

Should Rituximab Be Used to Prevent Relapse in Patients with ANCA-Associated Vasculitis?

Stephen P. McAdoo and Charles D. Pusey

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Rituximab is now licensed, both in the United States and Europe, for use as a remission-induction agent in the treatment of ANCA-associated vasculitis (AAV). Although the two randomized controlled trials on which this licensure is based did not demonstrate, at least in patients presenting with new disease, either superiority of rituximab to conventional treatment or a better short-term toxicity profile (1,2), the approval of this new agent is arguably the most significant development in the management of AAV since the introduction of cytotoxic therapy almost half a century ago, providing an effective alternative for patients who are intolerant, unresponsive, or aversive to cyclophosphamide and its proven toxicities (3).

Despite successful induction therapy, a significant proportion of patients go on to relapse, even on conventional maintenance therapy, resulting in accrual of disease-related damage and treatment side effects (4,5). More effective maintenance strategies are badly needed. No controlled studies have investigated the use of rituximab in this respect, although a number of centers are using this approach. The report from Pendergraft *et al.* in this issue of *CJASN* is the largest published experience to date (6). In this uncontrolled, retrospective study, Pendergraft *et al.* used rituximab for continuous B-cell depletion in 172 patients, with scheduled redosing every 4 months (or earlier if B-cell replete) for 2 years, and then every 6 months thereafter. They report very low relapse rates (5% major relapse during a median follow-up of 2.1 years) and impressive periods of disease-free survival in their cohort (similar to a matched general population) without identifying any unexpected safety signals. This approach enabled withdrawal of other immunosuppressive treatment, and was equally effective in patients who were treated after remission induction and in patients who were transitioned from another maintenance regimen.

These findings are consistent with previous reports of rituximab use as maintenance therapy. Smith *et al.* compared two historical cohorts from their center, comprising a total of 73 patients, all with relapsing disease. One group was routinely retreated with rituximab every 6 months for 2 years (regardless of disease activity or B-cell count) and one group was retreated at the time of disease flare (7). Routine retreatment was associated with significantly lower rates of relapse (12% versus 72% at 2 years). Notably, they did not

observe a difference in the total dose of rituximab per year between groups, suggesting that scheduled redosing did not result in excessive administration in a cohort of patients with relapsing disease. The French Vasculitis Study Group (FVSG) reported a long-term multicenter experience using rituximab for induction and maintenance in 80 patients (8). This was a highly heterogeneous cohort, using several different dosing schedules for maintenance, alone or combined with other treatments. However, the analysis did suggest that in patients who achieved remission by 6 months, subsequent use of rituximab in their maintenance regimen was again associated with improved rates of relapse-free survival. Cartin-Ceba *et al.* also reported a 10-year experience of rituximab use in 53 patients with refractory relapsing granulomatosis with polyangiitis (GPA), specifically (9). In patients who achieved remission and who were treated pre-emptively with rituximab for prevention of relapse (based on reconstitution of B cells and rising anti-proteinase 3 titers), remission was maintained in all cases. Other studies that included only patients with GPA suggested that rituximab may be a useful maintenance therapy, although they failed to demonstrate such an impressive rate of remission maintenance (10,11).

Although these studies suggest that rituximab may be of value in maintaining disease remission in AAV, several questions remain unanswered as to how it should be used most effectively and safely. Not all patients who achieve remission will go on to relapse, and it is recognized that one episode of relapse predicts future disease flare. Similarly, relapse is more frequent in patients with GPA and/or anti-proteinase 3 antibody positivity. Should maintenance rituximab be reserved for those patients who demonstrate a biologic tendency to relapsing disease, particularly in light of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial findings, which suggest that rituximab may be superior to conventional treatment in such cases (2,12)? The study by Pendergraft *et al.* included both new and relapsing patients, although the authors do not report the proportion of the latter (6). In addition, over half the patients in this study (57%) were positive for the anti-myeloperoxidase antibody. Although comparison of the subgroups did not reveal significant differences in outcome, it is possible that over-representation of patients at low risk of relapse may have contributed to the very low relapse rates that were observed. This is in contrast with some other

Renal and Vascular Inflammation Section, Department of Medicine, Imperial College London, London, United Kingdom; and Multidisciplinary Vasculitis Clinic, Hammersmith Hospital, Imperial College Healthcare National Health Service Trust, London, United Kingdom

Correspondence:

Dr. Stephen P. McAdoo, Renal and Vascular Inflammation Section, Department of Medicine, Imperial College London, Hammersmith Hospital, London W12 0NN, UK. Email: s.mcadoo@imperial.ac.uk

studies, which included much higher proportions of patients with relapsing disease and GPA (7–9).

