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ORIGINAL ARTICLE

The Off-Label Use of Rituximab for the Management of Inflammatory Disorders: American University of Beirut Medical Center Experience

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Objectives: This study aims to evaluate the efficacy of off-label use of rituximab with possible side effects.

Patients and methods: Records of the 44 American University of Beirut Medical Center pharmacies were searched for patients who used rituximab over the past 4.5 years, and data on rituximab dosage, protocol and side effects were documented. The majority of patients had systemic lupus erythematosus. Autoimmune thrombocytopenic purpura, antiphospholipid syndrome, Sjögren's syndrome, Wegener's granulomatosis, autoimmune hemolytic anemia, dermatomyositis, and pemphigus vulgaris were also reported. Outcome measures were improvement in signs and symptoms during a follow-up period of two years.

Results: Twenty-nine out of the 44 patients had complete response without relapse. Of those, 12 patients were in remission after the first cycle. Of the systemic lupus erythematosus cases, 12 had complete response without relapse; of which, five patients had remission after the first cycle. No significant toxicities were noted.

Conclusion: The off-label use of rituximab in various inflammatory diseases showed improvement in symptoms with no significant side effects in patients who have failed previous treatment with multiple conventional regimens.

Key words: Autoimmune disease; biologic therapy; inflammatory disorder; off-label; rituximab.

Biologists have been extensively investigating a promising therapy in the management of multiple inflammatory and autoimmune diseases. Rituximab is a chimeric (murine/human) monoclonal antibody, which targets a cluster of 20 different antigens (CD20) found on the surface of B-lymphocytes.

Rituximab is approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, non-Hodgkin's lymphoma[1] and recently of anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[2] In addition to these indications, rituximab is being used as an off-label treatment in a number of inflammatory and systemic autoimmune diseases. Off-label use dictates the prescription of a registered medicine for a use that is not included in the product information. It is considered appropriate when there is high-quality evidence, or where the use is within the context of a formal research proposal, or in exceptional cases, justified by clinical situations.[3] Rituximab has been tried as an off-label treatment for many conditions including systemic lupus erythematosus (SLE), Sjögren's syndrome, idiopathic thrombocytopenic purpura (ITP), systemic vasculitides, bullous dermatologic

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diseases, and others.[4] Rituximab use in a number of dermatological diseases has also been reported.[5]

Several reports have acknowledged the positive outcomes and efficacy of rituximab in the aforementioned diseases. In 2009, Ramos-Casals et al.[6] reported a review of the literature regarding the off-label use of rituximab in resistant SLE patients, revealing a 91% positive response. One year later, Murray and Perry[7] conducted a systematic review about the off-label use of rituximab in SLE, and found that it induced B-cell depletion in 95% of patients, and induced significant reduction in disease activity with a good safety profile. Since applicability of these results to our study population remains to be elucidated due to the current limited reports on rituximab use among this patient, we were enthusiastic to investigate our experience at the American University of Beirut Medical Center, with rituximab off-label use in a variety of inflammatory rheumatologic, dermatologic, and hematologic conditions, addressing efficacy in clinical response and side effects. The results of this study contribute to the worldwide experience in the off-label use of this drug.

PATIENTS AND METHODS

In this retrospective study, pharmacy records at the American University of Beirut Medical Center were evaluated for rituximab use over the past 4.5 years (January, 2006 - May, 2010). A total of 44 patients received rituximab for off-label conditions during the period were evaluated. All patients were of Caucasian origin (34 females versus 10 males), and were enrolled depending on whether there was treatment failure after conventional regimens and/or treatment side effects. Patients whose medical charts were noted in the pharmacy database and were reviewed in the medical records of the hospital (in- and out- patient) and the dermatology department, and those who received rituximab as an off-label use for an inflammatory disorder, were then enrolled in the study. The disorders include SLE, antiphospholipid syndrome (APS), Sjögren's syndrome, systemic sclerosis (SSc), Still's disease, AAV, Behçet's disease, cryoglobulinemia, poly/dermato-myositis, scleroderma, as well as pemphigus vulgaris, bullous pemphigoid, epidermolysis bullosa, ITP, and thrombotic thrombocytopenic purpura. Diagnosis of these diseases was based on clinical manifestations and serological markers.

