



HAL
open science

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

David Saadoun, Amine Ghembaza, Sebastien Riviere, Arsene Mekinian, Jonathan Boutemy, Gaelle Leroux, Fanny Domont, Helene Maillard, Mathieu Vautier, Patrice Cacoub

► To cite this version:

David Saadoun, Amine Ghembaza, Sebastien Riviere, Arsene Mekinian, Jonathan Boutemy, et al.. Rituximab plus belimumab in non-infectious refractory cryoglobulinemia vasculitis: A pilot study. Journal of Autoimmunity, 2021, 116, pp.102577 -. 10.1016/j.jaut.2020.102577 . hal-03493570

HAL Id: hal-03493570

<https://hal.science/hal-03493570v1>

Submitted on 2 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Rituximab plus Belimumab in non-infectious refractory cryoglobulinemia vasculitis: a pilot study.

Running head: Belimumab in cryoglobulinemia vasculitis

D. Saadoun^{1*}, A. Ghembaza^{1*}, S. Riviere², A. Mekinian², J. Boutemy³, G. Leroux¹, F. Domont¹, H. Maillard⁴, M. Vautier¹, P. Cacoub¹

1. Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France, Centre national de références Maladies Autoimmunes et systémiques rares et Centre national de références Maladies Autoinflammatoires. UPMC Université Paris 6, INSERM, UMR S 959, Immunology-Immunopathology- Immunotherapy (I3); F-75005, Paris, France;

2. Assistance Publique - Hôpitaux de Paris (AP-HP), Hôpital Saint-Antoine, Service de médecine interne, 75571 Paris Cedex 12, France.

3. Departments of Internal Medicine and Clinical Immunology, CHU de Caen, Caen, France, 14000.

4. Service de Médecine Interne, Centre de Référence des maladies systémiques rares du Nord et Nord-Ouest, CHU Lille, France.

*co-first author

Address correspondence to: Pr David Saadoun, MD, PhD

Département de Médecine Interne et d'Immunologie Clinique, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.

E-mail: david.saadoun@aphp.fr, Phone: +33(0)142178042, Fax: +33(0)142178080.

Word count: 1757

Tables: 2

Competing interests and funding info: The authors have no conflict of interest or financial support or other benefits from commercial sources for the work reported on in the manuscript.

Abstract

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

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

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

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

Keywords: cryoglobulinemia; vasculitis; biologic; rituximab; belimumab.

1. Introduction

Mixed cryoglobulinaemic vasculitis (CV) can cause manifestations ranging from purpura, arthralgia and constitutional symptoms to more serious lesions with skin ulcers, neurological and renal involvement. Immunosuppression has been traditionally considered as the first line intervention in severe non-infectious CV. Rituximab is the most widely used biologic agent for the management of CV. It has a safer profile than conventional immunosuppressants[1], and its use has substantially changed the natural history of CV by inducing long term remission[2]. However, CV remains a challenging disease to manage owing to frequent relapses and treatment failure[3]. Studies are needed to identify rescue treatments for refractory CV patients.

B-Lymphocyte stimulator (BLYS), also known as B cell activating factor (BAFF), is overexpressed in patients with CV[4]. Thus, a combination of rituximab and belimumab may result in improvements in CV. Here we report our experience of rituximab plus belimumab in patients with refractory CV.

2. Methods

We reviewed the chart of four consecutive patients with CV seen in Paris (Pitié Salpêtrière hospital and Saint Antoine hospital), Caen and Lille, in France between 2017 and 2020. CV was defined as serum cryoglobulinemia associated with the triad of purpura-arthralgia-asthenia sometimes associated with renal and/or neurologic involvement. Refractory cryoglobulinaemic vasculitis was defined as a clinical picture that does not improve within 4–6 weeks after the initial treatment, or that provides a < 50 % improvement after 12 weeks, or that shows chronic persistent manifestations after > 12 weeks of treatment. Belimumab was administered as intravenous infusions at a dose of 10 mg/kg on days 0, 14, 28 and then every

month in association with rituximab. Demographic, clinical, laboratory characteristics, treatment modalities and outcomes were recorded.

The study was conducted in compliance with the Declaration of Helsinki, no formal consent from participants was required according to local ethics committees. Belimumab was prescribed off-label after validation in a multidisciplinary meeting. All patients were orally informed before receiving belimumab.

3.Results

Table 1 and **2** summarizes main clinical and laboratory data and outcome of the four CV patients.

