



RITUXIMAB Y CRIOGLOBULINEMIA: CASO PRACTICO Y REVISION DE LA LITERATURA 2010-2011

¿Antivíricos o biológicos?

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Hospital Clínic, Barcelona*

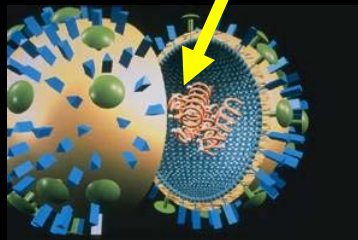
OPCIONES TERAPÉUTICAS: 2000-2010

**Tratamiento
antivírico
(Cacoub, 2003)**

Anti-VHC

Antivíricos

Eliminar el VHC o
carga viral

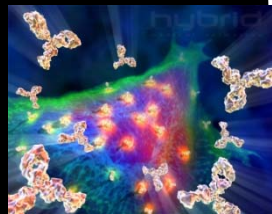


**Tratamiento
clásico**

Inmunodepresión

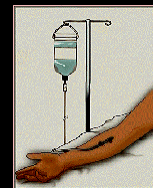
Corticoides

Manifestaciones
autoinmunes



Inmunosupr.

Dosis corticoides
Casos graves



Recambio plasmático

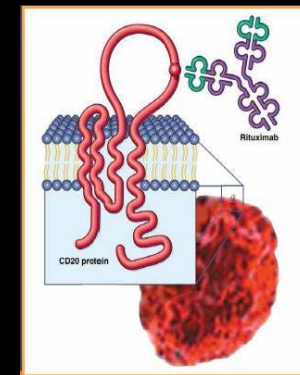
Eliminar inmunocomplejos

**Tratamiento
biológico
(De Vita, 2003)**

Anti-linfo B

Rituximab

Eliminar vs
controlar la
proliferación B



CASO CLINICO

Mujer de **49 años**, con infección crónica por **VHC**.

Fue tratada con **peg INF + RVB**, con negativización del RNA-VHC a las **12 semanas**.

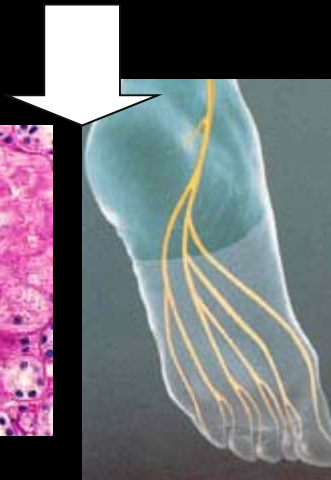
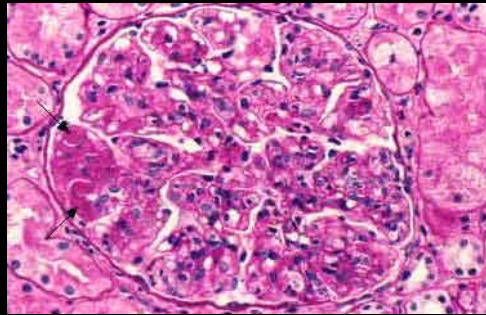
A la semana de la retirada del tratamiento antivírico por plaquetopenia y hepatitis, la paciente presenta:

- Fiebre
- Afección del estado general
- Púrpura cutánea
- Diarrea
- Proteinuria
- Parestesias

