Long-term disease control in granulomatosis with polyangiitis: is low-dose rituximab the cure?

This editorial refers to Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients by Xavier Puéchal et al., on pages 401–9.

Rituximab (RTX) is an anti-CD20 mAb that has gained a major role in the treatment of ANCA-associated vasculitis (AAV). In this issue of Rheumatology, Puéchal et al. [1] report the results of a single-centre cohort study of RTX as induction and maintenance therapy for granulomatosis with polyangiitis (GPA).

GPA is a type of AAV with a wide range of clinical manifestations, some of which are potentially life threatening. Although the disease prognosis has dramatically improved with the development of a staged treatment based on glucocorticoids (GCs) and immunosuppressive agents, AAV patients still experience a high incidence of relapses and therapy-related adverse events. Given that, RTX is seen as a valid alternative to conventional immunosuppressive therapy.

In 2010, two randomized controlled trials (RCTs), Rituximab versus Cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) and Rituximab versus Cyclophosphamide for ANCA-associated vasculitis (RAVE), demonstrated that RTX given at 4 weekly doses of 375 mg/m² is as effective as standard CYC among patients with new-onset severe AAV and superior to CYC among patients with relapsing severe AAV in achieving remission [2, 3]. Moreover, the safety profile of the two treatments was similar, probably because of a major contribution of GC toxicity in the short term.

Extended follow-up of the RITUXVAS and RAVE trials found similar relapse rates between the RTX and CYC arms, although the former did not receive any further infusions, while the latter was given daily AZA for maintenance [4, 5]. RTX efficacy in relapse prevention was also reported in retrospective studies with two different approaches: fixed RTX administration every 4–6 months and pre-emptive RTX at CD19⁺ B cell reconstitution and/or at ANCA titre increase [6, 7]. Sustained remission was achieved by nearly all patients, but B cell repopulation and ANCA titre modifications failed to reliably predict relapse.

A French RCT called MAINRITSAN reported the superiority of low doses of RTX (500 mg × 2 at month 6, then 500 mg every 6 months for 18 months) in preventing major relapses among AAV patients who had achieved remission with CYC (5% vs 29% at month 28; \( P = 0.002 \)) [8]. MAINRITSAN 2, a further RCT by the same group, recently found no significant differences in major relapse rates (7.4% vs 3.7%; \( P = 0.23 \)) between groups treated with systematic vs patient-tailored RTX administration (i.e. following B cell repopulation and/or ANCA titre increase), with the latter group receiving a lower RTX cumulative dose [9].

However, these trials have not clarified all of the issues regarding maintenance treatment in AAV. First, it remains unclear which regimen should follow RTX-based induction. Moreover, only a minority of the enrolled patients were relapsing (20% in MAINRITSAN, 34% and 37% in the arms of MAINRITSAN 2) and PR3-ANCA⁺, that is, the subgroup at highest risk of relapse. Finally, RTX-related complications and risk–benefit balance in the long-term have yet to be elucidated. An ongoing RCT called RITAZREM has enrolled relapsing AAV patients who achieved remission with RTX-based induction therapy, comparing 1 g RTX every 4 months for 24 months to AZA. Results of this trial are pending and will reveal if prolonged B cell depletion is the therapy of choice in AAV patients with relapsing disease, as supported by retrospective studies [6, 7].

The paper by Puéchal et al. [1] is the largest published experience of RTX combined with GCs for induction and maintenance therapy of GPA specifically. The authors studied 114 patients treated with one or more RTX courses for new-onset, relapsing or refractory/grumbling disease. Three quarters were PR3-ANCA⁺ and nearly 50% had pure granulomatous manifestations. Most patients received RTX 500 mg at month 6 as maintenance therapy, then every 6 months for 18 months [8]. Their median follow-up was 3.6 years.

At month 6, the remission rate was 84%. These findings are in line with the RAVE results, but patients in this study received a median GC induction dose that was about half of that in RAVE (30 mg/day vs 1 mg/kg/day). Moreover, the remission rate remained stable during the follow-up, with 85 and 83% relapse-free survival rates at months 24 and 36, respectively, although the authors used a lower dose RTX regimen compared with most previous studies (500 mg vs 1 g).

Multivariable analyses identified pure granulomatous disease and pachymeningitis as remission failure predictors, confirming observations from previous studies [10]. An estimated glomerular filtration rate \( \geq 60 \text{ ml/min/1.73 m}^2 \) also predicted remission failure, probably because this reflects a clinical phenotype of mainly granulomatous disease lacking severe renal involvement. Moreover, independent predictors of relapse were refractory/grumbling GPA, subglottic stenosis, ENT signs and skin involvement, but not PR3-ANCA positivity, likely because of too few PR3-ANCA⁺ patients. PR3-ANCA positivity was associated
with an increased risk of relapse in studies including both GPA and microscopic polyangiitis patients, not only in GPA.

The rate of serious adverse events was 8.1/100 patient-years, with predominance of severe infections, mainly pneumonia. Among patients with infections, 44% had hypogammaglobulinaemia, a well-known side effect of B cell depletion, but none of them had severe hypogammaglobulinaemia (IgG < 4 g/l), suggesting that this was not the only factor implicated in the development of infectious events.

This study corroborates the role of RTX combined with GCs for induction and maintenance therapy of GPA. The effectiveness and safety of this treatment were satisfactory in the examined cohort and have been evaluated over a long-term follow-up in a significant proportion of patients with pre-existing comorbidities. Low-dose pre-emptive RTX seems to succeed in maintaining remission even in relapsing PR3-ANCA+ patients with granulomatous disease, considered the most difficult-to-treat group. These results need to be carefully compared with those of the RITAZAREM trial to further understand the risks and benefits of low-dose vs high-dose RTX in the long term. Appropriate use of RTX probably depends on several factors, such as disease phenotype, history of relapse, patient characteristics and previous treatments. To assess these points, careful stratification of patients is essential, and so is the development of biomarkers able to predict relapse more reliably than the ones currently used (e.g., ANCA titre modifications, B cell reconstitution). Cohort studies will go on to confirm, anticipate and complete RCT results, offering new perspectives for optimal disease treatment.

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