Impact of rituximab trials on the treatment of ANCA-associated vasculitis

Federico Alberici and David R. W. Jayne
Vasculitis and Lupus Clinic, Addenbrooke’s Hospital, Cambridge, UK

Correspondence and offprint requests to: Federico Alberici; E-mail federico.alberici@gmail.com

ABSTRACT

ANCA-associated vasculitis (AAV) is a subgrouping of autoimmune disorders characterized by a chronic relapsing course. Induction therapy is usually effective, but 70% of patients will relapse and 20% develop refractory disease. In the relapsing and refractory subgroups, treatment is complicated by the cumulative exposure to toxic drugs that contribute to poor long-term outcomes. The anti-CD20 monoclonal antibody rituximab (RTX) depletes B cells, and the success of this targeted therapy has contributed to the evidence supporting a central role for B cells in AAV pathogenesis. Initial proof of RTX effectiveness originated from small, prospective trials and retrospective surveys conducted in AAV patients with relapsing and refractory disease; high remission rates permitted the reduction of glucocorticoids (GCS) doses and withdrawal of immunosuppressives. There has been controversy over the effectiveness of RTX in patients with predominantly granulomatous manifestations, where response rates have varied between studies, in part due to different RTX dosing regimens. These studies were followed by comparison of RTX against cyclophosphamide (CYC) for remission induction of new or relapsing AAV in two randomized trials, which led to the licensing of RTX for this indication. Subsequent attention has been turned to the use of RTX as a relapse prevention agent, to the potential for GCS sparing and to RTX-associated toxicity. We will discuss the impact that the results of RTX clinical trials have had on the management of AAV patients.

Keywords: ANCA, GPA, MPA, EGPA, rituximab, therapy, vasculitis

INTRODUCTION

ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) [1]. A trademark GPA and MPA feature is positivity in around 90% of patients for anti-neutrophil cytoplasm auto-antibodies (ANCAs) directed against neutrophil proteinase 3 or myeloperoxidase (PR3 or MPO-ANCA) [2] with PR3-ANCA more frequent in GPA and MPO-ANCA more typical of MPA; in EGPA patients ANCA positivity is less frequent and reported in around 40% [3]. Their common association with ANCA, similar histological features of inflammation and fibrinoid necrosis of small blood vessels and response to therapy has led to the GPA and MPA subgroups being combined for clinical studies. This convention has been challenged by a recent genome-wide association study, which found PR3 and MPO-ANCA subgroups to markedly differ in their genetic susceptibility [4]. Both GPA and MPA patients present with vasculitic manifestations, such as necrotizing crescentic glomerulonephritis, alveolar haemorrhage, purpura and peripheral neuropathy. GPA is further characterized by granulomatous involvement of the ear, nose and throat (ENT) and lungs; ENT involvement may be the only manifestation in the localized subset of the disease [1]. EGPA is defined by eosinophilia, necrotizing vasculitis and eosinophil-rich granulomatous inflammation [3, 5].

The treatment of AAV has developed into an induction phase of 3–6 months to stop vasculitis activity and prevent or reverse vital organ dysfunction and a longer maintenance stage. Current induction regimens are effective in 70–90% of the patients, but complicated by high adverse event rates. Subsequent maintenance therapy is better tolerated but relapse occurs in 70% despite initial disease control [6]. The natural history of AAV has evolved from one of high mortality, end-stage renal failure and high organ damage risk to a chronic relapsing disease [7], where a fine balance exists between the benefits and the risks of therapy.

Glucocorticoids (GCS) and cyclophosphamide (CYC) are the mainstays of the induction phase for AAV patients with vital organ, especially renal, involvement [8]; plasma exchange is recommended for presentations with severe renal impairment or lung haemorrhage [9]. Methotrexate and mycophenolate mofetil have been evaluated as alternatives to CYC, in particular for non-organ threatening disease [6]; although
effective these regimens are associated with a higher relapse risk [10]. Bladder, haematological and gonadal toxicity [11, 12] have limited the duration of CYC and inspired lower CYC dosing as used in intravenous (IV) protocols [13]. Azathioprine and methotrexate have been equally effective for preventing relapse, with weaker evidence for leflunomide or mycophenolate mofetil in this role [14, 15]. Other drugs that have been studied for AAV but are not in routine use include anti-TNF alpha blockers [16], gusperimun (deoxyspergualin) [17] and IV immunoglobulin [18]. Alemtuzumab is a humanized anti-CD52 monoclonal antibody that depletes lymphocytes, including B cells and monocytes. Compassionate use studies have indicated potential in AAV, but also immune suppressive complications especially in the elderly and those with renal impairment [19].