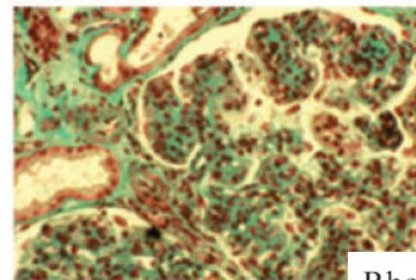
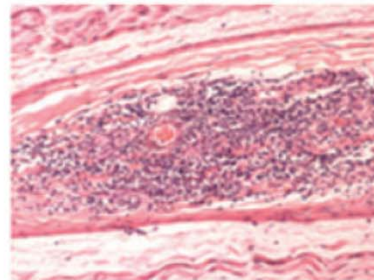
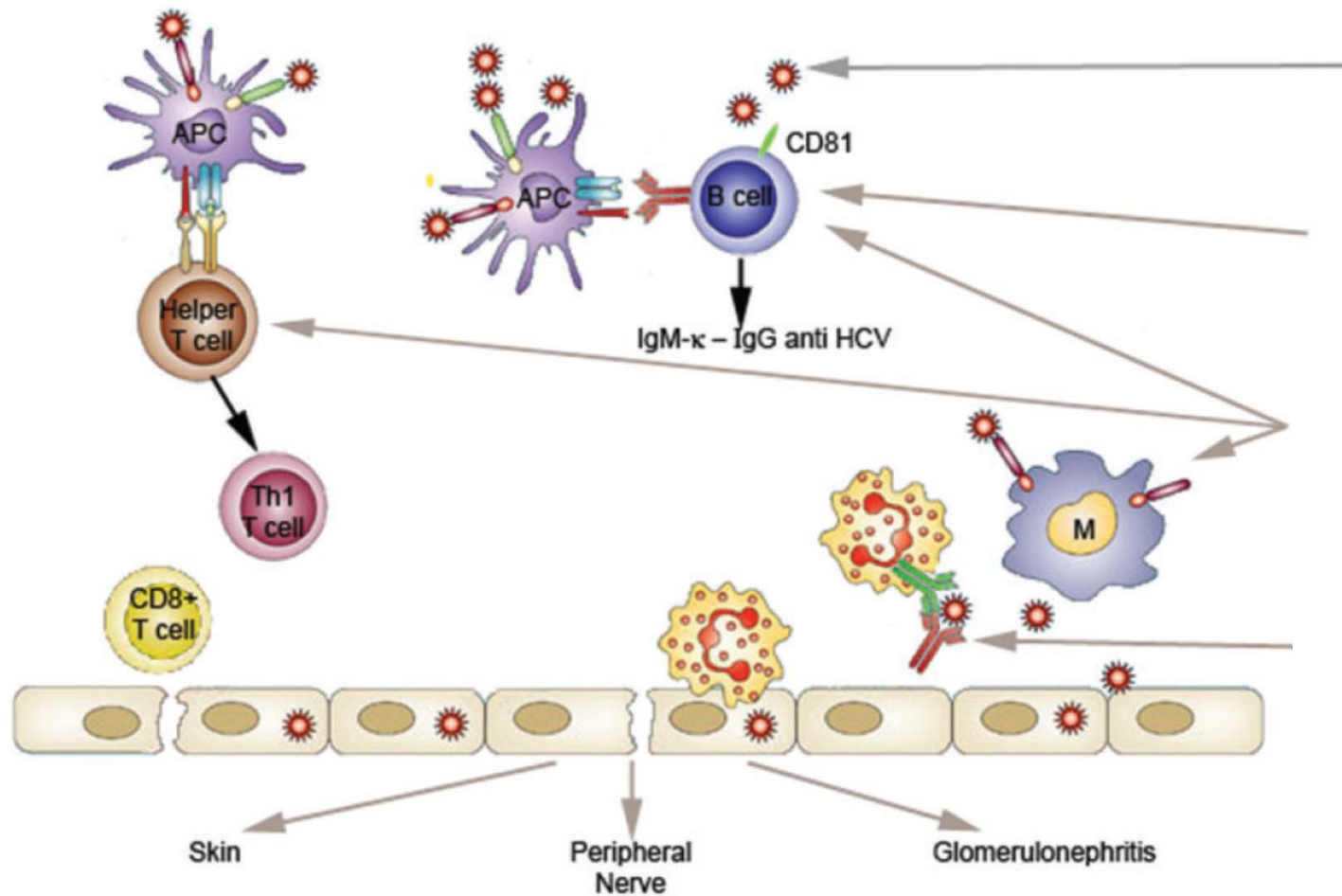
CASO CLINICO

En la analítica y exploraciones complementarias destaca:

- Crioglobulinas positivas
- Hipocomplementemia
- Proteinuria
- Reaparición de RNA circulante (130000 copias)
- Glomerulonefritis mesangiocapilar
- Mononeuritis múltiple
- Inflamación intestinal (TC)



