Despite the unanswered questions, in the fifteen years since rituximab was first introduced to the US market, it has become a well-established treatment option for AAV in the US. The FDA has recognized rituximab as a safe and effective alternative to cyclophosphamide for remission induction in severe GPA and MPA, and rituximab has become the preferred agent for the treatment of severe relapses in these syndromes. In addition, the early experience of US investigators with rituximab for remission maintenance in GPA and MPA, and for remission induction in EGPA, has been encouraging. While there remain areas of uncertainty that require further study, the US experience with rituximab for the treatment of AAV has been overwhelmingly positive, and it has established rituximab as a key agent in the armamentarium of AAV therapies.

Disclosure of interest: the authors have not supplied their declaration of conflict of interest.

References


S2. Rituximab for ANCA-associated vasculitis: The UK experience

Introduction
In 2000, key areas of unmet need in the treatment of ANCA-associated vasculitis (AAV) were relapsing or refractory granulomatosis with polyangiitis (GPA) and the toxicity of standard...
therapy for elderly patients presenting with severe renal vasculitis. There was preliminary experience of rituximab in rheumatoid arthritis and case reports of benefit in SLE and AAV [1]. Alemtuzumab, a pan-lymphocyte depleting antibody, had been used in 120 vasculitis patients in Cambridge although the therapeutic mechanism was considered to relate to T cell rather than B cell depletion. Anti-tumor necrosis factor blockade with infliximab or etanercept was being used on a compassionate basis for refractory GPA and trials in AAV were starting.

Preliminary studies in ANCA-associated vasculitis (AAV)
Following success in an 11 patient open label trial in refractory SLE, a further 11 refractory AAV patients were studied between 2002 and 2004 [2]. They received rituximab 375 mg/m²/week × 4 and a single cyclophosphamide dose of 500 mg with the first infusion, prednisolone and maintenance immunosuppressives were continued. Ten of 11 patients responded with full remission in nine, but six (60%) relapsed after a mean of 16.5 months. Disease free survival was associated with duration of B cell depletion.

Rituximab then entered routine clinic use for refractory disease or patients with multiple relapses and a retrospective survey was conducted on 65 patients from four centres, including children [3]. Improvements in disease activity were seen in all except one patient, with full remission in 49 (75%), withdrawal of immunosuppressives in the majority and steroid sparing effects. No differences in time to relapse or duration of B cell depletion were seen between the 375 mg/m²/week × 4 or 1000 mg × 2 rituximab regimens. Also, in retrospective comparisons, no benefit was detectable with concomitant cyclophosphamide or continued immunosuppressive. Relapses occurred in 57% after a mean of 11.5 months, some following a rise in ANCA and most, but not all, after B cell return, and rituximab re-treatment was effective. Late onset neutropenia and falls in IgM levels and infections were noted. Following this experience a regimen of fixed interval repeat dose rituximab was instituted, 1000 mg × 2 induction and 1000 mg/6 months × 4 for relapse prevention. The granulomatous manifestations of GPA, such as retro-orbital granulomata, have also responded to rituximab. However four of 34 GPA patients with ENT manifestations had no response to an initial course but responded to subsequent courses. This suggests that these presentations may require higher rituximab dosing and should not necessarily be regarded as failures after one rituximab course [4].

Rituximab for initial induction therapy
Previous EUVAS trials had standardised and optimized induction therapy for newly diagnosed AAV and demonstrated a high early mortality in older patients with renal failure [5]. The RITUVAS trial compared rituximab, 375 mg/m²/week × 4, to IV cyclophosphamide in newly diagnosed renal vasculitis and recruited 44 patients with a median age of 68 and GFR of 18 mL/min [6]. Patients in the rituximab group received two doses of cyclophosphamide 15 mg/kg without further immunosuppression. No differences in efficacy or safety end-points were observed at 12 months. Relapses occurred in 26% of rituximab patients at 24 months from both PR3 and MPO-ANCA subgroups. The RAVE trial also found no difference in efficacy and safety between rituximab and cyclophosphamide/azathioprine treatment groups [7]. The failure of rituximab to improve safety has been attributed to the high dose glucocorticoid regimens received by all patients and inherent safety risks of patients with severe AAV.

