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REVIEW ARTICLE

The potential utility of B cell-directed biologic therapy in autoimmune diseases

D. G. Arkfeld

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Abstract Increasing awareness of the importance of aberrant B cell regulation in autoimmunity has driven the clinical development of novel B cell-directed biologic therapies with the potential to treat a range of autoimmune disorders. The first of these drugs—rituximab, a chimeric monoclonal antibody against the B cell-specific surface marker CD20—was recently approved for treating rheumatoid arthritis in patients with an inadequate response to other biologic therapies. The aim of this review is to discuss the potential use of rituximab in the management of other autoimmune disorders. Results from early phase clinical trials indicate that rituximab may provide clinical benefit in systemic lupus erythematosus, Sjögren's syndrome, vasculitis, and thrombocytopenic purpura. Numerous case reports and several small pilot studies have also been published reporting the use of rituximab in conditions such as myositis, antiphospholipid syndrome, Still's disease, and multiple sclerosis. In general, the results from these preliminary studies encourage further testing of rituximab therapy in formalized clinical trials. Based on results published to date, it is concluded that rituximab, together with other B cell-directed therapies currently under clinical development, is likely to provide an important new treatment option for a number of these difficult-to-treat autoimmune disorders.

Keywords Biologic therapies · B-lymphocytes · CD20 · Lupus · Rituximab · Sjögren's syndrome · Thrombocytopenic purpura · Vasculitis

D. G. Arkfeld (✉)
Division of Rheumatology, Keck School of Medicine,
University of Southern California, HMR 711,
2011 Zonal Avenue, Los Angeles, CA 90033, USA
e-mail: arkfeld@usc.edu

Background

Autoimmunity is widely believed to be fundamental to the development and progression of many rheumatic diseases—rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) being the best-known examples. The function of B cells in autoimmunity is still not fully understood, although evidence is mounting that they play an essential role in the process. In addition to their well-known function in synthesizing antibodies, B cells act in antigen presentation and as critical regulators of the development and function of T cells [21]. B cells are also the source of rheumatoid factor, levels of which are strongly correlated with disease severity in RA [103]. These and other lines of evidence provided the rationale for testing whether B cell depletion would be an effective strategy for treating rheumatic diseases. The availability of rituximab (RITUXAN®; Genentech/Biogen-IDEC, South San Francisco, CA, USA), a genetically engineered monoclonal antibody directed against the B cell-specific antigen CD20 [60], enabled this hypothesis to be tested. The first results, demonstrating sustained clinical responses coupled with B cell depletion in 5 RA patients treated with rituximab [30], ignited intense interest in the wider potential of B cell depletion therapy in autoimmune diseases.

A full-scale clinical trial program led to the approval of rituximab in 2006 for the treatment of RA in patients with an inadequate response to anti-tumour necrosis factor (TNF) therapy. A number of other B cell-directed agents are currently in clinical development. Among the most advanced is epratuzumab, a humanized monoclonal antibody directed against CD22, another B cell-specific marker [90]. Epratuzumab has been tested in patients with Sjögren's syndrome (SS) [89] and results were published recently of an open-label clinical trial involving patients

with SLE [29]. Another strategy under investigation is the neutralization of B cell survival factors. BAFF (also known as B lymphocyte stimulator, BLyS) is essential for the survival of B cells and is involved in many other aspects of B cell biology, including germinal center maintenance, isotype switching, and regulation of B cell-specific markers [48]. Belimumab is an anti-BAFF monoclonal antibody that has reached Phase II trials in SLE and RA [27], while atacicept (previously known as TACI-Ig), a recombinant fusion protein that neutralizes both BAFF and APRIL (a related B cell survival factor) [41], has undergone Phase I evaluation in SLE. A more in-depth review was published recently of current B cell-targeted approaches that are being developed to treat autoimmune disorders [31].

The aim of this review is to discuss the potential utility of B cell-directed therapy in the management of autoimmune disorders. As the first of these agents to be approved for clinical use, rituximab will be the focus of this article. In addition, since several excellent reviews have been published recently covering the use of rituximab in RA [25, 31, 58], this review will discuss results from the clinical testing of rituximab in autoimmune disorders other than RA. Information from case reports, clinical trials, and other studies was gathered from a search of the Medline database up to and including June 2007.

