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# Pro: Should all patients with anti-neutrophil cytoplasmic antibody-associated vasculitis be primarily treated with rituximab?

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## ABSTRACT

Randomized controlled trials have shown that rituximab is non-inferior to cyclophosphamide followed by azathioprine (CYC/AZA) for remission induction in severe granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The efficacy of rituximab is on par with CYC/AZA for 18 months, for patients with GPA and MPA alike, and for patients with any degree of renal impairment. The Rituximab in ANCA-associated Vasculitis (RAVE) trial also showed superiority of rituximab for patients presenting with a severe disease relapse. An exploratory analysis of the RAVE data further suggests that rituximab may be preferable for PR3-ANCA-positive patients as superiority was also achieved in that subset. When considering treatment options for patients with disease presentations for which only non-inferiority has been documented, safety concerns, compliance issues, the overall cost of each treatment approach to the patient, to society and to insurers, as well as individual patient preferences all should affect the decision-making process. The trials failed to uncover any difference in adverse events between rituximab and CYC/AZA. However, daily oral cyclophosphamide given for 3–6 months has measurable negative effects on fertility. Rituximab has certain compliance and convenience advantages. When assessing cost, the overall cost of a treatment, the societal context of the individual patient and not merely the sticker price of the drug should be considered. For all of these reasons, the author believes that CYC/AZA should be reserved for patients with newly diagnosed, MPO-ANCA-positive disease who raise no fertility, compliance or malignancy concerns.

**Keywords:** ANCA, cyclophosphamide, rituximab, trial results, vasculitis

Those of us who received their medical education in the era of multiple choice testing know all too well that answers containing the words 'all', 'always' or 'never' are always wrong. With that in mind, let's take a more nuanced approach to the argument, integrating the current evidence derived from published results of randomized controlled trials with what we currently know about the spectrum of pathology afflicting individual patients united under the umbrella diagnosis of 'anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis' (AAV). For the purpose of this debate, 'primary therapy' is interpreted to mean 'the agent of choice for remission induction'. This debate focuses on the choice between rituximab and cyclophosphamide as primary remission induction agent for patients with severe, life- or organ-threatening granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). For information about the use of rituximab for refractory, non-severe or ANCA-negative GPA or MPA, as well as for maintenance of remission in GPA and MPA, or about the emerging role of rituximab in eosinophilic granulomatosis with polyangiitis (EGPA) the reader is referred elsewhere [1, 2].

Rituximab was first used in a patient with chronically relapsing PR3-ANCA-positive GPA when the patient suffered a systemic disease relapse that also affected the kidneys. This patient had previously experienced significant cyclophosphamide toxicity precluding further use of this agent [3]. The rationale for choosing rituximab was based on several assumptions. First, activated peripheral blood B-cells seemed to correlate with disease activity of GPA better than differences in markers of T-cell activation [4]. Second, since the 1980s the efficacy of cyclophosphamide for GPA had been attributed to its effect on B-cells [5, 6]. Consequently, an agent that targets B-cells more specifically and more effectively than cyclophosphamide appeared attractive. Third, there was emerging evidence at the time that rituximab could abolish autoantibody production and benefit patients with antibody-mediated autoimmune disease [7, 8]. Hence, this agent appeared attractive to anybody who believed that ANCA play an important pathogenic role in the development of small vessel vasculitis [9].

Other patients with refractory disease were subsequently treated on a compassionate basis and in a formal prospective

pilot trial with the rituximab dosing regimen of 375 mg/m$^2$ once a week times four, without the concomitant use of other immunosuppressive agents [3, 10–12]. All of these patients achieved stable complete remission with complete discontinuation of glucocorticoids. These preliminary data suggested that complete eradication of B-cells with this agent might restore tolerance to the ANCA autoantigens and thereby fundamentally alter the relapsing nature of the disease. Therefore, these results formed the basis for the design of randomized controlled trials [11, 12]. A decade and a half later, after completion of the trials, multiple single-center cohort studies, and several thousands of patients with AAV having been treated with this agent worldwide, it has become apparent that rituximab is very effective at controlling disease activity, in many instances superior to cyclophosphamide, and very well tolerated over time [13–19]. Yet, it has become quite clear that rituximab does not cure AAV, and that its effects on the immune system are broader than what is reflected by peripheral blood B-cell counts alone. This needs to be considered when discussing safety issues and the potential for adverse events with patients.

