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REVIEW

Rituximab in systemic autoimmune rheumatic diseases: indications and practical use

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ABSTRACT

Objectives: To review the therapeutic option of Rituximab, a chimeric anti-CD20 antibody, in systemic autoimmune rheumatic diseases (SARDs) such as systemic lupus erythematosus, systemic sclerosis, primary Sjögren syndrome and idiopathic inflammatory myopathy.

Methods: A non-systematic review was conducted.

Results: The specific role and indication of rituximab in SARDs has been the subject of multiple trials in recent years. Evidence supports the use of rituximab in moderate-to-severe refractory systemic lupus erythematosus, diffuse skin involvement in systemic sclerosis and systemic involvement in primary Sjögren syndrome. Several guidelines have adopted these indications. In addition, there is a consensus about the use of rituximab in refractory myositis. The role of rituximab in interstitial lung disease associated with these SARDs needs to be further explored.

Conclusion: Rituximab is a treatment option in several SARDs. Upcoming trials, use in daily practice and the safety profile are elaborated on.

KEYWORDS

Rituximab; systemic autoimmune rheumatic disease; systemic lupus erythematosus; systemic sclerosis; primary Sjögren syndrome; inflammatory myopathy; myositis

Introduction

Rituximab is a chimeric monoclonal anti-CD20 antibody. CD20 is an antigen expressed in all stages of B-cell development except for the earliest (pro-B-cells) and latest stages (plasma blasts and plasma cells). It is presumed to play a central role in the generation of B-cell responses against T-cell independent antigens [1]. Rituximab induces B-cell depletion through complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC) and direct signaling [2]. It was first approved for the treatment of indolent non-Hodgkin lymphoma (NHL) in 1994. It has been endorsed since for other hematological malignancies as chronic lymphatic leukemia (CLL) and more aggressive NHLs such as diffuse large B-cell lymphoma [3]. In this context, rituximab is administered in doses of 375 mg/m² body surface area (the 'lymphoma dose') using varying administration intervals. Furthermore, it has later been approved for remission induction and maintenance therapy of ANCA-associated vasculitis (AAV) [4,5] and for treatment of rheumatoid arthritis (RA), the most prevalent of systemic autoimmune rheumatic diseases (SARDs), after failing TNF blockers [6]. Considering the widely accepted indications for the use of rituximab in the treatment of RA, we do not cover the details on the use of rituximab in RA in this manuscript.

Over the last few years, rituximab has been used off-label in transplant rejection and immune-mediated

diseases such as multiple sclerosis, autoimmune hemolytic anemia, immune thrombocytopenic purpura, and SARDs other than RA. These SARDs include, 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 incompletely understood but an essential role for B cells in the autoimmune response in these diseases seems clear, providing a rationale for the use of rituximab, a B-cell depleting agent. In Belgium treatment with rituximab is partially and conditionally reimbursed in serious immune-mediated diseases since 1 January 2018 if this treatment is based on available scientific evidence supporting the efficacy and safety in the specific indication [7]. The reimbursement request needs to be done by the treating physician electronically via eHealth and one can apply for Mabthera® as well as for the biosimilar Truxima®. This new regulation paralleled the price reductions when the biosimilar came to the market.

In this review, we will discuss the current evidence, guidelines, and upcoming trials for rituximab in the abovementioned SARDs. In addition, the practical use and safety profile of rituximab will be discussed. The current overview can be used as a guidance for clinicians caring for patients with these diseases in Belgium, but might also be useful for physicians in other countries.

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Supplemental data can be accessed [here](#)

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Methodology

We conducted a non-systematic review. Briefly, a search was carried out in PubMed in January 2018 using the following search terms: rituximab AND (SLE), rituximab AND (SSc OR scleroderma), rituximab AND (pSS), rituximab AND (IIM OR myositis). All titles and abstracts were screened and relevant manuscripts were selected by the authors. Additional literature was obtained by searching references in the manuscripts. Relevant guidelines of the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and British Society for Rheumatology (BSR) were included. A search in ClinicalTrials.gov was performed using the above-mentioned search terms. Relevant trials were selected.