Case 1: A 71-year-old woman with a prior medical history of monoclonal gammopathy was diagnosed with CV in 2011 based on palpable purpura on lower extremities, polyneuropathy, type II monoclonal IgM Kappa serum cryoglobulinemia at 0.59 g/l and low complement C4 level at 0.08 g/l. The patient was successfully treated with four consecutive rituximab weekly infusions of 375 mg/m² and achieved complete resolution of her symptoms. In August 2018, purpura relapsed and polyneuropathy worsened. She was then treated with another infusion of rituximab 500 mg followed by intravenous administration of belimumab at 10 mg/kg on days 0, 14, 28 and then every month thereafter. Eight weeks after treatment, the patient had improvement of her neurologic symptoms and complete resolution of the cutaneous purpura. Laboratory test results showed normal complement C4 level (0.27 g/l), and negative cryoglobulinemia. This positive response was maintained during all treatment period. No side effect was reported.

Case 2: A 75-year-old woman with a medical history of primary Sjögren syndrome presented recurrent palpable purpura, arthralgia, myalgia, and polyneuropathy revealing CV. Laboratory investigations showed type II monoclonal IgM Kappa serum cryoglobulinemia, and low

complement C4 level at 0.02 g/l. Underlying infections and lymphoproliferative disorders were excluded. Between 2008 and 2017, she received multiple therapeutic regimens, including corticosteroids (1 mg/kg/day), cyclophosphamide (six cycles), azathioprine and rituximab (two bi-weekly infusions of 1000 mg intravenously in December 2014 and in September 2018). In 2018, CV relapsed leading to reintroduction of four weekly infusions of 375 mg/m² rituximab. Belimumab (at 10 mg/kg at days 0, 14, 28 and then every 28 days intravenously) was administered along with corticosteroids (20 mg/day) because of purpura and arthralgia recurrence. After ten infusions, belimumab yielded a good clinical response with complete resolution of arthralgia. However, some transient episodes of purpura were noted and the patient developed recurrent urinary tract infections.

Case 3: A 74-year-old woman was admitted to the emergency department because of palpable purpura with necrotic lesions on lower limbs, arthralgia and acute renal failure with nephritic range proteinuria (1.6 g/day) and microscopic hematuria. A renal biopsy was performed and showed membranoproliferative glomerulonephritis. The patient was diagnosed with CV. Type II monoclonal IgM Kappa cryoglobulinemia was positive and with low C4 complement level. Infectious (hepatitis B, hepatitis C and HIV), autoimmune and lymphoproliferative causes were excluded. The patient underwent seven plasma exchange sessions combined with rituximab and corticosteroids. Maintenance Rituximab infusions at 500mg every 6 months were given. Her kidney function recovered as serum creatinine returned to baseline level. In January 2017, due to purpura and skin ulcerations relapse, intravenous Belimumab 10 mg/kg on days 0, 14, 28 and then every month was added along with rituximab 500mg leading to the complete resolution of the cutaneous purpura and arthralgia. Nevertheless, the patient developed osteitis of the left hallux sesamoid bones and urinary tract infection, which were successfully treated with antibiotics. Three years after belimumab initiation, the patient

remained symptom-free, with negative cryoglobulinemia, normal serum creatinine and C4 level.

Case 4: A 65-year-old woman with a medical history of hepatitis C virus (HCV) infection successfully treated with sofosbuvir and daclatasvir was admitted because of purpura, arthralgia and polyneuropathy, which occurred despite a sustained virologic response for HCV. Electrophysiological studies demonstrated lower limbs sensorimotor axonal polyneuropathy. IgM-K type II cryoglobulinemia was positive at 5.2 g/l. Autoimmune and lymphoproliferative causes were excluded. CV was diagnosed and the patient received four weekly infusions of rituximab (375 mg/m²) and two cycles of rituximab 500mg as maintenance therapy every six months. However, purpura relapsed and belimumab was added at 10 mg/kg on days 0, 14, 28 and then every month along with rituximab 500mg. By the eighteenth month of treatment, the patient had sustained clinical remission, with resolution of purpura and arthralgia, clinical stabilization of the neuropathy, and decreased level of cryoglobulins. Belimumab was well tolerated without evidence of infectious complications.

4. Discussion

CV is a major cause of morbidity and mortality, especially in elderly patients with severe renal impairment[5]. Prompt treatment is mandatory to relieve patient's symptoms and avoid long-term complications. Treatments strategies are mainly based on the underlying cause and disease severity. To date, the available therapeutic options included antiviral therapy (in case of hepatitis C), rituximab, immunosuppressants, and plasmapheresis[6]. Despite these strategies, CV relapse is noted in up to 40% of patients[3]. Moreover, side effects, mainly infections and drug toxicity, are a serious concern.

