ANCA-associated vasculitis: mission incomplete

Over the last decades, introduction of high-dose corticosteroids and immunosuppressive agents and later rituximab into the current algorithms for remission induction and maintenance treatment resulted in a tremendous improvement in the survival of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). However, in the recent meta-analysis of observational studies, Tan et al showed a 2.7-fold increased risk of death in patients with AAV when compared with the general population.\(^1\) Notably, there was a trend towards lower mortality in the most recent compared with the earlier cohorts. In our own study in 242 patients with granulomatosis with polyangiitis, we also found a significant decrease in mortality in the recent years (2004–2012 vs 1970–2003; \(p=0.04\)) and a shift towards a higher percentage of cardiovascular events and complications of immunosuppression as the causes of death.\(^2\)

The results of Tan et al’s meta-analysis are not surprising and suggest that AAV, particularly if not promptly diagnosed and treated, remains a life-threatening disease and requires proper management. The pitfalls of the current treatment for AAV are well known and include relatively frequent relapses, especially in proteinase-3 (PR3) ANCA-positive patients (up to 50% within 5 years), delayed diagnosis and late initiation of treatment in a proportion of patients, high rate of end-stage renal disease (ESRD), which did not change significantly in the current era, unknown optimal duration of maintenance therapy, burden of immunosuppression (eg, infections and malignancy), and increased risk of cardiovascular and thromboembolic events, which may be related to persistent inflammation and/or corticosteroid treatment.

How can we improve outcomes in patients with AAV? Currently, rituximab seems to be the most promising agent both for remission induction and maintenance treatment. In the RAVE trial, rituximab appeared more effective than cyclophosphamide for relapsing disease and for PR3-ANCA-positive patients with AAV, while in the MAINRITSAN trial prolonged maintenance treatment with low-dose rituximab resulted in a significant reduction in the major relapses rate compared with azathioprine.\(^3\) A tailored approach to guide rituximab administration based on serial B lymphocyte and ANCA titre monitoring was studied in the MAINRITSAN 2 (NCT01731561) trial, while the MAINRITSAN 3 (NCT02433522) study will evaluate the need in the longer biological therapy to sustain remission. These trials will advance the understanding of optimal rituximab use for maintenance of remission in patients with AAV. In general, rituximab is regarded as more effective and safe option than cyclophosphamide. However, its advantages over standard immunosuppressives should not be overstated. In the RITUXVAS and RAVE trials, rituximab was equivalent to cyclophosphamide for remission induction of AAV among treatment-naïve patients, while in the MAINRITSAN trial the azathioprine dose was tapered starting at 12 months. The latter schedule of remission maintenance is not well accepted, and 41% of the relapses in the azathioprine group occurred after treatment cessation. Therefore, it can be speculated that the difference in relapse rates between rituximab and azathioprine groups would have been less significant if higher doses of the latter were maintained throughout the entire study. The RITAZAREM trial (NCT01697267) will help answer this question. Unlike cyclophosphamide, rituximab does not induce infertility or haemorrhagic cystitis. However, it can cause serious infections, late-onset neutropenia and hypogammaglobulinaemia. Moreover, in the randomised controlled trials retreatment with rituximab was not associated with a lower rate of adverse events compared with that in the other arms.

In the future, we can expect that targeted agents will continue to expand in the treatment arena. Avacopan (CCX168), an orally administered, selective C5a receptor inhibitor (CCX168), has recently completed phase 2 investigation in patients with AAV in Europe (CLEAR, NCT01363388). In this randomised, placebo-controlled trial, avacopan was effective in replacing high-dose corticosteroids in treating newly diagnosed or relapsing vasculitis.\(^6\) A randomised, double-blind, phase 3 ADVOCATE (NCT02994927) study will evaluate the safety and efficacy of avacopan as an alternative to prednisone in inducing and sustaining remission in patients with AAV treated concomitantly with rituximab or cyclophosphamide/azathioprine. Belimumab, a monoclonal antibody directed against B cell activating factor (BAFF), is currently being investigated in combination with azathioprine for maintenance of remission in AAV in a multicentre, randomised trial (BREVAS; NCT01663623). Belimumab may be probably combined with rituximab, for example, as a sequential therapy. Another ongoing multicentre, double-blind, placebo-controlled phase 3 trial aims to evaluate abatacept, a fusion protein that blocks the costimulatory signal needed for T cell activation, in relapsing non-severe AAV (ABROGATE; NCT02108860).

Renal prognosis is still unfavourable in AAV, as up to 20%–25% of patients reach ESRD within a few years after diagnosis. Adjunct plasma exchange is advocated for patients with a serum creatinine level of >500 mmol/L due to rapidly progressive glomerulonephritis in the setting of new or relapsing AAV. It can also be considered for the treatment of severe diffuse alveolar haemorrhage. Short-term results with plasma exchange in patients with ANCA-associated glomerulonephritis were encouraging, but the long-term benefits remain unclear.

Patients with AAV have an increased risk of cardiovascular events that may be determined by highly prevalent traditional risk factors, such as hypertension, dyslipidaemia and type 2 diabetes, vasculitis itself and/or atherogenic effects of corticosteroids. Therefore, in addition to vigorous risk factors, modification of steroid-sparing strategies may confer protective effects against atherosclerotic cardiovascular disease. However, a higher relapse rate may be a price we pay for a lower dose or too rapid tapering of prednisone. Several trials, that is, PEXIVAS, LoVAS and TAPiR, will add evidence regarding the efficacy of different corticosteroid regimens for remission induction and maintenance.

The recent EULAR/ERA-EDTA recommendations for the management of AAV did not address the risk of venous thromboembolic events\(^5\) that occur in up to 10% of patients within the first few months after diagnosis or relapse of vasculitis.\(^5\) Risk/benefit ratio of anticoagulation in patients with AAV is not established. Therefore, routine administration of oral anticoagulants cannot be recommended. In a large cohort of patients with AAV (n=377), we were unable to establish sufficiently strong predictors of venous thromboembolic events, except a short time after diagnosis, that would justify thromboprophylaxis with oral anticoagulants. Thus, it is currently unknown how to use this double-edged sword in real-life clinical practice.

In summary, observational studies have inherent limitations in terms of their susceptibility to bias and confounding. Risk of bias is particularly high in patients with AAV since they constitute a heterogeneous group and have variable course and response to treatment (eg, eosinophilic granulomatosis with
polyangiitis (EGPA) vs granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), renal vs non-renal vasculitis, localised vs generalised GPA), not to mention the ongoing discussion regarding classification of AAV (ANCA specificity based or a nosological scheme, the possible need to revise current definition for EGPA). However, observational studies give an idea about the prevalence and prognosis of the disease and reflect daily clinical practice more closely than randomised controlled trials. Tan et al’s meta-analysis suggests that there is room for further improvement in management of patients with AAV with the ultimate goal to reduce mortality and disability while avoiding both undertreatment and overtreatment. There is a need for longitudinal studies to evaluate mortality benefits of modern therapies and trends in the leading causes of death of patients with AAV. These data may facilitate decision making and support new preventive strategies.

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