Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases

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Abstract

Objectives

To analyse the safety and efficacy of the off-label use of rituximab in patients with severe, refractory systemic autoimmune diseases.

Methods

In 2006, the Study Group on Autoimmune Diseases of the Spanish Society of Internal Medicine created the BIOGEAS project, a multicentre study devoted to collecting data on the use of biological agents in adult patients with systemic autoimmune diseases refractory to standard therapies (failure of at least two immunosuppressive agents).

Results

One hundred and ninety-six patients with systemic autoimmune diseases treated with rituximab have been included in the Registry (158 women and 38 men, mean age 43 years). Systemic autoimmune diseases included systemic lupus erythematosus (107 cases), inflammatory myopathies (20 cases), ANCA-related vasculitides (19 cases), Sjögren's syndrome (15 cases) and other diseases (35 cases). A therapeutic response was evaluable in 194 cases: 99 (51%) achieved a complete response, 51 (26%) a partial response and 44 (23%) were classified as non-responders. After a mean follow-up of 27.56±1.32 months, 44 (29%) out of the 150 responders patients relapsed. There were 40 adverse events reported in 33 (16%) of the 196 patients. The most frequent adverse events were infections, with 24 episodes being described in 19 patients. Thirteen (7%) patients died, mainly due to disease progression (7 cases) and infection (3 cases).

Conclusion

Although not yet licensed for this use, rituximab is currently used to treat severe, refractory systemic autoimmune diseases, with the most favourable results being observed in Sjögren's syndrome, inflammatory myopathies, systemic lupus erythematosus and cryoglobulinemia.

Key words

Rituximab, systemic lupus erythematosus, Sjögren's syndrome, vasculitis

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Introduction

In recent decades, therapeutic approaches to systemic autoimmune diseases (SAD) have been based on the use of glucocorticosteroids and immunosuppressive agents, although scientific evidence of their efficacy and safety relies principally on data from uncontrolled studies. Clinically, therapeutic decisions are often based on personal experience and reported studies, since there are no standardised, international therapeutic guidelines, with the exception of some recent proposals (1-3). The complexity of therapy in SAD is increased by the large number of patients who do not respond to first-line therapies and by relapses after initial clinical remission. In these patients, there is even less scientific evidence available for the use of second-line drugs, which are often prescribed according to individual clinical decisions. The emergence of biological therapies has increased the therapeutic armamentarium available in these complex situations, but their use is limited by the lack of licensing.

Rituximab is a chimeric antibody against CD20, a surface antigen expressed by B cells. Rituximab was first approved for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma in 1997, and it has also recently been approved to treat rheumatoid arthritis (4, 5). In addition, rituximab is being used for a rapidly-increasing number of SAD (6) even though it remains unlicensed for this use by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). This off-label indication is mainly used to treat patients with either life-threatening situations or severe involvement refractory or intolerant to standard therapy (corticosteroids plus immunosuppressive agents). Available data on the use of biological agents in SAD rely on some randomised controlled trials (RCTs) but especially on a large number of observational studies and case reports (7). This poses many questions on when and how to use them, since there are no current recommendations/guidelines on their use in SAD.

The purpose of this study was to analyse the safety and efficacy of the off-label use of rituximab in patients with severe, refractory SAD by means of an observational multicentre study under the auspices of the Spanish Society of Internal Medicine.

Methods

In 2006, the Study Group on Autoimmune Diseases (GEAS) of the Spanish Society of Internal Medicine (SEMI) created the BIOGEAS project (www.biogeas.org), a multicentre study devoted to collecting data on the off-label use of biological agents in adult patients with severe, refractory SAD. By December 2008, the database included 196 consecutive patients treated with rituximab reported by 14 departments of internal medicine. The inclusion criteria were: i) diagnosis of SAD based on the current classification criteria internationally defined for each disease; ii) severe SAD, defined as the development of potentially life-threatening clinical manifestations; and iii) refractory SAD, defined as patients not achieving remission or relapsing or with progressive disease in spite of optimal doses of corticosteroids and who failed with at least two consecutive immunosuppressive agents.