For which patient with AAV should rituximab be the primary therapy? The clearest answers to this question are provided for remission induction in patients with severe, generalized, life- or organ-threatening GPA and MPA by results from two randomized controlled trials [13, 14]. The results of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial conducted in 197 patients with severe newly diagnosed or relapsed GPA or MPA led to the approval of rituximab for remission induction in GPA and MPA by the Food and Drug Administration and many other international regulatory agencies [13, 18, 20]. The RAVE trial results are complemented by those of the Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) trial conducted in 44 newly diagnosed ANCA positive patients with biopsy-proven active renal disease [14].

The RAVE trial has shown that rituximab is non-inferior to cyclophosphamide for remission induction in patients with severe GPA and MPA [13]. In addition, rituximab was found superior to cyclophosphamide in patients who presented with a severe disease relapse at baseline ($n = 101$) [13]. The effects of one course of rituximab consisting of four weekly infusions at a dose of 375 mg/m$^2$ were as enduring as 18 months of conventional therapy consisting of daily oral cytotoxic therapy with cyclophosphamide for 3–6 months followed by azathioprine out to month 18 [18].

The RAVE trial also bore out that there was no difference in efficacy among patients with major renal involvement at baseline ($n = 102$) [20]. The remission rates, relapse rates and average improvement of estimated glomerular filtration rate (eGFR) achieved with one course of rituximab were equivalent to cyclophosphamide followed by azathioprine at 6, 12 and 18 months, even though the eGFR at baseline was significantly lower among the patients randomized to rituximab compared with cyclophosphamide/azathioprine (41 versus 50 mL/min per 1.73 m$^2$, P = 0.05) [20]. There was no difference in these outcomes between patients with PR3-ANCA versus those with MPO-ANCA, patients with a diagnosis of GPA versus MPA and patients with a new diagnosis versus a severe disease relapse at baseline [20]. Similarly, the treatment responses and renal outcomes were equivalent in the subsets of patients with eGFR >60 mL/min per 1.73 m$^2$ ($n = 26$), eGFR of 30–60 mL/min per 1.73 m$^2$ ($n = 44$) or those with eGFR <30 mL/min per 1.73 m$^2$ ($n = 32$) [20]. These data indicate that in combination with glucocorticoids rituximab is as effective as daily oral cyclophosphamide followed by azathioprine for induction and maintenance of remission as well as preservation of renal function in patients with major renal disease activity at baseline.

The RITUXVAS trial featured major design differences compared with the RAVE trial [14]. Forty-four patients were randomized 3:1 to open label treatment with glucocorticoids in combination with one course of four weekly infusions of rituximab at a dose of 375 mg/m$^2$ compared with the standard EUVAS intravenous bolus treatment with cyclophosphamide at a dose of 15 mg/kg for 3–6 months followed by oral azathioprine out to month 18 [14]. It is of note that about a quarter of the patients had received plasma exchange prior to randomization, and the patients in the rituximab arm also received two intravenous boluses of cyclophosphamide at a dose of 15 mg/kg with the first and third rituximab infusions [14]. In contrast to the RAVE trial where prednisone was discontinued per protocol, patients in the RITUXVAS trial were maintained on low-dose prednisolone throughout the trial [13, 14, 18]. Whereas the primary outcome of the RAVE trial was the rate of complete remission (defined as BVAS/WG = 0 and prednisone dose of 0 mg) at 6 months, the primary outcomes of the RITUXVAS trial were sustained remission (defined as a BVAS of 0 for at least 6 months regardless of prednisone dose) and the rates of severe adverse events [13, 14].

