Reumatol Clin. 2015;11(3):165–169

Reumatología Clínica

www.reumatologiaclinica.org

Review Article

Rituximab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis☆

Sebastián Andrés Muñoz,[a,*] Ignacio Javier Gandino,[a] Alberto Omar Orden,[b] Alberto Allievi[c]

[a] Servicio de Clínica Médica División «A», Hospital General de Agudos Juan A. Fernández, Ciudad Autónoma de Buenos Aires, Argentina
[b] Servicio de Reumatología, Hospital Aeronáutico Central, Ciudad Autónoma de Buenos Aires, Argentina
[c] Exjefe del Servicio de Clínica Médica División «A», Hospital General de Agudos Juan A. Fernández, Ciudad Autónoma de Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 11 March 2014
Accepted 8 August 2014
Available online 14 February 2015

Keywords:
Rituximab
Eosinophilic granulomatosis with polyangiitis
Antineutrophil cytoplasmic antibodies associated vasculitis

ABSTRACT

Background: The general consensus is that for patients with EGPA with poor prognosis, intensive therapy with both GC and CF is indicated. The maintenance of remission is made with GC and AZA. A considerable number of patients with EGPA are refractory to first line therapy, experience dose-limiting side effects or relapse. In clinical trials, RTX was effective for the treatment of ANCA-associated vasculitis. However, patients with a diagnosis of EGPA were not included.
Objective: To review and analyze the published literature regarding the use of RTX in the treatment of EGPA.
Methods: The literature search was performed in MEDLINE and LILACS from 1965 and 1986 respectively until February 2014.
Results: 27 patients were included. RTX treatment was due to refractory disease (n = 20), relapse (n = 5) and with new diagnosis (n = 2). The affected organs were the lungs, peripheral nervous system, kidney and the eyes. Sixteen patients had clinical remission and 8 patients had clinical response.
Conclusions: RTX was effective and well tolerated for the treatment of EGPA.

Rituximab en el tratamiento de la granulomatosis eosinofílica con poliangitis

Palabras clave:
Rituximab
Granulomatosis eosinofílica con poliangitis
Vasculitis asociadas a anticuerpos anticitoplasma de neutrófilo

RESUMEN

Antecedentes: Algunos pacientes con granulomatosis eosinofílica con poliangitis (EGPA) y factores de mal pronóstico son refractarios o presentan efectos adversos al tratamiento de inducción (glucocorticoides [GC] y ciclofosfamida [CF]), o recaen durante el mantenimiento (GC y azatioprina), haciendo necesaria la búsqueda de alternativas terapéuticas. En ensayos clínicos, el RTX demostró ser eficaz para el tratamiento de las vasculitis asociadas al ANCA; sin embargo, los pacientes con EGPA no fueron incluidos.
Objetivo: Revisar y analizar la bibliografía sobre la uso de RTX para el tratamiento de la EGPA.
Métodos: La búsqueda se realizó en MEDLINE y LILACS (1965 y 1986, respectivamente, hasta febrero del 2014).
Resultados: Se incluyó a 27 pacientes. La indicación de RTX fue por enfermedad refractaria (n = 20), recaída (n = 5) y nuevo diagnóstico (n = 2). Los órganos afectados fueron los pulmones, el sistema nervioso periférico, el riñón y los ojos. Se observó remisión en 16 y respuesta en 8 pacientes.
Conclusiones: El RTX fue eficaz y bien tolerado para el tratamiento de la EGPA.

Introduction

EGPA is a necrotizing vasculitis that primarily affects small and medium caliber blood vessels, and is defined as a granulomatous inflammatory and necrotizing disease rich in eosinophils that often affects the airway and is characterized by the presence of asthma and eosinophilia. Along with granulomatosis

☆ Please cite this article as: Muñoz SA, Gandino IJ, Orden AO, Allievi A. Rituximab en el tratamiento de la granulomatosis eosinofílica con poliangitis. Reumatol Clin. 2015;11:165–169.

* Corresponding author.
E-mail addresses: sebastianamunoz@gmail.com, aoorden@yahoo.com.ar (S.A. Muñoz).

