On- and off-label use of rituximab in rheumatic diseases

Gilda Sandri, Carlo Umberto Manzini, Carlo Salvarani

Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy

Abstract

Steadily growing knowledge about pathogenetic mechanisms in autoimmune rheumatic diseases (RDs) has paved the way to different therapeutic approaches. In particular, the availability of biologics on the market has dramatically modified the natural history of rheumatic chronic inflammatory diseases with a meaningful impact on patients' quality of life. Among the wide spectrum of available biological treatments, rituximab (RTX), initially used in the treatment of non-Hodgkin's lymphoma, was later approved for rheumatoid arthritis and anti-neutrophil cytoplasmic antibodies-associated vasculitis. Currently, in rheumatology, RTX is also used with off-label indications in patients with systemic sclerosis, Sjögren's syndrome and systemic lupus erythematosus. RTX is a monoclonal antibody targeted to CD20 molecules expressed on the surface of pre-B and mature B lymphocytes. It acts by causing apoptosis of these cells with antibody- and complement-dependent cytotoxicity. As inflammatory responses to cell-associated immune complexes are key elements in the pathogenesis of several autoimmune RDs, such an approach might be effective in these patients. In fact, RTX promotes a rapid and long-term depletion of circulating and lymphoid tissue-associated B cells, thus leading to a lower recruitment of these effector cells at sites of immune complex deposition, therefore reducing inflammation and tissue damage. RTX is extremely interesting for rheumatologists, as it represents an important additional therapeutic approach. Therefore, the advent in clinical practice of approved RTX biosimilars, such as CT-P10, may help in improving treatment access as well as reducing costs.

Correspondence: Carlo Umberto Manzini, Rheumatology Unit, University of Modena and Reggio Emilia, Via del Pozzo 71, 41121, Modena, Italy.
Tel.: +39.059.4225663 - Fax: +39.059.4223007.
E-mail: manzini.carlo@aou.mo.it

Key words: Rituximab; rheumatoid arthritis; ANCA-associated vasculitis; systemic sclerosis; Sjögren's syndrome; systemic lupus erythematosus; biologics; biosimilars; myositis.

Conflict of interests: the authors declare no potential conflict of interests.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: Not required

Received for publication: 12 January 2021.
Revision received: 30 March 2021.
Accepted for publication: 31 March 2021.

Licensee PAGEPress, Italy
Beyond Rheumatology 2021; 3:56
doi:10.4081/br.2021.56

Introduction

Rituximab (RTX) is a chimeric monoclonal anti-CD20 antibody that induces B-cell depletion through complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC) and direct signaling. It is presumed to play a central role in the generation of B-cell responses against T-cell independent antigens.[1,2]

It was firstly approved for the treatment of indolent non-Hodgkin's lymphoma in 1994 and later for the treatment of rheumatoid arthritis (RA). Finally, it was approved for remission induction and maintenance therapy of associated vasculitis (AAV).[3,4] RTX has also been used in the most common systemic autoimmune rheumatic diseases (SARDs), such as, amongst others, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary Sjögren syndrome (pSS) and idiopathic inflammatory myopathy (IIM). The complex pathogenesis of most SARDs is not yet fully understood, but an essential role of B cells appears to be clear in the autoimmune response to these diseases, thus providing a rationale for the use of RTX, a B-cell depleting agent.

At the moment, RTX regimen is intravenous (IV) with slightly different dosages for RDs ranging from 1000 mg administered 2 weeks apart in RA to 375 mg/m^2 weekly for 4 weeks in AAV. In all patients, premedication with methylprednisolone 100 mg IV, acetaminophen and antihistamines is highly recommended before each infusion. Depending on convenience and safety considerations, RTX can be administered intravenously (IV) or subcutaneously. In autoimmune diseases, only IV administration has been studied. The most widely used schedule (the 'RA dose') consists of 1000 mg at weeks 0 and 1 or 2.[2] The number of courses (one or more) depends on the indication. The premedication consists of paracetamol (1 g), an antihistaminic (*e.g.*, diphenhydramine) and the equivalent of 100 mg methylprednisolone.

Methodology

We conducted a non-systematic review. The PubMed database was searched for any study associated with RTX in RD. Accordingly, the two terms 'Rheumatic disease' AND 'Rituximab' rituximab AND (SLE), rituximab AND (SSc or scleroderma), rituximab AND (pSS), rituximab AND (IIM OR myositis), RA AND 'Rituximab' AAV and Rituximab were used to find relevant studies. The

search was updated in March 2020. This review provides insights into the current on- and off-label use of RTX in RDs with a focus on the advent of biosimilars.

