

## Rituximab for ANCA-associated vasculitides

L. Guillevin

Service de Médecine Interne, Centre de Référence des Maladies Systémiques et Autoimmunes Rares, Université Paris-Descartes, AP-HP, Hôpital Cochin, Paris France.

Loïc Guillevin, MD

Please address correspondence to:

Loïc Guillevin, MD

Service de Médecine Interne, Centre de Référence des Maladies Systémiques et Autoimmunes Rares, Université Paris-Descartes, AP-HP, Hôpital Cochin, 27 Rue du Fbg. St. Jacques, 75014 Paris, France.

E-mail: loic.guillevin@orange.fr

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### ABSTRACT

*Among new treatments for ANCA-associated vasculitis, rituximab is the most promising. It has already been demonstrated that rituximab is not inferior to cyclophosphamide in inducing remission. This drug is therefore an alternative to cyclophosphamide for induction treatment. In the long term, it has been shown that patients who have received 4 infusions of rituximab to induce remission, not followed by a maintenance treatment, have the same relapse rate as patients who have been treated with azathioprine for maintenance. This high relapse rate supports a maintenance treatment which could also be rituximab. The results obtained with rituximab vs. azathioprine are encouraging and could favour rituximab use, but long-term results are still needed. Rituximab is safe and side effect frequency and severity are comparable to the side effects observed in patients treated with cyclophosphamide for induction, and azathioprine or methotrexate for maintenance. New studies are needed to evaluate the long-term side effects of this biotherapy.*

### 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). Rituximab has been given to increasing numbers of patients, especially after the publication of the two randomised-controlled trials showing that it was as effective as cyclophosphamide (CYC) at inducing AAV remission (2, 3).

We describe herein the experience with rituximab in two situations: first, in prospective trials for flaring patients, and, second, as a maintenance treatment. The benefit/risk ratio of rituximab in

vasculitis therapeutic strategy is also reported and discussed.

### Studies in flaring patients

Since 2001, numerous uncontrolled observations reporting the efficacy of the chimeric monoclonal anti-CD20 antibody, rituximab (RTX), against MPA, GPA and EGPA have sparked enthusiasm and hope that targeted B-cell therapy might cure ANCA-associated vasculitides. First, reports on small numbers of patients focused on the efficacy of rituximab in inducing remission of relapsing or refractory AAV. In a study on 8 patients followed for 6 months (4), 3 achieved complete remission, 3 partial remission and 2 were non-responders. As rituximab use expanded, a large, multicentre, retrospective study was conducted on 80 patients in France (5). The results of that study showed that the modalities of rituximab prescription and use were highly heterogeneous: 4 different infusion protocols when rituximab was given for remission induction and more than 5 schedules for maintenance therapy, alone or combined with other immunosuppressants.

The first randomised-controlled trial included 17 patients and was conducted between 2004 and 2007 (6). It compared rituximab to infliximab for remission induction of refractory granulomatosis with polyangiitis (Wegener) (GPA). The rituximab protocol was 1 infusion (375 mg/m<sup>2</sup>) every week for 4 weeks, followed, when clinical improvement was observed at month 2, by an infusion of 375 mg/m<sup>2</sup> 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 8 patients receiving rituximab, 4 were in complete remission, 1

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in partial remission, 1 had died and 2 were therapeutic failures. Among the 9 patients on infliximab, 2 were in complete remission, 1 in partial remission, 1 had died and 5 were non-responders. The results of this trial indicated the potential contribution of this biologic in the treatment for refractory AAV.

In 2010, two randomised clinical trials, RTX in ANCA-associated vasculitis (RAVE) (2) and RTX *versus* CYC for ANCA-associated vasculitis (RITUXVAS) (3), provided the first controlled evidence that, at 6 or 12 months of follow-up, respectively, RTX was not inferior and as safe as conventional immunosuppressive therapy (CYC) to control active MPA and GPA. In a subgroup analysis of RAVE data, RTX proved to be even more effective at inducing disease remission for those patients enrolled at the time of a relapse (2). Tolerance of rituximab or cyclophosphamide was comparable (14% severe adverse events in both groups). The RITUXVAS study reached the same conclusions (3). However, one cyclophosphamide pulse was combined with rituximab to induce remission and side effects were observed more frequently (36% of the rituximab group) than in the RAVE study (2).

