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REVIEW

Current perspective on rituximab in rheumatic diseases

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Abstract: The steadily increasing knowledge regarding pathogenetic mechanisms in autoimmune rheumatic diseases has paved the way to different therapeutic approaches. In particular, the market entry of biologics 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), first used in the treatment of non-Hodgkin's lymphoma, was later approved for rheumatoid arthritis and anti-neutrophil cytoplasmic antibodies-associated vasculitis. Nowadays, 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 directed to CD20 molecules expressed on the surfaces 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 rheumatic diseases, such an approach might be effective in these patients. In fact, RTX, by promoting the rapid and long-term depletion of circulating and lymphoid tissue-associated B cells, leads to a lower recruitment of these effector cells at sites of immune complex deposition, thus reducing inflammation and tissue damage. RTX is of the most interest to rheumatologists as it represents an important additional therapeutic approach. Thus, the advent in clinical practice of approved RTX biosimilars, such as CT-P10, may be of help in improving treatment access as well as in reducing costs.

Keywords: rituximab, rheumatoid arthritis, ANCA-associated vasculitis, systemic sclerosis, Sjögren's syndrome, systemic lupus erythematosus, biologics, biosimilars, myositis, pregnancy, vaccination

Introduction

Rituximab (RTX) is a chimeric mouse/human monoclonal antibody that targets the transmembrane protein CD20 molecule on the surfaces of some but not all B cells. RTX by binding to CD20, that is expressed on pre-B and mature B lymphocytes, leads to apoptosis of these cells with antibody- and complement-dependent cytotoxicity (Figure 1). This mechanism of action leads, in most patients, to a selective peripheral B cell depletion for more than 24 weeks. However, other niches of B cells (eg, those in the synovium) are variably depleted. RTX has no or little effects on autoantibody levels, which are mainly secreted by mature plasma cells, but it is active on memory and mature B cells. Repopulation of peripheral B cells occurs after 6–9 months from RTX course, and it can be of particular utility in patients with scarce adherence to daily therapy.

Nowadays, RTX is a well-established biologic agent for the treatment of some rheumatic autoimmune diseases such as refractory rheumatoid arthritis (RA)[1,2] and anti-neutrophil cytoplasmic antibodies (ANCAs)-associated vasculitis (AAV).[3]

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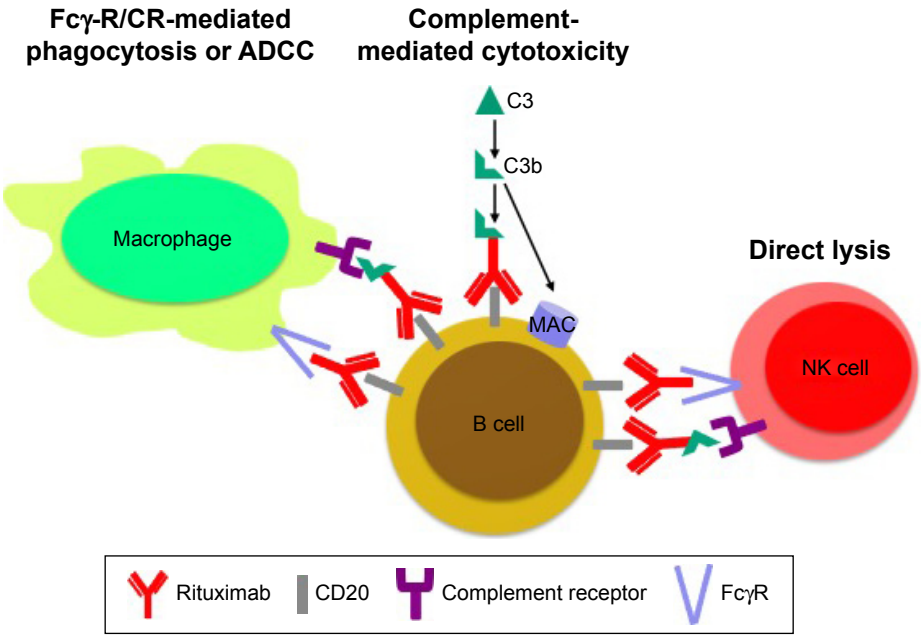

Figure 1 RTX has different mechanisms of action through activation of the complement cascade which leads to a direct lyse B cells by complement-mediated cytotoxicity, the recognition by both Fcγ receptors and complement receptors 1 and 3 on macrophages causes phagocytosis and antibody-dependent cell-mediated cytotoxicity and interaction with NK cells via FcγRIII and complement receptor 3.
Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer; RTX, rituximab.

