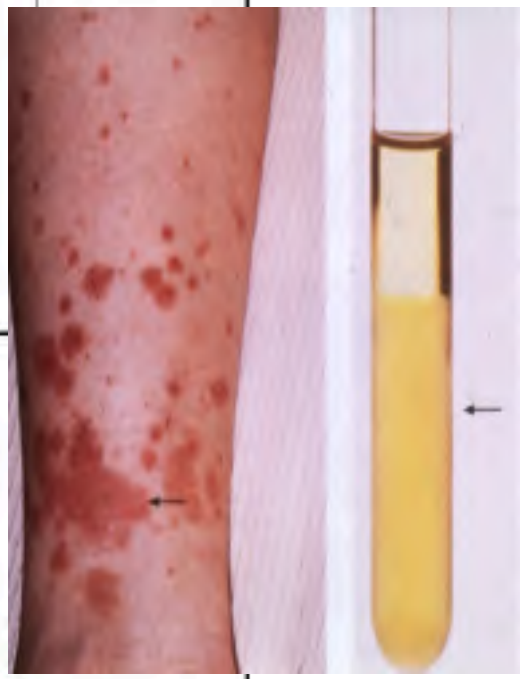
Atteinte rénale au cours des cryoglobulinémies mixtes: quels traitements en 2012

Pr Patrice CACOUB

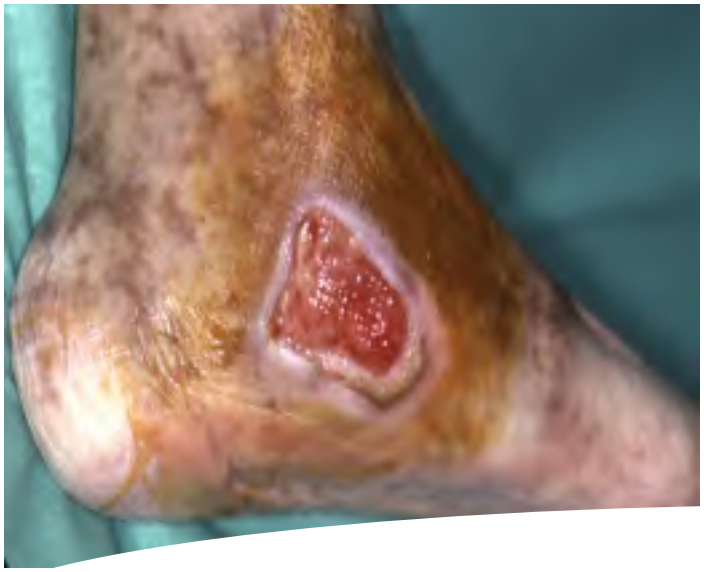
Service de Médecine Interne, et CNRS UMR 7087
Université Pierre et Marie Curie
Centre National de Référence Maladies Auto-immunes
Hôpital La Pitié-Salpêtrière, Paris, FRANCE

Cryoprecipitation

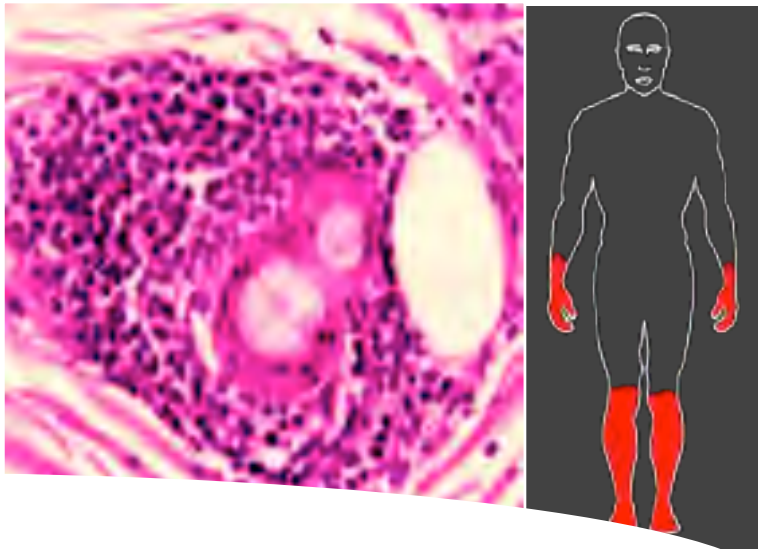




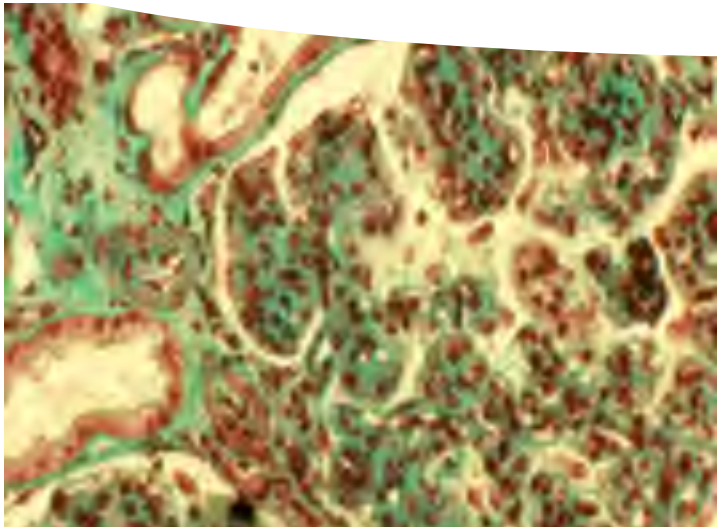
Skin Purpura



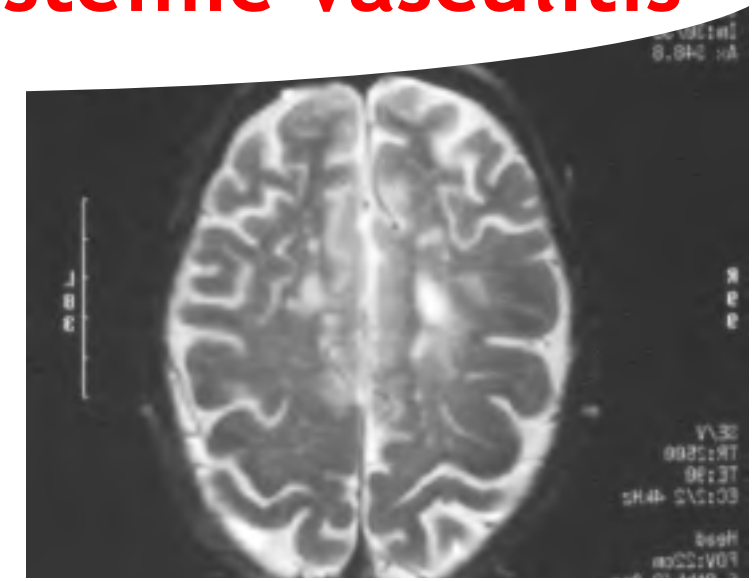
Neuropathy



Cryoglobulinemia-Systemic Vasculitis

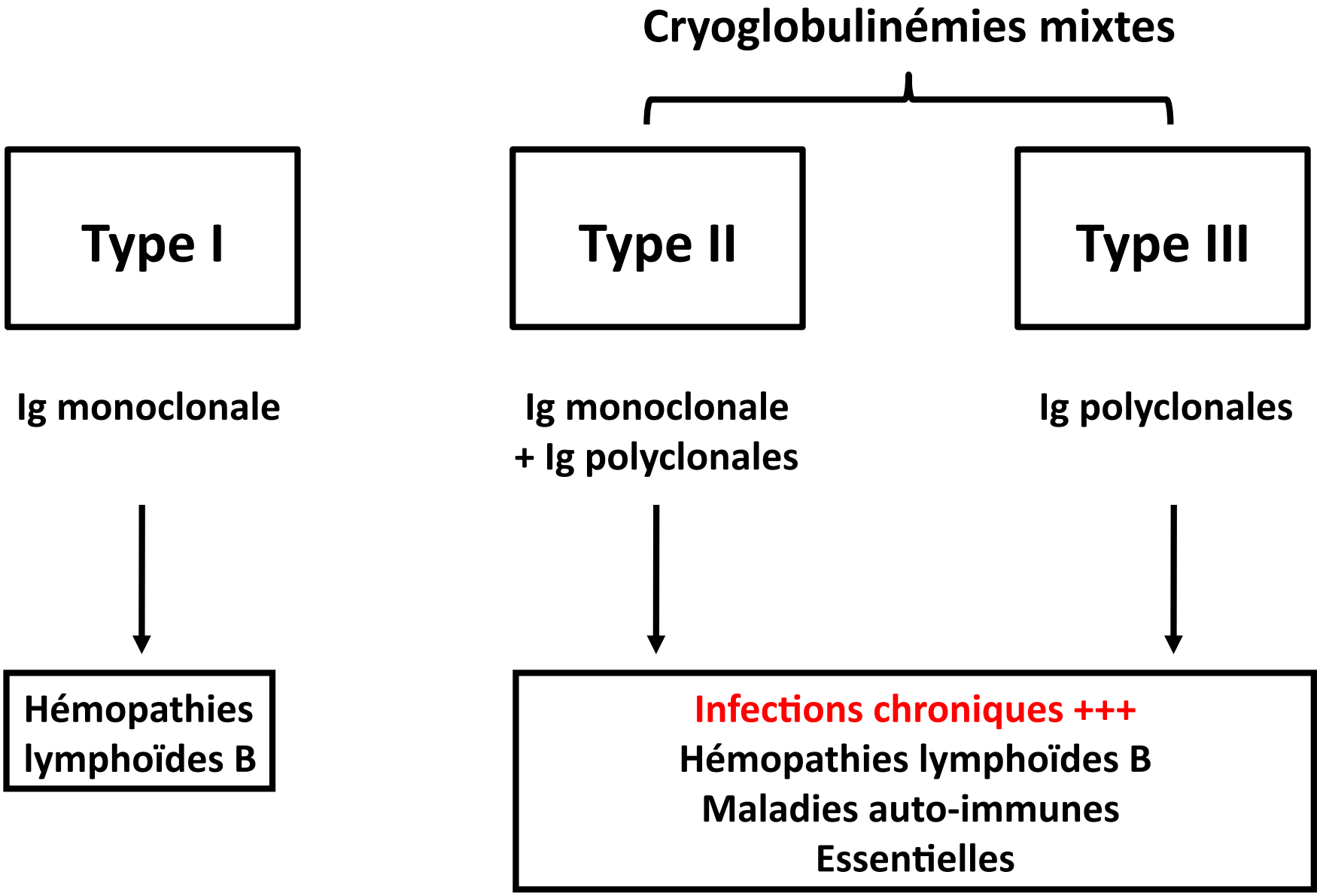


Membrano-proliferative Glomerulonephritis

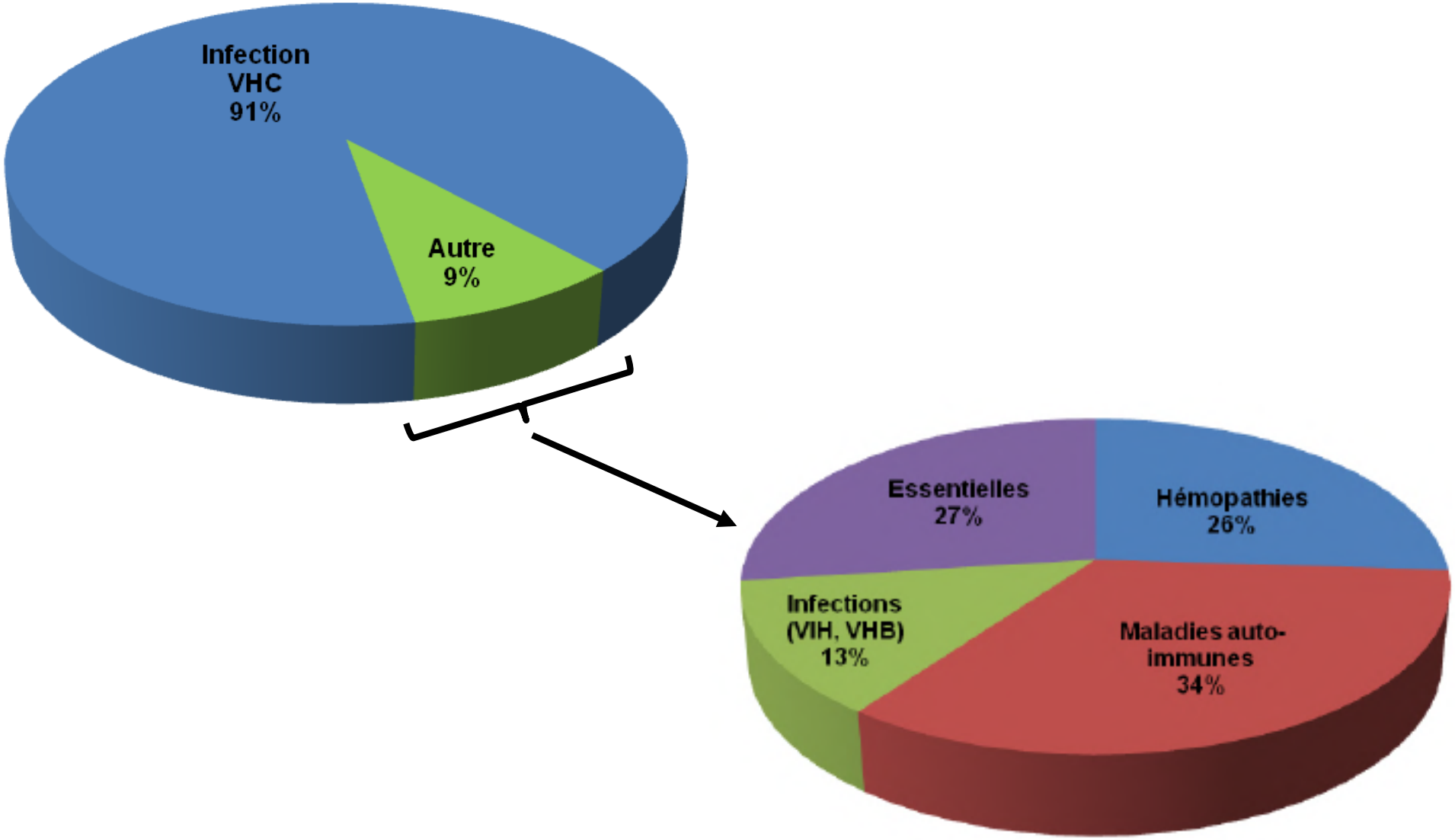


CNS Vasculitis

Cryoglobulinémies



Cryoglobulinémies mixtes



Saadoun, Arch Intern Med, 2006

Cryoglobulinémies mixtes liées au virus de l'hépatite C

Features of 250 Mixed Cryoglobulinemic Patients

Age at disease onset	54 ± 13 (29-72)
Female/Male ratio	3
Purpura	**98 %**
Weakness	**98 %**
Arthralgias	**91 %**
Arthritis (non-erosive)	8 %
Raynaud's phenomenon	32 %
Sicca syndrome	51 %
Peripheral neuropathy	**81 %**
Renal involvement	**31 %**
B-cell non-Hodgkin's lymphoma	11 %
Hepatocellular carcinoma	3 %

Ferri C, Mascia MT, Saadoun D, Cacoub P. 2009

HCV & glomerulonephritis

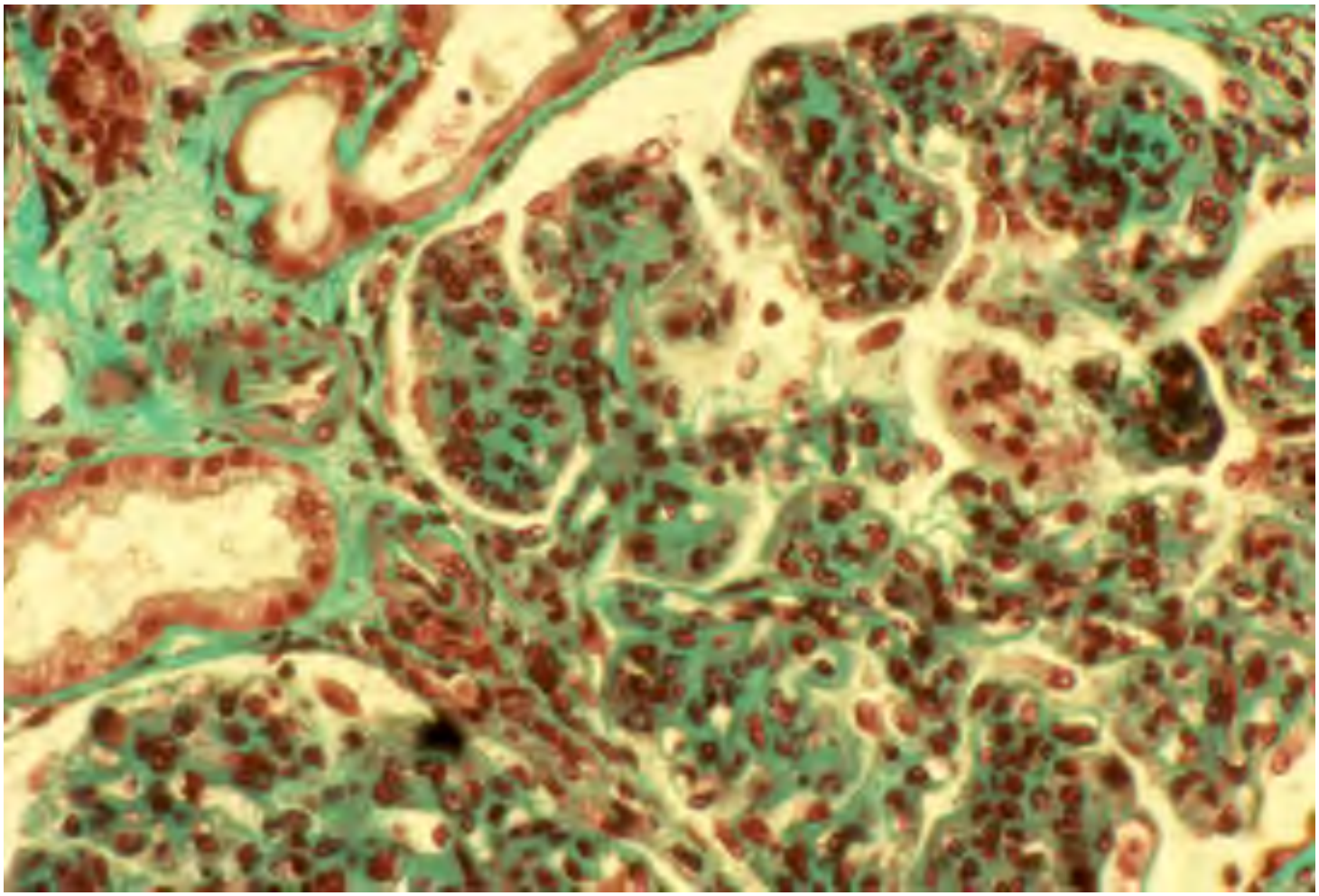
• Proteinuria (g/d)	3.1 ± 2.2
• Albumin (g/L)	29 ± 5
• Creatinine (μmol/L)	118 ± 41
• Cryoglobulin (II/III)	16 / 2
• Cryoglobulin level (g/L)	1.4 ± 1.8
• ALT (IU x N/ml)	1.5 ± 1
• Genotype 1/ 2/ 3/ 4	11/ 3/ 2/ 2
• Treatment of nephrotic sd	
plasmapheresis	132 (66%)
steroids	8 (44%)
furosemide	18 (100%)
ACE	12 (66%)

Alric L. Am J K Dis, 2004

Cryoglobulinemic GN vs Idiopathic type I Membranoproliferative GN.