Clinical use of rituximab

Rituximab has been tested in a wide range of autoimmune conditions, with clinical trials being most advanced in SLE and SS. A summary of the published clinical data in these and other autoimmune disorders is presented in Table 1.

Systemic lupus erythematosus

Traditional treatments for SLE include nonsteroidal anti-inflammatory drugs, antimalarials, corticosteroids, methotrexate, mycophenylate, and cytotoxic drugs such as cyclophosphamide (often in combination). However, these therapies are associated with many potential side effects and are usually only partially effective in the long term [46]. The wide body of evidence indicating that B cells play a central role in the etiopathology of SLE has focused attention on the potential benefits of rituximab and other B cell-targeted therapies in the disease [33, 57, 78].

Individual case reports and case series, together with encouraging results from early phase clinical trials, indicate that rituximab is likely to provide significant clinical benefit for at least a subset of SLE patients. For example, in a dose-escalation study involving 17 patients, significant improvements in the systemic lupus activity measure (SLAM) score were observed in those patients (11/17) who achieved concomitant profound B cell depletion; efficacy persisted for 12 months and no significant adverse events were reported [59]. Analysis of some of the patients in this trial revealed that clinical response to rituximab correlated closely with the FcγI-IIa genotype of individual patients [6], as observed previously in studies involving the rituximab responses of patients with follicular lymphoma [96]. In another open-label study, 23/24 patients achieved depletion of B cells following treatment with rituximab (two 1,000 mg infusions of rituximab separated by 2 weeks); depletion lasted for 3–8 months—except in 1 individual, who remained depleted after 4 years [55]. Clinical improvements observed in this study occurred in each of the 8 organs/systems assessed using the British Isles Lupus Assessment Group (BILAG) system. A recent update from the same group—covering a total of 41 patients with a mean (range) follow-up period of 37 (6–79) months—reported that one-third of patients remained well following B cell depletion, without the need for immunosuppressive agents [64]. Thirteen patients had been re-treated with rituximab. Three serious adverse events (1 pneumococcal sepsis, 1 severe serum sickness-like reaction, and 1 seizure related to hyponatremia) and 2 deaths (1 involving varicella pneumonitis and the other involving pancarditis) had occurred in this cohort over the 7-year observation period.

In another trial involving patients with active or refractory SLE, with a follow-up period of 2 years, all 11 patients in the study responded to a single course of rituximab, with 6 achieving a full response and 5 a partial response; although relapse was common (64%), re-treatment was rapidly effective [85].

In a recently reported case series of six patients with aggressive refractory SLE, rituximab therapy (doses of rituximab and use of combination drugs varied between patients) resulted in partial clinical improvements in five cases [40]. Rituximab has also shown effectiveness in pilot studies involving patients with the common severe complication lupus nephritis [42, 84, 95] and in patients with refractory SLE involving the central nervous system [92].

Although most studies to date indicate that B cell depletion therapy is likely to be useful in SLE, the variability of responses to rituximab therapy observed in SLE trials published to date remains to be explained. Ongoing Phase II/III randomized controlled trials should provide some insight into this question. In addition, although the overall tolerability of rituximab in SLE appears to be good, the Food and Drug Administration recently issued an alert concerning two spontaneous fatal cases of progressive multifocal leukoencephalopathy (PML) due to JC polyomavirus reactivation in two patients with SLE who had received rituximab therapy [38]. It is unclear whether these cases were related to rituximab treatment, since only two cases have been reported and PML has also been reported in >20 SLE patients not treated with rituximab.

Table 1 Summary of published data from clinical studies of rituximab in autoimmune disorders other than RA