#### Rituximab for maintenance treatment

Few data are available on the interest of rituximab as a maintenance treatment. The French retrospective study results (5) were consistent with other retrospective series (7-10): 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% (5). Rituximab tended to be a superior maintenance therapy: 9/45 (20%) patients relapsed *versus* 7/14 (50%) ( $p=0.13$ ) prescribed other therapies. Another study evaluated rituximab as maintenance therapy (11). Among the 28 patients who received a median of 4 rituximab infusions, only 2 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, 2 severe allergic manifestations (asthma) after rituximab infusions have been described (12).

The FSVG's main research axis is using rituximab as AAV maintenance therapy. The MAINRITSAN study (NCT00748644) was completed in October 2012 (13). That open-label randomised-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 (5 infusions)). At 28 months, rituximab efficacy looked promising. 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, the use of less rituximab obviously lowered the cost of treatment and because usual doses (*e.g.* 1 g or 375 mg/m<sup>2</sup>) had been determined empirically.

An ongoing randomised trial (MAINRITSAN 2: NCT01731561) is comparing 2 rituximab-administration strategies for maintenance therapy (5). 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  $>0/\text{mm}^3$  or the ANCA titer becomes positive or rises.

The 18-month results of the RAVE study were recently published and showed that the same number of relapses occurred when patients have been treated for induction of remission with 4 weekly infusions of rituximab or when they received azathioprine for maintenance (14). In our view, the results obtained 18 months after starting the RAVE study did not show that induction treatment with rituximab, not followed by a maintenance therapy was able to maintain remission. In our view, this study favours the need for a maintenance treatment. This study showed also that the relapse rate is different according to clinical and immunological

parameters. Patients with GPA, who are anti-PR3 positive, relapse more than those with anti-MPO MPA. The large variations regarding the relapse rate observed in ANCA-associated vasculitides could contribute to choosing different durations for maintenance treatment according to the risk of relapses.

#### Safety issues

Results of the RAVE and RITUXVAS studies showed a comparable number of infections in patients who received cyclophosphamide and rituximab. As for cyclophosphamide, 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, 9). In our 80-patient study, 12 (15%) severe infectious complications were reported and led to 4 (5%) deaths. Some patients present also neutropenia which can persist for several weeks. Other complications have been rarely reported, *e.g.* macular oedema (15).

#### Recommendations of the French Vasculitis Study Group

Recommendations for RTX use to treat ANCA-associated vasculitides were elaborated by some authors (16). First, RTX was proposed as an alternative to CYC remission-induction therapy for previously untreated ANCA-associated vasculitides. Moreover, the authors considered that, in this context, RTX should be preferred when it would be advisable to avoid CYC because of its high gonadal toxicity and carcinogenicity, or an ongoing infection. Second, RTX was considered effective therapy against refractory/relapsing ANCA-associated vasculitides.

Several questions must be answered before substituting rituximab for cyclophosphamide. Notably, rituximab efficacy needs to be evaluated in the most severely ill patients requiring intensive care for renal failure and/or alveolar haemorrhage and elderly patients, and its activity against orbital tumours and tracheal stenoses (17).

The FVSG has recently published recommendations on rituximab in AAV. They are summarised below (18):