Systemic lupus erythematosus

B lymphocytes have proven to play a major role in the pathogenesis of SLE.[5] Therefore, B-cell depletion therapy has gained much interest in management of SLE and lupus nephritis (LN). Isenberg *et al*.[6] led the early studies on B-cell depletion therapy with RTX for lupus treatment.[5,6] The first trial of RTX in SLE patients with active disease reported promising clinical efficacy and a favorable safety profile.[7] This was followed by wide adoption of RTX in clinical practice, and many case reports were published confirming its usefulness.[8] However, unexpectedly, RTX did not meet the primary endpoints in two large trials of non-renal (EXPLORER) and renal (LUNAR) SLE.[9,10] These trials were later criticized for their poor design, particularly the concomitant administration of high doses of corticosteroids, which may have hidden the clinical response attributable to RTX.[11-13] RTX remains a common off-label prescription for the treatment of SLE in spite of conflicting evidence in clinical studies.[14-16] Thereby, we aimed to generate robust evidence on the clinical efficacy of RTX in SLE and LN patients, refractory to conventional treatment. Our findings suggest a potential therapeutic efficacy of RTX in both SLE and LN patients. RTX achieved a 73% global response rate, a 51% complete remission and a 34% partial remission in SLE and LN patients. Moreover, it decreased significantly the BILAG and SLEDAI scores as well as proteinuria. Additionally, RTX demonstrated a significant corticosteroid sparing effect with a remarkable reduction of the prednisone dose in both SLE and LN patients. These effects are consistent with evidence from recent clinical trials.[17] RTX displayed promising effects in cases of neuropsychiatric SLE (NPSLE) leading to a rapid improvement of cognitive dysfunction, psychosis and seizures. NPSLE patients on RTX had a long-lasting significant reduction of SLEDAI. However, these effects were revealed in one study on 10 patients, therefore so further assessment of the role of RTX in NPSLE in larger studies is warranted. In non-renal moderate-to-severe SLE, RTX can be considered in refractory cases, as mentioned in the guidelines of the British Society of Rheumatology.[18] In terms of adverse reactions, RTX was well tolerated by most of the patients enrolled in the included studies. The most common adverse reactions were infections, acute or delayed infusion reactions and thrombocytopenia.[19-21] Sepsis-like syndrome and serum sickness-like reaction occasionally occurred in three patients overall.[22,23] Although not yet authorized for the treatment of SLE and LN, RTX is widely used in these patient groups. Data from Ryden-Aulin *et al*.[24] study of the off-label use of RTX for SLE in Europe indicated that RTX is used in 4% to 20% of SLE patients in Sweden, up to 11% in Spain, and 7% in the U.K. Moreover, adoption of RTX for management of SLE ranged from 1% to 4% in other European countries. Clinicians have high expectations for RTX therapy owing to the favorable data from clinical practice and observational studies as well as some promising exploratory outcomes from the LUNAR trial, such as potential advantage in African Americans.[6,25,26] Furthermore, off-label use of RTX is supported by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines, which include it as a treatment option for patients with refractory LN.[27,28] Several uncontrolled open-label studies and cohort studies (systematically reviewed by other authors[29,30]) also reported this glucocorticoid-sparing effect. Furthermore, these uncontrolled studies suggest efficacy of RTX in patients with refractory SLE disease activity. When considering organ-specific refractory disease manifestations, RTX seems effective in LN, arthritis and immune thrombocytopenic purpura, with weaker evidence for an effect in autoimmune hemolytic anemia, cutaneous and neurological involvement. ACR and EULAR guidelines state that RTX can be used in LN when conventional treatment with glucocorticoids and cyclophosphamide and/or mycophenolate mofetil has failed.[27,28] In short, our findings demonstrate that RTX treatment achieved significant clinical efficacy and a favorable safety profile in SLE and LN patients refractory to conventional treatment. Further large well-designed multicenter randomized controlled trials are warranted with the aim of approving RTX as a standard therapy for lupus.