In EGPA, an evidence-based therapeutic approach is harder to establish because of its rarity: GCS alone are effective for non-severe presentations, but relapses are frequent during tapering [20]. Severe subsets of EGPA (e.g. cardiac involvement) require CYC and GCS [21]. The anti-IL-5 monoclonal antibody mepolizumab has controlled EGPA in preliminary studies with a GCS sparing effect, although disease flares recur after drug cessation [22].

Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody [23] that depletes circulating and tissue resident B cells by direct induction of apoptosis, complement-dependent cytotoxicity (CDCC) and antibody-dependent cytotoxicity (ADCC) [23]. The in vitro observation of RTX-induced apoptosis through caspase activation [24] suggested programmed cell death as a possible mechanism of action providing a high degree of cross-linking between the monoclonal antibody molecules [25]; however, the actual in vivo contribution of this mechanism is still debated. The role of CDCC, which is mediated by the complement protein C1q, is also unclear: a reduction in complement levels has been described after RTX infusion in vivo and the ex vivo complement supplementation has been able to reactivate RTX [26, 27]; however, at the same time C3b deposition seems to facilitate RTX removal and to interfere with ADCC, leading to conflicting conclusions regarding the complement role [24]. ADCC is mediated by effector cells, mainly natural killers [28], able to bind RTX through their Fcγ receptors: ADCC is thought to be the main pathway leading not only to B cell cytotoxicity or phagocytosis but also facilitating antibodies cross linking on the B cell surface and cytokine production [24]. The observation that Fcγ receptors single nucleotide polymorphisms (SNPs) may influence response to RTX [29, 30] could be a support for the centrality of ADCC in the mechanism of RTX.

There has been an extensive experience of RTX following its approval in 1997 for B-cell lymphoma and in 2005 for rheumatoid arthritis [31, 32]. A rationale for its use in AAV has been based on the pathogenicity of ANCA [33]; however, being the precursor of ANCA producing plasma cells and CD20+ plasmablasts is not the only role of B cells in AAV. Their presence in vasculitic lesions and the association of their activation with clinical disease activity [34] suggested other functions. B cells may act as antigen presenting cells for T lymphocytes [35] as well as producing pro-inflammatory cytokine useful for T cell hyperactivity and neutrophil priming (Figure 1). The complex relationship between B and T cells could explain RTX effectiveness in T cells driven diseases such as EGPA, which is characterized by a lower rate of ANCA

**FIGURE 1:** Role of B cells in the pathogenesis of AAVs. The interaction between CD20+ B cells and T lymphocytes leads to (i) the development of ANCA-producing plasmablasts (CD20+) and plasma cells (CD20−), (ii) the maturation of T effector memory cells (TEM) and (iii) the production of pro-inflammatory cytokines. The priming of neutrophils is facilitated by the circulating cytokines and by microorganisms including *Staphylococcus aureus*. The primed neutrophils are activated by the binding of ANCA on the surface and together with TEM cells are responsible for vessel inflammation and tissue damage. The activated neutrophils may produce BAFF contributing to further B lymphocyte activation. In the peripheral tissues, a further interaction between B and T cells occurs inside the tertiary lymphoid tissues sites where B cells are more protected compared with the circulation due to stromal cell adhesion molecules and BAFF production.
positivity compared with GPA and MPA. Moreover, it is interesting to note how in EGPA the Th2 immune response may eventually lead to an abnormal B-cell activity as demonstrated by the increased levels of IgG4 in patients with active disease [36]. Further evidence of a central B-cell role is that the efficacy of CYC in vasculitis has been linked with its anti-B-cell effects [33], and B-cell autoreactivity is linked with the T-cell dysregulation seen in AAV [35].