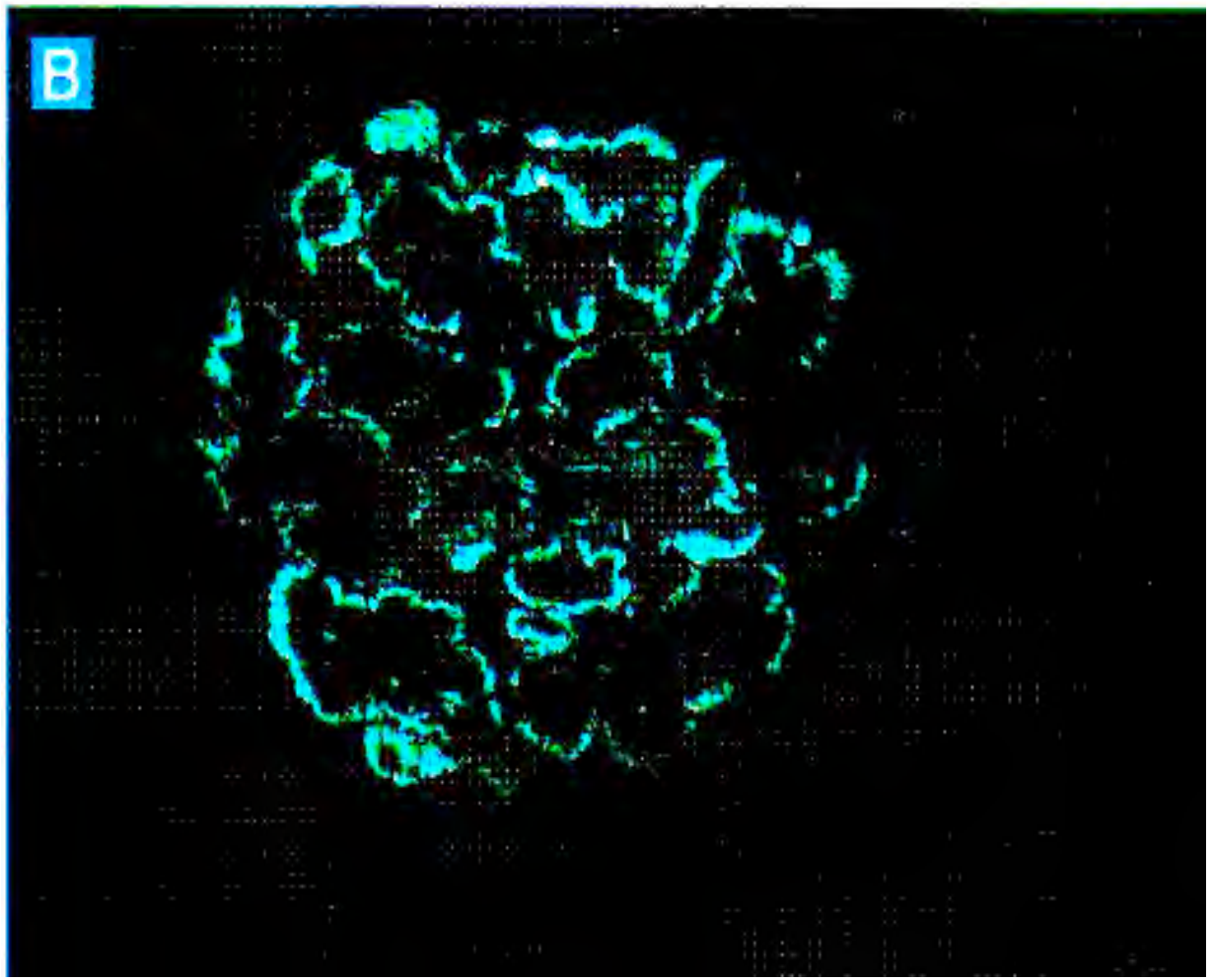
- **Glomérulonéphrite membrano-proliférative**
  - infiltrat monocytaire (+++)
  - thrombi intra-luminaux
  - basale glomérulaire = double contour
  - vascularite vaisseaux petits-moyen calibre ± nécrose fibrinoide
  - IF : dépôts sous-endothéliaux et intra-luminaux d'Ig (= cryo)
  - ME : dépôts cristalloïdes pathognomoniques

Cryoglobulinemic Membrano-Proliferative Glomerulonephritis

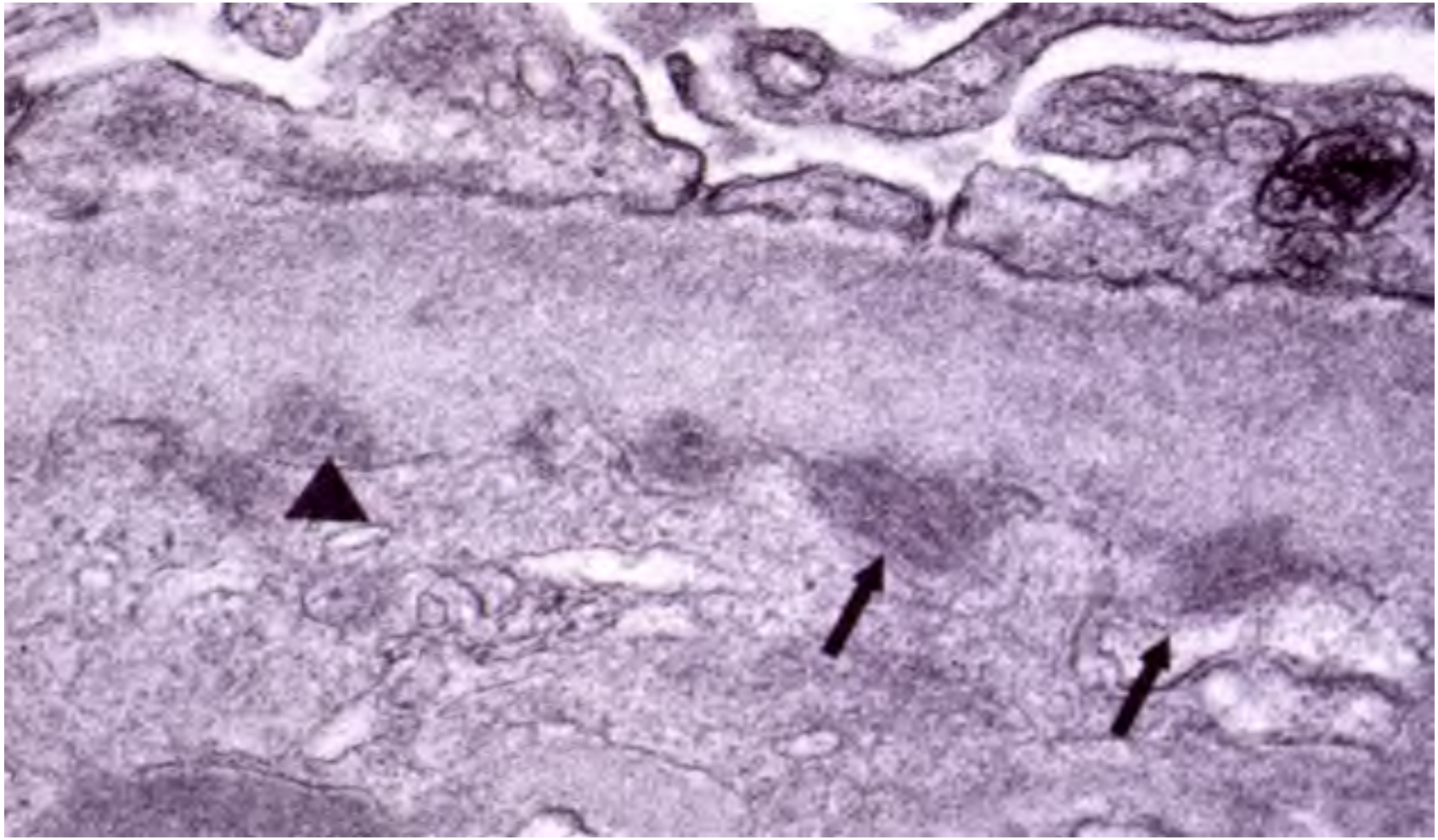


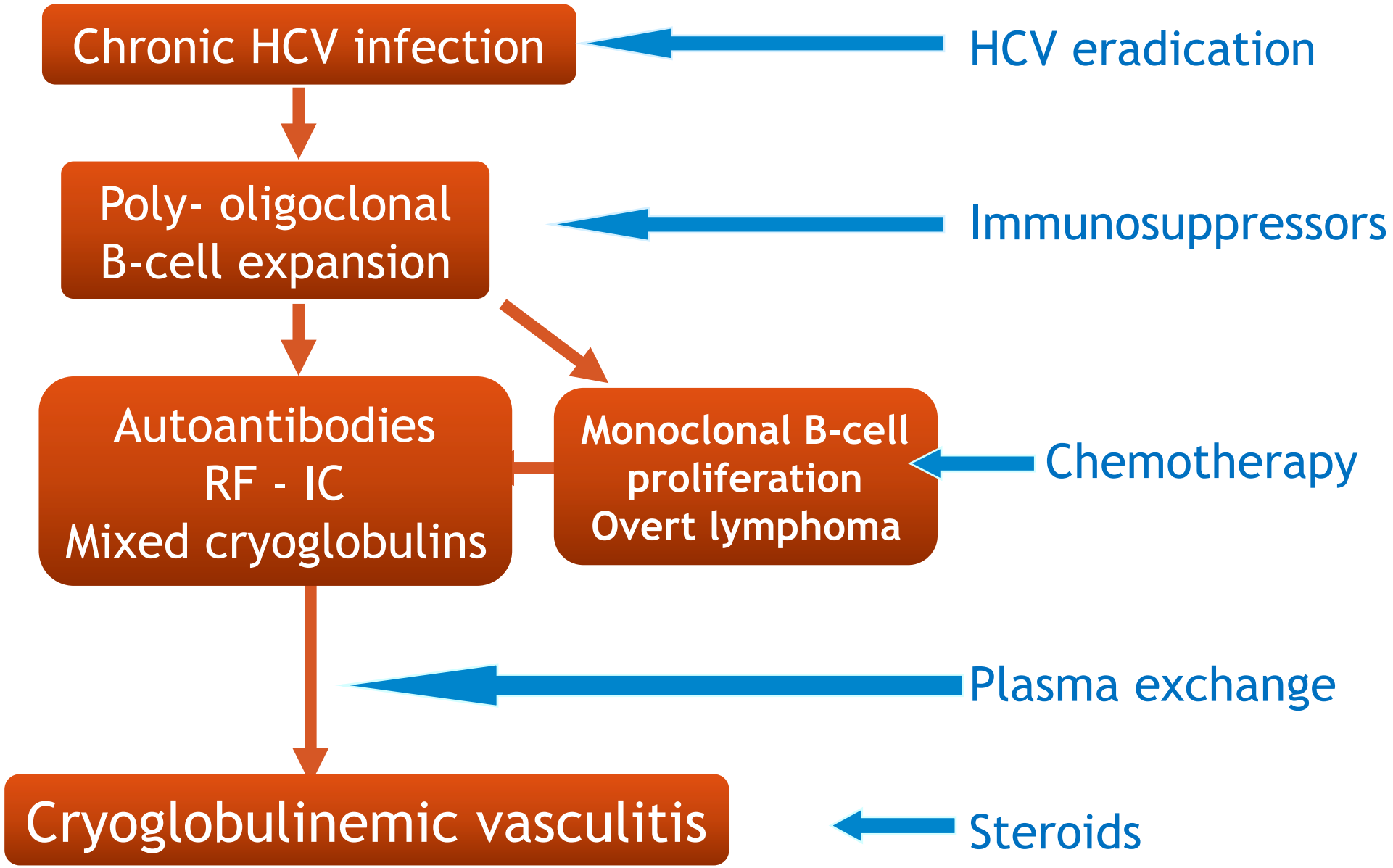
HCV & membranoproliferative glomerulonephritis

Immunofluorescence : endoluminal deposits of IgG, eosinophils, PAS + (thrombi)

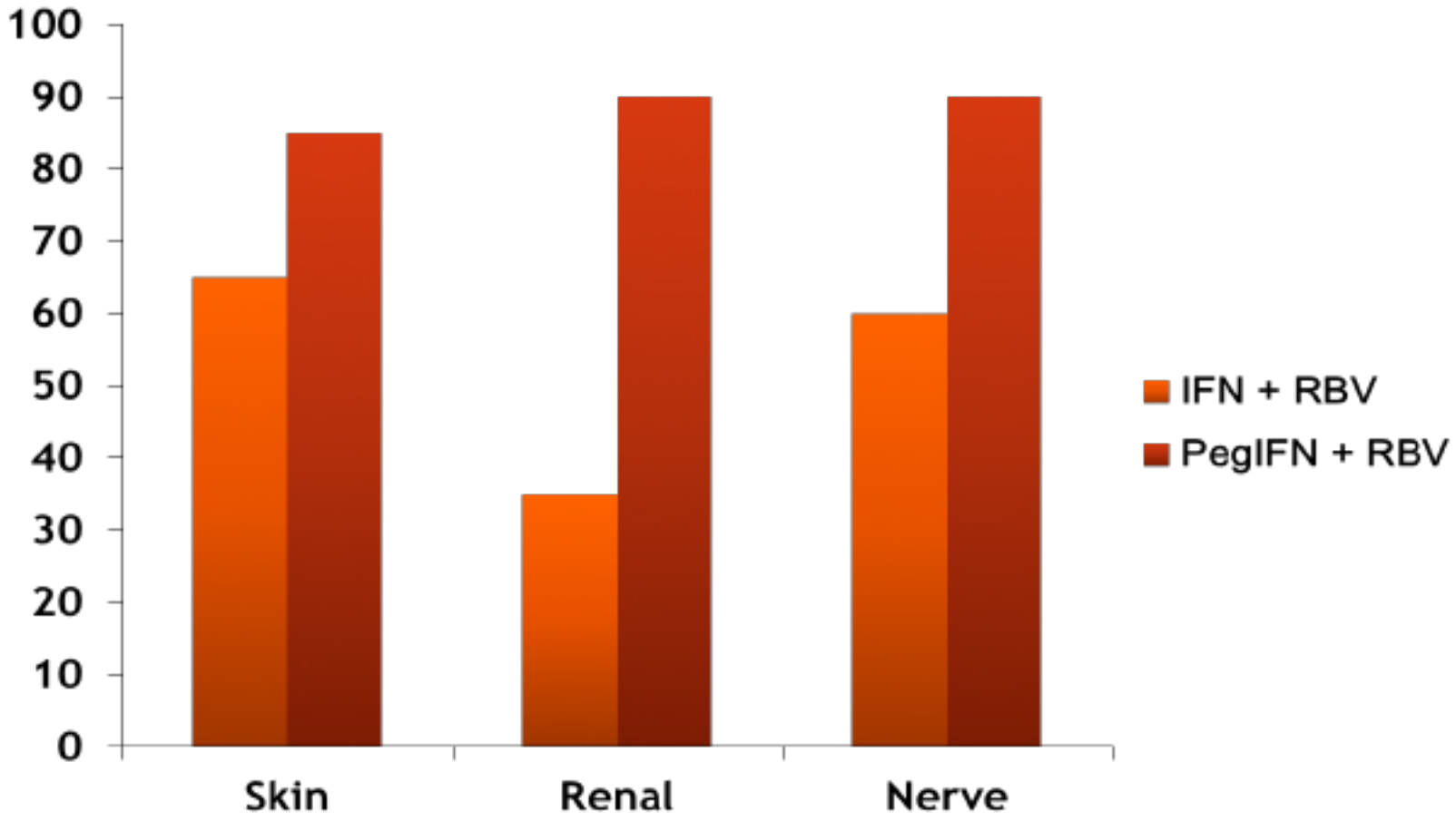


Cryoglobulinemic Membrano-Proliferative Glomerulonephritis (EM)




Chronic HCV infection
HCV eradication
Poly- oligoclonal
B-cell expansion
Immunosuppressors
Autoantibodies
RF - IC
Mixed cryoglobulins
Monoclonal B-cell
proliferation
Overt lymphoma
Chemotherapy
Plasma exchange
Cryoglobulinemic vasculitis
Steroids

HCV Treatment Efficacy in HCV-Vasculitis



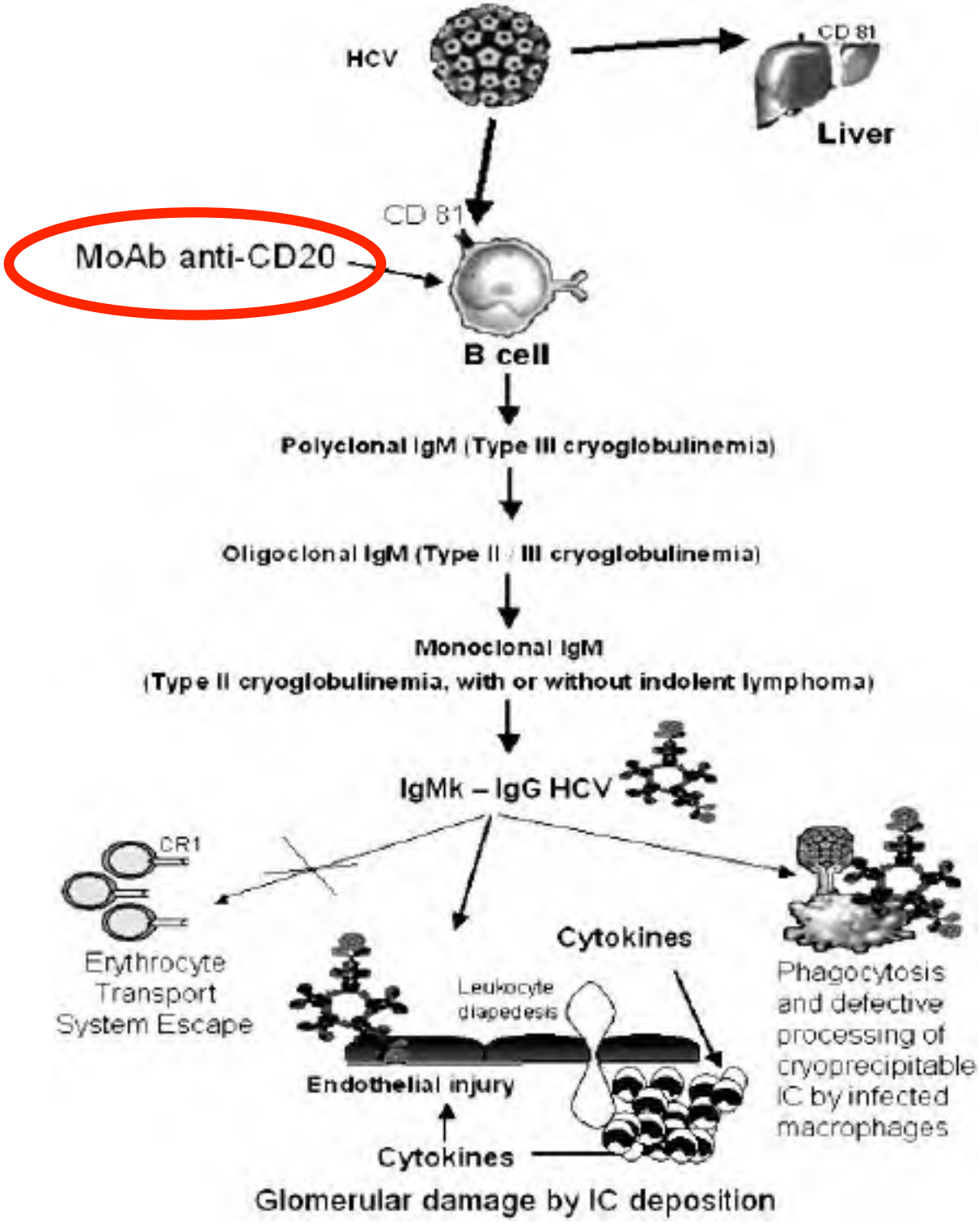
Zuckerman, J Rheumatol 2000. Naarendorp, J Rheumatol 2001. Cacoub, Arthritis Rheum 2002, Zaja F, Blood 2003. Sansonno D, Blood 2003 , Cacoub, Arthritis Rheum 2005, Saadoun, Arthritis Rheum 2007

