Editorial

Optimising ANCA-associated vasculitis management and infectious risks during the COVID-19 pandemic

L. Guillevin, B. Terrier

Department of Internal Medicine, Hôpital Cochin, Université Paris-Descartes, Paris, France.

Loïc Guillevin, MD
Benjamin Terrier, MD, PhD

Please address correspondence to:
Loïc Guillevin,
Department of Internal Medicine,
Hôpital Cochin,
27 Rue du Faubourg Saint-Jacques,
75679 Paris Cedex, France.
E-mail: loic.guillevin@orange.fr

Received and accepted on April 27, 2022; accepted on April 28, 2022.

Clin Exp Rheumatol 2022; 40: 688-690.

Competing interests: none declared.

Over the last few decades, treatment of vasculitides, especially antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs), has been revolutionised by extensive use of combinations of steroids and cytotoxic agents (1, 2). Since 2010, rituximab has been approved to treat AAVs (3-5) and other biologic therapies are emerging, e.g. mepolizumab (6), an anti-IL5 to treat eosinophilic granulomatosis with polyangiitis. To prevent corticosteroid adverse events (AEs), dose reduction has been successfully applied and a steroid-sparing drug, avacopan (7), a C5a-receptor antagonist, has been prescribed as adjunctive therapy for AAV patients. These new standard-of-care molecules are aimed at improving patient survival and quality of life, and minimising drug-induced AEs.

Unfortunately, most of those agents also impair the immune response against pathogens, rendering patients more susceptible to infections. A careful prophylactic policy, combining long-term antibiotics in some circumstances, vaccination and drug-dose minimisation, has certainly lowered the risk of lethal infections but has not been able to prevent severe AEs. Infection with the severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) viral infection has killed patients worldwide, especially those immunocompromised and/or elderly (8).

AAV therapy usually comprises 2 phases: induction, to obtain remission, and maintenance, to prevent relapses. The 2 phases of this therapeutic strategy cannot be dissociated and the choice of maintenance regimen is largely influenced by that of remission-induction treatment. When cyclophosphamide is prescribed for induction, maintenance therapy is mandatory (9) and regimens of short duration are associated with relapses (10). The efficacy of rituximab for maintenance has been thoroughly demonstrated and is clearly superior to that of azathioprine and other conventional drugs (5), like methotrexate or mycophenolate mofetil.

In contrast, when rituximab is the first remission-induction agent, clinicians have several available options. The first is the "wait-and-see" option, which was strategy tested in the RAVE trial (3, 4). Patients who had received rituximab for induction received a placebo for maintenance; they were retreated only when their AAV relapsed (3). That strategy has the advantage of facilitating immune reconstitution and, subsequently, lowering the risk of infectious AEs. It was effective at 18 months but the relapse risk during long-term follow-up cannot be ignored. The second alternative is to systematically prescribe maintenance therapy, even for patients who had initially received rituximab. The MAINRITSAN trial design (5), conceptualised initially for patients whose remissions had been obtained with a combination of corticosteroids and pulse cyclophosphamide, can be applied to patients with rituximab-induced remissions. The MAINRITSAN protocol was effective, with ~5% of rituximab recipients suffering major relapses *versus* 28% of those given azathioprine at 28 months. However, choosing that strategy has a clear impact on the occurrence of infectious AEs. Notably, 1–2% of rituximab recipients developed Pneumocystis jiroveci pneumonia and the fatality rate of rituximab-treated coronavirus disease-2019 (COVID-19) patients was higher (11).

The COVID-19 pandemic has highlighted the risk of increasing AE numbers and severity with new therapeutics that have demonstrated efficacy against AAVs. For this reason, clinicians must

try to determine how to optimise AAV-treatment management, while keeping the advantages provided by new agents together with their better safety profiles. Treatment doses and durations, prophylactic measures, and corticosteroid-sparing are the main points to consider. The rituximab induction dose is codified and 2 dosing schedules are commonly prescribed: 375 mg/m^2 every week for 3 weeks (4 infusions) has been validated by prospective trials (3, 4) or 1 g every 2 weeks, which has been prescribed empirically but has not been confirmed by prospective trial results. Lowering doses for induction during the induction-remission phase – with the objective of minimising toxicities – has not been explored.