Rituximab in anti-neutrophil cytoplasmic antibodies-associated vasculitis

AAV are rare diseases classified on the basis of both vascular inflammation distribution and the presence or absence of granulomatosis and asthma. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis) and eosinophilic GPA (also known as Churg-Strauss syndrome).[3] RTX has been approved by the U.S. Food and Drug Administration (FDA) for two types of AAV: GPA and MPA. In AAV patients, RTX works by decreasing the levels of harmful anti-neutrophil cytoplasmic antibodies (ANCA) autoantibodies, which normally target the proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) proteins in certain types of immune cells. Two retrospective open-label studies reported remission (Birmingham Vasculitis Activity Score Modified for GPA: 0) in all 21 AAV patients enrolled. Based on these successful results, the first seminal multicenter randomized double-blind controlled trial on RTX in AAV (RAVE) was designed. The study was based on data from 99 AAV patients who participated in the RAVE Phase 2/3 trial (NCT00104299), a multi-center, randomized, double-blind, placebo-controlled study designed to evaluate the effectiveness of RTX in GPA and MPA patients, compared with conventional therapies. The RAVE trial demonstrated that a single course of RTX was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remission in AAV. Further analysis of the RAVE trial revealed that an increase in PR3-ANCA levels during remission was related to an increased risk of relapse, particularly among patients with renal involvement or alveolar hemorrhage.[3,31-34] The MAINRITSAN trial, which was the first randomized controlled trial to compare the efficacy of RTX and azathioprine in AAV remission maintenance, demonstrated a superior outcome using RTX. The randomized controlled studies MAINRITSAN and RITAZEREM demonstrated that RTX was superior to azathioprine for remission maintenance in AAV, without increasing the adverse event rate.[34-36] This study suggests that repeated course of RTX might improve clinical response.

Rheumatoid arthritis

Although the etiology and the pathogenesis of RA are complex, various new biologics have revolutionized therapeutic approaches. They usually suppress the immune system by targeting particular

signaling pathways and act in a more specific manner. It was suggested that biologic agents, such as tumor necrosis factor-alpha (TNFα) inhibitors and RTX, could significantly reduce the mortality risk in RA patients, as compared with disease-modifying antirheumatic drugs.[37]

Overall, among the different biologic drugs to target B cells, such as ocrelizumab, ofatumumab, belimumab and atacicept, RTX is the only one with promising results and an acceptable safety profile for the treatment of RA patients. Despite the approval of RTX for RA patients, promising results and fewer adverse effects compared to conventional treatments, there are growing concerns over the safety of this drug. Additionally, there is no consensus regarding optimum dosage, biomarkers for RTX response and treatment of pregnant women with RTX, which are issues that need to be addressed. Comprehensive insights into these matters could open an avenue for developing more effective and safer treatments for RA patients.[38] In 2004, the first randomized double-blind placebo-controlled trial in patients with long-standing active RA, despite methotrexate treatment, demonstrated that a single course of two infusions of RTX, alone or in combination with either cyclophosphamide or continued methotrexate, provided significant improvement in clinical response at weeks 24 and 48.4. The efficacy and safety of different RTX doses plus methotrexate, with or without glucocorticoids, in patients with active RA who did not respond to disease-modifying antirheumatic drugs were tested in the DANCER study.[5] Both RTX doses (*i.e.*, 500 mg or 1000 mg on Days 1 and 15) were effective and well tolerated.[39] Moreover, the MIRROR study demonstrated that RTX dose escalation from two doses of 500 mg to two doses of 1000 mg did not improve clinical response. A retreatment strategy from Week 24 promoted a sustained suppression of disease activity through to Week 48.6.[40] The Phase III SERENE study investigated the efficacy and safety of RTX plus methotrexate in patients with active RA who were naive to prior biological treatment. RTX both 2×500 mg and 2×1000 mg plus methotrexate significantly improved clinical outcomes at Weeks 24 and 48.[41] Further studies in patients with RA with inadequate response to antitumor necrosis factor (anti-TNF) therapies demonstrated that a single course of RTX associated with methotrexate provided significant improvements in disease activity and progression of radiological damage.[42-46] Sustained clinical efficacy was better maintained after two courses of RTX about 6 months apart.[10] In 2011, a Phase IIIb open-label prospective study (RESET) confirmed that RTX is an effective treatment option for patients who have not responded to a single TNF-α inhibitor, particularly for seropositive patients.[47] The MIRAR study and real-life data indicate that switching to RTX is a successful treatment option for patients with RA who are failing on TNF antagonists.[48] Treatment with RTX (2×1000 mg) in combination with MTX has proven to be effective for patients with MTX-naive RA, leading to sustained improvements in radiographic, clinical and functional outcomes over 2 years.[49]