2173-5743/

with polyangiitis (Wegener's granulomatosis [GPA]) and microscopic polyangiitis (MPA), they are part of the antineutrophil cytoplasm antibodies (ANCA) associated vasculitis (AAV).[1]

The general consensus is to treat severe forms of EGPA, defined as those with a score on the 5 factor score (FFS) equal to or greater than 1, with glucocorticoids (GC) and cyclophosphamide (CYP) to achieve clinical remission. Maintaining remission is achieved using GC and AZA. Mild forms (FFA of 0) are treated with GC alone. However, the high rate of adverse events, lack of response to induction treatment or frequent relapses with first line treatments require the study of therapeutic alternatives.[2–4]

Rituximab (RTX) is a chimeric monoclonal antibody that specifically binds the CD20 antigen, a non-glycosilated transmembrane phosphoprotein expressed on pre-B and B lymphocytes. The reasonable use of this drug in EGPA is mainly based on its good results in case reports and small series of patients who have been refractory to first line treatment and, in addition is supported by its proven efficacy in clinical trials for AAV patients (GPA and MPA).[5–8] As patients with EGPA were not included in these trials, RTX approval was not extended to EGPA.

The purpose of this study is to review and analyze the studies published in the literature on the use of RTX in the treatment of EGPA.

Materials and Methods

Literature search strategy: we consulted the databases of the Medical Literature Analysis and Retrieval System on Line (MEDLINE)/National Library of Medicine (NLM)-Library of Medicine of the United States and the Latin American and Caribbean Literature in Health Sciences (LILACS) library, since 1965 and 1986 respectively, until February 2014. Search terms in English and Spanish were Churg-Strauss (síndrome de Churg-Strauss) syndrome, eosinophilic granulomatosis with polyangiitis (granulomatosis eosinofílica conpoliangitis), allergic granulomatous angiitis (angeí-tis granulomatosa alérgica), RXT and monoclonal anti-CD20 (anti-CD20 monoclonal antibody).

The following data were analyzed: age, sex, affected organs/systems when RTX was indicated, clinical disease state (defined as relapse, treatment resistant or new diagnosis), ANCA determination, eosinophil and B lymphocyte counts in peripheral blood, number of immunosuppressive used before and after treatment with RTX, clinical patient progression and adverse events.

We excluded all those publications that did not have detailed data from the final analysis.

Statistical analysis: Qualitative variables were presented as percentages, and quantitative variables as means ± standard deviations or median with minimal and maximum values.

Results

Table 1 shows the general characteristics of 27 patients with a diagnosis of EGPA included for analysis. Fifteen (55.5%) were male and 12 (44.5%) were female. Median follow-up was 15 months (3–60 months). The indication for RTX treatment was refractory

Table 1
General Characteristics of the 27 EGPA Patients Treated With RTX Until February 2014.