To minimise possible inter-observer bias, the inclusion criteria and variables of the protocol were agreed by all the participating physicians. The following variables were collected and computerised according to a standard protocol designed by the GEAS Study Group: previous therapies, number of rituximab infusions, dosage and time of infusions, concomitant drugs, therapeutic response, adverse events and outcomes. Rituximab was administered according to the following definitions included in the SEMI clinical guidelines (www.fesemi.org):

a) Off-label use of biological agents in SAD: patients must fulfil the inclusion criteria mentioned above. Failure of previous immunosuppressive therapies was considered if there was no response after at least 6 months of continued use of the immunosuppressive agents and oral corticosteroids at a dose of ≥0.5 mg/kg/day.

c) Classification of therapeutic response: due to the heterogeneous clinical presentation and organ involvement in the different SAD, we used a homogeneous definition for all diseases and involvements, according to the EULAR and ACR recommendations (9-13).

c1. Complete response was defined as no disease activity (disappearance of all symptoms and signs that led to the use of rituximab) combined with a low level of acceptable standard therapy (prednisone <10mg/d and/or stable immunosuppressive therapy);

c2. Partial response was defined as an improvement considered significant (>50% of initial disease activity based on clinical judgment) but not reaching complete remission;

c3. No response was defined as no significant improvement (<50% of initial disease activity based on clinical judgment) or a worsening of the disease in spite of treatment.

d) Therapeutic response to rituximab was evaluated at 12 months.

Information collected by protocol forms was transferred to a computerised database program (SPSS for Windows, Chicago, IL, USA). The design of the protocol included written consent from patients and conformed to the ethical standards currently applied for the off-label use of biological therapies in the different centres involved.

Results

General characteristics

A total of 196 SAD patients treated with rituximab were included in the Registry. There were 158 (81%) women and 38 (19%) men, with a mean age of 42.61±1.09 (range 16-82) years. SAD included systemic lupus erythematosus (SLE) in 107 (55%) cases, inflammatory myopathies in 20 (10%), ANCA-related vasculitis in 19 (10%), Sjögren syndrome in 15 (8%), cryoglobulinemia in 9 (5%) and other autoimmune diseases in the remaining 26 cases (Table I). In 189 cases, rituximab was administered for an SAD refractory to corticosteroids and immunosuppressive drugs; in 7 cases, it was administered for B-cell lymphoma, although all patients also had systemic manifestations related to SAD. Previous therapies included corticosteroids in 182 (93%) patients, cyclophosphamide in 120 (61%), methotrexate in 62 (32%), intravenous immunoglobulins in 56 (29%), azathioprine in 48 (24%) and mycophenolate in 40 (20%). Twelve (6%) patients had received other biological therapies (Table I). Forty-five (23%) patients had failed three therapies and 23 (12%) five or more.

Table I. Main characteristics of 196 patients with SAD treated with rituximab.

	n=196
Females	158 (81%)
Mean age (years)	42.61 ± 1.09 (16-82)
Mean time of follow-up (months)	27.56 ± 1.32 (1-104)
Autoimmune diseases	
- Systemic lupus erythematosus	107 (55%)
- Inflammatory myopathies	20 (10%)
- Wegener's granulomatosis	17 (9%)
- Primary Sjögren's syndrome	15 (8%)
- Cryoglobulinemia	9 (5%)
- Idiopatic thrombocytopenic purpura	7 (4%)
- Primary antiphospholipid syndrome	5 (3%)
- Polyarteritis nodosa	3 (2%)
- Microscopic polyangitis	2 (1%)
- Mixed connective tissue disease	2 (1%)
- Thrombotic thrombocytopenic purpura	2 (1%)
- HCV-related autoimmune features	2 (1%)
- Behçet's disease	1 (0.5%)
- Systemic sclerosis	1 (0.5%)
- Urticaria vasculitis	1 (0.5%)
- Takayasu arteritis	1 (0.5%)
- Polyneuropathy + hyperIgM	1 (0.5%)
Previous therapies	
- Corticosteroids	182 (93%)
- Cyclophosphamide	120 (61%)
- Methotrexate	62 (32%)
- Intravenous immunoglobulins	56 (29%)
- Azathioprine	48 (24%)
- Mycophenolate	40 (20%)
- Cyclosporine A	19 (10%)
- Other biologic therapies	12 (6%)
- Plasma exchange	6 (3%)
- Splenectomy	5 (3%)
- Antiviral therapy	4 (2%)
- Tacrolimus	3 (2%)
- Leflunomide	3 (2%)
- Thalidomide	2 (1%)
- Other therapies	14 (7%)
RTX regimens	
- 375 mg/m^2/week (x4)	169 (86%)
- 1g/15 days (x2)	27 (14%)
Response (n=195)	
- Complete	99 (50%)
- Partial	51 (27%)
- No response	44 (23%)
Relapses	44/150 (29%)