At the moment, RTX regimen is intravenous (IV) with slightly different dosages in rheumatic diseases ranging from 1,000 mg administered 2 weeks apart in RA to 375 mg/m^2 weekly for 4 weeks in AVV. In all patients, premedication before each infusion with methylprednisolone 100 mg IV, acetaminophen and antihistamines is highly recommended.

This review provides insight into the current on- and off-label use of RTX in rheumatic diseases with a focus on the advent of biosimilars.

RTX in RA

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 (DMARDs) were tested in the DANCER study.[5] Both RTX doses (ie, 500 mg or 1,000 mg on days 1 and 15) were effective and well tolerated.[5]

Moreover, the MIRROR study showed that RTX dose escalation from two doses of 500 mg to two doses of 1,000 mg did not improve clinical response. Retreatment strategy from week 24 supported a sustained suppression of disease activity through to week 48.[6]

The Phase III SERENE study showed 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 2×1,000 mg plus methotrexate significantly improved clinical outcomes at weeks 24 and 48.[7]

Further studies in patients with RA with inadequate response to antitumor necrosis factor (anti-TNF) therapies showed that a single course of RTX associated with methotrexate therapy provided significant improvements in disease activity and progression of radiological damage.[8–10] A 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.[11–13]

The MIRAR study and real-life data indicate that switching to RTX is a successful treatment option for patients with RA failing on TNF antagonists.[12,14,15]

Treatment with RTX (2×1,000 mg) in combination with MTX has been shown to be an effective treatment for patients with MTX-naive RA, leading to sustained improvements in radiographic, clinical and functional outcomes over 2 years.[16–18]

RTX in AAV

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).[19]

RTX was approved by the Food and Drug Administration (FDA) for the treatment of patients with GPA and MPA in 2011.[3]

Two retrospective open-label studies reported remission (Birmingham Vasculitis Activity Score Modified for Wegener's Granulomatosis: 0) in all the 21 AAV patients enrolled.[20,21] Based on these successful results, the first seminal multicenter randomized double-blind controlled trial on RTX in AAV (RAVE) trial was designed.[22] This study demonstrated that RTX therapy was not inferior to daily cyclophosphamide for induction of remission in severe AAV as a higher percentage of remission occurred in RTX-treated patients (64% vs 53%).[22] Moreover, RTX appeared to be superior in patients with relapsing RA.

Results from 18-month extension of 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.[23]

Further analysis of the RAVE trial showed 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.[24]

RTX was also studied for remission maintenance. 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.[25,26]

RTX in systemic lupus erythematosus (SLE)

Since B cells play a critical role in SLE, in the past 10 years, targeted B cell therapies have been proposed in these patients.[27]

B cell depletion therapy based on RTX is still unlicensed for SLE, but it is used to treat early onset and refractory disease. The most important studies on RTX in SLE are reported in Table 1. RTX has not been designed for SLE patients, but many uncontrolled studies described its utility in SLE patients who are refractory to conventional treatments.[28–33] In fact, RTX is a recommended option in SLE nephritis in both European League Against Rheumatism (EULAR) and American College of Rheumatology guidelines.[34]

RTX failed primary end points in two randomized clinical trials (RCTs; EXPLORER in non-renal SLE and LUNAR

Table 1 Results from the off-label use of RTX in SLE

Studies	Study design	Number of patients	Drug regimen	Results
Merrill et al[35]	Prospective Randomized (2:1) Double-blind Placebo-controlled	257 SLE	RTX 1 g or placebo on days 1, 15, 168 and 182	Extra-renal manifestations: no difference between RTX and placebo
Rovin et al[36]	Prospective Randomized (1:1) Double-blind Placebo-controlled	144 SLE	RTX 1 g or placebo on days 1, 15, 168 and 182	Primary end point: no renal response at week 52 Reduction in anti-dsDNA and C3/C4 levels
Leandro et al[28]	Prospective Open-label study	24 SLE	In most cases: RTX 1 g, CYC 750 mg and MPD 250 mg 2 weeks apart	At 6 months: BILAG, anti-dsDNA and C3 improved
Lu et al[29]	Retrospective	50 SLE (45 with available follow-up at 6 months)	46 of 50: RTX 1 g, CYC 750 mg and MPD 100–250 mg 2 weeks apart	BILAG Remission: 42% Partial remission: 47% Anti-dsDNA antibody titers: decreased C3: increased
Diaz-Lagares et al[30]	Retrospective Multicenter Registry	164 biopsy-proven lupus nephropathy	RTX with corticosteroids (99%) and immunosuppressive agents (76%, CYC and MMF)	At 6 and 12 months: Complete response: 27% and 30% Partial response: 40% and 37% No response: 33% At 12 months, significant improvement in proteinuria, albumin and protein/creatinine ratio Better response in type III lupus nephropathy Worse response in nephrotic syndrome and renal failure at the time of RTX administration

