

B Cell Strategy to Maintain Remission in ANCA-associated Vasculitides?



During the past decades therapeutic regimens in the anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides (AAV) aiming at induction or maintenance of remission have undergone substantial changes. Glucocorticoids plus cyclophosphamide as standard therapy for induction have been challenged by monoclonal tumor necrosis factor blocking antibodies; and maintenance therapy with azathioprine has been expanded by methotrexate, leflunomide, and mycophenolate mofetil^{1,2}.

Regarding pathogenesis, numerous recent studies have suggested a central role of the ANCA³. In line with this hypothesis, plasma exchange aiming at a reduction of antibody titer showed positive results in life-threatening vasculitis⁴. Along this line, rituximab (RTX), a chimeric monoclonal anti-CD20 antibody primarily used for therapy of B cell lymphomas, proved to be highly effective in the induction of remission, successfully challenging cyclophosphamide^{5,6,7}. With the US Food and Drug Administration approval of RTX for a single course treatment in both granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) and microscopic polyangiitis (MPA) in April of 2011, a novel induction regimen was established⁸.

Notably, RTX is the only treatment approved so far. Disease relapses after induction — irrespective of the agent — are to be expected in AAV. In the RITUXVAS study, which included 2 infusions of cyclophosphamide additionally to the first course of RTX, relapses during a 2-year followup occurred in 21% (7/33) of the RTX-treated patients and in 18% (2/11) in the cyclophosphamide-only treated group. Remarkably, in the RTX arm no maintenance therapy was given, whereas the cyclophosphamide-only treated patients were followed by maintenance azathioprine⁹. At this point it is unclear which of 3 options will perform best: watch-and-wait, standard regimen, or repeated cycles of RTX. If the latter is favored, it remains to be determined whether RTX is given in fixed intervals or based on biomarkers and/or clinical judgment.

So far a few studies have addressed the question of pre-

vention of relapse using RTX. A recent retrospective analysis showed efficacy of RTX as maintenance therapy with 1-gram applications in 4-monthly intervals, with flares in only 3/39 patients within 2 years after RTX. In this study patients with complete or partial remission were included; all were induced by RTX¹⁰. Another study reported on 49 patients with AAV receiving per-protocol RTX maintenance therapy every 6 months for 2 years versus 34 non-protocol RTX applications repeated only at relapse¹¹. Relapse rates after 2 years were reported in 22% of per-protocol patients versus 71% of non-protocol patients. The high relapse rate in the latter treatment arm may, at least in part, be due to low or no concomitant glucocorticoids. Remarkably, infectious complications were less frequent in the protocol group (14% vs 18%).

In this issue of *The Journal*, Roubaud-Baudron, *et al*¹² address the question of efficacy and side effects of preemptive RTX as maintenance therapy in patients with GPA and MPA, a retrospective single-center study covering a period of 7 years. Patients administered standard induction treatment with cyclophosphamide (21 of 28 patients) also received the novel treatment with RTX, leading to maintenance of remission in 15/28 patients (53%) over a mean period of 38 months. The studied patients had typical disease characteristics of a referral center: high cumulative doses of cyclophosphamide (mean 48 g), longstanding disease (median of 84 mo), different organ manifestations, and varying preceding therapeutic regimens.

The dosages of RTX maintenance therapy varied from 375 mg/m² biannually to 1 g biannually and 1 g annually; dosages changed intra-individually based on the judgment of the treating physician, severity of disease, and available evidence in the literature. Remarkably, regardless of RTX dosage, only 2 patients suffered relapse within 6 and 11 months after RTX maintenance infusion, respectively. One of these had a CD19+ lymphocyte reconstitution at the time of relapse. The percentage of relapses in their study is lower than the relapse rate of the above-mentioned studies. This

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may be explained by frequent comedication or by the individualized treatment strategy. A further interesting finding of their study is the lack of a prognostic value of ANCA titers and CD19+ B cell numbers. This is in line with recent studies in AAV, as well as numerous studies in rheumatoid arthritis (RA), where autoantibodies and B cell numbers did not help identify relapses at an early stage.

Regarding side effects, 1 patient who suffered relapse died because of an H1N1 infection. Whereas she had normal immunoglobulin levels, 2 patients who had infections (cutaneous abscess and otitis media) were hypogammaglobulinemic. The data about immunoglobulin levels are remarkable. Eleven of the 21 patients with repetitive measurements had immunoglobulin levels below normal limits before first RTX administration. RTX led to a further, significant decrease. However, despite this humoral immune-deficit and frequent immunosuppressive comedication, no increase in infections was noted, in particular bronchopulmonary infections with encapsulated bacteria.

Considering the data of Roubaud-Baudron, *et al*¹² as well as data from other recently published studies, at this stage RTX retreatment at fixed intervals of 6 months at a dose of 1 g can be suggested, with close monitoring of efficacy and safety to maintain remission. As proposed by Roubaud-Baudron, *et al*, prospective trials of patients with AAV to compare conventional immunosuppressive agents versus pro-protocol RTX treatment will need to be performed. The MAINRITSAN study initiated by Loïc Guillevin, which is under way, compares repeated RTX to continuous azathioprine as maintenance therapy.

Despite the negative data regarding biomarkers, efforts should be undertaken to study the value of B lymphocyte cytokines such as B cell activating factor of the tumor necrosis factor family¹³ and B lymphocyte subpopulations, for example, switched memory B cells. The latter have recently been shown to predict relapses in RA¹⁴. It appears likely that more sophisticated variables possess predictive value and will help to tailor therapy.

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