Editorial

How to prescribe rituximab wisely for antineutrophil cytoplasmic antibody-associated vasculitides

L. Guillevin

French Vasculitis Study Group, Cochin Hospital, University Paris Cité, Paris, France.

Loïc Guillevin, MD

Please address correspondence to:
Loïc Guillevin
French Vasculitis Study Group, Cochin Hospital, University Paris Cité, 27 rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France.
E-mail: loic.guillevin@orange.fr

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Remission-induction and -maintenance treatments for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) have been revolutionised by rituximab, an anti-CD20 antibody, combined with corticosteroids (CS). Its efficacies to induce granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) remissions are not inferior to cyclophosphamide (1, 2). As maintenance therapy for those diseases, rituximab is superior to all other therapeutic options (3): CS and/or conventional immunosuppressants.

Treating eosinophilic granulomatosis with polyangiitis (EGPA) must be distinguished from other AAVs for various reasons: heterogeneity of pathogenetic mechanisms; different phenotypes (4, 5), according to ANCA-positivity or -negativity and genotypes (6); no previously published prospective therapeutic remission-induction or -maintenance trials potentially demonstrating a place for rituximab (7); and the possible use of other biotherapies targeting, particularly, interleukin (IL)-5 (8) or IL4/IL13. Therefore, in this update, we will address two AAV groups, GPA and MPA together and then EGPA.

Rituximab for GPA and MPA

The RAVE study analysis at 6 and 18 months (1, 2) of remission-induction efficacy of rituximab (375 mg/m^2 every week for 3 weeks; 4 infusions) *versus* oral cyclophosphamide showed it not inferior. MAINRITSAN-trial maintenance results showed that rituximab (500 mg) administered every 6 months for 18 months was superior, at 28 months, to azathioprine prescribed for 22 months (3), with respective major relapse rates of 5% *versus* 29%. The RAVE and MAINRITSAN trials contributed to establishing a new treatment paradigm for GPA and MPA but many questions remain unanswered.

In light of new therapeutic guidelines, the persisting main concerns are to determine the optimal rituximab dose and when to infuse it, whether should it be infused at fixed intervals or on-demand, treatment duration, whether it should it be combined with other immunosuppressants and CS management, and the availability of new drugs like avacopan (9). Treatment tolerance is also a major concern worthy of investigation.

Rituximab dose and infusion intervals

The remission-induction dose adopted by consensus (see above) followed initially guidelines for lymphoma treatment. Alternatively, retrospectively obtained short-term results supported two 1-g rituximab infusions, at a 2-week interval, as being as effective as the 4-infusion regimen with similar tolerance (10). We chose a maintenance regimen of 500 mg every 6 months for the MAINRITSAN-trial; it is now the Food and Drug Administration and European Medications Agency recommended schedule and has been adopted by several National Health Authorities. As the principal MAINRITSAN investigator, I would like to explain that that dose was chosen for two main reasons: a "logic-driven" decision to use less drug for maintenance than for induction and the objective to limit long-lasting rituximab-induced immunodepression-related adverse events (AEs).

The authors of the prospective RITAZAREM study (11, 12) treated AAV patients in relapse with rituximab after having received the conventional dose for induction, followed by five 1-g infusions, administered every 4 months. Because all RITAZAREM patients *versus* 23% of MAINRITSAN1 participants had already relapsed at inclusion, they were at higher risk of relapse. At 4 months, 90% of 188 RITAZAREM

patients were in remission, confirming rituximab's continued effectiveness in patients who relapsed, independently of their first-line therapy (cyclophosphamide or rituximab) (11). Maintenance rituximab (1 g) was infused every 4 months. After five rituximab infusions post-RITAZAREM enrolment and the 48-month follow-up (12) maintenance phase, 13/85 (15%) rituximab-treated patients relapsed *versus* 32/85 (38%) azathioprine recipients; their respective relapse-free survival rates were 85% [95% confidence interval (CI) 78% to 93%] *vs*. 61%, [95% CI 51% to 73%]. During follow-up, five rituximab-treated patients experienced major relapses *versus* 11 azathioprine recipients. Those results confirmed rituximab superiority over azathioprine for remission maintenance. Relapse prevention was comparable to that obtained in MAINRITSAN1 (3). RITAZAREM outcomes also demonstrated that rituximab-dose intensification from 500 mg to 1 g to prevent relapses and shortening the infusion interval from 6 to 4 months was not beneficial for most patients but could be retained, as a possible option, for patients responding poorly to rituximab.

Predictors of relapse and their impact on the treatment schedule

How to manage remission maintenance

Although the rituximab remission-induction regimen for GPA and MPA is now codified, the maintenance-infusion schedule warrants additional studies. The "ideal" long-term reinfusion schedule would be to treat patients at risk of relapse and to stop treatment after approximately 2 years for patients without risk factors for relapse. Unfortunately, those factors are only partially known and, at our present level of knowledge, it seems difficult to apply a "calculated-decision algorithm" to guide these therapeutic decisions. Confirmed relapse predictors are previous relapse, anti-proteinase-3 (PR3) ANCA-positivity at diagnosis (2, 13) and their persistent presence 12 months after the first rituximab infusion (13). Relapse rates were also higher for patients whose ANCA disappeared then reappeared (13), but lower for patients positive for anti-myeloperoxidase (MPO) than anti-PR3 ANCA, and higher than that of ANCA-negative patients (13, 14). However, keep in mind that renal disease evolution is more severe in patients with anti-MPO-ANCA than those anti-PR3-positive (15).