(*Continued*)

Table 1 (*Continued*)

Studies	Study design	Number of patients	Drug regimen	Results
Condon et al[32]	Cohort study Prospective Observational Monocentric	50 biopsy-proven lupus nephropathy	RTX 1 g and MPD 500 mg 2 weeks apart, with MMF as maintenance therapy	At 52 weeks: Responders: 90% Complete biochemical remission: 52% Partial biochemical remission: 34% Relapses after 65.1 weeks (20–112) from remission: 12 Systemic flares: 6
Witt et al[33]	Registry Retrospective Multicenter Noninterventional	85 active SLE	RTX 1 g 2 weeks apart 67: 1 course 6: 2 courses 2: 3 courses	Complete response: 46.8% Partial response: 34.2% No response: 19.0% SLEDAI: 12.2 → 3.3 Clinical (tender and swollen joint counts, fatigue, myalgia, general well-being, Raynaud's phenomenon) and laboratory (anti-dsDNA, complement factors, hematologic parameters, proteinuria): improvement
Albert et al[37]	Prospective Open-label Multicenter	24 mild and moderate SLE without concomitant immunosuppressive therapy	RTX 1 g 2 weeks apart	1-year follow-up In 18 patients, B cell levels in peripheral blood were available: Effective CD19+ B cell depletion: 17 B cell return before 24 weeks: 6 SLEDAI: improvement by week 55 in 70% Approximately one-third of the patients developed human anti-chimeric antibody titers correlated with poor B cell depletion
Lindholm et al[38]	Retrospective Monocentric	26 SLE with active nephritis (17) or autoantibody-mediated cytopenias (thrombocytopenia: 10 and hemolytic anemia: 4) refractory to conventional immunosuppressive treatment	RTX 375 mg/m^2/week for 4 weeks added to conventional immunosuppressive therapy	Complete B cell depletion in all patients Complete or partial response in 11 patients with lupus nephritis was achieved after 6–12 months Significant increase in platelet count after 1 month Complete platelet count normalization at 6 weeks in five patients
Ramos-Casals et al[39]	Multicenter Registry	196 with systemic autoimmune diseases refractory to standard therapies 107 SLE	91: RTX 375 mg/m^2/week for 4 weeks 16: RTX 1 g 2 weeks apart	Mean follow-up of 26.05±1.62 months Complete response: 47% Partial response: 34% No response: 24% Relapses in responders: 25% Deaths: 5%
Vital et al[40]	Open-label Monocentric Observational	39 active SLE	RTX 1 g 2 weeks apart	BILAG: significantly reduced Major clinical response: 51% Partial clinical response: 31% Relapse after 6–18 months: 50% B cell numbers: no response in 21 patients after RTX (included seven patients with no response) Memory B cell and plasmablast repopulation after 26 weeks faster in patients with earlier relapse
Fernandez-Nebro et al[41]	Multicenter Retrospective Longitudinal study	116 SLE nonresponder to standard therapy	65%: RTX 1 g 2 weeks apart 30%: RTX 375 mg/m^2/week for 4 weeks 5%: others	After 6 months: Complete response: 17% Partial response: 44% After a mean follow-up of 20.0±15.2 months: Responses: 77.6% Relapses: 38%
Terrier et al[42]	Registry Observational Prospective	136 SLE	60%: RTX 1 g 2 weeks apart 36%: RTX 375 mg/m^2/week for 4 weeks 4%: others	Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-SLEDAI: improvement in 71% Relapses in 41% of responders with a good response in 91% to retreatment

(*Continued*)

Table 1 (*Continued*)

Studies	Study design	Number of patients	Drug regimen	Results
Pinto et al[45]	Prospective Observational Multicenter	42 severe and refractory SLE	RTX 1 g 2 weeks apart	Reduction in steroid requirement at 24 months At 12-month follow-up, remission according to proteinuria: Complete: 28% Partial: 36% At 12-month follow-up, remission according to creatinine clearance: Complete: 12.5% Partial: 33% No RTX reinfusion required: 80%

Abbreviations: BILAG, British Isles Lupus Assessment Group; CYC, cyclophosphamide; MMF, mycophenolate mofetil; MPD, methylprednisolone; RTX, rituximab; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

in renal SLE).[35,36] In recent years, interest in B cell therapies has been maintained as demonstrated by the approval of belimumab.