In recent years, different RTX biosimilars have been introduced, and many clinical trials are being conducted to evaluate their efficacy and safety compared with the originator.[50] These alternative drugs, such as Truxima (CT-P10) and Rixathon (GP2013), are increasingly being used due to availability and lower cost. It was revealed that switching from reference RTX to GP2013 is not associated with any additional safety or immunogenicity problems.[51] Regarding CT-P10, there was no significant difference between the efficacy, safety and immunogenicity of reference RTX and biosimilar RTX at 24, 48 and 72 weeks' follow-up.[50,51] Similar findings in terms of efficacy, safety and immunogenicity were reported for PF-m05280586, another RTX biosimilar.[52]

Biosimilars have no clinical meaningful differences, in terms of efficacy and safety, with respect to the originator; thanks to cost saving, they should be considered, and their use should be promoted. The availability of biosimilars would allow patients to receive medications that might otherwise be unaffordable to them.[53]

Systemic sclerosis

Systemic sclerosis (SSc) is a chronic collagen disease, with a complex pathogenesis, characterized by autoimmune disorders and excessive extracellular matrix deposition in the skin and visceral organs.[54]

The major pathognomonic abnormalities are represented by: widespread collagen deposition in several organs, resulting in fibrosis; vascular damage, which mainly consists of Raynaud's phenomenon; presence of immune activity.

As to latter context in particular, we recognize, in SSc patients, an autoimmune disorder, supported by abnormal function of B cell and autoantibody synthesis.[55] Moreover, many cellular activities, such as cytokine production, peripheral T cell subpopulations activity and antigen presenting cells including dendritic cells and macrophage, are regulated by B cells themselves. Therefore, their alteration can be responsible for the induction and evolution of SSc;[56-59] also T cells may be centrally involved in the pathogenesis of SSc.[60]

Based on the above, over the last few years, RTX, a chimeric monoclonal antibody which targets and depletes B cells, is successfully used in the treatment of resistant SSc with beneficial results.[61-67]

Interestingly, in patients with SSc, RTX treatment reduces circulating as well as skin CD4+IL4+ T cells, which contribute to the fibrosis of the heart, liver, kidneys, and skin.[68]

In a recent careful investigation conducted by a systemic review on this topic,[69] some studies on the efficacy of RTX on lung function and skin fibrosis in patients with SSc are reported,[62-64,70,71] while others do not confirm or reject potential efficacy of RTX in these patients.[72] SSc-associated arthritis is generally susceptible to RTX therapy, while digital ulcers result scarcely responsive.[73]

Regarding the possible side effects of RTX treatment, the main ones are mild infusion reactions, sepsis, urinary and pulmonary infections, herpes zoster and cardiovascular involvement.[62,64,71,74] However, available experience related to side effects derives especially from RTX treatment of RA, in which severe reactions are uncommon, less than 1%, and the risk of malignancy (solid tumor or lymphoma) is similar to other conditions.[75]

In fact, a limited number of open-label, uncontrolled trials are generally referred to SSc patients, while only one multicenter study tested a large number of scleroderma patients.[76]

Nowadays, RTX really seems to be a safety and effective therapy for SSc patients.

Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a systemic *autoimmune disease* of unknown etiology, characterized by xerophtalmia and xerostomia. Histologically a lymphocytic infiltration of exocrine glands is detected.

The pathogenesis of pSS is notoriously related to T cells,[77] as well as to a major contribution of B cells.[78-80]

More specifically, dysregulation of B cells causes an alteration of peripheral B-cell homeostasis and depletion of circulating CD27+ memory cells; accumulation and retention of autoantibody-producing B cells in the inflamed glands are noticeable.[81] In addition, B lymphocytes can stimulate a wide range of cytokines such as IL-1, IL-6, IL-7, and TNF-□.[82]Moreover, pSS patients present an increased risk for B-cell lymphoma, if compared with other autoimmune diseases.[83,84]

Nonetheless, the efficacy of RTX therapy in pSS appears quite elusive compared to other autoimmune diseases. A well conducted review on this question[85] analyzed many papers considering the efficacy of this therapy on various clinic and serologic pSS parameters (salivary and tear gland function, fatigue, dryness VAS; pain; IgG; RF; anti-salivary glands B Ro/La cells).[86-96]

Not all studies converge towards the same results; in fact, though some smaller works evidenced promising results of RTX therapy in pSS, the two major randomized control trials (TEARS and TRACTISS) did not achieve their primary outcomes.[92,93]

Indeed, different criteria were adopted in selecting patients and in the study design, furthermore patients with low baseline disease activity were treated.

