

The role of rituximab in the treatment of ANCA-associated vasculitides (AAV)

Thomas Daikeler^a, Andreas D. Kistler^b, Pierre-Yves Martin^c, Bruno Vogt^d, Uyen Huynh-Do^d

^a Rheumatology, University Hospital Basel, Switzerland

^b Division of Nephrology, University Hospital, Zürich, Switzerland

^c Nephrology Division, University Hospital and School of Medicine, Geneva, Switzerland

^d Department of Nephrology and Hypertension, Inselspital, University of Bern Medical School, Switzerland

Summary

The antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a group of primary vasculitides that affect predominantly small- to medium-sized blood vessels. AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Disease severity is dictated by the location and extent of the blood vessels affected. If left untreated, systemic forms of AAV are often fatal. The advent of immunosuppressive therapy (cyclophosphamide plus glucocorticoids) has revolutionised the prognosis for patients with AAV, transforming the course of the disease from fatal to one that can be managed, though not without significant treatment-related toxicity. Recently, the monoclonal antibody rituximab was approved for the treatment of GPA and MPA, providing the first major alternative to cyclophosphamide for induction

therapy of AAV. This review explores the emerging role of rituximab in the management of this complex disorder.

Key words: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV); first-line treatment; maintenance; relapsed/refractory disease; cyclophosphamide; glucocorticoids; methotrexate; rituximab

Introduction

The antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are chronic, relapsing, primary vasculitides characterised by leucocyte infiltration of blood vessel walls, fibrinoid necrosis and vascular damage [1]. Three heterogeneous syndromes fall under the term AAV: granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) [2]. In addition, AAV can present as single-organ vasculitis, e.g. renal-limited AAV. A hallmark of these disorders is the presence of circulating antibodies to neutrophil cytoplasmic antigens, specifically, proteinase 3 (PR3) and myeloperoxidase (MPO) [1]; hence they are called ANCA-associated vasculitides. Granulomatous lesions in the upper and lower respiratory tract often precede the appearance of symptoms in other organs, a feature which distinguishes GPA from MPA [3]. When first described, severe systemic forms of these disorders were mostly fatal. In the absence of treatment, the mean survival for patients with systemic GPA was 5 months, and the 1-year mortality rate was 82% [4]. The combination of cyclophosphamide (CYC) and glucocorticoids heralded a landmark in the management of AAV, transforming this fatal disease into one that could be managed, though not entirely cured [5, 6]. Despite this improvement, however, a proportion of patients either do not respond to CYC, or relapse after initial treatment [7]. Another major obstacle in the management of AAV is the substantial toxicity associated with the repeated use of CYC, which includes infertility, cytopenia, infections, or malignancies.

Abbreviations

AAV	ANCA-associated vasculitides
ANCA	antineutrophil cytoplasmic antibody
BSA	body surface area
CYC	cyclophosphamide
EGPA	eosinophilic granulomatosis with polyangiitis
EUVAS	European Vasculitis Study Group
FDA	Food and Drug Administration
GDCN	Glomerular Disease Collaborative Network
GFR	glomerular filtration rate
GPA	granulomatosis with polyangiitis
MPA	microscopic polyangiitis
MAINRITSAN	maintenance using rituximab in remission after vasculitis
MPO	myeloperoxidase
NORAM	non-renal Wegener's granulomatosis treated alternatively with methotrexate
PML	progressive multifocal leukoencephalopathy
PR3	proteinase 3
RAVE	rituximab for ANCA-associated vasculitis
RITAZAREM	rituximab vasculitis maintenance study
RTX	rituximab
RITUXVAS	rituximab versus cyclophosphamide in ANCA-associated vasculitis.

Indeed, these significant treatment-related adverse effects have now moved to the forefront as more patients have lasting remissions with CYC. This underscores the need for less toxic treatment modalities.

Rituximab (RTX) is a monoclonal anti-CD20 antibody that selectively targets B cells. RTX is an established treatment for rheumatoid arthritis and B cell lymphomas. RTX in combination with glucocorticoids was recently approved by the US Food and Drug Administration (FDA) for the induction treatment of GPA and MPA. Amongst the European countries, Switzerland led the way in approving the use of RTX in combination with glucocorticoids for the treatment of these diseases. Rather than a comprehensive literature overview, our objective with this review is to place RTX in the context of the current therapies used for AAV. As such, this review will be organised around several key questions relevant to the physicians who manage this challenging disease.

Pathogenesis, clinical presentation and standard therapy: how does rituximab act in the pathogenesis of AAV?

ANCAs are assumed to be important in the pathogenesis of AAV. In mouse models, ANCAs have been shown to induce glomerulonephritis [8]. The interaction of ANCA and MPO or PR3 on the surface of neutrophils may result in the activation and degranulation of neutrophils and monocytes within capillaries, leading to inflammation and destruction of vascular endothelium [9–11]. In addition, the number of activated B cells is associated not only with disease activity, but also correlates with the severity of disease symptoms [12] and autoantigen-specific B cells have been identified at sites of inflammation [11, 13, 14]. Collectively, these data provided a strong rationale for the use of a B cell-depleting agent such as RTX in AAV [15]. Importantly, there are also data on the presence of ANCA-specific T cells and the complement pathway also plays an important role in the initiation of vessel inflammation (reviewed in [16]).