Despite these design differences, the RITUXVAS trial provides valuable complementary information to the RAVE trial results. No differences in any of the efficacy or safety outcome measures were found between the treatment groups in the RITUXVAS trial which comprised a substantially sicker patient population than the RAVE trial [14]. The RITUXVAS subjects were older (median of 68 years, IQR 56–76) versus the RAVE subjects (median of 52, range 15–92), and they all had more severe renal disease at baseline with a median eGFR of 12 mL/min per 1.73 m$^2$ (IQR 9–33) in the control group and 20 mL/min per 1.73 m$^2$ (IQR 5–44) in the rituximab group [13, 14, 20]. One (9%) patient in the control group and eight (24%) in the rituximab group required hemodialysis at baseline [14]. The nature of this more severely ill patient population may explain the higher mortality observed in RITUXVAS (18% in each treatment group in the first 12 months) versus RAVE (2% in each treatment arm by common close out date) [14, 18].

Taken together, the RAVE and RITUXVAS trial results indicate that rituximab and cyclophosphamide are equivalent for remission induction in patients with major renal disease, even if the baseline eGFR is <30 mL/min per 1.73 m$^2$ [14, 20].

Fifty-one subjects enrolled in the RAVE trial (26%) had documented alveolar hemorrhage at baseline, even though patients who required mechanical ventilation due to hemorrhage related respiratory failure were excluded from enrollment [13]. There was no difference in primary outcome between the two treatment arms in this disease subset [13].

An important exploratory analysis looking at the patient demographics, organ manifestations and treatment responses by ANCA-type (PR3-ANCA versus MPO-ANCA) showed that rituximab was also superior to cyclophosphamide among the PR3-ANCA-positive patients in the RAVE trial ($n = 131$), and non-inferior among the MPO-ANCA-positive patients ($n = 66$) [21]. This is not a surprise as PR3-ANCA positivity and relapse risk are closely related, and PR3-ANCA-positive patients were enriched among the patients who enrolled into the RAVE trial with a severe disease relapse [13, 18].

In aggregate, the efficacy data from the RAVE and RITUXVAS trials justify the use of rituximab for remission induction in any patient with severe GPA and MPA, and for a severe disease relapse rituximab is clearly the preferred agent because of proven superior efficacy, regardless of ANCA-type and diagnosis.

In my opinion, there is also a case to be made to treat all PR3-ANCA-positive patients with severe disease with rituximab as primary remission induction therapy based on available data. Several signals of biological efficacy from the RAVE trial favor the use of rituximab in PR3-ANCA-positive patients over cyclophosphamide. First, when making a choice between rituximab versus cyclophosphamide as primary treatment for a PR3-ANCA-positive patient the exploratory analysis from the RAVE trial showing superiority of rituximab over cyclophosphamide for the PR3-ANCA-positive subset of patients is hard to ignore even though the analysis by ANCA-type was not a pre-specified one [21]. Second, among PR3-ANCA-positive patients at baseline a significantly higher ANCA negativity rate was achieved at 6 months compared with the cyclophosphamide group (50 versus 17%, $P < 0.001$), a phenomenon not observed among MPO-ANCA-positive patients (40 versus 41%, $P = 0.95$) [13]. Several studies have shown that patients with PR3-ANCA are genetically different from patients with MPO-ANCA, have different disease phenotype and are at much higher risk of relapse than patients with MPO-ANCA [18, 22–25]. Moreover, standard remission maintenance therapy is fraught with a significant break-through relapse rate among newly diagnosed PR3-ANCA-positive patients [18, 19, 26, 27]. So, why should we expose newly diagnosed PR3-ANCA-positive patients to cytotoxic therapy that is associated with the need for much more involved laboratory monitoring with all its associated inconvenience and cost, when there is evidence that rituximab may have a more profound biological effect and possibly superior efficacy in all PR3-ANCA-positive patients taken together?