Disorder/study type	No. of pts	Treatment regimen	Summary of clinical results
Systemic lupus erythematosus			
Phase I/II dose escalation [59]	18	Single RTX infusion of 100 mg/m^2 (low dose [$n = 6$]) or 375 mg/m^2 (intermediate dose [$n = 6$]), or 4 weekly RTX infusions of 375 mg/m^2 (high dose [$n = 6$])	Improved SLAM score at 12 months in 11/17 (65%) evaluable pts
Open-label pilot [84]	10[a]	RTX (375 mg/m^2) once weekly for 4 weeks + prednisolone (0.5 mg/kg/day for 10 weeks, tapered by 4 mg every 2 weeks thereafter)	Partial remission (improvement in renal parameters) in 8/10 pts within a median (range) of 2 (1–4) months; of these, 5 pts had complete remission at 3 months (median); this was sustained for ≥12 months in 4 pts
Open-label pilot [55]	24	RTX (1,000 mg) + CyP (750 mg): two infusions, 2 weeks apart	Improvements in global and all 8 individual BILAG scores at 6 months in 23/24 pts (96%)
Open-label pilot [85]	11	RTX (375 mg/m^2) once weekly for 4 weeks + CyP (500 mg) co-administered at first infusion; immunosuppressive therapy at baseline had been unchanged for ≥3 months prior to study and was continued until Month 6, following which dose reduction was allowed	6 complete and 5 partial responses (follow-up through 2 yrs) (overall, significant reduction in median BILAG scores)
Sjögren's syndrome			
Single-centre, open-label Phase II [73]	15	RTX (375 mg/m^2) once weekly for 4 weeks	Improvements in subjective and objective parameters of disease activity (salivary and lacrimal gland function) in all 14 pts who completed the study. Of the 7 pts with MALT-type lymphoma, 3 had complete remission, while disease was stable in 3 pts and progressive in 1 pt.
Retrospective [83]	16	RTX (375 mg/m^2) once weekly for 4 weeks (6 weeks in 1 pt with lymphoma); 1 pt with systemic manifestations received RTX 2 × 1,000 mg. All pts received methylprednisone (100 mg) and either oral certirizine (20 mg) or dexchloropheniramine (5 mg) before the RTX infusion	Efficacy observed in 9/11 pts with systemic manifestations (improvement in systemic symptoms) and in 4/5 pts with lymphomas (disease remission)
Open-label pilot [26]	16	RTX (375 mg/m^2) once weekly for 2 weeks	Significant improvement in mean VAS scores for fatigue and dryness, tender point count, and quality of life (at Week 12) and for all 4 VAS scores, tender joint count, tender point count, and quality of life (at Week 36)
Vasculitis			
Case series [34]	9[b]	RTX (500 mg [375 mg/m^2 in 1 patient]) once weekly for 2 weeks ($n = 3$) or 4 weeks ($n = 6$)	Remission (BVAS = 0) in 8 pts and partial remission (BVAS = 1) in 1 pt at 6 months
Case series [50]	11[c]	RTX (375 mg/m^2) once weekly for 4 weeks + prednisone (≤1 mg/kg/day, tapering once disease activity improved)	Remission (BVAS/WG = 0) in all 11 pts (10 pts within 6 months); tapering of prednisone dose (median = 0; range 0–1.5 mg/kg/day) in all pts
Open-label pilot [51]	10[d]	RTX (375 mg/m^2) once weekly for 4 weeks + prednisone (≤1 mg/kg/day, tapering once disease activity improved)	Remission (BVAS/WG = 0) in all pts within 3 months; tapering of prednisone dose to 0 in all pts by 6 months
Case series [88]	10[e]	RTX (375 mg/m^2) once weekly for 4 weeks + prednisone (≤2 mg/kg/day, tapering once disease activity improved)	Complete response (BVAS/WG = 0) in 9 pts and partial response (BVAS/WG = 1) in 1 pt at 6 months. Follow-up (median 34 months; range 26–45 months): 3 pts relapsed but had new sustained response following re-treatment