RTX is a chimeric IgG1 antibody that binds to CD20 expressed exclusively on all cells of the B cell lineage except the very early B cell precursors and the plasma cells [17, 18]. B cell depletion from peripheral blood, spleen and lymph nodes is achieved by antibody-dependent cellular cytotoxicity (ADCC), complement-dependent toxicity (CDC) and apoptosis. However, the relevance of the different pathways remains a matter of debate [18]. The early B cell progenitor ‘sparing effect’ ensures repletion of B cells after treatment. Plasma cells are not depleted and thus established protective immune responses are not affected by RTX treatment.

Treatment of AAV

Today, standard therapy consists of high-dose glucocorticoids plus intravenous or oral CYC over a period of 3–6 months for induction of remission [19]. Plasma exchange has also been used to treat cases characterised by alveolar haemorrhage and acute renal insufficiency [20]. With these

treatments, remission rates are between 30–93% in GPA and 75–89% in MPA [19].

Once remission is achieved, this treatment is usually followed by maintenance therapy, since AAV are chronic diseases with a high risk of relapse. The use of azathioprine or methotrexate has replaced CYC in remission maintenance [21, 22]. Despite current maintenance treatments, around 50% of responders still relapse within 3–5 years and the 1-year mortality remains at around 12–18% [23]. Furthermore, around 20% of survivors develop end-stage renal disease, adding to the clinical burden, which already includes increased incidence of cardiovascular disease, infections and malignancies [24]. The latter two are associated with the use of immune suppressive agents, e.g. CYC and glucocorticoids. Hence, a major focus has been to develop novel therapeutic strategies that reduce toxicity while retaining efficacy.

What is the role of rituximab for remission induction in AAV?

The earliest clinical evidence supporting the use of RTX came from a case study in which a 66-year old man with GPA, who relapsed despite treatment with azathioprine and mycophenolate mofetil, and developed severe CYC-induced bone marrow toxicity was treated with a combination of glucocorticoids plus RTX [25]. After four weekly doses of 375 mg/m² RTX, he experienced clinical remission, allowing discontinuation of glucocorticoids. RTX alone was later used to treat another relapse in the same patient, thus introducing a new line of treatment for AAV.

Data for RTX in the induction therapy of patients with newly-diagnosed AAV comes from two pivotal trials, RAVE (rituximab for ANCA-associated vasculitis) [26–28] and RITUXVAS (rituximab versus cyclophosphamide in ANCA-associated vasculitis) [29]. Both trials were designed to compare the efficacy and safety of RTX versus CYC in the treatment of AAV.

RITUXVAS was an open-label study in which 44 patients with newly-diagnosed ANCA-associated glomerulonephritis were randomised in a 3:1 ratio to receive either RTX (375 mg/m² per week for 4 weeks) or intravenous CYC (3–6 months), followed by azathioprine for maintenance of remission in the CYC group [29]. It is important to note that patients in the RTX group also received intravenous CYC (15 mg/kg) along with the first and third RTX infusions; those who had progressive disease within the first 6 months were given an additional third dose of CYC. The RTX group did not receive maintenance azathioprine. The RTX arm achieved similar results to the CYC cohort, with respect to complete remission (82% in the RTX arm versus 91% in the CYC-only controls; $p = 0.68$). At the 2-year follow-up, relapse had occurred in 21% of the RTX arm (who had not received maintenance therapy) as compared with 18% in the control group who had received azathioprine maintenance treatment; $p = 1.00$ [30]). It is important to note, however, that the RITUXVAS trial was underpowered to detect clinically relevant differences between the two treatments.

The RAVE trial differed from RITUXVAS in several important points, including in the study treatment protocol, where RTX without the addition of CYC was compared

directly to CYC. This multicentre, double-blind, placebo-controlled trial included 197 patients with severe GPA and MPA who were randomised to receive treatment with RTX (375 mg/m² per week for 4 weeks) or daily oral CYC (2 mg/kg) for 3–6 months [26]. All patients in the CYC group received a further 12–15 months' treatment with azathioprine. Another relevant distinction between RAVE and RITUXVAS is the clinical profile of the patients. Only half of the RAVE patients had glomerulonephritis and the mean GFR was above 50 ml/min/1.73 m² (vs all patients in RITUXVAS, with mean GFR of 18 ml/min/1.73 m²); patients with serum creatinine levels >4 mg/dl were excluded from the study and half of the patients had relapsing disease. Results from RAVE showed that RTX was non-inferior to CYC for achieving glucocorticoid-free remission at 6 months (64% vs 53%; *p* = 0.09). Subgroup analysis indicated that RTX appeared to be equally effective in those patients with glomerulonephritis or pulmonary haemorrhage and that RTX induced a higher rate of remission than CYC amongst patients with relapsing disease. Longer follow-up (18 months) of the RAVE cohort confirmed that the initial single course of RTX was as effective as CYC induction plus azathioprine maintenance [31, 32].

Thus, the findings from both trials demonstrate that RTX has an efficacy in remission induction comparable to that of CYC and is likely superior in relapsing patients.

What maintenance immunosuppression to choose after remission induction with RTX?