The most-frequently used rituximab regimen was that recommended for the treatment of lymphoma (375 mg/m^2 of rituximab weekly for 4 weeks), which was used in 169 (86%) patients. In the remaining 27 cases (14%), rituximab was administered as two 1000 mg doses separated by fifteen days. After induction therapy with rituximab, 184 patients continued maintenance therapy with corticosteroids, 107 of whom were also receiving immunosuppressive agents.

The therapeutic response was evaluated in all but two patients (a SLE

Table II. Main adverse events of 196 patients with SAD treated with rituximab.

	n=196
Adverse events	33 (16%)
Type	
- Infections	24 (12%)
- Infusion-related	7 (4%)
- Neoplasia	1 (0.5%)
- Haematological	2 (1%)
- Other	6 (3%)
Classification of infections	
- Respiratory infections	9 (5%)
- Urinary tract infections	6 (3%)
- Cutaneous infections	3 (2%)
- Neutropenia	2 (2%)
- Bacteriemia/sepsis	2 (2%)
- Vaginitis	1 (0.5%)
- Osteomielitis	1 (0.5%)
- Endocarditis	1 (0.5%)
- Viral encephalitis	1 (0.5%)
Microorganisms	
- Staphylococcus aureus	2 (2%)
- Herpes zoster	2 (2%)
- Streptococcus pneumoniae	1 (0.5%)
- Pseudomonas aerugynosa	1 (0.5%)
- Escherichia coli	1 (0.5%)
- Stenotrophomonas maltophila	1 (0.5%)
- Trichomonas sp	1 (0.5%)
- Mycobacterium tuberculosis	1 (0.5%)
- Aspergyllus fumigatus	1 (0.5%)
- Cytomegalovirus	1 (0.5%)
Deaths	13 (7%)
Causes of death	
- Disease progression	7
- Endocarditis	1
- Sepsis	2
- Sudden death	1
- Other causes	2

Table III. Main characteristics of 107 patients with systemic lupus erythematosus treated with rituximab.

	n=107
Females	94 (88%)
Mean age (years)	35.96 ± 1.15 (16-70)
Mean time of follow-up (months)	26.05 ± 1.62 (1-87)
RTX regimens	
- 375 mg/m^2/week (x4)	91 (85%)
- 1g/15 days (x2)	16 (15%)
Concomitant therapies	
- Corticosteroids	107 (100%)
- Immunosuppressive agents	64 (60%)
Overall response (n=105)	
- Complete response	47 (45%)
- Partial response	34 (32%)
- Non-responders	24 (23%)
Organ-specific response (n=105)	
- Cytopenias	27/37 (73%)
- Type III/IV nephritis	21/25 (85%)
- Nephritis not classified	17/23 (74%)
- Arthritis	7/9 (78%)
- Cutaneous features	3/9 (33%)
- CNS involvement	5/6 (80%)
- Serositis	4/6 (67%)
- Thrombotic features	5/5 (100%)
- Pulmonary involvement	3/5 (60%)
- Digestive involvement	4/4 (100%)
- Vasculitis	3/3 (100%)
- Muscular involvement	1/3 (33%)
- Type V nephritis	1/1 (100%)
- Lymphoma	0/1 (0%)
Adverse events	18 (17%)
Relapses	20/81 (25%)
Deaths	5 (5%)

patient who developed necrotising fasciitis a few hours after the first dose of rituximab, which was discontinued, and a second patient classified as missing one month after rituximab administration). Of the remaining 194 patients, 99 (51%) achieved a complete response, 51 (26%) a partial response and 44 (23%) were classified as non-responders. After a mean follow-up of 27.56±1.32 months, 44 (29%) out of the 150 responding patients had relapsed. There were 40 adverse events reported in 33 (16%) of the 196 patients (Table II). Thirteen (7%) patients died, with 7 (54%) due to disease progression.