Predictive Factors of Clinical Response to HCV Therapy in Mixed Cryoglobulinemia Vasculitis

Multivariate Analysis

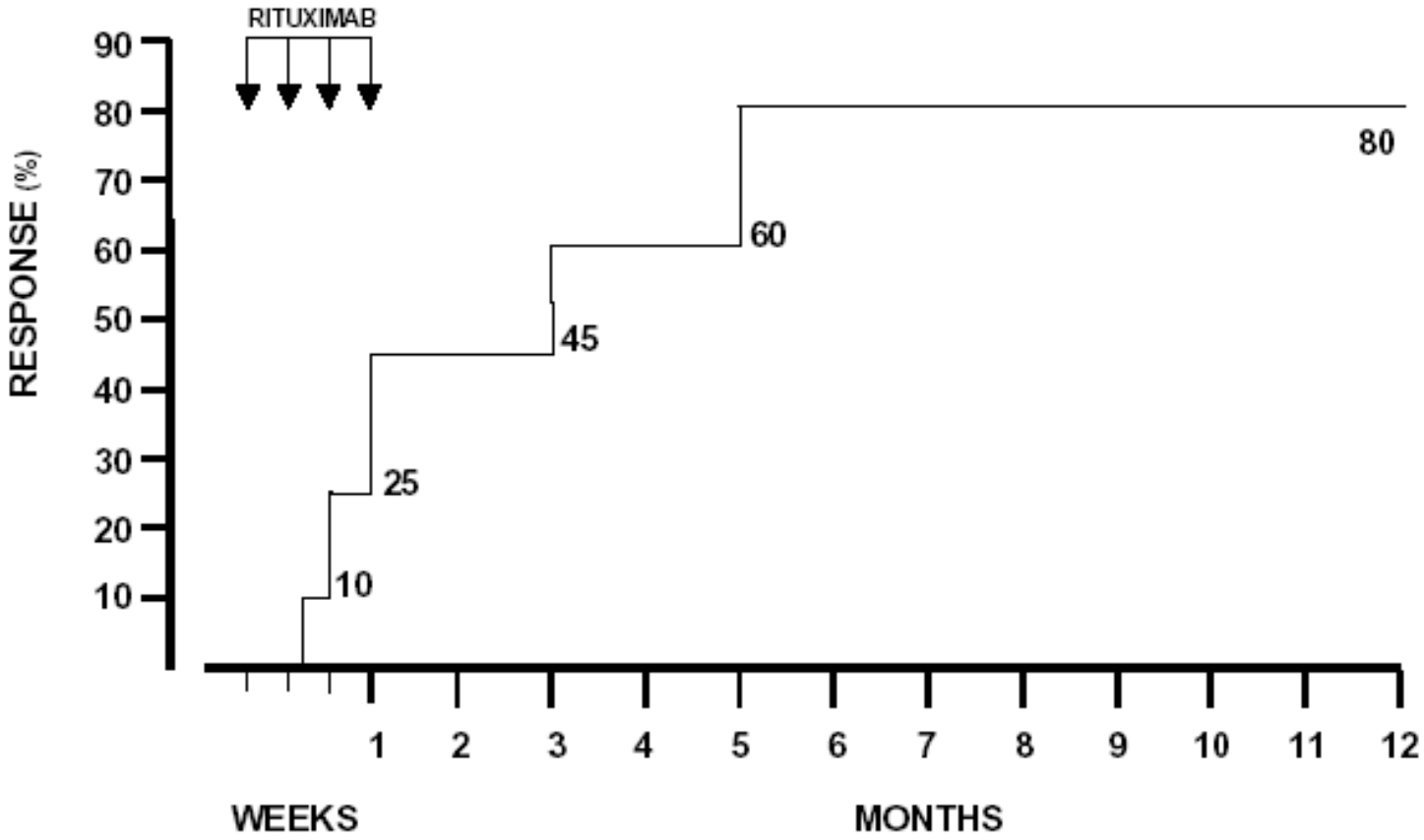
	Odds ratio	[95%CI]	p
• Renal involvement	0.27	[0.08-0.87]	0.02
• **Renal insufficiency (GFR<70)**	**0.18**	**[0.05-0.67]**	**0.01**
• Daily proteinuria > 1g	0.32	[0.09-1.11]	0.05
• **Early virological response**	**3.53**	**[1.18-10.59]**	**0.02**

Rationale for Rituximab treatment in cryoglobulinemic vasculitis



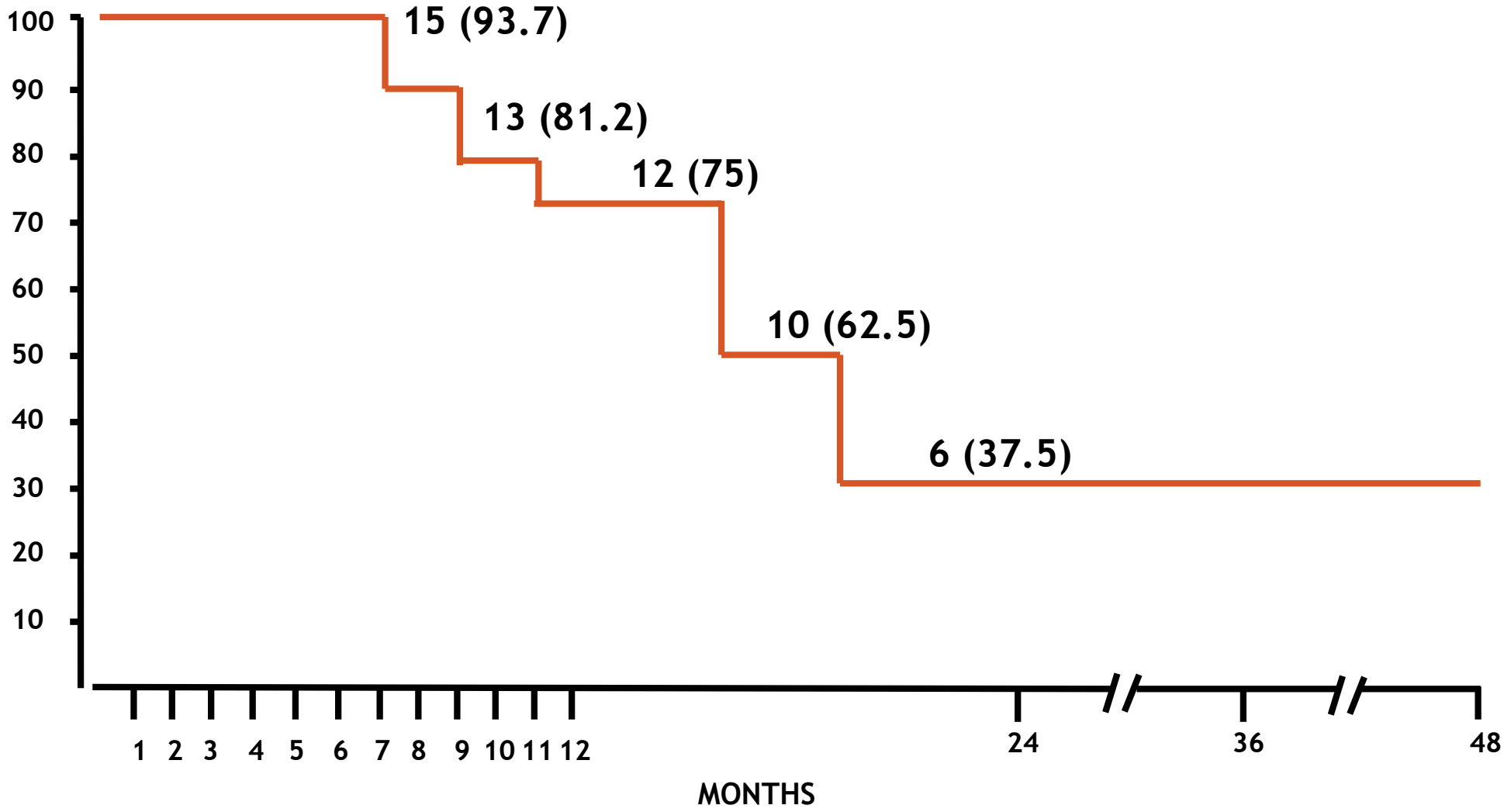
Roccatello, D. et al. Nephrol. Dial. Transplant. 2004

Treatment of Mixed Cryoglobulinemia Resistant to Interferonα with Rituximab



Sansonno D et al, Zaja F et al, Blood 2003

Cryoglobulinemia Vasculitis: Response Maintenance after Discontinuation of Rituximab



Sansonno D et al, 2007

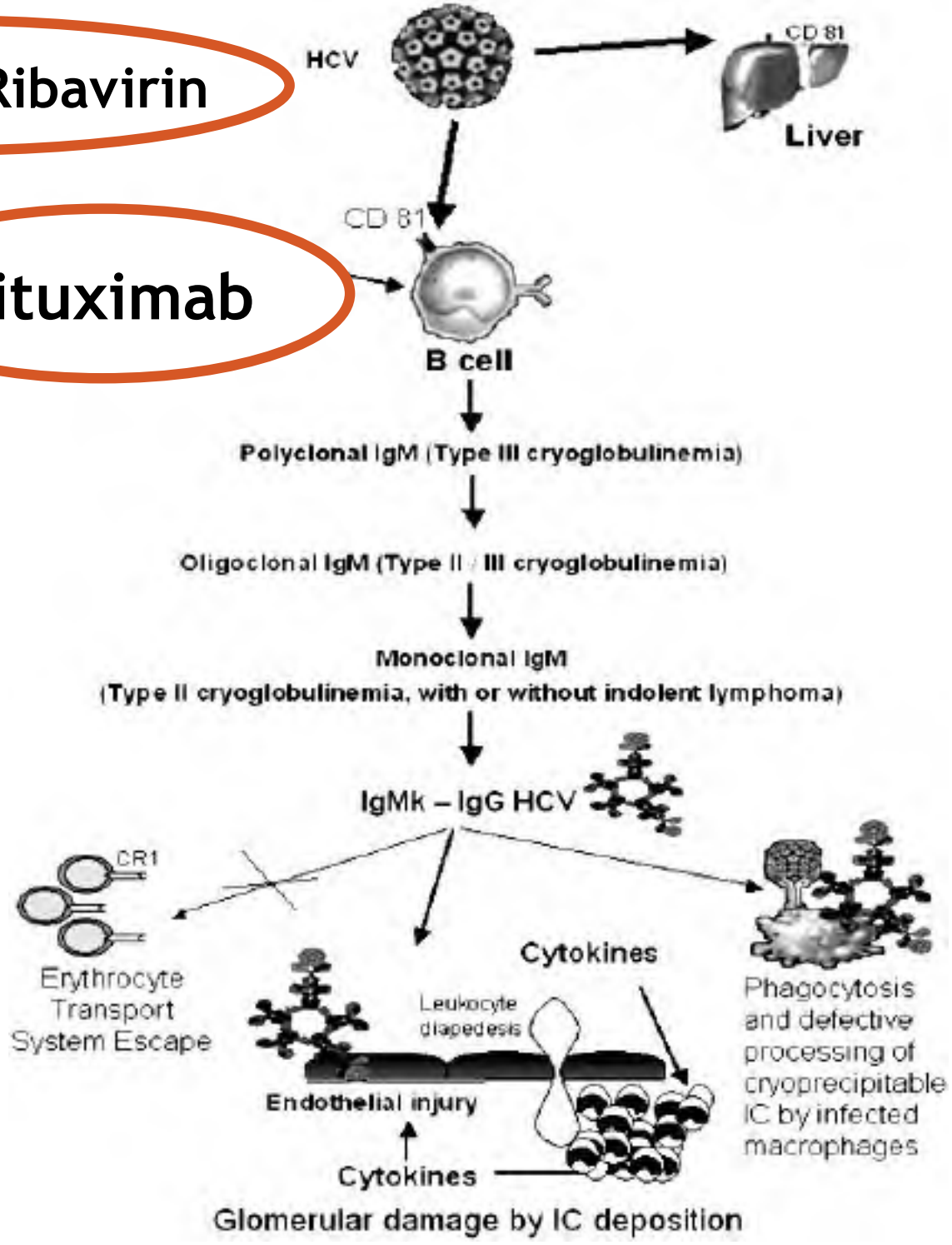
PegIFN plus Ribavirin

Rituximab

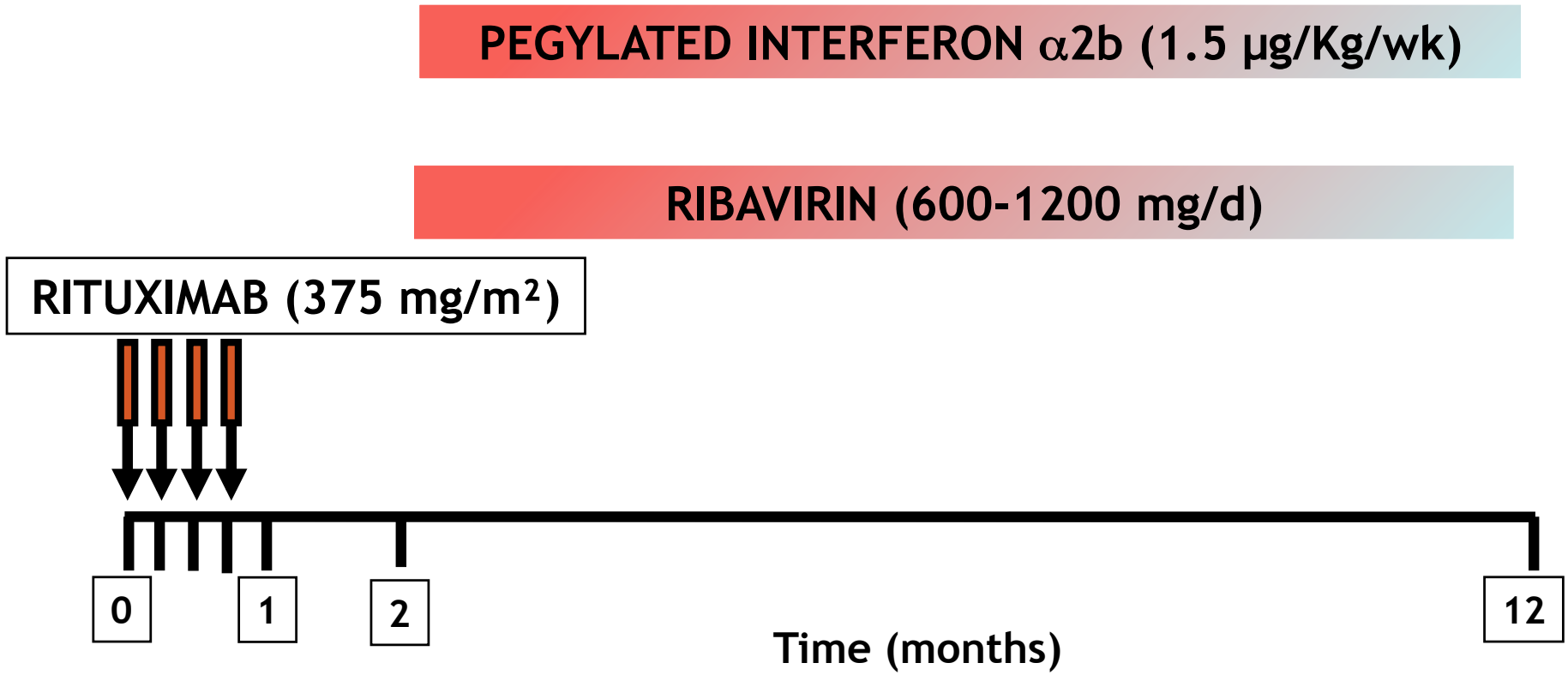
HCV Vasculitis: a Two-Faces Disease

…

Needs a Two Faces Treatment Strategy



Rituximab plus Peg-IFNα2b-Ribavirin in Refractory HCV-Related Systemic Vasculitis