Medical records were reviewed and general information regarding race, sex, and age at onset of disease, as well as disease chronicity and manifestations as per system review were collected. Current medications and previous treatment received were recorded along with thoroughly explored comorbidities. The total dose of rituximab, protocol of drug administration, and side effects were documented.

The responsible treating physician identified the patient's response to rituximab in dermatologic and rheumatologic diseases according to symptoms and signs. Response rate was categorized as: *(i)* complete response without relapse meaning that the patient attained remission by regression of symptoms and signs without the appearance of other signs and symptoms, *(ii)* complete response with relapse, *(iii)* partial response meaning improvement in one or more of the symptoms and signs, and *(iv)* no response. Improvement in cell counts and remission was documented for ITP and thrombotic thrombocytopenic purpura patients. Patients were evaluated for a follow-up period of two years. Data analysis was performed using the PASW Statistics version 18.0 for Windows software program (SPSS Inc., Chicago, IL, USA). On the other hand, frequencies were extracted using descriptive statistics, while means were compared using the paired sample T test. A P-value less than or equal to 0.05 was considered statistically significant.

RESULTS

The mean age at diagnosis was 36.4±19.8 years, and the mean age at study enrollment was 44.5±19.1 years. The mean chronicity of the disease is 7.4±6.4 years. Seventeen patients had SLE. Patients with other inflammatory diseases were also reported in decreasing frequency as follows: ITP (n=8), APS (n=5), Sjögren's syndrome (n=5), polymyositis (n=4), Wegener's granulomatosis (n=3), autoimmune hemolytic anemia (AIHA) (n=2), scleroderma (n=2), Still's disease (n=1), dermatomyositis (n=1), pemphigus vulgaris (n=1), bullous pemphigoid (n=1), ankylosing spondylitis (n=1), polyarteritis nodosa

Table 1. Summary of patient's diagnosis, clinical manifestations, pertinent laboratory markers, and previous medications used

Patient number	Age at protocol	Age at diagnosis	Sex	Diagnosis	Clinical manifestations	Positive laboratory markers	Medications used
1	26	21	F	Polymyositis, scleroderma	Sclerodactyly, telangiectasia, skin thickness, pericarditis, muscle weakness, osteopenia, myositis, myalgia, osteoporosis, raynauld's	ANA Scl70	Antimalarials Cyclophosphamide Methotrexate
2	-	-	F	SLE	Malar rash, epilepsy, small vessel vasculitis	ANA Anti-DNA Anticardiolipin (IgG, IgM)	Antimalarials Azathioprine Steroid Mycophenolate mofetil
3	35	34	M	Polymyositis	Swelling, arthralgia, myalgia, muscle weakness	–	Azathioprine, steroid
4	56	46	F	Sjögren's syndrome	CVA, swelling, xerostomia, arthralgia, eye dryness, loss of vision	Anti-SSA	Antimalarials, NSAIDs
5	57	55	F	Wegener's granulomatosis	Headache, interstitial lung disease, diarrhea, ascites, sinusitis	RF, c-ANCA	Methotrexate
6	-	-	F	SLE, APS	Arthralgia	Anticardiolipin	Antimalarials
7	14	13	F	SLE	Malar rash, psychotic disorder, cardiomyopathy, pleural effusion, nephritic syndrome, renal failure, arthralgia, thrombocytopenia, microangiopathic hemolytic, anemia		
8	-	-	F	Polymyositis, scleroderma	Skin ulcer, telangiectasia	ANA, Scl70	Steroid, methotrexate
9	40	34	F	SLE	Photosensitivity, alopecia, malar rash, skin dryness, discoid rash, headache, arthralgia, muscle weakness, eye dryness, Raynaud's phenomenon,	ANA, Anti-SSA	Antimalarials, Azathioprine, Steroid, Methotrexate
10	18	10	F	SLE	Livedo reticularis, malar rash, swelling, nephritic syndrome, anemia	ANA, Anti-DNA	Steroid, NSAIDs Mycophenolate mofetil
11	17	15	F	SLE, APS	Photosensitivity, malar rash, swelling, headache, arthralgia, myalgia, morning stiffness, anemia, splenomegaly	ANA, Anti-DNA, anti-smith, anticardiolipin, lupus anticoagulant, RF	Antimalarials, steroid, NSAIDs, methotrexate
12	80	76	F	Polymyositis	Telegiectasia, cardiomyopathy, muscle weakness, Raynauld's	ANA	Steroid, NSAIDs
13	19	14	F	SLE, APS	Malar rash, headache, arthralgia, polyarthritis, muscle weakness, morning stiffness, vertigo, myalgia, AIHA	ANA, Anti-DNA Anticardiolipin (IgG, IgM) Anti-β2GP1, Anti-RNP	Antimalarials, aspirin, steroid
14	39	26	M	Sjögren's syndrome	Xerostomia, Parotid swelling, Myalgia, Eye dryness	ANA, Anti-SSA, RF	Antimalarials, steroid, infliximab, NSAIDs
15	29	24	F	SLe	Alopecia, swelling, pericardial effusion, nephritic syndrome, arthralgia, thrombocytopenia, leucopenia, anemia	ANA, Anti-DNA, anticardiolipin	Antimalarials, azathioprin, steroid, mycophenolate mofetil NSAIDs