RTX AS INDUCTION TREATMENT IN GPA AND MPA

The first report of successful treatment of GPA with RTX was in 2001 [37], in a patient with PR3-ANCA positivity and refractory disease. Fourteen studies have examined RTX and GCS as induction treatment in GPA and MPA of more than five patients, six prospective [38–44] and two randomized [38, 39] and eight retrospective (45–51) (Table 1). Thirteen included patients with refractory-relapsing disease [38, 40–43, 45–51], one newly diagnosed patient [39] and one both relapsing and new-onset AAV [44].

Relapsing patients treated with RTX had had previous CYC exposure and most were receiving another immunosuppressive at the time of treatment with RTX [40–43, 45–49]. There was variable use of CYC with RTX and continuation or withdrawal of other immunosuppressives. Although not formally compared, no obvious benefit of concomitant CYC on response rates, or continued immunosuppression on relapse rates, was seen. RTX has been dosed at 375 mg/m² a week for four consecutive weeks [38, 39, 41–43, 46, 49–51] or two doses of 1000 mg with a 2-week interval [40, 44, 45, 47, 48] without noticeable differences in the duration of B-cell depletion or disease-free interval.

The remission rates (partial and complete remission) after RTX have varied from 62 to 90%, with differences in remission definitions influencing the results; in particular, the lower response rates were observed in the two randomized trials [38, 39], which employed more stringent remission definitions and were not subject to publication bias. Most patients achieve B-cell depletion, with rates of 94% [38] and 82% [39] seen in two randomized trials; ANCA levels fall predictably after 6 weeks and parallel the achievement of remission [40, 41, 43–48, 50, 51]. Relapses following RTX respond successfully to further anti-CD20 treatment [40–51]. All the studies contained a majority of PR3-ANCA-positive GPA patients, for this reason some caution is required in extrapolating the results to MPO-ANCA-positive or MPA patients.

The two randomized trials, RITUXVAS [39] and RAVE [38], definitely answered the question whether RTX could have the same profile of effectiveness compared with CYC as induction treatment. Forty-four patients with new onset of disease and 197 patients with either relapsing or newly diagnosed AAV, respectively, were enrolled. The RTX groups in both studies received RTX 375 mg/m² a week for 4 weeks. RITUXVAS patients also received two IV CYC (15 mg/kg) infusions; neither study gave maintenance treatment after RTX. The control arms received as induction daily oral CYC in RAVE (2 mg/kg) and IV CYC in RITUXVAS (15 mg/kg) followed by azathioprine as maintenance treatment. From the GCS prospective, both RITUXVAS and RAVE allowed up to 3 g of IV methylprednisolone at the study entry with a prednisolone starting dose of 1 mg/kg; differences were recorded in the tapering schedule with the aim of reaching 5 mg at month 6 to be kept until month 12 in RITUXVAS and 0 mg at month 5 in RAVE. Response was assessed at month 12 in RITUXVAS and at month 6 in RAVE. Both trials [38, 39] found similar efficacy between RTX- and CYC-based regimens for patients with new diagnosis of vasculitis; moreover, the RAVE trial [38] found a higher remission rate in the subgroup with relapsing, as opposed to newly diagnosed, disease at entry that received RTX. There were no differences in the time to remission for nephritis or pulmonary manifestations between the RTX and CYC groups. The similar remission rates between the two trials confirmed no advantages with the concomitant administration of CYC and RTX. Despite the reduction or removal of CYC in the RTX treatment groups, there were no differences in severe adverse events rates [38, 39]. The reasons for this are unclear but a major contribution of GCS to adverse events in these short term studies appears likely. Attention is now turning to whether RTX permits early GCS reduction, and this has been tested in a cohort study of 23 patients with ANCA-associated renal vasculitis when all remitted on a regimen of RTX, reduced dose CYC, and prednisolone starting at 20 mg/day [44]. Thus, therapy in the future may be more finely adjusted, or stratified, according to severity and comorbidity [52].