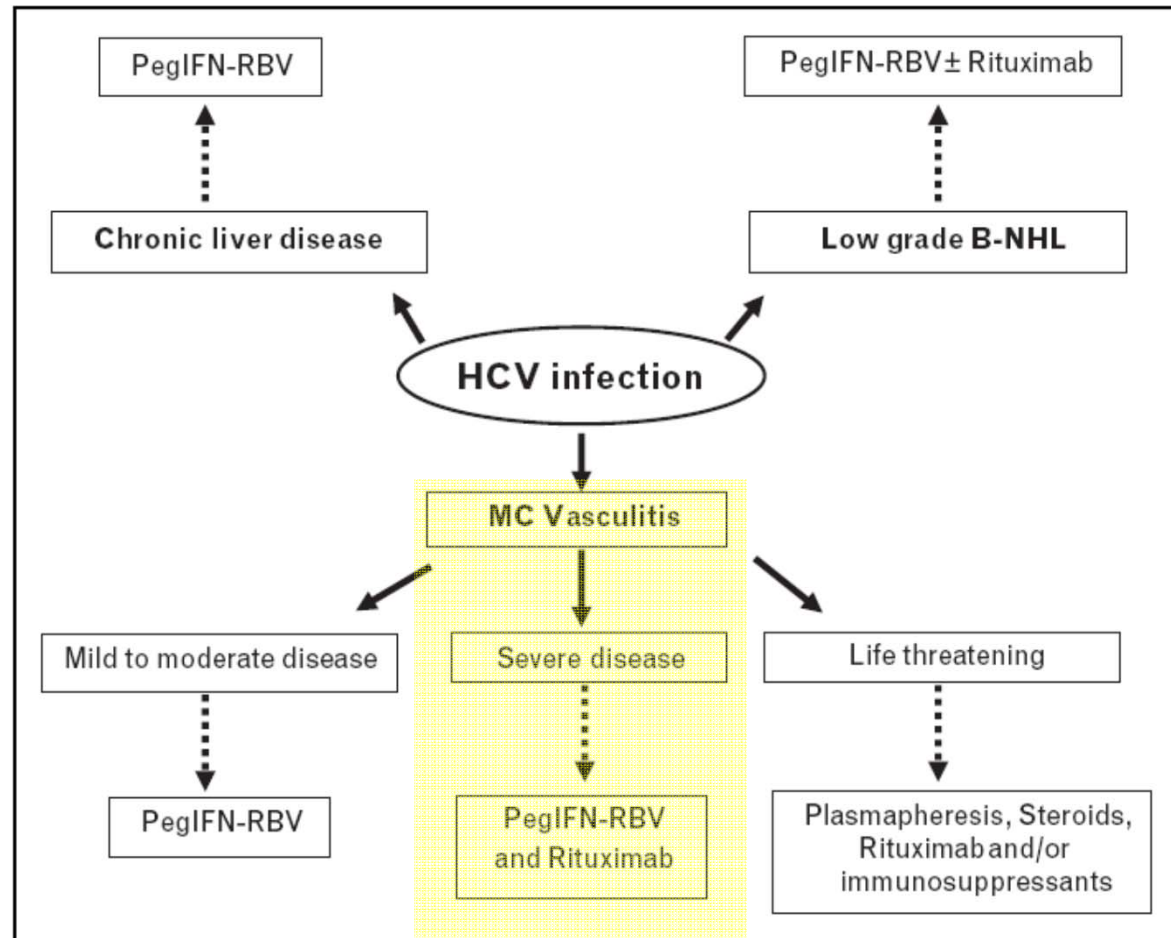
1. OPCIONES TERAPÉUTICAS



2. SITUACIÓN CLÍNICA

Figure 1 Therapeutic strategies in patients with hepatitis C virus-associated mixed cryoglobulinemia

HCV, hepatitis C virus; MC, mixed cryoglobulinemia; RBV, ribavirin; NHL, non-Hodgkin's lymphoma.



3. TRATAMIENTO ANTIVÍRICO

1. Monoterapia o terapia combinada?
2. INF estándar o pegilado?
3. Dosis y duración?

3. TRATAMIENTO ANTIVÍRICO

1. Monoterapia o terapia combinada?
2. INF estándar o pegilado?
3. Dosis y duración?

Pegylated interferon-alpha-2a

180 micrograms subcutaneously per week

+

Ribavirin

1000 mg orally per day (body weight \leq 75 kg.)

1200 mg orally per day (body weight $>$ 75 kg.)

Pegylated interferon-alpha-2b

1.5 micrograms/kg. subcutaneously per week

+

Ribavirin

800 mg orally per day (body weight \leq 65 kg.)

1000 mg orally per day (body weight 65-85 kg.)

1200 mg orally per day (body weight 85-105 kg.)

1400 mg orally per day (body weight $>$ 105 kg.)

DURACIÓN

Genotypes 1 and 4: **48 weeks**

Genotypes 2 and 3: **24 weeks**

4. TRATAMIENTO DEPLETIVO B



Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev



Review

Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: Results of multicenter cohort study and review of the literature

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A. Tavoni ^f, A.L. Zignego ^g, S. De Vita ^h

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^b Department of Internal Medicine, AP HP, Hopital La Pitié Salpêtrière and UMR 7211 (UPMC/CNRS), UMR S-959 (INSERM), Université Pierre Marie Curie, Paris, France

^c Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy

^d Divisione di Nefrologia e Dialisi, Ospedale Giovanni Bosco, Turin, Italy

^e UO Nefrologia, Spedali Civili, Brescia, Italy

^f Department of Internal Medicine, University of Pisa, Medical School, Pisa, Italy