RTX is currently used for more severe forms and to achieve disease control rather than corticosteroid-sparing strategy in patients with lupus nephritis. Moreover, probably due to its efficacy in idiopathic autoimmune hemolytic anemia and idiopathic thrombocytopenia purpura (ITP), RTX is also used in patients with SLE complicated by thrombocytopenia and hemolytic anemia. RTX is less used in cutaneous and musculoskeletal SLE involvement. The efficacy of RTX in mucocutaneous manifestations is unclear, while RTX seems to be effective in articular manifestations.[37–42]

RTX has been also described as an effective therapy in antiphospholipid syndrome secondary to SLE in the prevention of recurrent thrombotic events.[43] Scarce and non-conclusive data are available on neuropsychiatric SLE.[39–41,44,45]

A study demonstrated that a single infusion of RTX was as effective as multiple doses with a reduction in cost therapy.[46] Reports suggest RTX as an induction therapy followed by belimumab as maintenance.[47] Two prospective clinical trials (NCT02260934 and NCT02284984 on ClinicalTrials.org) are currently ongoing to assess the efficacy of the sequential therapy with RTX followed by belimumab in SLE patients.

RTX is used differently all across Europe also for economical reasons.[48]

RTX in Sjögren syndrome (SS)

Traditional immunosuppressive therapies did not show effectiveness in RCTs. Nowadays, SS therapy is essentially based on symptomatic and supportive measures. As B cells play a pivotal role in SS pathogenesis, RTX has been suggested to be potentially useful.[49] The most important studies on RTX in SS are listed in Table 2.

A meta-analysis published in 2016 evaluated 276 subjects (145 RTX and 131 placebo) from four RCTs: no statistically significant change regarding lacrimal gland function, as assessed by Schirmer test, was noted while an improvement in salivary gland production and fatigue were described at 24 weeks.[50–53]

Carubbi et al[54] reported on 41 patients with SS an improvement at 120 weeks in unstimulated saliva flow rate and a decrease in labial salivary gland lymphocytic infiltration as assessed by focus score in patients treated with RTX compared to patients treated with conventional therapies.

RTX has been demonstrated to be effective at 6 months as assessed by both the SS responder index and ultrasonography.[55,56]

According to recently published SS treatment recommendations, RTX should be used in selected patients who have not responded to conventional therapies for sicca syndrome and for some extra-glandular manifestations (vasculitis, arthritis, lung involvement, peripheral neuropathy and parotid involvement).[57]

Treatment with belimumab could decrease B cell-activating factor (BAFF) levels, B cell hyperactivation and salivary gland B cell infiltration. Sequential treatment with belimumab and RTX has been suggested.[58,59] Synergic action of RTX and belimumab is now under investigation also in other rheumatic conditions (NCT02260934, NCT02631538 and NCT02284984 on ClinicalTrials.org).

A retrospective study by a Taiwanese group on 10 patients with SS complicated by interstitial lung disease treated with RTX reported pulmonary involvement stabilization.[60]

RTX retreatment seems to be reasonable in patients who responded to first course with RTX, as reported by two different groups.[61,62]

It would be extremely important to identify predictor factors for RTX response. Moreover, the most adequate RTX regimen should be assessed throughout a specific trial.