RTX IN VASCULITIC AND GRANULOMATOUS MANIFESTATIONS

The manifestations of GPA can be divided into those with predominant vasculitis: glomerulonephritis, alveolar haemorrhage, arthritis and polyneuropathy; and those with granulomata: orbital and pulmonary masses, granulomatous sinusitis, subglottic stenosis, tracheobronchial and meningeal involvement. Granulomatous lesions are more difficult to treat: in localized (ENT and lung) GPA, relapse rates exceed 50% at 5 years, and two-thirds have damage due to vasculitis [53]. Furthermore, orbital involvement leads to frequent visual impairment and blindness in 20% [54].

CD20+ B cells contribute to granulomatous inflammation and have been identified locally in tissue biopsies [55, 56]; moreover, in patients who achieved remission after RTX, tissue B cells were depleted along with circulating cells [55]. However, the rates of response of granulomatous manifestations to RTX have been variable among different reports, and the effectiveness of RTX in this subgroup of patients is still unclear [51, 55, 57–62]. In a cohort of 59 patients, the response of granulomatous manifestations was low with a higher rate of refractory-unchanged disease compared with vasculitic manifestations (41.8 and 9.4%); moreover, some localizations (e.g. pulmonary masses) had a better outcome compared with orbital and meningeal involvement which had the highest rate of refractivity [63]. In another study, 34 patients with mainly ENT granulomatous disease showed an 88% response rate...
Table 1. Clinical trials of more than five patients exploring the effectiveness of RTX as induction treatment in GPA/MPA