Systemic lupus erythematosus

SLE is a multisystem autoimmune disease with a high female predominance and heterogeneous clinical manifestations (constitutional, cutaneous, hematological, musculoskeletal, gastro-intestinal, neurological, renal, cardiorespiratory and serological) [8]. The disease is characterized by frequent flares and remissions. B-cells are central in the pathogenesis through the production of autoantibodies and cytokines [9].

Current treatment of mild-to-moderate SLE consists of antimalarials, low dose glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid-sparing agents such as methotrexate, azathioprine and mycophenolate mofetil. Moderate and severe disease activity is addressed with medium-to-high-dosed glucocorticoids, ciclosporin, belimumab or cyclophosphamide. Defined regimens including cyclophosphamide or mycophenolate mofetil are the first-line treatment for lupus nephritis [10–12].

The efficacy of rituximab has been explored in two randomized placebo-controlled trials (Table 1). In the EXPLORER trial, in which patients with extra-renal SLE activity were treated with rituximab or placebo on top of standard of care, no difference in major or partial clinical response was observed, except in the African-American and Hispanic subgroup [13]. Rituximab did have a biological effect, with increased recuperation of complement levels and decreased anti-double-stranded DNA antibody titers. *Post-hoc* analysis of the data show that more rituximab-treated patients

achieved low disease activity without major British Isles Lupus Assessment Group A (BILAG A) flares, suggesting a beneficial effect of rituximab [14]. It is argued that The EXPLORER trial was too stringent in the criteria for non-responders, allowing a relatively minor disease flare to be classified as non-response. The LUNAR trial, a randomized placebo-controlled trial evaluating the efficacy of rituximab on top of standard of care (mycophenolate mofetil and glucocorticoids) in patients with class III or IV lupus nephritis, did not meet its primary outcome and showed similar renal response rates at week 52 in both groups [15]. The exploratory endpoints did illustrate a trend to a reduction in proteinuria, improvement in renal function, a lower daily oral glucocorticoid dose and less need for rescue therapy with cyclophosphamide. Rituximab could therefore be considered an efficient glucocorticoid-sparing therapy. Several uncontrolled open-label studies and cohort studies (systematically reviewed in [16] and [17]), also show this glucocorticoid-sparing effect. Furthermore, these uncontrolled studies suggest efficacy of rituximab in patients with refractory SLE disease activity. When considering organ-specific refractory disease manifestations, rituximab seems effective in lupus nephritis, 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 rituximab can be used in lupus nephritis when conventional treatment with glucocorticoids and cyclophosphamide and/or mycophenolate mofetil have failed [10,11]. In non-renal moderate-to-severe SLE, rituximab can be considered in refractory cases, as mentioned in the guidelines of the British Society of Rheumatology [12].

Systemic sclerosis

SSc is a rare auto-immune disease characterized by progressive fibrosis of skin and internal organs, vascular alterations and immunological dysfunction [18]. Patients can be classified as limited (lSSc), limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc) SSc, depending on the extent of the skin involvement. In this heterogeneous disease, not only the skin but also the gastro-intestinal, renal, cardiac, pulmonary and musculoskeletal system can be affected. The pathogenesis is

Table 1. Randomized controlled trials in systemic lupus erythematosus.

Study	N	RTX dose and interval	Primary end point	Follow-up	SOC	Primary end point met?
EXPLORER (extra-renal) [13]	257 (169 RTX vs. 88 placebo)	1 g IV W 0–2 W 24–26	Major or partial clinical response	52 weeks	AZA, MMF, MTX, GC	No
LUNAR (nephritis) [15]	144 (72 RTX vs. 72 placebo)	1 g IV W 0–2 W 24–26	Renal response	42 weeks	MMF, GC	No

RCT, randomized controlled trial; N, number of patients included; SOC, standard of care; IV, intravenously; W, week; RTX, rituximab; vs., versus; AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; GC, glucocorticoids.

incompletely understood, but emerging evidence points to the role of B cells, acting through secretion of cytokines, production of autoantibodies and direct B-cell contact with fibroblasts and dendritic cells [19].

