Terapias biológicas

SJÖGREN

CRIOGLOBULINEMIA

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Autoimmune Diseases Dep, Hospital Clínic, Barcelona, Spain

Terapias biológicas

SJÖGREN

CRIOGLOBULINEMIA

Biological therapies & primary SS

Introduction

Rheumatology 2007;46:1389–1396
Advance Access publication 22 June 2007

doi:10.1093/rheumatology/kem078

Review

Emerging biological therapies in primary Sjögren's syndrome

M. Ramos-Casals and P. Brito-Zerón

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes. SS primarily affects white perimenopausal women, with an incidence of 4–5 cases per 100 000. Recent studies have analysed new therapeutic approaches, focusing mainly on the use of biological agents. B-cell targeted therapies seem to be the most promising agents in primary SS, especially rituximab, which has been used in more than 50 reported cases. Other promising B-cell targeted therapies include epratuzumab and belimumab, while T-cell targeted agents (efalizumab, abatacept, alefacept) should currently be considered as possible future options. In the near future, biological agents will play key roles in the treatment of severe involvement, broadening the therapeutic options in primary SS and offering a more optimistic point of view of the treatment of this disease, which, at present, is often considered to lack adequate specific therapy. However, the possible risks and benefits of using these agents should be carefully balanced, and a reasonable assessment of the risk of serious adverse events versus the benefits of treatment should be made. The use of biological agents targeting molecules and receptors involved in the aetiopathogenesis of primary SS opens a new era in the therapeutic management of patients with primary SS.

TABLE 2. Therapeutic role of biological agents in primary SS: reported studies

Biological agent	Authors [reference]	Patients	Study design	Efficacy
Infliximab	Steinfeld *et al.* [68]	16	Open-label	Response
	Mariette *et al.* [72]	103	Randomized, double-blind, placebo-controlled	No response
Etanercept	Sankar *et al.* [73]	28	Randomized, double-blind, placebo-controlled	No response
	Zandbelt *et al.* [74]	15	Open-label	No response
Rituximab	Gottenberg *et al.* [16]	6	Retrospective	Response
	Pijpe *et al.* [17]	15	Open-label	Response
	Seror *et al.* [18]	16	Retrospective	Response
	UMCG	–	Randomized, double-blind, placebo-controlled	Recruiting patients
Epratuzumab	Steinfeld *et al.* [46]	16	Phase I/II	Response
Efalizumab	NIDCR	–	Phase II	Recruiting patients

Treatment of Primary Sjögren Syndrome
A Systematic Review

Manuel Ramos-Casals, MD, PhD
Athanasios G. Tzioufas, MD
John H. Stone, MD, MPH
Antoni Sisó, MD, PhD
Xavier Bosch, MD, PhD

SJÖGREN SYNDROME IS A SYSTEMIC autoimmune disease that presents with sicca symptomatology of mucosal surfaces,[1] mainly dry mouth and dry eyes. There is often systemic involvement (extraglandular manifestations) and lymphoma is a recognized complication.[2] Sjögren syndrome is one of the most prevalent autoimmune diseases (with an estimated 0.5 million to 3 million affected persons in the United States,[3] primarily perimenopausal women). When sicca symptoms appear in a previously healthy person, this is classified as primary Sjögren syndrome.[4]

Standard management focuses on controlling sicca features using substitute topical agents, and extraglandular features are managed with glucocorticoids and immunosuppressive drugs.[5] However, there are no evidence-

Context A variety of topical and systemic drugs are available to treat primary Sjögren syndrome, although no evidence-based therapeutic guidelines are currently available.

Objective To summarize evidence on primary Sjögren syndrome drug therapy from randomized controlled trials.

Data Sources We searched MEDLINE and EMBASE for articles on drug therapy for primary Sjögren syndrome published between January 1, 1986, and April 30, 2010.

Study Selection Controlled trials of topical and systemic drugs including adult patients with primary Sjögren syndrome were selected as the primary information source.

Results The search strategy yielded 37 trials. A placebo-controlled trial found significant improvement in the Schirmer and corneal staining scores, blurred vision, and artificial tear use in patients treated with topical ocular 0.05% cyclosporine. Three placebo-controlled trials found that pilocarpine was associated with improvements in dry mouth (61%-70% vs 24%-31% in the placebo group) and dry eye (42%-53% vs 26%). Two placebo-controlled trials found that cevimeline was associated with improvement in dry mouth (66%-76% vs 35%-37% in the placebo group) and dry eye (39%-72% vs 24%-30%). Small trials (<20 patients) found no significant improvement in sicca outcomes for oral prednisone or hydroxychloroquine and limited benefits for immunosuppressive agents (azathioprine and cyclosporine). A large trial found limited benefits for oral interferon alfa-2a. Two placebo-controlled trials of infliximab and etanercept did not achieve the primary outcome (a composite visual analog scale measuring joint pain, fatigue, and dryness); neither did 2 small trials (<30 patients) testing rituximab, although significant results were observed in some secondary outcomes and improvement compared with baseline.

Conclusions In primary Sjögren syndrome, evidence from controlled trials suggests benefits for pilocarpine and cevimeline for sicca features and topical cyclosporine for moderate or severe dry eye. Anti–tumor necrosis factor agents have not shown clinical efficacy, and larger controlled trials are needed to establish the efficacy of rituximab.

JAMA. 2010;304(4):452-460 www.jama.com

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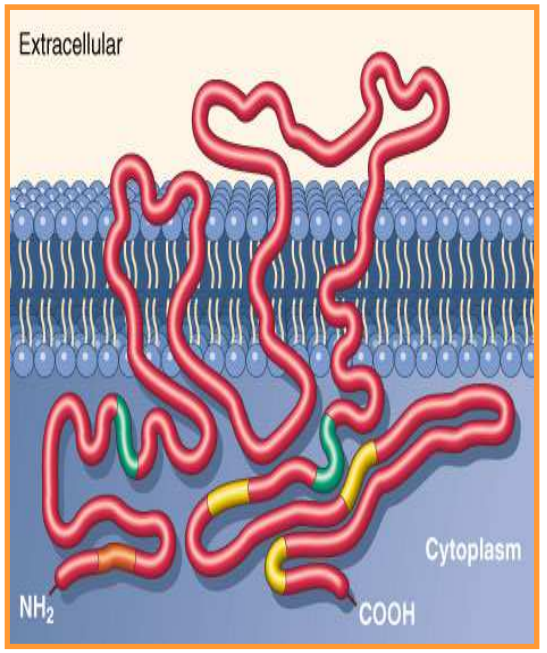
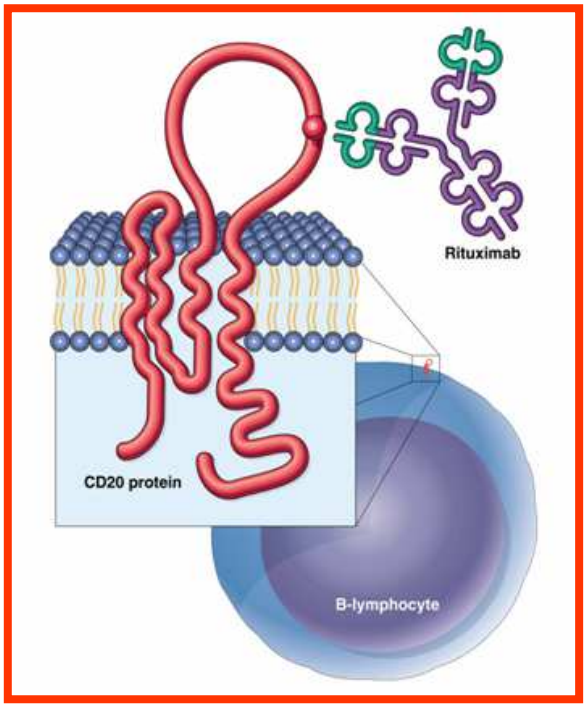
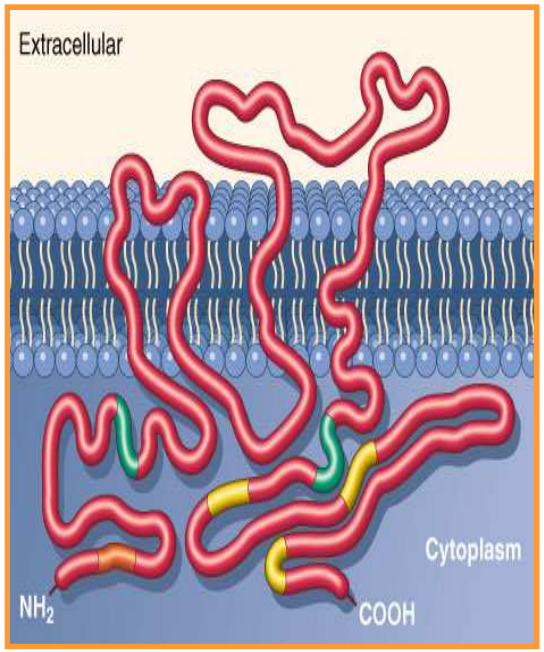
Voulgarelis et al. (2012)	Rituximab	Retrospective	17
Steinfeld et al. (2006)	Epratuzumab	Open-label	16
Mariette et al. (2012)	Belimumab	Open-label	30
De Vita et al. (2012)		Open-label	

B-cell depletion in primary SS

- Epratuzumab (anti-CD22)
- Rituximab (anti-CD20)
- Belimumab (anti-Blys)





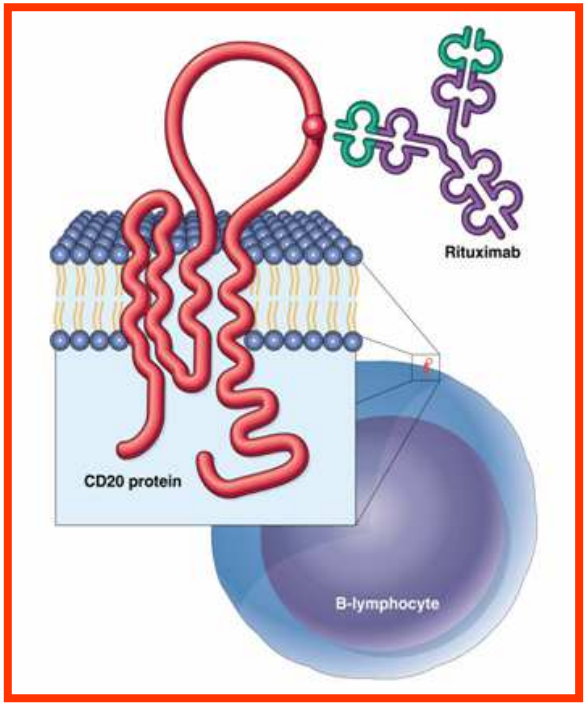


B-cell depletion in primary SS

Epratuzumab
(anti-CD22)

Belimumab
(anti-Blys)

**Rituximab
(anti-CD20)**



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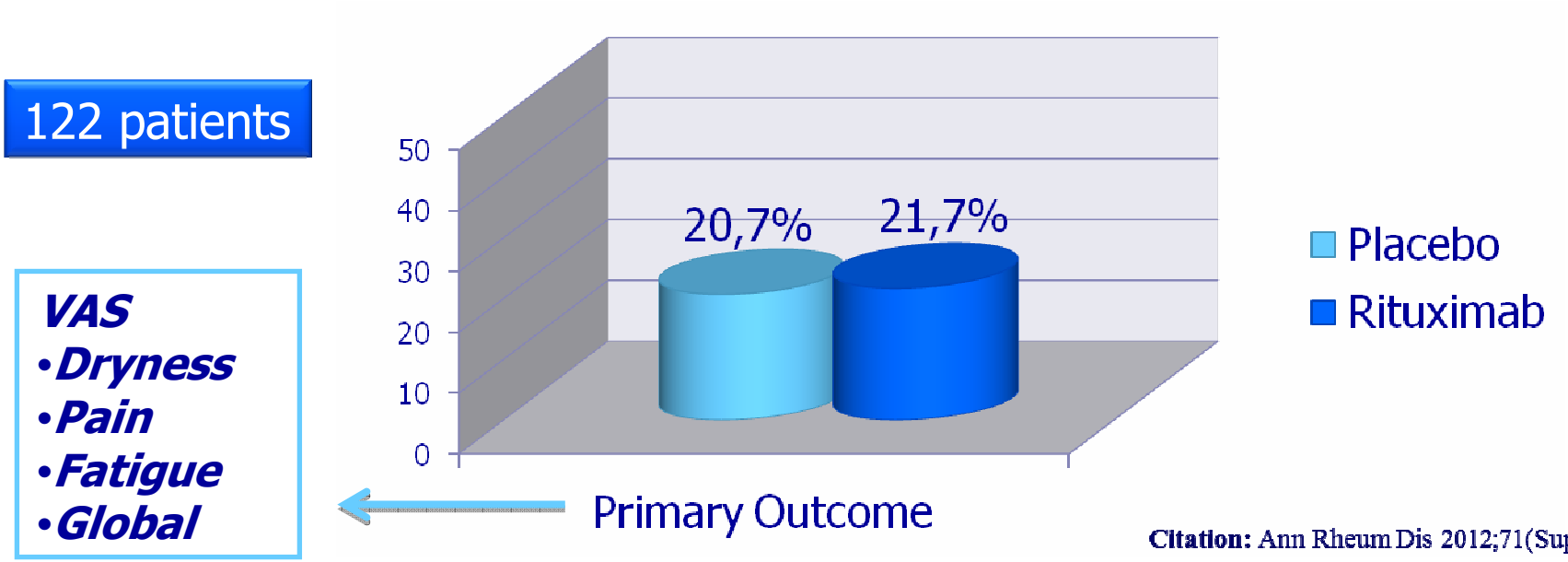
[2012] [OP0065] TOLERANCE AND EFFICACY OF RITUXIMAB IN PRIMARY SJOGREN SYNDROME (TEARS): RESULTS OF A RANDOMIZED CONTROLLED TRIAL