BAFF, a member of tumor necrosis factor superfamily, is expressed by monocytes, dendritic cells, T cells, and neutrophils. It promotes B lymphocytes differentiation, proliferation and

survival and thus increases immunoglobulin secretion[7]. BAFF up-regulation may favor both autoimmunity and B-cell lymphoproliferation. This finding has been strengthened by BAFF overexpression found in many autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome, and its related B-cell lymphoma[8]. In patients with hepatitis C, BAFF was significantly overexpressed in patients with mixed cryoglobulinemia than those without which lead to presume that suppression of BAFF may be a promising therapeutic option for patients with CV[9,10]. In transgenic mouse strain that expresses the human CD20 antigen on B cells, while splenic B cells subset were resistant to anti-CD20 monotherapy, targeting both CD20 and BAFF resulted in a marked decrease in B cell number[11].

Belimumab is a human anti-BAFF monoclonal IgG antibody that inhibits BAFF binding to its receptor. In a case report, monotherapy with rituximab first then followed by belimumab infusions were ineffective in a patient with Sjögren syndrome complicated with low-grade parotid B-cell lymphoma and CV. However, healing of a refractory skin ulcer, normalization of C4 and disappearance of cryoglobulin were observed when rituximab was administered shortly (six weeks) after belimumab infusions[12]. An open label study, assessing the efficacy and the safety of belimumab in 30 patients with primary Sjögren syndrome, showed that in three patients with positive cryoglobulinemia at baseline, circulating cryoglobulins disappeared at the end of follow-up[13].

The use of the association of rituximab plus belimumab in patients with CV is based on data from SLE patients with the hypothesis that decreasing the number of naïve B-cells after complete depletion could be an option in controlling disease activity.

In fact, BAFF levels have been consistently described as increased after B-cell depletion via anti-CD20[14]. Furthermore, patients who relapsed after rituximab administration were more likely to have greater BAFF levels[14]. Thus, dual therapy with rituximab plus belimumab

provides an opportunity to target the surge in circulating BAFF levels after B-cell depletion, thereby minimizing the survival of autoreactive B cells.

In a Phase 2, single-arm, open-label proof-of-concept, study including 15 patients with severe, refractory SLE, dual therapy with rituximab plus belimumab showed encouraging results. This effect was more prominent in patients with prolonged suppression of autoreactive B cells[15]. These findings support the potential benefit of dual B-cell immunomodulation, also known as “Synergetic B-cell immunomodulation” over individual anti-CD20 depletion or BAFF blockade and pave the way for the use of this dual therapy in patients with CV, especially those with refractory forms. Recently, Chevalier et al. reported a good response to rituximab followed by belimumab administered as a 200 mg subcutaneous injection every week, in three patients with primary Sjögren syndrome complicated by CV[16].

In our case series, belimumab along with rituximab improved markedly the patient's symptoms after failure of several immunosuppressants including rituximab. This treatment combination led to complete resolution of cutaneous and/or articular manifestations in three out of four patients, polyneuropathy stabilized in two patients and improved in another. However, two patients who previously received multiple lines of immunosuppressive therapy, and presented hypogammaglobulinemia, experienced recurrent infections. Patients two and three experienced recurrent urinary tract infections that were well controlled with adapted antibiotics. Patient three developed severe hypogammaglobulinemia with soft tissue infections that required hospitalization with intravenous antibiotic administration along with immunoglobulin replacement therapy. In a previous report of 15 SLE patients treated with dual B-cell immunomodulation, serious and minor infections occurred in three and eight

patients, respectively[15]. More recently, a phase II clinical trial, including 43 SLE patients who were randomized to receive prednisone, cyclophosphamide and rituximab with or without additional belimumab, showed no significant differences between the two groups with respect to serious infections after a 48 week follow-up period[17].

Well-conducted randomized controlled studies should be conducted to elucidate the effect of that combination therapy in patients with CV.

In refractory cryoglobulinemic vasculitis, belimumab could represent a promising option in combination with rituximab. This treatment showed a good efficacy in our experience. However, patients should be closely monitored to avoid serious infections because of profound B cell depletion, especially in patients who have received multiple lines of immunosuppressive therapy.