Although cyclophosphamide remains the routine induction immunosuppressive for new AAV patients in our centre, those with a contra-indication, such as desire to preserve fertility, have received rituximab. Eight AAV patients with severe intercurrent infection treated with rituximab and glucocorticoids achieved remission without further severe infections or death [8].

Rituximab for maintenance therapy
Patients receiving rituximab for relapsing AAV have a high rate of subsequent relapse that is not effectively prevented by conventional maintenance immunosuppression. In a retrospective comparison of 73 patients relapse rates were reduced from 75% to 22% by fixed interval repeat rituximab in the absence of an immunosuppressive and with prednisolone withdrawal in 40% [9]. After the end of the 2 year rituximab re-treatment period relapses occurred in 16/51 patients (32%) followed for a mean of 15.5 months. The RITAZAREM trial (ClinicalTrials.gov NCT01697267) aims to demonstrate that maintenance rituximab is more effective than azathioprine for the prevention of relapse after rituximab induction for relapsing AAV over a 2 year period. It will also examine the relapse rates for up to 2 years following withdrawal of rituximab or azathioprine to detect prolonged effects of these therapies. The falls in IgG levels observed in some patients receiving repeated rituximab prompted a further review of 177 patients receiving rituximab for SLE or vasculitis. Twenty per cent of this cohort had low IgG levels before the first rituximab infusion, reflecting prior immunosuppression, and this proportion rose to 40% by 4 years after the first rituximab infusion. There was no clear evidence of increased infective risk in those with IgG levels between 3 and 7 g/L but all those with IgG levels < 3 g/L and occasional patients with higher levels required maintenance intravenous immunoglobulin due to recurrent infections.

Rituximab for other forms of vasculitis
Following the success of rituximab in GPA and MPA, there has been compassionate use of rituximab for non-AAV vasculitides. Good responses have been seen in eosinophilic GPA (Churg-Strauss, EGPA) similar to those in GPA/MPA [10]. Four
of five patients with Behçet’s syndrome had clinical improvement after rituximab with a full remission in one. Two have remained controlled on repeat rituximab but two have required other therapies. Experience in large vessel vasculitis, cryoglobulinaemia, polyarteritis nodosa, Henoch–Schönlein purpura and urticarial vasculitis has been too limited to draw meaningful conclusions.

Conclusions
The addition of rituximab to the management of AAV has been of major benefit to our patients permitting improved disease control and reduced immunosuppressive and glucocorticoid exposure. The published experience has been sufficient to enable treatment recommendations that emphasise the place of rituximab for relapsing or refractory disease and those in whom cyclophosphamide is contra-indicated [11]. Although we have found associations between B cell return and ANCA rises [3], there is considerable variability and some relapses are seen without changes in these indices. Falling immunoglobulin levels are a concern as patient exposure to rituximab increases, that will limit further use of this agent in such patients.

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References

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S3. Rituximab for ANCA-associated vasculitides: The French experience

Introduction
Rituximab is a chimeric murine–human monoclonal IgG1 antibody directed against CD20 expressed on lymphocytes. It was used to treat antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) for the first time in 2001 [1]. In France, rituximab treatment of refractory AAV started in 2002. Rituximab has been given to increasing numbers of patients, especially after the publication of the two randomized–controlled trials showing that it was as effective as cyclophosphamide (CYC) at inducing AAV remission [2,3]. We describe the French experience with rituximab in two situations: first, in prospective trials organized by the French Vasculitis Study Group (FVSG), and, second, in routine hospital practice, reported as retrospective studies.

Prospective studies organized by the French Vasculitis Study Group (FVSG)
The first randomized–controlled trial included 17 patients and was conducted between 2004 and 2007 [4]. It compared rituximab to infliximab for remission induction of refractory granulomatosis with polyangiitis (Wegener) (GPA). The rituximab protocol was one infusion (375 mg/m²) every week for 4 weeks, followed, when clinical improvement was observed at month 2, by an infusion of 375 mg/m² at months 4, 8 and 12. The infliximab protocol was 3 mg/kg on days 1 and 14. If complete remission was achieved, patients received 3 mg/kg every month, but if the remission was only partial, patients were given 5 mg/kg every month. At month 12, among the eight patients...