Current treatment options for SSc are limited and are highlighted in the recently updated EULAR treatment recommendations. Methotrexate can be used as treatment for skin manifestations in early diffuse SSc. Mycophenolate mofetil and cyclophosphamide are recommended in progressive interstitial lung disease (ILD), the former being equally efficient and better tolerated [20]. In selected cases with rapid progressive disease, autologous hematopoietic stem cell transplantation could be considered [21].

The effect of rituximab has been evaluated in descriptive cohorts [22–24], two case-control studies [25,26] and various interventional studies: several uncontrolled open-label studies [27–35], one randomized open-label trial [36] and one placebo-controlled randomized trial [37] (Supplemental Table 1). In these studies, considerable heterogeneity exists in the severity of skin and lung involvement, disease duration and concomitant treatment. The only randomized controlled trial comparing rituximab with placebo was underpowered, including only 8 patients per group, but showed a trend towards improvement in skin and lung involvement [37]. Overall, rituximab seems to stabilize and might improve skin involvement and lung function tests, when given on top of standard of care. Based on the available evidence, the BSR guidelines indicate possible use of rituximab in refractory skin disease [38]. Overall, one can consider the use of rituximab in early diffuse cutaneous SSc to stabilize or decrease skin fibrosis and attempt stabilization of lung volumes.

Primary Sjögren syndrome

pSS is the second most frequent autoimmune rheumatic disease after RA. The incidence is estimated to be 3–11/100.000 individuals per year [39]. The most common symptoms are oral and ocular dryness, pain and fatigue. Systemic involvement is present in 50–60% [39]. Sjögren

syndrome can be present on its own (primary SS) or in association with other connective-tissue diseases and is then referred to as secondary Sjögren syndrome and outside the scope of this article. According to the ‘auto-immune epithelitis’ theory, epithelial cells are in the center of the autoimmune response, in which B-cells play an important role [39]. Standard treatment for sicca symptoms includes local symptomatic treatment with tear substitution, oral moisturizers and pilocarpine. In systemic involvement glucocorticoids and hydroxychloroquine are often used [40,41].

Four RCTs have been published on the use of rituximab in the treatment of pSS, mostly focusing on sicca symptoms and fatigue (Table 2). The first two small studies met their primary end point whereas the last larger two did not. In the first trial Dass et al. noted a significant effect on the mean fatigue reduction compared to baseline after 6 months, but not on the proportions of patients achieving 20% reduction in fatigue from baseline [42]. In the second trial only changes in stimulated salivary flow at 12 weeks, and not at later time points, and ocular dryness at 36 and 48 weeks were significant [43]. The larger TEARS trial did not meet its primary end point (≥ 30 mm change in ≥ 2 of 4 VAS) at 24 weeks but an early effect (weeks 6 to 16), particularly on fatigue, was noted [44]. To demonstrate a long-term effect, a second course of rituximab was administered at week 26 and 28 in the TRACTISS trial [45]. However, no early effect on fatigue (as in the TEARS trial) or late effect on ocular dryness (as reported by Meijer et al.) or other long-term effect was seen. Additionally, a cost-effectiveness analysis was negative. The baseline treatment in these trials differed: in the TRACTISS trial 55,6% used hydroxychloroquine, whereas in the other trials use of other immunosuppressive agents outside of treatment intervention was not allowed.

A first criticism on both the TEARS and TRACTISS trials are the low baseline EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) scores. A second point of critique was the choice of end points, though the ESSDAI, a secondary end point in the last two trials, should be able to detect a treatment effect of rituximab in RCTs, even at low mean ESSDAI scores [46].

Table 2. Randomized controlled trials in primary Sjögren syndrome.