V. Devauchelle-Pensec1, X. Mariette2, S. Jousse-Joulin1, J.-M. Berthelot3, A. Perdriger4, E. Hachulla5, X. Puéchal6, V. Le Guern7, J. Sibilia8, J.-E. Gottenberg8, L. Chiche9, V. Goeb10, G. Hayem11, J. Morel12, C. Zarnitsky13, J.-J. Dubost14, J.-O. Pers15, E. Nowak16, A. Saraux1, and the TEARS study group (Institutional grant support from the French Health ministry PHRC 2007) 1Rheumatology and EA 2216, CHU, Brest; 2Rheumatology, CHU Bicêtre, Paris; 3Rheumatology, CHU, Nantes; 4Rheumatology, CHU, Rennes; 5Rheumatology, CHU, Lille; 6Rheumatology, CH, Le Mans; 7Internal medicine, Cochin, Paris; 8Rheumatology, CHU, Strasbourg; 9Internal Medicine, CHU, Marseille; 10Rheumatology, CHU, Rouen; 11Rheumatology, CHU Bichat, Paris; 12Rheumatology, CHU, Montpellier; 13Rheumatology, CH, Le Havre; 14Rheumatology, CHU, Clermont-Ferrand; 15Ea 2216; 16CIC, CHU, Brest, France

Background: Current pharmacological treatments can improve the sicca symptoms but they are unable to modify the course of of primary Sjogren's syndrome (pSS). There is evidence for a critical role of B cells in the pathogenesis of pSS. Both open labelled and small controlled studies suggested the efficacy of Rituximab (RTX) in specific subgroups of pSS.
Objectives: We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of RTX in a large group of patients with active primary Sjögren's syndrome (pSS).
Methods: 122 Patients were assigned to receive either RTX infusions (1g) or placebo (P) at weeks 0 and 2. They were followed up for 24 weeks. All patients fulfilled the new American-European Consensus Group criteria for pSS, had an active disease as assessed by mean values of the 2 highest visual analog scales (VAS) ≥50 evaluating dryness, pain, fatigue and global (disease activity assessed by the patient), and had either a recent (less than 10 years since first clinical sign) and a biologically active pSS [Auto antibodies (SSA or RF) or cryoglobulinaemia, or hypergammaglobulinaemia, or high level of beta 2-microglobulinemia or hypo-complementaemia] or at least one extra-glandular manifestation. The primary end point was an improvement of at least a 30 mm on 2 of 4 VAS between weeks 0 and 24.



Citation: Ann Rheum Dis 2012;71(Suppl3):75

CONCISE REPORT

Ann Rheum Dis 2012;**0**:1–6. doi:10.1136/annrheumdis-2012-202293

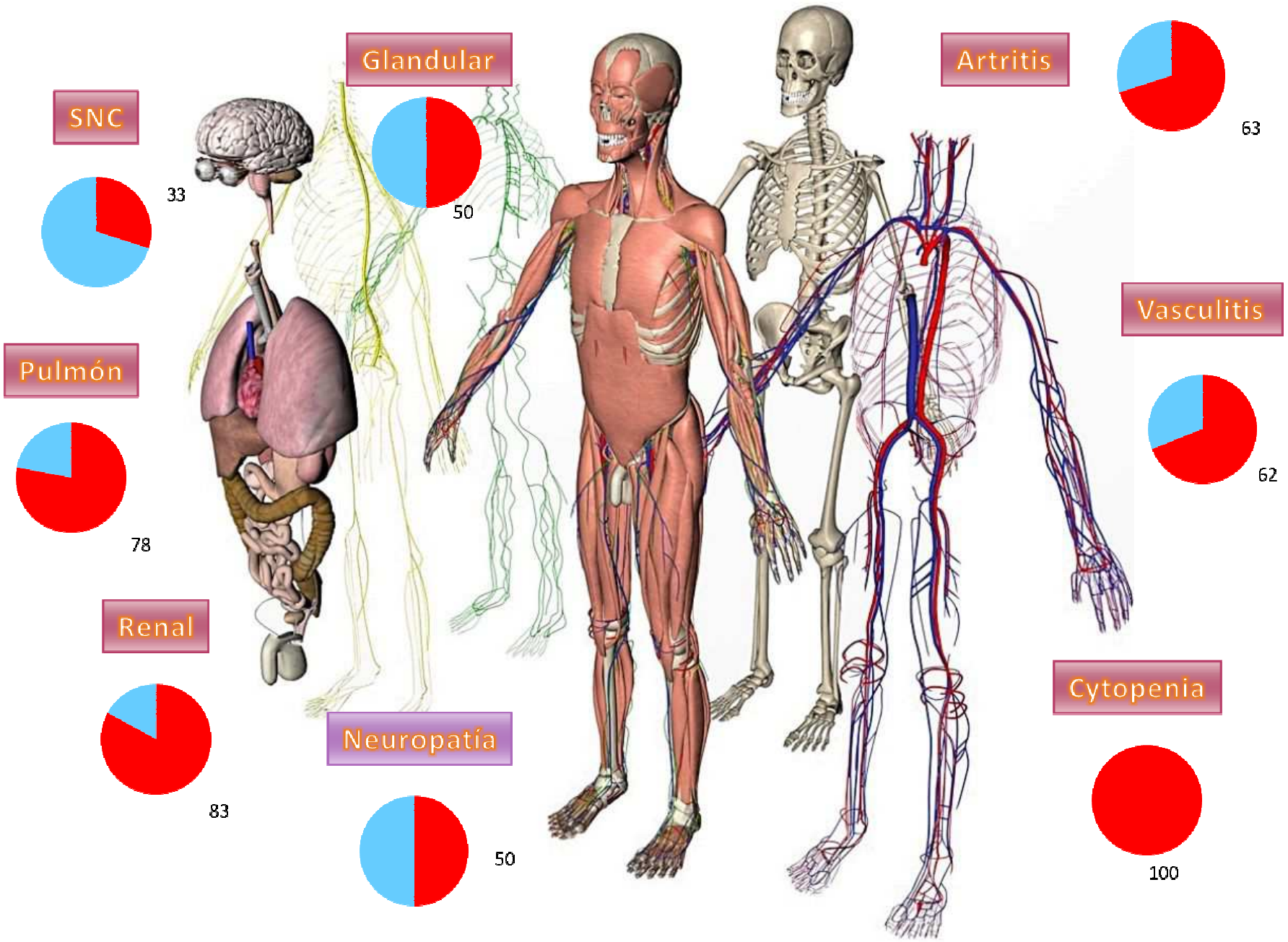
Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry

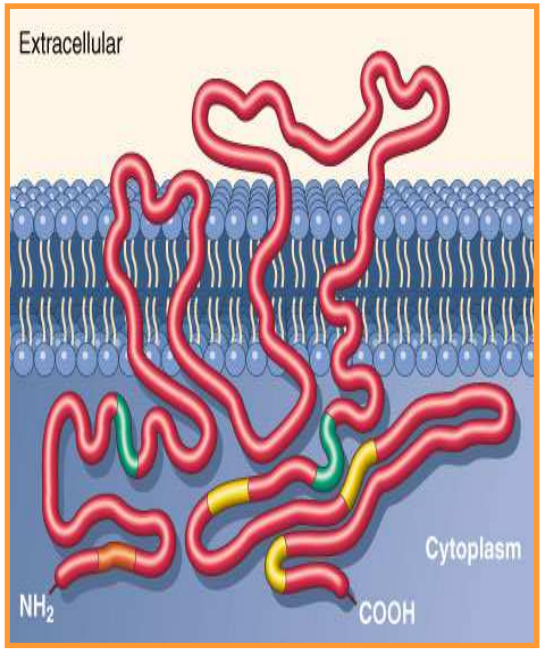
Jacques-Eric Gottenberg,[1] Gael Cinquetti,[2] Claire Larroche,[3] Bernard Combe,[4] Eric Hachulla,[5] Olivier Meyer,[6] Edouard Pertuiset,[7] Guy Kaplanski,[8] Laurent Chiche,[8] Jean-Marie Berthelot,[9] Bruno Gombert,[10] Philippe Goupille,[11] Christian Marcelli,[12] Séverine Feuillet,[13] Jean Leone,[14] Jean Sibilia,[1] Charles Zarnitsky,[15] Philippe Carli,[16] Stephanie Rist,[17] Philippe Gaudin,[18] Carine Salliot,[17] Muriel Piperno,[19] Adeline Deplas,[20] Maxime Breban,[21] Thierry Lequerre,[22] Pascal Richette,[23] Charles Ghiringhelli,[24] Mohamed Hamidou,[25] Philippe Ravaud,[26] Xavier Mariette,[27] for the Club Rhumatismes et Inflammations and the French Society of Rheumatology

Table 2 Efficacy of rituximab on the various predominant organ involvements

Before rituximab		After rituximab	
Systemic organ involvement	74	Systemic efficacy	44 (59%)
Articular	27		17 (63%)
Nervous system	18		8 (44%)
CNS	6		2 (33%)
Multiple sclerosis-like manifestations	4		0
Transverse myelitis	1		1
Anxiety/depression	1		1
PNS	12		6 (50%)
Mixed sensorimotor polyneuropathy	6		3
Sensory painful neuropathy (including sensory ataxic neuropathy)	4		2
Mononeuritis multiplex	2		1
Pulmonary	9		7 (78%)
Vasculitis	8		5 (62.5%)
Renal	6		5 (83.3%)
Muscular	3		0 (0%)
Haematological	2		2 (100%)
Autoimmune pancreatitis	1		1 (100%)
Glandular involvement	4	Glandular efficacy	2 (50%)
Hypertrophy of lachrymal glands	1		0
Sclera vasculitis	1		0
parotid hypertrophy	2		2
ESSDAI before rituximab (n=72)	11.0 (2–31)	ESSDAI after rituximab (n=72)	7.5 (0–26)
Corticosteroids (mg/day) (n=29)	17.6	Corticosteroids after rituximab (n=23)	10.8

% de respuesta a rituximab por órgano





B-cell depletion in primary SS

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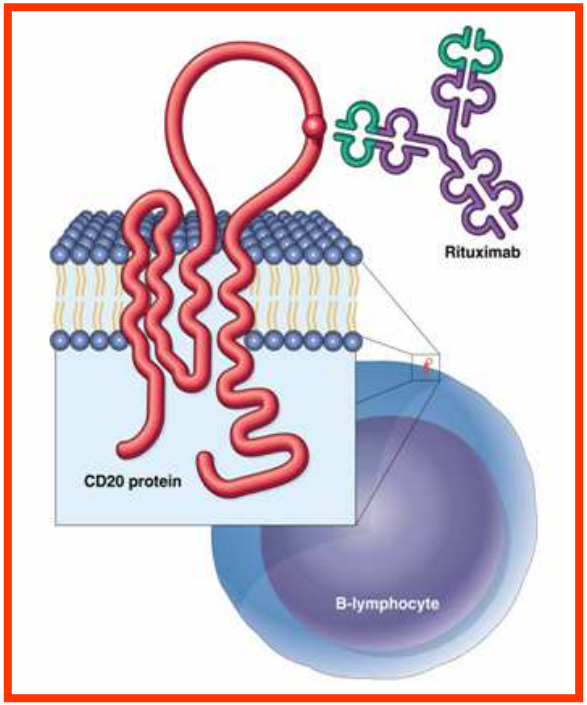
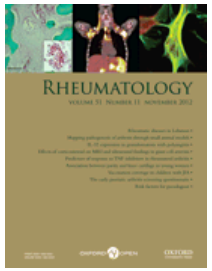




Manuel Ramos-Casals[1]

[1]*Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS, Department of Autoimmune Diseases, ICMiD, Hospital Clínic, University of Barcelona, Barcelona, Spain.*

Rheumatology Advance Access published October 4, 2012

RHEUMATOLOGY

Editorial

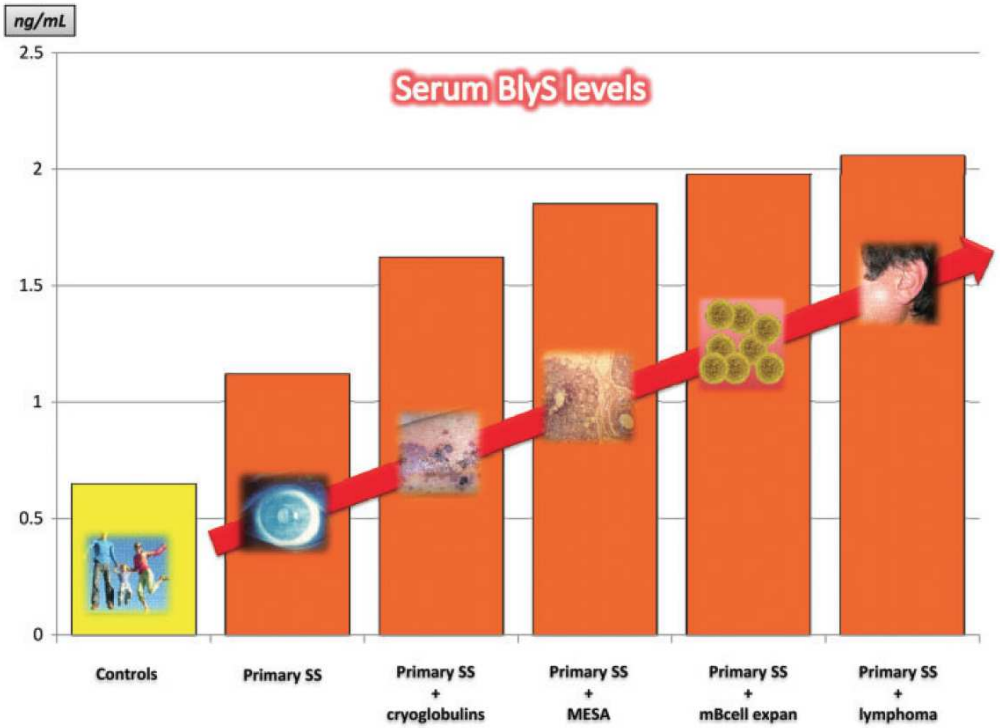
doi:10.1093/rheumatology/kes235

The B-lymphocyte stimulator connection in Sjögren's syndrome

Is there a place for using BLyS as a potential therapeutic target?

EDITORIAL

Fig. 1 Serum BLyS levels in patients with pSS [1].