For newly diagnosed patients and for MPO-ANCA-positive patients for which all available data suggest that rituximab is of non-inferior or equivalent efficacy for remission induction compared with cyclophosphamide, the choice of agent comes down to considerations of safety, compliance, cost and patient-specific preferences.

Neither the RAVE trial nor the RITUXVAS trial has documented any difference in adverse events between treatment arms [14, 18]. However, in these trials the overwhelming majority of serious adverse events could not be clearly attributed to either rituximab or cyclophosphamide, but were rather attributable to the underlying disease or immunosuppressive therapy in aggregate. In that context, the currently inevitable use of high-dose glucocorticoids as part of any remission induction regimen may overshadow any subtle differences that might exist between rituximab and the short-term use of cyclophosphamide. Regarding the safety of rituximab, what we have seen in the RAVE trial is what we get in practice [18]. In contrast, the safety of cyclophosphamide is highly dependent on rigorous monitoring and the experience of the provider managing the patient with this drug. We need to consider that cyclophosphamide use may be safer in the context of a clinical trial than in routine clinical practice because of strict protocol proscribed laboratory monitoring of blood counts and resulting appropriate dose adjustments; this is not a concern with rituximab use. While the most dreaded cyclophosphamide-associated malignancy risk is dose dependent, and therefore may be low in association with a single 3–6 months course [28], the risk of losing fertility is measurable and significant [29, 30]. Consequently, rituximab is the preferred agent for young patients, both male and female, who do not want to sacrifice their fertility during the first course of remission induction therapy of newly diagnosed AAV.

Compliance is another major concern in the management of patients with AAV. Daily oral cyclophosphamide can only be applied effectively and safely if the patient can be trusted to take the medication as prescribed and follow instructions for bladder protection and regular laboratory monitoring. In patients for whom compliance cannot be guaranteed, directly observed therapy may be the only way to ensure efficacy and safety. Therefore, for patients with questionable compliance, rituximab is clearly the preferred agent. All necessary treatments can be applied over a 3-week period, and the effect is as lasting as 18 months of conventional therapy [18]. Before rituximab was available, the only alternative to daily oral cyclophosphamide for non-compliant patients was intravenous bolus therapy. Even though the intravenous bolus application of cyclophosphamide following the EUVAS regimen of 15 mg/kg every 2 weeks times three, followed by every 3 weeks to 6 months, has been shown to be non-inferior to daily oral cyclophosphamide for remission induction in a randomized controlled trial, the long-term follow up data from this trial have indicated a higher relapse rate in the bolus treatment group compared with the daily oral application [31, 32]. Moreover, a 3–6-month course of intravenous bolus treatment with cyclophosphamide with its requirements for anti-emetics and MESNA application for bladder protection is more expensive than a course of rituximab in almost all reimbursement systems in the USA.

This brings us to the argument of cost. When two available treatments are equivalent in efficacy and safety, preference should certainly be given to the cheaper alternative. However, one could argue that the primary economic considerations for the physician as patient advocate should be the overall aggregate cost of a specific treatment to the patient, followed by the economic cost to society, rather than the simple cost of the drug, which is usually the primary short-term, and one might argue short-sighted, concern of the insurer. No trial comparing rituximab to cyclophosphamide followed by azathioprine was designed to address the question of overall cost-effectiveness of the compared treatments. As alluded to

in the previous paragraph, cost-effectiveness of any given treatment needs to be considered in the context of the reimbursement system in which the treatment is applied. When doing so, the intravenous bolus application of cyclophosphamide is often not a financially sound alternative to rituximab treatment. The cost of regular laboratory monitoring billed to the insurer and the cost of work absenteeism to the patient and employer should be factored in when considering the use of daily oral cyclophosphamide followed by azathioprine over the course of 18 months.