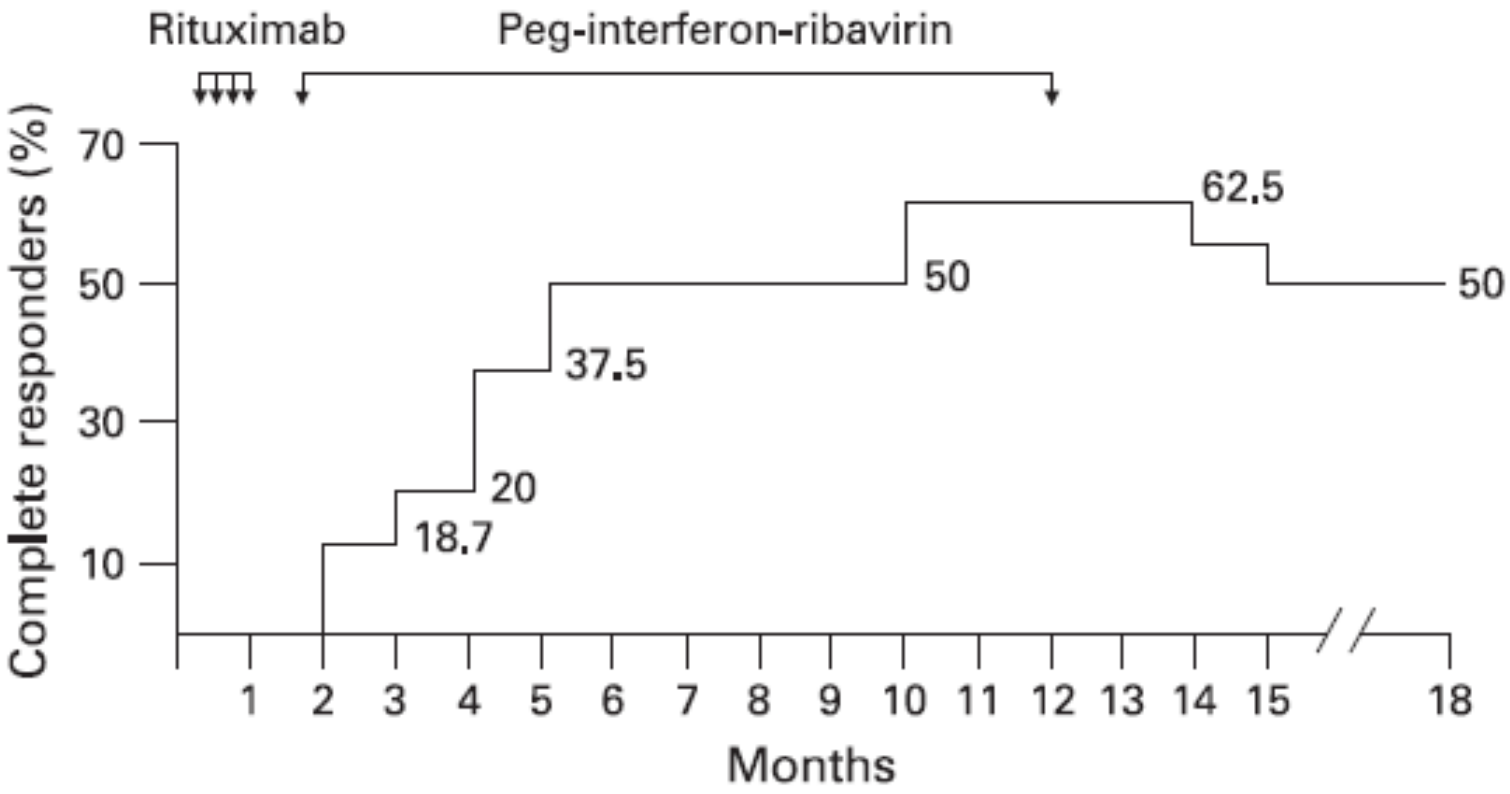
Saadoun D et al, Ann Rheum Dis 2008

Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis

D Saadoun, M Resche-Rigon, D Sene, L Perard, A Marras and P Cacoub

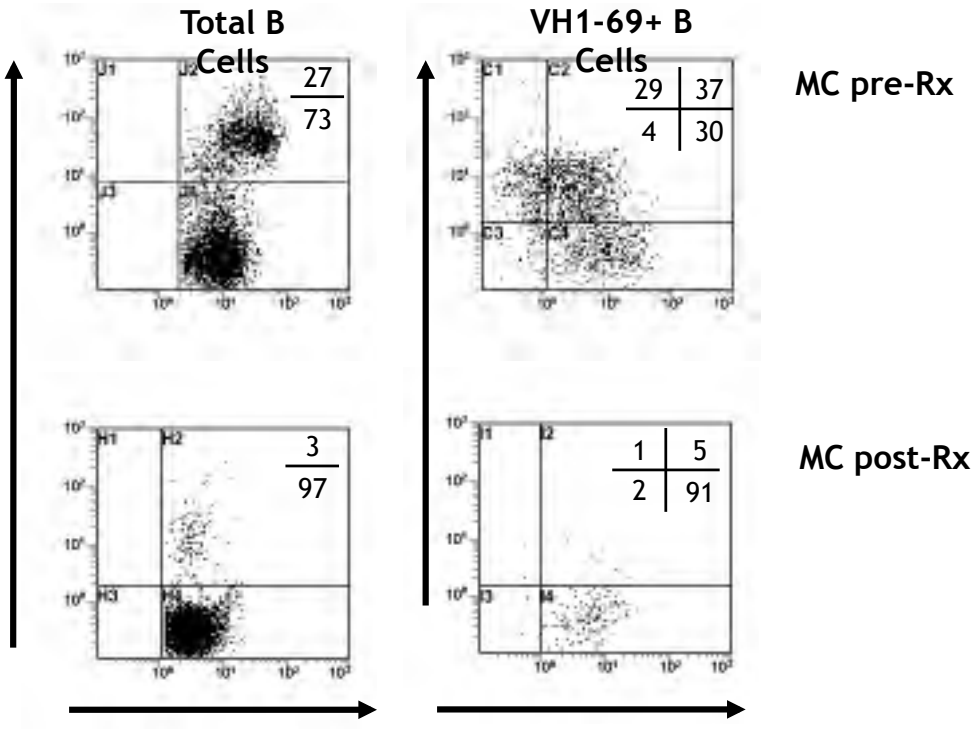
Ann Rheum Dis 2008;67:1431-1436; originally published online 4 Jan 2008;
doi:10.1136/ard.2007.061663

Response rate of HCV-cryoglobulinemia vasculitis with Rituximab plus Peg-IFNα2b + Ribavirin.

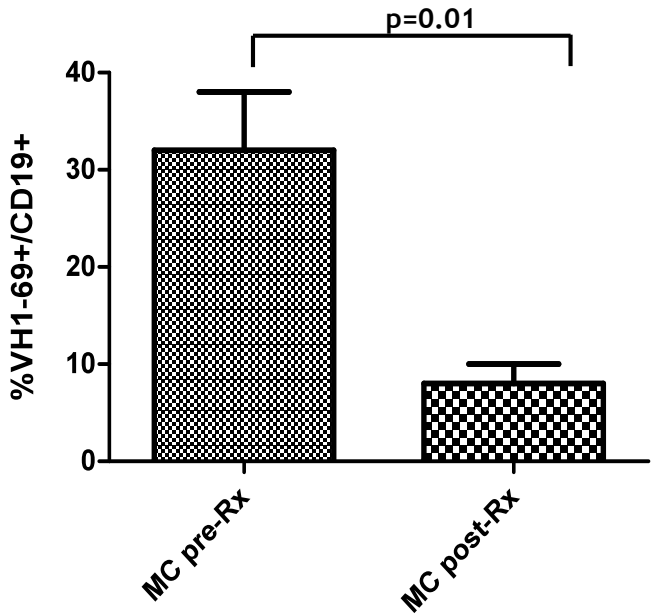


Saadoun D, Ann Rheum Dis, 2008

Effects of rituximab on VH1-69 clonal B cells



A patient with HCV-MC-vasculitis demonstrating staining with anti-Vh1-69 gene product mAb (MC pre-Rx) and disappearance of VH1-69+ B cells following rituximab (MC post-Rx).



VH1-69+ cells among CD19+ B cells in patients with HCV-MC vasculitis (n=11) before and after rituximab

Rituximab plus Peg-interferon-α/ribavirin compared with Peg-interferon-α/ribavirin in hepatitis C–related mixed cryoglobulinemia

David Saadoun,[1,2] Mathieu Resche Rigon,[3] Damien Sene,[1] Benjamin Terrier,[1,2] Alexandre Karras,[4] Laurent Perard,[5] Yoland Shoindre,[1] Brigitte Coppéré,[5] François Blanc,[6] Lucile Musset,[7] Jean-Charles Piette,[1] Michele Rosenzwajg,[2] and Patrice Cacoub[1,2]

BLOOD, 22 JULY 2010 • VOLUME 116, NUMBER 3

Outcome of HCV-MC according to treatment

Parameters	All n=93	PegIFNα-ribavirin n=55	RTX-PegIFNα-ribavirin n=38	*P*
Time clinical response, months	**6.8 ± 4.7**	**8.4 ± 4.7**	**5.4 ± 4.0**	0.004
Clinical response				
CR	**68 (73.1)**	**40 (72.7)**	**28 (73.7)**	**0.98**
PR	22 (23.6)	13 (23.6)	9 (23.7)	
NR	3 (3.2)	2 (3.6)	1 (2.6)	
Relapse	17 (18.3)	10 (18.1)	7 (18.4)	
Immunological response				
CR	**49 (52.7)**	**24 (43.6)**	**26 (68.4)**	**0.001**
PR	35 (37.6)	25 (45.4)	10 (26.3)	
NR	8 (8.6)	6 (10.9)	2 (5.2)	
Relapse	17 (18.3)	10 (18.1)	7 (18.4)	
Virological response				
SVR	**55 (59.1)**	**33 (60)**	**22 (57.9)**	**0.94**
Death	5 (5.4)	2 (3.6)	3 (7.9)	0.70

Course of kidney parameters in HCV-MC according to the type of treatment

	PegIFNα-ribavirin n=10	*p*	RTX-PegIFNα-ribavirin n=21	*p*
Kidney inv. CR	4 (40)		17 (80.9)	0.04

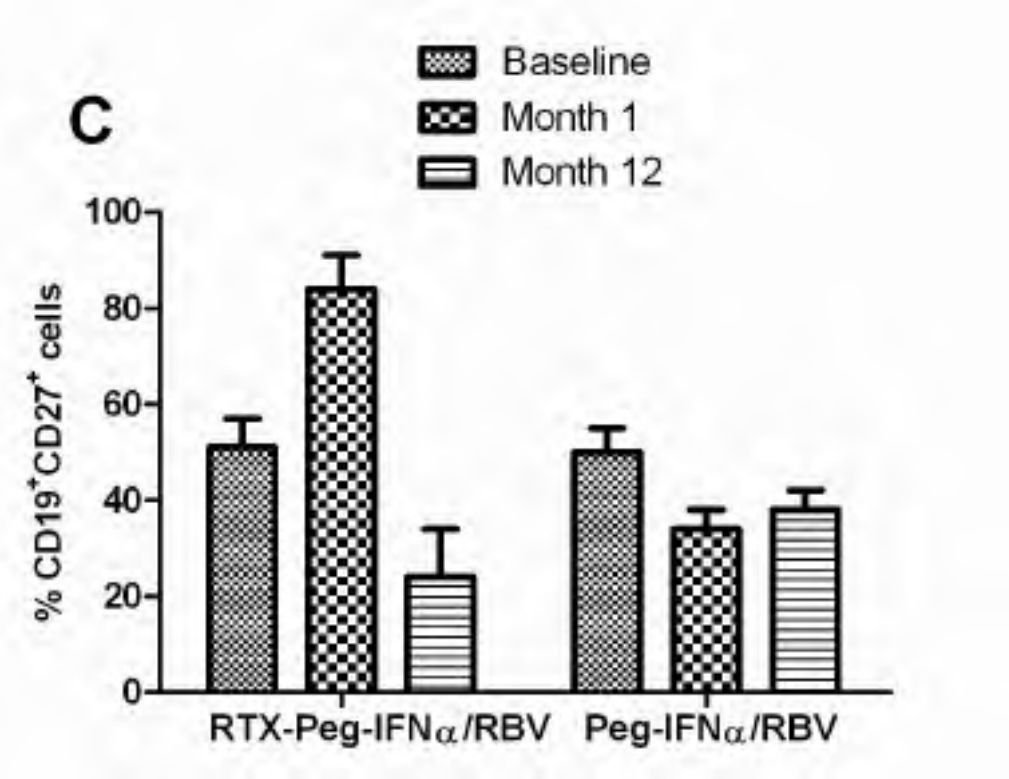
Course of kidney parameters in HCV-MC according to the type of treatment

	PegIFNα-ribavirin n=10	*p*	RTX-PegIFNα-ribavirin n=21	*p*
Kidney inv. CR	**4 (40)**		**17 (80.9)**	**0.04**
Creatininemia (µmol/l)				
Baseline	150 ± 30		**217 ± 47**	
EOF	169 ± 44	0.28	**136 ± 27**	0.03
GFR (ml/min)				
Baseline	58 ± 7		**42 ± 5**	
EOF	59 ± 9	0.41	**57 ± 4**	0.01

Course of kidney parameters in HCV-MC according to the type of treatment

	PegIFNα-ribavirin n=10	*p*	RTX-PegIFNα-ribavirin n=21	*p*
Kidney inv. CR	**4 (40)**		**17 (80.9)**	**0.04**
Creatininemia (µmol/l)				
Baseline	150 ± 30		217 ± 47	
EOF	169 ± 44	0.28	136 ± 27	0.03
GFR (ml/min)				
Baseline	58 ± 7		42 ± 5	
EOF	59 ± 9	0.41	57 ± 4	0.01
Daily Proteinuria (gr/d)				
Baseline	**3.1 ± 0.9**		**3 ± 1**	
EOF	**1.2 ± 0.5**	0.046	**0.4 ± 0.1**	<0.001
Hematuria (n,%)				
Baseline	**10 (100)**		**19 (90.5)**	
EOF	**2 (20)**		**2 (10.5)**	<0.001

Antiviral therapy alone decreases the memory B cells

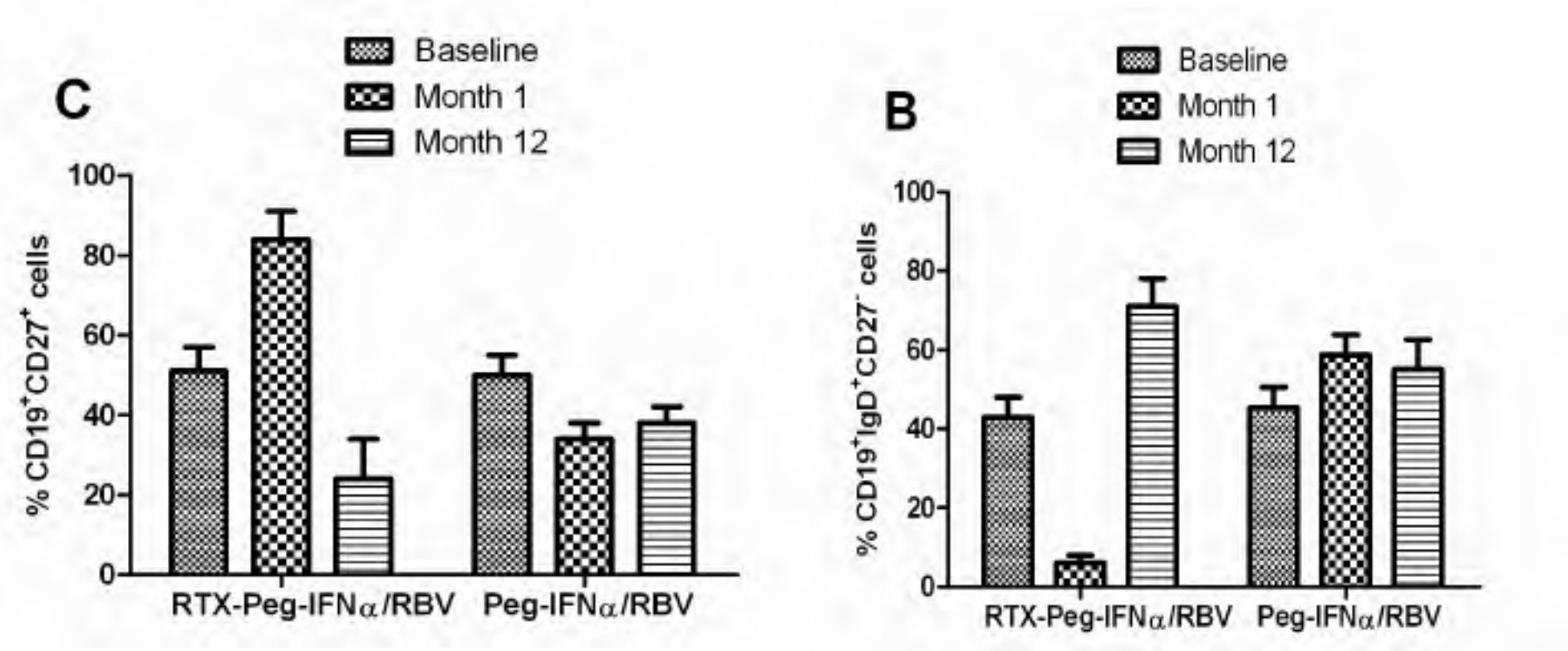


n=38 **n=55**

Saadoun D et al, Blood 2010

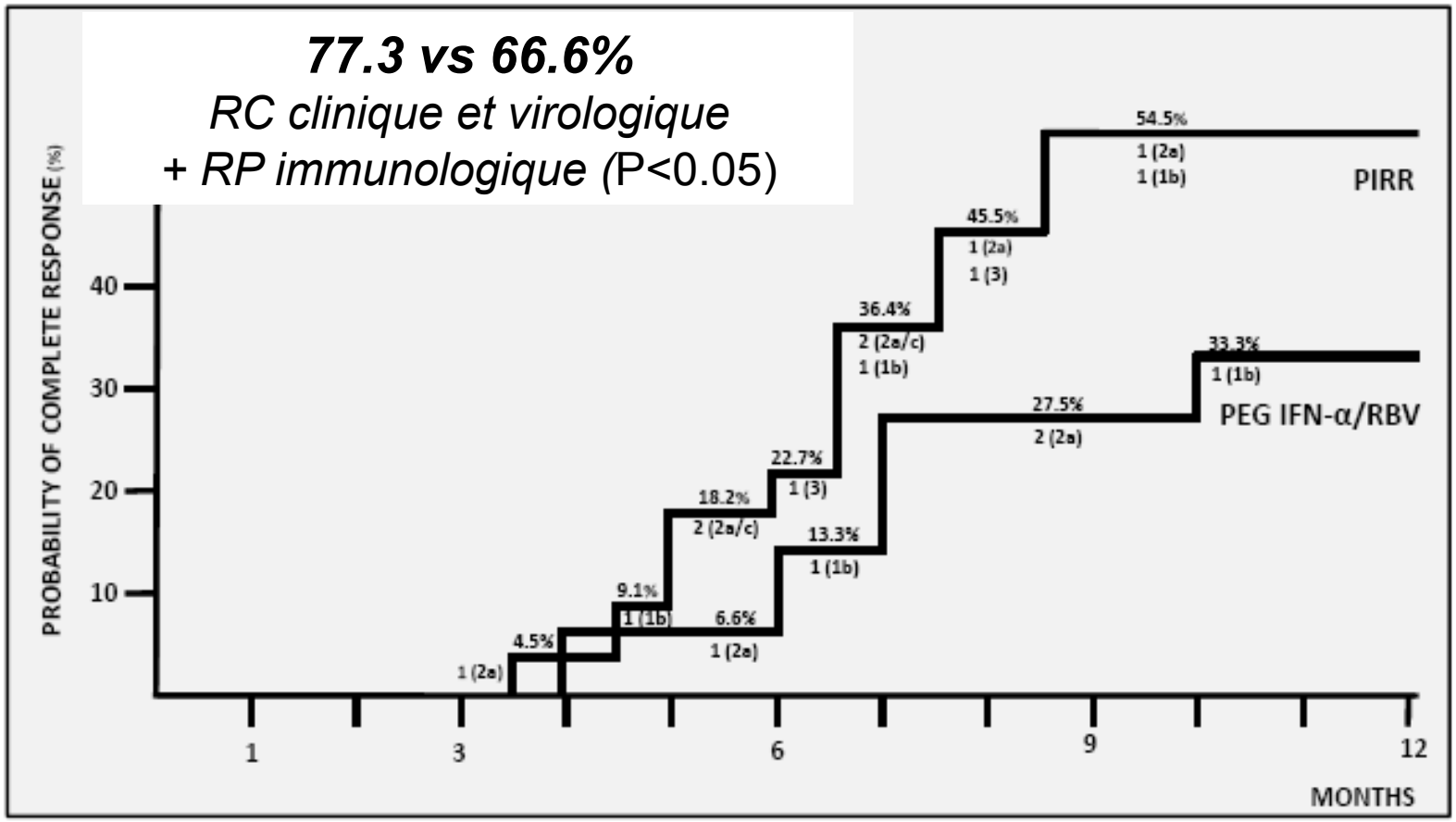
Antiviral therapy alone decreases the memory B cells

