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Moderator’s view: Should all patients with ANCA-associated vasculitis be primarily treated with rituximab?

Vladimir Tesar

Department of Nephrology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

Correspondence and offprint requests to: Vladimir Tesar; E-mail: vladimir.tesar@vfn.cz

ABSTRACT

Experience with rituximab in patients with new ANCA-associated vasculitis (AAV) is still very limited, especially in patients with severe (organ- or life-threatening) AAV. Rituximab may be more effective in anti-PR3 AAV, but potentially less effective in some granulomatous manifestations of AAV. We do not know what the response is to rituximab on the tissue level. Rituximab induction needs to be followed by maintenance treatment, and potentially very long rituximab maintenance may result in higher risk of rituximab-related complications (e.g. decrease in IgG levels). Long-term experience with rituximab in AAV is insufficient. Treatment with rituximab is more expensive than the standard treatment with cyclophosphamide and corticosteroids and seems to be cost-effective only in patients primarily treated with cyclophosphamide. Rituximab can be used in some newly diagnosed patients with AAV (e.g. women with child-bearing potential, or patients with active vasculitis and severe infection), but with the available information, it may be too early to use it as a first-line treatment in all new AAV patients.

Until the end of the last century all patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were treated with conventional standard immunosuppression (cyclophosphamide with gradually tapered corticosteroids as an induction and azathioprine with low-dose corticosteroids as a maintenance treatment) with remission rates frequently exceeding 90% [1], but still with high relapse rate (50% within 5 years), relatively high long-term mortality (5-year mortality of 22% in patients recruited to European randomized controlled trials [2]) and high short-term mortality especially in patients with severe renal (1-year mortality 25% [3]) and lung involvement, at least partly related to the toxicity of the treatment.

Major attention was thus paid to minimizing or completely avoiding the exposure to cyclophosphamide and corticosteroids and at the same time keeping the high efficacy of this treatment. Unfortunately, lower cumulative dose of cyclophosphamide and corticosteroids during the first 6 months of treatment seemed to be always associated with higher risk of relapses during the long-term follow-up, especially in patients with anti-PR3 antibodies [1, 4], some of these relapses being organ- or even life-threatening, or at least further increasing the accumulated organ damage.

On one hand, the long-term outcome of the patients with AAV has definitely improved [5–7], but, on the other hand, the risk of increasing lifelong exposure to both corticosteroids and cytotoxic drugs due to still high relapse rate despite maintenance treatment, especially in anti-PR3-positive patients, has remained a difficult therapeutic challenge.

The only way to completely escape from this vicious cycle of early (putative) undertreatment resulting in (repeated) relapses with finally similarly high cumulative doses of both cyclophosphamide and corticosteroids was to find some new potentially more specific and less toxic mode of treatment. Very positive experience with rituximab in a small series of patients with mostly refractory or relapsing ANCA-associated vasculitis [8]
was confirmed by the results of two randomized controlled trials [9, 10] which demonstrated that rituximab is similarly effective as cyclophosphamide in patients with new AAV and better than cyclophosphamide in patients with relapsing AAV and that it can be used (with only two cyclophosphamide pulses) also in patients with severe renal vasculitis. Rituximab was well tolerated, but the short-term (6 months) adverse event rate in patients treated with rituximab was not lower compared with patients treated with cyclophosphamide. Importantly, even rituximab has been unable to cure AAV, and the patients treated with rituximab induction still require either conventional (most often azathioprine) or rituximab maintenance treatment to prevent relapses of the disease [11]. Recently, rituximab was also shown to be more effective than azathioprine in preventing relapses of AAV [12].

Introduction of rituximab definitely changed the paradigm of induction and maintenance treatment of AAV. With the availability of more effective treatment of relapses, it is no longer appropriate to treat relapses repeatedly with cyclophosphamide, and rituximab became a plausible alternative of azathioprine in the maintenance treatment [12]. Use of rituximab as a first-line induction treatment in newly diagnosed AAV remains, however, more controversial as illustrated in the Polar Views papers by Dr Specks and Drs Kronbichler and Jayne.

First of all, as nicely demonstrated by Kronbichler and Jayne, the experience with rituximab in patients with new ANCA-associated vasculitis is still very limited. With the exception of the RAVE trial, only very small series of patients with newly diagnosed AAV were treated with rituximab. As there is now no randomized controlled trial recruiting patients with newly diagnosed AAV to rituximab treatment, we desperately need the observational real life data possibly from AAV registries [13].