^g Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Florence, Italy

^h Rheumatology Clinic, DPMSC, AOU S. Maria della Misericordia, Udine, Italy

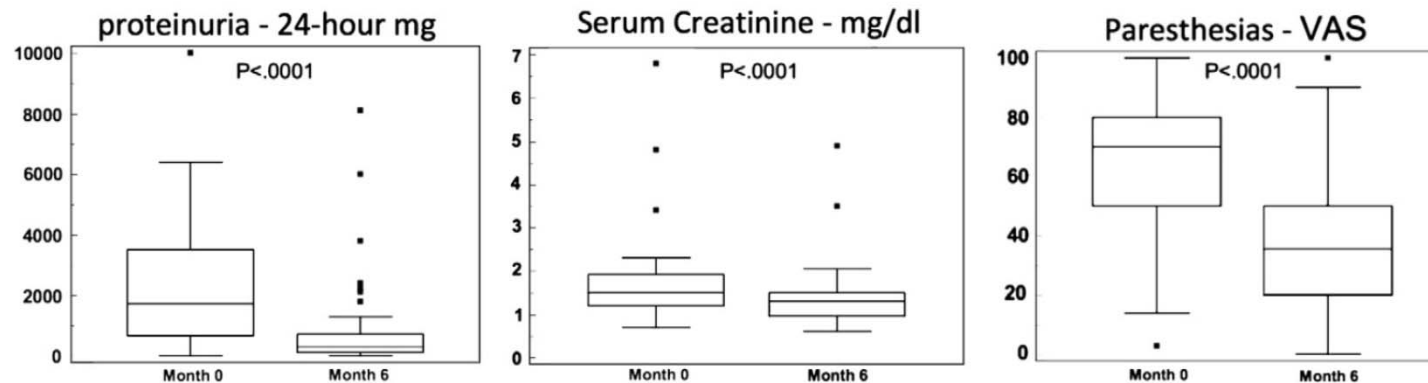
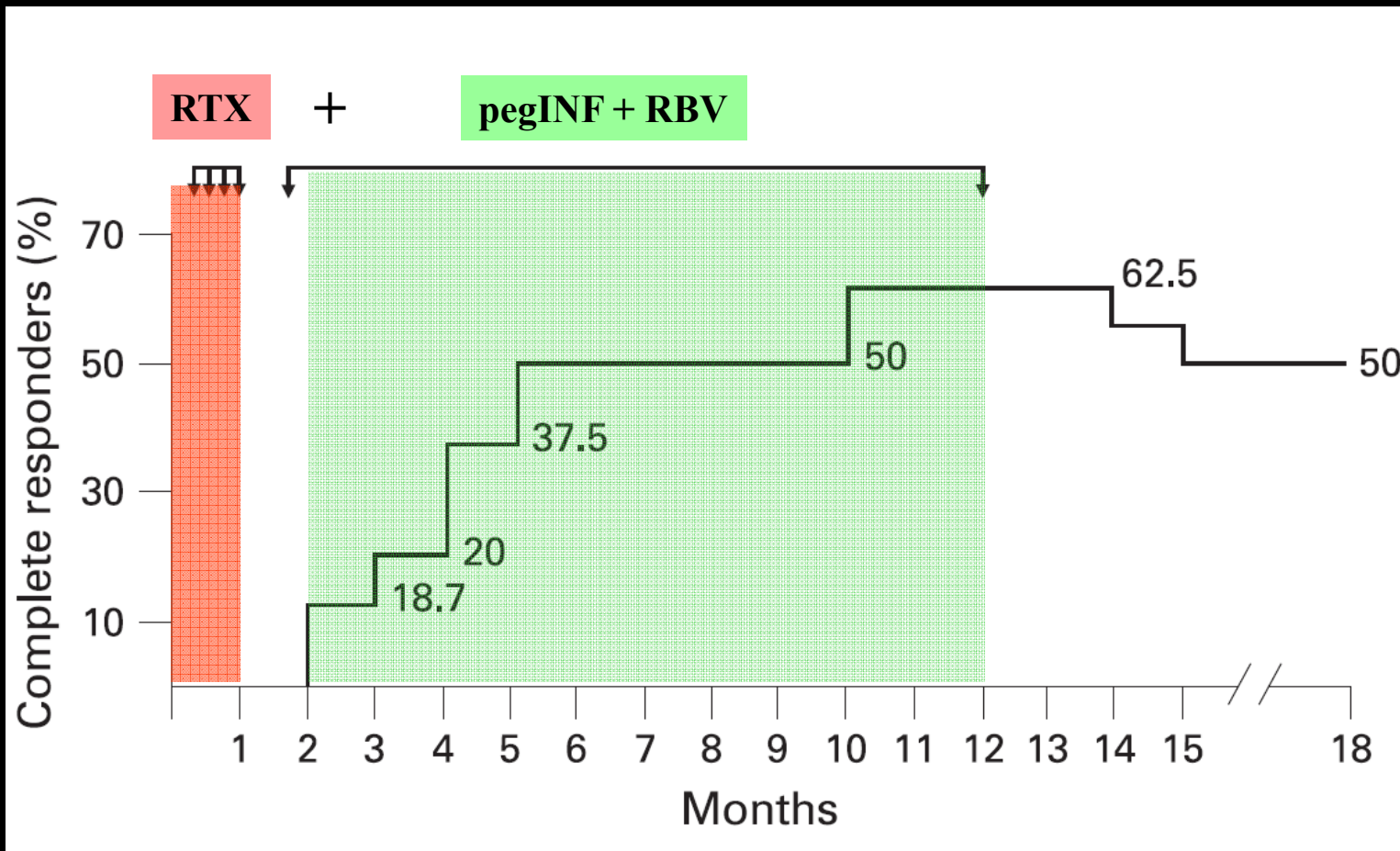


Fig. 1. In 38 patients with cryoglobulinemic nephropathy the 24-hour proteinuria and serum creatinine significantly improved after rituximab treatment; namely, mean values of 24-hour proteinuria decreased from 2.2 ± 2.1 SD to 0.9 ± 1.7 SD g/24 h, and serum creatinine from 1.8 ± 1.1 SD to 1.4 ± 0.8 SD mg/dl). In 69 patients with sensory peripheral neuropathy the treatment positively affected the paresthesias (patient's visual analogical scale from 62 ± 25 SD to 37 ± 27 SD).

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

D Saadoun,¹ M Resche-Rigon,² D Sene,¹ L Perard,³ A Karras,⁴ P Cacoub¹

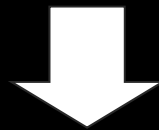


CASO CLINICO

OPCIONES TERAPÉUTICAS

Tratamiento con rituximab + corticoides 1mg/Kg/d

MANTENIMIENTO: introducción de tratamiento antivírico, con monitorización estricta junto con hepatología



REMISIÓN COMPLETA

Clínica

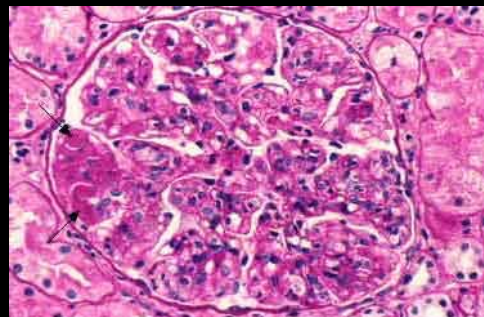
Inmunológica

Vírica

CASO CLINICO: Rebrote

En la analítica y exploraciones complementarias destaca:

- Crioglobulinas positivas
- Hipocomplementemia
- Proteinuria
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- Mononeuritis múltiple



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

D Saadoun,¹ M Resche-Rigon,² D Sene,¹ L Perard,³ A Karras,⁴ P Cacoub¹

16 pacientes (11 refractarios, 5 rebrotos)

Edad media = 58 años

No respuesta a tratamiento antivírico combinado (al menos 6 meses)



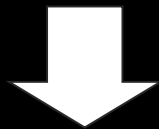
The therapeutic schedule consisted of the weekly administration of four intravenous infusions of rituximab at 375mg/m² (on days +1, +8, +15, 22) over a period of one month; this was followed one month later by an antiviral combination with Peg-IFN α 2b (1.5 μ g/kg/week subcutaneously) plus ribavirin (600-1,200 mg/day orally) for 12 months.

