Editorial

Combination of rituximab and cyclophosphamide for induction of remission in ANCA-associated vasculitis: the stronger, the better?

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Despite advances in treatment such as the introduction of rituximab (RTX) as a standard of care for induction and maintenance therapy, the clinical course of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is still characterised by increased mortality and frequent permanent end-organ damage (1, 2). Long-term follow-up of 848 patients who had been enrolled in seven randomised controlled clinical trials (RCTs) conducted by the European Vasculitis Society (EUVAS) showed a cumulative excess mortality compared with the matched general population of 7.9% at 1 year, 14.2% at 5 years and 19.9% after 10 years (3). In this cohort, the cumulative incidence of end-stage kidney disease (ESKD) at 5 and 10 years was 17% and 22%, respectively (4). A low estimated glomerular filtration rate (eGFR) at baseline was found to be a strong baseline predictor of death in the multivariate Cox regression analysis and infection was identified as the most common cause of death (26%) in the first year of treatment (4). Therefore, there is a strong need to find treatment regimens that are faster acting and more effective with the aim to reduce permanent organ damage, but which are also safer with the aim to reduce mortality due to infections (5).

Current guidelines recommend a combination of high-dose glucocorticoids (GC) with either RTX or cyclophosphamide (CYC) for induction of remission in life- or organ-threatening granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) (6-9). Adjunctive plasma exchange reduces the risk of end-stage kidney disease (ESKD) in MPA or GPA with severe active glomerulonephritis after one year. However, this beneficial effect seems to get lost over time and there is no impact on mortality while the risk for severe infections is increased (10). In two RCTs, GC-taper regimens with a faster dose reduction compared to previous standards were associated with significantly lower infections risk without compromising primary efficacy endpoints (11, 12). As a retrospective multicentre observational study found a non-significant trend towards a higher risk for disease progression before achieving remission, the faster GC taper should not be commenced before seeing an early treatment response (13). In the RCT ADVOCATE, the use of the complement-5a receptor (C5aR) antagonist avacopan instead of high-dose GCs as part of a CYC- or RTX-based induction regimen was similarly effective in terms of remission induction at 6 months and associated with lower GC-related toxicity, although the risk of severe infections and mortality was not significantly reduced (14). In patients with impaired renal function, a better recovery of renal function after one year was observed with avacopan compared to the GC-based control group (15). However, renal recovery in this control group appeared to be somewhat reduced compared to other studies, potentially due to early stopping of GCs at week 20 and the lack of maintenance therapy in patients who had received RTX for remission induction. Despite these advances, additional efforts to reduce early mortality and risk of ESKD are required.

In this context, a scientific debate is evolving on whether a more aggressive induction therapy with a combination of RTX and CYC might be superior to induction regimens that are based on either RTX or CYC only. Recent guidelines from the Kidney Disease

Improving Global Outcomes group (KDIGO) (8) recommend to consider a combination of RTX and CYC for remission induction in patients presenting with active AAV and a markedly reduced or rapidly declining renal function (serum creatinine [SCr] >4 mg/dl [>354 mmol/l]) and the British Society of Rheumatology (BSR) recommends to consider the RTX/CYC combo even more broadly in organ-threatening or life- threatening disease (9). But what is the evidence behind these recommendations? An observational study from the United Kingdom (UK) has reported the outcome of 49 patients with GPA or MPA who received a combination of RTX (2 x 1g) plus 6 pulses of CYC at doses of 500-750 mg per pulse combined with one or two methylprednisolone pulses and oral prednisone of 30-60 mg/day for 1-2 weeks only, followed by azathioprine or RTX for maintenance of remission (16). At 6 months, 96% of patients were in GC-free remission and only 3 patients experienced a disease relapse within the first year. Renal function improved and no patient developed ESKD. Compared to a matched historic cohort from the RITUXVAS trial (17), cumulative GC exposure and rates of severe infections and diabetes mellitus were lower with the RTX/CYC combination. A second report from this cohort with additional patients and longer follow-up confirmed the initial observations (18). Major limitations of this cohort study were its observational design and the lack of a randomised control group. Now, results of a large observational study reported by von Allwörden *et al*. in this issue of *Clinical and Experimental Rheumatology* provide additional evidence on the role of RTX/CYC combination therapy compared to standard induction therapy in AAV (19).