It is noteworthy that in both RAVE and RITUXVAS, those patients in the RTX arms had similar long-term relapse rates compared with those in the CYC arms, despite the fact that they did not receive maintenance immunosuppressive agents. Therefore, it could be concluded that maintenance immunosuppression is not required after RTX treatment. However, the relapse rates in both the RAVE and the RITUXVAS studies remained considerable. During the 12-month follow-up period in RITUXVAS, 15% of patients in the RTX group versus 10% of those in the CYC group had a relapse (non-significant; *p* = 0.70) [29]. In RAVE, 32% of patients in the RTX arm versus 29% in the CYC-azathioprine arm had a relapse between month 6 and month 18 [27]. A subgroup analysis of the RAVE trial confirmed several previously known, strong risk factors for relapse: relapsing disease (vs newly diagnosed) and PR3-ANCA positivity (vs MPO-ANCA) [27]. Thus, maintenance immunosuppression with either azathioprine or repeated courses of RTX should be considered at least in high-risk patients.

RTX for maintenance of remission

Apart from its use for remission induction, RTX has been tested as an alternative to azathioprine for maintenance treatment.

Several independent nonrandomised studies tested the option of pre-emptive RTX treatment to maintain remission [33–39]. Multiple courses of RTX have been shown to induce additional remissions after relapse, and pre-emptive RTX retreatment can result in sustained remissions [33, 34]. In the 2-year follow-up of a study comparing 6-monthly, pre-emptive protocolised retreatment with RTX

(2 x 1g followed by 1 x 1g every 6 months for 2 years) against nonprotocolised retreatment according to clinical need (either 2 x 1g or 4 x 375 mg/m² only upon relapse), Jones et al. demonstrated that at 2 years relapse occurred in 11 of 49 (22%) protocol patients versus 24 of 34 (71%) nonprotocol patients (*p* < 0.01) [34] and at the 44-month follow-up, relapses had occurred in 22 of 26 (85%) of nonprotocol patients compared with 11 of 43 (26%) of those who received pre-emptive RTX treatment (*p* < 0.001) [39]. Glucocorticoid dosages were decreased and immunosuppressive therapy was withdrawn in the majority of patients. These results have been supported by other studies [35, 36, 40], including a recent one that examined the feasibility of continuous B cell depletion via administration of one RTX dose every 4 months [37]. This regimen not only resulted in a low relapse rate (average follow-up 28 months; 9 of 72 patients, 13%), but also allowed most patients to be weaned off additional immunosuppressive medications [37]. Very recently, the results of MAINRITSAN (maintenance using RTX in remission after vasculitis), the first randomised controlled trial that evaluated RTX for maintenance treatment of AAV, have been published. In this study, 115 patients (mainly with GPA) were randomised to receive either azathioprine or RTX after remission induction with CYC and steroids. RTX was given at a reduced dose of 500 mg on days 1 and 15 followed by repeat doses of 500 mg after 6, 12 and 18 months. At month 28, major relapses had occurred in 29% of patients in the azathioprine group compared with only 5% of the RTX group (*p* = 0.002) [41]. The rate of adverse events was similar. The ongoing RITAZAREM study (RTX vasculitis maintenance study) is testing the efficacy of RTX at a higher dose (1,000 mg every 4 months) in relapsing patients after remission induction with RTX.

In summary, current data support the use of RTX to maintain remission in patients at high risk of relapse or in patients who have experienced multiple relapses, or relapses while on alternative maintenance regimens. The optimal dosing schedule, however, remains to be determined. It is also unknown whether retreatment following a fixed schedule is superior to treatment upon reconstitution of CD19+ cells or rise of ANCA titre. This question will be addressed by the ongoing MAINRITSAN II study (NCT01731561). In the RAVE study, relapses were only seen after B cell recovery in peripheral blood, whereas the rise in ANCA titre was not predictive of relapse in these patients [27].

The characteristics and results of the randomised trials on RTX in AAV are summarized in table 1.

The role of RTX in AAV patient subgroups

Refractory/relapsing disease

Despite aggressive induction regimens and maintenance therapy, AAV is still plagued by a high rate of relapses, with reported relapse rates ranging from 20% up to 50% after 2 years [42]. Relapsing patients pose a special challenge to the physician, who has to manage symptoms of recurrent disease alongside the accrual of organ damage and the side effects of prolonged CYC and steroid exposure [43]. Although refractory and relapsing disease are often treated in the same context, it is important to note the dis-

inction between refractory and relapsing disease. Disease relapses occur after achieving remission with induction therapy, whereas refractory disease does not actually respond to initial therapy [44].

The bulk of supporting evidence comes from case series and individual studies published over the last decade, mainly in patients with GPA [3, 15]. More recent reports further support the feasibility of RTX as rescue therapy in patients with MPA and GPA, including in those with refractory renal and ocular manifestations [45–49]. Results from a prespecified subgroup analysis in the RAVE trial favoured RTX plus prednisolone over standard CYC therapy for patients with relapsing disease (6-month remission rates 67% vs 42%, respectively; $p = 0.01$). The superiority of RTX-prednisolone in this patient subgroup persisted even after adjusting for differences in ANCA type and clinical site (odds ratio 1.40; 95% confidence interval 1.03–1.91; $p = 0.03$) [26].