CASO CLINICO

OPCIONES TERAPÉUTICAS

Tratamiento con rituximab + corticoides 1mg/Kg/d

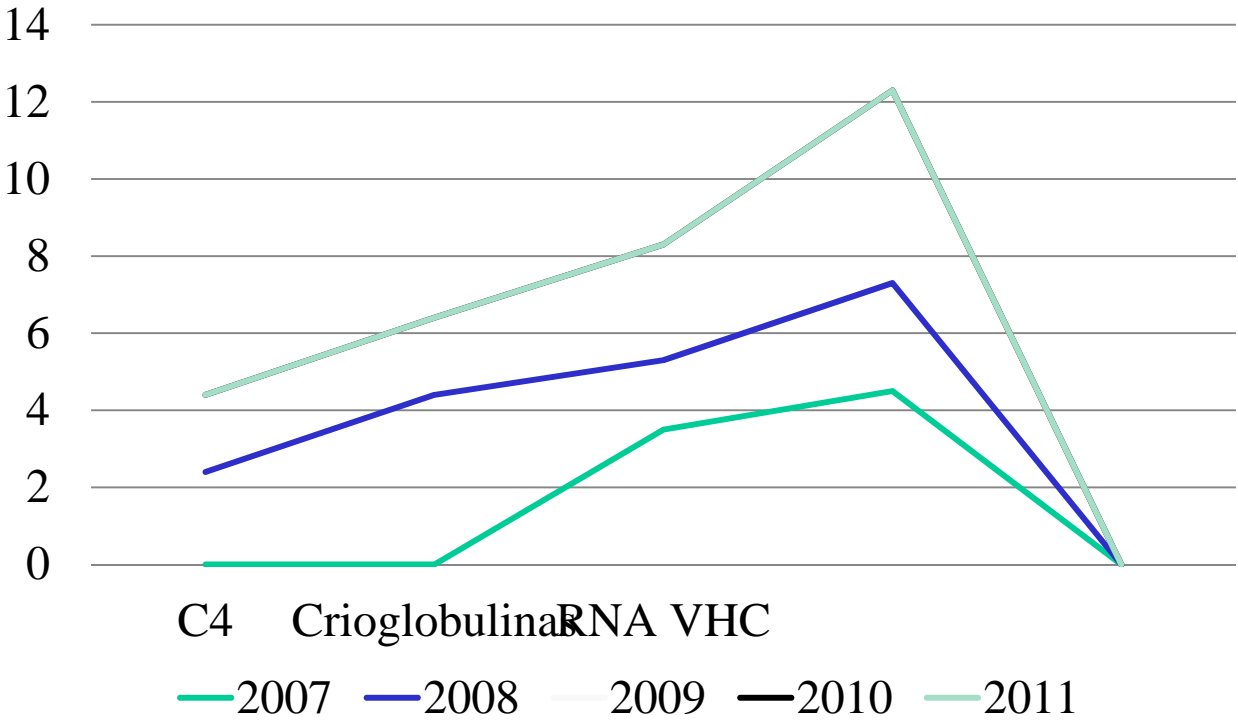
MANTENIMIENTO: introducción del tratamiento antivírico



REMISIÓN COMPLETA

ULTIMA VISITA (Octubre 2011): remisión clínica e inmunológica, carga viral 5600, transaminasas < 80UI/L. En tratamiento con Peg INF+RBV (desde diciembre 2010).

Título del gráfico



ULTIMOS TRABAJOS

1. Antivírico o antivírico + rituximab?
2. Rituximab en cirróticos?



Pegylated interferon- α , ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study

Franco Dammacco,¹ Felicia Anna Tucci,¹ Gianfranco Lauletta,¹ Pietro Gatti,¹ Valli De Re,² Vincenza Conteduca,¹ Silvia Sansonno,² Sabino Russi,¹ Maria Addolorata Marigiò,³ Maria Chironna,⁴ and Domenico Sansonno¹

Sections of ¹Internal Medicine and Clinical Oncology, ³General Pathology and Experimental Oncology, and ⁴Hygiene, Department of Biomedical Sciences and Human Oncology, University of Bari Medical School, Bari; and ²Clinical and Experimental Pharmacology, Department of Molecular Oncology and Translational Research, Centro di Riferimento Oncologico Aviano, Pordenone, Italy