Table 1. Continued

Patient number	Age at protocol	Age at diagnosis	Sex	Diagnosis	Clinical manifestations	Positive laboratory markers	Medications used
16	44	41	F	Sjögren's syndrome	Rheumatoid nodules, xerostomia, arthralgia, myalgia, morning stiffness, eye dryness	Anti-SSA	Antimalarials, infliximab, methotrexate, NSAIDs
17	–	–	F	Wegner's Granulomatosis	Sinusitis, saddle nose deformity, anemia	ANA, p-ANCA	Methotrexate
18	42	39	F	SLE	Demyelinated syndrome, arrhythmia, gastrointestinal hypomotility, arthralgia, muscle weakness	ANA	Antimalarials, steroid, plasmapheresis
19	46	36	F	SLE	Alopecia, malar rash, urticaria, skin dryness, subdural hematoma, valvular heart disease, migraine, arryhthmia, nephritic syndrome, oral candidiasis, arthralgia, muscle weakness, morning stiffness, osteopenia, leucopenia, anemia, Raynauld's phenomenon	Anti-DNA	Antimalarials, azathioprine, steroid, cyclophosphamide, NSAIDs, mycophenolate mofetil
20	53	49	F	SLE	Cerebral vasculitis, nephritic syndrome, polyarthritis, TMJ involvement, osteoporosis, keratitis, anemia	ANA, c-ANCA	Steroid, cyclophosphamide, NSAIDs
21	84	69	F	Still's disease	Rheumatoid nodule, ulnar deviation, arthralgia, polyarthritis, morning stiffness, osteoporosis, anemia	–	Steroid, infliximab, methotrexate, NSAIDs
22	40	19	M	Ankylosing spondylitis	Arthralgia, Morning stiffness	RF	Infliximab, NSAIDs, sulfasalazine
23	48	33	M	SLE, Bullous pemphigoid	Photosensitivity, alopecia, discoid rash, arthralgia, Raynauld's phenomenon	ANA, RF	Antimalarials, azathioprin, steroid, methotrexate
24	30	19	F	SLE	Photosensitivity, malar rash, headache, steroid induced diabetes mellitus, arthralgia, morning stiffness, myalgia, thrombocytopenia, anemia, splenomegaly	ANA, anti-SSA, anticardiolopin (IgM)	Antimalarials, azathioprine, steroid, IVIG, NSAIDs
25	26	18	F	SLE, APS	Alopecia, headache, cerebral venous sinus thrombosis, cognitive disorder, pericardial effusion, interstitial lung disease, arthralgia, polyarthritis, gastrointestinal bleed, muscle weakness, morning stiffness, myalgia, leukopenia, DVT	ANA, anti-DNA, anti-smith, anti-SSA, lupus anticoagulant, anti-RNP	Antimalarials, azathioprine, steroid, cyclophosphide, NSAIDs
26	38	25	F	SLE	Malar rash, discoid rash, pleuritis, pleural effusion, nephritic syndrome, renal failure, arthralgia, polyarthritis,	ANA, anti-DNA, anti-smith	Antimalarials, azathioprine, steroids, NSAIDs, mycophenolate mofetil