In particular, the two trials mentioned above do not include the baseline systemic disease activity assessment tool ESSDAI (EULAR SS disease activity index),[97] which will hopefully be introduced in future studies.

However, RTX therapy in pSS seems particularly effective in the early stage of the disease and before permanent loss of glandular function,[9] appearing to be generally safe with an incidence of adverse events comparable to other groups of patients.

However further trials including more patients are needed to reach a clear conclusion.

Idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies are a group of rheumatic autoimmune diseases which involve skeletal muscles and internal organs such as lung, heart, esophagus.

They include dermatomyositis, polymyositis, necrotizing autoimmune myositis, inclusion-body myositis.

In the last 15 years, RTX therapy has frequently been proposed in many uncontrolled studies, for the treatment of the myopathies, in particular when therapy with steroids and at least one other immunosuppressive agent failed.

The results do not completely agree among the various trials, underlining the complexity of these diseases so that, at the current time, RTX is not probably the decisive drug for the treatment of myopathies.

The various subsets of patients of the different trials did not respond only to RTX.

Interestingly, Fasano e Coll, in a careful review,[98] extracted some results from some meaningful trials and reported that patients with myositis-specific autoantibodies, especially anti-Mi-2 and anti-Jo1, evidenced a considerable improvement compared to other subsets of patients. However, it should be noted that anti-Jo1 levels do not tend to decrease after the treatment, maybe because long-lived plasma cells producing autoantibodies are CD20 negative, thus raising some uncertainties about the use of RTX.[98-100] In addition, the pathogenic role of these antibodies is still currently unclear.[101]

As to the complications of myopathies, the interstitial lung disease, which is one the most frequent and worrying complication, in patients with anti-synthetase syndrome appears to be responsive to RTX therapy, unlike other drugs which were not effective.[99,100,102]

Skin manifestations of patients with dermato-polymyositis would be sensitive to RTX only in some cases or not at all.[103-106]

Dysphagia essentially proves unresponsive to RTX.[107]

In short, off-label RTX therapy can be useful in several patients affected by refractory myositis.

Conclusions

RTX is definitely an effective therapy for many rheumatic conditions, both in label and off label, and is often employed when other immunosuppressive agents failed.

As to the risk of infection, patients must be vaccinated against influenza and *Pneumococcus*[108] and against severe acute respiratory syndrome-related coronavirus disease 2 (SARS-CoV-2) as soon as possible.

For the SARS-CoV-2 vaccination, the vaccine series must be initiated approximately 4 weeks prior to next scheduled rituximab cycle; after vaccination, it is recommended to delay RTX by 2-4 weeks after the 2nd vaccine dose, if disease activity allows [ACR COVID-19 Vaccine Clinical Guidance Task Force. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases; March 4, 2021. Unpublished data, in peer review].

References

1. Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest 2010;120:214-22.
2. Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010;47:115-23.
3. Stone PA, Spiera R, Seo P, et al. RAVE-ITN Research Group. SR. S. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
4. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771-80.
5. Mota P, Reddy V, Isenberg D. Improving B-cell depletion in systemic lupus erythematosus and rheumatoid arthritis. Expert Rev Clin Immunol 2016:1-10.
6. Ramos L, Isenberg D. Rituximab: the lupus journey. Curr Treatm Opt Rheumatol 2015;1:30-41.
7. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum 2004;50:2580-9.
8. Díaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012;11:357-64.
9. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum 2012;64:1215-26.
10. Merrill J, Furie R, Latinis K, et al. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). Lupus 2011;20:709-16.

