
The field of ANCA-associated vasculitis therapy is currently undergoing probably the most momentous change since the effectiveness of adjunctive CYC to treat granulomatosis with polyangiitis (Wegener’s) was discovered in the early 1970s [1, 2]. Since 2001 [3], the numerous uncontrolled observations reporting the efficacy of the chimeric monoclonal anti-CD20 antibody rituximab against granulomatosis with polyangiitis, microscopic polyangiitis and Churg–Strauss syndrome have sparked enthusiasm and hope that targeted B-cell therapy might cure ANCA-associated vasculitides. In 2010, the New England Journal of Medicine published two randomized clinical trials, Rituximab in ANCA-associated vasculitis (RAVE) and Rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) [4, 5], that provided the first controlled evidence that at 6 or 12 months of follow-up, respectively, rituximab was as effective and safe as conventional immunosuppressive therapy to control active granulomatosis with polyangiitis and microscopic polyangiitis. In a subgroup analysis of RAVE data, rituximab proved to be even more effective at inducing disease remission for those patients enrolled at the time of a relapse [4].

While inclusion of rituximab in the armamentarium of highly effective compounds to treat ANCA-associated vasculitides represents a major advancement, caregivers are now confronted with the dilemma of deciding how to incorporate rituximab into the previously defined therapy algorithms. In particular, the crucial question arises as to whether rituximab should henceforth dethrone CYC as the first-line drug combined with glucocorticoids for ANCA-associated vasculitides.

The article by Guerry et al. [6] published in this issue of Rheumatology is a welcome reflection, as it aims to provide rheumatologists and other physicians involved in the care of ANCA-associated vasculitides with guidance on answering these questions. Based on a systematic literature review and using a modified Delphi study design involving a panel of 11 vasculitis experts, the authors elaborated recommendations for using rituximab to treat ANCA-associated vasculitides. They then formulated 15 statements covering five pre-specified categories of interest. The strength of each recommendation was graded on a scale ranging from 1 (strong evidence) to 4 (poor evidence).

The panel was able to identify two key recommendations, which were accorded the highest grade 1 levels of evidence. First, the authors think that rituximab is an alternative to CYC as remission-induction therapy for previously untreated ANCA-associated vasculitides. Moreover, the panel considered that, in this context, rituximab should be preferred when it would be advisable to avoid CYC because of its high gonadal toxicity and carcinogenicity, or an ongoing infection. The second strong recommendation pertained to the approval of rituximab as an effective therapy against refractory/relapsing ANCA-associated vasculitides. The remaining recommendations, e.g. to use rituximab to treat Churg–Strauss syndrome and paediatric ANCA-associated vasculitides, reached only poor-grade evidence, as they were based exclusively on observational data from small numbers of patients.

Since the extent to which these newly proposed guidelines [6] are fully supported by available data is uncertain, all experts might not be ready to partake of them. This rapid positioning of rituximab as an alternative equal to conventional CYC-based immunosuppressive therapy for newly diagnosed ANCA-associated vasculitides could be too premature, in light of the lack of head-on comparative data beyond 6–12 months. Follow-up data from the RAVE and RITUXVAS trials, to determine whether the rituximab effect is sustained over the longer term, are awaited. Advancing the opinion that rituximab should be chosen for patients at risk of malignancy or with an ongoing infection reflects a conviction that rituximab has a better safety profile than CYC. Compared with the original treatment modality [1, 2], CYC administered as intermittent i.v. pulses and for a restricted 3- to 6-month remission-induction period has resulted in substantially lower exposure to CYC and, thus, its toxicity. Conversely, recently reported long-term follow-up results from patients with haematological malignancies suggest that rituximab may not be free of long-term side effects with respect to severe infections [7] and solid cancers [8]. Those observations urge for further monitoring of rituximab safety over the longer term.

For the time being, we are not yet as firmly committed to the unrestricted use of rituximab to treat ANCA-associated vasculitis patients as Guerry et al. [6] seem to be. Awaiting the accumulation of more clinical trial data obtained over longer observation periods, we still
recommend and prescribe CYC as the first-line glucocorticoid-combined drug for patients with newly diagnosed ANCA-associated vasculitides. As acknowledged by the authors, careful assessment of the cost-benefit balance will become another important parameter in therapeutic decision-making, especially for countries or care settings where access to more expensive biologic therapies is limited.

In contrast, that rituximab appears to be an effective agent for relapsing/refractory ANCA-associated vasculitides seems a very reasonable statement, even though this recommendation is also derived from relatively short-term follow-up data. Whether rituximab could satisfy the unmet need for an effective therapy of smouldering ear, nose and throat disease, retro-orbital pseudotumours or subglottic and tracheal stenoses in patients with granulomatosis with polyangiitis remains to be seen.

The arrival of rituximab in the universe of ANCA-associated vasculitis has revolutionized the approach to ANCA-associated vasculitis care and our understanding of its pathophysiology. We are perhaps only at the beginning of a new era, with more effective targeted therapies to come. Expert opinion surveys, such as the one reported by Guerry et al. [6], are crucial contributions to implementing new agents in daily clinical practice in the most accurate and objective manner without dismissing the knowledge gained on conventional therapies over many decades.

Disclosure statement: L.G. is a principal investigator for an institutional trial for which Roche has provided, in part, rituximab. L.G. is a member of the Scientific Council of the National Registry on the Use of Rituximab in Autoimmune Diseases (AIR), which is sponsored by Roche Pharma. A.M. is an investigator of an institutional trial for which Roche has provided, in part, rituximab.

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Accepted 15 April 2011
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