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Number of Patients (GPA%)</th>
<th>Type of disease</th>
<th>Other add-on immunosuppressive with RTX</th>
<th>Disease Score</th>
<th>Follow-up (months)</th>
<th>Remission rate (%)</th>
<th>Remission rate in relapsing patients re-treated with RTX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone et al., 2010⁴⁸</td>
<td>Prospective, Randomized</td>
<td>99 (75%)</td>
<td>New Onset (48%)</td>
<td>None</td>
<td>Mean BVAS 8.5 (SD ± 3.2)</td>
<td>Trial follow-up 6</td>
<td>65</td>
<td>NA</td>
</tr>
<tr>
<td>Jones et al., 2010⁵⁹</td>
<td>Prospective</td>
<td>33 (55%)</td>
<td>New Onset (100%)</td>
<td>CYC 100%⁶¹</td>
<td>Median BVAS 19 (IQR 14–24)</td>
<td>Trial follow-up 12</td>
<td>76</td>
<td>NA</td>
</tr>
<tr>
<td>Mansfield et al., 2011⁴⁴</td>
<td>Prospective</td>
<td>23 (57%)</td>
<td>New Onset (96%)</td>
<td>CYC 100%, AZA 100%</td>
<td>Median BVAS 21 (range 12–27)</td>
<td>Median (range) 39 (8–51)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Smith et al., 2006⁴⁰</td>
<td>Prospective</td>
<td>11 (45%)</td>
<td>Relapse (4%)</td>
<td>CYC 100%⁶¹</td>
<td>BVAS &gt;8</td>
<td>Median (range) 24 (12–31)</td>
<td>82</td>
<td>100</td>
</tr>
<tr>
<td>Stasi et al., 2006⁴¹</td>
<td>Prospective</td>
<td>10 (80%)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 5.5 (range 3–11)</td>
<td>Median (range) 33.5 (26–45)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Keogh et al., 2006⁴⁴</td>
<td>Prospective</td>
<td>11 (91%)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 6 (range 5–10)</td>
<td>Median (range) 14 (10–42)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Keogh et al., 2005⁴⁴</td>
<td>Prospective</td>
<td>10 (NA)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 5 (range 3–11)</td>
<td>Median (range) 20 (3–55)</td>
<td>98⁶⁵</td>
<td>84–95</td>
</tr>
<tr>
<td>Jones et al., 2009⁴⁵</td>
<td>Retrospective</td>
<td>65 (71%)</td>
<td>Relapsing Refractory</td>
<td>CYC 43%⁶¹</td>
<td>Median DEI 4 (range 2–11)</td>
<td>Median (IQR) 21 (14–31)</td>
<td>62</td>
<td>100</td>
</tr>
<tr>
<td>Pullerits et al., 2012⁴⁶</td>
<td>Retrospective</td>
<td>29 (97%)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 6 (IQR 3–8)</td>
<td>Median (range) 20 (3–48)</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Wendt et al., 2012⁴⁷</td>
<td>Retrospective</td>
<td>16 (88%)</td>
<td>Relapsing Refractory</td>
<td>CYC 19% Other (69%)</td>
<td>Median BVAS 9.5 (range 2–27)</td>
<td>Median (range) 15 (3–39)</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Lovric et al., 2009⁵¹</td>
<td>Retrospective</td>
<td>15 (87%)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 12 (range 6–21)</td>
<td>Median (IQR) 32 (19–47)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Rees et al., 2011⁴⁸</td>
<td>Retrospective</td>
<td>12 (92%)</td>
<td>Relapsing Refractory</td>
<td>CYC 67%⁶¹</td>
<td>Median BVAS 13.5 (range 7–26)</td>
<td>Median (IQR) 40 (36–52)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Roccatello et al., 2011⁵⁰</td>
<td>Retrospective</td>
<td>11 (82%)</td>
<td>Relapsing Refractory</td>
<td>None</td>
<td>Median BVAS 18 (IQR 15–20)</td>
<td>Median (IQR) 40 (36–52)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Henes et al., 2007⁷⁹</td>
<td>Retrospective</td>
<td>6 (100%)</td>
<td>Relapsing Refractory</td>
<td>LEF 83%</td>
<td>Median BVAS 5 (range 3–8)</td>
<td>Mean (range) 16 (12–21)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Remission rate includes complete and partial response. If not specified, the remission rate was assessed 6 months after the RTX administration.
IQR, interquartile range; LEF, leflunomide; BVAS, Birmingham Vasculitis Activity Score; NA, not available.
⁶⁵Study assessing the response to therapy before the sixth month after RTX treatment.
⁶¹CYC administered in a low-dose fashion (low dose defined in case of cumulative dose <50% of what suggested by EUVAS guideline).
cells have been associated with relapse in AAV [70, 71]. Al-
rheumatoid arthritis and SLE, while falls in regulatory CD5+ B
covering population has been associated with relapse in
predictors [45]. A memory CD27+ B-cell phenotype in the re-
though both B cells and ANCA lack sensitivity as relapse
is usually preceded by B cell return and a positive ANCA assay
again with a median time to relapse of 12 months; the relapse
duction for relapsing or refractory disease, 75% will relapse
creased vasculitis-induced damage [69]. Following RTX in-
ent doses with intervals ranging between 3 and 12 months:
though RTX treatment of relapse is effective, relapse avoidance
is preferable. RTX has then been given pre-emptively at differ-
role of biomarkers are uncertain. Relapses have occurred after
optimal duration of maintenance therapy with RTX and the
azathioprine after RTX induction for relapsing AAV. The
NCT01697267) compares RTX 1000 mg every 4 months with
azathioprine after CYC induction for new and relapsing pa-
(500 mg × 2 at 6 months then 500 mg every 6 months) with
(72–76). The MAINRITSAN trial (Clinicaltrials.gov NCT00748644) compares lower dose RTX
after one RTX course, and the failing patients improved after a
second RTX dose; moreover, repeated RTX administration
was effective in preventing relapse [64]. The differences in re-
response rates may have been influenced by patient selection
and the level of non-healing tissue damage [63]. Ongoing in-
fection, such as with Staphylococcus aureus, provides a local
stimulus to vasculitis and hinders efforts to attain disease
control [65]; routine ENT assessment and nasal swab culture
should be performed and an aggressive treatment of local colo-
nizations and infections is suggested. The microenvironment
within granulomatous lesions may protect B cells from RTX-
associated depletion: both tissue B cell activating factor levels
(BAFF) and adhesion molecules have prevented depletion, and
persisting tissue B cells have been demonstrated in pa-
patients despite depletion of the circulating ones [66]; this may
explain why higher RTX dosing may be necessary to achieve
remission in some GPA patients [64, 67].