Table 2 Results from the off-label use of RTX in SS

Studies	Study design	Number of patients	Drug regimen	Results
Dass et al[50]	Randomized Double-blind Placebo-controlled	17 pSS and fatigue VAS >50	RTX 1 g 2 weeks apart or placebo	At 6-month follow-up: Fatigue VAS: reduction >20% in RTX HRQOL: SF-36 better in RTX
Meijer et al[51]	Randomized (2:1) Double-blind Placebo-controlled	30 active pSS and a rate of SWS secretion ≥0.15 mL/minute	RTX 1 g 2 weeks apart or placebo	Follow-up at 5, 12, 24, 36 and 48 weeks Primary end point: SWS: better in RTX Secondary end points: Laboratory (B cell and RF): better in RTX Subjective variables (MFI and VAS): better in RTX Extra-glandular manifestations: better in RTX Better when compared to baseline values: SWS, B cell, RF, UWS, lacrimal gland function, MFI, SF-36 and sicca VAS
Devauchelle-Pensec et al[52]	Randomized (1:1) Placebo-controlled Multicenter	120 recent-onset or systemic pSS with 50 mm or greater on at least 2 of 4 VAS (global disease, pain, fatigue, dryness)	RTX 1 g 2 weeks apart or placebo	At 24 weeks Primary end points: Improvement of at least 30 mm in 2 of 4 VAS by week 24: no difference Some subjective efficacy with RTX before 24 weeks
Carubbi et al[54]	Prospective Multicenter	41 pSS with early and active disease (ESSDAI ≥6)	RTX or DMARDs	Follow-up for 120 weeks (at weeks 12, 24, 48, 72, 96 and 120): ESSDAI: better in RTX Other clinical parameters (self-reported global disease activity pain, sicca symptoms and fatigue VAS, UWS and Schirmer's I test): better with RTX Minor salivary gland biopsies at baseline and at week 120: glandular infiltrate receded with RTX
Jousse-Joulin et al[56]	Randomized (1:1) Double-blind Placebo-controlled Multicenter	28 recent-onset or systemic pSS with 50 mm or greater on at least 2 of 4 VAS (global disease, pain, fatigue, dryness)	RTX 1 g 2 weeks apart or placebo	At 6-week follow-up: Salivary gland echostructure: better in RTX (50% vs 7%) Gland sizes: no change Vascularization: no change
Gottenberg et al[61]	Registry Prospective	78 pSS with systemic or severe glandular involvement	86%: RTX 1 g 2 weeks apart 14%: RTX 375 mg/m^2/week for 4 weeks	Follow-up every 6 months for 5 years (78 patients with at least one follow-up) ESSDAI: decreased Median dosage of corticosteroid: decreased 41 retreatments
Meiners et al[62]	Retrospective	15 pSS	RTX 1 g 2 weeks apart for two courses Median interval between courses: 103 weeks	Follow-up at 24 and 48 weeks after RTX treatment Better after both courses with RTX: ESSDAI, B cells, RF, MFI, IgG Improved significantly after first course but with a trend after second one: patient GDA and oral dryness VAS Improved significantly only after first course: ocular dryness VAS SWS: stable during the first 24 weeks of both courses, but with a significant at week 48 of the first course Less pronounced deterioration after the treatment course
Cornec et al[63]	Open-label (group I) Placebo (group II)	45 pSS	Group I (14): low-dose RTX (two 375 m^2) Group II: full-dose RTX (two 1,000 g) (17) vs placebo (14)	At 24 weeks: SSRI-30: 50% in both RTX groups BCD duration: similar in both groups BCD duration: not associated with clinical response Responders: lower baseline proportions of SG B cells Baseline serum BAFF: correlated with the proportion of SG B cells and clinical response (higher levels in nonresponders)
Delli et al[64]	Randomized (2:1) Double-blind Placebo-controlled	20 RTX-treated and 10 placebo-treated pSS	RTX 1 g 2 weeks apart or placebo	Biopsies at baseline and 12 weeks after treatment: B cells, number and the severity of lymphoepithelial lesions and germinal centers: reduced in RTX T cells (CD3+): no change CD20+ higher in responders

Abbreviations: BAFF, B cell-activating factor; BCD, B cell depletion; DMARDs, disease-modifying antirheumatic drugs; ESSDAI, EULAR Sjögren's syndrome disease activity index; EULAR, European League Against Rheumatism; GDA, global disease activity; HRQOL, health-related quality of life; MFI, multidimensional fatigue inventory; pSS, primary SS; RF, rheumatoid factor; RTX, rituximab; SF-36, 36-Item Short Form Health Survey; SG, salivary gland; SS, Sjögren syndrome; SSRI, SS responder index; SWS, stimulated whole saliva; UWS, unstimulated whole saliva; VAS, Visual Analog Scale.

Salivary gland B cell infiltration would be important to determine the efficacy of RTX even if its role has not yet been completely elucidated; the studies published are difficult to be compared as they report opposite results but they do significantly differ about methodology.[63,64]

Many reasons could be evoked to explain why biological therapies are ineffective in SS randomized trials. In a recent paper, the authors gave many possible explanations: incorrect diagnosis, nonrepresentative SS population enrolled in clinical trials, antinuclear antibody (ANA) false negativity, lack of marker for fatigue and other benign symptoms, and an unknown link between immune system and central nervous system.[65]

RTX in systemic sclerosis (SSc)

B cells play a central role in SSc pathogenesis. A mounting quantity of evidences provides a rationale for the use of RTX in SSc patients.[66–68] The most significant studies on RTX in SSc are reported in Table 3.

RTX was initially administered in patients affected by chronic graft-versus-host disease with a good response on skin fibrosis but not on extra-cutaneous manifestations.[69]

Uncontrolled studies and case reports described the efficacy of RTX in SSc patients with regard to pulmonary function, skin fibrosis, and less frequently arthritis, calcinosis and quality of life.[70–80]

A retrospective case–control analysis performed by the European Scleroderma Trial and Research Group described 63 SSc patients treated with RTX matched to 25 controls; authors described an improvement in skin involvement as assessed by modified Rodnan skin score and a stabilization of lung function as assessed by pulmonary lung function.[81]

Bosello et al[82] described, in a cohort of 20 SSc patients, the effectiveness of RTX with regard to skin fibrosis and disease activity.