Patients with SLE

The main characteristics of the 107 SLE patients treated with rituximab are summarised in Table III. Forty-seven (45%) patients achieved a complete response, 34 (32%) a partial response and 24 (23%) were classified as non-responders. With respect to renal involvement, complete response was defined as normal serum creatinine and serum albumin levels, inactive urinary sediment and 24-hour urinary albumin <0.5 g, and partial response as a >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter (12, 13). For severe thrombocytopenia, complete response was defined as platelet count >50,000/mm^3, and partial response as a count >30,000/mm^3, while for haemolytic anemia complete response was defined as haemoglobin >11g/dL and partial response >10g/dL. The remaining types of involvement were evaluated according to the homogeneous definition of response stated in the *Methods* section.

Previous immunosuppressive therapies included cyclophosphamide in 78 (73%) patients, mycophenolate in 40 (45%), methotrexate in 30 (28%), azathioprine in 30 (28%) and intravenous immunoglobulins in 30 (28%). After induction therapy with rituximab, all patients continued maintenance therapy with corticosteroids; 76 patients were also receiving immunosuppressive agents, mainly cyclophosphamide (n=50) and mycophenolate (n=14).

According to SLE manifestations, a therapeutic response of >80% was observed for proliferative nephritis, CNS involvement, vasculitis, digestive involvement and thrombotic complications. In contrast, a response of <50% was observed for cutaneous and muscular involvement and lymphoma. In addition to the clinical response, there was a reduction in anti-dsDNA titers after rituximab therapy in 59% of patients and a reduction in the corticosteroid dose in 79% (including withdrawal in 14%).

Table IV. Main characteristics of 20 patients with inflammatory myopathies treated with rituximab.

	n=20
Females	15 (75%)
Mean age	49.20 ± 2.98 (23-77)
Mean time of follow-up	19.00 ± 2.65 (1-52)
RTX regimens	
- 375 mg/m^2/week (x4)	18 (90%)
- 1g/15 days (x2)	2 (10%)
Concomitant therapies	
- Corticosteroids	20 (100%)
- Immunosuppressive agents	18 (90%)
Overall response	
- Complete response	11 (55%)
- Partial response	6 (30%)
- Non-responders	3 (15%)
Overall response by disease	
- Dermatomyositis	9/11 (82%)
- Polymyositis	4/4 (100%)
- Antisynthetase syndrome	4/5 (80%)
Organ-specific response	
- Muscular involvement	15/16 (94%)
- Cutaneous features	5/6 (80%)
- Pulmonary involvement	3/4 (75%)
- Arthritis	1/1 (100%)
- Cytopenias	1/1 (100%)
Adverse events	2 (10%)
Relapses	8/17 (47%)
Deaths	1 (100%)

Twenty-two adverse events were reported in 18 (17%) patients. The most frequent adverse events were infections in 12 patients, including respiratory infection (5 cases, 3 of which were pneumonia), urinary tract infection (3 cases, one pyelonephritis) and cutaneous infection (2 cases). Severe infusion reactions were reported in 2 cases and neutropenia in one. After a mean follow-up of 26.05±1.62 months, 20/81 (25%) responders relapsed, and 5/107 (5%) patients died (4 due to disease progression and one due to pneumonia).

Patients with inflammatory myopathies

The main characteristics of the 20 patients with inflammatory myopathies (11 with dermatomyositis, 4 with polymyositis and 5 with antisynthetase syndrome) are shown in Table IV. With respect to muscular involvement, complete response was defined as the disappearance of weakness and normalisation of CK levels, and partial response as significant improvement of muscular weakness and >50% improvement in CK levels (14, 15). The remaining types of involvement were evaluated according to the homogeneous definition of response stated in the Methods section.

Eleven (55%) patients achieved a complete response, 6 (30%) a partial response and 3 (15%) were classified as non-responders. In addition to the clinical response, there was a reduction in the corticosteroid dose in 85% of patients. The therapeutic response was excellent for muscular (94%), pulmonary (75%) and cutaneous involvement (80%). There were 2 (10%) adverse events (urinary tract infections). After a mean follow-up of 19.00±2.65 months, 8/17 (47%) responders relapsed. One patient (5%) with antisynthetase syndrome died due to disease progression.