Antiviral therapy plus Rituximab decrease naive B-cells



Saadoun D et al, Blood 2010

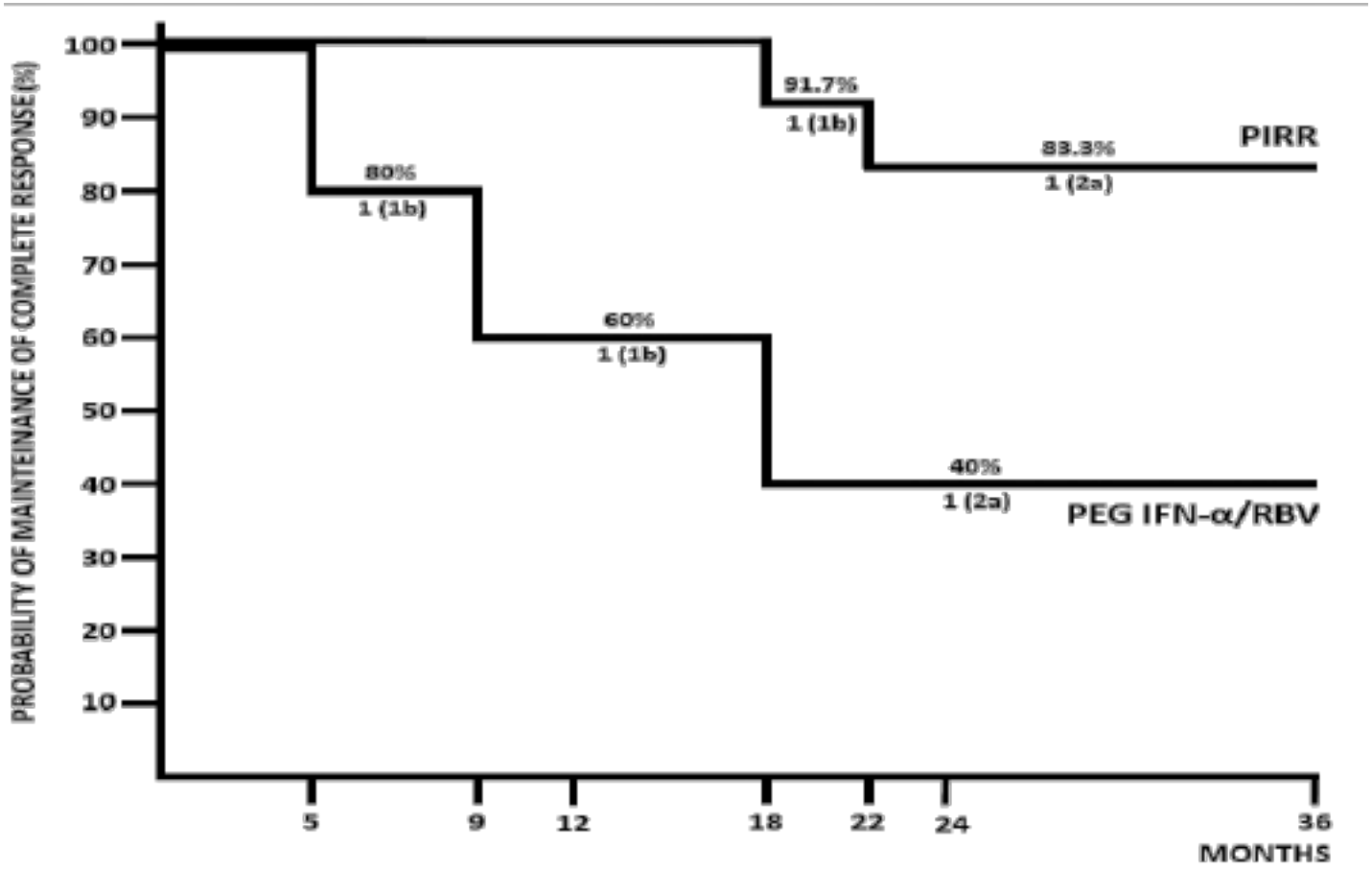
RTX/Peg-IFNα-Ribavirin vs. Peg-IFNα-Ribavirin in HCV Systemic Vasculitis



Dammacco F et al, Blood, 2010

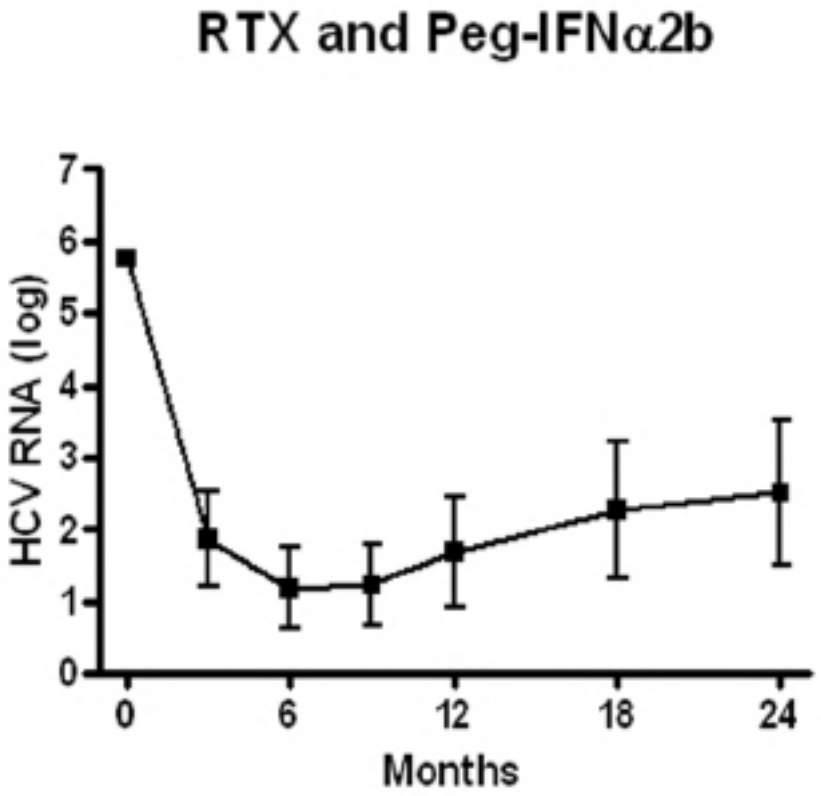
RTX/Peg-IFNα-Ribavirin vs. Peg-IFNα-Ribavirin in HCV Systemic Vasculitis

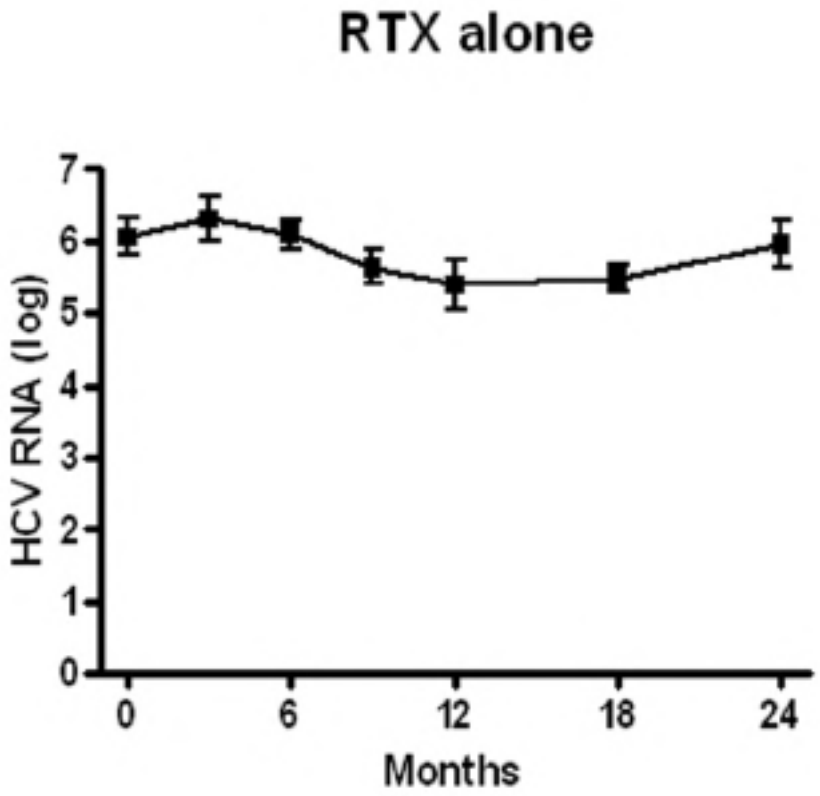
Maintien de la Réponse clinique complète



Dammacco F et al, Blood 2010

Reassuring Time Course of HCV Viral Load with Rituximab





Terrier B et al. Arthritis Rheum 2009

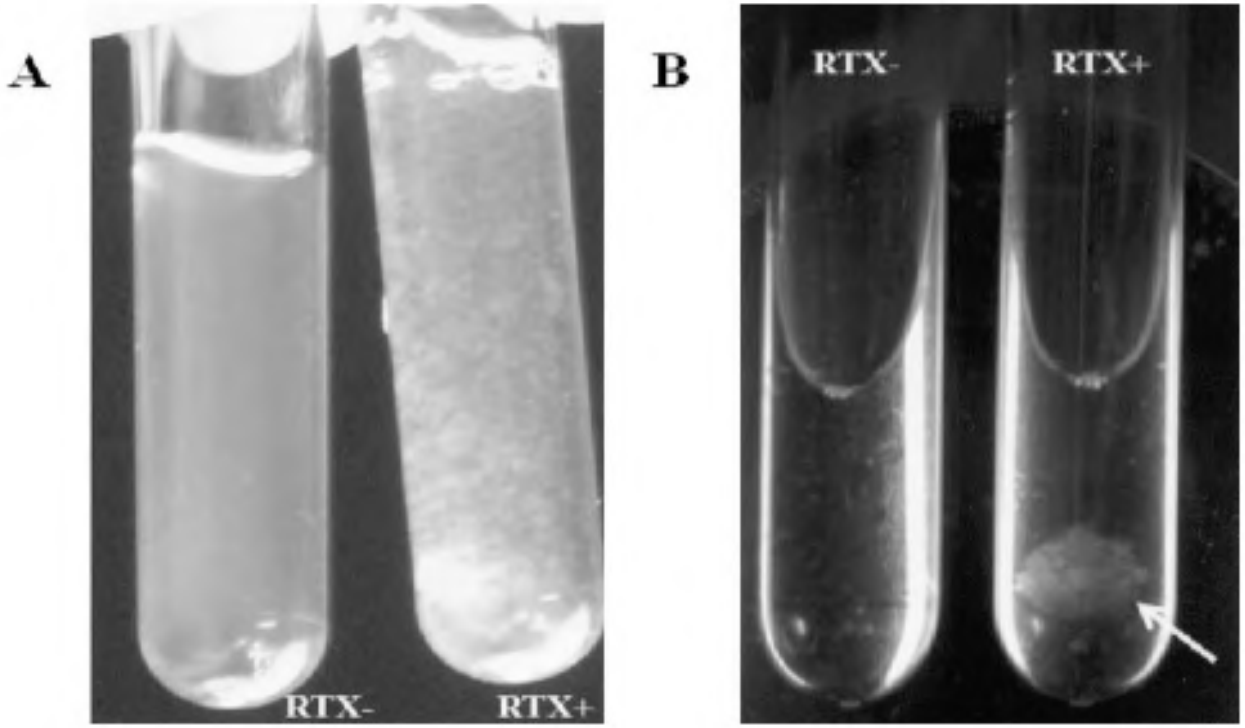
ARTHRITIS & RHEUMATISM
Vol. 60, No. ●, Month 2009, pp 000–000
DOI 10.1002/art.●

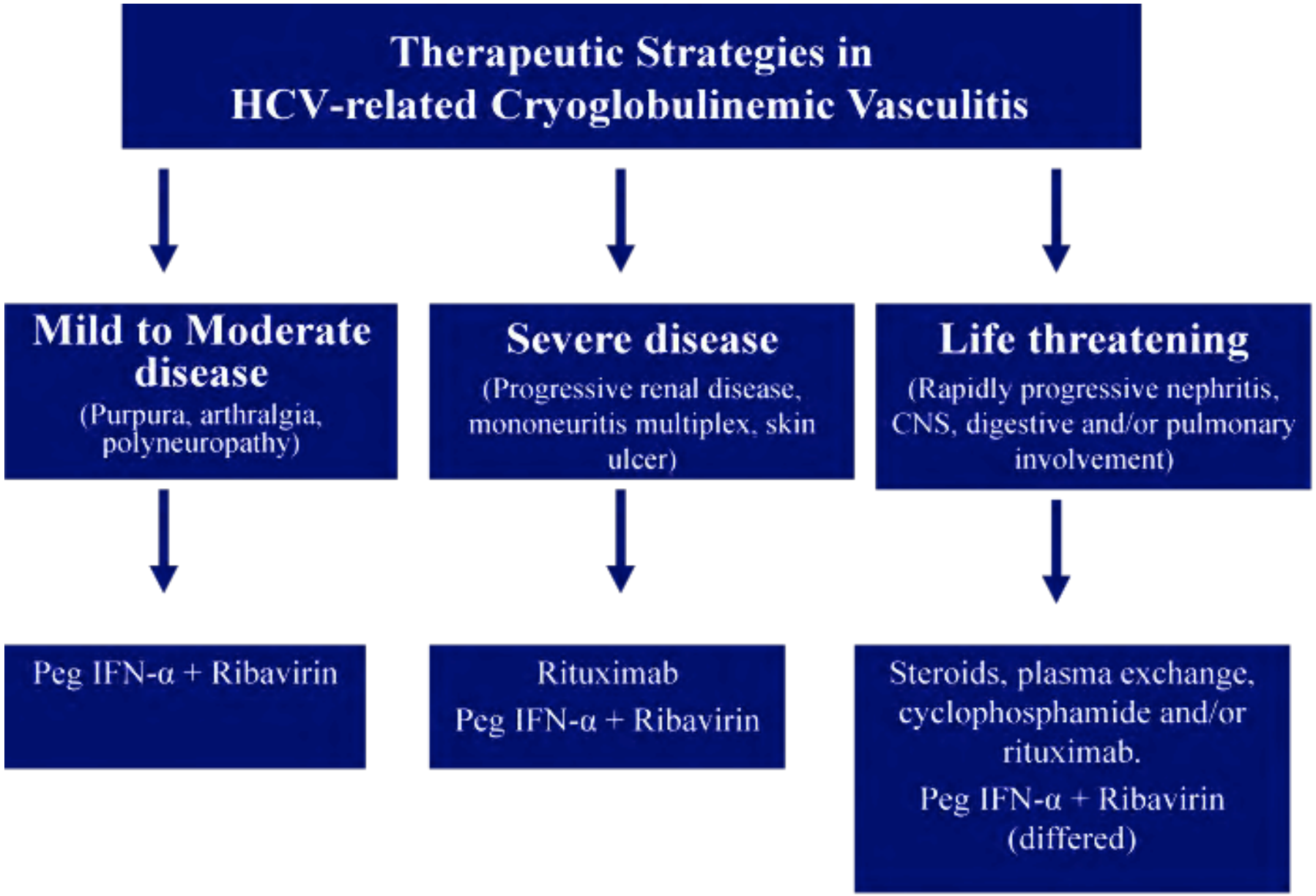
Rituximab May Complex With IgMκ Mixed Cryoglobulin and Induce Severe Systemic Reactions in Patients With Hepatitis C Virus–Induced Vasculitis

Damien Sène, Pascale Ghillani-Dalbin, Zahir Amoura, Lucile Musset, and Patrice Cacoub

2°) The 6 patients with RTX related severe systemic drug-reaction, compared to those without were characterized by:

- *higher MC levels : 1.4 ± 0.8 g/L vs 0.71 ± 0.77 g/L; P = 0.0475*
- *lower C4 levels: 0.02 ± 0.006 vs 0.07 ± 0.07 g/L; P = 0.02*
- *more frequent receipt of the RTX-1000 high dose protocol (3/6 = 50% vs 1/15 = 6.7%; P = 0.05)*





- **If failure or CI to PegINF/riba: RTX alone**
- **Place to be defined for PegIFN/Riba/Previr**

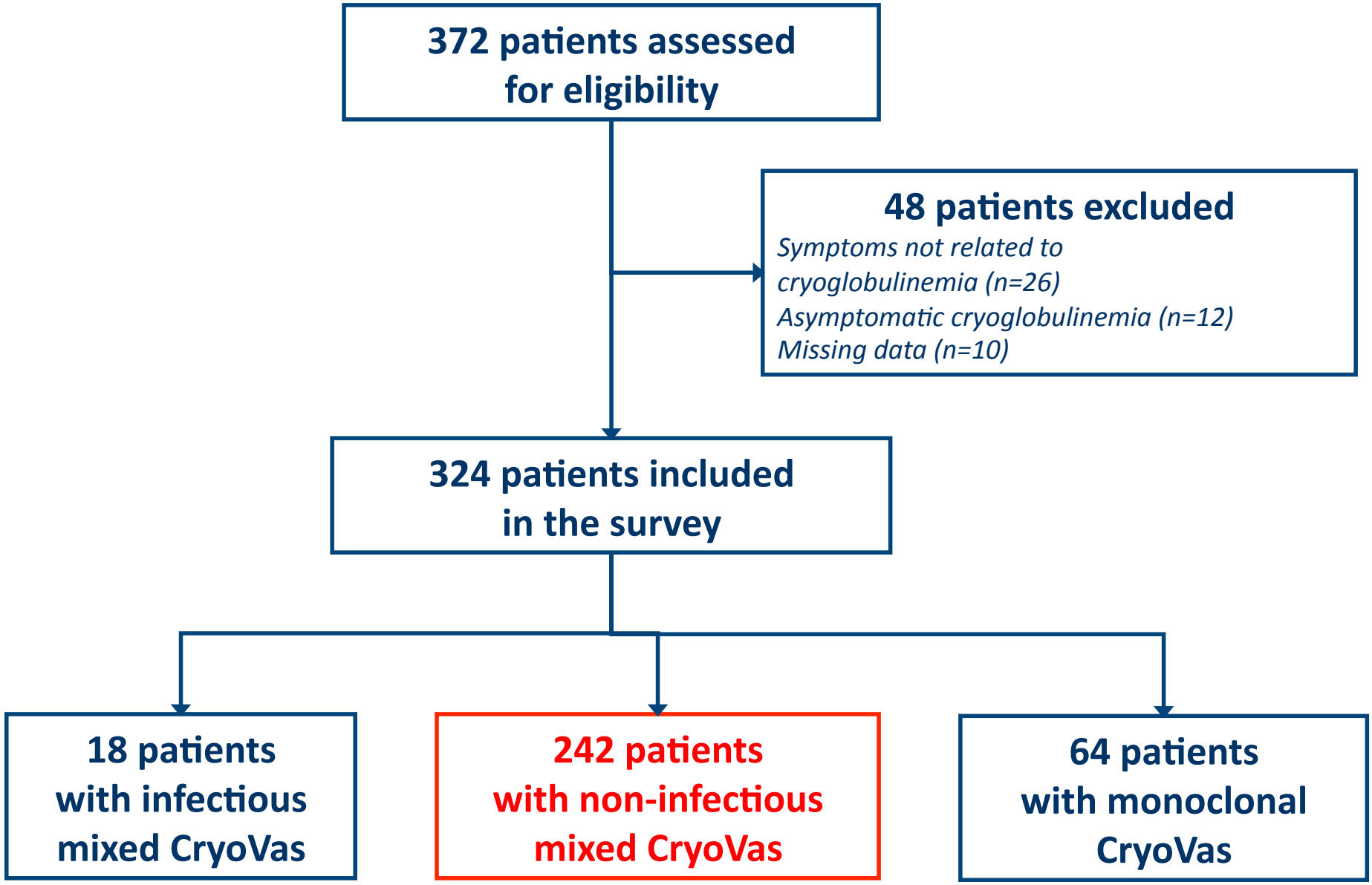
Cryoglobulinémies mixtes non infectieuses