Table 1 continued

Disorder/study type	No. of pts	Treatment regimen	Summary of clinical results
Open-label [85]	11[c]	RTX (375 mg/m^2) once weekly for 4 weeks + CyP (500 mg) co-administered at first infusion; immunosuppressive therapy at baseline had been unchanged for ≥3 months prior to study and was continued until Month 6, following which dose reduction was allowed	Remission in 9/11 pts (BVAS = 0) and partial remission in 1 pt (BVAS = 2); 6/10 pts subsequently relapsed but had new sustained response following re-treatment with RTX (2 × 1000 mg, 2 weeks apart)
Case series [8]	8[d]	RTX (375 mg/m^2) once every 4 weeks for 4 cycles + standard treatment (CyP 2 mg/kg once daily or 15–20 mg/kg every 18–21 days or methotrexate 0.3 mg/kg once weekly)	Remission (BVAS = 0) in 2 pts, partial remission in 1 pt, unchanged disease activity in 3 pts, and progression in 2 pts 1 month after final cycle
Myositis			
Open-label pilot [56]	7[f]	RTX (375 mg/m^2) once weekly for 4 weeks + standard treatment (included azathioprine, corticosteroids, CyP, and intravenous immunoglobulin)	Clinical improvement (increased muscle strength relative to baseline [assessed using dynomometry]) in all 6 evaluable pts
Idiopathic thrombocytopenic purpura			
Open-label pilot [87]	25	RTX (375 mg/m^2) once weekly for 4 weeks	Clinical response (rise in platelet counts) at end of therapy without need for further treatment in 13/25 (52%) pts. Responses were sustained for ≥6 months in 7 pts
Pooled data from two pilot trials [22]	57	RTX (375 mg/m^2) once weekly for 4 weeks; 17 pts received prednisone (60 mg with Infusion 1 and 20 mg with Infusion 2)	Clinical response (rise in platelet counts) at end of therapy without need for further treatment in 31/57 (54%) pts; 29/31 responses occurred within 8 weeks of initiating RTX therapy. 15/16 pts with complete clinical response (rise in platelet counts to normal levels) maintained response for ≥12 months
Retrospective national multicenter [13]	35	RTX (375 mg/m^2) once weekly for 4 weeks + prednisone; 6 pts received a fixed dose of 500 mg supplemented by 100 mg methylprednisone or 50–100 mg prednisone + antihistamine prior to RTX infusion	Clinical response (rise in platelet counts) within 3–8 weeks for 17/39 (44%) treatments (4 pts received 2 cycles); pts with complete or partial responses had been in remission for a median of 47 weeks
Retrospective national multicenter[g] [71]	89	RTX (375 mg/m^2) once weekly for 4 weeks (n = 77) or for 1–6 weeks (n = 12); 31 pts received RTX with other therapies (corticosteroids [n = 20], IVIG [n = 2], corticosteroids + IVIG [n = 3], others [n = 6])	Clinical response (rise in platelet counts) in 49/89 (55%) pts; 31 pts maintained response for a median (range) of 9 (2–42) months, 12 pts for >12 months
Thrombotic thrombocytopenic purpura			
Open-label prospective multicenter [35]	11	RTX (375 mg/m^2) once weekly for 4 weeks + premedication with IV steroids (30 mg), IV dexchlorpheniramine (10 mg), and IV paracetamol (1 g). Patients with acute TTP (n = 5) continued plasma infusions for ≥3 weeks followed by tapering at the onset of remission	Clinical remission (regression of visceral ischemic signs and normalization of blood parameters) in all patients with acute TTP; continued remission in patients with disease remission at enrolment (6–11 months' follow-up). Biologic remission (≥10% recovery of ADAMTS-13 activity and disappearance of anti-ADAMTS-13 antibodies) in all pts

Table 1 continued

Disorder/study type	No. of pts	Treatment regimen	Summary of clinical results
Open-label prospective multicenter [82]	25	RTX (375 mg/m^2) once weekly for 4 weeks + premedication with IV hydrocortisone (100 mg), IV dexchlorpheniramine (10 mg), and oral paracetamol (1 g) immediately following PEX; PEX was continued until clinical remission was achieved	All patients achieved clinical remission (sustained normal platelet count, absence of clinical manifestations of TTP, and cessation of PEX) in a median of 11 days after initiating rituximab. ADAMTS-13 activity returned to normal levels in 21/25 pts; anti-ADAMTS-13 antibodies disappeared in 23/25 pts
Retrospective comparative 2-center [45]	15	RTX (375 mg/m^2) once weekly for 1–8 weeks + standard therapy (PEX + corticosteroids + various agents added as second-line therapy, if needed) ($n = 8$) or standard therapy alone ($n = 7$)	Clinical remission (absence of clinical manifestations of TTP and normalization of blood parameters): 100% (RTX group) vs. 66% (standard therapy group) ($p = 0.0025$)
Mixed cryoglobulinemia			
Open-label prospective [80]	20[h]	RTX (375 mg/m^2) once weekly for 4 weeks	Complete response (improvement of clinical signs and decline in cryocrit) in 16/20 (80%) pts; response was maintained for ≥12 months in 12/16 responders
Case series [101]	15[i]	RTX (375 mg/m^2) once weekly for 4 weeks + prednisone (<0.5 mg/kg/day), if already administered at recruitment	Improved clinical symptoms (including cutaneous manifestations, lymphoma features, neuropathic symptoms) in all 15 pts
Cold agglutinin disease			
Open-label Phase II [11]	27	RTX (375 mg/m^2) once weekly for 4 weeks. Re-treatment (if required): RTX (same regimen) plus interferon-α (5 million units three-times weekly for 20 weeks)	Clinical response (improvement in anaemia, clinical symptoms, and histopathology) in 14/27 (52%) pts after first treatment and in 6/10 pts after re-treatment; median (range) time to response was 1.5 (0.5–4) months
Phase II multicenter [81]	20[j]	RTX (375 mg/m^2) once weekly for 4 weeks	One pt showed a complete response (normalization of hemoglobin levels, absence of signs of hemolysis, and loss of clinical symptoms), 8 pts had a partial response (increase in hemoglobin levels ≥1.0 g/dl for ≥1 month, no need for erythrocyte transfusions, improvement in clinical symptoms); of the 9 responders, 8 relapsed and 1 remained in remission at 48 weeks