Mean levels in the control population and in patients with B-cell-related processes (cryoglobulinaemia, myoepithelial sialoadenitis, monoclonal B cell histopathological expansion and overt lymphoma). Labels for *x*-axis (subset of patients) and *y*-axis (serum BlyS levels, ng/ml). MESA: myoepithelial sialoadenitis; mBcell expan: monoclonal B-cell expansion in salivary glands.

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COMUNICACION ORAL
Abstract#: 2555
Results of the Beliss Study, the First Open Phase 2 Study of Belimumab in Primary Sjogren's Syndrome
Presenter: Xavier Mariette: Université Paris-Sud

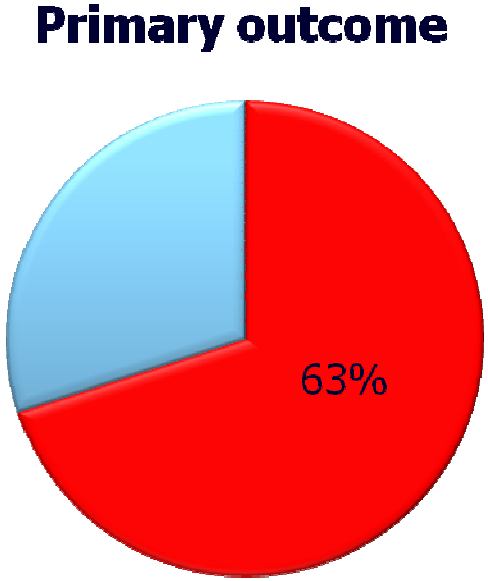
Abstract#: 2189

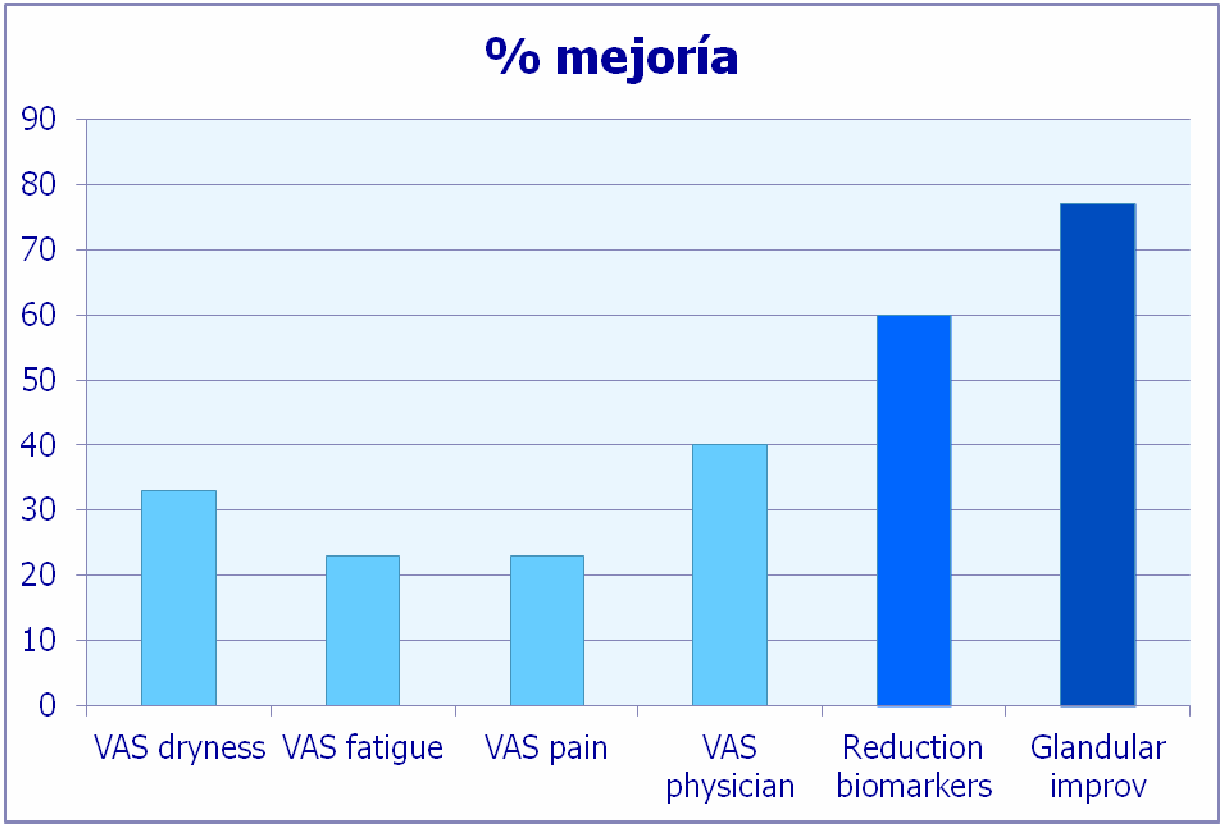
Efficacy of Belimumab On Non-Malignant Parotid Swelling and Systemic Manifestations of Sjögren's Syndrome: Results of the Beliss Study

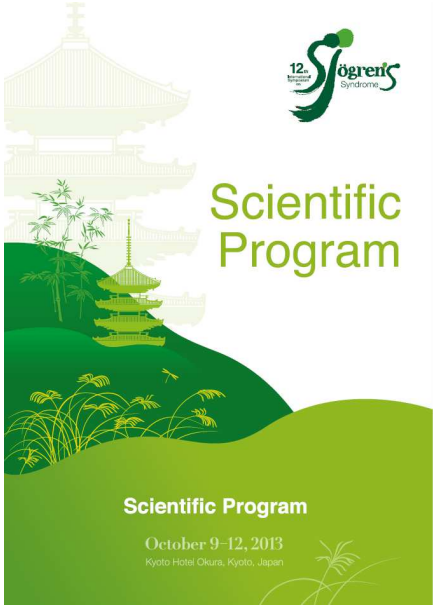
Presenter: Salvatore De Vita: Rheumatology Clinic, DSMB, University of Udine

Estudio abierto a 28s
30 pacientes
Primary outcome = composite

Reducción VAS (dryness, fatigue, pain, global) + biomarkers







12th International Symposium on Sjögren's Syndrome

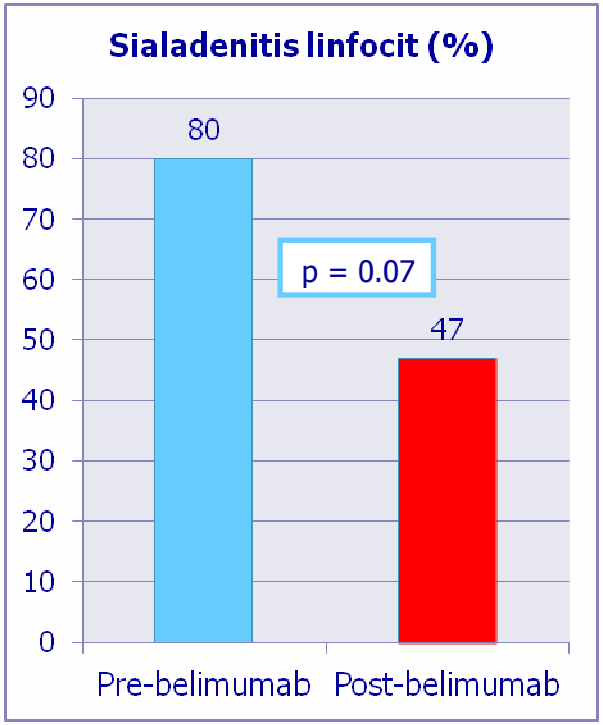
Workshop 8 : *Clinical & Treatment I*

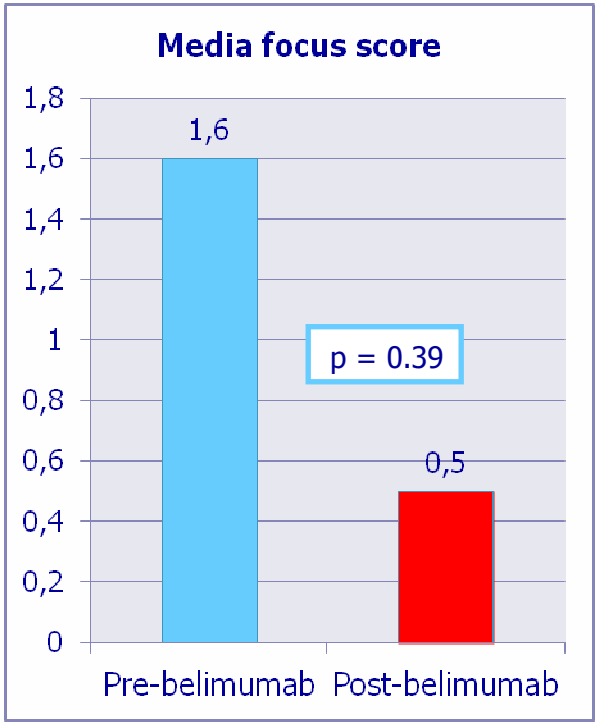
WS8-3 **Salivary gland lymphocyte pattern associated with response to belimumab in primary Sjögren's syndrome: results of the BELISS study**

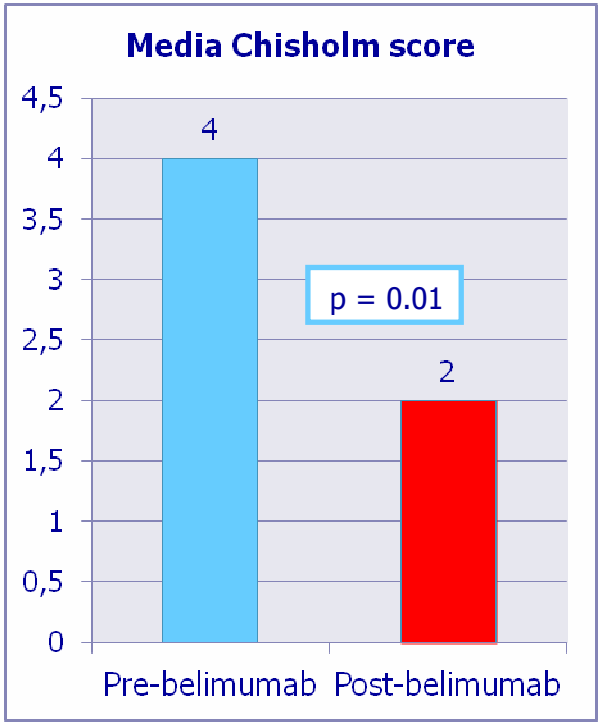
Raphaele Seror[1], Thierry Lazure[2], Frederic Desmoulins[1,3], Stephan Pavy[1], Corinne Miceli-Richard[1], Philippe Ravaud[3], Xavier Mariette[1]

[1] *department of rheumatology, Hopital Bicetre, Le kremlin Bicetre, France,*
[2] *department of pathology, Hopital Bicetre, Le kremlin Bicetre, France,*
[3] *department of clinicla epidemiology, Hopital Hotel Dieu, Paris, France*

Re-biopsias en 15 pacientes antes y después del tx con belimumab

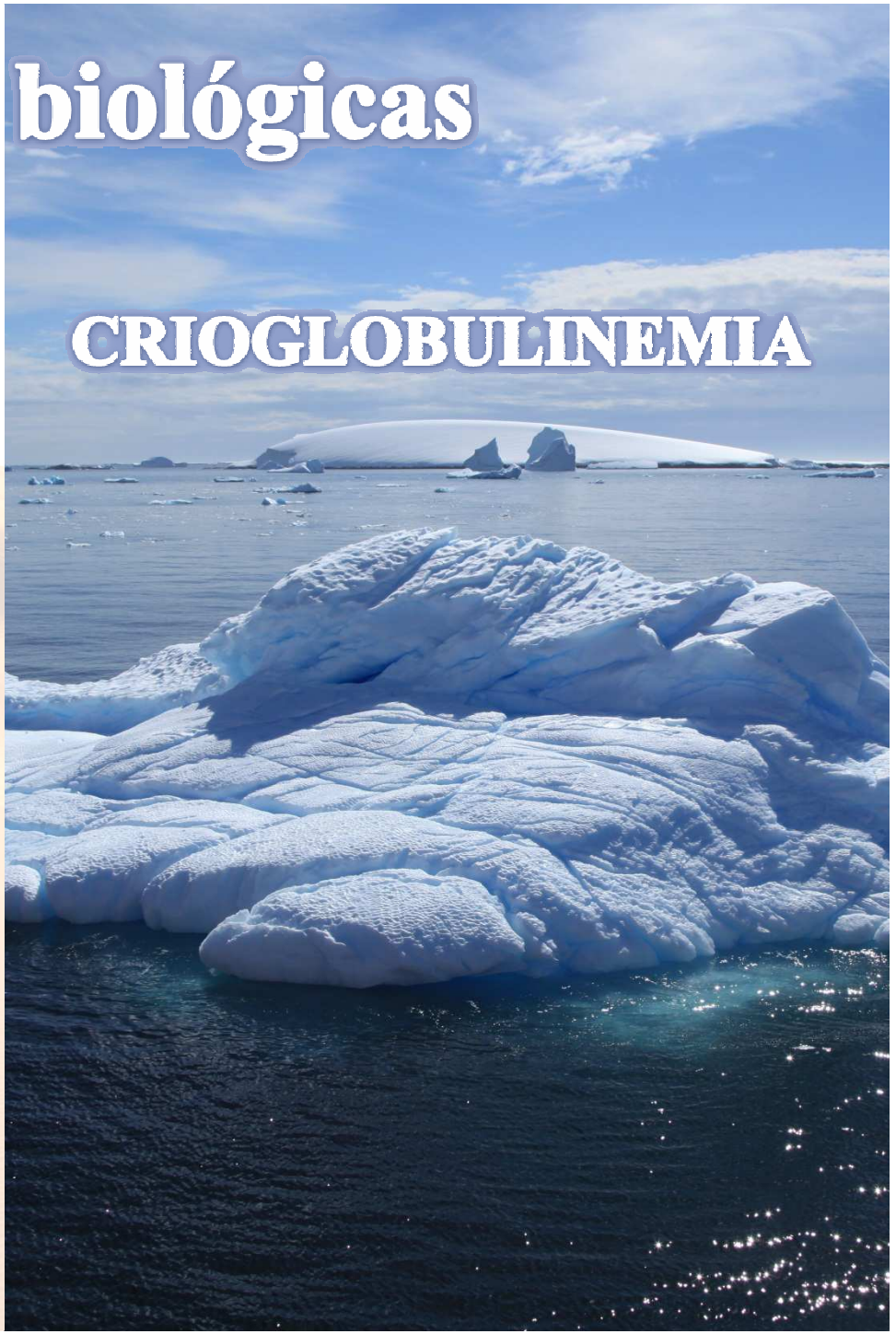






Terapias biológicas

SJÖGREN



OPCIONES TERAPÉUTICAS: 2000-2013

Tratamiento antivírico (Cacoub, 2003)

Tratamiento clásico

Tratamiento biológico (De Vita, 2003)

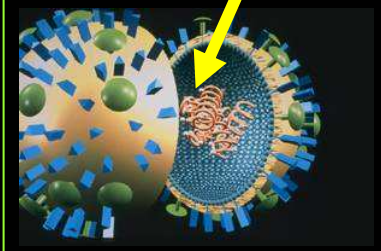
Anti-VHC

Inmunodepresión

Anti-linfo B

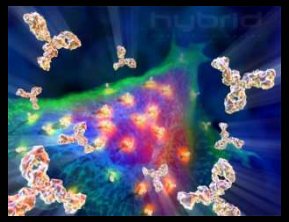
Antivíricos

Eliminar el VHC o carga viral



Corticoides

Manifestaciones autoinmunes



Inmunosupr.