The above-described studies, being uncontrolled and retrospective, are heterogeneous in many other respects. They used a range of rituximab doses during the remission maintenance phase, administered either at fixed intervals (which ranged from 4 to 12 months in individual studies) or depending on B-cell reconstitution. In all studies, peripheral B-cell depletion was achieved, regardless of the dose used. Cartin-Ceba *et al.* did not find a difference in the time to B-cell repopulation between patients treated with a four-dose versus a two-dose regimen, although it is notable that no relapses were observed in this cohort, who were treated with generally higher doses for remission maintenance [either $4 \times 375 \text{ mg/m}^2$ or $2 \times 1 \text{ g}$, versus $1 \times 1 \text{ g}$ in the other cohorts (6,7)]. This might suggest that higher rituximab doses have effects on noncirculating B cells, particularly those at sites of disease (13), which may contribute to disease activity and relapse. The same group found that B-cell reconstitution was a useful predictor of flare and, thus, a guide to redosing, whereas others have not found this to be the case, with relapses occurring in the absence of B cells. Smith *et al.* (7) used a fixed redosing schedule regardless of B-cell count, whereas Pendergraft *et al.* aimed to achieve sustained B-cell depletion by more frequent dosing at 4-monthly intervals, or earlier if required (6). Further studies are clearly needed to identify the optimum dose and regimen for rituximab administration in the maintenance phase.

Similarly, the ideal duration of maintenance treatment is unknown. Current guidelines suggest that immunosuppression should be continued for at least 18 months (14), although in practice there is considerable variation. The European Vasculitis Study Group (EUVAS) REMAIN (Randomized Trial of Prolonged Remission-Maintenance Therapy in Systemic Vasculitis) study may shed some light on the potential benefit of extended maintenance therapy (comparing 2 versus 4 years of treatment with azathioprine), although its design and recruitment predates the widespread use of rituximab. Smith *et al.* observed extended periods of remission after completing a 2-year course of rituximab treatment (7), although other studies have continued regular redosing beyond the 2-year time point, with a significant number of patients receiving >10 courses in some cohorts (6,8,9). It seems likely that continued rituximab administration will lead to an increased incidence of adverse events, including hypogammaglobulinemia, late-onset neutropenia, and infections, each of which was reported in these cohort studies. However, it is difficult to define the precise role of rituximab in these adverse events in patients with a burden of previous immunosuppression and disease-related damage. Reassuringly, atypical or opportunistic infections were not a frequent observation in these studies, and progressive multifocal leukoencephalopathy has not, to our knowledge, been reported in patients with AAV treated with rituximab.

How, or whether, rituximab should be used in conjunction with conventional maintenance treatments is also unknown—again, their use was highly variable in these studies. Notably, the recently reported follow-up from the RAVE study showed that remission induction with a single course of rituximab showed sustained benefit, without maintenance immunosuppression, at 18 months (12). Perhaps the synergistic effects of combined therapy might further improve efficacy?

Conversely, concomitant use of other immunosuppressants at the time of rituximab administration may impair the function of phagocytic cells that are required for antibody-mediated clearance of B cells (15). The approach of most centers, including that of Pendergraft *et al.*, is to withdraw other immunosuppressants, although this was associated with a relapse in the small number of patients who did proceed to flare (6).