Patient/ reference	Age/ gender	Status	Organs affected	**Previous** and concomitant treatments	Time of follow up (Months)	No. of cycles of RTX and indication	Result	Adverse events
1[9]	49/F	Rf	Skin, lung	**PS,** CF, AZA	3	1	RM	Pneumonia, herpes zoster
2[10]	37/F	Rl	Lung, PNS, VAS	**PS,** CF, Ig, MFM, Alemtuzumab	18	3 (relapse)	RM	NR
3[10]	35/F	Rf	Lung, VAS, PNS, articular	**PS,** CF, AZA, MFM, INF Alemtuzumab	15	1	RM	Respiratory infection
4[11]	40/M	Rf	Skin, kidney, eye	MP, **PS, CF,** PF	9		RM	NR
5[11]	66/M	Rf	PNS, heart	MP, **PS,** Ig, CF	3	1	RM	NR
6[12]	60/M	Rf	PNS, joints, skin	MP, **PS,** CF, Ig	12	1	RM	NR
7[13]	44/F	Rf	PNS, lung	PS, AZA, MTX, CF	–	–	NA	Bronchospasm
8[13]	33/F	Rl	Joint	PS, CF, MFM, AZA	–	–	NA	Bronchospasm
9[14]	46/M	Rf	CNS	**PS,** CF, **MFM**	4	1	RM	NR
10[15]	50/M	Rf	Lung, ear	**PS,** AZA, **MTX,** CSP, infliximab, anakinra	19	5 (prophylaxis)	RM	NR
11[15]	35/F	Rl	Lung VAS	**PS, AZA**	6	2 (prophylaxis)	RM	NR
12[16]	35/M	Rf	Lung, joint	**PS**	36	2 (relapse)	RM	NR
13[17]	54/M	Rl	PNS, kidney	**PS,** CF	12	2 (relapse)	RM	NR
14[17]	54/F	ND	PNS, kidney, lung	**PS**	12	1	RM	NR
15[17]	64/F	ND	PNS, kidney, muscle	**PS**	12	1	RM	NR
16[18]	59/F	Rf	PNS, kidney	**PS, CF,** AZA	16	1	RM	NR
17[19]	44/F	Rf	PNS, febrile syndrome	MP, **PS,** Ig, CF	6	1	RM	NR
18[20]	70/M	Rf	Lung, kidney	MP, CF, PF	60	1	RM	NR
19[21]	F	Rf	Lung, eye, ear, heart	**PS, CF, AZA**	19	1	RP	NR
20[21]	F	Rf	Lung, eye, ear, heart, PNS	**PS, AZA**	6	1	RP	NR
21[21]	F	Rf	Lung, eye, ear, PNS, SNC	**PS,** MTX, **AZA**	6	1	RP	NR
22[21]	M	Rf	Lung, eye, ear, heart, CNS, skin	**PS, CF, AZA**	32	2 (prophylaxis)	RP	NR
23[21]	M	Rf	Lung, eye, ear, heart	**PS, CF, AZA** AZA	34	4 (prophylaxis)	RP	Seminoma
24[21]	M	Rf	Lung, eye, ear, PNS, skin, kidney	**PS,** CF, **MFM,** MTX, LF	36	6 (prophylaxis)	RP	NR
25[21]	M	Rf	Lung, eye, ear, heart, skin, PNS, CNS, kidney	**PS, AZA,** CF, MTX	13	1	RP	NR
26[21]	M	Rf	Lung, PNS, kidney	**PS, CF, AZA**	6	1	RP	NR
27[21]	M	Rc	Lung, eye, ear, PNS	**PS, MTX**	6	1	RM	NR

AZA: azathioprine; CF: cyclophosphamide; CSP: cyclosporin; ND: new diagnosis; F: female; Ig: immunoglobulin; M: male; MFM: mycohenolate mofetil; MP: methylprednisolone; MTX: methotrexate, NA: not applicable; NR: not reported; PF: plasmapheresis; PS: prednisone; Rl: relapse; Rf: refractory; RP: response; RM: remission; CNS: central nervous system; PNS: peripheral nervous system; RTX: rituximab; UA: upper airway.

Table 2
Details of the Presence of ANCA, Eosinophils and Lymphocytes CD20+ Before and After Treatment With RTX.

	Patients studied/total prior rituximab	Patients studied/total after rituximab
ANCA/specificity	24/27 C (+): 12% P (+): 46% C and P (−): 42%	10/27 C (+): 0% P (+): 10% C and P (−): 90%
Eosinophil	22/27 High: 100%	22/27 Descent: 55% Normal: 45%
CD20+lymphocytes	16/27 Normal: 100%	19/27 Undetectable: 100%

disease in 20 (74.1%), relapse in 5 (18.5%) and a new diagnosis in 2 (7.4%) patients.

The affected organs that prompted the use of RTX were the lungs (n=18, 66.6%) (asthma, pulmonary infiltrates or alveolar hemorrhage), the peripheral nervous system (n=16, 59.3%) (mono- or polyneuropathy), kidneys (n=9, 33.3%), eyes (n=9, 33.3%) and heart (n=6, 22.2%) (Table 1).