Patients with ANCA-related vasculitis

The main characteristics of the 19 patients with ANCA-related vasculitis (17 with Wegener's granulomatosis and 2 with microscopic polyangiitis) treated with rituximab are shown in Table V. With respect to Wegener's granulomatosis, complete response was defined as the absence of new disease activity in the major organ involvements defined in the BVAS/WG score (16), while partial response was defined by persistent disease activity for no more than one of these items.

Ten (53%) achieved a complete response, three (16%) a partial response and 6 (31%) were classified as non-responders. The therapeutic response was higher for renal (100%), neurological (80%) and pulmonary (78%) involvement, and lower for ENT (67%) and cutaneous (33%) involvement. In addition to the clinical response, there was a reduction of ANCA titers after rituximab therapy in 40% of patients and a reduction in the corticosteroid dose in 74% of patients (including withdrawal in 8%).

There were 12 adverse events in 6 (32%) patients. The most frequent adverse events were infections, with 5 episodes (vaginitis, herpetic keratoconjunctivitis, pneumonia, pulmonary aspergillosis and bacteremia) being described in 3 patients, severe infusion reactions in two cases, neutropenia in one and pulmonary embolism in one. After a mean follow-up of 31.37±3.25 months, 9/13 (69%) responders relapsed. One (5%) patient died due to pulmonary embolism.

Patients with Sjögren's syndrome

Fifteen patients with SS were treated with rituximab due to extraglandular involvement which was associated with B-cell lymphoma in 6 cases (these patients also had SS activity including purpura, arthralgia, myalgia, parotid swelling, fatigue and/or fever). Organ-specific involvements that led to the use of rituximab included neurological involvement in 4 cases (CNS involvement, mixed polyneuropathy, ataxic neuronopathy and myelitis), haematological involvement in 2 cases (severe thrombocytopenia and acquired C1 inhibitor deficiency) and severe, refractory glomerulonephritis, arthritis and protein-losing enteropathy (one case each).

Ten (67%) patients achieved a complete response, 3 (20%) a partial response (ataxic neuronopathy, CNS involvement and arthritis) and 2 (13%) were

Table V. Main characteristics of 19 patients with ANCA-related vasculitis treated with rituximab.

	n=19
Females	10 (53%)
Mean age	46.21 ± 3.72 (16-73)
Mean time of follow-up	31.37 ± 3.25 (1-50)
RTX regimens	
- 375 mg/m^2/week (x4)	18 (95%)
- 1g/15 days (x2)	1 (5%)
Concomitant therapies	
- Corticosteroids	19 (100%)
- Immunosuppressive agents	12 (63%)
Overall response	
- Complete response	10 (53%)
- Partial response	3 (16%)
- Non-responders	6 (31%)
Overall response by disease	
- Wegener's granulomatosis	12/17 (71%)
- Microscopic polyangitis	1/2 (50%)
Organ-specific response	
- Pulmonary involvement	11/14 (79%)
- ENT involvement	4/6 (67%)
- CNS involvement	3/4 (75%)
- Cutaneous features	1/3 (33%)
- Renal involvement	2/2 (100%)
- Peripheral neuropathy	2/2 (100%)
- Arthritis	1/1 (100%)
- Cytopenias	1/1 (100%)
- Digestive involvement	1/1 (100%)
Adverse events	6 (31%)
Relapses	9/13 (69%)
Deaths	1 (5%)

classified as non-responders (glomerulonephritis and myelitis). There were no significant changes in the autoantibody profile after rituximab therapy, except for reduced ANA titers in 4 patients and reduced RF titers in two. There were 2 (13%) adverse events (urinary tract infection and interstitial pneumonitis). After a mean follow-up of 42.07±8.45 months, 5/13 (38%) responders relapsed.