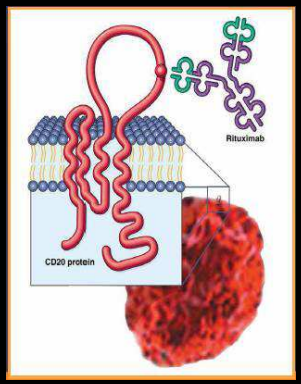
Dosis corticoides Casos graves

Recambio plasmático

Eliminar inmunocomplejos

Rituximab

Eliminar vs controlar la proliferación B



Retamozo S, Brito-Zerón P, Bosch X, Stone JH, Ramos-Casals M. Cryoglobulinemic Disease. Oncology 2013 (in press)

Author, year (reference)	N (female)	Patient profile	Study design (duration)	Intervention drug (patients)	Control group (patients)
Zaja et al , 2003	15 (11)	HCV related MC refractory to antiviral therapy (n=12) Essential MC (n=2), VHB (n=1)	Prospective open-label study (Follow up 24 w)	**RTX** 375 mg/m² intravenously weekly 4 w (n= 15).	-
Sansonno et al, 2003	20 (16)	HCV related MC refractory to INF-α	Prospective open-label study	**RTX** 375 mg/m² intravenously weekly 4 w (n=20)	-
Saadoun et al, 2008	16 (13)	HCV related MC refractory or relapser to antiviral therapy	Prospective open-label study (48 w)	**RTX** 375 mg/m² intravenously weekly 4 w combined with Peg-INF-α 2b plus RBV (n= 16).	-
Terrier et al, 2009	32 (18)	HCV related MC (severe vasculitic involvement),INF-α naïve, refractory or relapser to antiviral therapy	Case-control prospective study (Follow up 48 w).	**RTX** (375 mg/m² intravenously weekly 4) plus Peg-IFN-α/RBV for 48 w (n=20).	RTX alone (375 mg/m² intravenously weekly 4): (n=12).
Dammacco et al, 2010	37 (15)	HCV related MC no previous administration of IFNs or immunosuppressive drugs.	Case-control prospective study (Follow up 48 w).	**RTX** 375 mg/m² intravenously weekly 4 w followed by two 5-monthly infusions combined with Peg-IFN-α/RBV for 48 w (n=22).	Peg-IFN-α/RBV for 48 w (n=15).
Petrarca et al, 2010	19 (13)	HCV related MC with advanced CLD.	Prospective study (follow up 24 w)	**RTX** 375 mg/m² intravenously weekly 4 w (n= 19).	-
Saadoun et al, 2010	93 (55)	HCV related MC	Case-control prospective stud (Follow up 48 w).	**RTX** 375 mg/m² intravenously weekly 4 w combined with Peg-IFN-α/RBV for 48 weeks (n=38).	Peg-IFN-α/RBV for 48 w (n=55).
Ferri et al, 2011	87 (68)	HCV related MC (n=80), essential MC (n=5), SSp (n=2) Refractory or intolerant to previous treatments	Retrospective and Pubmed search (Follow up 24 w)	-**RTX** 375 mg/m² intravenously weekly 4 w (n=87).	-
Saadoun et al, 2011	10 (5)	HCV related MC refractory or intolerant to other previous treatments (antiviral treatment and/ or RTX)	Prospective open label study, phase I/II study. (Follow up 27 mo).	One **IL-2** course of 1.5 million IU/day for 5 days followed by three 5-day courses of 3 million IU/day at weeks 3, 6 and 9 (n= 10).	-
Visentini et al, 2011	27 (20)	HCV related MC refractory or intolerant to antiviral treatment and no previous use of RTX.	Phase II single-arm controlled study	**RTX** 250 mg/m² was given twice at one-week interval (n= 27).	-
De Vita et al, 2012	59 (46)	Severe HCV related MC refractory or intolerant to antiviral treatment.	RCT-d (24 m)	**RTX** 2 infusions of 1 gm each, with a lowering of PDN dosage when possible, and with a second course of RTX at relapse (n=28).	Immunosuppressive therapy (glucocorticoids, azathioprine or cyclophosphamide, or plasmapheresis) (n=29)
Sneller et al, 2012	24 (18)	HCV related MC refractory or intolerant to antiviral treatment	RCT-d (early stop)	**RTX** (375 mg/m2/w for 4 w) (n=12).	Immunosuppressive therapy (n=12)
Saadoun et al, 2013	7 (3)	HCV related MC with LL refractory or intolerant to antiviral treatment and/or RTX) (n=6), SSp plus LL (n=1)	Retrospective study (mean 27 mo)	Fludarabine (40 mg/m2) and cyclophosphamide (250 mg/m2) orally on days 2–4), and **RTX** (375 mg/m2 on day 1), given every 4 w, for 3 to 6 courses (n= 7).	-

BLOOD, 22 JULY 2010 • VOLUME 116, NUMBER 3

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 Rosenzwajg,[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 μg/week, n = 5; or 2b, 1.5 μg/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/m^2 (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

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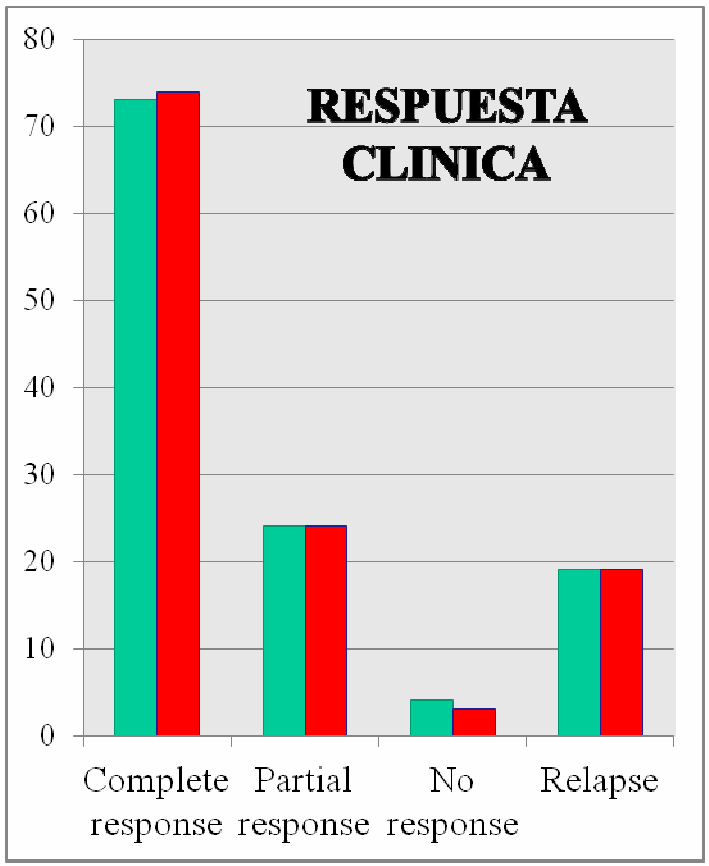
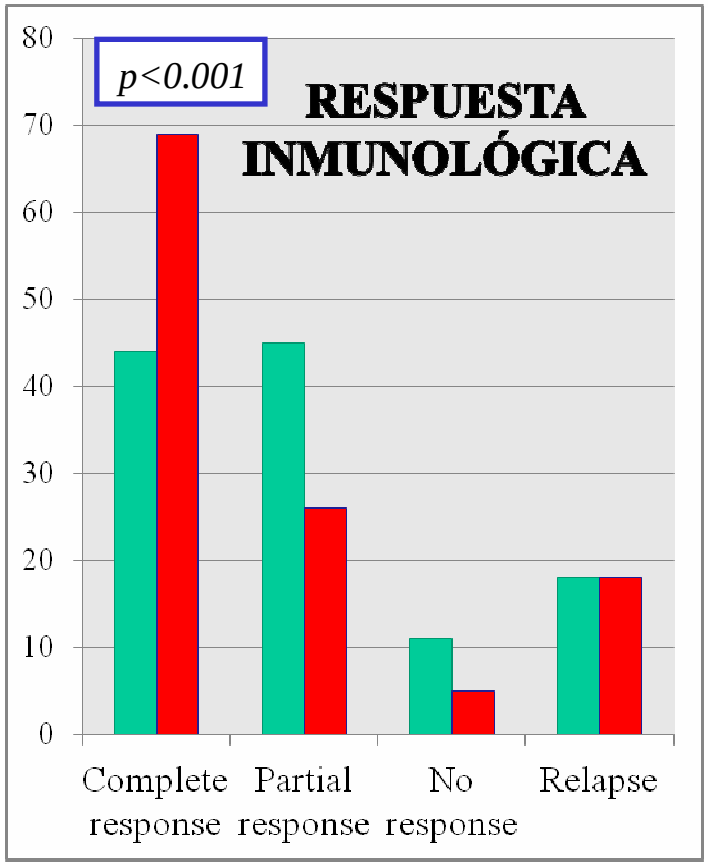
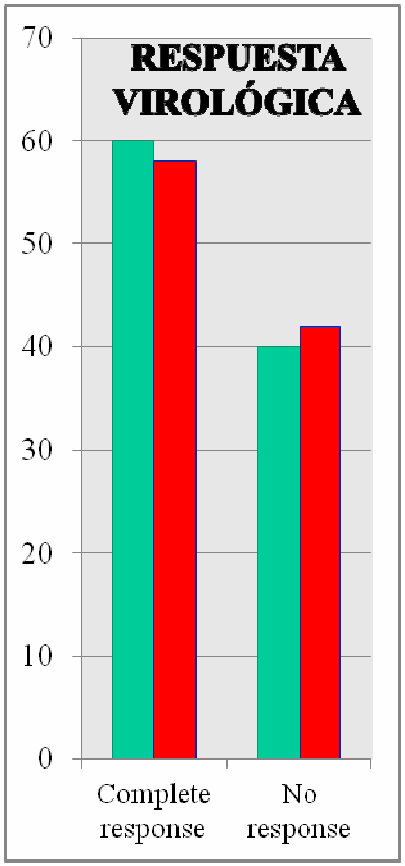


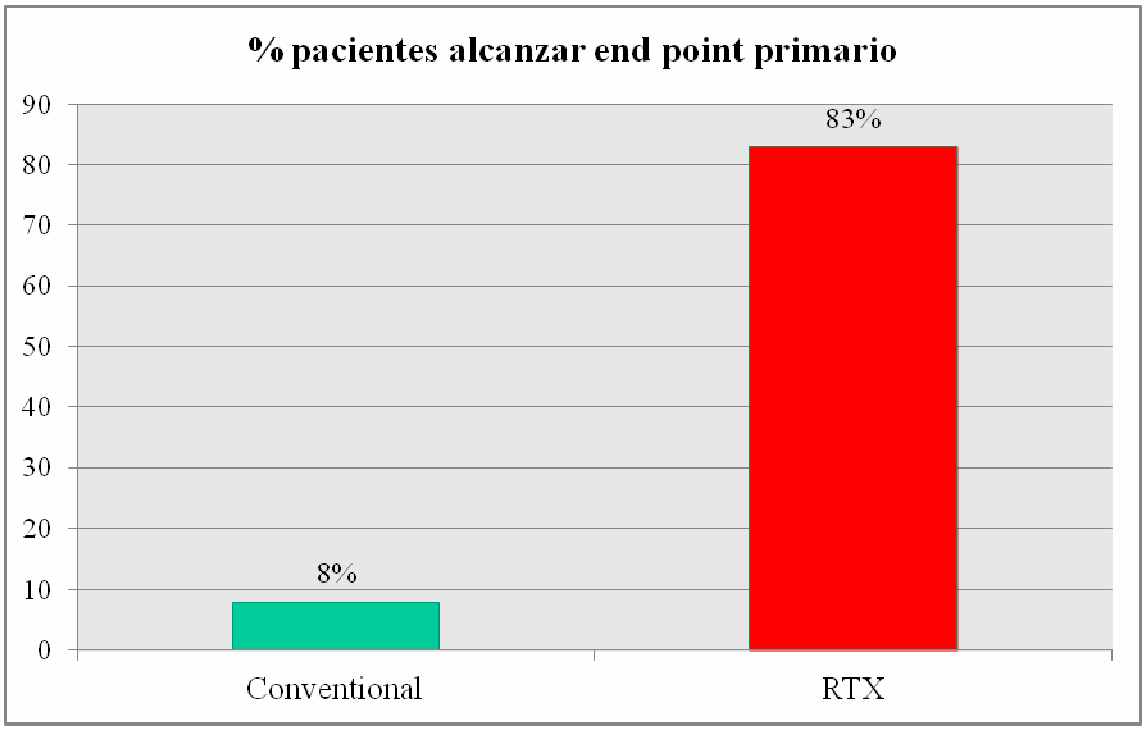




ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 835–842
DOI 10.1002/art.34322

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. Langford[2]



Efficacy assessments. *Primary end point.* The primary end point of the study was the number of patients whose disease was in remission at study month 6. Ten of the 12 patients in the rituximab group (83.3% [95% CI 51.6–97.9]) reached the primary end point, as compared with 1 of the 12 patients in the control group (8.3% [95% CI 2.0–38.6]), indicating significantly higher remission with rituximab treatment ($P < 0.001$).