[a] Proliferative lupus nephritis, [b]ANCA-positive microscopic polyangitis ($n = 2$) and ANCA-positive Wegener's granulomatosis ($n = 7$), [c]ANCA-associated vasculitis

[d] ANCA-positive refractory Wegener's granulomatosis, [e]ANCA-positive microscopic polyangitis ($n = 2$) and ANCA-positive Wegener's granulomatosis ($n = 8$), [f] Dermatomyositis, [g] Clinical results were obtained from physicians via a questionnaire (original patient data were not analyzed), [h] HCV-positive type II or type III mixed cryoglobulinemia, [i] Type II mixed cryoglobulinemia (HCV-positive [$n = 12$]; associated with SS [$n = 1$]; "essential" disease [$n = 2$]), [j] Idiopathic CAD ($n = 13$) and CAD associated with malignant B-cell lymphoproliferative disease ($n = 7$)

ADAMTS-13 a disintegrin-like and metalloproteinase with thrombospondin-like type I motif 13, *ANCA* anti-neutrophil cytoplasmic antibody, *BILAG* British Isles Lupus Assessment Group, *BVAS* Birmingham vasculitis activity score, *BVAS/WG* BVAS modified for Wegener's granulomatosis, *CAD* cold agglutinin disease, *CyP* cyclophosphamide, *HCV* hepatitis C virus, *IVIG* intravenous immunoglobulin, *MALT* mucosa-associated lymphoid tissue, *PEX* plasma exchange, *pts* patients, *RTX* rituximab, *SLAM* systemic lupus activity measure, *VAS* visual analog scale

Sjögren's syndrome

Sjögren's syndrome is a chronic autoimmune disorder of the exocrine glands affecting approximately 1% of the adult US population. The syndrome often occurs in the presence of another autoimmune disorder such as RA or SLE [37]. The etiopathology of SS is not fully understood; however, disturbances in B cell biology are considered to play an important role [43].

A number of case reports and pilot studies have been published that describe the successful treatment of SS with rituximab [2, 73, 76, 93]. In a recent trial involving 16 female patients with systemic complications of primary SS, rituximab therapy led to B cell depletion and decreased levels of various B cell markers; with a median follow-up period of 14.5 months, clinical efficacy was observed in 4/5 patients with lymphomas and in 9/11 patients with other systemic manifestations [83].

Another recent study investigated the effects of rituximab (two infusions of 375 mg/m^2 separated by 1 week) in 16 patients with primary SS [26]. Rituximab therapy, which was administered using a slow initial rate of infusion without steroid premedication, was well tolerated and overall improvements were observed in subjective parameters of disease activity and in quality of life after both 12 and 36 weeks' follow-up.

Results were presented recently from the first double-blind, randomized, controlled study of rituximab in SS [24]. In this 20-patient pilot study, subjects received either rituximab (two 1,000 mg infusions separated by 2 weeks) or placebo. Although patient responses were highly variable and there was a marked placebo effect, a higher proportion of patients in the rituximab group achieved improvement in fatigue (the primary efficacy endpoint) than in the placebo group (48 vs. 20%); this difference was not statistically significant. Significantly greater improvements with rituximab over placebo in the social functioning aspect of the quality of life assessment were also noted.