Study	N	RTX dose and interval	Primary end point	Follow-up	SOC	Primary end point met?
Dass et al. [42]	17 (8 RTX vs. 9 placebo)	1 g IV W 0–2	Reduction of fatigue ($> 20\%$ on VAS)	6 months	Not further defined	Yes (RTX $p < 0,001$ vs. placebo $p = 0,147$)
Meijer et al. [43]	30 (20 RTX vs. 10 placebo)	1 g IV W 0–2	Improvement of stimulated salivary flow rate (ml/min)	48 weeks	Stop concomitant medication before baseline	Yes ($p = 0,038$)
TEARS [44]	120 (63 RTX vs. 57 placebo)	1 g IV W 0–2	Significant effect (≥ 30 mm) on ≥ 2 VAS (fatigue, sicca symptoms, global disease, pain)	24 weeks	Stop all immunosuppressive medication 4 weeks before baseline	No
TRACTISS [45]	133 (67 RTX vs. 66 placebo)	1 g IV W 0–2 W 24–26	Significant effect on fatigue, oral dryness (VAS)	48 weeks	Stable dose GC and hydroxychloroquine	No

RCT, randomized controlled trial; N, number of patients included; SOC, standard of care; IV, intravenously; W, week; VAS, visual analog scale; RTX, rituximab; ml, milliliter; GC, glucocorticoids.

Prospective non-randomized trials (recently reviewed in [47]) with more active disease and systemic involvement show efficacy of rituximab. There was a significant effect of rituximab vs. DMARD treatment on ESSDAI scores in a prospective follow-up study of 41 early active pSS patients with a higher mean ESSDAI at baseline (20,3 in the rituximab group, 19,8 in the DMARD group) [48]. This study was characterized by frequent systemic involvement, a long follow-up period (120 months) and repeated use of rituximab. Another prospective registry study of 78 patients, of whom 74 had systemic involvement, demonstrated a good effect of rituximab according to the treating physician in 60% of patients. Articular, hematological, pulmonary, and renal involvement and vasculitis benefited most [49]. Rituximab shows some effect in peripheral neuropathy related to vasculitis and cryoglobulinemia but not in central neurological manifestations (such as multiple sclerosis-like symptoms) or peripheral non-vasculitis neuropathy [50,51].

According to the guidelines of the ACR, rituximab can be used for treatment of oral and ocular dryness after failure of conventional treatment although the strength of the recommendation was weak and the last and largest RCT, which was negative, had not yet been published [45,52]. As such, rituximab for sicca symptoms based on the current evidence remains highly debatable. The use of rituximab as a therapeutic option in systemic involvement is accepted and is recommended in the guidelines of the ACR and the British Society of Rheumatology [40,52].

Idiopathic inflammatory myopathy

The IIMs are a rare and heterogeneous group of diseases, including polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myositis, inclusion-body myositis and overlap myositis (overlapping with other CTDs). Muscle weakness is the central, though not-obligatory, feature. Skin features are typical of dermatomyositis, but skin involvement also occurs in other subtypes. Arthritis and ILD are frequently present, often as part of the antisynthetase syndrome (ASS). This syndrome is associated with antisynthetase antibodies (including anti-Jo-1, PL7, PL12, KS, OJ and EJ), the most prevalent myositis-specific antibodies (MSA). MSA-defined syndromes provide the base for a newly proposed clinico-serological classification [53]. The presence of autoantibodies in serum (up to 60% has MSAs) and T cells, macrophages, and dendritic cells in muscle tissue support involvement of immune mechanisms in the pathogenesis [54]. Glucocorticoids are the standard treatment, with immunosuppressive treatment as second-line therapy, though there is no high-quality evidence supporting their use [55,56].

The only randomized rituximab trial, the Rituximab in Myositis (RIM) trial, was negative. The primary end point was the time to achieve the International Myositis

Assessment and Clinical Studies Group preliminary definition of improvement (DOI), a composite of 6 core set measures [57]. This trial included refractory juvenile and adult PM and DM patients in a randomized placebo-phase study design. One arm received rituximab at weeks 0 and 1 and the other arm at weeks 8 and 9. The slower-than-expected onset of action of rituximab in combination with a short 8-week placebo phase may explain the negative result. Though the primary end point was not met, 83% of all randomized patients met the DOI [57], a number in line with a response rate of 78.3% in a recent review which includes open label studies and case series [58]. The presence of autoantibodies, especially antisynthetase and anti-Mi-2 (another MSA), predicted clinical improvement at 20 weeks. The clinico-pathological subtype (PM and DM) and age group (juvenile vs. adult) did not [59].