Taken together, and despite the heterogeneity of the treatment regimens and patient populations in the studies so far, RTX treatment has yielded consistently positive results [50]. Indeed, the patient heterogeneity, varying disease statuses and often severe comorbidities seen in the subset of patients with refractory disease reflects the diverse clinical spectrum routinely encountered in a real-life setting. However, it must be kept in mind that many of the studies used other immunosuppressive agents along with RTX, including glucocorticoids.

Refractory granulomatous disease

Granulomatous disease in GPA is mostly localised and manifests in the upper and lower airways [19]. Localised GPA can also present in the form of inflammation restricted to the eye [51]. The potentially destructive nature of localised GPA should not be underestimated [43]; moreover, these manifestations are often resistant to treatment. Indeed, patients with refractory disease are most often those who suffer from granulomatous disease.

Individual case reports have shown that RTX treatment can achieve clinical remission in GPA patients with pachymeningitis, a rare manifestation of GPA [52, 53]. There is some evidence that RTX may be used to treat orbital involvement, although this matter is still under discussion [46, 54–56]. Case series in patients with refractory ophthalmic GPA have reported that RTX is effective at inducing remission [47, 48], with efficacy in both vasculitic and granulomatous manifestations [47]. However one retrospective single-centre study of more than 50 patients with refractory GPA hints at a lower response rate with granulomatous disease manifestations compared with vasculitic manifestations, after RTX treatment [46]. The uncertainty associated with RTX treatment of localised disease emphasises the need to have more data before recommending the use of RTX as an alternative to CYC.

Severe renal impairment

The presence of symptoms and laboratory features indicating kidney inflammation not only dictates an unfavourable clinical course leading to end-stage renal disease if left untreated, it also diminishes the odds of survival [57]. Renal

involvement is present in around 70% of patients with GPA and affects nearly all patients with MPA [57].

Both RAVE and RITUXVAS revealed that RTX was noninferior to CYC in patients with glomerulonephritis, defined according to the inclusion criteria of the respective study protocols. However, it must be noted that the RITUXVAS study was underpowered to detect a clinically significant difference between the two groups and included two intravenous CYC pulses, whereas in the RAVE trial, although around half the patients had glomerulonephritis, those with severe renal dysfunction (serum creatinine levels >4 mg/dl, corresponding to $354 \mu\text{mol/l}$) were excluded [26]. In the West London Renal and Transplant Centre study, a non-randomised prospective study, 23 patients with newly diagnosed or relapsing renal AAV (excluding those with creatinine levels $>500 \mu\text{mol/l}$ or previous RTX treatment), patients were treated with two pulses of 1 g RTX (2 weeks apart) and 6 fortnightly doses of CYC (10 mg/kg body-weight instead of 15 mg/kg bodyweight as given in the CYCLOPS trial [58]), followed by a sequentially reducing protocol of daily prednisolone beginning with 20 mg and azathioprine maintenance. All patients achieved prolonged disease-free remission (median follow-up 39 months), with three major and two minor relapses occurring in five patients at a median of 30 months [59]. However, the study did not include a control group. Thus, firm data on the use of RTX in patients with severe renal impairment (creatinine $>354 \mu\text{mol/l}$) are lacking. For these patients, plasmapheresis followed by CYC has been shown to reduce the risk of end-stage renal disease in the MEPEX trial [60]. However, during longer follow-up the mortality in both groups was high and did not differ significantly [61].

Whether plasmapheresis combined with RTX is effective in patients with severe renal impairment has not yet been shown. This approach may be feasible if plasmapheresis is delayed for 24 hours after RTX, to ensure complete binding of RTX to CD20.

RTX for eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome, EGPA)

It should be emphasised that EGPA patients were excluded from RAVE and RITUXVAS trials and results cannot be extrapolated to this category of patients. Only few data are available for the treatment of EGPA with RTX. Case reports and small case series reported the efficacy of RTX in refractory or relapsing patients with EGPA [62].

What is the optimal dosage for rituximab when used as an induction regimen?

According to the lymphoma protocol, RTX is administered at a dose of $375 \text{ mg/m}^2/\text{week}$ for 4 weeks. The rheumatoid arthritis protocol calls for two infusions of 1 g each, given 2 weeks apart, resulting in a lower total dose. The majority of published studies, including the RAVE and RITUXVAS trials, have employed the 4-dose lymphoma regimen for remission induction [63]. In contrast, the 1 g fortnightly protocol has mainly been used to treat patients with refractory disease [33, 54]. In an attempt to shed light on the optimal dosing schedule, Jones et al. [33] compared these two regi-

mens in a retrospective, multicentre study. Complete remission was achieved in 75% (57% of whom experienced another relapse), and partial remission in 23% of patients; the rate of remission was not related to the RTX regimen used. Achieving sufficient RTX exposure may be important for obtaining a clinical effect; a report citing the lack of efficacy used a less frequent dosing regimen [55], possibly resulting in a lower cumulative exposure. In Switzerland, the approved regimen for use in AAV is the four-dose schedule (4 x 375 mg/m² BSA/week), but due to the comparable results obtained with the 2 x 1 g regimen, many clinicians have adopted this dosing schedule for practical reasons. A very recent trial used a single dose of 375 mg/m² as induction regimen in a small group of AAV patients. Within this heterogeneous population, B cell depletion could be achieved in 90% of patients and the 3-month probability of reaching a complete remission was 80% [64].