Second, patients treated initially with rituximab induction will also need a maintenance treatment, and we currently have a positive experience with rituximab maintenance after cyclophosphamide induction [12], but until the data from the RITAZAREM study (https://clinicaltrials.gov/ct2/show/NCT01697267) are available, our experience with rituximab maintenance after rituximab induction will also remain very limited. Should it mean that we should start in new patients with rituximab induction and then switch most of them to azathioprine (possibly less effective) maintenance, or based on opinion (and belief) treat the patients with rituximab induction also with rituximab maintenance? As even the patients who were treated for 2 years with rituximab maintenance may relapse after rituximab withdrawal (although the relapse rate after rituximab maintenance seems to be much lower than after rituximab induction only [14]) we will now be more and more often confronted with a difficult decision of very prolonged (many years) treatment with rituximab with somewhat unpredictable and potentially higher risks of some of rituximab-related complications (e.g. decrease of IgG levels [15]).

Third, we have almost no data on rituximab (without cyclophosphamide) in severe (organ- or life-threatening) AAV and it is very difficult to know what the real contribution was (if any) of cyclophosphamide in rituximab-treated patients with severe renal vasculitis in RITUXVAS [9]. Recent analysis of patients with renal involvement from RAVE suggests that rituximab is similarly effective as cyclophosphamide also in patients with renal vasculitis, but in RAVE there were no patients with severe renal involvement [16].

Fourth, we are still uncertain if rituximab is similarly effective in vasculitic and granulomatous manifestations of AAV. Some studies suggest that especially some manifestations, e.g. tracheal stenoses or orbital disease may have a much poorer response than pulmonary or renal disease [17]. On the other hand, these manifestations are not so frequent initial presentations of AAV, they are usually also refractory to the conventional treatment and rituximab often represents for these patients the only feasible alternative.

Fifth, post hoc analyses from the RAVE trial suggest that rituximab may be more effective than cyclophosphamide in patients with anti-PR3 AAV [11] further underlining the ever more shared view that anti-PR3 and anti-MPO AAV are different diseases with a different pathogenesis, clinical presentation and outcome and should be treated in a different way. As anti-PR3 patients are much more prone to relapses compared with anti-MPO patients the subsequent maintenance treatment and its length remain a very important issue.

Sixth, we have no clinical data on the response to rituximab in AAV on the tissue level. In an analysis of renal biopsies from the RITUXVAS trial, not infiltration of the kidney with CD20-positive B cells which could be (temporarily?) depleted with rituximab, but rather CD3-positive tubulitis (so the presence of T cells) was a negative predictor of renal outcome [18]. In our protocol, renal biopsies, infiltration of the kidney with CD20 cells almost diminished after cyclophosphamide treatment, but CD3 infiltration persisted even in patients in clinical remission [19]. Rituximab may not be able to have a significant impact on the presence of CD3 in the kidney with uncertain impact on the long-term renal outcome of rituximab-treated patients.

Seventh, there is insufficient long-term experience with rituximab. Although one would expect that using rituximab might help in avoiding the long-term complications of corticosteroids (e.g. cataracts, osteoporosis, obesity, diabetes, cardiovascular complications, etc.) and cyclophosphamide (namely myelodysplasia and secondary malignancies) we must be aware that our expectations may not necessarily be fulfilled [20] and great attention is to be paid to the evaluation of the real risk of cancer. We must also keep in mind the rare, but potentially life-threatening complications of rituximab, including serum sickness, thromboses, pulmonary fibrosis or progressive multifocal leukoencephalopathy (PML) which may, however, also occur after conventional treatment with cyclophosphamide [21].

Eighth, treatment with rituximab is more expensive than the standard treatment with cyclophosphamide and corticosteroids and can hardly be used as a first-line treatment in countries with low gross domestic product, and cost-effectiveness of the treatment will always be discussed even in richer countries. In a recent NICE analysis [22] cited by Kronbichler and Jayne, rituximab may be cost-effective only in patients primarily treated with cyclophosphamide.

On the other hand, as rituximab is really comparably effective as cyclophosphamide, it can be used as a first-line treatment more and more often at least in selected groups of AAV patients, e.g. young women with child bearing potential, patients at higher risk of infection or with infection in the setting of active
vasculitis or in patients with myelodysplasia. In my opinion, we need more data to be sure that rituximab is really a first-line treatment for patients with anti-PR3 AAV. Anyway, rituximab gives us another option to the until recently unavoidable cyclophosphamide and further underlines that it is reasonable to consult each new patient with AAV in a clinical centre with the experience with AAV and its treatment, so that the treatment of our patients could be optimized.

Nice overviews of Drs Specks and Kronbichler and Jayne give to the reader a good insight in to this quickly moving area. In my opinion, rituximab can be used in some newly diagnosed patients with AAV, but with the available information it is too early to use it as a first-line treatment in all new AAV patients. Undoubtedly, within several years we will have much more data to base our choice of primary treatment of newly diagnosed AAV more on evidence than mostly on opinion.

**CONFLICT OF INTEREST STATEMENT**

I obtained lecture fees from Roche, Medonet, Baxter, Fresenius Medical Care, B. Braun and Amgen and consultancy fees from Abbvie, Chemocentryx and Boehringer Ingelheim. I have been the member of the Advisory Board of Abbvie, Amgen, Fresenius Medical Care and Baxter.


**REFERENCES**


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