ANCA were reported in 14 patients (51.8%), 11 (78.6%) with a perinuclear pattern (P-ANCA) and 3 (21.4%) with a cytoplasmic pattern (C-ANCA). In 10 (33.1%) patients, ANCA were negative and in 3 (11.1%) the ANCA status was not reported. The number of eosinophils, before the start of treatment with RTX, was elevated in all patients (Table 2).

The median of immunosuppressive drugs (including GC) used before the start of treatment with RTX was 3 (range 1–6).

The treatment strategies with RTX employed were: 375 mg/m^2 of total body surface every 7 days, a total of 4 infusions (n=8; 2) 1000 mg every 15 days, a total of 2 infusions (n=13) and variants of these (n=4).

In 2 patients the RTX infusion was suspended due to adverse reactions, making it unable to finish the therapy.

Excluding the use of GC, 14 patients used another immunosuppressive drug concomitantly with RTX (CYP, AZA, methotrexate and mycophenolate mofetil).

Response to Treatment

Clinical disease remission was seen in 16 (59.2%) patients and response in 8 (29.6%) patients (Tables 1 and 3).

In 3 (12%) patients a relapse was observed and in 2 of them this coincided with the reappearance of CD20+B lymphocytes in peripheral blood. All 3 patients were retreated with RTX, with a clinical response.

Table 2 shows the evolution of ANCA, eosinophil counts and the determination of CD20+B lymphocytes in patients before and after the administration of RTX.

Adverse events reported are detailed in Table 1. In 2 patients the first infusion of RTX had to be suspended due to serious bronchospasm; the remaining adverse events were respiratory infections and an episode of herpes zoster. One patient was diagnosed with a seminoma 12 months after receiving RTX. There were no deaths.

Discussion

EGPA belongs to the group of AAV along with GPA and MPA; however, it differs from them in several ways. The current treatment of EGPA is similar to that of the remaining AAV, but differs in that RTX has no defined indication as in GPA and MPA, as the randomized clinical trials such as the RAVE and RITUXVAS[5,6] did not include patients with EGPA. So far, there are only anecdotal reports of EGPA patients treated with RTX, which makes it difficult to assess the effectiveness of this drug in this disease.

An analysis of the literature shows that most EGPA patients treated with RTX were refractory to first line treatment or relapsed during maintenance immunosuppressive therapy. Only 5 patients received RTX as first line induction treatment (Table 3).

In all patients there was a rapid response observed after treatment with RTX; 2 patients did not complete the infusion of the drug due to a severe adverse reaction.[12] Clinical disease remission was seen in most patients. Three patients had one or more relapses, but responded to a new cycle of RTX. Table 3 shows the response to treatment with RTX of cases analyzed along with 2 sets of cases recently reported as abstracts.[22,23]

A major problem in patients with EGPA is the persistence of symptoms of asthma, despite treatment and the morbidity dependent on long-term GC treatment. While the studies did not analyze the therapeutic response of asthma to RTX, a recent communication presented at the 16th International Vasculitis & ANCA Workshop (Paris, France) by Hot et al. found that 39% of patients treated with RTX for EGPA continued with GC requirements due to persistent asthma.[23]

Decreased values of peripheral blood eosinophil were reduced or normal after treatment with RTX regardless of the dosage regimen used, in most patients. This finding puts the close relationship that the different cells of the immune system, and especially the strong Th2 lymphocyte interaction through the secretion of cytokines (IL-4, IL-5 and IL-13), with the B cell and the subsequent production and secretion of eotaxin-1, IgG4, IgE and ANCA in perspective.[2,24] IgE is elevated in the serum of patients with EGPA. This immunoglobulin, which is produced by plasma cells, is bound to receptors (FcεR1) on the surface of eosinophils, which, by

Table 3
Details of Response to Treatment With RTX in EGPA Cases Analyzed and 2 Recent Series Reported in Abstracts.