Table 1. Continued

Patient number	Age at protocol	Age at diagnosis	Sex	Diagnosis	Clinical manifestations	Positive laboratory markers	Medications used
27	68	67	F	Sjögren's syndrome	Morning stiffness, osteoporosis, eye dryness	ANA, Anti-SSA	Steroids, NSAIDs
28	35	29	F	Dermatomyositis	Photosensitivity, myocarditis, arrhythmia, Steroid induced DM, dysphagia, arthralgia, muscle weakness, TMJ involvement, myalgia, osteoporosis, eye dryness, anemia, splenomegaly, Raynauld's phenomenon		
29	–	–	F	Sjögren's syndrome	Headache, acute ischemic encephalopathy, xerostomia, arthralgia, muscle weakness, eye dryness	–	Antimalarials, steroid, methotrexate, NSAIDs
30	37	20	F	Polyarteritis nodosa	Skin ulcer, livedo reticularis, mononeuritis multiplex, carpel tunnel syndrome, arthralgia, Raynauld's phenomenon, lower extremity arterial thrombosis	–	Anti-coagulation, aspirin, azathioprine, steroid, NSAIDs
31	86	79	M	Wegener's granulomatosis	Osteoporosis	–	Steroids, azathioprine, NSAIDs
32	32	25	F	SLE	Malar rash, nephritic syndrome, arthralgia, anemia	ANA, anti-DNA, anticardiolipin (IgG, IgM)	Steroid, Mycophenolate mofetil
33	55	51	F	SLE, APS	CVA, headache, epilepsy, diffuse alveolar hemorrhage, pleural effusion, hemoptysis, epistaxis, thrombocytopenia, leukopenia, anemia, DVT	Anticardiolipin (IgG, IgM) lupus anticoagulant	Steroid, cyclophosphamide, cyclosporin, plasmapheresis,
34	49	46	M	ITP	Thrombocytopenia	Anti-B2GP1 (IgG, IgM)	Steroid
35	75	74	F	AIHA	Leukemia, anemia	–	Steroid
36	35	34	F	ITP	Arthralgia	ANA	Steroid
37	69	63	M	ITP	Osteoporosis, epistaxis, thrombocytopenia, AIHA, splenomegaly	–	Azathioprine, steroid, IVIG
38	32	29	M	ITP	Epistaxis	–	Steroid, IVIG
39	40	26	F	ITP	Epistaxis, thrombocytopenia, splenomegaly	ANA	Steroid, IVIG
40	43	39	F	ITP	Thrombocytopenia	–	Steroid
41	37	35	F	ITP	Thrombocytopenia	–	Steroid
42	39	7	F	Sickle cell disease	Osteoporosis, thrombocytopenia, microangiopathic hemolytic anemia, splenomegaly	–	Steroid, NSAIDs
43	21	15	M	ITP	Headache, hemoptysis, arthralgia, myalgia, thrombocytopenia, splenomegaly	ANA	Steroid, leflunomide
44	69	64	M	AIHA	Oral candidiasis, arthralgia, splenomegaly	–	Azathioprine, steroid

ANA: Antinuclear antibodies; Scl70: Anti-topoisomerase I; NSAIDs: Non-steroidal anti-inflammatory drugs; CVA: Cerebrovascular accident; c-ANCA: Cytoplasmic antineutrophil cytoplasmic antibodies; RF: Rheumatoid factor; Anti-β2GP1: Anti-β2 glycoprotein1; Anti-RNP: Anti-ribonucleoprotein antibody; SLE: Systemic lupus erythematosus; APS: Antiphospholipid syndrome; AIHA: Autoimmune hemolytic anemia; p-ANCA: Peripheral antineutrophil cytoplasmic antibodies; TMJ: Temporomandibular joint; IVIG: Intravenous immunoglobulin; DVT: Deep vein thrombosis; ITP: Idiopathic thrombocytopenic purpura.