11. Ramos-Casals M, Soto M, Cuadrado M, Khamashta M. Rituximab in systemic lupus erythematosusA systematic review of off-label use in 188 cases. Lupus 2009;18:767-76.
12. Isenberg DA, Merrill JT. Why, why, why de-lupus (does so badly in clinical trials). Expert Rev Clin Immunol 2016;2:95-8.
13. Ramos-Casals M, Díaz-Lagares C, Khamashta MA. Rituximab and lupus: good in real life, bad in controlled trials. Comment on the article by Lu et al. Arthritis Care Res 2009;61:1281-2.
14. Terrier B, Amoura Z, Ravaud P, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 2010;62:2458-66.
15. Díaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012;11:357-64.
16. Furie R, Looney R, Rovin B, et al. Efficacy and safety of rituximab in subjects with active proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study. Arthritis Rheum 2009:60.
17. Gracia-Tello B, Ezeonyeji A, Isenberg D. The use of rituximab in newly diagnosed patients with systemic lupus erythematosus: long-term steroid saving capacity and clinical effectiveness. Lupus Sci Med 2017;4:000182.
18. Gordon C, Gayed M, Brown S, et al. British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatol 2017;epub(6 October):1-45.
19. Lindholm C, Börjesson-Asp K, Zendjanchi K, et al. Longterm clinical and immunological effects of anti-CD20 treatment in patients with refractory systemic lupus erythematosus. J Rheumatol 2008;35:826-33.
20. Reynolds J, Toescu V, Yee C, et al. Effects of rituximab on resistant SLE disease including lung involvement. Lupus 2009;18:67-73.
21. Tanaka Y, Yamamoto K, Takeuchi T, et al. A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. Mod Rheumatol 2007;17:191-7.
22. Davies R, Sangle S, Jordan N, et al. Rituximab in the treatment of resistant lupus nephritis: therapy failure in rapidly progressive crescentic lupus nephritis. Lupus 2013;22:574-82.
23. Gottenberg J-E, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913-20.
24. Rydén-Aulin M, Boumpas D, Bultink I, et al. Off-label use of rituximab for systemic lupus erythematosus in Europe. Lupus Sci Med 2016;3:e000163.
25. Moroni G, Raffiotta F, Trezzi B, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. Rheumatology 2014;53:1570-7.
26. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215-26.
27. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012;64:797-808.
28. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-82.
29. Fernandez-Nebro A, de la Fuente JM, Carreno L, et al. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus 2012;21:1063-76.
30. Vital EM, Dass S, Buch MH, et al. B cell biomarkers of rituximab responses in systemic lupus erythematosus. Arthritis Rheum 2011;63:3038-47.
31. Iaccarino L, Bartoloni E, Carli L, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. Clin Exp Rheumatol 2014;33:449-56.
32. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.
33. Keogh KA, Ytterberg SR, Fervenza FC, et al. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006; 173:180-7.
34. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417-27.
35. Fussner LA, Hummel AM, Schroeder DR, et al. Factors determining the clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3. Arthritis Rheumatol 2016;68:1700-10.
36. Gopaluni S, Smith RM, Lewin M, et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials 2017;18:112
37. Edwards JC, Szczepański L, Szechiński J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Eng J Med 2004;350:2572-81.
38. BuchMH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909-20.
39. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54: 2793-806.
40. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-400.
41. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX inadequate responders (SERENE)). Ann Rheum Dis 2010;69:1629-35.
42. Coutant F, Rouzaire P, Soubrier M. An unexpected response to rituximab in a patient with rheumatoid arthritis. Rheumatology (Oxford) 2017;57:580-2.
43. Vital EM, Dass S, Rawstron AC, et al. Management of nonresponse to rituximab in rheumatoid arthritis: predictors and outcome of re-treatment. Arthritis Rheum 2010;62:1273-9.
44. Henry J, Gottenberg JE, Rouanet S, et al. Doses of rituximab for retreatment in rheumatoid arthritis: influence on maintenance and risk of serious infection. Rheumatology (Oxford) 2017;57:538-47.