	No. patients (M/F)	Age (years)	Mean follow up (months)	Indication disease (No.)	Response n (%)
Cases analyzed[9–21]	27 (15/12)	48.6	14.7	Refractory (20) Relapse (5) New diag. (2)	Remission: 16 (59) Responded: 8 (29)
Dubrau et al.[22]	11 (NR)	NR	8	Refractory (5) Relapse (3) New diag. (3)	Remission: 1 (9) Responded: 7 (64) No response 1 (9) Lost: 2 (18)
Hot et al.[23]	30 (16/14)	NR	40	Refractory or relapsed	Remission: 26 (88) Responded: 2 (6) No response: 2 (6)

NR: not reported.

binding to antigen, induces their involvement in the inflammatory response. Furthermore, eotaxin-1 participates in the recruitment of eosinophils to the site of inflamation.[2] These mechanisms could explain in part the decline of eosinophils after treatment with RTX.

Circulating CD20+lymphocytes after RTX use were undetectable and thus persisted for variable time. The period until the repopulation of CD20+B cells was not uniform and in some patients was not correlated with the clinical evolution of the disease. In the RAVE[6] study, a high percentage of patients had undetectable CD20+B cell counts after the infusion of RTX (as occurred in the group using CYP) and the time to repopulation thereof was variable. Of greater importance was the finding regarding the repopulation of CD20+B lymphocytes as an isolated variable that did not predict the relapse risk in the individual patient. However, patients who after the use of RTX persisted with undetectable CD20+B lymphocyte levels and negative ANCA were unlikely to relapse.

ANCA are not the only pathogenic mechanism involved in the genesis of this vasculitis; EGPA patients have a strong IgG4 response regardless of the status of ANCA; evidence of a dialog between the B lymphocytes and eosinophils, and the ability of the B cell to secrete eotaxin-1, which is involved in the recruitment of eosinophils at sites of inflammation[24–26] could be another pathogenic mechanism involved in the response mediated by RTX; therefore the fact that a patient is ANCA negative does not predict a failure to respond to treatment with RTX.

RTX was well tolerated; only 2 patients experienced adverse reactions during infusion. Adverse events were minor, usually respiratory infections in outpatient care. No deaths directly attributed to RTX were reported. This is consistent with the adverse effects reported in large series and extensive clinical studies demonstrating the safety of RTX in the treatment of AAV.[5–8]

The most commonly used treatment strategies were: RTX 1000 mg every 15 days (total 2 infusions) and 375 mg/m^2 of RTX per week (total of 4 infusions). Although both strategies were not formally compared, they appear to be equally effective for the induction of remission in the AAV; the expert recommendation on the use of RTX in AAV is to use both strategies interchangeably.[27]

This study has limitations: the number of patients is small, follow-up time is limited, definitions of activity and damage were not uniform – only in some studies was the Birmingham Vasculitis Activity Score used, and in different versions, immunosuppressive drugs and use of RTX differed between patients. In addition, we did not find publications regarding EGPA patients who did not respond to RTX.

However, there is a widespread tendency to reconsider the standards of treatment for AAV, including EGPA, both in the induction as well as in the maintenance.[28,29]

Finally, RTX appears to be effective and safe for the treatment of refractory EGPA, relapses or newly diagnosed, independent ANCA status. Randomized clinical trials are necessary to confirm this observation.

Ethical Responsibilities

Protection of people and animals. The authors declare that this research did not perform experiments on humans or animals.

Data privacy. The authors state that no patient data appear in this article.

Right to privacy and informed consent. The authors state that no patient data appear in this article.