The MAINRITSAN2 trial (16) attempted rituximab-dose adaptation to CD19-B-cell positivity and/or ANCA titre. It failed to individualise parameters predictive of relapse but indeed demonstrated that it was possible, during the 28-month follow-up, that rituximab was able to prevent relapses with an on-demand dose (1.5 g) *versus* a fixed-dose (2.5 g). In the RITAZAREM study, CD19-positive B-cell counts were low in rituximab and azathioprine groups. The search for indicators predicting relapses is certainly the first step to guide the choice between a fixed-infusion schedule and an on-demand tailored one.

More recently, the prospective MAINTACAVAS study (17) compared rituximab-maintenance administration based on B-cell repopulation *versus* serological ANCA flare. All patients had already received rituximab for at least 2 years. Patients were randomised based on ANCA titre or B-cell reconstitution. After randomisation, rituximab (1 g) was reinfused into patients with B-cell repopulation or an ANCA-titre rise. The primary endpoint was clinical relapse. Because the relapse rate was lower for the B-cell strategy than the ANCA-titre strategy, the authors recommended basing dose adaptation on B cells. In fact, MAINRITSAN2 and MAINTACAVAS reinfusion strategies reflect different approaches to disease follow-up. B-cell repopulation reflects immunosuppression intensity, but ANCA titres reflect the presence and sometimes AAV activity.

All discussions addressing parameters predicting AAV relapse focus on two different pathogenetic mechanisms to control disease evolution: should we try to obtain continuous B-cell depletion or control disease activity? At the moment, the answer to that question remains unknown. We know that: longer rituximab therapy maintains remissions (18) and a low CD19-positive B-cell count indicates prolonged immunosuppression, but the latter does not indicate disease activity, unlike ANCA presence or titre increase. ANCA variations could help guide reinfusing rituximab on-demand, based on minor clinical changes. Like in MAINRITSAN2, rituximab (500 mg)-infusion intervals spaced 1-year apart had the advantage of minimising the risk of immunodepression-related infections, without losing rituximab efficacy to prevent relapse. However, long-term follow-up of the MAINRITSAN trials (19) showed that 3 semestrial rituximab infusions without CS were associated with a high relapse rate, meaning that short-term rituximab therapy has only short-term efficacy, but does not preclude reinfusing rituximab at successively longer intervals according to clinical or biological signs (e.g., every 8 months based on CD19 repopulation as in the MAINTACAVAS study).

How to manage immunosuppression and its AEs

No doubt persists that prolonged rituximab administration prevents relapses. However, it does have the disadvantage of inducing major immunosuppression. Fifty-six months fixed-dose (36 months rituximab + 20-month follow-up in MAINRITSAN2 and -3; 500 mg); rituximab (1 g) every 4 months (RITAZAREM), rituximab (1 g) adapted to B-cell repopulation (MAINTACAVAS) had deleterious effects. Although prolonged immunosuppression represents a high infection risk, the number of infections has never been prospectively collected; it should be a future task. Since the first rituximab trials for AAV (RAVE, MAINRITSAN1), more information has become available on infections developing in rituximab-, corticosteroid- and conventional immunosuppressant-treated patients but most is fragmented, having been collected during prospective studies, and does not give sufficient importance to discern impact on future treatment decisions. Also, the real COVID pandemic's effect on AAV mortality and how it influenced therapeutic strategies are unknown. New pandemics and other

infections will certainly arise in the future and clinicians should collect data on what happened during the last one and subsequently formulate preventive and therapeutic recommendations.

CS-dose reduction and duration contribute to limiting AEs, and all guidelines now recommending lower CS doses have been implemented in prospective trials. That strategy was validated by Furuta *et al*. (20) who compared patients given rituximab for remission-induction and full-dose or half-dose CS. Their respective outcomes at 6 months were: 45/65 (69.2%) *versus* 49/69 (71.0%) achieved remission; 41 serious AEs (SAEs) occurred in 24 (36.9%) patients *versus* 21 in 13 (18.8%) (p=0.02); and 20 serious infections in 13 (20.0%) patients *versus* 7 in 5 (7.2%) (p=0.04). It should also be kept in mind that although CS-dose reduction effectiveness has been shown, prolonged low-dose CS lowers the risk of relapse and, subsequently, could minimise long-term AEs possibly occurring during a relapse and requiring new remission-induction. In a meta-analysis, Walsh *et al*. (21) comparison of non-zero *versus* zero CS-target doses demonstrated respective relapse rates of 14% (95% CI 10 to 19%) and 43% (95% CI 33 to 52%). The TAPIR study (22) randomised patients within 1 year of having received remission-induction for active GPA and in remission after tapering CS to 5 mg/day to continue for 6 months that dose or totally discontinue CS in 4 weeks and then stay off CS while pursuing other immunosuppressive therapy: relapses were more frequent in those off CS, except for rituximab-treated patients.