Efficacy and safety of treatments in patients with non-infectious mixed cryoglobulinemia vasculitis

Results from the French CryoVas survey

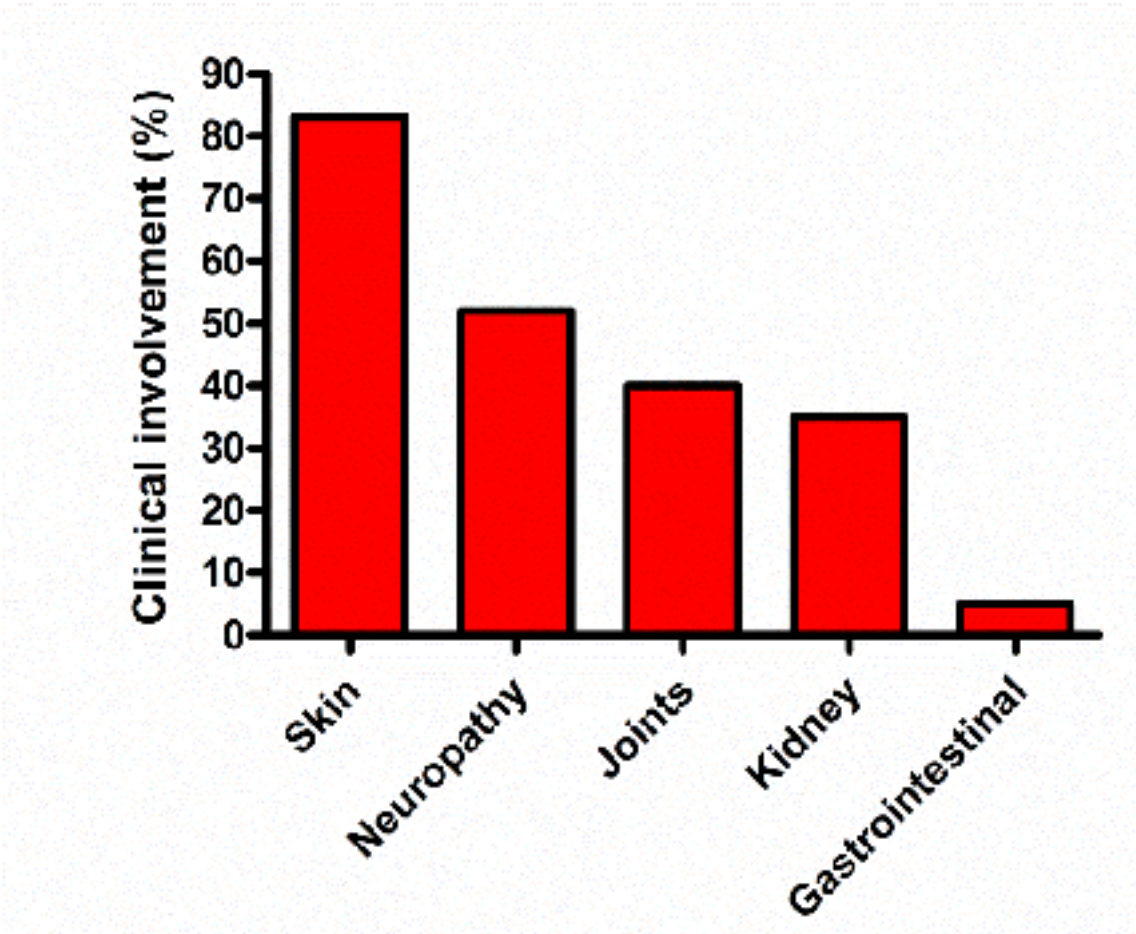
Benjamin Terrier, Evguenia Krastinova, Isabelle Marie, Adeline Lacraz, David Launay, Emmanuelle Plaisier, Luc de Saint-Martin, Fabrice Bonnet, Pauline Belenotti, Jean-Emmanuel Kahn, Olivier Hinschberger, Patricia Rullier, Patrice Cacoub

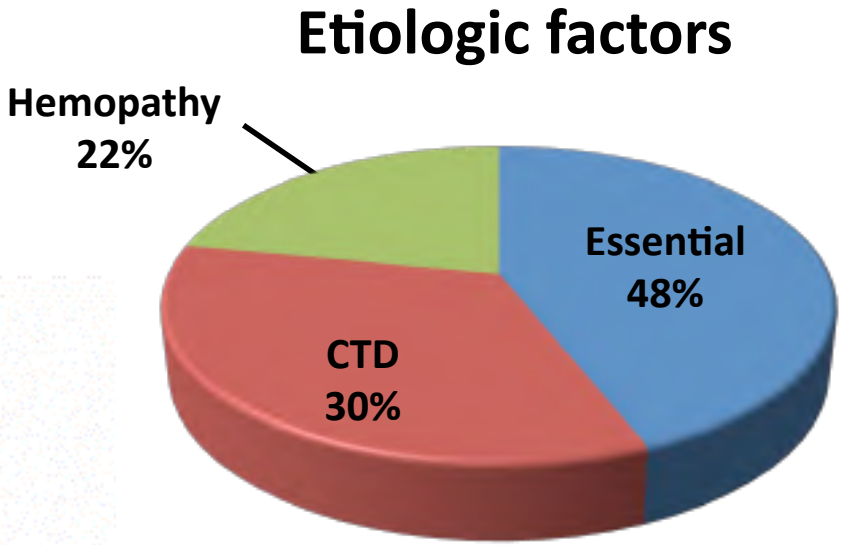
Internal Medicine Department,
Groupe Hospitalier Pitié-Salpétrière
Université Pierre et Marie Curie, Paris 6, Paris, France


372 patients assessed for eligibility
48 patients excluded
Symptoms not related to cryoglobulinemia (n=26)
Asymptomatic cryoglobulinemia (n=12)
Missing data (n=10)
324 patients included in the survey
18 patients with infectious mixed CryoVas
242 patients with non-infectious mixed CryoVas
64 patients with monoclonal CryoVas

Baseline characteristics

62.6 ± 14.5 years
Females : 69%





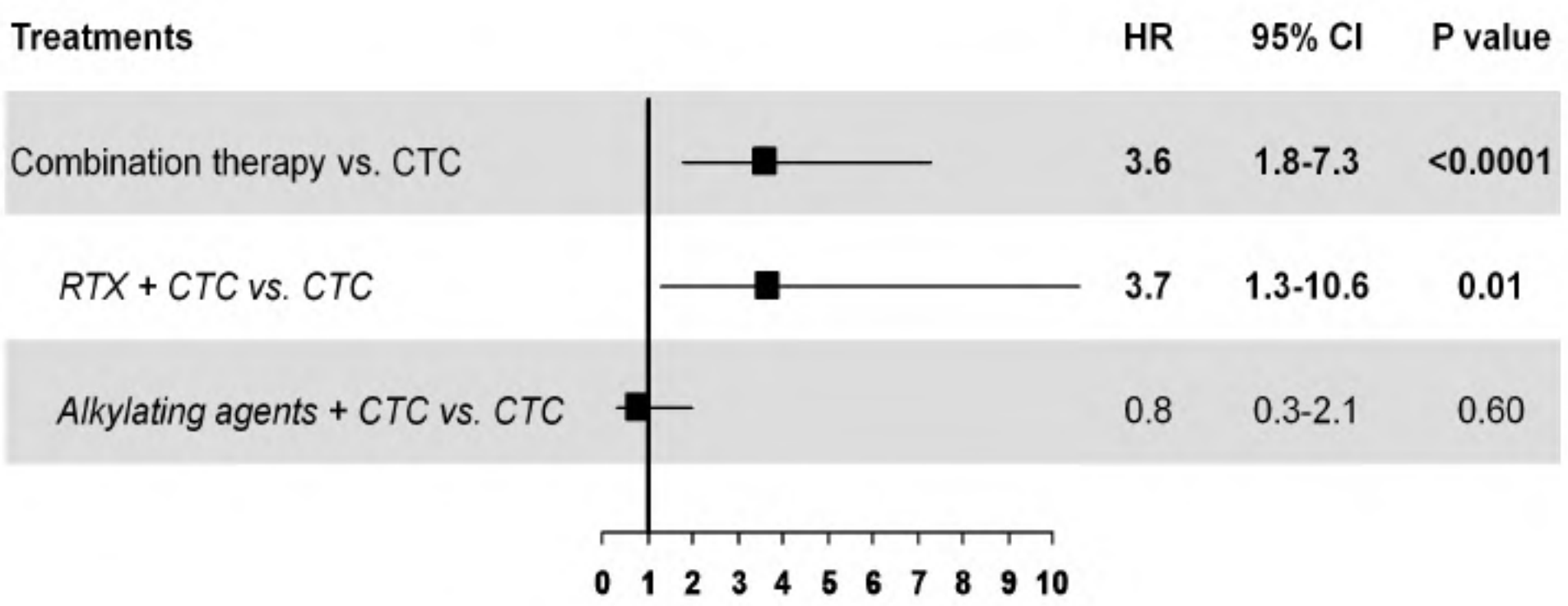
Therapeutic regimens in non-infectious mixed CryoVas

	n=209
Lines of treatment, n (%)	1.8 ± 1.2
Corticosteroids	209 (100%)
Rituximab	104 (50%)
Alkylating agents	97 (46%)
Plasmapheresis	43 (21%)
Azathioprine/MMF	31 (15%)

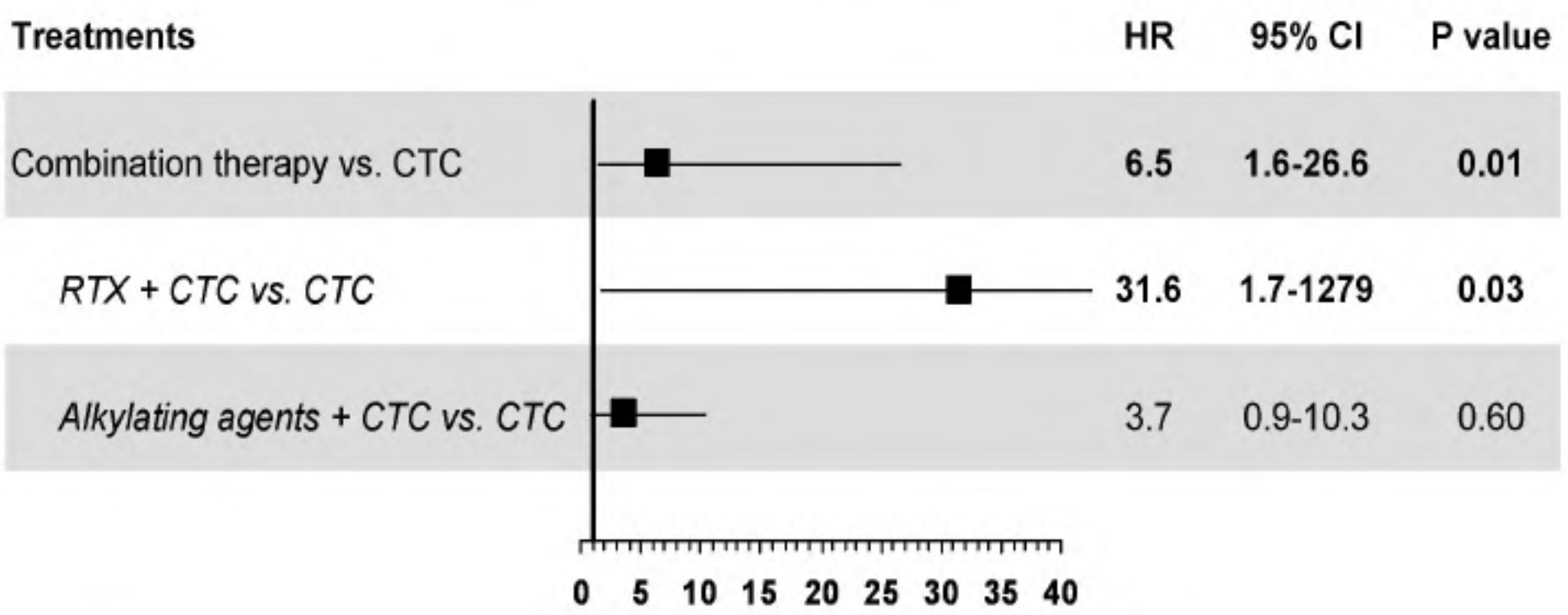
Assessment of treatment efficacy and safety

1. **Randomized controlled trials :** difficult in rare diseases
2. **Observational studies** using **marginal structural models :** evaluation of efficacy and safety of treatments after adjustment on confounding factors (baseline characteristics, treatment used, response to therapy…)

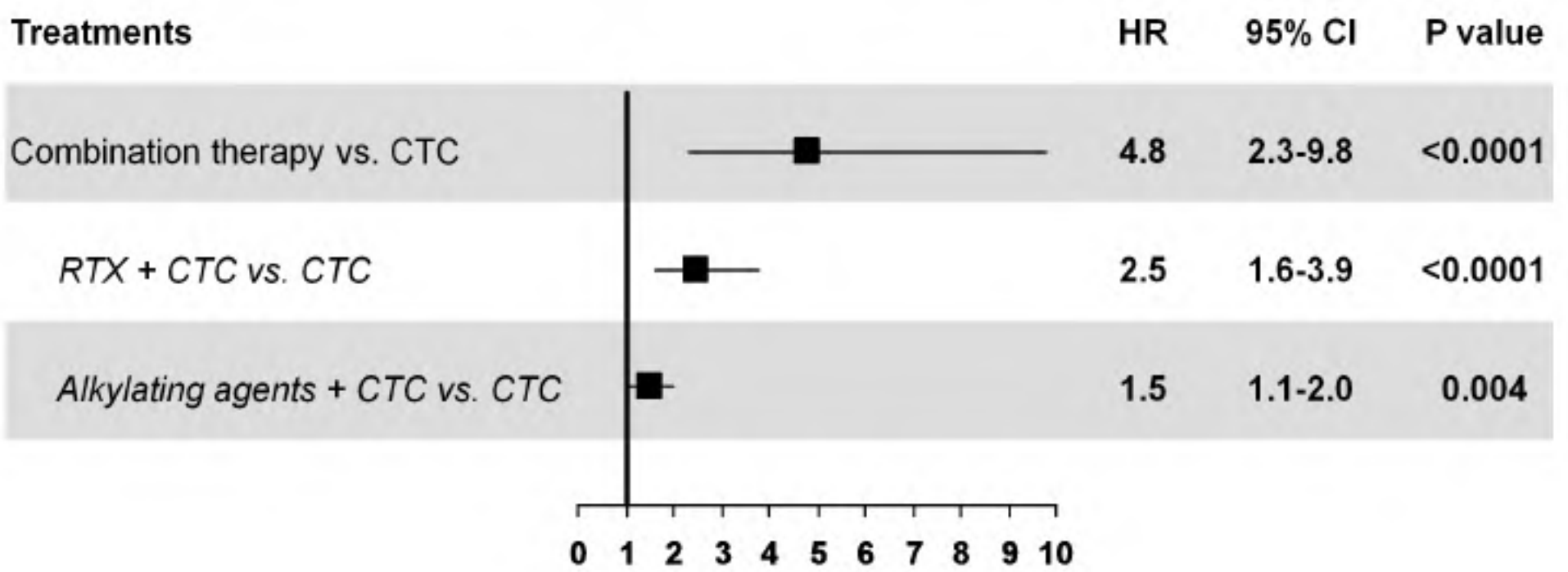
Therapeutic strategies associated with a complete clinical response in non-infectious mixed CryoVas



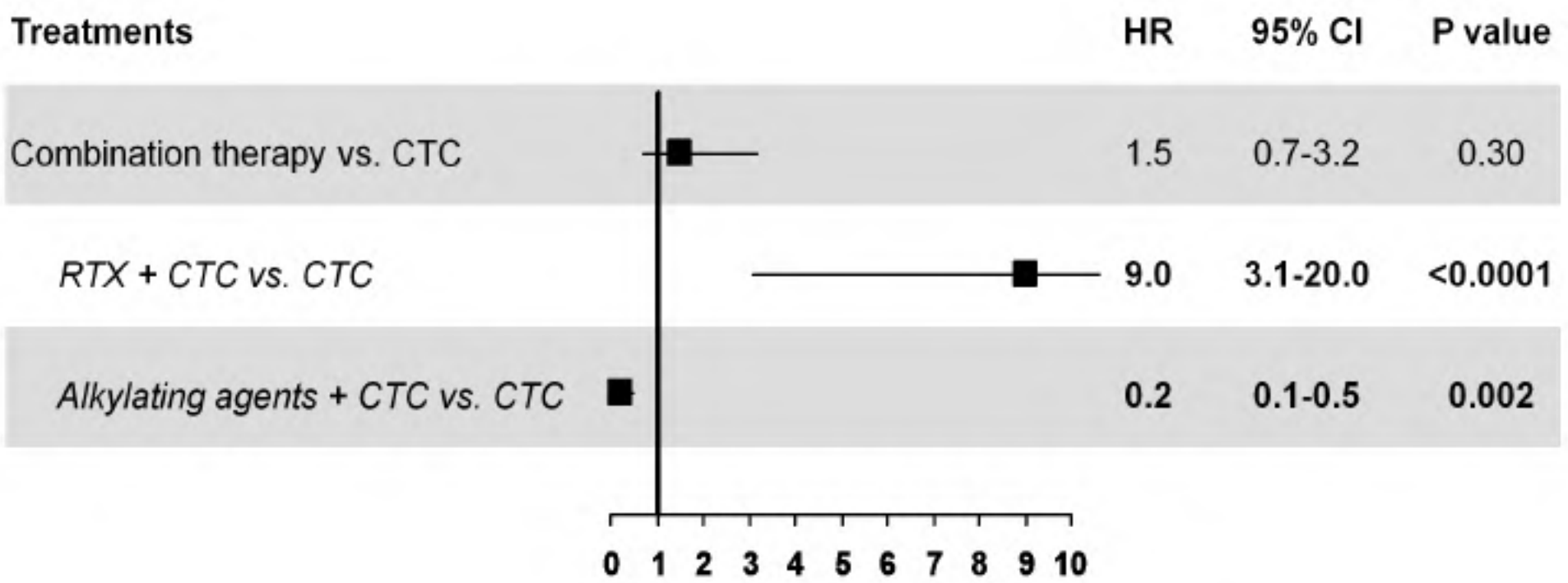
Greater efficacy of rituximab plus corticosteroids on renal response vs. other regimens