Safety of rituximab in patients with AAV

Although the safety profile of RTX in lymphoma and rheumatoid arthritis is well established, the situation in AAV is less clear-cut. Recently, data on over 3,190 RTX-treated rheumatoid arthritis patients who had received up to 17 courses of RTX over 9.5 years in the global clinical trial programme were published [65]. This long-term safety dataset revealed no evidence of an increased safety risk or increased incidence of any adverse events with prolonged exposure to RTX, including no increased risk of malignancy over this timeframe. In general, adverse effects associated with RTX use include infusion reactions, hypogammaglobulinaemia especially after repeated courses, infections, reactivation of hepatitis B virus hepatitis and late-onset neutropenia, which may manifest months after therapy and is mostly asymptomatic and reversible [66]. In patients with AAV, infections are a major cause of morbidity and mortality, particularly during remission induction when the most intensive immunosuppressive regimens are administered [67–69]. The use of systemic glucocorticoids as concomitant therapy with RTX or CYC enhances immunosuppression. In many patients, B cell levels are depleted for prolonged periods even after clinical recovery [70]. Although its main action is depletion of B cells, RTX has a significant impact on the immune and inflammatory systems, and thus enhances susceptibility to infection [70]. Hypogammaglobulinaemia can be associated with development of mostly bacterial infections [71, 72]. Interestingly, data from the RAVE trial showed that the rates of overall and serious infections at 18 months were similar in patients who exhibited low immunoglobulin levels at any point in time compared with those with normal immunoglobulin levels [73]. Another potential risk factor for infections is late-onset neutropenia, an adverse effect that is associated with RTX. Recent data from patients with rheumatoid arthritis suggest that late onset neutropenia is more prevalent than expected but is not associated with neutropenic infections. However this has to be proven in AAV [74, 75].

There have been reports on *Pneumocystis jirovecii* pneumonia in patients receiving RTX for autoimmune diseases other than AAV [76]. Most of these cases had received prior cytostatic therapy or RTX was paralleled by high doses of steroids. Therefore PCP prophylaxis at least during induction therapy with RTX for AAV should be considered. Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the brain caused by a ubiquitous polyomavirus, the JC virus. In a recently published review Molloy and Calabrese [77] reported 34 confirmed cases of PML in the setting of autoimmune rheumatic diseases: 14 of these patients were under RTX; however none of these patients had AAV.

There is an increased incidence of either previous or concurrent malignancies in patients with AAV [78], and the risk of cancer augments with the use of conventional CYC-based therapy [79, 80]. Malignancy is of special concern when treating patients with severe glomerulonephritis. This subset has often undergone heavy pretreatment, and the risk of malignancy is a long-term safety issue. In the RAVE and RITUXVAS trials, a similar incidence of malignancies

There is an increased incidence of either previous or concurrent malignancies in patients with AAV [78], and the risk of cancer augments with the use of conventional CYC-based therapy [79, 80]. Malignancy is of special concern when treating patients with severe glomerulonephritis. This subset has often undergone heavy pretreatment, and the risk of malignancy is a long-term safety issue. In the RAVE and RITUXVAS trials, a similar incidence of malignancies

Table 1: Summary of results from randomised trials on rituximab in antineutrophil cytoplasmic antibody-associated vasculitis.

Study	RAVE [26–28]	RITUXVAS [29]	MAINRITSAN [41]
Patient number (randomisation)	197 (1:1)	44 (3:1)	118 (1:1)
GPA / MPA / RL (%)	76/24/0	50/36/14	76/20/4
Renal involvement (%)	66	100	70
Newly diagnosed (%)	49	100	80
Treatment			
Induction (all plus PDN)	RTX 375 mg/m ² day 0, 7, 14 and 21 vs p.o. CYC	RTX 375 mg/m ² day 0, 7, 14 and 21 + i.v. CYC day 0 and 14 vs IV CYC + PDN	i.v. CYC (both groups)
Maintenance	No maintenance (RTX group) vs azathioprine	No maintenance (RTX group) vs azathioprine	RTX 500 mg day 0, 14, month 6, 12 and 18 vs azathioprine until month 22
Outcome	Steroid-free remission in 64% (RTX) vs 53% (CYC-AZA) at month 6 and in 39% vs 33% at month 18; RTX noninferior RTX superior in relapsing disease p = 0.01	Sustained remission at month 12 in 76% (RTX) vs 82% (CYC-AZA) not significant	Major relapses at month 28 in 5% (RTX) vs 29% (AZA) p = 0.002
CYC = cyclophosphamide; GPA = granulomatosis with polyangiitis; i.v. = intravenous; MPA = microscopic polyangiitis; PDN = prednisone RL = renal limited; RTX = rituximab			