45. Mena-Vazquez N, Manrique-Arija S, Urena-Garnica I, et al. Efficiency of different doses of rituximab in rheumatoid arthritis. Reumatol Clin 2016;12:139-45.
46. Sellam J, Hendel-Chavez H, Rouanet S, et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study. Arthritis Rheum 2011;63:933-8.
47. Haraoui B, Bokarewa M, Kallmeyer I, et al. RESET Investigators Safety and Effectiveness of Rituximab in Patients With Rheumatoid Arthritis Following an Inadequate Response to 1 Prior Tumor Necrosis Factor Inhibitor: The RESET Trial J Rheumatol 2011;38:2548-56.
48. Gomez-Reino JJ, Maneiro JR, Ruiz J, et al. Comparative Effectiveness of Switching to Alternative Tumour Necrosis Factor (TNF) Antagonists Versus Switching to Rituximab in Patients With Rheumatoid Arthritis Who Failed Previous TNF Antagonists: The MIRAR Study. Ann Rheum Dis 2012;71: 1861-4.
49. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.
50. Yoo DH, Park W, Suh CH, et al [webpage on the Internet]. Efficacy and safety of switched CT-P10 from innovator rituximab compared to those of maintained CT-P10 in patients with rheumatoid arthritis up to 56 weeks. Arthritis Rheumatol 2015;67(suppl 10).
51. Smolen J, Scheinberg M, Tony H, et al. FRI0222 pharmacokinetics, pharmacodynamics, safety and efficacy of proposed rituximab biosimilar (GP2013) vs EU-approved rituximab (RTX) in patients with rheumatoid arthritis: results from a randomized controlled trial (GP13-201) over 52 weeks. Ann Rheum Dis 2016;75:512-3.
52. Cohen S, Emery P, Greenwald M, et al. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. Br J Clin Pharmacol 2016;82:129-38.
53. Dorner T, Strand V, Cornes P, et al. The changing landscape of biosimilars in rheumatology. Ann Rheum Dis 2016;75:974-82.
54. Yoshizaki A. Pathogenic roles of B lymphocytes in systemic sclerosis. Immunol Lett 2018;1-7.
55. Whitfield ML.Systemic and cell type-specific gene expression patterns in scleroderma skin, Proc Natl Acad Sci U S A 2003;100;12319-24.
56. Bouaziz JD, Yanaba K, Tedder TF. Regulatory B cells as inhibitors of immune responses and inflammation. Immunol Rev 2008;224:201-4.
57. Yoshizaki A. B lymphocytes in systemic sclerosis: abnormalities and therapeutic targets. J Dermatol 2016;43:39-45.
58. Yoshizaki A, Sato S. Abnormal B lymphocyte activation and function in systemic sclerosis. Ann Dermatol 2015;27:1-9.
59. Liossis SN, Sfikakis PP. Rituximab-induced B cell depletion in autoimmune diseases: potential effects on T cells. Clin Immunol 2008;127:280-5.
60. Sakkas LI, Xu B, Artlett CM, et al. Oligoclonal T cell expansion in the skin of patients with systemic sclerosis. J Immunol 2002;168:3649-59.
61. Daoussis D, Liossis SN, Tsamandas AC, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol 2011;30:S17-22.
62. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparativestudy of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum 2017;46:625-31.
63. Jordan S, Distler JHJHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis 2015,74:1188-94.
64. Bosello SL, De Luca G, Rucco M et al. Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. Semin Arthritis Rheum 2015;44:428-36.
65. Smith V, Piette Y, Van Praet JT, et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. J Rheumatol 2013;40:52-7.
66. Keir GJ, Maher TM, Hansell DM et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescuetherapy. Eur Respir J 2012;40:641-8.
67. Keir GJ, Maher TM, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology 2014;19: 353-9.
68. Antonopoulos I, Daoussis D, Lalioti M−E, et al. B cell depletion treatment decreases CD4+IL4+ and CD4+CD40L+ Tcells in patients with systemic sclerosis. Rheumatol Int 2019;39:1889-98.
69. de Figueiredo Caldas MMV, Bezerra Neto FA, de Azevedo KPM, et al. Rituximab in systemic sclerosis. A protocol for systematic review. Medicine 2019;98:38:1-4.
70. Daoussis D, Liossis SNC, Tsamandas AC, et al. Experience with rituximab in scleroderma: Results from a 1-year, proof-of-principle study. Rheumatology (Oxford) 2010;49:271-80.
71. Melsens K, Vandecasteele E, Deschepper E, et al. Two years follow-up of an open-label pilot study of treatment with rituximab in patients with early diffuse cutaneous systemic sclerosis. Acta Clin Belg 2018;73:119-25.
72. Boonstra M, Meijs J, Dorjée AL, et al. Rituximab in early systemic sclerosis. RMD Open 2017;3:e000384.
73. Giuggioli D, Lumetti F, Colaci M, et al. Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature. Autoimmun Rev 2015;7.
74. Smith V, Piette Y, Van Praet JT, et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. J Rheumatol 2013;40:52-7.
75. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909-20.
76. Jordan S, Distler JH, Maurer B, et al; EUSTAR Rituximab study group. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis 2015;74:1188-94.
77. Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. Clin Immunol Immunopathol 1994;72:162-5.
78. Le Pottier L, Devauchelle V, Pers JO, et al. The mosaic of B-cell subsets (with special emphasis on primary Sjögren's syndrome). Autoimmun Rev 2007;6:149-54.
79. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary Sjögren's syndrome. Nat Rev Rheumatol 2013;9:544-56.
80. Kroese FG, Abdulahad WH, Haacke E, et al. B-cell hyperactivity in primary Sjögren's syndrome. Expert Rev Clin Immunol 2014;10:483-99.
81. Ibrahem HM. B cell dysregulation in primary Sjögren's syndrome: A Review. Jpn Dent Sci Rev 2019;55:139-44.