1. For first-line treatment, rituximab may be prescribed for the same indications as cyclophosphamide to induce remission of certain GPA and MPA forms. It should preferentially be prescribed to women of child-bearing age, especially when they are over 30 years old (Committee consensus).
2. Considering treatment for GPA or MPA relapse, rituximab should preferentially be chosen for patients who have received at least one full cyclophosphamide cycle (either 6–9 infusions or a cumulative dose >10 g), as the recommended in the French National Guidelines endorsed by the Haute Autorité de Santé (HAS) (19). Our group now recommends replacing cyclophosphamide with intravenous rituximab and prescribing oral cyclophosphamide as third-line therapy, *i.e.* after total or partial rituximab failure.
3. Rituximab is not recommended for patients with low disease activity or non-systemic disease, which can be treated without cytotoxic drugs.
4. The FVSG recommends choosing rituximab and not cyclophosphamide to treat a relapse of GPA or MPA previously treated with conventional immunosuppressant(s) (level 2).
5. The FVSG considers that rituximab should be preferred for women of childbearing age, especially when they are >30 years old. In the absence of data on a potentially prolonged rituximab impact on the descendents and in accordance with marketing authorisation recommendations, contraception is recommended during the year following rituximab administration.
6. Regardless of the regimen chosen to treat AAV, the risk of infection is higher among those over 65 years receiving high-dose corticosteroids and conventional immunosuppressant(s) (20, 21). Hence, today, preferentially prescribing rituximab for elderly patients is not justified.
7. Despite conflicting data (9, 22), some GPA forms seem to respond incompletely to rituximab (level 4):
  8. The benefit/risk ratio of an immunosuppressant-and-rituximab combination prescribed at lower doses has not been evaluated, particularly with immunosuppressant(s) usually prescribed for vasculitis, like methotrexate or azathioprine. The Committee does not exclude the option of combining rituximab and conventional immunosuppressant(s) for patients not responding (or responding incompletely) to immunosuppressant(s) or rituximab alone. However, it is not recommended to combine rituximab and cyclophosphamide at full doses in fragile patients with AAV.
  9. Rituximab induces a decrease of serum gammaglobulins, especially IgM. Over the long term, prolonged low immunoglobulin levels might increase the infectious risk. The FVSG does not recommend routine prescription of immunoglobulins at a replacement dose. The recommendations established to treat secondary immunodeficiencies, *e.g.* multiple myeloma (23), chronic lymphoid malignancies or others, should be followed.
  10. In light of our present knowledge, rituximab maintenance therapy can apparently be prescribed (level 4). The preliminary results of the MAINRITSAN trial, comparing azathioprine to rituximab for maintenance, indicate fewer relapses in the rituximab arm (13). The optimal duration of AAV treatment has not yet been established. The total treatment duration is 18 months to 2 years, by analogy with the results of clinical trials evaluating immunosuppressant(s) but some authors recommend prescribing more prolonged treatment in order to prevent relapses (24).
  11. Monitoring gammaglobulin levels might identify a population at increased risk of infection. The value of renewed or persistent positivity of ANCA or CD19<sup>+</sup> B lymphocytes to predict relapse remains controversial (25, 26). At present, these parameters are not taken into account when making therapeutic decisions for AAV patients. An ongoing clinical trial is assessing the contribution of adapting treatment(s) to ANCA and CD19 expression ([www.vascularites.org](http://www.vascularites.org)).
  12. Several cases of *Pneumocystis jiroveci* pneumonia (PJP) have been reported during rituximab treatment (8-10). Prophylactic cotrimoxazole (400 mg/80 mg) is recommended for all patients. A first case of progressive multifocal leukoencephalopathy has been reported in a rituximab-treated patient (unpublished), who also had other causes of immunosuppression. Treatment recommendations have been proposed for HBV-infected patients taking immunosuppressants (27). For patients with circulating HBs antigens or a positive virus load (>2000 copies/mL), we recommend preemptive tenofovir or entecavir, beginning on the first day of rituximab infusion. For anti-HBc-positive/HBsAg-negative patients (regardless of their anti-HBs status) with a negative virus load, preemptive antiviral therapy is not required but monitoring of transaminases and virus load is mandatory every 1–3 months. If such monitoring cannot be assured, pre-emptive treatment is recommended. It has not been demonstrated that rituximab aggravates HCV infection, *i.e.* induces virus replication or new manifestations of infection attributable to such enhanced replication. Rituximab has been used to treat cryoglobulinaemia associated with HCV infection, without detrimentally affecting liver function.
  13. The ability of rituximab-treated patients to produce protective antibodies is poor (28, 29). Therefore, patients who will receive rituximab should, when possible, be vaccinated before starting treatment. It is recommended that immunisations be updated as soon as possible, and preferably 3 weeks before the first

rituximab infusion, if possible. Live vaccines are contraindicated for patients treated with rituximab alone or in combination with corticosteroids and/or conventional immunosuppressants.

### 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 found to be superior at inducing AAV remission, 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. Because of infectious concerns, we think that rituximab future use means lower doses to a large AAV population.

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