was reported in the RTX-treated and control arms. An important confounding factor is the concomitant use of CYC in these studies, alongside the short follow-up periods. In contrast, recent analysis of the long-term safety outcomes of RTX in 370 patients from the German Registry of Autoimmune Diseases, including 15.7% of which had AAV, did not report any increased incidence of malignancy across the entire study population [81]. Ten-year follow-up of 108 AAV patients treated with RTX for remission induction or maintenance reported infusion-related reactions (7 patients; 6%) and infections (8 patients; 7%), but no occurrence of malignancies [82]. Nevertheless, this point deserves careful attention during long-term follow-up of the RAVE and RITUXVAS data. Cumulative toxicity with CYC bears a dose- and age-dependent risk of inducing infertility and may induce premature menopause [83]. In contrast to CYC, RTX is not associated with infertility. Pregnancies under RTX treatment have been reported. A retrospective study analysed pregnancy outcome in women that conceived whilst being treated with RTX. From 153 pregnancies in patients with various autoimmune and malignant diseases treated with RTX with known outcomes, 90 resulted in live births. Twenty-two infants were born prematurely; with one neonatal death at 6 weeks. Eleven neonates had haematological abnormalities; none had corresponding infections. Four neonatal infections were reported (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis). Two congenital malformations were identified: clubfoot in one twin, and cardiac malformation in a singleton birth. These findings may have been confounded by the concurrent use of other potentially teratogenic agents [84].

In a more recent paper, five out of six pregnancies in patients with vasculitis treated with RTX were uneventful and one early abortion occurred (in week 15). Of note, in all of the three foetal cord blood samples tested, B cells were present [85].

Owing to the potential risk for the newborn, contraception after RTX treatment is mandatory and should be performed according to existing guidelines.

Despite an apparently better toxicity profile, the rate of infections at least during short term follow-up in the RAVE and RITUXVAS trials in both the CYC- and RTX-treated arms did not differ significantly [26, 30].

Conclusions

The approval of RTX not only provides a valuable alternative treatment modality, but encourages us to rethink the way in which we approach AAV. Today, the clinical challenge is shifting; in addition to reducing the disease burden, a key goal is to minimise treatment-related damage. RAVE, RITUXVAS and MAINRITSAN provide us with an important vantage point from which to assess the potential of RTX from a randomised, controlled perspective. Overall, the currently available data suggest (a.) equivalence of RTX to CYC for induction treatment with potential superiority of RTX in relapsing disease (after induction with CYC) and the potential to reduce some of the long term adverse effects of CYC and (b.) possible superiority of repeat RTX compared with azathioprine for maintenance

therapy. The main disadvantages of RTX are the considerably higher price and the lack of very long-term data. When balancing the risks and benefits of AAV treatment the following conclusions can be drawn from the discussed evidence to aid in patient-tailored treatment decisions:

1. RTX is equivalent to CYC in inducing remission in severe AAV.
2. RTX could be considered as the preferred regimen in relapsing AAV (at least in RTX-naïve patients).
3. There is limited evidence for the use of RTX as induction regimen in patients with creatinine >354 µmol/l or pulmonary haemorrhage requiring mechanical ventilation at presentation. If RTX is used in these patients, the addition of low dose CYC and/or plasmapheresis should be considered.
4. RTX should be preferred over CYC in premenopausal women whenever possible, because of the potential induction of infertility (dose- and age-dependent in women) [83].
5. The efficacy of RTX in localised and granulomatous disease needs to be further studied.
6. RTX can be used as maintenance therapy as an alternative to azathioprine or MTX. The best treatment regimen will need to be defined as suggested strategies vary widely.
7. Contraception is mandatory in fertile women after RTX treatment owing to the lack of robust information on the effect of RTX on newborns.

Acknowledgement: The authors would like to thank Karen Yeow (Biomedicomm Ltd.) for editorial assistance during the preparation of the manuscript.

Funding / potential competing interests: This article summarizes the consensus of an advisory board meeting on the role of rituximab in the treatment of AAV held in November 2012 with an update of data that have been published since then. The advisory board was organised and financed by Roche Pharma (Schweiz) AG, Reinach, Switzerland. The sponsor had no influence on the content of this article, nor its approval before submission.

Correspondence: Thomas Daikeler, MD, Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland, [thomas.Daikeler\[at\]usb.ch](mailto:thomas.Daikeler[at]usb.ch)

References

- 1 Flint J, Morgan MD, Savage CO. Pathogenesis of ANCA-associated vasculitis. *Rheum Dis Clin North Am.* 2010;36:463–77.
- 2 Gomez-Puerta JA, Bosch X. Anti-neutrophil cytoplasmic antibody pathogenesis in small-vessel vasculitis: an update. *Am J Pathol.* 2009;175:1790–8.
- 3 Cartin-Ceba R, Fervenza FC, Specks U. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab. *Curr Opin Rheumatol.* 2012;24:15–23.
- 4 Wolff SM, Fauci AS, Horn RG, Dale DC. Wegener's granulomatosis. *Ann Intern Med.* 1974;81:513–25.
- 5 Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine (Baltimore).* 1973;52:535–61.
- 6 Novack SN, Pearson CM. Cyclophosphamide therapy in Wegener's granulomatosis. *N Engl J Med.* 1971;284:938–42.