(n=1), and sickle cell disease (n=1). The diagnoses, clinical manifestations, previous treatments and outcome are summarized in Table 1. Previous treatment modalities were documented; and the most widely used drugs were corticosteroids in 39 patients, non-steroidal anti-inflammatory drugs (NSAIDs) in 23 patients, anti-malarial drugs (n=17), azathioprine (n=15) and methotrexate (n=14). Other regimens such as mycophenolate (n=7), cyclophosphamide (n=6), cyclosporine, infliximab (n=5), and IVIG (n=5) were also used, but to a lesser extent.

The use of rituximab in the above reported cases was off-label, thus there was no consensus as to the dosing and number of cycles needed to attain a cure. The most commonly used protocol was either a 500 mg weekly dose for four weeks or two doses only of 1000 mg for every other week. The number of cycles administered was decided by the treating physician depending on the clinical and laboratory response to treatment by the patients. Twenty-two patients received 1 cycle, 10 patients received 2 cycles, whereas eight patients received a third cycle.

The efficacy of rituximab was retrospectively assessed according to improvement of clinical signs and symptoms of patients. Of all the patients found to be treated with rituximab, 38 patients documented response to treatment. The degree of response was divided into complete response without relapse, complete response with relapse, partial response or no response. Twenty-nine patients had complete response without relapse, three patients had relapse, while four patients had partial response (Figure 1). Out of 44 cases, only two patients had no response. To achieve complete remission, 12 patients required only 1 cycle of the drug, while 14 patients required a second or a third cycle for maintenance of remission every six to eight months. Figure 2 shows the number of cycles required to achieve remission. Patients receiving steroids as initial treatment for autoimmune and inflammatory processes were followed-up clinically and the dose of steroid was tapered over 8 to 12 weeks. Table 2 provides a summary of the response to rituximab for each disease reported, while Figure 3 shows the response rate in selected diseases. The most common autoimmune disease for which rituximab was used in this series was SLE. Of the 17 patients with SLE included in this study, 13 patients had complete response without relapse, two patients had partial response whereas one patient had no response. Of these patients, only one patient died during follow-up.

The efficacy of rituximab use as an off-label treatment of hematologic diseases was separately studied. The number of patients receiving rituximab for hematologic causes was 11, eight of whom were diagnosed with ITP. It was crucial to compare the level of platelet count before and after rituximab therapy among patients with ITP, in order to check for treatment response. The data revealed that the mean change in platelet count among the eight patients was significantly important with an increase from 46 thousands before rituximab treatment to 184 thousands after rituximab treatment, and a p-value of 0.012. The apparently significant increase in platelet count indicates response to therapy and a possibly disease remission. The remission rate in ITP was 67% (four out of six patients).