Conflict of Interest

None.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1–11.
2. Vaglio A, Moosig F, Zwerina J. Churg-Strauss syndrome: update on pathophysiology and treatment. Curr Opin Rheumatol. 2012;24:24–30.
3. Mukhyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Groos W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310–7.
4. Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Stern M, et al. Long-term outcome of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. J Autoimmun. 2013;43:60–9.
5. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009;60:2156–68.
6. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
7. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–20.
8. Charles P, Néel A, Tieulié N, Hot A, Pugnet G, Decaux O, et al. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study of 80 patients. Rheumatology (Oxford). 2014;53:532–9.
9. Kaushik VV, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome. Ann Rheum Dis. 2006;65:1116–7.
10. Koukoulaki M, Smith KGC, Jayne DRW. Rituximab in Churg-Strauss syndrome. Ann Rheum Dis. 2006;65:557–9.
11. Pepper RJ, Fabre MA, Pavesio C, Gaskin G, Jones RB, Jayne D, et al. Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology (Oxford). 2008;47:1104–5.
12. Roccatello D, Baldovino S, Alpa M, Rossi D, Napoli F, Naretto C, et al. Effects of anti-CD20 monoclonal antibody as rescue treatment for ANCA-associated idiopathic systemic vasculitis with or without overt renal involvement. Clin Exp Rheumatol. 2008;26 3 (Suppl. 49):S67–71.
13. Bouldouyre MA, Cohen P, Guillevin L. Severe bronchospasm associated with rituximab for refractory Churg-Strauss syndrome. Ann Rheum Dis. 2009;68:606.
14. Saech J, Owczarzyk K, Rösgen S, Petereit H, Hallek M, Rubbert-Roth A. Successful use of rituximab in a patient with Churg-Strauss syndrome and refractory central nervous system involvement. Ann Rheum Dis. 2010;69:1254–5.
15. Dønvik KK, Omdal R. Churg-Strauss syndrome successfully treated with rituximab. Rheumatol Int. 2009;31:89–91.
16. Roccatello D, Sciascia S, Rossi D, Alpa M, Naretto C, Russo A, et al. Long-term effects of rituximab added to cyclophosphamide in refractory patients with vasculitis. Am J Nephrol. 2011;34:175–80.
17. Cartin-Ceba R, Keogh KA, Specks U, Sethi S, Fervenza FC. Rituximab for the treatment of Churg-Strauss syndrome with renal involvement. Nephrol Dial Transplant. 2011;26:2865–71.
18. Rees F, Yazdani R, Lanyon P. Long-term follow-up of different refractory systemic vasculitides treated with rituximab. Clin Rheumatol. 2011;30:1241–5.
19. Umezawa N, Kohsaka H, Nanki T, Watanabe K, Tanaka M, Shane PY, et al. Successful treatment eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome) with rituximab in a case refractory to glucocorticoids, cyclophosphamide, and IVIG. Mod Rheumatol. 2012:12 [Epud ahead of print].
20. Martínez-Villaescusa M, López-Montes A, López-Rubio E, de la Vara-Iniesta L, Méndez-Molina M, Donate-Ortiz D, et al. Treatment-resistant Churg-Strauss syndrome: progression after five years using rituximab. Nefrologia. 2013;33:737–9.
21. Thiel J, Hässler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Arthritis Res Ther. 2013;15:R133.
22. Dubrau C, Arndt F, Wolfgang L, Gross WL, Moosig F. Successful treatment of Churg-Strauss syndrome with rituximab. Arthritis Rheum. 2012;64:S:1002 [Cited in Moosig F. Eosinophilic granulomatosis with polyangiitis: Future therapies. Presse Med. 2013;42(4Pt2):510–2].
23. Hot A, Guerry MJ, Smith R, Sivasothy P, Guillevin L, Merkel P, et al. A multicenter survey of rituximab for eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Presse Med. 2013;42(4P2):698, http://dx.doi.org/10.1016/j.lpm.2013.02.109.
24. Vaglio A, Strehl JD, Manger B, Maritati F, Alberici F, Beyer C, et al. IgG4 immune response in Churg-Strauss syndrome. Ann Rheum Dis. 2012;71:390–3.
25. Rehman MQ, Beal D, Liang Y, Noronha A, Winter H, Farraye FA, et al. B cells secrete eotaxin-1 in human inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:922–33.

26. Bochner BS, Gleich GJ. What targeting eosinophil has taught us about their role in diseases. J Allergy Clin Immunol. 2010;126:16–25.
27. Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, et al. Recommendation for the use of rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2012;51:634–43.
28. Knight A, Hallenberg H, Baecklund E. Efficacy and safety of rituximab as maintenence therapy for relapsing granulomatosis with poliangiitis—a case series. Clin Rheumatol. 2013 [Epub ahead of print].
29. Hoffman GS. L52. Vasculitis treatment: is it time to change the standard of care for ANCA-associated vasculitis? Presse Med. 2013;42(4Pt2):643–50.