82. Bikker A, van Woerkom JM, Kruize AA, et al. Increased expression of IL-7 in labial salivary glands of patients with primary Sjögren's syndrome correlates with increased inflammation. Arthritis Rheum 2010;62:969-77.
83. Weng MY, Huang YT, Liu MF, Lu TH. Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjögren's syndrome in Taiwan. Ann Rheum Dis 2012;71:524.
84. Johnsen SJ, Brun JG, Goransson LG, et al. Risk of non-Hodgkin's lymphoma in primary Sjögren's syndrome: A population based study. Arthritis Care Res 2013;65:816-21.
85. Grigoriadou S, Chowdhury F, Pontarini E, et al. B-cell depletion with rituximab in the treatment of primary Sjögren's syndrome: what have we learnt? Clin Exp Rheumatol 2019;37:S217-24.
86. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.
87. Pijpen J, Van Imhoff GW, Spijkervert FKL, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.
88. Carubbi F, Cipriani P, Marrelli A, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther 2013;15:R172.
89. Clairew S, Levesque MC, Prak ETL, et al. Rituximab therapy for primary Sjögren's syndrome: an open-label clinical trial and mechanistic analysis. Arthritis Rheum 2013;65:1097-106.
90. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4.
91. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.
92. Devauchelle-Pensec V, Mariette X, Jousse-Joulins J, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 2014;160:233-42.
93. Bowman SJ, Everett CC, O'Dwyer JL, et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome. Arthritis Rheumatol 2017;69:1440-50.
94. Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.
95. Meiners PM, Arends S, Brouwer E, et al. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-02.
96. Gottemberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. Ann Rheum Dis 2013;72:1026-31.
97. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.
98. Fasano S, Gordon P, Hajji R, et al. Rituximab in the treatment of inflammatory myopathies: a review. Rheumatology 2016;56:26-36.
99. Sem M, Molberg O, Lund MB, et al. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology (Oxford) 2009;48:968-71.
100. Allenbach Y, Guiguet M, Rigolet A, et al. Efficacy of rituximab in refractory inflammatory myopathies associated with anti-synthetase auto-antibodies: an open-label, phase II Trial. PLoS One 2015;10:e0133702.
101. Ascherman DP. The role of Jo-1 in the immunopathogenesis of polymyositis: current hypotheses. Curr Rheumatol Rep 2003;5:425-30.
102. Vandenbroucke E, Grutters JC, Altenburg J, et al. Rituximab in life threatening antisynthetase syndrome. Rheumatol Int 2009;29:1499-502.
103. Rider LG, Yip AL, Horkayne-Szakaly I, et al. Novel assessment tools to evaluate clinical and laboratory responses in a subset of patients enrolled in the rituximab in myositis trial. Clin Exp Rheumatol 2014;32:689-96.
104. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol 2007;143:763-7.
105. Barsotti S, Cioffi E, Tripoli A, et al. The use of rituximab in idiopathic inflammatory myopathies: description of a monocentric cohort and review of the literature. Reumatismo 2018;70:1011.
106. Aggarwal R, Loganathan P, Koontz A, et al. Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. Rheumatology 2016;56:247-54.
107. De Souza FHC, Miossi R, de Moraes JCB, et al. Favorable rituximab response in patients with refractory idiopathic inflammatory myopathies. Adv Rheumatol 2018;58:31.
108. Landewé RBM, Machado PM, Kroon F, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2 Ann Rheum Dis [published online June 5, 2020]. doi:10.1136/annrheumdis-2020-217877.