Cyclophosphamide for remission induction: the results of several prospective trials showed that it is possible to prescribe lower cyclophosphamide doses by shortening the duration of oral treatment to 3–6 months (usually 3), rather than 12 (12), or to administer 6 pulses within 4 months (13), which is now widely applied in Europe. This regimen remains the gold standard for patients with severe renal insufficiency and the most severe forms of AAV. We suggest maintaining this strategy preferring pulses to oral intake.

Rituximab for maintenance: the dose matters. Our *post-hoc* analysis of MAINRITSAN trial data showed that 4 infusions, spaced 6 months apart, sufficed to prevent relapses, instead of the 5 initially scheduled to achieve that goal (14). For most patients, each 500-mg infusion was sufficient and we do not recommend higher doses. The RITAZAREM trial (15) focused on more severely-ill patients than those enrolled to participate in the MAINRITSAN trial; 1 g of rituximab was administered every 4 months for 24 months. Rituximab recipients did not have more AEs than patients given azathioprine but, in the context of the COVID-19 pandemic, such dose escalation to maintain remission does not seem appropriate to us.

Rituximab on-demand could make a comeback: it was the option implicitly privileged in the RAVE trial (4) and evaluated in the MAINRITSAN2 trial (16), comparing a fixed rituximab-administration schedule to on-demand infusions, based on CD19-positive B-cell status or ANCA titres. The latter's findings showed that similar efficacy to prevent relapses could be achieved with 3, 500-mg infusions versus 5. This strategy has the advantage of limiting immune depression and probably the risk of developing infectious AEs, but its main disadvantage is that relapses are treated not prevented.

Optimal treatment duration is still not known. Conventional drug administration for 12 months or less is associated with enhanced relapse risk (10). Most patients are treated for 18 months to 2 years but some need a more prolonged therapy, perhaps even life-long. Prolonged azathioprine treatment, given in the randomised trial by Karras *et al*. (17), showed its superiority to the withdrawal arm. The MAINRITSAN3 trial results (18) also demonstrated that 2 more years of rituximab were associated with fewer relapses than for the placebo group. Our policy is now to try to identify patients at higher risk of relapse and to treat them for longer times. It is probably one of the best ways to protect most patients against prolonged therapy-induced immunosuppression.

Which patients are at risk of relapse? The long-term follow-up results of the RAVE (4) and MAINRITSAN1 (19) trials partly answered that question. Patients who were anti-proteinase-3-positive at diagnosis relapsed more frequently than those anti-myeloperoxidase-positive. Patients ANCA-negative at diagnosis had a low risk of relapse. Patients ANCA-positive after 12 months of follow-up post-induction relapsed more frequently than patients whose ANCA had disappeared or did not reappear. Patients who relapse once, are obviously at risk of relapsing again. We now need to modellise patients' profiles and more precisely define the subpopulation(s) that require long-term treatment, so as to differentiate them from "non-relapsers" to avoid over-treatment of the latter.

Systematic prophylaxis policy against infections. Pneumocystis jiroveci prophylaxis with co-trimoxazole has been recommended for decades. It should be prescribed not only until the end of immunosuppressant, corticosteroid and/or rituximab administration, but stopped only once immune reconstitution has been documented. Some patients may also need prophylaxis against tuberculosis. Systematic prophylaxis against fungal infection is not recommended and has been validated only for patients who had received a bone-marrow transplant for haematological diseases.