Declaration of interest

Nothing to declare

References:

- [1] M.C. Sneller, Z. Hu, C.A. Langford, A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis, *Arthritis Rheum.* 64 (2012) 835–842. <https://doi.org/10.1002/art.34322>.
- [2] L. Quartuccio, F. Zuliani, L. Corazza, P. Scaini, R. Zani, M. Lenzi, A. Tavoni, M. Sebastiani, S. Baldovino, T. Urraro, F. Saccardo, C. Sbreglia, C. Mazzaro, P. Pioltelli, P. Fraticelli, D. Filippini, A. Gabrielli, O. Perrella, S. Scarpato, D. Roccatello, A.L. Zignego, C. Ferri, S. Bombardieri, M. Pietrogrande, G. Monti, M. Galli, S. De Vita, Retreatment regimen of rituximab monotherapy given at the relapse of severe HCV-related cryoglobulinemic vasculitis: Long-term follow up data of a randomized controlled multicentre study, *J. Autoimmun.* 63 (2015) 88–93. <https://doi.org/10.1016/j.jaut.2015.07.012>.
- [3] P. Cacoub, A. Delluc, D. Saadoun, D.A. Landau, D. Sene, Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand?, *Ann. Rheum. Dis.* 67 (2008) 283–287. <https://doi.org/10.1136/ard.2006.065565>.
- [4] M. Fabris, L. Quartuccio, S. Sacco, G. De Marchi, G. Pozzato, C. Mazzaro, G. Ferraccioli, T.S. Migone, S. De Vita, B-Lymphocyte stimulator (BLyS) up-regulation in mixed cryoglobulinaemia syndrome and hepatitis-C virus infection, *Rheumatology (Oxford)*. 46 (2007) 37–43. <https://doi.org/10.1093/rheumatology/ke1174>.
- [5] D. Sansonno, V. De Re, G. Lauletta, F.A. Tucci, M. Boiocchi, F. Dammacco, Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20, *Blood*. 101 (2003) 3818–3826. <https://doi.org/10.1182/blood-2002-10-3162>.
- [6] E. Muchtar, H. Magen, M.A. Gertz, How I treat cryoglobulinemia, *Blood*. 129 (2017) 289–298. <https://doi.org/10.1182/blood-2016-09-719773>.
- [7] B. Nardelli, O. Belvedere, V. Roschke, P.A. Moore, H.S. Olsen, T.S. Migone, S. Sosnovtseva, J.A. Carrell, P. Feng, J.G. Giri, D.M. Hilbert, Synthesis and release of B-lymphocyte stimulator from myeloid cells, *Blood*. 97 (2001) 198–204. <https://doi.org/10.1182/blood.v97.1.198>.
- [8] G.S. Cheema, V. Roschke, D.M. Hilbert, W. Stohl, Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases, *Arthritis Rheum.* 44 (2001) 1313–1319. [https://doi.org/10.1002/1529-0131\(200106\)44:6<1313::AID-ART223>3.0.CO;2-S](https://doi.org/10.1002/1529-0131(200106)44:6<1313::AID-ART223>3.0.CO;2-S).
- [9] D. Sène, N. Limal, P. Ghillani-Dalbin, D. Saadoun, J.-C. Piette, P. Cacoub, Hepatitis C virus-associated B-cell proliferation--the role of serum B lymphocyte stimulator (BLyS/BAFF), *Rheumatology (Oxford)*. 46 (2007) 65–69. <https://doi.org/10.1093/rheumatology/ke1177>.
- [10] D.-A. Landau, M. Rosenzweig, D. Saadoun, D. Klatzmann, P. Cacoub, The B lymphocyte stimulator receptor-ligand system in hepatitis C virus-induced B cell clonal disorders, *Ann. Rheum. Dis.* 68 (2009) 337–344. <https://doi.org/10.1136/ard.2007.085910>.
- [11] Q. Gong, Q. Ou, S. Ye, W.P. Lee, J. Cornelius, L. Diehl, W.Y. Lin, Z. Hu, Y. Lu, Y. Chen, Y. Wu, Y.G. Meng, P. Gribling, Z. Lin, K. Nguyen, T. Tran, Y. Zhang, H. Rosen, F. Martin, A.C. Chan, Importance of cellular microenvironment and circulatory dynamics in B cell immunotherapy, *J. Immunol.* 174 (2005) 817–826. <https://doi.org/10.4049/jimmunol.174.2.817>.
- [12] S. De Vita, L. Quartuccio, S. Salvin, L. Picco, C.A. Scott, M. Rupolo, M. Fabris, Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy, *Clin. Exp. Rheumatol.* 32 (2014) 490–494.