Skin and pulmonary involvement seem to benefit from rituximab. An analysis of skin rashes of DM patients in the RIM trial showed a significant effect on a cutaneous visual analog scale. Classical DM signs, the heliotrope rash and Gottron papules; and erythematous rashes without ulceration or necrosis improved most [60]. Rituximab shows promise in IIM-associated ILD. In a retrospective analysis of the RIM trial, improvement of pulmonary function testing, was noted in 6 of 8 patients with ILD [61]. In a case series of 7 anti-Jo-1 patients with ILD treated with rituximab in combination with glucocorticoids only, after 1 year the pulmonary symptoms, pulmonary function tests (forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO)) and high-resolution computed tomography were significantly better [62]. In detail, the median level of FVC increased from 66% to 74% ($p = 0,04$) and the median level of DLCO increased from 39% to 59% ($p = 0,001$).

No guidelines on treatment of IIM by the ACR, EULAR or BSR have been published, but there is a consensus for use of rituximab in refractory myositis. Autoantibody status is the most useful predictor of treatment success with rituximab for now. The use of rituximab in IIM-associated ILD will be explored, together with other CTD-ILD, in the RECITAL trial [63].

Practical use and safety

Rituximab can be administered intravenously (IV) or subcutaneously. In autoimmune disease, only IV administration has been studied. The most widely used course (the 'RA dose') consists of 1000 mg at week 0 and 1 or 2 [13,15,26,37,44,45,57]. The number of courses, one or more, depends on the indication (Table 3). The premedication consists of paracetamol (1 g), an antihistaminic (e.g. diphenhydramine) and the equivalent of 100 mg methylprednisolone. During the first infusion, the initial infusion rate is 50 mg/hour and can be increased by 50 mg/hour

Table 3. Indications for rituximab in systemic autoimmune rheumatic disease.

SARD	Indication	Combination therapy?	Single course or to be repeated?	Guidelines endorsement (LOE, SOR)
SLE	Refractory moderate-to-severe SLE	On top of SOC	To be repeated	BSR (2+, C) [12] ACR (C)
SSc	Refractory skin involvement	On top of SOC	To be repeated	BSR (III, C) [38]
	SSc-associated ILD	On top of SOC	To be repeated	No formal recommendation
pSS	Systemic involvement	On top of SOC	To be repeated	ACR (Moderate) [52]
				BSR (IIb, B) [40]
IIM	Refractory myositis	On top of GC	Single course	No guidelines available

SARD, systemic autoimmune rheumatic disease; LOE, level of evidence; SOR, strength of recommendation; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; pSS, primary Sjögren syndrome; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; SOC, standard of care; GC, glucocorticoids; BSR, British Society of Rheumatology; ACR, American College of Rheumatology.

every 30 min to a maximal infusion rate of 400 mg/hour. In RA, a faster infusion rate can be used if the first infusion is well tolerated. The initial infusion rate in this accelerated scheme is 250 mg/hour during the first 30 min and 600 mg/hour during the next 90 min which translates to a total infusion time of approximately 2 h [64].

Infusion-related reactions (IRRs) are common, especially when no premedication is given, and may be related to release of cytokines. IRRs include hypertension and hypotension, nausea, rash, pyrexia, urticaria and in more severe cases generalized edema or angioedema, bronchospasm and anaphylaxis. The overall incidence of IRR in RA trials was 36% but < 1% was serious. IRRs occurred most frequently during the first infusion. The number of IRRs in the previously discussed RCTs varied between 1 and 16,4% [13,15,44,45,57]. In case of an IRR rituximab should be stopped and supportive care provided. If the IRR is not severe and symptoms resolve completely, rituximab can be resumed at a slower infusion rate (50% reduction).

Infections are the most prevalent side effect next to IRRs. In the RA trials, overall infection rate was 94 per 100 patient years of which only 4 (out of 94) were serious or required intravenous antibiotics. Respiratory and urinary tract infections occurred most often. In the previously mentioned RCTs, in which combination therapy with DMARD was frequent, a serious infectious adverse event was noted in 3–19.2% [13,26,45,57]. Cases of

progressive multifocal leukoencephalopathy in treatment of autoimmune diseases with rituximab have been reported [65,66]. Hypogammaglobulinemia has been observed but is not associated with an increased infection risk in RA, in contrast to rituximab use in hematological malignancies [67]. Mild-to-moderate neutropenia occurs, but severe neutropenia is rare.