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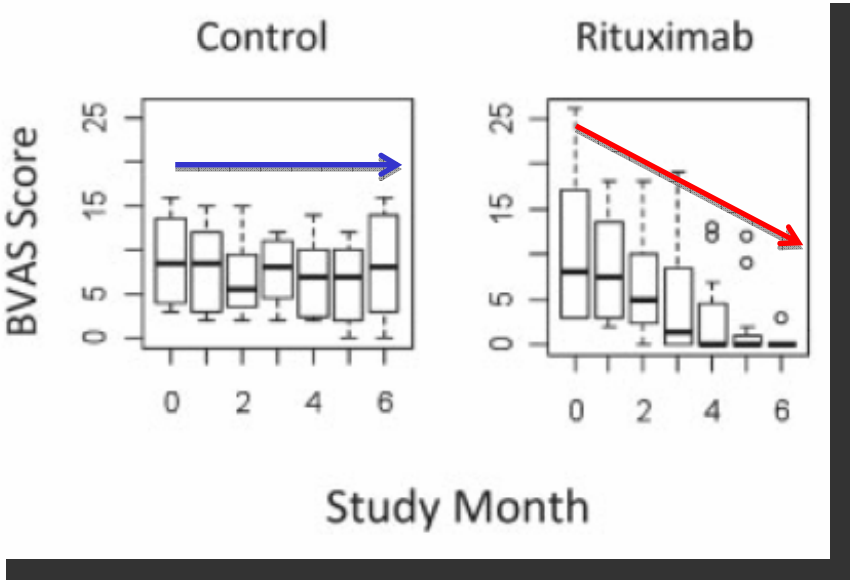
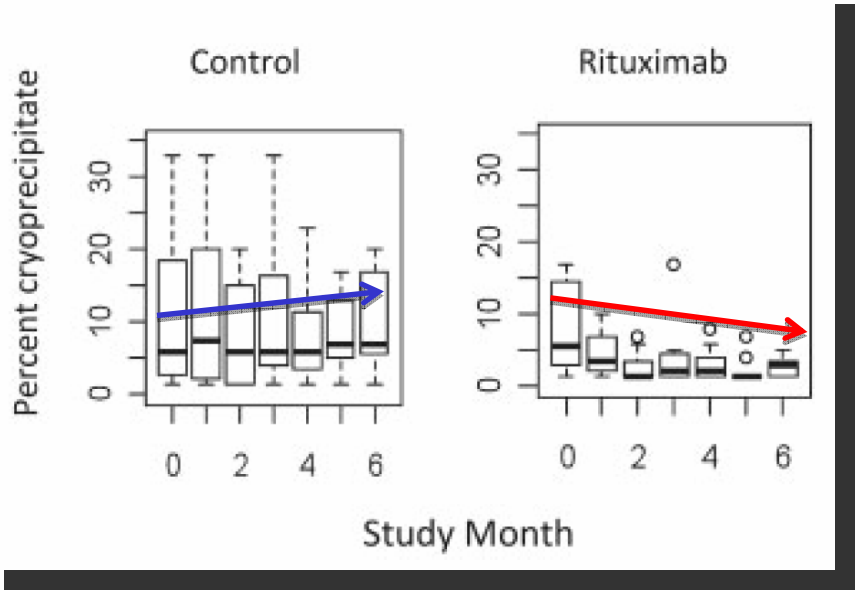




ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 843–853
DOI 10.1002/art.34331

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. Monti[19]

Table 1. Characteristics of the patients who were randomized into the study, by treatment group*

	All patients (n = 57)	Non-RTX group (n = 29)	RTX group (n = 28)
Age, mean ± SD years	63.27 ± 10.78	63.0 ± 10.6	62.85 ± 11.36
Sex, no. female/male	46/11	22/7	24/4
No. HCV positive/no. tested	53/57	28/29	25/28
Antiviral therapy failure/not indicated	28/25	14/14	14/11
BVAS at baseline, mean ± SD	10.51 ± 4.49	9.55 ± 3.64	11.89 ± 5.42
No. with skin ulcers	7	2	5
No. with nephritis	17	10	7
No. with neuropathy	33	17	16
Rheumatoid factor, mean ± SD IU/ml	528.55 ± 840.12	556.58 ± 784.04	501.38 ± 891.81
C4, mean ± SD mg/dl	6.62 ± 8.05	6.81 ± 7.37	6.27 ± 8.7

* There were no significant differences between the two treatment groups. RTX = rituximab; HCV = hepatitis C virus; BVAS = Birmingham Vasculitis Activity Score.

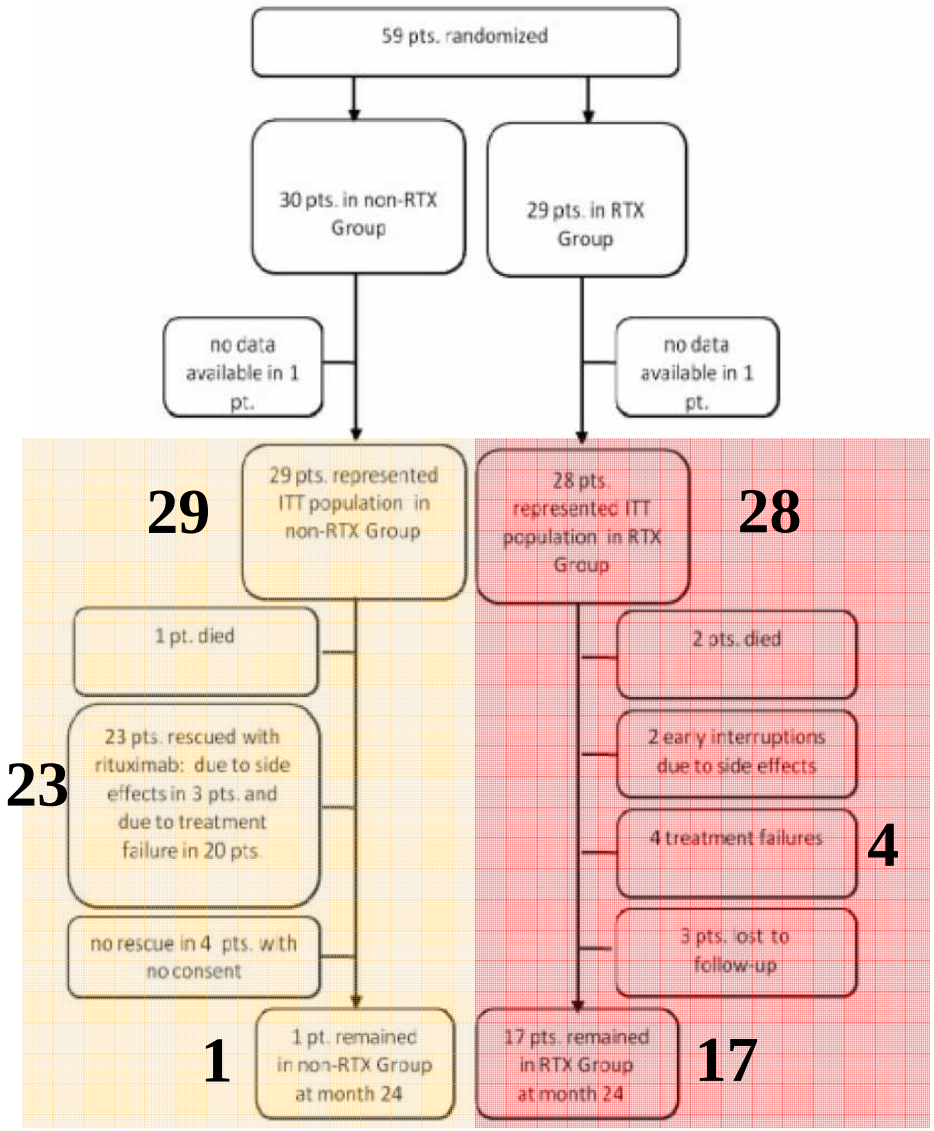


Figure 1. Flow chart showing the distribution of study patients from randomization, over the subsequent course of the study, and to completion of the study in patients randomized to receive rituximab (RTX) or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis. ITT = intent-to-treat.

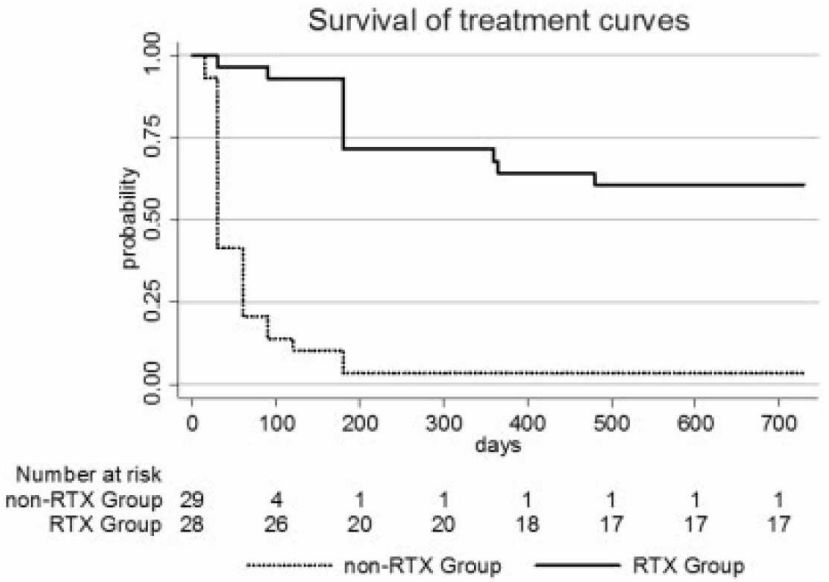


Figure 2. Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.


CONCLUSIONES

Rituximab en el paciente con SSp

¿Cuándo?

REVIEWS

Topical and systemic medications for the treatment of primary Sjögren's syndrome

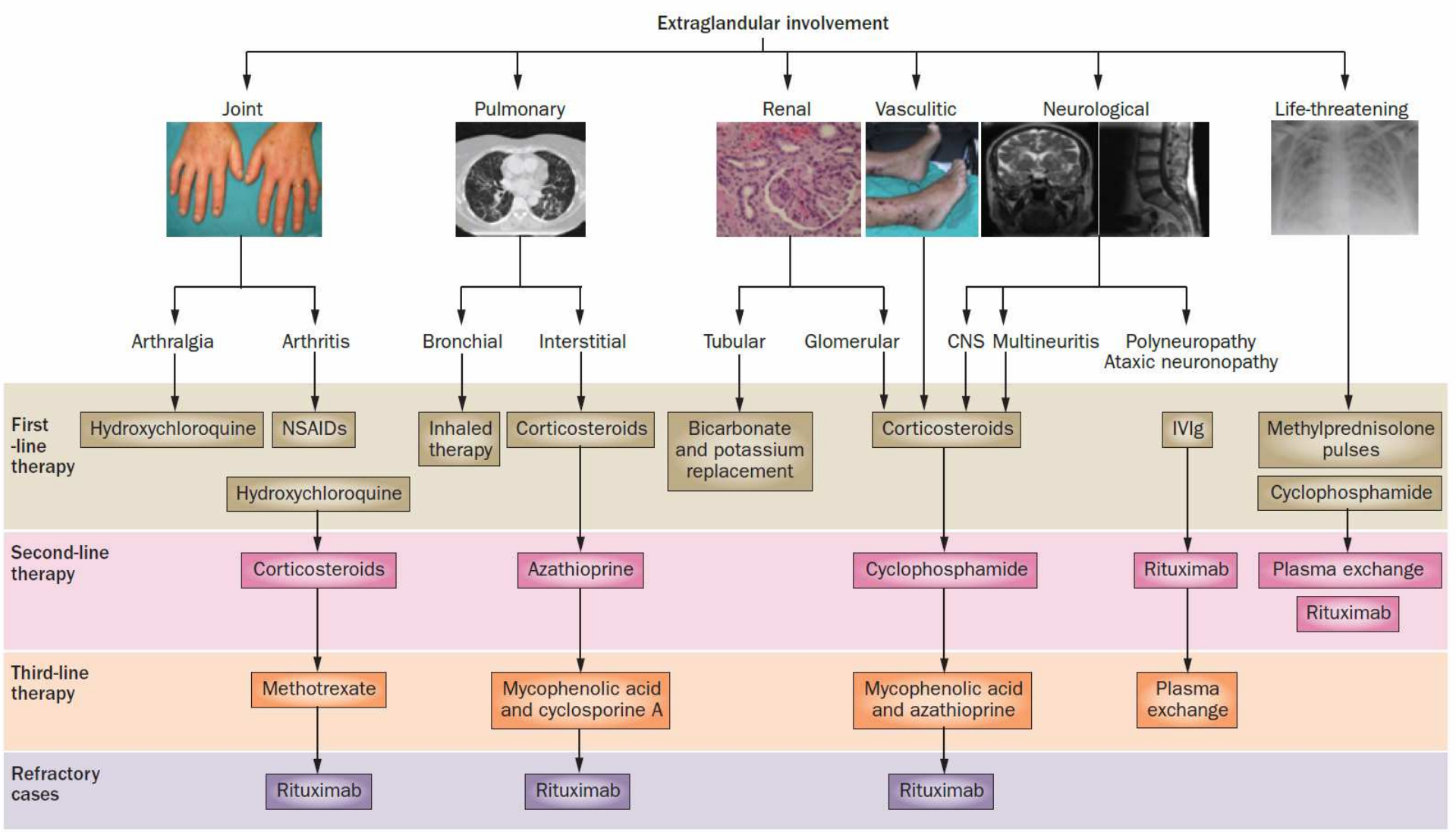
Manuel Ramos-Casals, Pilar Brito-Zerón, Antoni Sisó-Almirall, Xavier Bosch and Athanasios G. Tzioufas

Abstract | The treatment of primary Sjögren's syndrome (SS) is based principally on the management of sicca features and systemic manifestations. Sicca manifestations are treated symptomatically through administration of topical therapies, such as saliva substitutes and artificial tears; in patients with residual salivary gland function, stimulation of salivary flow with a sialogogue is the therapy of choice. The management of extraglandular features must be tailored to the specific organ or organs involved; however, limited data have been obtained from controlled trials in SS to guide the treatment of systemic symptoms using therapies including antimalarials, glucocorticoids, immunosuppressive drugs and biologic agents. Nevertheless, randomised controlled trials of biologic agents that target molecules and receptors involved in the aetiopathogenesis of primary SS have initiated a new era in the therapeutic management of the disease, although the potential risks and benefits of these agents must be carefully considered. In this Review, we analyse the evidence regarding the efficacy of the therapeutic agents currently available to treat the manifestations of SS. On the basis of this evidence, we provide guidance on the use of these agents in different clinical scenarios.