Another strategy to reduce CS is avacopan, an anti-C5a agent. In the prospective randomised ADVOCATE trial (9), all the patients received either cyclophosphamide or rituximab and took oral avacopan (30 mg twice daily) or oral prednisone on a tapering schedule. Sustained remission at week 52 (the second primary endpoint) was observed in 109/166 (65.7%) patients taking avacopan and in 90/164 (54.9%) patients on prednisone (p<0.001 for non-inferiority; p=0.007 for superiority). Despite that significant between-group difference, it should be recalled that patients did not receive rituximab maintenance, which could have favoured relapses in both groups.

Combining rituximab, CS and conventional immunosuppressants

Although that combination therapy is often prescribed, no prospective trial results have confirmed its superiority *versus* rituximab alone. The prospective trial evaluating rituximab + cyclophosphamide + CS before randomisation between CS + cyclophosphamide *versus* CS + rituximab did not demonstrate superiority of remission-induction regimen intensification (23) but may increase the risk of developing infections when conventional immunosuppressants were added to rituximab. Therefore, we recommend that this combined therapy not be generalised.

The infectious risk for rituximab-treated patients

Information from prospective trials is available but was published before the COVID-19 pandemic (1-3, 12), which was responsible for the deaths of some profoundly immunocompromised patients with hypogammaglobulinaemia decades after receiving the last rituximab infusion. Serious infectious AEs occurred in 18% of rituximab-treated patients in the RITAZAREM trial *versus* 22% given azathioprine (12) (endpoint 24 months).

Twenty-seven percent of the patients included in the long-term follow-up (84 months) of the 3 MAINRITSAN trials developed at least one serious infection, including 9 opportunistic infections (4 Pneumocystis jiroveci pneumonia) (PJP) equally balanced in both groups. However, PJP seems to occur more frequently in rituximab-treated patients, without initial low CD4-T-cell counts. PJP may occur at any time during treatment and this risk factor disappears only when immune reconstitution has been achieved, *i.e*. several months after completing rituximab infusions. Infection prophylaxis should be prescribed to all patients receiving rituximab: vaccination against pneumonia, herpes zoster, COVID-19, etc.) and systematic co–trimoxazole (400 mg/day adapted to renal function). Unfortunately, because rituximab quickly depletes B cells, vaccination efficacy is poor when given after or immediately before rituximab infusion.

COVID-19 is also a concern (24). Several patients in AAV remission died during the pandemic, sometimes several months or years after having received rituximab. Because no data have been systematically collected, it is impossible to quantify the real numbers of COVID-19-attributable deaths. We are aware among AAV patients that prophylactic measures are often poorly prescribed to patients or were prescribed too late to be effective. Severe infections can best be prevented by CS-dose reduction, avoiding, if possible, combined rituximab and conventional immunosuppressants, and prescribing long-term treatments only to patients at high risk of relapse, *i.e*. those with prior relapse and/or ANCA presence, mainly PR3.

Some GPA subgroups are also frequent relapsers, like those with ear, nose & throat (ENT) manifestations. So, expected relapse severity should also be considered. Patients with ENT manifestations frequently develop minor relapses with only rhinitis or chronic otitis and, even during incomplete remission, have symptoms that do not require intense B-cell depletion or aggressive immunosuppression. Less toxic treatments like co–trimoxazole, low-dose methotrexate or CS <5 mg could suffice to control the disease. Hence, low-level grumbling disease of minor relapse is acceptable and should not be treated with rituximab. Long-term rituximab infusions should also be avoided in patients with comorbidities and factors favoring infection, *e.g*. denutrition or prior treatments engendering immune-system modification (like anticancer chemotherapy, but also previous immunosuppressants or rituximab for earlier relapses).

Rituximab for EGPA

Although rituximab indication for GPA and MPA is now partly codified, that is not the case for EGPA. Several explanations clarify why: EGPA rarity, heterogeneity and the availability of several new drugs targeting IL5.

The forthcoming results of the randomised REOVAS study, organised by the French Vasculitis Study Group (7), evaluated rituximab induction-remission, comparing CS + rituximab *versus* a control group stratified according to the Five Factor Score (FFS) (25): CS alone for patients with FFS=0 or CS + cyclophosphamide for FFS≥1. The two groups obtained responses comparable to those of GPA and MPA patients (1, 2, 23). Retrospective study results showed rituximab induction-remission efficacy for EGPA (26), with responses for ANCA-positive or -negative patients. The rituximab indication for maintenance has not been yet examined but a prospective study is ongoing.

It is also probable that the questions and answers regarding rituximab management detailed above will be validated for EGPA.

Conclusion

Rituximab has revolutionised vasculitis patient care and improved outcomes. A new paradigm emerged, answering many questions about AAV management, while raising new concerns about long-term follow-up and patient management, urging clinicians to define which patients could clearly benefit from rituximab use.

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