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 receiving rituximab, four were in complete remission, one in partial remission, one had died and two were therapeutic failures. Among the nine patients on infliximab, two were in complete remission, one in partial remission, one had died and five were non-responders. That was the first trial to investigate rituximab and its results indicated the potential contribution of this biologic in the treatment for refractory AAV.

The FVSG’s main research axis is using rituximab as AAV maintenance therapy. The MAINRITSAN study (NCT00748644) was completed in October 2012. That open-label randomized–controlled trial, conducted on 117 AAV (GPA or microscopic polyangiitis (MPA)] patients, compared azathioprine (2 mg/kg/day) to rituximab (500 mg on days 1 and 15) and then every 6 months (five infusions). At 28 months, 5% of the rituximab-treated patients had suffered a major relapse versus 25% of those taking azathioprine. No major safety issue was raised. For that trial, a rituximab dose of 500 mg was chosen for several reasons: fewer side effects were expected by lowering the dose, use of less rituximab obviously lowered the cost of treatment and because usual doses (e.g. 1 g or 375 mg/m²) had been determined empirically.

An ongoing randomized trial (MAINRITSAN 2: NCT01731561) is comparing two rituximab-administration strategies for maintenance therapy. In one arm, patients receive the same rituximab regimen as in the original MAINRITSAN study, while in the second arm, after a first 500-mg infusion, rituximab is given again only if a patient’s CD19 count is > 0/mm³ or the ANCA titer becomes positive or rises.

The French experience reported in retrospective studies

As for other investigators, first reports on small numbers of patients focused on rituximab efficacy at inducing remission of relapsing or refractory AAV. In a study on eight patients followed for 6 months [5], three achieved complete remission, three partial remission and two were non-responders. Rituximab was also used to treat rare and life-threatening manifestations, e.g. cardiac GPA involvement [6]. As rituximab use expanded, a large, multicenter, retrospective study was conducted on 80 patients (submitted). The results of that study showed that the modalities of rituximab prescription and use were highly heterogeneous: four different infusion protocols when rituximab was given for remission induction and more than five schedules for maintenance therapy, alone or combined with other immunosuppressants. Moreover, despite available recommendations on rituximab use for rheumatoid arthritis [7], only 19% of our patients had been vaccinated against pneumococcal infections before the first rituximab infusion and immunoglobulin dosages were available for only 56%. Rituximab efficacy for remission induction and maintenance was consistent with other retrospective series [8–11]: respective 1-, 2- and 3-year relapse-free survival rates after the first rituximab infusion were 80% (95% CI 72–89), 63% (51–77) and 52% (39–70). Rituximab tended to be a superior maintenance therapy: 9/45 (20%) patients relapsed versus 7/14 (50%) (P = 0.13) prescribed other therapies. Rituximab safety is of concern. Even though, unlike other vasculitides, multifocal encephalopathy has never been reported in AAV, the infectious complications of RTX are frequent, ranging
from 7 to 28.9% (2,10). In our 80-patient study, 12 (15%) severe infectious complications were reported and led to four (5%) deaths. Other complications have been reported, e.g. macular edema [12].

Another study evaluated rituximab as maintenance therapy [13]. Among the 28 patients who received a median of 4 rituximab infusions, only two have relapsed, with a median follow-up of 38 months since diagnosis. Rituximab efficacy against GPA and MPA has been demonstrated but not for eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA). Some patients, particularly those with renal involvement, might respond better than others with granulomatous disease (personal data), but no study has examined this possibility. However, two severe allergic manifestations (asthma) after rituximab infusions have been described [14].

**Conclusion**

Rituximab efficacy for induction remission and as maintenance therapy of GPA and MPA has been demonstrated. The addition of this biotherapy to AAV management is a major benefit to patients, particularly those with refractory or relapsing disease and already exposed to high cumulative cyclophosphamide doses, or for women < 40 years old to avoid cyclophosphamide-related ovarian failure. Nevertheless, rituximab was not superior at inducing AAV remission [2], was not compared to cyclophosphamide in patients with acute renal failure or severe granulomatous disease, and had no impact on the frequency of infectious complications. Under the auspices of FVS6, we are devising recommendations determining rituximab indications and the modalities of its use, particularly for infectious complications: systematic vaccinations, immunoglobulin dosages and co-trimoxazole prophylaxis.

Because of infectious concerns and rituximab efficacy even at a low dose (500 mg), we think that its future use means lower doses to a large AAV population.

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**References**