- 7 Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* 1996;7:33–9.
- 8 Coughlan AM, Freeley SJ, Robson MG. Animal models of anti-neutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Immunol.* 2012;169:229–37.
- 9 Kallenberg CG. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: where to go? *Clin Exp Immunol.* 2011;164(Suppl 1):1–3.
- 10 Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med.* 1992;116:488–98.
- 11 Lamprecht P, Gross WL, Kabelitz D. T cell alterations and lymphoid neogenesis favoring autoimmunity in Wegener's granulomatosis. *Arthritis Rheum.* 2007;56:1725–7.
- 12 Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW. Differential B- and T-cell activation in Wegener's granulomatosis. *J Allergy Clin Immunol.* 1999;103:885–94.
- 13 Csernok E, Moosig F, Gross WL. Pathways to ANCA production: from differentiation of dendritic cells by proteinase 3 to B lymphocyte maturation in Wegener's granuloma. *Clin Rev Allergy Immunol.* 2008;34:300–6.
- 14 Lamprecht P, Wiczorek S, Epplen JT, Ambrosch P, Kallenberg CG. Granuloma formation in ANCA-associated vasculitides. *APMIS Suppl.* 2009;127:32–6.
- 15 Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, et al. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology (Oxford).* 2012;51:634–43.
- 16 Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol.* 2014;10:463–73.
- 17 Weiner GJ. Rituximab: mechanism of action. *Semin Hematol.* 2010;47:115–23.
- 18 McDonald V, Leandro M. Rituximab in non-haematological disorders of adults and its mode of action. *Br J Haematol.* 2009;146:233–46.
- 19 Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis.* 2009;68:310–7.
- 20 Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis – a clinical randomized controlled trial. *Nephrol Dial Transplant.* 2011;26:206–13.
- 21 Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadonienė J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003;349:36–44.
- 22 Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med.* 2008;359:2790–803.
- 23 Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis.* 2008;67:1004–10.
- 24 Cohen Tervaert JW. Rituximab in ANCA-associated vasculitis: a revolution? *Nephrol Dial Transplant.* 2011;26:3077–9.
- 25 Specks U, Fervenza FC, McDonald TJ, Hogan MC. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. *Arthritis Rheum.* 2001;44:2836–40.
- 26 Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med.* 2010;363:221–32.
- 27 Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med.* 2013;369:417–27.
- 28 Miloslavsky EM, Specks U, Merkel PA, et al. Rituximab for the treatment of relapses in ANCA-associated vasculitis. *Arthritis Rheumatol.* 2014; epub ahead of print.
- 29 Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med.* 2010;363:211–20.
- 30 Jones RB, Walsh M, Jayne DR, et al. Two-year follow-up results from a randomized trial of RTX versus Cyp for ANCA-associated renal vasculitis: RITUXVAS. *Clin Exp Immunol.* 2011;164(Supplement 1):57–8.
- 31 Kallenberg CG, Specks U, Stone JH, et al. Long-term efficacy and safety results of the RAVE trial. *Clin Kidney J (Supplement).* 2011;4:Abstract.
- 32 Geetha D, Fervenza FC, and The RAVE Research Group. The Efficacy of Rituximab Vs Cyclophosphamide for Treatment of Renal Disease in ANCA-Associated Vasculitis: The RAVE Trial. American College of Rheumatology Annual Meeting, Washington, DC, November 10–14. 2012; Abstract 1542.
- 33 Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2009;60:2156–68.
- 34 Jones RB, Smith R, Guerry MJ, et al. Protocolized versus non-protocolized RTX treatment for refractory ANCA-AAV. *Clin Exp Immunol.* 2011;Suppl. 1:58.
- 35 Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sánchez-Menéndez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. *Arthritis Rheum.* 2012;64:3770–8.
- 36 Rees F, Yazdani R, Lanyon P. Long-term follow-up of different refractory systemic vasculitides treated with rituximab. *Clin Rheumatol.* 2011;30:1241–5.
- 37 Niles J, McGrath M, Laliberte KA. Continuous RTX therapy for ANCA-AAV. *Clin Exp Immunol.* 2011;164:62.
- 38 Roubaud-Baudron C, Pagnoux C, Meaux-Ruault N, et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. *J Rheumatol.* 2012;39:125–30.
- 39 Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2012;64:3760–9.
- 40 Guillevin L, Pagnoux C, Karras A, et al. Rituximab Versus Azathioprine for Maintenance in Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis. American College of Rheumatology Annual Meeting, Washington, DC, November 10–14. 2012; Abstract 1652.
- 41 Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med.* 2014;371:1771–80.
- 42 Walsh M, Flossmann O, Berden A, Westman K, Höglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2012;64:542–8.
- 43 Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, et al. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). *Arthritis Rheum.* 2005;52:2168–78.
- 44 Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis.* 2007;66:605–17.
- 45 Holle JU, Gross WL, Holl-Ulrich K, Ambrosch P, Noelle B, Both M, et al. Prospective long-term follow-up of patients with localised Wegener's granulomatosis: does it occur as persistent disease stage? *Ann Rheum Dis.* 2010;69:1934–9.
- 46 Holle JU, Dubrau C, Herlyn K, Heller M, Ambrosch P, Noelle B, et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. *Ann Rheum Dis.* 2012;71:327–33.
- 47 Joshi L, Lightman SL, Salama AD, Shirodkar AL, Pusey CD, Taylor SR. Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective. *Ophthalmology.* 2011;118:2498–503.