Before the start of rituximab, a screening for latent infections (tuberculosis, hepatitis B and C, HIV) and review of the vaccination status should be performed. Yearly vaccination against seasonal flu and pneumococcal vaccination (the 13-valent conjugated vaccine PCV13, followed after at least 8 weeks by the 23-valent non-conjugated vaccine PPV23, this latter being repeated every 5 years) are recommended. Vaccines should be given 4 weeks before the start or at least 6 months after the last administration of rituximab, because of potential reduced response rate. Live viral vaccines (e.g. yellow fever, herpes zoster) can only be administered at least 4 weeks before the start of rituximab. There are currently no data available to support a recommendation on the minimal interval between the stop of rituximab and the administration of live vaccines. According to the half-life of rituximab and the studies about immunogenicity of inactivated vaccines [68,69], it could be safe at least 12 months after the last rituximab administration, if immunoglobulin levels and CD 19 + B-cells are normal. However, until more data are available, the use of live vaccines is contraindicated.

Table 4. Upcoming phase-2 and -3 trials of rituximab in systemic autoimmune rheumatic disease.

Trial	Phase	Indication	Intervention + comparison if applicable	Primary outcome measure (time)	Status
RECITAL [63]	2/3	CTD-ILD	RTX vs. CYC	Absolute change in FVC (W 48)	Recruiting
BLISS-BELIEVE [72]	3	SLE	BEL + RTX + SOC vs. BEL + placebo + SOC vs. BEL + SOC	Disease control (W 52)	Not yet recruiting
ROOTS [73]	2	SLE: skin disease, arthritis	RTX + CS vs. CS	Feasibility of trial (W 24)	Recruiting
RITUXILUP [74]	3	Lupus nephritis	RTX + CS + MMF vs. CS + MMF	Complete renal response without need of PO CS (W 52)	Terminated
SYNBloSe [75]	2	Lupus nephritis	BEL + RTX	Reduction of pathogenic autoantibodies (W 24)	Enrolling
RECOVER [76]	2/3	SSc: articular symptoms	RTX vs. placebo	Number of tender and swollen joints out of 53 joints (W 26)	Completed
NC02631538 [77]	2	pSS	BEL + RTX vs. BEL vs. RTX vs. placebo	Number of SAEs and AESIs (W 104)	Recruiting
EvER-ILD [78]	3	ILD, NSIP pattern	RTX + MMF vs. MMF	Change in FVC (W 24)	Recruiting

CTD, connective tissue disease; ILD, interstitial lung disease; RTX, rituximab; CYC, cyclophosphamide; FVC, forced vital capacity; W, week; SLE, systemic lupus erythematosus; BEL, belimumab; CS, corticosteroids; PO, peroral; MMF, myophenolate mofetil; SSc, systemic sclerosis; SAE, severe adverse event; AESI, adverse events of special interest; NSIP, non-specific interstitial pneumonia; vs., versus.

once rituximab is started [70]. Pregnancy and breastfeeding is not recommended up to 12 months after the last administration of rituximab, although unintentional rituximab exposure early in the first trimester is unlikely to be harmful [71]. At present, there are no recommendations on the use of rituximab in patients with a history of or active malignancy. Rituximab is contraindicated in active, severe infections, severely immunocompromised patients and patients with severe heart failure or other uncontrolled cardiac disease [64].

Conclusion

Rituximab is a treatment option in several SARDs (Table 3). Current evidence supports use of rituximab in refractory moderate-to-severe SLE, SSc with refractory skin involvement, and pSS with systemic involvement. There is a consensus for use in refractory myositis. The role of rituximab in ILD will be further explored in the RECITAL and EvER-ILD trial. Several other trials of rituximab in SARD are upcoming or ongoing (Table 4). Rituximab has a good safety profile, but the treating physician should be aware of possible infusion reactions and their appropriate treatment, as well of the increased risk of infection.

Disclosure statement

No potential conflict of interest was reported by the authors.

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