Vaccination is strongly indicated for AAV patients, at least against pneumococcal pneumonia, seasonal flu and, more generally against all potential seasonal infections. Unfortunately, it is often too late to vaccinate once vasculitis has been diagnosed and treatment started, because immunosuppressants may diminish vaccine efficacy or live-virus vaccine inoculation may be contraindicated. At present, 4 doses of anti-COVID-19 vaccine are recommended. However, antibody responses of rituximab-treated patients are usually very low (20), especially against COVID-19 vaccines. For those rituximab-treated patients, anti-COVID prophylaxis comprises systematic monoclonal antibody administration. In Europe, where the Omicron variant is dominant, patients should receive tixagevimab/cilgavimab (Evusheld), a long-acting combination of monoclonal antibodies serving as replacement therapy for the lack of antibody production post-vaccination. The recommendations of the French Vasculitis Study Group to optimally treat vasculitis patients with biotherapies are available (21).

The choice of agents and their potential combinations, prudent selection of prophylactic measures and, when necessary, management of infections contribute to the complexity of therapeutic strategies for AAVs.

References

1. HAUBITZ M, SCHELLONG S, GÖBEL U *et al*.: Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998; 41: 1835-44.
2. GUILLEVIN L, CORDIER JF, LHOTE F *et al*.: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997;

40: 2187-98.
3. STONE JH, MERKEL PA, SPIERA R *et al*.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
4. SPECKS U, MERKEL PA, SEO P *et al*.: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369: 417-27.
5. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab vs azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80
6. WECHSLER ME, AKUTHOTA P, JAYNE DRW*et al*.: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376: 1921-32.
7. JAYNE DRW, MERKEL PA, SCHALL TJ *et al*.: Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384: 599-609.
8. MONREAL E, SAINZ DE LA MAZA S, FERNANDEZ-VELASCO JI *et al*.: The impact of immunosuppression and autoimmune disease on severe outcomes in patients hospitalized with COVID 19. *J Clin Immunol* 2021; 41(2): 315-23.
9. PAGNOUX C, MAHR A, HAMIDOU M *et al*.: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359: 2790-803.
10. DE GROOT K, RASMUSSEN M, BACON PA *et al*.: Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 2461-9.
11. SATTUI S, CONWAY R, PUTMAN MS *et al*.: Outcomes of COVID-19 in patients with primary vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study. *Lancet Rheumatol* 2021; 3(12): e855-64.
12. JAYNE D, RASMUSSEN N, ANDRASSY K *et al*.: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil-associated antibodies. *N Engl J Med* 2003; 349: 36-44.
13. GUILLEVIN L, CORDIER JF, LHOTE F: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. A*rthritis Rheum* 1997; 40: 2187-98.
14. CHARLES P, DECHARTRES A, TERRIER B *et al*.: Reducing the initial number of rituximab maintenance-therapy infusions for ANCA-associated vasculitides: randomized-trial post-hoc analysis. *Rheumatology* 2020; 59: 2970-75.
15. SMITH RM, JONES RB, SPECKS U *et al*.: Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis* 2020; 79: 1243-49.
16. CHARLES P, TERRIER B, PERRODEAU E *et al*.: Comparison of individually tailored versus fixed schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 2018; 77(8): 1143-9.
17. KARRAS A, PAGNOUX C, HAUBITZ M: Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 2017; 76: 1662-8.
18. CHARLES P, PERRODEAU E, SAMSON M *et al*.: Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis. A randomized trial. *Ann Intern Med* 2020; 173(3): 179-87.
19. TERRIER B, PAGNOUX C, PERRODEAU E *et al*.: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 2018; 77: 1150-6.
20. AVOUAC J, DRUMEZ E, HACHULLA E *et al*.: COVID 19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. *Lancet Rheumatol* 2021; 3(6): e419-26.
21. TERRIER B, CHARLES P, AUMAITRE O *et al*.: ANCA-associated vasculitides: Recommendations of the French Vasculitis Study Group on the use of immunosuppressants and biotherapies for remission induction and maintenance *Presse Med* (Q Med Rev) 2020; 49(3): 104031.