n = 37

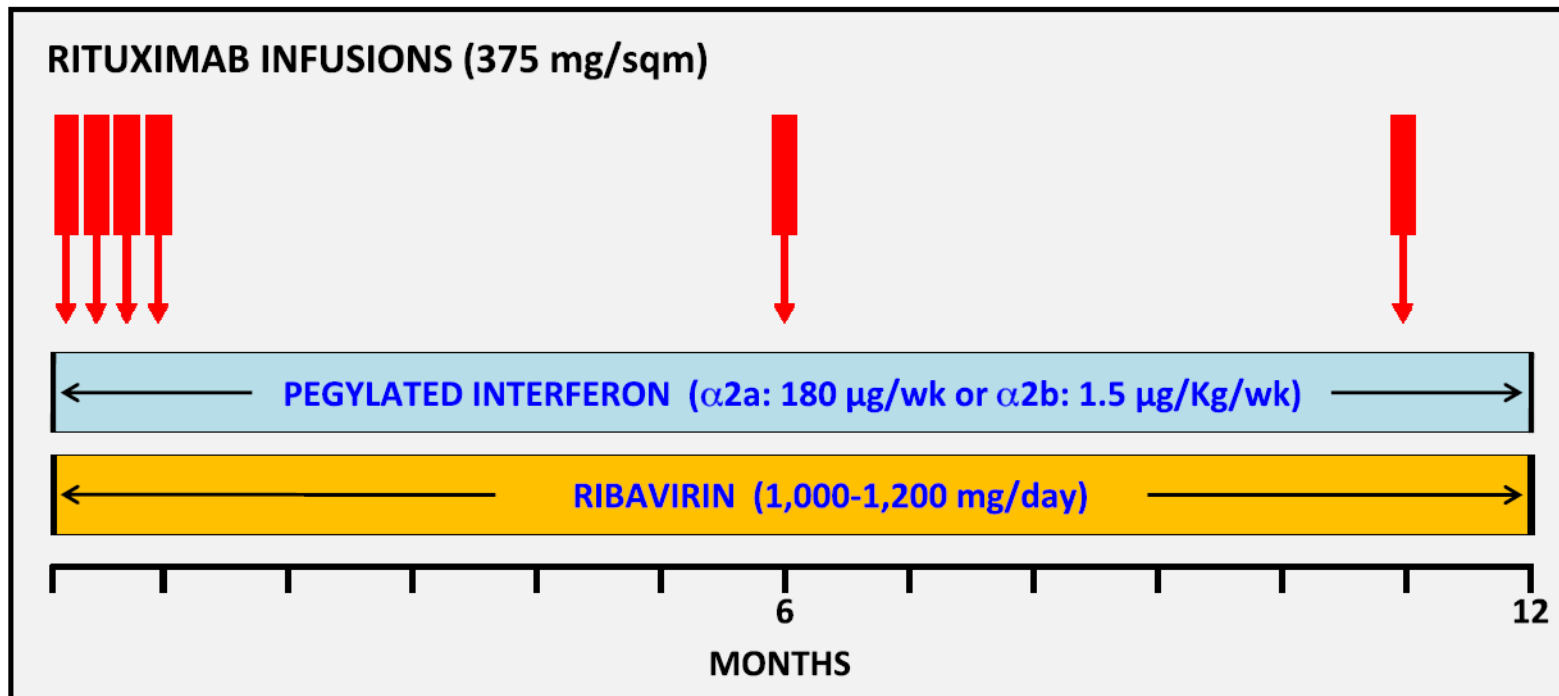


Figure 1. Design of PIRR schedule.

Pegylated interferon- α , ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study

Franco Dammacco,¹ Felicia Anna Tucci,¹ Gianfranco Lauletta,¹ Pietro Gatti,¹ Valli De Re,² Vincenza Conteduca,¹ Silvia Sansonno,² Sabino Russi,¹ Maria Addolorata Marigliò,³ Maria Chironna,⁴ and Domenico Sansonno¹

Sections of ¹Internal Medicine and Clinical Oncology, ³General Pathology and Experimental Oncology, and ⁴Hygiene, Department of Biomedical Sciences and Human Oncology, University of Bari Medical School, Bari; and ²Clinical and Experimental Pharmacology, Department of Molecular Oncology and Translational Research, Centro di Riferimento Oncologico Aviano, Pordenone, Italy

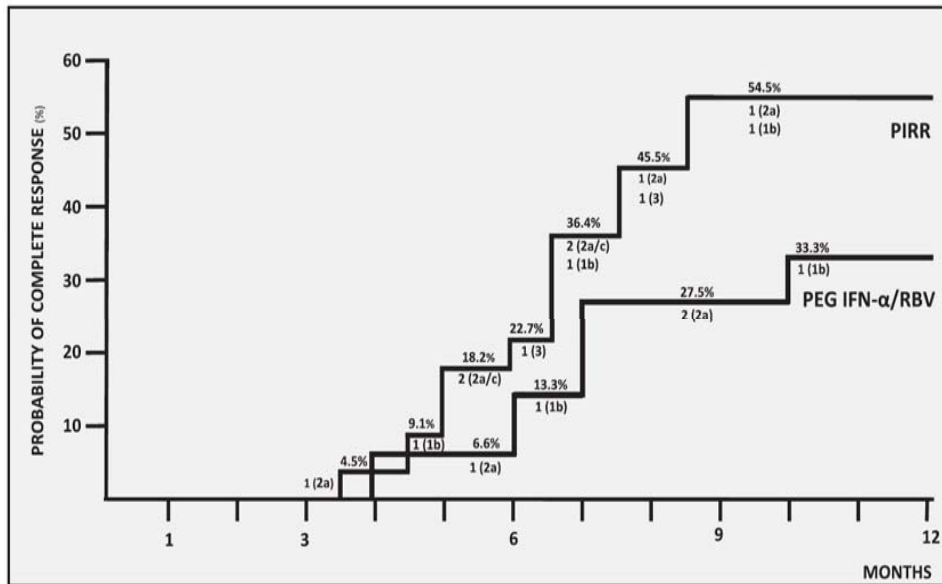
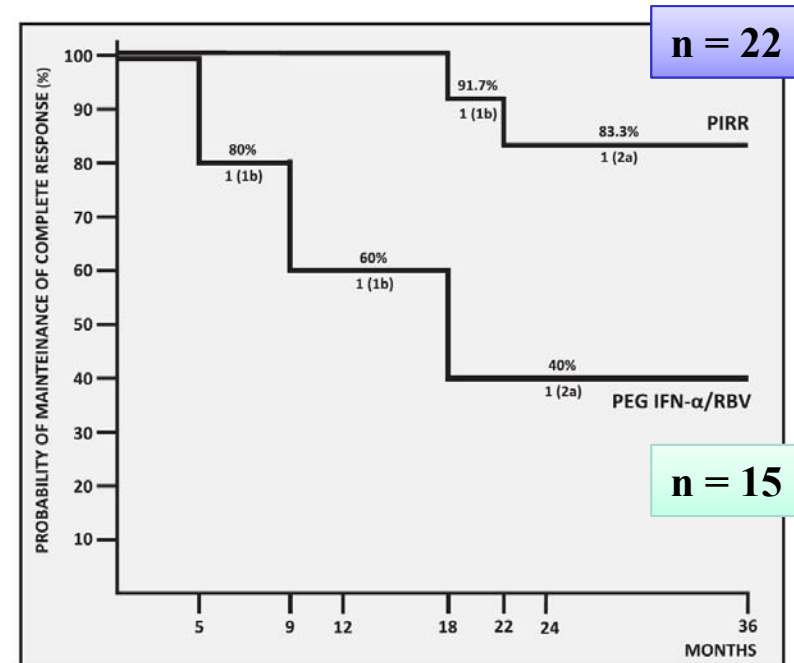