Corticosteroid-sparing effect of rituximab plus corticosteroids and alkylating agents plus corticosteroids



Increased risk of severe infections using rituximab plus corticosteroids in non-infectious mixed CryoVas



Prednisone > 50 mg/d associated with serious infections (71% vs. 39%, P=0.008) +++

Conclusion

- **Rituximab plus corticosteroids showed a greater efficacy than alkylating agents plus corticosteroids and corticosteroids alone**

Merci

- D. Saadoun, Paris
- D. Sene, Paris
- B. Terrier, Paris
- G. Géri, Paris
- P. Hausfater, Paris
- O. Lidove, Paris
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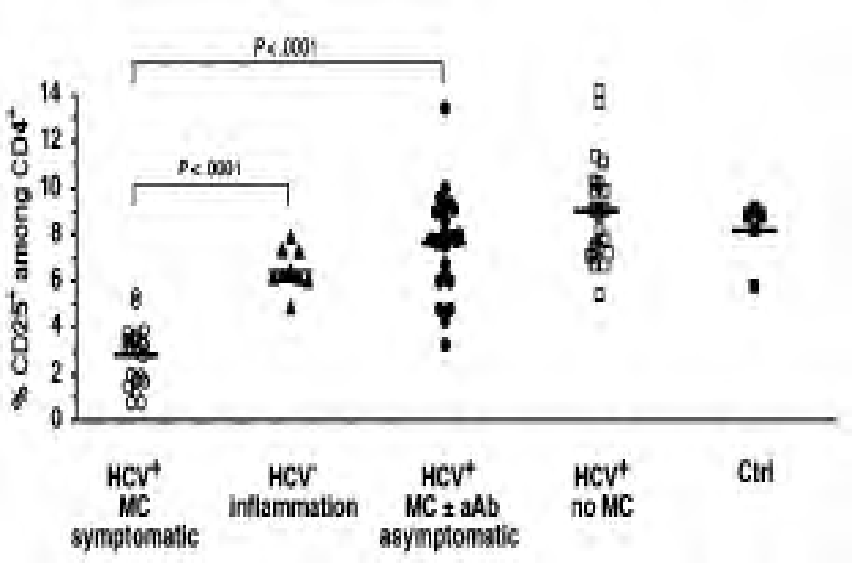
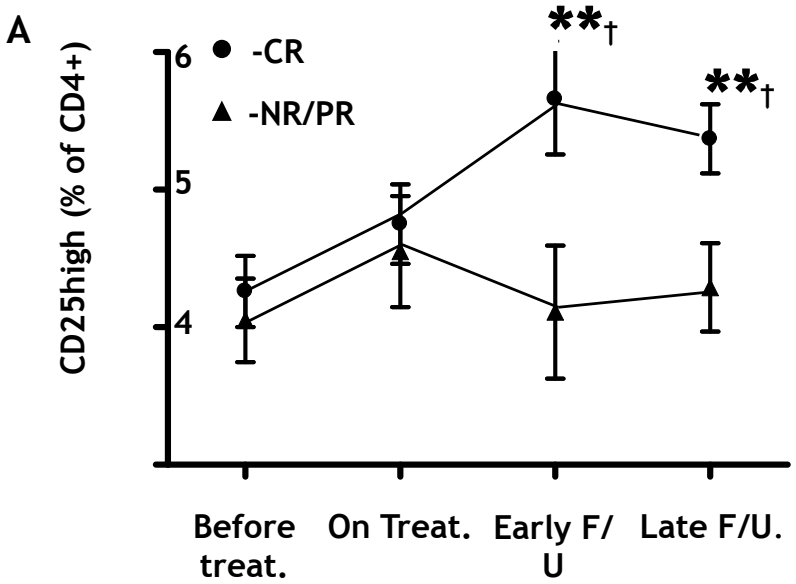
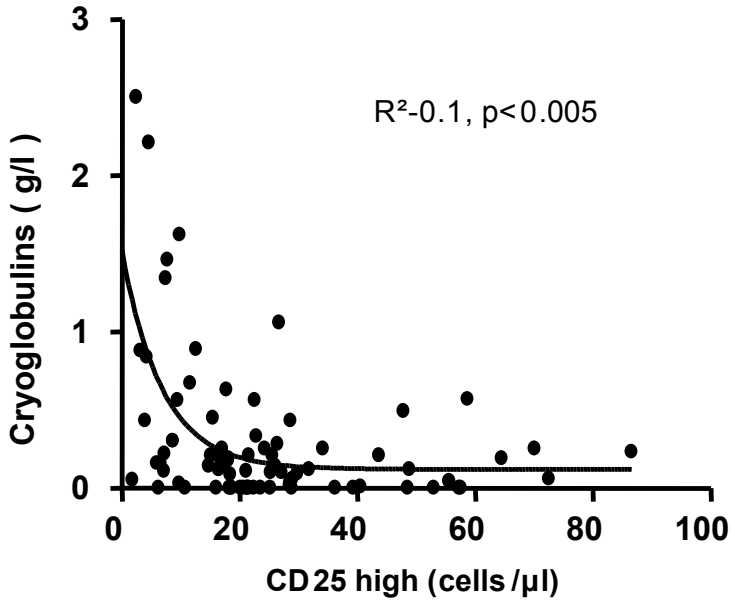
- P. Ghillani, Paris
- D. Klatzmann, Paris
- L. Musset, Paris
- M. Rosenzwajg, Paris

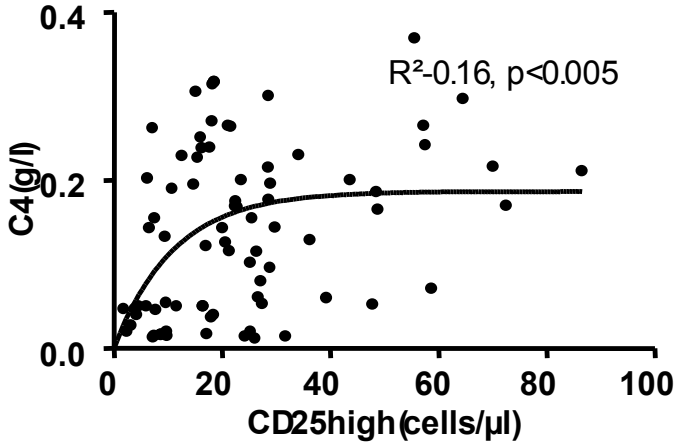
- P. Halfon, Marseille
- E. Plaisier, Paris
- S. Pol, Paris
- T. Poynard, Paris
- V. Thibault, Paris
- Les membres du GERMIVIC

Reversible Quantitative Deficit in Treg Lymphocytes (CD4+CD25+) in HCV-Systemic Vasculitis









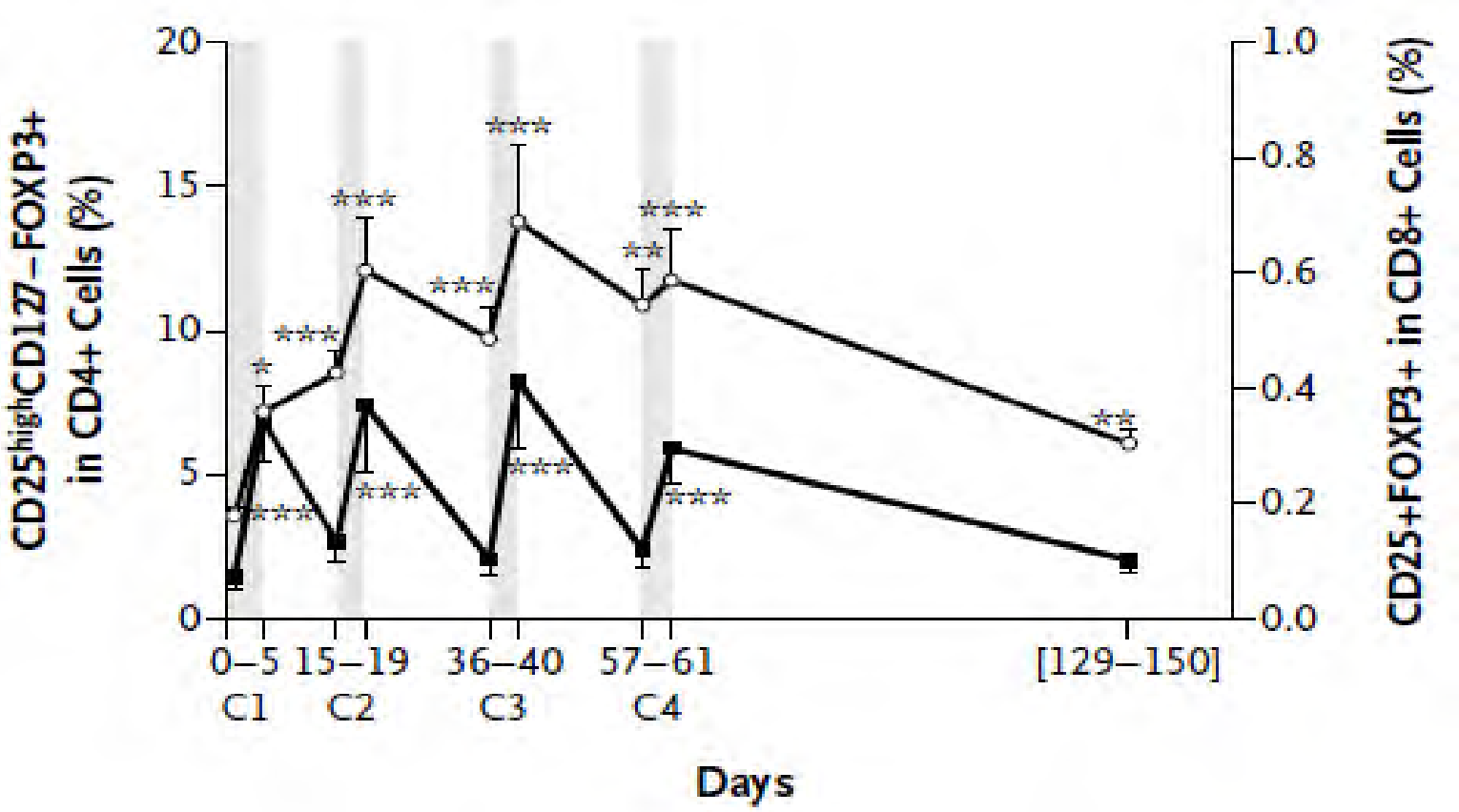
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

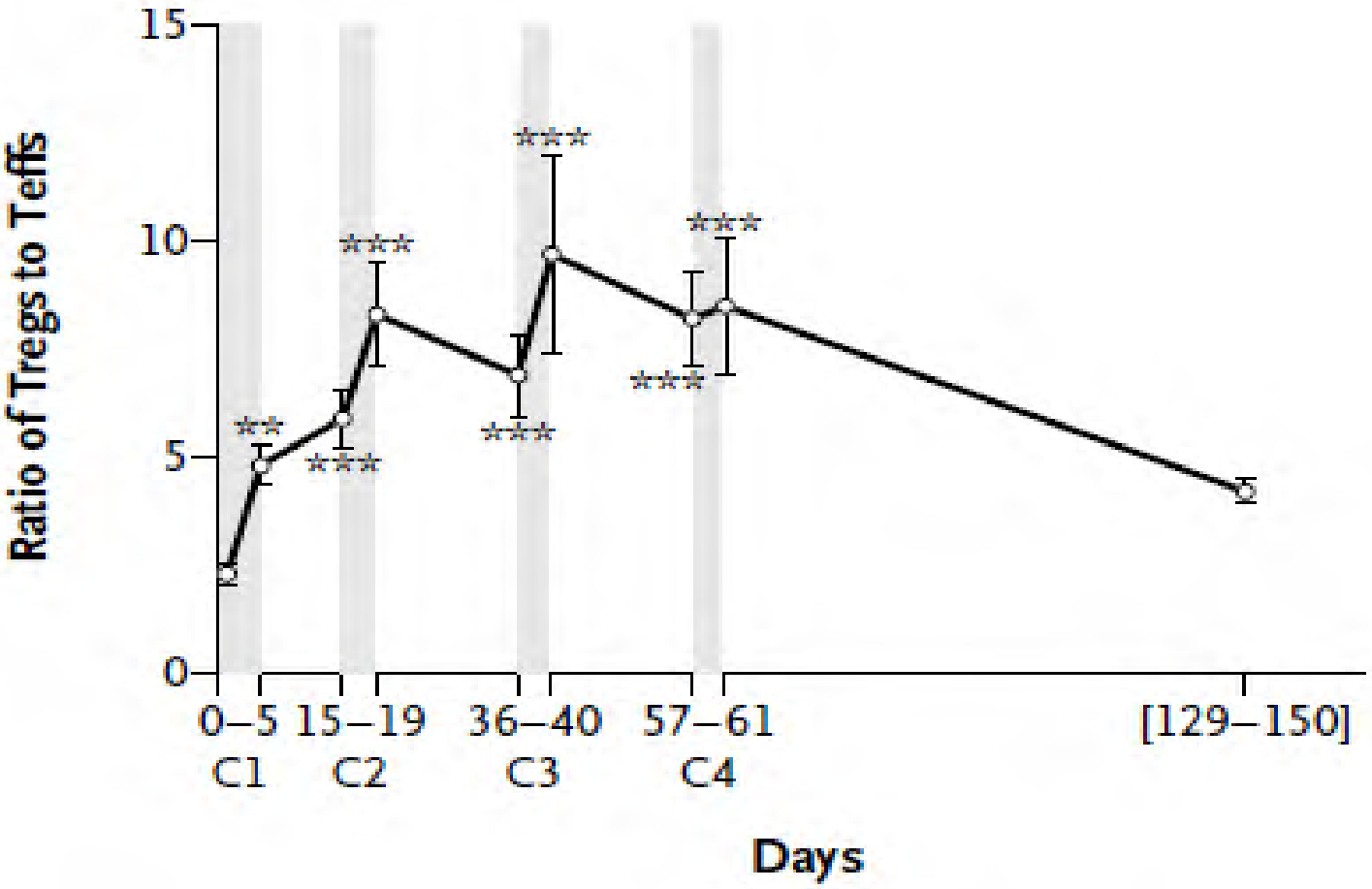
Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

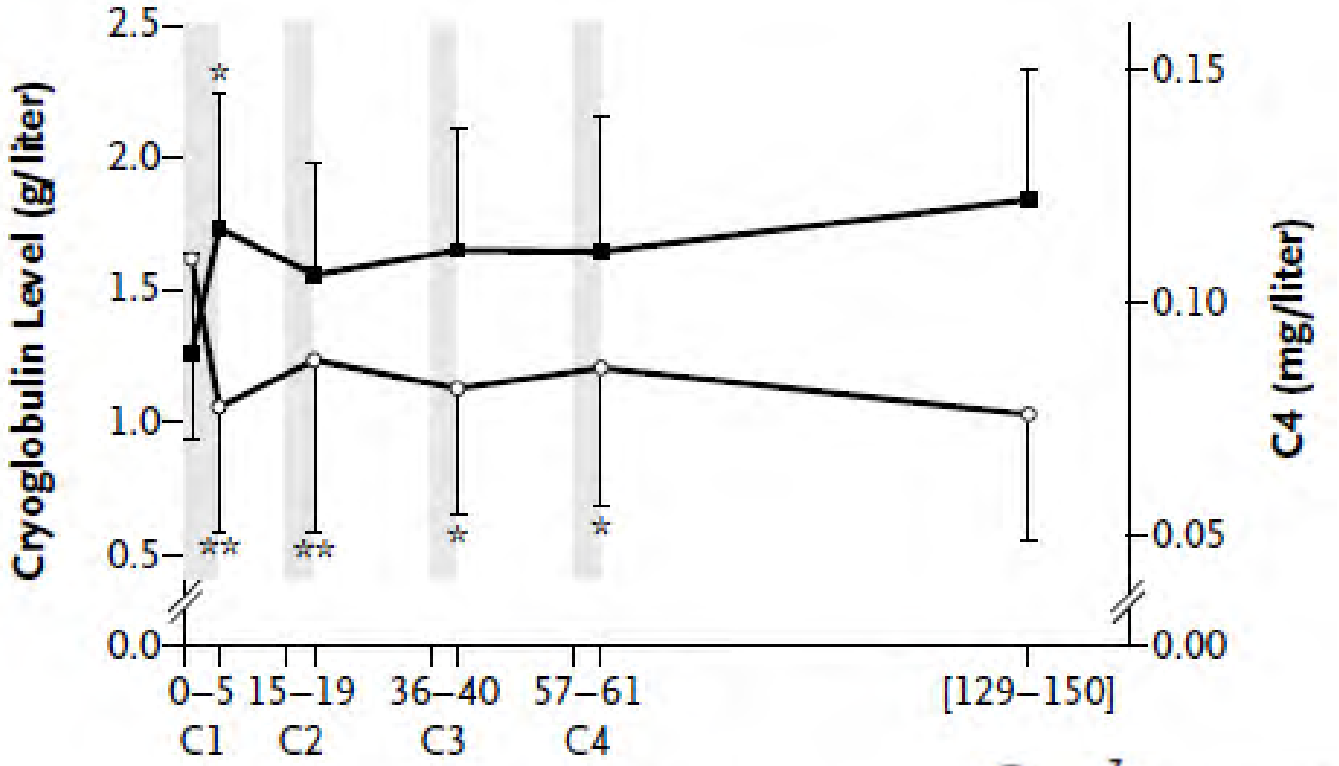
David Saadoun, M.D., Ph.D., Michelle Rosenzwajg, M.D., Ph.D., Florence Joly, Ph.D., Adrien Six, Ph.D., Fabrice Carrat, M.D., Ph.D., Vincent Thibault, Pharm.D., Damien Sene, M.D., Ph.D., Patrice Cacoub, M.D., and David Klatzmann, M.D., Ph.D.

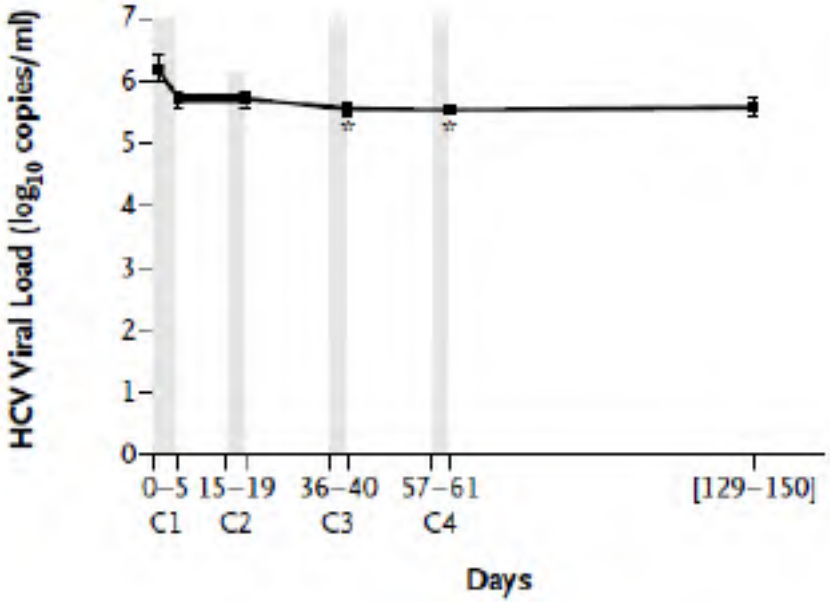
Effects of Low-Dose Interleukin-2 on Levels of CD4-Treg (c) and CD8-Treg (sq) in Patients with HCV-Vasculitis, According to Treatment Course.