- [13] X. Mariette, R. Seror, L. Quartuccio, G. Baron, S. Salvin, M. Fabris, F. Desmoulins, G. Nocturne, P. Ravaud, S. De Vita, Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study, *Ann. Rheum. Dis.* 74 (2015) 526–531. <https://doi.org/10.1136/annrheumdis-2013-203991>.
- [14] L.M. Carter, D.A. Isenberg, M.R. Ehrenstein, Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus, *Arthritis Rheum.* 65 (2013) 2672–2679. <https://doi.org/10.1002/art.38074>.
- [15] T. Kraaij, E.J. Arends, L.S. van Dam, S.W.A. Kamerling, P.L.A. van Daele, O.W. Bredewold, A. Ray, J.A. Bakker, H.U. Scherer, T.J.W. Huizinga, T.J. Rabelink, C. van Kooten, Y.K.O. Teng, Long-term effects of combined B-cell immunomodulation with rituximab and belimumab in severe, refractory systemic lupus erythematosus: 2-year results, *Nephrol Dial Transplant.* (n.d.). <https://doi.org/10.1093/ndt/gfaa117>.
- [16] K. Chevalier, R. Belkhir, R. Seror, X. Mariette, G. Nocturne, Efficacy of a sequential treatment by anti-CD 20 monoclonal antibody and belimumab in type II cryoglobulinaemia associated with primary Sjögren syndrome refractory to rituximab alone, *Ann. Rheum. Dis.* (2020). <https://doi.org/10.1136/annrheumdis-2020-217481>.
- [17] Y. Atisha- Fregoso, S. Malkiel, K.M. Harris, M. Byron, L. Ding, S. Kanaparthi, W.T. Barry, W. Gao, K. Ryker, P. Tosta, A.D. Askanase, S.A. Boackle, W.W. Chatham, D.L. Kamen, D.R. Karp, K.A. Kirou, S.S. Lim, B. Marder, M. McMahon, S.V. Parikh, W.F. Pendergraft, A.S. Podoll, A. Saxena, D. Wofsy, B. Diamond, D.E. Smilek, C. Aranow, M. Dall'era, CALIBRATE: A Phase 2 Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis, *Arthritis & Rheumatology.* n/a (n.d.). <https://doi.org/10.1002/art.41466>.

Table 1. Main demographic, clinical characteristics and treatment of CV patients treated with belimumab.

Patients	Cryoglobulin type/composition	Cryoglobulinemia etiology	Treatment before belimumab	Clinical manifestations at diagnosis			
				Skin	Joints	Neurologic	GN
1	II IgM/Kappa	essential	RTX	Purpura	No	polyneuropathy	No
2	II IgM/Kappa	SS	Cs,Cyc,AZA, RTX	Purpura	Arthralgia	polyneuropathy	No
3	II IgM/Kappa	essential	Cs, PE, RTX	Purpura, skin ulcer	Arthralgia	No	Yes
4	II IgM/Kappa	HCV	RTX,Cs	Purpura	Arthralgia	polyneuropathy	No

AZA=Azathioprin; Cs=corticosteroids; Cyc=cyclophosphamide; GN=glomerulonephritis; HCV=hepatitis C virus; IgM=immunoglobulin M; NA=not available ; PE=plasma exchange; PN=peripheral neuropathy; RTX=rituximab; SS=Sjögren syndrome

Table 2. Main demographic, clinical characteristics and treatment of CV patients treated with belimumab.

	Clinical manifestations at belimumab initiation				Medications at belimumab initiation			Outcome at month 3					Outcome at month 6					Outcomes end of follow up					Follow up from belimumab initiation (months)	Adverse events	
	Skin	Joints	Neuropathy	GN	Cryoglobulin (g/l)	Belimumab dose (mg/kg)*	RTX dose (mg)	CS dose (mg)	Skin	Joints	Neuropathy	GN	Cryoglobulin (g/l)	Skin	Joints	Neuropathy	GN	Cryoglobulin (g/l)	Skin	Joints	Neuropathy	GN			Cryoglobulin (g/l)
1	Purpura	No	PN	No	0.59	10	500 x 1	0	-	No	stabilization	No	0	-	No	improvement	No	0	-	No	improvement	No	0	18	No
2	Purpura	+	PN	No	NA	10	375/m2 x 4	20	+	-	stabilization	No	positive	+	-	stabilization	No	positive	+	-	stabilization	No	positive	14	urinary tract infections
3	Purpura, skin ulcer	No	No	No	0.83	10	500x 1	5	-	-	No	No	0	-	-	No	No	0	-	-	No	No	0	35	osteomyelitis, skin and urinary tract infections
4	Purpura	+	PN	No	1.32	10	375/m2 x 4	10	-	-	stabilization	No	0.11	+	-	stabilization	No	0.86	-	-	stabilization	No	0.29	24	No

AZA=Azathioprin; Cs=corticosteroids; Cyc=cyclophosphamide; GN=glomerulonephritis; HCV=hepatitis C virus; IgM=immunoglobulin M; PE=plasma exchange; PN=peripheral neuropathy; RTX=rituximab; SS=Sjögren syndrome