**RTX AS MAINTENANCE TREATMENT**

With conventional therapy, 50% of AAV patients will relapse
by 5 years and 15–20% will experience a refractory disease
course [6, 13, 68], resulting in high GCS exposure and in-
creased vasculitis-induced damage [69]. Following RTX in-
duction for relapsing or refractory disease, 75% will relapse
again with a median time to relapse of 12 months; the relapse
is usually preceded by B cell return and a positive ANCA assay
although both B cells and ANCA lack sensitivity as relapse
predictors [45]. A memory CD27+ B-cell phenotype in the re-
covering population has been associated with relapse in rheumatoid arthritis and SLE, while falls in regulatory CD5+ B
cells have been associated with relapse in AAV [70, 71]. Al-
though RTX treatment of relapse is effective, relapse avoidance
is preferable. RTX has then been given pre-emptively at differ-
ent doses with intervals ranging between 3 and 12 months:
high rates of sustained remission have been obtained during
the treatment period, suggesting a role of RTX also as ma-
inance treatment (Table 2) [72–76]. The MAINRITSAN trial (Clinicaltrials.gov NCT00748644) compares lower dose RTX
(500 mg × 2 at 6 months then 500 mg every 6 months) with
azathioprine after CYC induction for new and relapsing pa-
tients; and the RITAZAREM trial (Clinicaltrials.gov NCT01697267) compares RTX 1000 mg every 4 months with
azathioprine after RTX induction for relapsing AAV. The
optimal duration of maintenance therapy with RTX and the
role of biomarkers are uncertain. Relapses have occurred after
a 2-year course of RTX 1000 mg every 6 months, but at a
lower rate than occurred after a single RTX course, suggesting
a potential wear-off effect in the time since the last infusion
in some but not in all patients [72].

**RTX IN EGPA**

Patients with EGPA have been excluded from most RTX AAV
studies, and the evidence for B cells in pathogenesis is weaker.
Eosinophilia results from T-cell dysregulation mediated by

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**Table 2. Clinical trials exploring the effectiveness of the pre-emptive RTX administration as maintenance treatment in GPA and MPA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of infusions</th>
<th>Infusion schedule</th>
<th>Infusion frequency</th>
<th>Response before treatment (%)</th>
<th>Response after treatment (%)</th>
<th>Reasons for re-treatment</th>
<th>Type of maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 2017</td>
<td>25</td>
<td>1g twice a year</td>
<td>Median 6 (range 2–11)</td>
<td>88</td>
<td>100</td>
<td>62</td>
<td>89</td>
<td>Other (40%)</td>
</tr>
<tr>
<td>Roubaud-Baudron et al. 2012</td>
<td>28</td>
<td>1g twice a year</td>
<td>Median 4 (range 2–10)</td>
<td>93</td>
<td>82</td>
<td>57</td>
<td>87</td>
<td>Other (40%)</td>
</tr>
<tr>
<td>Cartin-Ceba et al. 2012</td>
<td>53</td>
<td>1g twice a month</td>
<td>Median 4 (IQR 3–5)</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>De Menthon et al. 2011</td>
<td>10</td>
<td>Median 4 (IQR 3–5)</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rhee et al. 2010</td>
<td>39</td>
<td>1g every 4 months</td>
<td>Median 6.5 infusions per year</td>
<td>92</td>
<td>87</td>
<td>30</td>
<td>41</td>
<td>NA</td>
</tr>
</tbody>
</table>

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IQR, interquartile range; NA, not available.

RTX re-treatment was given pre-emptively, for intolerance of more conventional maintenance treatment, for grumbling disease despite treatment with other drugs and for kidney failure. Only 64% of the RTX courses were given pre-emptively.
IL-4, IL-5 and IL-13 [77, 78]; however, B cells appear to support T-cell autoreactivity [35]. RTX has led to remission in refractory-relapsing EGPA whether or not ANCA was positive [45, 48, 79–84]; moreover, RTX has been also effective in reducing eosinophil counts and IL-5 levels [83]. Subsequent flares responded to repeated RTX dosing [45, 80, 81].