Ramos-Casals, M. *et al. Nat. Rev. Rheumatol.* **8**, 399–411 (2012); published online 1 May 2012; doi:10.1038/nrrheum.2012.53

Rituximab en el paciente con SSp

¿Cuándo?



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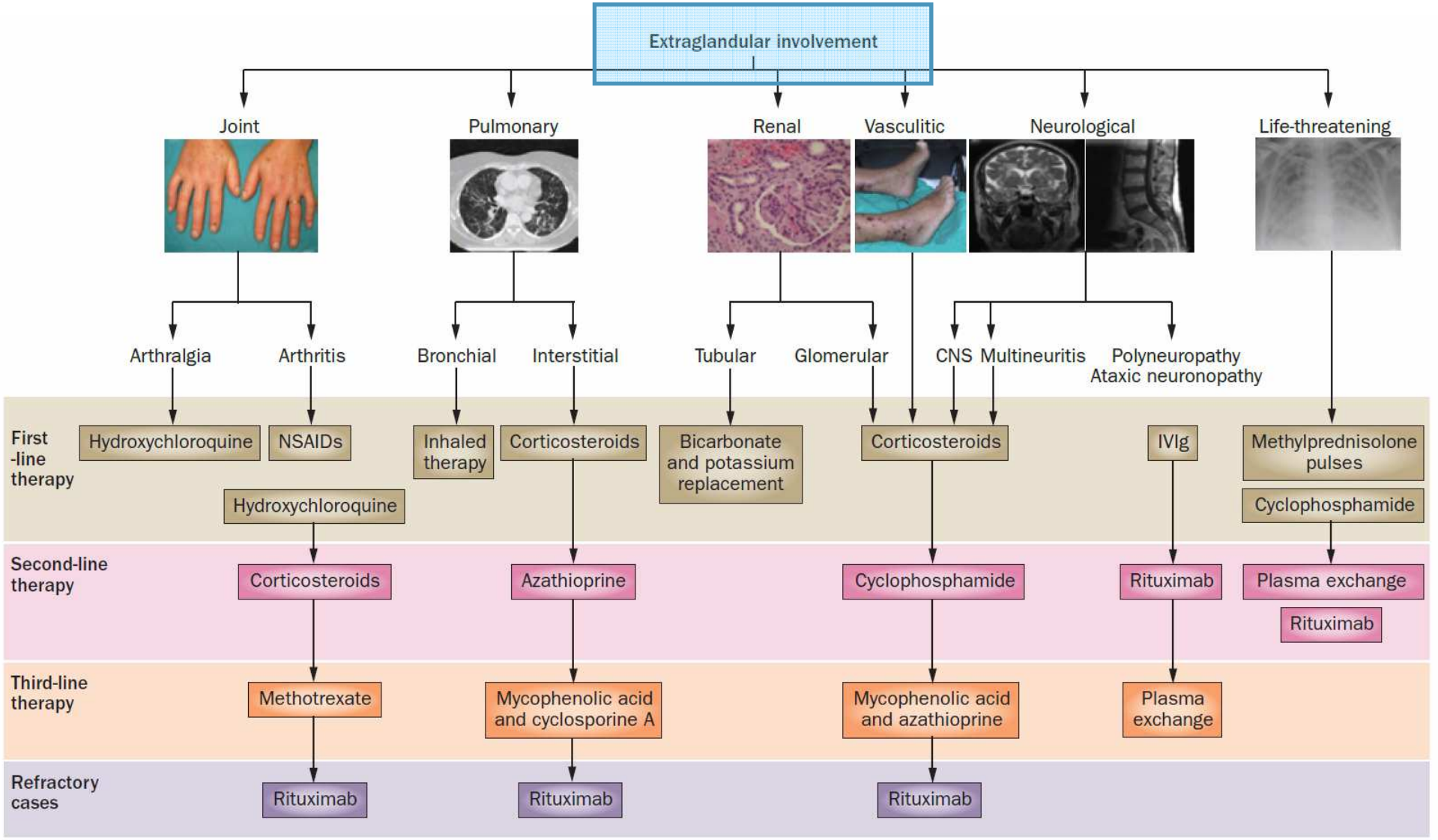

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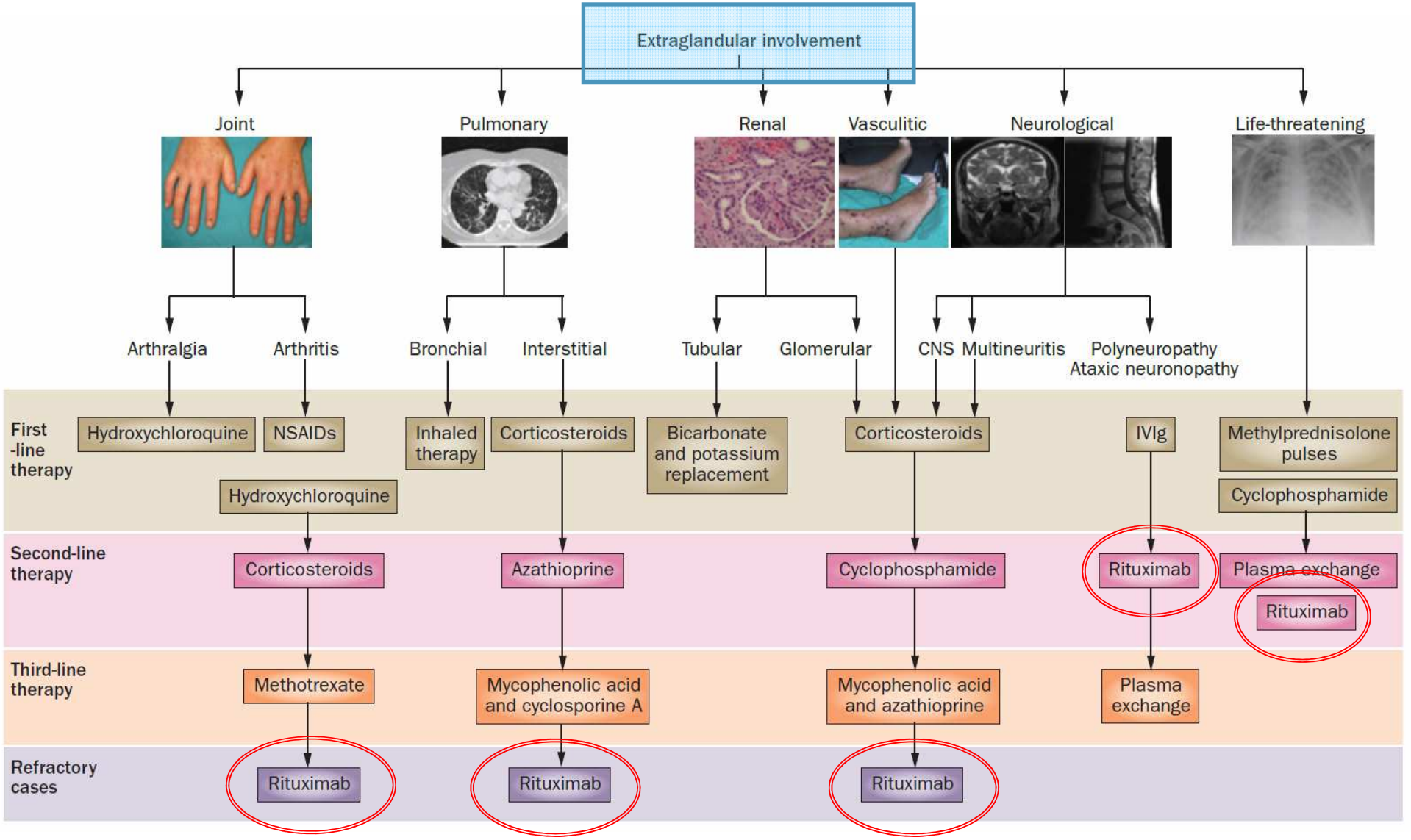


Rituximab en el paciente con HCV-crio

¿Cuándo?

Seminar

The cryoglobulinaemias

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

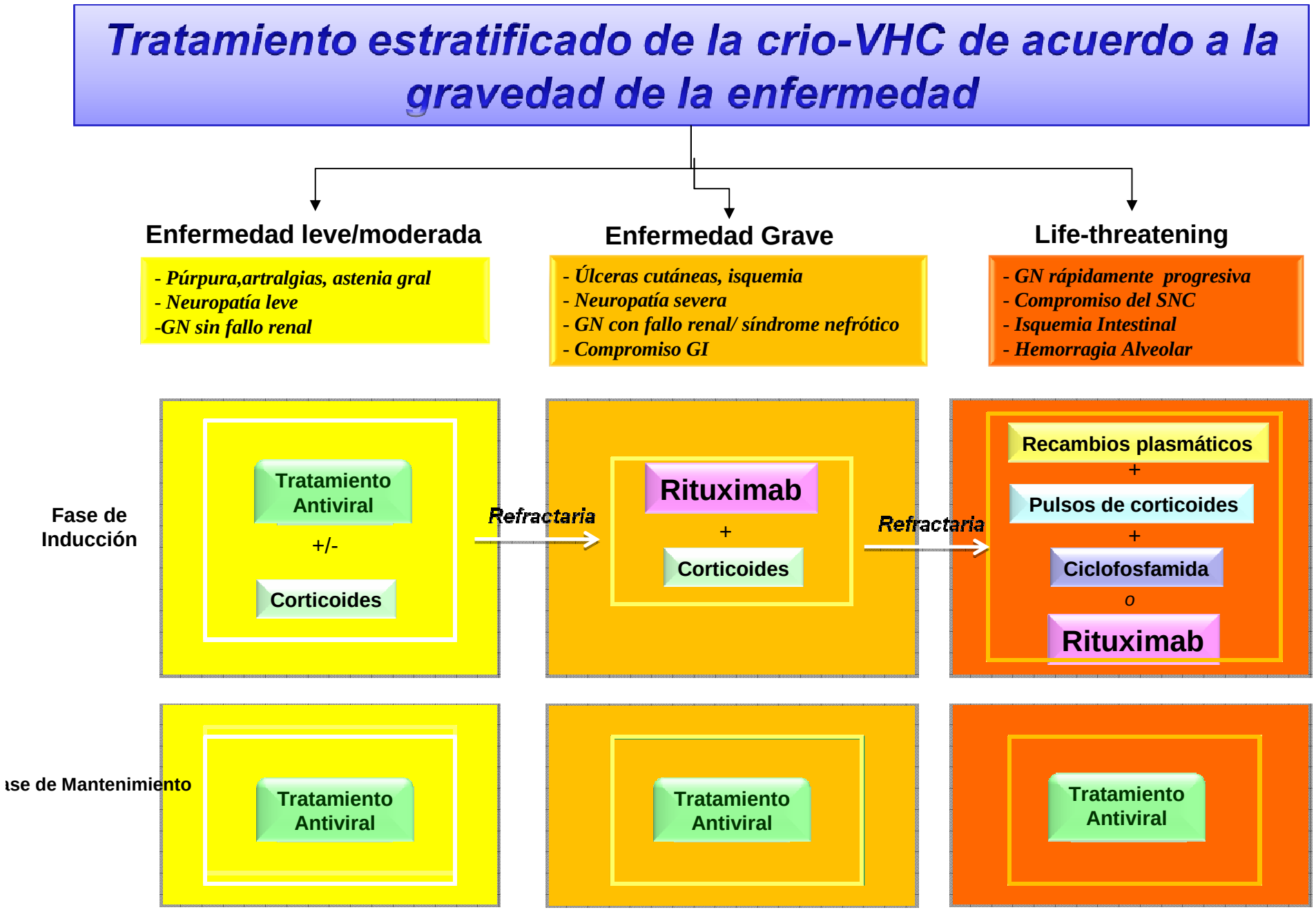
Lancet 2012; 379: 348–60

Published Online August 24, 2011 DOI:10.1016/S0140-6736(11)60242-0

Josep Font Laboratory of Autoimmune Diseases (M Ramos-Casals MD) and Vasculitis Research Unit, Department of Autoimmune Diseases (M C Cid MD), and Department of Internal Medicine (X Bosch MD), Institut Clínic de Medicina I Dermatologia, Hospital Clínic, Institut d'Investigacions

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C and produce organ damage through two main pathways: vascular sludging (hyperviscosity syndrome, mainly in type I cryoglobulinaemia) and immune-mediated mechanisms (principally vasculitis, in mixed cryoglobulinaemia). Cryoglobulinaemia is associated with many illnesses, which can be broadly grouped into infections, autoimmune disorders, and malignancies; the most common cause is infection with hepatitis C virus. Mixed cryoglobulinaemic syndrome is diagnosed when a patient has typical organ involvement (mainly skin, kidney, or peripheral nerve) and circulating cryoglobulins. Cutaneous purpura is the most common manifestation of cryoglobulinaemic vasculitis. The most frequently affected internal organs are the peripheral nerves, kidneys, and joints. The course varies widely and prognosis is influenced by both cryoglobulinaemic damage to vital organs and by comorbidities associated with underlying diseases. More than 90% of cases of cryoglobulinaemia have a known underlying cause; therefore treatment is focused on the cause of the disorder rather than merely symptomatic relief. Studies suggest that both combined or sequential antiviral therapies and targeted biological treatments might be more effective than monotherapy.