Discussion

In the last three decades, therapeutic approaches in SAD have been based on the use of glucocorticosteroids and immunosuppressive agents. Therapeutic decisions are based on a mix of personal experience and reported studies, although scientific evidence of the efficacy and safety of standard therapies relies principally on data from uncontrolled studies. The small number of RCTs carried out in SAD patients may be explained by the low prevalence of most SAD, their heterogeneous clinical presentation (often multiorganic) and the absence of consensual endpoints for evaluation in each disease. The complexity of the therapeutic approach in SAD is increased by the large number of patients who do not respond to first-line therapies and the occurrences of relapses after initial clinical remission. In these patients, there is even less scientific evidence available than for first-line therapies and second-line drugs are often used according to individual clinical decisions. The emergence of biological therapies has increased the therapeutic armamentarium available in these complex situations, but is significantly limited by the lack of licensing for SAD.

Since its recent introduction, rituximab has been increasingly used in patients with SAD and there are now nearly 500 reported cases (www.biogeas.org). The majority of reports involve SLE (172 patients), cryoglobulinemia (88 patients), primary SS (69 patients) and Wegener's granulomatosis (68 patients): the therapeutic response was >80% in each disease. This study reports a complete or partial therapeutic response in 77% of patients with severe, refractory SAD (no response to corticosteroids and at least two immunosuppressive agents) overwhelmingly treated with four weekly infusions of 375 mg/m^2 of rituximab, suggesting that rituximab may be considered a promising therapy in these patients.

Nearly half the patients included in our Registry had SLE. To date, available data on the use of rituximab in SLE rely on a large number of case reports and some observational studies. The largest available clinical studies of rituximab in SLE include a retrospective evaluation of eight series including 137 patients (17-24). Lindholm *et al*. (7) reported a beneficial effect of adding rituximab to immunosuppressive therapy in 31 refractory SLE patients. Leandro *et al*. (18) reported 24 patients with SLE refractory to standard immunosuppressive therapy (mean of 3 agents) who were started on two 500 mg infusions of rituximab together with two 750 mg infusions of cyclophosphamide and high-dose oral corticosteroids for 2 weeks. The global BILAG score, serum C3 levels and antidsDNA antibodies improved significantly 6 months after rituximab initiation. Gottenberg *et al*. (19) described a clinical response in 9 of 13 patients with SLE, including seven who achieved complete remission and two who achieved partial remission. The mean SLEDAI score decreased in the 11 surviving patients. In the study by Tanaka *et al*. (20) of 14 SLE patients treated with rituximab, a significant improvement in the BILAG score was observed at 4 and 28 weeks, compared to baseline scores. In our 107 SLE patients treated with rituximab, the clinical features that led to rituximab administration consisted mainly of severe cytopenia and internal organ involvement (cardiopulmonary, digestive, renal or CNS manifestations), with mucocutaneous and musculoskeletal involvement being less frequent (<20% of patients). Positive clinical response was more frequent in patients with internal organ involvement: efficacy was lower in patients with cytopenias, cu-

taneous and articular involvement. Our results suggest a potential benefit of using rituximab as rescue therapy in SLE patients with severe, refractory disease, especially those with renal, digestive, vasculitic and CNS involvement.

The promising results of rituximab in uncontrolled studies of refractory SLE patients (25) are in clear contrast to the poor results of the recently completed EXPLORER and LUNAR randomised controlled trials (RCT) (26, 27). Before concluding that B-cell depletion is not a good therapy for SLE, a careful evaluation of the design of these trials is necessary, especially with respect to the level of disease severity of patients included or the possible influence of ethnicity or concomitant therapies such as the high doses of corticosteroids permitted in both arms of these trials whose use could lead to significant differences not being apparent in a short-term evaluation. The characteristics of the patients included in these RCTs seem to differ completely from those of the refractory SLE patients who have received rituximab since 2000: this may explain the different results obtained (28). In addition, the possible synergistic effect of immunosuppressive agents (cyclophosphamide or mycophenolate) in combination with rituximab, suggested by some authors to have significant advantages in complicated SLE cases (29, 30), was not evaluated in these RCTs.