**RTX SAFETY**

Mild-to-moderate infusion reactions, including bronchospasm, occur in 20% during or after RTX and prophylaxis with 100 mg IV methylprednisolone and antihistamine is recommended [85]. Severe reactions are rare [86]. It is unclear the extent to which RTX increases infection risk: there was no reduction in infections with RTX in the randomized trials [38, 39], and although infections were seen in the non-randomized surveys, the impact of RTX could not be determined. Progressive multifocal leucoencephalopathy is a very rare complication of RTX that may be more common in patients who have received several immunosuppressive treatment [87]. The serology for hepatitis C (HCV) and B viruses (HBV) should be checked before starting treatment with RTX. HCV-positive patients have in fact an increased risk of hepatic flares after RTX treatment [88]. HBV reactivation has been described after RTX and pre-emptive lamivudine may be considered [89]. Prophylactic treatment of *pneumocystis jiruvecii pneumonia* is recommended [90]. A reduction in immunoglobulin levels has been noted in longer term observational studies in 33–71% of patients, especially in those with prior CYC exposure and mainly after RTX repeated dosing; a small number of patients have required IV immunoglobulin replacement [72–74, 91, 92].

**THE PLACE OF RTX IN CURRENT THERAPY**

CYC and GCS remain the standard induction therapy for newly diagnosed AAV but where there is a contraindication to CYC, such as the desire to protect fertility or in the context of concomitant infection, RTX is a reasonable alternative [52, 93]. RTX has been shown to be superior to CYC for relapsing disease [38] and prevents increased exposure to CYC. It is uncertain whether RTX should be used for a first relapse in a patient with a low CYC exposure; however, RTX is indicated for subsequent relapses and for refractory disease and it may be considered when CYC has been poorly tolerated, is contraindicated or the malignancy risk due to a high CYC exposure is a concern [94] (Figure 2). The licensed RTX regimen is 375 mg/m² for four consecutive weeks, but 1000 mg administered 2 weeks apart has a similar efficacy [39]. Concomitant CYC is not routinely administered with RTX and does not appear to improve remission rates [38, 39]; however, it may be considered for the more aggressive disease flares or with a steroid-sparing purpose. RTX maintenance treatment does not require continued immunosuppression, and GCS withdrawal should be achieved in over 50% by 6–12 months; however, advice on maintenance RTX awaits the results of ongoing trials. In the absence of RTX re-treatment, relapse is common; therefore, maintenance immunosuppression may be considered and the patients should be monitored accordingly [72]. Immunoglobulin levels should be checked and marked falls indicate a risk of a clinically relevant acquired immunodeficiency

**FIGURE 2:** Flowchart suggesting the therapeutic approach in patients with AAVs. AAV, ANCA-associated vasculitis; CYC, cyclophosphamide; AZA, azathioprine; RTX, rituximab; MTX, methotrexate.
and a relative contraindication to further RTX. The response to RTX in EGPA and paediatric AAV patients appears similar to that of adults with GPA/MPA but further data are required. There is also a paucity of data on long-term outcomes after RTX induction in AAV, and patients should be recruited to registries where possible.

**FUTURE PROSPECTIVE**

Other anti-CD20-depleting agents have not been evaluated in AAV, but increased ADCC–CDCC activity and target avidity may improve the completeness of B-cell depletion, especially in granulomatous disease; moreover, a fully humanized structure would reduce rates of antitoglobulin formation, although this has not been a major issue in AAV [95, 96]. High levels of BAFF are associated with a shorter duration of the RTX-induced B-cell depletion [97]; the anti BAFF monoclonal antibody belimumab has efficacy in SLE, and its role as a relapse prevention agent in AAV is being assessed in a randomized trial (BREVAS, ClinicalTrials.gov number NCT01663623).

Improved biomarkers would aid in the selection of RTX dose and dosing interval: Fcy receptors and C1QA are involved in the RTX mechanism of action; SNPs of their genes predict clinical response in haematological malignancies and rheumatoid arthritis [29, 30, 98]. Other possible prognostic factors are IL-6 [99], plasmablast mRNA markers [100], interferon type I signature [101], BAFF receptor expression on B cells [102], CCR5 density on blood T4 cell surface [103] and the phenotype of the returning B cells [70].

Beneficial effects of RTX over standard therapy have not been shown on vasculitis-related damage, such as loss of GFR, on mortality or on quality of life. Improvement in these outcomes is required to justify the costs of RTX and before the displacement of CYC in routine therapy.

**CONFLICT OF INTEREST STATEMENT**

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