Tratamiento estratificado de la crio-VHC de acuerdo a la gravedad de la enfermedad



Expert Opin. Pharmacother. (2013) **14**(3)

Review

EXPERT OPINION

Primary Sjögren syndrome: an update on current pharmacotherapy options and future directions

Pilar Brito-Zerón, Antoni Sisó-Almirall, Albert Bové, Belchin A Kostov & Manuel Ramos-Casals[†]

[†]*Servei de Malalties Autoimmunes, Hospital Clínic, Barcelona, Spain*

Table 4. Ongoing pharmacotherapeutic studies in primary SS (clinicaltrials.gov, accessed October 31, 2012).

Drug	Disease	Intervention	Recruitment	Code
Dexamethasone	Primary Sjögren syndrome	Dexamethasone irrigation of the parotid glands	Recruiting	NCT01316770
Hydroxychloroquine	Dry eyes in patients with primary Sjögren syndrome	Hydroxychloroquine vs placebo	Recruiting	NCT01601028
Low-dose Cyclosporin A	Primary Sjögren syndrome	Cyclosporine A	Recruiting	NCT01693393
Baminercept (lymphotoxin inhibitor)	Sjögren syndrome	Baminercept vs placebo	Recruiting	NCT01552681
Rituximab	Sjögren syndrome	Rituximab	Active, not recruiting	NCT00101829
Rituximab	Sjögren syndrome	Rituximab vs placebo	Active, not recruiting	NCT00740948
Hydroxychloroquine	Primary Sjögren syndrome	Hydroxychloroquine vs placebo	Completed	NCT00632866
Drug 552-02 (Methasulfonate, ENaC inhibitor)	Dry mouth associated with Sjögren syndrome	Drug 552-02 vs placebo	Completed	NCT00852839
Belimumab	Primary Sjögren syndrome	Efficacy and Safety of Belimumab	Completed	NCT01160666
Belimumab	Primary Sjögren syndrome	Efficacy and Safety of Belimumab	Completed	NCT01008982

ENaC: Airway epithelial sodium channels.

Expert Opin. Pharmacother. (2013) **14**(3)

Review

EXPERT OPINION

Primary Sjögren syndrome: an update on current pharmacotherapy options and future directions

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2013

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ENaC: Airway epithelial sodium channels.


Muchas gracias por su atención

[2012] [OP0065] TOLERANCE AND EFFICACY OF RITUXIMAB IN PRIMARY SJOGREN SYNDROME (TEARS): RESULTS OF A RANDOMIZED CONTROLLED TRIAL

V. Devauchelle-Pensec1, X. Mariette2, S. Jousse-Joulin1, J.-M. Berthelot3, A. Perdriger4, E. Hachulla5, X. Puéchal6, V. Le Guern7, J. Sibilia8, J.-E. Gottenberg8, L. Chiche9, V. Goeb10, G. Hayem11, J. Morel12, C. Zarnitsky13, J.-J. Dubost14, J.-O. Pers15, E. Nowak16, A. Saraux1, and the TEARS study group (Institutional grant support from the French Health ministry PHRC 2007) 1Rheumatology and EA 2216, CHU, Brest; 2Rheumatology, CHU Bicêtre, Paris; 3Rheumatology, CHU, Nantes; 4Rheumatology, CHU, Rennes; 5Rheumatology, CHU, Lille; 6Rheumatology, CH, Le Mans; 7Internal medicine, Cochin, Paris; 8Rheumatology, CHU, Strasbourg; 9Internal Medicine, CHU, Marseille; 10Rheumatology, CHU, Rouen; 11Rheumatology, CHU Bichat, Paris; 12Rheumatology, CHU, Montpellier; 13Rheumatology, CH, Le Havre; 14Rheumatology, CHU, Clermont-Ferrand; 15Ea 2216; 16CIC, CHU, Brest, France

Background: Current pharmacological treatments can improve the sicca symptoms but they are unable to modify the course of of primary Sjogren's syndrome (pSS). There is evidence for a critical role of B cells in the pathogenesis of pSS. Both open labelled and small controlled studies suggested the efficacy of Rituximab (RTX) in specific subgroups of pSS.
Objectives: We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of RTX in a large group of patients with active primary Sjögren's syndrome (pSS).
Methods: 122 Patients were assigned to receive either RTX infusions (1g) or placebo (P) at weeks 0 and 2. They were followed up for 24 weeks. All patients fulfilled the new American-European Consensus Group criteria for pSS, had an active disease as assessed by mean values of the 2 highest visual analog scales (VAS) ≥50 evaluating dryness, pain, fatigue and global (disease activity assessed by the patient), and had either a recent (less than 10 years since first clinical sign) and a biologically active pSS [Auto antibodies (SSA or RF) or cryoglobulinaemia, or hypergammaglobulinaemia, or high level of beta 2-microglobulinemia or hypo-complementaemia] or at least one extra-glandular manifestation. The primary end point was an improvement of at least a 30 mm on 2 of 4 VAS between weeks 0 and 24. Secondary end points included values on each VAS separately, the number of tender and swollen joints, the basal salivary flow rate, Schirmer test, the focus score on labial salivary gland biopsy, biological and extra glandular improvement evaluated from baseline to week 24.
Results: 24 of 122 patients (19.5%) had a recent pSS without systemic symptoms, 67 (54.9%) had a recent pSS with systemic signs and 31 (25.4%) had a chronic systemic pSS. Concerning systemic manifestations, 33 (28%) had pulmonary involvement, 63 (53%) articular involvement and 34 (28.5%) parotidomegaly. 113 patients had an evaluation at week 24. 11/53 (20.7%) patients receiving P and 13/60 (21.7%) treated with RTX had a favourable overall response (P=0.9). The 30 points VAS improvement for fatigue and sicca were numerically better in the RTX than in the P group [11/60 (18%) vs 5/53 (9%) (p: 0.16) and 15/60 (25%) vs 6/53 (11%) (p:0.06), respectively] but the differences did not reach significance. 9/54 (16.7%) and 9/61 (14.7%) were considered as improved by physicians in P and RTX group, respectively. The two groups did not differ in term of salivary unstimulated flow rate improvement in both recent and chronic pSS.
Conclusions: This randomized, double blind, placebo controlled study suggest that the efficacy of RTX is not sufficient enough to allow its prescription in a large population of pSS. Further studies are needed to select which subgroups may justify this treatment.

Citation: Ann Rheum Dis 2012;71(Suppl3):75

CONCISE REPORT

Ann Rheum Dis 2012;**0**:1–6. doi:10.1136/annrheumdis-2012-202293

Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry

Jacques-Eric Gottenberg,[1] Gael Cinquetti,[2] Claire Larroche,[3] Bernard Combe,[4] Eric Hachulla,[5] Olivier Meyer,[6] Edouard Pertuiset,[7] Guy Kaplanski,[8] Laurent Chiche,[8] Jean-Marie Berthelot,[9] Bruno Gombert,[10] Philippe Goupille,[11] Christian Marcelli,[12] Séverine Feuillet,[13] Jean Leone,[14] Jean Sibilia,[1] Charles Zarnitsky,[15] Philippe Carli,[16] Stephanie Rist,[17] Philippe Gaudin,[18] Carine Salliot,[17] Muriel Piperno,[19] Adeline Deplas,[20] Maxime Breban,[21] Thierry Lequerre,[22] Pascal Richette,[23] Charles Ghiringhelli,[24] Mohamed Hamidou,[25] Philippe Ravaud,[26] Xavier Mariette,[27] for the Club Rhumatismes et Inflammations and the French Society of Rheumatology

Table 2 Efficacy of rituximab on the various predominant organ involvements

Before rituximab		After rituximab	
Systemic organ involvement	74	Systemic efficacy	44 (59%)
Articular	27		17 (63%)
Nervous system	18		8 (44%)
CNS	6		2 (33%)
Multiple sclerosis-like manifestations	4		0
Transverse myelitis	1		1
Anxiety/depression	1		1
PNS	12		6 (50%)
Mixed sensorimotor polyneuropathy	6		3
Sensory painful neuropathy (including sensory ataxic neuropathy)	4		2
Mononeuritis multiplex	2		1
Pulmonary	9		7 (78%)
Vasculitis	8		5 (62.5%)
Renal	6		5 (83.3%)
Muscular	3		0 (0%)
Haematological	2		2 (100%)
Autoimmune pancreatitis	1		1 (100%)
Glandular involvement	4	Glandular efficacy	2 (50%)
Hypertrophy of lachrymal glands	1		0
Sclera vasculitis	1		0
parotid hypertrophy	2		2
ESSDAI before rituximab (n=72)	11.0 (2–31)	ESSDAI after rituximab (n=72)	7.5 (0–26)
Corticosteroids (mg/day) (n=29)	17.6	Corticosteroids after rituximab (n=23)	10.8

WS8-3 Salivary gland lymphocyte pattern associated with response to belimumab in primary Sjögren's syndrome: results of the BELISS study

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Purpose: To address changes in labial salivary gland (LSG) inflammation after Belimumab (BAFF inhibitor) in pSS patients and identify predictor of response to treatment.

Methods: Patients were included in 2identical studies in 2 European centers. Patients fulfilled AECG criteria, were anti-SSA/SSB positive and had at the time of inclusion either systemic complications or early disease (<5 yrs of symptoms), or the presence of biomarker of B-cell activation. Minor labial salivary gland (LSG) biopsies (W0 and W28) of the 15 patients from the French center were analyzed .Response to treatment was defined according to a composite primary end-point and systemic response according to a decrease of the ESSDAI>3 points.

Results: Lymphocytic sialadenitis was observed in 12 (80%) patients, before treatement and 7 (47%) at w28 (p=0.07). The median focus score decreased from 1.6 to 0.5 (p=0.39) and Chisholm score from 4 to 2 (p=0.01). Median B-cell /T cell ratio decreased (p=0.055). Before treatment, BAFF staining was detected in 11/14 (78.6%) patients, and in 7/14 (50.0%) after belimumab (p=0.07). The median percentage of BAFF positive cells in foci decreased from 27.5% to 5% (p=0.03). NK cells infiltrate was predominantly located in interstitium rather than in foci (p=0.0003), and did not change after belimumab.8/15 patients (53%) achieved the primary end-point, and 6 (40%) patients had a significant systemic improvement. The only histological parameter associated with response to belimumab (p=0.028) and improvement of systemic disease activity (p=0.019) was the NK infiltrate in periphery of the foci which was lower in responders than in non-responders () Also, there was a trend to observe lower focus score in responders than in non responders (p=0.08). The rate of salivary BAFF-positive cells was not associated with the response. Dosage of serum BAFF levels and their association to response to belimumab will be presented at the meeting.

Conclusion: After belimumab therapy, there was a tendency in favour of a decrease of lymphocytic infiltration, and of B-cell/T-cell ratio within LSG. Also the percentage of BAFF positive cells significantly decreased, suggesting either a decrease of the BAFF expressing cells, or a decrease in B cells. The patients with a higher number of foci and a higher number of NK cells at the periphery of the foci had a poor response to Belimumab, suggesting that these forms of the disease may be more linked to the IL-12/IFNg TH1/ NK axis and less linked to BAFF/B-cell axis than others

COMUNICACION ORAL

Abstract#: 2555

Results of the Beliss Study, the First Open Phase 2 Study of Belimumab in Primary Sjogren's Syndrome

Presenter: Xavier Mariette: Université Paris-Sud

Background/Purpose:

The BAFF (or BLyS) cytokine plays a key role in pathogenesis of primary Sjogren's syndrome (pSS). Belimumab, the first biological treatment inhibiting soluble BAFF, has proved its effectiveness and has been recently approved in systemic lupus. Lupus and pSS share a lot of pathogenic mechanism including interferon signature and BAFF involvement. Thus we run the first open label study of belimumab in pSS patients.

Methods:

Patients were included in 2 simultaneous and identical studies in 2 European Centres. Patients had to fulfill AECG criteria, to be anti-SSA/SSB positive and had to have at the time of inclusion either systemic complications, early disease (≤ 5 years), or the presence of at least one other biomarker of B-cell activation (increase in IgG, free light chains or of beta2-microglobulin, decrease of C4, presence of cryoglobulinemia or monoclonal component).The patients were treated with belimumab 10 mg/kg W0, W2, W4 and then every four weeks until W24.

The primary end-point was evaluated at W28 and consisted of improvement of 2 of the 5 following items : 1- ≥ 30% reduction of patient's dryness VAS, 2- ≥ 30% reduction of patient's fatigue VAS, 3- ≥ 30% reduction of patient's musculoskeletal pain VAS, 4- ≥ 30% reduction of physician's systemic activity VAS , 5- ≥ 25% reduction of any of the following B cell activation biomarkers (free light chains of immunogobulins, beta2-microglobulin, monoclonal component, cryoglobulinemia, IgG) or ≥ 25% C4 increase

Results:

Thirty patients were included, 15 in each center (all female, mean age = 49.5 yrs ±16.5, mean disease duration = 5.7 yrs ± 5.6). 15 patients had systemic complications, 11 had early disease and 20 had at least one other biomarker of B-cell activation. 19/30 (63%) reached the primary end-point. For each individual component the response was as follows: VAS dryness: 10 (33%), VAS fatigue: 7 (23%), VAS pain: 7 (23%), VAS physician's systemic activity: 12 (40%), biological component: 18 (60%). The percentage of responders was 8/11 (73%) in early disease and 7/15 (47%) in systemic disease.