Figure 2. Probability of complete response during PIRR and combination therapies. Below the line: number and HCV genotype of responders.



CME article**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 Schoindre,¹ Brigitte Coppéré,⁵ François Blanc,⁶ Lucile Musset,⁷ Jean-Charles Piette,¹ Michele Rosenzweig,² and Patrice Cacoub^{1,2}

n = 93**Study design**

This was a prospective cohort study, including consecutive, unselected HCV-MC patients. All patients received antiviral therapy with Peg-IFN- α (2a, 180 μ g/week, n = 5; or 2b, 1.5 μ g/kg per week, n = 88, subcutaneously) plus ribavirin (600-1200 mg/day orally) for 48 weeks. For the 38 patients who received the combination of rituximab plus Peg-IFN- α /ribavirin, the therapeutic schedule consisted of: (1) weekly administration of 4 intravenous infusions of rituximab at 375 mg/m² (on days 1, 8, 15, and 22; n = 31) or 2 intravenous infusions of rituximab at 1000 mg (on days 1 and 15; n = 7) followed 1 month later by the antiviral combination with Peg-IFN- α /ribavirin for 48 weeks.

CME article

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 Yolande Schoindre,¹ Brigitte Coppéré,⁵ François Blanc,⁶ Lucile Musset,⁷ Jean-Charles Piette,¹ Michele Rosenzweig,² and Patrice Cacoub^{1,2}

Table 2. Outcomes of the 93 HCV-MC patients according to the type of treatment

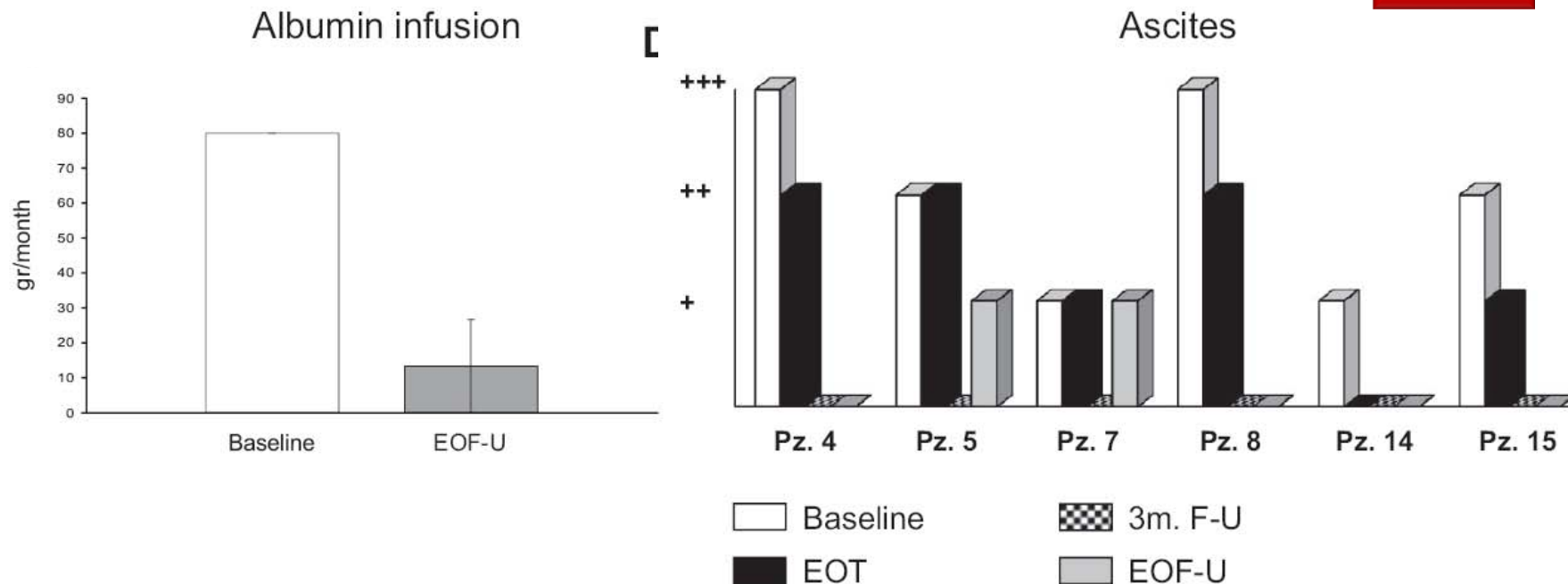
Parameter	All MC patients (n = 93)	Peg-IFN- α /ribavirin (n = 55)	RTX-Peg-IFN- α /ribavirin (n = 38)	P
Delay to clinical response, mo	6.8 \pm 4.7	8.4 \pm 4.7	5.4 \pm 4.0	.004
Clinical response				
CR	68 (73.1)	40 (72.7)	28 (73.7)	.98
PR	22 (23.6)	13 (23.6)	9 (23.7)	
NR	3 (3.2)	2 (3.6)	1 (2.6)	
Relapse	17 (18.8)	10 (18.8)	7 (18.9)	
Immunologic response				
CR	49 (52.7)	24 (43.6)	26 (68.4)	.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)	
Virologic response				
SVR	55 (59.1)	33 (60)	22 (57.9)	> .999
NR	38 (40.8)	22 (40)	16 (42.1)	
Death				
Cirrhosis	1 (1.1)	—	1 (2.6)	.70
Liver carcinoma	3 (3.2)	2 (3.6)	1 (2.6)	
Unknown	1 (1.1)	—	1 (2.6)	