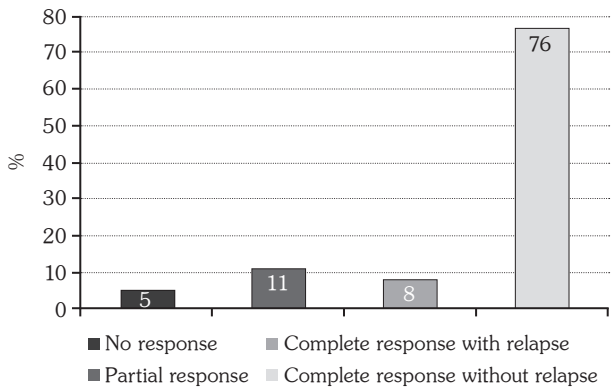

Figure 1. Summary of rate of response

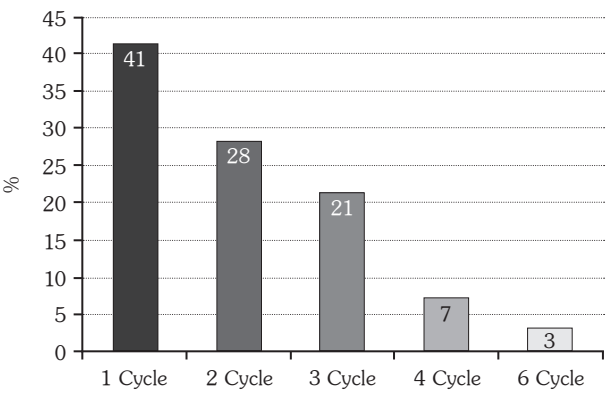

Figure 2. Number of cycles to achieve remission.

Table 2. Number of cycles used with corresponding level of response

	Number of patients			
Degree of response	No response	Partial response	Complete response with relapse	Complete response without relapse
Number of cycles				
1	2	2	1	12
2	0	1	1	8
3	0	1	1	6
4	0	0	0	2
6	0	0	0	1
Total number of patients	2	4	3	29

Skin infusion reactions were the most common side effects reported, which were observed in six out of 44 patients. The other patients did not have any reportable side effects of the medication. No serious hematological, renal, or hepatic toxicities were documented in our treated cohort.

DISCUSSION

In the past decades, therapeutic approaches to systemic autoimmune and inflammatory diseases have been based on the use of glucocorticosteroids and immunosuppressive agents. Available data on the use of biological agents in patients with these conditions rely mainly on a large number of observational studies and case reports. The almost total lack of randomized clinical trials may be explained by the low prevalence of systemic autoimmune diseases, their diverse clinical presentation, and the absence of consensual endpoints to be evaluated in each disease. This poses multiple questions on when and how to use these agents, since there are no current recommendations or guidelines on their use in such circumstances.[8]

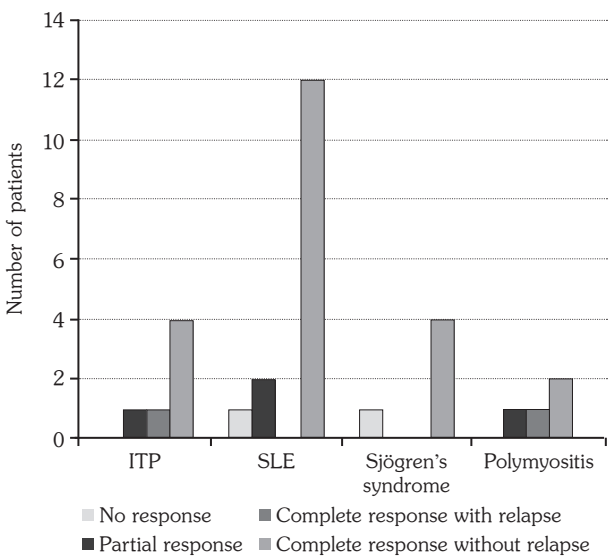

Figure 3. Degree of response for selected diseases. ITP: Idiopathic thrombocytopenic purpura; SLE: Systemic lupus erythematosus.

B cells play important roles in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, SLE, and Sjögren's syndrome. They exert their pathogenic effect by producing autoantibodies which target self antigens and induce inflammation and tissue injury, disrupting T cell tolerance, activating autoreactive memory T cells, attracting and activating dendritic cells, inhibiting regulatory T cells, and recruiting follicular B-helper T cells, among many other functions. It is important to note that all these effects are independent of antibody secretion, but are mediated instead through antigen-presentation, co-stimulation and production of proinflammatory cytokines. Hence, one would expect that the elimination of B cells by blocking CD20, the molecular target of rituximab, should be of therapeutic benefit in SLE.[9]

There was a predominance of females over males in the population studied, which is expected, given the fact that a large number of autoimmune diseases are more prevalent in women.[10] Moreover, studies have shown that the more frequent the autoimmune disease and the later it appears, the more women are affected.[11]