Vasculitis

Vasculitis refers to a collection of rare inflammatory diseases that involve the blood vessel walls and surrounding interstitium. A subset of these diseases, including Wegener's granulomatosis (WG), microscopic polyangitis, and Churg–Strauss syndrome, is characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) [97]. The mainstay of current therapies in vasculitis involves glucocorticoids, cyclophosphamide, and—more recently—methotrexate and azathioprine [54]. However, these approaches are not always effective and are often limited by significant toxicity. B cells have been implicated in the pathogenesis of ANCA-associated vasculitis [20], indicating that rituximab may be an effective treatment option.

In addition to a number of individual case reports, results have been published recently from several small open-label trials of rituximab in vasculitis. In a report of a series of nine individual cases of ANCA-positive vasculitis resistant to conventional therapy in which rituximab therapy was attempted, eight patients achieved complete responses, while the other patient showed a partial response [34]. Keogh and colleagues have conducted small, prospective, open-label trials in both ANCA-associated vasculitis and WG. The vasculitis trial involved 11 patients whose disease was either refractory to cyclophosphamide or in whom cyclophosphamide was contraindicated [50]. Following infusions with rituximab, circulating B cells became undetectable in all patients and ANCA titers decreased significantly. Clinical remission was achieved in all patients and was maintained while B cells were undetectable. In ten patients with refractory WG treated with prednisone (1 mg/kg/day) plus rituximab (four consecutive weekly infusions of 375 mg/m^2) [51], therapy was well tolerated and—after 3 months—all patients had achieved clinical remission (reduction in disease activity score to 0); in addition, all patients were able to stop glucocorticoids by 6 months. Following the recurrence of raised ANCA titers, five patients in the trial were successfully re-treated with rituximab. Results were also recently published of long-term follow-up of ten patients with ANCA-associated vasculitis who had been treated with rituximab [88]: patients had received four consecutive weekly doses of rituximab (375 mg/m^2) and all experienced rapid clinical improvement at 6 months. Although three patients subsequently relapsed, re-treatment was effective. In addition, ANCA titers decreased significantly in all patients. Of 11 patients with refractory ANCA-associated vasculitis who were treated with rituximab in another recently published pilot study, 10 showed either complete or partial responses to a course of rituximab together with a single dose of cyclophosphamide [85].

In contrast to the above findings, one recent study found that rituximab was less effective in a cohort of eight patients with refractory WG [8]. In this trial, rituximab was given every fourth week. Interestingly, all patients in this study had particular granulomatous manifestations, consisting of retro-orbital granulomata ($n = 5$), nodules of the lungs ($n = 1$), and subglottic stenosis ($n = 2$). Although three patients experienced some clinical improvement, ANCA titers were not affected by rituximab therapy (except in a single patient). A smaller Norwegian study had also previously found only temporary responses to rituximab in three patients with WG, two of whom had granulomatous masses [68].

In a recent review of published studies in this area, it was concluded that rituximab may be an effective treatment in patients with refractory ANCA-associated vasculitis (with the probable exception of WG patients with retro-orbital granulomas, who tended to be less responsive to rituximab therapy) [98]. Since then, however, case reports have appeared describing the successful use of rituximab in patients with granulomatous involvement [79, 91]. In addition, results from a recent case series of eight WG patients indicated that, while vasculitis symptoms tended to disappear relatively quickly, granulomatous manifestations usually regressed more slowly (sometimes over several months) [14].

With regard to other forms of ANCA-associated vasculitis, two individual case reports have been published recently detailing the successful treatment of Churg–Strauss syndrome with rituximab [49, 52].

Thrombocytopenic purpura and other hematologic disorders

A number of autoimmune disorders of hemostasis, most notably idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP), have been examined for their potential responsiveness to rituximab in several small trials.