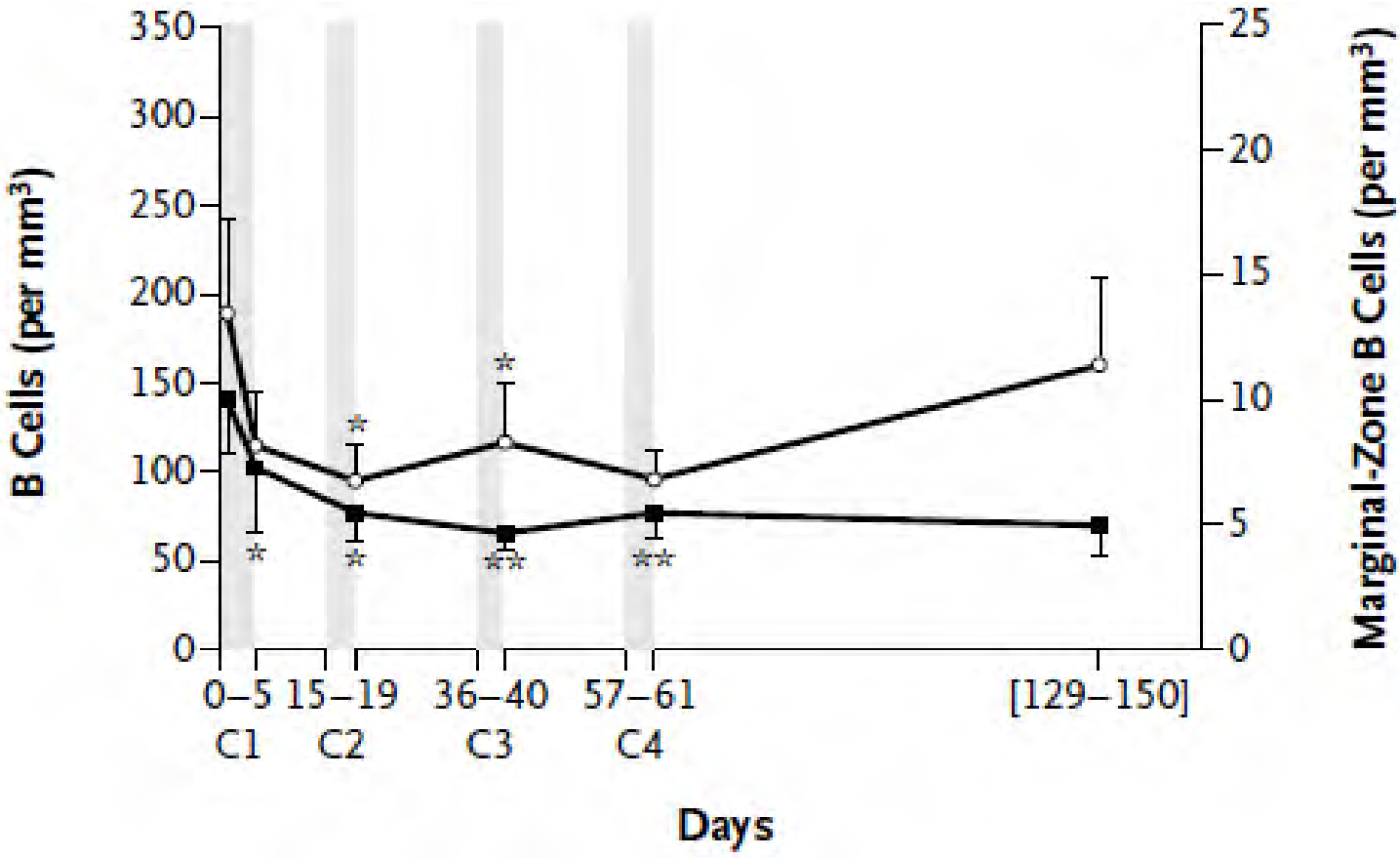
Effects of Low-Dose Interleukin-2 on Levels on the Ratio of Treg Cells to the sum of Effector T Cells CD4 + CD8 in Patients with HCV-Vasculitis, According to Treatment Course.



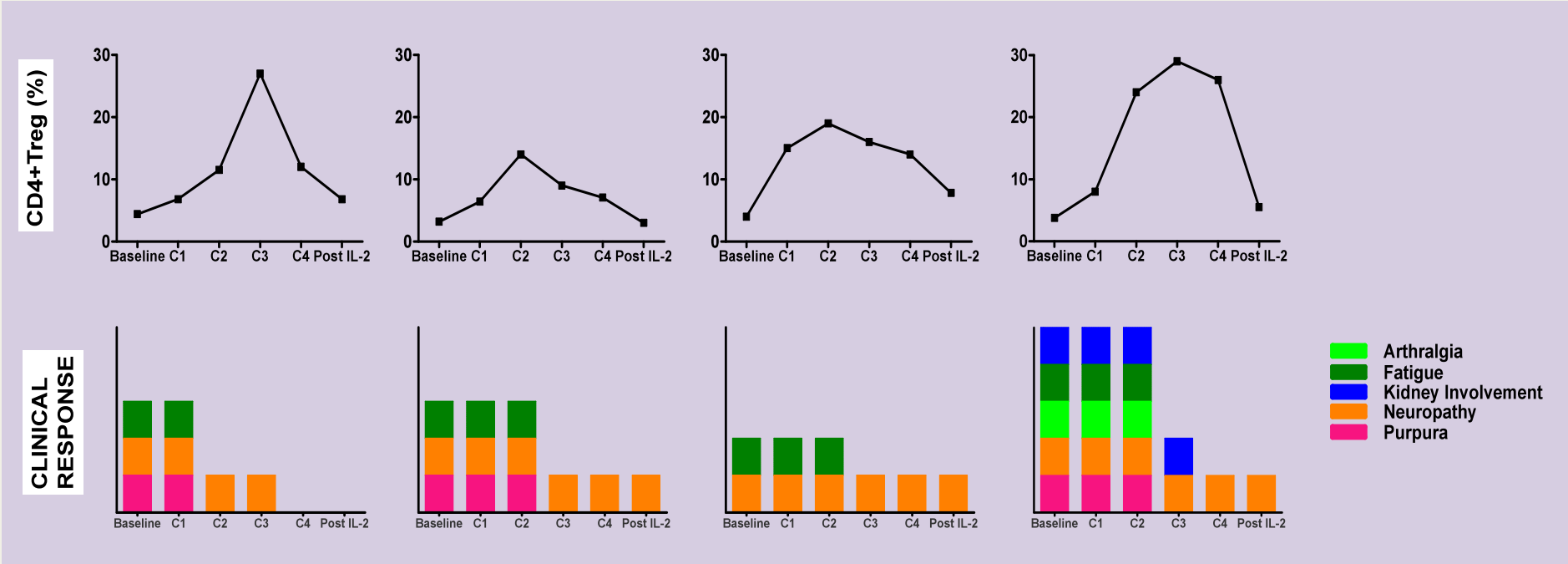

Cryoglobulin Level (g/liter)
2.5
2.0
1.5
1.0
0.5
0.0
0.15
0.10
0.05
0.00
C4 (mg/liter)
*
**
**
*
*
0–5
C1
15–19
C2
36–40
C3
57–61
C4
[129–150]
Days


HCV Viral Load (log_{10} copies/ml)
7
6
5
4
3
2
1
0
*
*
0–5
C1
15–19
C2
36–40
C3
57–61
C4
[129–150]
Days

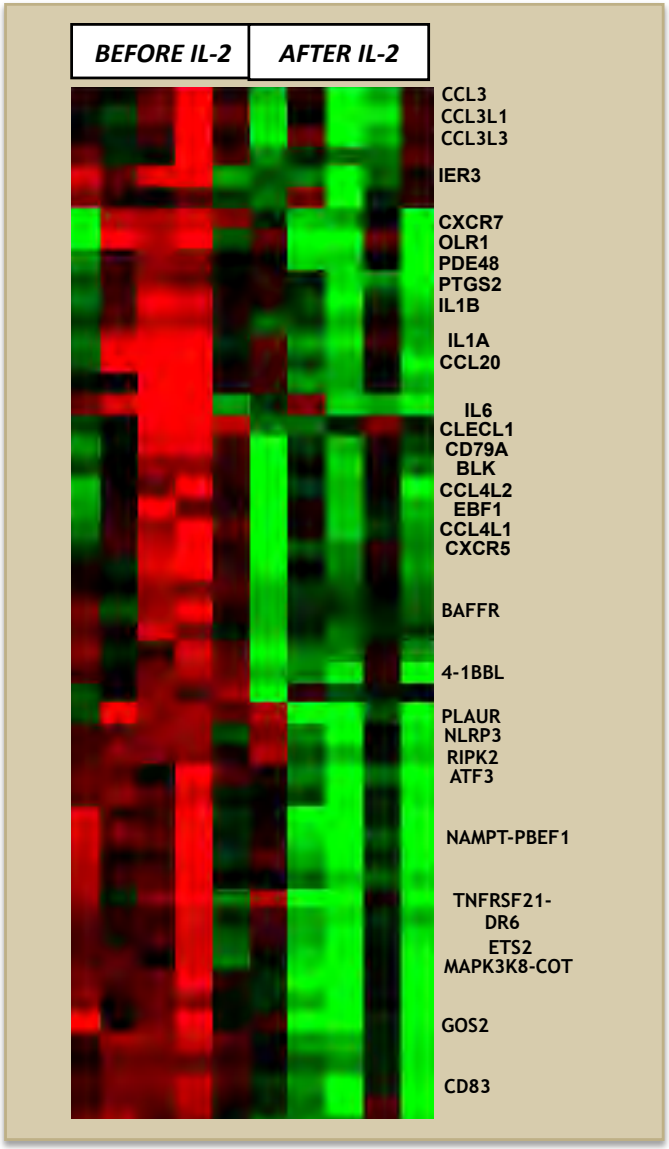
Effects of Low-Dose Interleukin-2 on Levels on CD19+ total B Cells (c) and Marginal-Zone B Cells (sq) in Patients with HCV-Vasculitis, According to Treatment Course.



Temporal Effects of Low-Dose Interleukin-2 on Clinical Features, Levels of Regulatory T Cells, and Cryoglobulin for Each Study Patient



Anti-inflammatory Effects of Low-Dose Interleukin-2 Revealed through Unsupervised Transcriptome Analyses of PBMCs.



	Up	Down	*Khi2 test*
Inflammation	**0**	**251**	*1,30E-40*
Immune Response	**16**	**684**	*3,40E-94*
Lymphocyte	**77**	**555**	*7,00E-49*
Cell Cycle	**1701**	**208**	*1,50E-138*
Control	**226**	**343**	*2,50E-01*
Autoimmune & transplantation pathologies	**0**	**46**	*7,60E-09*
Inflammatory infectious diseases	**6**	**242**	*7,60E-36*
Other diseases	**190**	**211**	*4,15E-02*

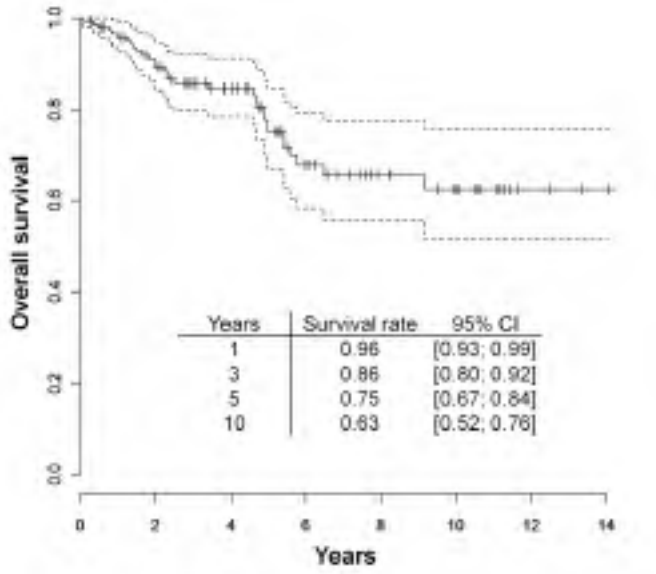
Saadoun D et al. NEJM 2011

Regulatory T Cell Recovery in HCV-Vasculitis through Low-Dose IL-2 Treatment

- We provide the first evidence of Treg recovery through low-dose IL-2 therapy in a human autoimmune disease.
- Low-dose IL-2 dramatically increases $CD4^{+}CD25^{high}CD127^{-}$ $Foxp3^{+}$ Treg cells that are functional
- Treg expansion persists after IL-2 therapy.
- IL-2 therapy was well tolerated with no flare of vasculitis.

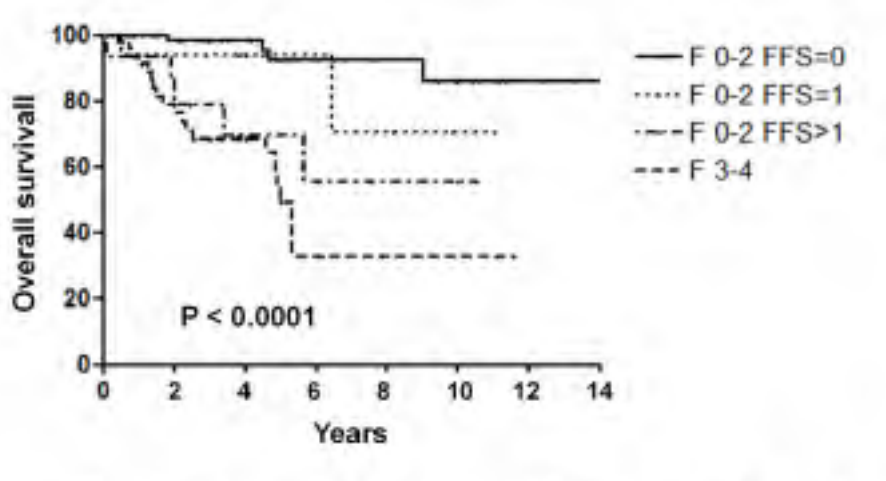
Saadoun D et al. NEJM 2011

Prognosis of HCV-related mixed cryoglobulinemia vasculitis



Causes of death

End-stage liver disease
Serious infection



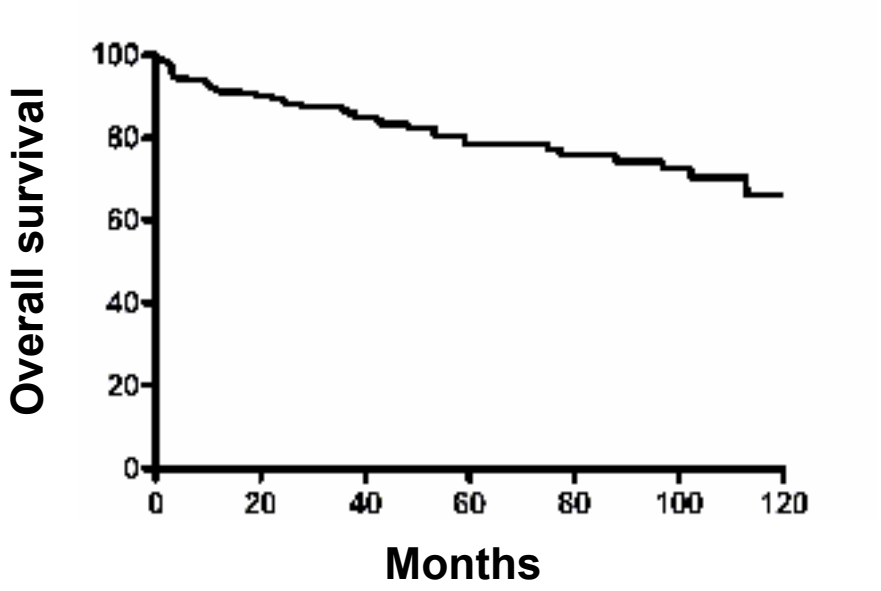
Prognostic factors of survival

Liver fibrosis
Vasculitis severity
Use of immunosuppressants

Antiviral therapy

Terrier B, Arthritis Rheum, 2011

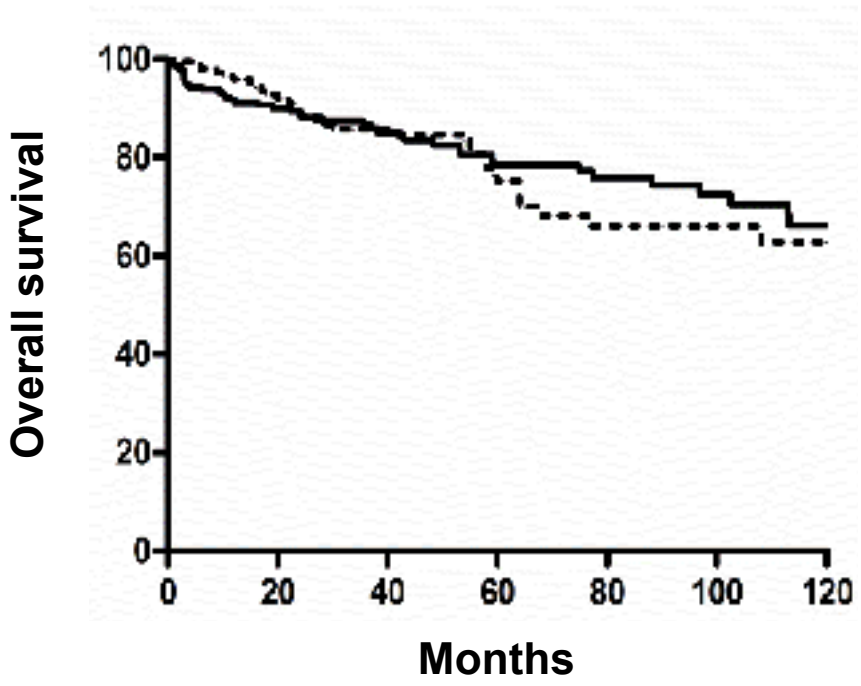
Overall survival in mixed cryoglobulinemia



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%*

Independent factors associated with survival in non-infectious mixed CryoVas

	Univariate analysis	
	HR 95% CI	P value
Age > 65 years	2.96 (1.5-5.2)	0.0008
Male gender	2.8 (1.7-7.1)	0.0005
Renal involvement	2.0 (1.1-4.0)	0.026
GFR < 60 ml/min	2.2 (1.3-4.5)	0.007
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

Independent factors associated with survival in non-infectious mixed CryoVas

	Univariate analysis		*Multivariate analysis*	
	HR 95% CI	P value	HR 95% CI	P value
Age > 65 years	2.96 (1.5-5.2)	0.0008	1.04 (1.02-1.08)	0.001
Male gender	2.8 (1.7-7.1)	0.0005	2.13 (1.01-4.11)	0.02
Renal involvement	2.0 (1.1-4.0)	0.026		
GFR < 60 ml/min	2.2 (1.3-4.5)	0.007	1.90 (1.01-3.56)	0.04
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	2.29 (0.99-5.31)	0.05