A recent published work by Daoussis et al[83] showed a beneficial effect on lung involvement of RTX on 33 patients with a follow-up up to 7 years.

Due to heterogeneity of these studies (different dosages and modalities of administration, number of cycles and follow-up period, indications and end points) it would be very problematic to draw definitive conclusions. Not enough data are currently available in the literature to prescribe

Table 3 Results from the off-label use of RTX in SSc

Studies	Study design	Number of patients	Drug regimen	Results
Lafyatis et al[71]	Open-label Observational	15 dcSSc	RTX 1 g 2 weeks apart	Primary outcome: Change in mRSS at 6 months: no change Secondary outcomes: PFTs: stable Organ involvement: stable B cell infiltrates: depleted (vs baseline) Autoantibodies: modest changes
Bosello et al[72]	Open-label	9 SSc	RTX 1 g 2 weeks apart	Follow-up up to 36 months (skin biopsy at baseline and during the follow-up): After 6 months; skin score, disease activity index and disease severity index: decreased IL-6: reduced Serum B cells: reduced in seven patients B cells at baseline in three patients
Daoussis et al[73]	Open-label	8 dcSSc with ILD	RTX 375 mg/m^2/week for 4 weeks	Long-term (2 years) safety and efficacy: Lung involvement (PFTs and HRCT): improved Skin involvement (mRSS and myofibroblast): improved
Smith et al[74]	Open-label	8 dcSSc	RTX 1 g 2 weeks apart	24-week follow-up: Peripheral CD19+: reduced Skin sclerosis score: reduced Biopsies (dermal hyalinized collagen content and dermal myofibroblast numbers): change
Smith et al[75]	Open-label	8 dcSSc	RTX 1 g 2 weeks apart at baseline and after 6 months	2-year follow-up: mRSS: decreased DAS: decreased Internal organ involvement: stable B cell depletion Biopsies (hyalinized collagen score): change

(*Continued*)

Table 3 (*Continued*)

Studies	Study design	Number of patients	Drug regimen	Results
Moazedi-Fuerst et al[76]	Open-label	5 SSc with ILD nonresponders to CYC	RTX 500 mg 2 weeks apart every 3 months for 1 year	mRSS: decreased DLCO and FVC: increased Lung fibrosis (three patients): decreased Digital ulcerations: healed Severity of Raynaud's phenomenon and vascular pain: decreased Number of capillary bleeds and megacapillaries: decreased B-lymphocyte count decreased Serum immunoglobulins, autoantibody titers or CRP levels: no change
Giuggioli et al[77]	Open-label	10 SSc	One or more cycles of RTX 375 mg/m^2/week for 4 weeks	Follow-up at 6 months and at last follow-up (up to 72 months): mRSS: decreased at 6 months Other cutaneous manifestations (hypermelanosis, pruritus, calcinosis): improved Arthritis: improved ILD: stable in 6 and worsened in 2 Pro-inflammatory cytokines: a more or less pronounced reduction after the first RTX cycle
Daoussis et al[78]	Randomized	14 SSc	8: RTX 375 m^2 weekly for 4 weeks at baseline and at 24 weeks plus standard therapy 6: standard treatment alone	1-year follow-up: FVC, DLCO and skin involvement: increased
Jordan et al[81]	Registry Case–control	88 SSc	63: RTX 1 g 2 weeks apart 25: controls	Primary end point: mRSS: reduced better in RTX Secondary end points: FVC: no further decline Safety measures: good
Bosello et al[82]	Open-label	29 dcSSc with or without ILD	RTX 1 g 2 weeks apart (more courses when needed)	Follow-up up to 68.9 months: Skin score, activity and severity indices improved significantly after 12 months and at final follow-up compared to baseline FVC and TLC: increased DLCO: stable HRCT: stable in 80% of patients
Daoussis et al[83]	Multicenter Open-label	51 SSc with ILD	33: RTX 375 m^2 weekly for 4 weeks 18: conventional therapy	Median follow-up 4 years (up to 7 years): FVC: increased at 2-year follow-up, results confirmed at 7 years mRSS: outcome favorable to RTX at all times

Abbreviations: CRP, C-reactive protein; CYC, cyclophosphamide; DAS, Disease Activity Score; dcSSc, diffuse cutaneous SSc; DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL-6, interleukin-6; ILD, interstitial lung disease; mRSS, Rodnan skin thickness score; PFTs, pulmonary function tests; RTX, rituximab; SSc, systemic sclerosis; TLC, total lung capacity.