The ESSDAI (EULAR Sjogren's Syndrome Disease Activity Index) score decreased from 8.8±7.39 to 5.59±5.49 ($p<0.0001$). The ESSPRI (EULAR Sjogren's Syndrome Patients Reported Index) score decreased from 6.44 ±1.11 to 5.56 ($p=0.01$). There was no significant change of salivary flow (0.62±1.23 to 0.75±1.23;$p=0.43$) and Schirmer test (4.09±7.23 to 4.72±8.08; $p=0.17$).

The treatment induced significant changes of some biological data: serum IgG from 20.92±10.25 to 18.53 ±7.21 ($p<0.0001$); serum IgA from 4.08 ±3.02 to 3.23 ±1.87 ($p=0.001$), kappa free light chain from 33.15±24.65 to 25.59 ±23.42 ($p<0.0001$), lambda free light chain from 28.31 ±16.59 to 20.85 ±12.24 ($p<0.0001$), rheumatoid factor from 146 ±174 to 97 ±91 ($p<0.0001$).

Concerning safety, we observed 1 severe adverse event which was a pneumococcus meningitis after 6 infusions of the drug. This patient, who was responder to belimumab, recovered completely without any sequellae.

Conclusion:

Results of this first open phase 2 study of belimumab in pSS patients are very encouraging and justify the realization of randomized control trials with the drug in selected populations of patients with pSS.

Abstract#: 2189

Efficacy of Belimumab On Non-Malignant Parotid Swelling and Systemic Manifestations of Sjögren's Syndrome: Results of the Beliss Study

Presenter: Salvatore De Vita: Rheumatology Clinic, DSMB, University of Udine

Background/Purpose: to report the effects of anti-BAFF/BLyS antibody belimumab (BEL) on the different ogan manifestations of primary Sjögren's syndrome (pSS), by evaluating the ESSDAI score and the single ESSDAI domains.

Methods: Thirty patients (15+15) with pSS (positive classification criteria and positive anti-SSA/SSB antibodies) were investigated in two European Centres to assess the efficacy and safety of BEL in pSS. They were all females (49.5±16.5 years). At least one of the following items was needed for enrolment: a) parotid swelling and/or systemic involvement; b) objective sicca with at least one laboratory sign of B-cell hyperactivation in serum (increased IgG, increased free Ig light chains, increased beta2-microglobulin, decreased C4, monoclonal gammopathy or cryoglobulinemia); c) recent onset of sicca symptoms (<5 years). Belimumab 10 mg/kg was administered intravenously on days 0, 14, 28 and then every 28 days through 48 wks, with a final evaluation at wk52, and after drug suspension. Concomitant therapies were left unchanged.

Results: 29/30 patients completed the 28 wk infusions, and 1 case with lymphoma and cryoglobulinemic vasculitis was withdrawn at w12 for worsening. Wk52 data are available in one Centre.
At wk 28, the ESSDAI score decreased from a median of 7 (1-33) to 4 (0-23) (p= 0.0001, Wilcoxon) with a decrease of ≥ 3 points in 14/29 (48.3%) and of ≥ 2 points in 18/29 (62.1%). The following domains mainly contributed to the ESSDAI score at baseline: glandular, biological, lymphadenopathy, articular, haematological and pulmonary. Activity (low-moderate-high) was present (baseline vs. wk28) in these domains as follows: glandular 15/30 vs. 7/29; biologic 27/30 vs. 20/29; lymphadenopathy 9/30 vs. 3/29; articular 9/30 vs. 3/29; haematological 5/30 vs. 3/29; pulmonary 4/30 vs. 5/29.
At wk 28 the glandular domain improved in 10/13 (76.9%) patients with non-malignant parotid swelling (confirmed by biopsy, whenever possible), while no improvement occurred in 2/2 patients with parotid low-grade lymphoma (stage IE). Data available at wk52 showed persistent disappearance of swelling in 4/5 patients and further amelioration in 1/5. After BEL suspension parotid swelling relapsed in 2/5 of these responders (4 and 14 months later).
Overall, 13/15 patients completed the trial at w52 in one Centre. The median ESSDAI at wk52 was 2 (0-12) [vs. 3 (1-16) at w28 vs. 8 (2-33) at baseline; p=0.003, wk52 vs. baseline, Wilcoxon)], with activity in the ESSDAI domains (baseline vs. wk28 vs. wk52) as follows: glandular 7/15 vs. 2/14 vs. 2/13; biologic 13/15 vs. 11/14 vs. 10/13; lymphadenopathy 8/15 vs. 3/14 vs. 0/13; articular 4/15 vs. 0/14 vs. 0/13; 1/15 vs. 1/14 vs. 0/13; pulmonary 2/15 vs. 2/14 vs. 2/13.
At wk52 we no additional side effects, if compared to wk28, were observed in the available cases.

Conclusion: Belimumab proved to be beneficial for non malignant glandular swelling in pSS. Recently, BAFF serum level were significantly increased in this subset of patients (Quartuccio L. et al., Rheumatology 2012, in press), supporting the rationale and the results observed. Other systemic features of pSS might also improve with BEL therapy. A controlled randomized trial is advisable.

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 Rosenzwajg,[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 μg/week, n = 5; or 2b, 1.5 μg/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/m^2 (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

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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 ± 4.7	8.4 ± 4.7	5.4 ± 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	5 (5.4)	2 (3.6)	3 (7.9)	.70
Cirrhosis	1 (1.1)	—	1 (2.6)	
Liver carcinoma	3 (3.2)	2 (3.6)	1 (2.6)	
Unknown	1 (1.1)	—	1 (2.6)	

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 843–853
DOI 10.1002/art.34331

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. Can
C. Naclerio,[7] A. Tavoni,[8] M. Pietrogrande,[9] C. Ferri,[10] M. T. Mascia,[10] P. Masc
A. Zabotti,[1] M. Maset,[1] D. Roccatello,[11] A. L. Zignego,[12] P. Pioltelli,[13] A. Gabri
D. Filippini,[15] O. Perrella,[16] S. Migliaresi,[17] M. Galli,[18] S. Bombardieri,[8] and G. M

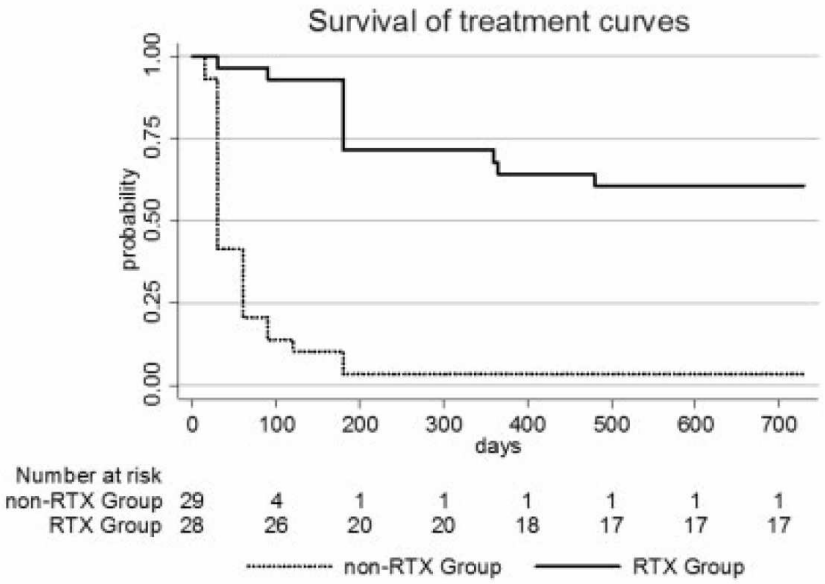

Figure 2. Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.

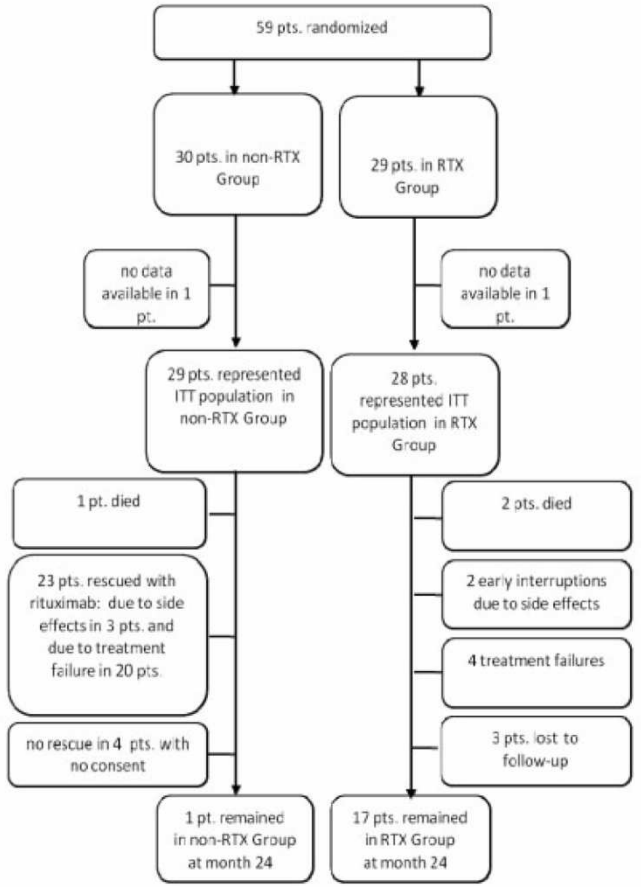

Figure 1. Flow chart showing the distribution of study patients from randomization, over the subsequent course of the study, and to completion of the study in patients randomized to receive rituximab (RTX) or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis. ITT = intent-to-treat.

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Table 1. Characteristics of the patients who were randomized into the study, by treatment group*

	All patients (n = 57)	Non-RTX group (n = 29)	RTX group (n = 28)
Age, mean ± SD years	63.27 ± 10.78	63.0 ± 10.6	62.85 ± 11.36
Sex, no. female/male	46/11	22/7	24/4
No. HCV positive/no. tested	53/57	28/29	25/28
Antiviral therapy failure/not indicated	28/25	14/14	14/11
BVAS at baseline, mean ± SD	10.51 ± 4.49	9.55 ± 3.64	11.89 ± 5.42
No. with skin ulcers	7	2	5
No. with nephritis	17	10	7
No. with neuropathy	33	17	16
Rheumatoid factor, mean ± SD IU/ml	528.55 ± 840.12	556.58 ± 784.04	501.38 ± 891.81
C4, mean ± SD mg/dl	6.62 ± 8.05	6.81 ± 7.37	6.27 ± 8.7

* There were no significant differences between the two treatment groups. RTX = rituximab; HCV = hepatitis C virus; BVAS = Birmingham Vasculitis Activity Score.

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 835–842
DOI 10.1002/art.34322

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

Michael C. Sneller,[1] Zonghui Hu,[1] and Carol A. Langford[2]

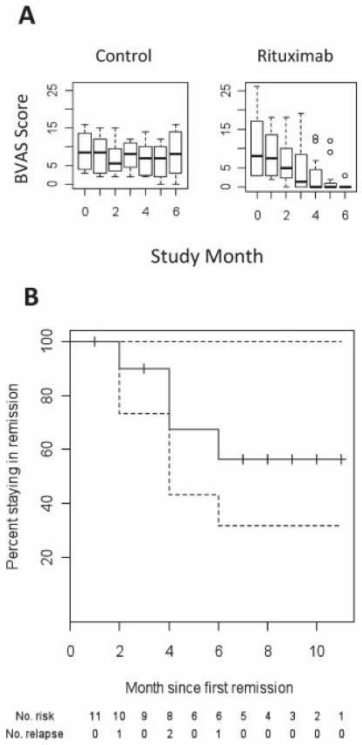

Figure 1. Birmingham Vasculitis Activity Score (BVAS) scores and duration of remission in patients with hepatitis C virus–associated mixed cryoglobulinemic vasculitis randomized to receive rituximab or control therapy (maintenance or increase in immunosuppressive therapy) (n = 12 per group). **A,** BVAS scores in the two treatment groups during the 6-month study period. Data are shown as box plots. The horizontal line within each box indicates the median, the bottom and top lines of the box indicate the 25th and 75th quartiles, respectively, the whiskers show the maximum and minimum values within 1.5 interquartile ranges from the 25th and 75th quartiles, respectively, and the circles represent values outside the range and are considered outliers. **B,** Kaplan-Meier curve for the duration of remission among patients in whom remission was achieved with rituximab therapy. Solid line indicates the percentage of patients whose disease remained in remission; broken lines indicate the 95% confidence intervals. Only a single patient in the control group achieved remission (data not plotted).

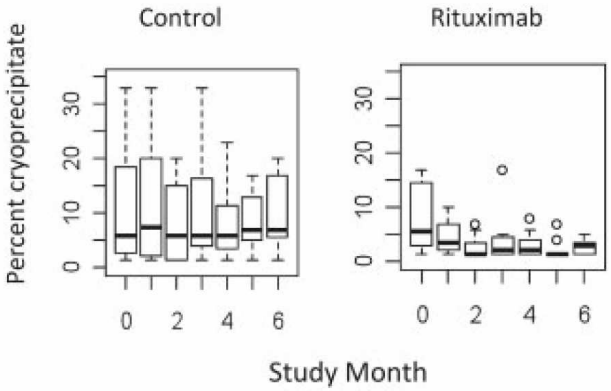

Figure 2. Cryoglobulin levels in patients with hepatitis C virus–associated mixed cryoglobulinemic vasculitis randomized to receive rituximab or control therapy (maintenance or increase in immunosuppressive therapy) (n = 12 per group). Cryoglobulin levels are expressed as a percentage of cryoprecipitate during the 6-month study period (normal <3%). Data are shown as box plots. The horizontal line within each box indicates the median, the bottom and top lines of the box indicate the 25th and 75th quartiles, respectively, the whiskers show the maximum and minimum values within 1.5 interquartile ranges from the 25th and 75th quartiles, respectively, and the circles represent values outside the range and are considered outliers.

Efficacy assessments. *Primary end point.* The primary end point of the study was the number of patients whose disease was in remission at study month 6. Ten of the 12 patients in the rituximab group (83.3% [95% CI 51.6–97.9]) reached the primary end point, as compared with 1 of the 12 patients in the control group (8.3% [95% CI 2.0–38.6]), indicating significantly higher remission with rituximab treatment ($P < 0.001$). Disease