The last, not least, consideration when choosing between rituximab versus cyclophosphamide followed by azathioprine is patient preference. Admittedly, there are no published scientific data to help us with this aspect. Beyond the inconvenience of regular laboratory testing required with cyclophosphamide and azathioprine use, more subtle, non-severe and often neither recorded nor acknowledged adverse events and inconveniences may weigh heavily on patients' overall sense of well-being while exposed to a certain treatment. Many patients' lives are negatively affected by the constant need to drink fluids to prevent bladder toxicity, the transient diffuse alopecia or the frequent loss of appetite and metallic taste associated with cyclophosphamide use. Patients who have experience with both cyclophosphamide and rituximab are usually quite vocal about such issues and would vote hands-down in favor of rituximab because of these issues alone.

For all of these reasons, ranging from solid data over soft data to patient-specific considerations, rituximab has taken over the place of cyclophosphamide in the management of GPA and MPA in my practice. Cyclophosphamide is only considered in compliant, newly diagnosed, MPO-ANCA positive patients, without cancer history, who have already outlived any fertility concerns, as well as for the rare patient who does not have an adequate prompt response to rituximab.



## CONFLICT OF INTEREST STATEMENT

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(See related article by Kronbichler and Jayne. Con: Should all patients with anti-neutrophil cytoplasmic antibody-associated vasculitis be primarily treated with rituximab? *Nephrol Dial Transplant* 2015; 30: 1075–1081; See related article by Tesar. Moderator's view: Should all patients with ANCA-associated vasculitis be primarily treated with rituximab? *Nephrol Dial Transplant* 2015; 30: 1088–1090.)

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# Opponent's comments

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We agree with Dr Specks that rituximab increases our therapeutic armamentarium in the treatment of patients with ANCA-associated vasculitis, especially those with a relapsing and refractory disease course. In contrast, we believe that a general recommendation to initiate rituximab as 'first-line treatment' is not supported by the randomized controlled trials leading to approval.

Follow-up data of the Rituximab in ANCA-associated Vasculitis (RAVE) study did not show superiority of rituximab compared with the control group. Of importance, the authors of the RAVE trial did not provide concise data on patients with newly diagnosed ANCA-associated vasculitis after 18 months of follow-up. Overall, the primary end point was met by 39% in the rituximab and 33% in the control group. Patients included with a relapsing disease course achieved the primary end point in 37 and 20%, respectively. This may indicate that newly diagnosed patients in fact had a numerically better outcome after 18 months in the control group compared with the rituximab treated patients. This would be in line with the observation after 6 months when 63% in the control group achieved the primary end point compared with 61% in the rituximab group [1, 2].

Our aim in the 'con' debate was to focus on 'primary treatment' of rituximab and most post hoc analyses of the RAVE trial included both newly diagnosed and relapsing patients. Since a majority of patients with a relapsing disease course in the RAVE trial received cyclophosphamide prior to relapse (82% in the rituximab and 74% in the control group) which indicate a failure of this agent to achieve long-term remission, validity of these reports is questionable. A recent post hoc analysis revealed superiority of rituximab in PR3-positive patients to achieve complete remission after 6 months, but this effect ceased after 18 months ($P = 0.39$). No information about disease course prior to enrollment is provided and we believe recommendation of rituximab as 'first-line treatment' in this indication needs more evidence.

Notably, patients receiving rituximab in the Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) trial had two concomitant cyclophosphamide pulses and plasma exchange was allowed [3]. Since patients with respiratory failure were excluded from both trials and concomitant immunosuppression may have influenced results in the RITUXVAS trial, rituximab's efficacy in treatment-naïve patients with severe disease forms has to be assessed. In conclusion, several more investigations have to be conducted to recommend rituximab as the preferable choice in the 'first-line treatment' of ANCA-associated vasculitis.

We remain concerned about the relatively low rates of remission and high glucocorticoid exposures with either RTX or CYC induction and feel that neither provides optimal therapy. There is also a paucity of information on RTX induction in patients with low glomerular filtration rate. Observational studies have indicated acquired immunodeficiency is an important late adverse effect of RTX with 4.2% requiring immunoglobulin replacement [4]. Uncertainty over the long-term outcomes of these patients and cost of replacement need to be considered when balancing the attractiveness of RTX as compared with CYC.

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