In a study involving a cohort of 25 patients with chronic ITP that had proved resistant to conventional therapies [87], patients received weekly rituximab at a dose of 375 mg/m^2 for 4 weeks. The overall response rate (comprising those with complete, partial, and minor responses) was 52%; responses were sustained for at least 6 months in 7 patients. Complete and partial responses were associated with rapid normalization of platelet concentrations. A similar initial response rate (54%) was reported from a larger follow-up trial involving 57 patients; sustained responses were observed in 32% of the study participants [22]. Other reports include a multicenter trial in 35 adults with refractory ITP conducted in Denmark, which resulted in a 44% overall success rate based on predefined rises in platelet concentrations [13]. An indirect retrospective survey of findings from 89 ITP patients treated at multiple centers in Spain indicated that rituximab therapy led to sustained responses in 35% of patients with a median follow-up of 9 months (range 2–42 months) [71].

A review was published recently of the clinical outcomes of patients with chronic ITP who were re-treated with rituximab following an initial response to therapy [72]. All 9 second responses recorded in this report were classified as complete. An interesting additional finding was the higher female:male ratio of the nine re-treated patients compared with the population of patients originally treated across the published studies identified, suggesting that female ITP patients are more likely than male patients to respond to rituximab therapy. In a recently published letter, early administration of rituximab was reported to be associated with a higher response rate in chronic ITP [102].

The efficacy and safety of rituximab in adults with ITP were the subject of a recently published systematic review [9]. Based on 19 reports (313 patients) deemed eligible for the analysis up to April 2006, rituximab therapy was associated with mean complete response (platelet count $>150 \times 10^9$ cells/l) and overall response (platelet count $>50 \times 10^9$ cells/l) rates of 44 and 63%, respectively. Significant toxicities including death occurred in 3% of included cases, although the deaths were not necessarily attributable to rituximab therapy. The authors noted the lack of randomized controlled studies of rituximab therapy in ITP.

A number of studies have also been conducted in patients with refractory or relapsing TTP. In addition to several case reports and small case series [3, 17, 69, 70, 74, 99], results from the first prospective trial have been published [35]. This study recruited 11 patients (6 enrolled during an acute refractory phase and 5 during a remission phase); following rituximab therapy (375 mg/m^2 once weekly for 4 weeks), clinical remission was observed in all 6 acute cases, while all 5 patients enrolled during remission remained in clinical remission during the 6–11 month follow-up period. Biologic remission (disappearance of anti-ADAMTS-13 [a disintegrin and metalloproteinase with thrombospondin motif 13] antibodies, which occur in the great majority of patients with acquired TTP [75]) was achieved in all patients 7–24 weeks after the final rituximab infusion.

Another more recent study involved 25 patients with acute refractory/relapsing idiopathic TTP, who were given rituximab in conjunction with plasma exchange (PEX) because of progressive clinical disease [82]. It was reported that all 25 patients in this trial achieved complete clinical and laboratory remission (sustained normal platelet count, absence of clinical manifestations of TTP, and cessation of PEX) in a median of 11 days following the initiation of rituximab therapy. Restoration of ADAMTS-13 activity and disappearance of anti-ADAMTS antibodies occurred in the vast majority of cases. At the time of publication, it was stated that none of the patients had clinically relapsed, with a median (range) follow-up of 10 (1–33) months.

In another recent retrospective study, the clinical outcome of patients who had received rituximab (375 mg/m^2 once weekly for a maximum of 8 weeks) together with standard therapy (PEX + corticosteroids) was compared with that of patients who had received standard therapy alone [45]. The remission rate in the rituximab group was significantly greater than that observed in the standard therapy group (100 vs. 66%; $P = 0.0025$). Interestingly, all

three of the TTP studies described above reported good tolerability to rituximab therapy.

There have also been sporadic case reports describing the successful use of rituximab in a number of other rare hematologic disorders, including Evans' syndrome [61, 65], mixed type II cryoglobulinemia [15, 80, 101], and cold agglutinin disease [11, 81]. In addition, we have recently reported on the successful use of rituximab in RA patients with life-threatening hemorrhage due to the presence of Factor VIII inhibitor [67]. By contrast, a case report describing the failure of rituximab therapy in a hemophiliac patient with Factor VIII inhibitor has also been published [18]. A recent analysis of published case reports of patients with acquired antibodies to Factor VIII indicated that rituximab therapy was associated with a similar rate of clinical remission (approximately 80%) compared with the standard treatment modality (cyclophosphamide + prednisolone) [86].

Myositis

Myositis comprises a group of inflammatory myopathies, of which polymyositis, dermatomyositis, and inclusion body myositis are the best defined clinically. The etiopathologies of this group of diseases are currently poorly understood, although autoimmunity is thought to play an important role [19].