Patients with active new-onset or relapsing GPA (n=97) or MPA (n=69) were treated with a combination of GC plus either a) RTX alone, or b) the combination of RTX/CYC for remission induction, followed by RTX maintenance therapy, or c) CYC followed by AZA maintenance therapy. In contrast to the study from the UK (16), GCs were not stopped after two weeks but were tapered according to the treating physician's discretion. Patients with prior RTX and/or CYC therapy were excluded and follow-up was 24 months. The primary endpoint was complete remission, defined as absence of vasculitis activity without concomitant GC therapy at 12 and 24 months. After 12 months, 20% of patients in the RTX group and 22% in the RTX/CYC group achieved a complete response, compared to only 3% in the CYC-AZA group (p=0.008). Most patients achieved remission at some point during the 24-month follow-up period (RTX, 88%; RTX/CYC, 87%; CYC-AZA, 81%; p=0.097). Relapse rates were similar between the three groups, including the subgroup of patients with severe kidney disease. Renal outcomes such as the percentage of patients with ESKD or recovery of renal function have not been reported. The use of plasma exchange may have had impact on renal outcomes, but the use of plasma exchange has not been reported in this study. As disease activity at baseline was higher in patients receiving either the RTX/CYC+GC combination or CYC only+GC compared to patients treated only with RTX+GC, a selection bias towards more aggressive treatment in patients with higher disease activity is likely, what may have favoured outcomes in the RTX-only group. GC exposure over time was highest in patients receiving CYC-AZA, most likely reflecting changes of practice and guidelines towards faster GC taper regimens, as the CYC-AZA was commonly prescribed in the first years of the study which included patients who were treated between 2010 and 2021. Further, the authors do not mention whether a portion of patients received plasma exchange which is not entirely unlikely, since patients in this study were seen by nephrologists and the greater part was diagnosed in the pre-PEXIVAS era. These and other limitations such as the retrospective monocentric design preclude a strong conclusion about the efficacy of the RTX/CYC combination compared to RTX alone. Despite these limitations, the study does not provide evidence supporting preferential use of an up-front RTX/CYC combination versus RTX only. So far, the RCT RITUXVAS provides the best available evidence on the use of RTX/CYC combination in patients with severe AAV with renal involvement (17). Although small, the trial showed no superiority of combining RTX induction with 2 pluses of CYC compared to standard CYC induction. The argument has been made that data on the use of RTX in severe renal AAV is limited as patients with a creatinine >354 μmol/l had been excluded in the phase-3 RCT RAVE comparing RTX and CYC for remission induction (20). However, in a *post-hoc* analysis of this trial, RTX was not inferior to CYC in patients with less severe renal disease (21) and mechanistically there are no strong reasons to assume that RTX targets B lymphocytes less effectively with more advanced renal disease. In fact, results from a large observational study showed similar efficacy of RTX compared to CYC in patient with severe renal disease (22).

In summary, the large observational study reported by von Allwörden *et al*. (19) provides no arguments supporting a routine use of an up-front use of a RTX/CYC combination therapy in preference of either CYC or RTX alone in patients with AAV, but clinicians may consider the combination in selected patients with refractory disease over monotherapy. Potential benefits of combination therapy such as a reduction in GC toxicity must be weighed against potential toxicity resulting from CYC use such as bladder cancer and only a proper RCT can finally define the role of this early multi-target therapy. As faster acting and less toxic induction therapies are clearly needed and the rationale for a more aggressive early treatment strategy is compelling, results of the currently recruiting RCT ENDURANCE-1 comparing combination therapy with RTX 2 x 1 plus 6 pulses of CYC to RTX (2 x 1 g) alone (NCT03942887) will be of great interest.

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