RTX in SSc patients who are naive to conventional therapy. RTX treatment seems to be promising in lung, skin and articular involvement secondary to SSc. There are little data on calcinosis, where RTX can be considered as a rescue therapy. A prospective, placebo-controlled, randomized trial is needed to definitively assess the efficacy of RTX in SSc. Meanwhile, RTX can be considered as a valid option in those patients who cannot tolerate or have contraindications for conventional therapies (ie, cyclophosphamide) or in patients where conventional therapies have already failed. RTX would be useful in pulmonary involvement as a maintenance therapy after induction with cyclophosphamide.

RTX in spondyloarthritis

The efficacy of RTX has also been tested in spondyloarthritis. A prospective open-label study showed that, among 20 patients with ankylosing spondylitis, 40% of anti-TNF-naive patients (N=10) achieved an improvement in Assessment of SpondyloArthritis international Society (ASAS) and 50% in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), while RTX did not seem to be effective in the TNF failure (N=10).[84] Moreover, the same authors reported that five patients who flared on follow-up responded again when retreated with RTX.[85]

Thus, these studies include a small number of patients and are open label, and no clear conclusions can be drawn.

Further studies are needed to ascertain the real therapeutic role of RTX.

Idiopathic inflammatory myopathies (IIMs)

IIMs include adult polymyositis (PM) and dermatomyositis (DM), juvenile PM and DM, anti-synthetase syndrome (ASS) and inclusion body myositis.

According to 2012 Cochrane review focused on therapy in DM and PM, no adequately designed study is present in the literature to assess which immunosuppressive drug is the best corticosteroid-sparing agent.[86] As a result, the drug choice is often based on empirical considerations.

Since up to 80% of patients with IIMs show circulating autoantibodies and B cells that are found within inflamed muscle fibers, RTX therapy seems to be reasonable.[87]

Although the use of RTX in IIMs is rational and several uncontrolled trials suggested its utility, the RTX in myositis (RIM) trial, conducted on 195 patients, failed to reach both primary and secondary end points;[88] however, almost 80% of patients responded to RTX treatment.

A subanalysis of RIM trial also demonstrated RTX as effective in refractory skin involvement in patients with both adult and juvenile DM.[89]

Some evidence suggests that RTX might be useful in interstitial lung disease secondary to IIMs, especially when related to ASS.[90–93]

The presence of antibodies predicts a good response to RTX.[94,95] Moreover, their titers decrease after therapy with variable correlation with disease activity and muscle enzyme.[96]

RTX biosimilars

RTX patents expired in Europe in 2013 and in the USA in 2016. Various Phases I, II and III clinical trials are ongoing (JHL1101, ABP 798, MabionCD20, PF-05280586, RTXM83, SAIT101, CT-P10, GP-2013).

European Medicines Agency (EMA) has recently approved the first RTX biosimilar, CT-P10, in RA. In the pivotal trial, patients with active RA were randomly assigned (2:1), to receive CT-P10 1,000 mg or RTX 1,000 mg 2 weeks apart. Patients were randomized to receive the treatment (50 patients for each group). Additional 50 patients were recruited to the CT-P10 group to better assess its safety. CT-P10 was demonstrated to be equivalent regarding pharmacokinetics and efficacy with similar immunogenicity and safety profiles as the originator.[97]

Moreover, patients who completed the follow-up at 72 weeks (N=87: 58 in the CT-P10 group and 29 in the RTX group) entered into the open-label extension study for 56 weeks. Patients of each group received CT-P10 according to DAS28. Patients who switched from RTX to CT-P10 demonstrated comparable efficacy and safety profiles compared to those who maintained CT-P10. In RA patients, maintained CT-P10 was also well tolerated and effective up to 2 years.[98]

EMA is also currently evaluating GP2013 in RA. GP2013 has been demonstrated to be comparable to the originator in a trial recently published as an abstract.[99]

PF-05280586 was proven to be similar to the EU and US originator with regard to pharmacokinetics, CD19 depletion, antidrugs antibodies production and adverse events in RA patients.[100]

Moreover, RTX biosimilars (BCD-020, Baball and MabTas) have been licensed in countries where regulatory processes are not as strict as FDA and EMA recommendations.