- 48 Lower EE, Baughman RP, Kaufman AH. Rituximab for refractory granulomatous eye disease. *Clin Ophthalmol*. 2012;6:1613–8.
- 49 Wendt M, Gunnarsson I, Bratt J, Bruchfeld A. Rituximab in relapsing or refractory ANCA-associated vasculitis: a case series of 16 patients. *Scand J Rheumatol*. 2012;41:116–9.
- 50 Rutgers A, Kallenberg CG. Refractory vasculitis. *Autoimmun Rev*. 2011;10:702–6.
- 51 Pagnoux C, Stubbe M, Lifermann F, Decaux O, Pavic M, Bérezné A, et al. Wegener's granulomatosis strictly and persistently localized to one organ is rare: assessment of 16 patients from the French Vasculitis Study Group database. *J Rheumatol*. 2011;38:475–8.
- 52 Just SA, Knudsen JB, Nielsen MK, et al. Wegener's granulomatosis presenting with pachymeningitis: clinical and imaging remission by rituximab. *ISRN Rheumatol*. 2011; epub June 8.
- 53 Bawa S, Mukhtyar C, Edmonds S, Webley M I. Refractory Wegener's meningitis treated with rituximab. *J Rheumatol*. 2007;34:900–1.
- 54 Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum*. 2009;60:1540–1547.
- 55 Aries PM, Hellmich B, Voswinkel J, Both M, Nölle B, Holl-Ulrich K, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis*. 2006;65:853–8.
- 56 Omdal R, Wildhagen K, Hansen T, Gunnarsson R, Kristoffersen G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. *Scand J Rheumatol*. 2005;34:229–32.
- 57 Sinico RA, Di TL, Radice A. Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis. *Autoimmun Rev*. 2012; epub ahead of print.
- 58 de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2009;150:670–80.
- 59 Mansfield N, Hamour S, Habib AM, Tarzi R, Levy J, Griffith M, et al. Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. *Nephrol Dial Transplant*. 2011;26:3280–6.
- 60 Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007;18:2180–8.
- 61 Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int*. 2013;84:397–402.
- 62 Thiel J, Hassler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Arthritis Res Ther*. 2013;15:R133.
- 63 Holle JU, Gross WL. Rituximab in AAV: when and how to use it. *Nat Rev Rheumatol*. 2011;7:566–7.
- 64 Turner-Stokes T, Sandhu E, Pepper RJ, et al. Induction treatment of ANCA-associated vasculitis with a single dose of rituximab. *Rheumatology (Oxford)*. 2014;53:1395–403.
- 65 van Vollenhoven RF, Emery P, Bingham CO, III, Keystone EC, Fleischmann RM, Furst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. *Ann Rheum Dis*. 2012;(epub).
- 66 Jayne D. Rituximab treatment for vasculitis. *Clin J Am Soc Nephrol*. 2010;5:1359–62.
- 67 Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis*. 2010;69:1036–43.
- 68 Charlier C, Henegar C, Launay O, Pagnoux C, Bérezné A, Bienvenu B, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. *Ann Rheum Dis*. 2009;68:658–63.
- 69 Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nölle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum*. 2000;43:1021–32.
- 70 Shetty S, Ahmed AR. Preliminary analysis of mortality associated with rituximab use in autoimmune diseases. *Autoimmunity*. 2013;46:487–96.
- 71 Venhoff N, Effelsberg NM, Salzer U, Warnatz K, Peter HH, Lebrecht D, et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides. *PLoS One*. 2012;7:e37626.
- 72 Helena M, Jones RB, Smith RM, et al. Hypogammaglobulinemia and infections following RTX therapy for systemic vasculitis and SLE. *Clin Exp Immunol*. 2011;164(Suppl. 1):59–60.
- 73 Specks U, Merkel PA, Seo P, et al. Immunoglobulin concentrations and infection risk among patients with ANCA-associated vasculitis treated with rituximab or cyclophosphamide. American College of Rheumatology Annual Meeting, Chicago, November 4–9. 2011; Abstract 789.
- 74 Goupil R, Brachemi S, Nadeau-Fredette AC, et al. Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. 2012;8:416–23.
- 75 Tesfa D, Palmblad J. Late-onset neutropenia following rituximab therapy: incidence, clinical features and possible mechanisms. *Expert Rev Hematol*. 2011;4:619–25.
- 76 Martin-Garrido I, Carmona EM, Specks U, Limper AH. Pneumocystis pneumonia in patients treated with rituximab. *Chest*. 2013;144:258–65.
- 77 Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. *Arthritis Rheum*. 2012;64:3043–51.
- 78 Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2004;43:1532–5.
- 79 Hejl C, Harper L, Flossmann O, Stücker I, Scott DG, Watts RA, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. *Ann Rheum Dis*. 2011;70:1415–21.
- 80 Faurusou M, Sorensen IJ, Mellemejaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol*. 2008;35:100–5.
- 81 Tony HP, Burmester G, Schulze-Koops H, Grunke M, Henes J, Kötter I, et al. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). *Arthritis Res Ther*. 2011;13:R75.
- 82 Cartin-Ceba R, Golbin JM, Keogh KA, et al. Rituximab for remission induction and maintenance in ANCA-associated vasculitis: a single-center ten-year experience in 108 patients. *Arthritis Rheum*. 2010;62:S283–S284.
- 83 Harward LE, Mitchell K, Pieper C, Copland S, Criscione-Schreiber LG, Clowse ME. The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease. *Lupus*. 2013;22:81–6.
- 84 Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood*. 2011;117:1499–506.
- 85 Pendergraft WF III, McGrath MM, Murphy AP, Murphy P, Laliberte KA, Greene MF, et al. Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. *Ann Rheum Dis*. 2013;72:2051–3.