As highlighted by the RAVE follow-up data, as well as several of the early controlled studies (16,17), the effect of the induction regimen must also be considered. Although remission can be induced with a number of different agents, subsequent relapse rates vary, and “not all remissions are equal.” In this study, patients were treated with 2 mg/kg of cyclophosphamide per day along with intravenous and high-dose oral glucocorticoids (6), and these additional treatments may have contributed to the low rate of relapse. We previously reported, in a cohort of patients with renal AAV, that prolonged disease-free remission could be achieved after induction with a combination of steroids, low-dose cyclophosphamide (median dose 3.4 g), and rituximab, although numbers in this study are small (18). In a larger cohort of all our AAV patients treated with rituximab, regardless of the pattern of organ involvement, we found that not receiving cyclophosphamide as part of the induction regimen was a significant risk factor for subsequent relapse (unpublished data). We believe that the interaction of rituximab with other agents warrants further investigation, and that it may have a role not only in maintenance of remission in AAV, but also as a potential glucocorticoid-sparing agent when coadministered with low-dose cyclophosphamide at induction.

Three prospective controlled studies will investigate the use of rituximab as maintenance therapy. The Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN; ClinicalTrials.gov NCT00748644), conducted by the FVSG, is an open-label study that compares conventional maintenance using azathioprine with 6-monthly scheduled readministration of rituximab for 18 months, with a further 10-month follow-up period. The study completed in October 2012 and preliminary results were presented at the 16th International Vasculitis and ANCA Workshop in Paris, France, in 2013 (19). At 28 months, 5% of the rituximab-treated patients had experienced a major relapse versus 25% of patients taking azathioprine, with no major safety issues being identified. MAINRITSAN 2 (ClinicalTrials.gov NCT01731561) is ongoing and will compare two rituximab administration strategies for maintenance therapy: fixed schedule 6-monthly redosing versus redosing dependent on B-cell repopulation and/or ANCA titers. Finally, the Rituximab Vasculitis Maintenance Study (ClinicalTrials.gov NCT01697267), a multicenter international study designed in collaboration between EUVAS and the Vasculitis Clinical Research Consortium, is currently aiming to recruit 190 participants with relapsing AAV, again to compare conventional maintenance using azathioprine versus 4-monthly rituximab for 2 years, with a further 2-year follow-up period. The results of these studies will clarify many of the issues we have raised, and should inform future practice. These and future studies will, however, require careful design, stratification, and interpretation to control for the multitude of factors that can influence the occurrence of disease flare in AAV, and it is likely that appropriate use of rituximab will vary depending on the disease phenotype, history of relapse, or other patient characteristics.

To this end, the identification of novel biomarkers that can better predict relapse in AAV is clearly needed. ANCA titers have not been reliably shown to anticipate flare, and B-cell repopulation after rituximab does not consistently predict relapse. More detailed analysis of B-cell phenotypes, however, may be informative. In rheumatoid arthritis and SLE, repopulation with higher proportions of B cells with a memory phenotype, as opposed to a naïve phenotype, is associated with subsequent relapse (20,21). In AAV, repopulation with a lower proportion of CD5⁺ B cells, a purported regulatory subset, was observed in patients who flared earlier after rituximab (22). In rheumatoid arthritis, an initial rise in serum B-lymphocyte stimulator levels was observed after treatment with rituximab, followed by a decline that was consistently associated with the re-emergence of B cells in peripheral blood, which in turn predated clinical relapse (23). The phenomenon of elevated B-lymphocyte stimulator levels after rituximab is also reported in AAV (24), and the utility of this marker as a predictor of B-cell repopulation and relapse should be investigated. In addition, recently identified non-B cell markers that predict relapsing disease, such as calprotectin or CD8⁺ T-cell transcription signature, may prove useful (25,26).

The available evidence certainly suggests that rituximab has the capacity to maintain remission in AAV. Little is known, however, about the potential long-term effects of this agent, and it is well recognized that much of the damage inflicted by cyclophosphamide, a comparable therapy, comes after repeated exposure and increasing cumulative dose (27). Future controlled trials, and the use of biologic registries for long-term follow-up, should identify how best to use this agent in the maintenance of remission, those patients that really require ongoing therapy, and the potential long-term toxicities. Pending this information, our current approach is to use rituximab for maintenance therapy in those patients (usually with GPA) who frequently relapse despite conventional maintenance treatment, and in whom avoidance of further cyclophosphamide or steroid exposure is desirable.

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