The aim of a recent open-label pilot study involving seven patients with dermatomyositis was to test the hypothesis that B cells play a critical role in this disease [56]. The results of this trial, in which patients received four infusions of rituximab (375 mg/m^2) at weekly intervals, showed that rituximab therapy was well tolerated and led to significant clinical improvements in the six evaluable patients who completed 1 year of follow-up. A number of other small pilot studies and case reports have also appeared recently detailing the generally successful use of rituximab in patients with dermatomyositis or polymyositis [7, 12, 16, 28, 53, 62, 66].

Antiphospholipid syndrome

Antiphospholipid syndrome (APS), a rare disorder mostly affecting young adults, is defined by the presence of autoantibodies against phospholipids; the main clinical manifestations are venous or arterial thrombosis and obstetric complications, although the link between antiphospholipid antibodies and these clinical features has not been firmly established [39]. The traditional approach to treatment mainly involves the use of anticoagulation therapies. However, data indicating a link between raised circulating CD5+ B cells and high levels of antiphospholipid antibodies in APS patients [100] suggest that APS may be amenable to B cell-directed therapies.

To date, only a small number of case reports have been published which detail attempts to manage APS with rituximab. Three of these studies [5, 77, 94] reported successful clinical outcomes following rituximab therapy, while the other [4] reported only a limited effect of rituximab on thrombocytopenia and anticardiolipin antibodies in a patient with primary APS. Although the data are currently limited, the striking clinical successes seen in some patients suggest that pilot studies with rituximab in APS should be conducted in the near future.

Still's disease

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology. Traditional therapies include NSAIDs, corticosteroids, and—more recently—disease-modifying anti-rheumatic drugs [47]. A number of trials have also been conducted with biologic agents (including TNF inhibitors), with some promising results [32].

One case report was published recently that described the successful use of rituximab in a patient with AOSD [1]. This report, together with the author's unpublished observations of two patients with AOSD refractory to cytotoxic agents who benefited from repeated rituximab infusion therapy, suggests that rituximab may be a future treatment option for this disease.

Neurologic disorders

As reviewed recently by Finsterer [36], rituximab has been tested in a number of immune-mediated peripheral neuropathies with promising results. Its potential clinical utility in neurological diseases of the central nervous system such as multiple sclerosis (MS) remains to be explored. Encouragingly, pilot studies have shown that rituximab therapy results in partial depletion of B cells from the cerebrospinal fluid of patients with progressive MS [23, 63]. The results of the first Phase I and II trials of rituximab in progressive MS were presented recently [10, 44]. In the placebo-controlled Phase II study [44], involving 104 patients with relapsing remitting MS, a single course of rituximab (two infusions of 1,000 mg given 2 weeks apart) resulted in significantly fewer inflammatory brain lesions and relapses over the 6-month observation period compared with placebo. Rituximab treatment was reported to have been well tolerated.

Conclusions

Recent advances in our understanding of autoimmunity have opened up new avenues for exploring novel targeted

therapies in a wide range of diseases. The role of B cells in many autoimmune disorders is now widely accepted, in many cases through the demonstration that B cell depletion using rituximab can often be very effective clinically. The potential utility of rituximab and other B cell-directed therapies is currently being studied in several of these diseases, including SLE, SS, and vasculitis. Although to date most of the findings have been encouraging, a significant proportion of the information derives from case reports and small case series. Together with the lack of randomized controlled trials in most of the diseases discussed in this review, it is likely that there has been a degree of positive reporting bias. Therefore, until large-scale clinical trial data are available, it would be prudent to proceed with caution regarding the use of rituximab outside its approved indications. Although rituximab tolerability was generally reported as favorable in most of the studies covered in this review, the true incidence of associated adverse events (e.g., serious infections, serum sickness-like reactions, and PML) will only become clear when larger numbers of patients have been treated in each disease entity. Important questions also remain regarding the optimal rituximab dosing modalities for each disease (for example, the dose and frequency of treatment, when re-treatment should be considered, and whether to use combination therapies). Nevertheless, based on the information published to date, it seems likely that B cell depletion therapy, using rituximab and—in the future—agents currently under development, will offer an effective new approach for the management of many of these burdensome and difficult-to-treat conditions.

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