Of note, other biosimilars (ie, infliximab and etanercept) have been successfully introduced in the treatment of RA. 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.[101]

RTX in pregnancy

RTX was shown not to have any teratogenic effect in animals.[102] In human beings, when RTX is administered during the second and third trimester, similar levels are found in mother and cord blood.[103,104]

Chakravarty et al[105] reported 153 pregnancies exposed to RTX in patients affected by RA, non-Hodgkin lymphoma and other autoimmune diseases: 90 live births (22 premature and one extremely premature births), 33 miscarriages, 28 elective terminations, one late fetal loss and one maternal death due to cerebral hemorrhage in idiopathic thrombocytopenic purpura. Among live births, two congenital malformations, one death for unknown causes (at 6 months), 11 hematological abnormalities without infectious complication and four neonatal infections were reported.[105] In particular, 21 patients received RTX during the second or third trimester, among them no maternal death, neonatal death or congenital malformations were noted, whereas cytopenia was reported in seven newborns.[105]

RTX exposure before conception or during early pregnancy does not provoke B cell depletion in newborns, whereas during the late stage of pregnancy (second and third trimester) RTX is able to reduce B cells that usually normalize after 3–6 months. Mothers and newborns, exposed

to RTX during second and third trimester, should be monitored for the risk of infections since neutropenia and B cell depletion have been described in newborns.[104,106–108]

Although no fetus damage has been reported in pregnancies exposed to RTX during the first trimester, this therapy, according to EULAR recommendations, should be considered only when no other therapeutic option is available.

According to the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology(BHPR) guidelines on prescribing drugs in pregnancy and breastfeeding, an effective contraception is recommended while taking RTX and for 12 months following treatment.[109]

According to EULAR recommendations, when RTX is administered before week 22, vaccinations can be performed according to local guidelines (live vaccines included). When administered later in pregnancy, live vaccines should be avoided till 6 months of life. Due to the lack of data, lactation should be avoided.[110]

Miscellaneous

RTX has been shown to impact on vaccine immunogenicity, thus highlighting the importance of the right timing of vaccines in relation to RTX administration.[111] For this reason, the better results in terms of humoral response are reported 6 months or more after RTX dosing.[112,113] Vaccinations should be considered at least 4 weeks before RTX administration. In particular, a significant humoral response impairment has been reported for influenza and pneumococcal vaccinations.[112–117] No data are available on the effects of RTX on hepatitis B virus (HBV), human papilloma virus or yellow fever vaccines. Safety for live vaccines has not been studied in patients treated with RTX; thus, these vaccines are considered contraindicated in this setting.

Screening serologies for HBV and hepatitis C virus (HCV) must be undertaken even if resolved HBV hepatitis reactivation has been rarely reported.[118,119]

In patients with HBsAg and anti-HBc negativity, vaccination should be considered before RTX initiation. By contrast, patients who are HBsAg and/or anti-HBc positive should be referred to a hepatologist for consideration of a prophylactic therapy, and HBV DNA levels have to be closely monitored if RTX is administered.[118,119]

With regard to HCV, RTX is used in the treatment of HCV-induced cryoglobulinemia. HCV should be screened, and for chronic HCV carriers, collaboration with a hepatologist is mandatory to plan a treatment strategy.[18,120]

Before RTX administration, routine screening for tuberculosis is suggested, even if it is not currently believed to be necessary. Patients with active tuberculosis should be appropriately treated and RTX should not be initiated.[121]

The long-term RTX safety report highlighted that serious opportunistic infections were rare. Among these, the reactivation of the John Cunningham (JC) virus leading to progressive multifocal leukoencephalopathy has been reported in patients with autoimmune diseases who should be informed of this risk.[122]

Finally, it is well known that long-term RTX administration is associated with hypogammaglobulinemia whose consequences are still unclear. It is recommended to evaluate baseline immunoglobulin levels and to consider cessation of therapy when the IgG level drops progressively.[123]

Moreover, attention should be paid to late-onset neutropenia that has been described as a potential RTX-related adverse event.[124]

Conclusion

RTX is currently considered useful and a relatively safe biological agent in the treatment of some rheumatic diseases.

Although RTX has been demonstrated to be relatively safe for infections, particular attention should be paid in the presence of HBV for the risk of reactivation.

Pregnancy during RTX treatment should be avoided since RTX, especially when administered during second and third trimester, increases the risk of infection in the mother and in the newborn.

RTX has been demonstrated useful in RA and AAV, and it is currently approved in many countries with these indications. RTX is also administered in other rheumatic conditions, such as SLE, SS and SSc, refractory to conventional therapies, but its utility in these conditions has not yet been completely and fully elucidated.

Moreover, further studies are needed to clarify some controversial points such as the association with concomitant DMARDs, RTX dosage and the optimal interval for retreatment. The availability of approved RTX biosimilars, such as CT-P10, would allow a widespread access of this treatment with cost saving. More likely, the harmonization of guidelines and recommendations on the use of biosimilars will be of help in clinical practice.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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