Safety and efficacy of rituximab in patients with hepatitis C virus–related mixed cryoglobulinemia and severe liver disease

Antonio Petrarca,¹ Luigi Rigacci,² *Patrizio Caini,¹ Stefano Colagrande,³ Paolo Romagnoli,⁴ Francesco Vizzutti,⁵ Umberto Arena,⁵ Carlo Giannini,¹ Monica Monti,¹ Paolo Montalto,⁶ Marco Matucci-Cerinic,⁷ Alberto Bosi,⁸ Giacomo Laffi,¹ and Anna Linda Zignego¹

¹Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Florence; ²Haematology Unit, AOU Careggi, Florence; ³Department of Clinical Physiopathology, Section of Radiodiagnostics, ⁴Department of Anatomy, Histology and Forensic Medicine, and ⁵Department of Internal Medicine, University of Florence, Florence; ⁶U.O. Gastroenterologia e Endoscopia Digestiva, Ospedale SS Cosma e Damiano, Pescia; ⁷Department of Biomedicine, Division of Rheumatology AOU Careggi, Florence; and ⁸Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy

n = 19





Terapias biológicas en enfermedades sistémicas autoinmunes

MENSAJE FINAL



Biological
Therapeutics
for Autoimmune
Diseases

5. TRATAMIENTO ESTRATIFICADO

THE LANCET

Volume 376 - Number 9734 - Pages 1-68 - July 3-9, 2010

www.thelancet.com

Seminar

The cryoglobulinaemias



Manuel Ramos-Casals, John H Stone, Maria C Cid, Xavier Bosch

Tratamiento estratificado del síndrome crioglobulinémico asociado a VHC de acuerdo a la gravedad de la enfermedad

Enfermedad leve/moderada

- Púrpura, artralgias, astenia gral
- Neuropatía leve
- GN sin fallo renal

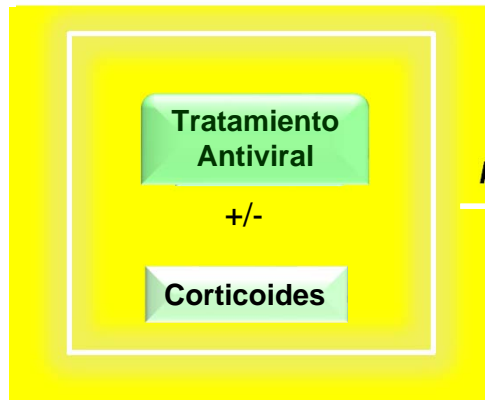
Enfermedad Grave

- Úlceras cutáneas, isquemia
- Neuropatía severa
- GN con fallo renal/ síndrome nefrótico
- Compromiso GI

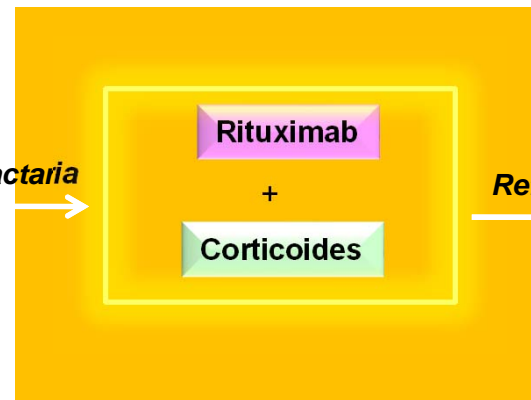
Life-threatening

- GN rápidamente progresiva
- Compromiso del SNC
- Isquemia Intestinal
- Hemorragia Alveolar

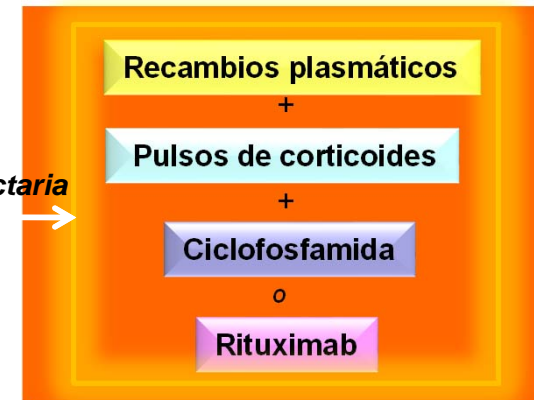
Fase de Inducción



Refractaria



Refractaria



Fase de Mantenimiento





Muchas gracias!!