The three other diseases in which we have a significant number of patients receiving off-label use (15-20 patients) are inflammatory myopathies, Wegener's granulomatosis and SS. We found a good balance between efficacy and adverse events in our patients with inflammatory myopathies (85%/10%) in contrast to uncontrolled studies carried out in 13 patients (69%/39%) (7). A recent study (31) has suggested that this variable response to rituximab may be related to the inclusion of non-inflammatory muscular diseases such as inclusion body myopathy or muscular dystrophies. However, these results are clearly better than those reported for other biological agents such as etanercept, which has been used in 14 patients with a therapeutic response of 21% (7). In patients with Wegener's granulomatosis, we found an efficacy of 71% and a rate of adverse events of 35%, figures less promising than those found in the overall analysis of 49 patients included in 6 uncontrolled studies –UCS- (efficacy 84%, adverse events 27%) and 19 case reports (efficacy 95%, adverse events 11%) (7). Similar promising results have also been shown in 3 recent observational studies including a total of 30 patients with ANCA-related vasculitis (32-34).

We have used rituximab to treat twelve other severe SAD with less than 10 patients in each disease, with an excellent rate of therapeutic response. Similar promising results have been reported in recent studies in the majority of these diseases, including thrombotic thrombocytopenic purpura (35-37), systemic sclerosis (38-40), antiphospholipid syndrome (41-43), autoimmune neurological (44) or haematological (45-47) processes and cryoglobulinemia (48).

Adverse events were reported in 16% of our SAD patients treated with rituximab. The most-frequent adverse event was infection, which was predominantly mild and involved the respiratory and urinary tracts and was caused by common microorganisms. No patient developed progressive multifocal leukoencephalopathy or cytokine release syndrome. Only 3 patients developed opportunistic infections (tuberculosis, systemic cytomegalovirus infection and aspergillosis), which other reports confirm are infrequent in SAD patients treated with rituximab (7, 49, 50). However, there were difficulties in attributing a direct causal role to rituximab in the development of adverse events in nearly 30% of our patients. The majority of patients who received rituximab had severe, refractory disease with a long-term history of corticosteroid and immunosuppressive agent use which, *per se,* increases the risk of infections, cytopenias, neoplasia and death. In a pooled analysis of SAD patients included in RCTs to date (7), although the global percentage of adverse events was significantly higher in patients treated with rituximab compared with placebo, there were no significant differences in the percentages of the main adverse outcomes, including total infections, severe infections, neoplasia and death (7). Interestingly, two recent studies (51, 52) have found that the use of rituximab in RA is not associated with an increased rate of severe infections.

Definitive recommendations for the off-label use of rituximab in SAD after overall analysis of consecutive cases included in a multicentre, uncontrolled study, with widely diverse individual characteristics and clinical features, is not yet possible. However, this global analysis of all cases reported in Spain provides relevant data on the efficacy/safety ratio of the off-label use of rituximab in individual SAD in clinical practice. In patients with severe, refractory SAD, rituximab may currently be considered the first-choice biological agent in diseases characterised predominantly by B-cell hyperactivity (SLE, primary SS and cryoglobulinemia) and may be a good option in patients with inflammatory myopathies and Wegener's granulomatosis.

Possible concerns in retrospective studies include those of selection bias (in our study, only refractory/severe patients were included). This makes it impossible to compare our results with those of controlled studies, a bias that, in our opinion, is very difficult to avoid due to the lack of licensed approval for rituximab in autoimmune diseases. In addition, the lack of use of objective activity scores may limit the accurate evaluation of therapeutic response in our patients. Nevertheless, in spite of these limitations, we believe that the recruitment of 196 patients with SAD treated with rituximab is a significant number and permits useful information on the off-label use of rituximab in patients with severe, refractory disease to be obtained.

Rituximab is currently used in patients with severe, refractory SAD even though it is not yet licensed for this use by the FDA and EMEA. Available scientific data rely on some RCT but principally on a large number of observational studies and case reports, which may overstate the efficacy and understate the risks. While awaiting the results of current, large RCTs, the off-label use of rituximab should cen-

tre on treating SAD patients with either life-threatening situations or severe involvement refractory to standard therapy (lack of response or intolerance to corticosteroids and at least two immunosuppressive agents). In this context, we have observed a very acceptable balance between clinical efficacy (nearly 80%) and adverse events (16%) in patients treated off-label. However, the uncontrolled design of our study makes it mandatory for the possible risks and benefits of using rituximab to be carefully balanced. A reasonable assessment of the risk of serious adverse events versus the benefits of treatment should be made on an individual basis.

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APPENDIX A.
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