In this study, the indication for starting rituximab therapy was either treatment failure

after conventional regimens or treatment side effects. As expected, the preceding therapy for almost all patients with the diseases included in this study consisted of glucocorticosteroids (88%), NSAIDs (51%), and immunosuppressants (67%). Since no solid guidelines and recommendations are available for the rituximab dosing protocol, the number of cycles administered was decided by the treating physician depending on the clinical and laboratory response to treatment by the patients. The most commonly used protocol was either repeated cycles of a 500 mg weekly dose for four weeks or 1000 mg every two weeks whereby each cycle consisted of two doses. It was considerably promising that 84% of the patients showed clinical improvement after receiving rituximab, with 67% showing complete remission and 29% requiring only 1 cycle.

Systemic lupus erythematosus was the autoimmune disease with the highest reported use of rituximab in this study (17/44 patients, 38.6%). Although Merrill et al.[12] showed no difference in primary or secondary end points between placebo and rituximab treatment over 52 weeks of treatment in patients with moderate-to severe SLE in the EXPLORER trial, other studies have shown more promising results. Ramos-Casals et al.[8] in 2008 showed that the best results were observed in the use of rituximab for Sjögren's syndrome, SLE, and cryoglobulinemia. A recent review suggested that rituximab induces B-cell depletion in 95% of patients, and a significant reduction in disease activity is achieved with a relatively good safety profile in patients with SLE[7] However, there is always a difficulty in assessing the status of SLE patients and response rate in any research, given the heterogeneity of the disease. Hence, grouping patients according to types of organ systems affected in SLE shows that some have better response rates to rituximab than others, for example, cutaneous lesions/discoid lupus shows less improvement than neuropsychiatric or renal, and multi-system diseases are more responsive than single organ diseases.[13]

However, the encouraging results contrast with the poor outcome reported from the two randomized clinical trials (the Explorer and the Lunar) which tested the efficacy of rituximab in SLE. The contradictory findings can be attributed to several reasons including patient selection. The next issue is the method used to assess clinical activity. The British Isles Lupus Assessment Group (BILAG) index score is a transitional index developed for the intention-to-treat analysis, and may not be perfect for use in regular clinical practice.

The statistically significant increase in platelet count in patients with ITP after receiving rituximab therapy also emphasizes its therapeutic efficacy in hematological diseases. Similar results were found in a study conducted by Dierickx et al.[14] in 2009. They showed that the overall response rates were 79.2% in AIHA and 70% in ITP, with a median follow-up since the first rituximab administration was 15 month in AIHA and 11 months in ITP. Progression-free survival at one and two years were respectively 72% and 56% in AIHA, and 70% and 44% in ITP.

Concerning the safety profile of rituximab, this study showed no statistically significant change in liver, kidney or bone marrow laboratory markers before and after treatment. The most common side effects observed were benign and consisted mainly of infusion reactions. This safety profile has been highlighted in many other studies. Ceccarelli's safety study on SLE found adverse event rates comparable to the placebo, with the only differences being leukopenia (12.3% vs. 4.2%), neutropenia (5.5% vs. 1.4%) and hypotension (11% vs. 4.2%).[15] Medeot et al.,[16] on the other hand, ascertained a rituximab safety profile in patients with refractory ITP. They found that rituximab administration was associated with two episodes of short-term toxicity, namely a mild infusion reaction and a case of serum sickness syndrome, which improved rapidly with steroids; no infectious or other significant long-term complications were documented.

To conclude based on our study results, the off-label use of rituximab carries a promising cure for debilitating and relapsing autoimmune and inflammatory disorders with a relatively good safety profile. However, the fact that we still have conflicting results from various observational studies, reviews and case reports, dictates the necessity for large randomized control trials on the efficacy and safety of rituximab therapy in various autoimmune and inflammatory diseases. This is crucial to set forth solid and reliable guidelines and recommendations for the dosing of rituximab and its prescription protocol.

Declaration of conflicting interests

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