Experience with rituximab in the treatment of antineutrophil cytoplasmic antibody associated vasculitis

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Abstract: Prior to the 1970s, severe cases of antineutrophil cytoplasmic antibody associated vasculitis (AAV) were thought to be invariably fatal. However, the use of cyclophosphamide-based treatment regimens fundamentally altered disease outcomes, transforming AAV into a manageable, chronic illness. Despite the tremendous success of cyclophosphamide in the treatment of AAV, there remained a need for alternative therapies, due to high rates of treatment failures and significant toxicities. In recent years, with the introduction of targeted biologic response modifiers into clinical practice, many have hoped that the treatment options for AAV could be expanded. Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte protein CD20, has been the most successful biologic response modifier to be used in AAV. Following the first report of its use in AAV in 2001, experience with rituximab for treatment of AAV has rapidly expanded. Rituximab, in combination with glucocorticosteroids, is now well established as a safe and effective alternative to cyclophosphamide for remission induction for severe manifestations of granulomatosis with polyangiitis and microscopic polyangiitis. In addition, initial experiences with rituximab for remission maintenance in these diseases have been favorable, as have experiences for remission induction in eosinophilic granulomatosis with polyangiitis.

Keywords: antineutrophil cytoplasmic antibody, antineutrophil cytoplasmic antibody associated vasculitis, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), granulomatosis with polyangiitis (Wegener’s granulomatosis), microscopic polyangiitis, rituximab, vasculitis

Introduction

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) syndromes are clinically heterogeneous conditions characterized by pauci-immune, necrotizing, small-vessel vasculitis, along with an association with circulating ANCA autoantibodies [Jennette *et al.* 2013]. In all three of the major AAV syndromes, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome), the vasculitic activity preferentially affects the kidneys, lungs, and peripheral nervous system [Jennette *et al.* 2013]. The AAV syndromes are distinguished on the basis of clinicopathologic features and their associated ANCA. Typically, GPA involves necrotizing granulomatous inflammation of the

respiratory tract, which separates it from MPA, while EGPA is differentiated by the presence of asthma and peripheral eosinophilia [Jennette *et al.* 2013]. ANCAs that react with proteinase 3 and cause a cytoplasmic immunofluorescence pattern on ethanol-fixed neutrophils predominate among patients with GPA. In contrast, the majority of patients with MPA and EGPA are found to have ANCAs that react with myeloperoxidase and cause a perinuclear immunofluorescence pattern on ethanol-fixed neutrophils [Hoffman and Specks, 1998].

Historically, severe cases of AAV followed a progressive course leading to death [Walton, 1958]. However, with the introduction of cyclophosphamide (CYC) combined with glucocorticosteroids (GCS) as a standard therapy for remission induction, AAV was transformed into a manageable,

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chronically relapsing illness for the vast majority of patients [Walton, 1958; Fauci *et al.* 1983]. Despite this success, treatment with CYC and GCS remained problematic. About 10% of patients with severe AAV fail to achieve remission with CYC and GCS, and up to half of those who do achieve remission go on to develop disease relapse within 5 years. In addition, CYC is associated with substantial toxicity, especially with long-term and repeated use [Hoffman *et al.* 1992; Nachman *et al.* 1996; Talar-Williams *et al.* 1996].

Due to the limitations and toxicities of CYC-based therapies, alternative treatment modalities have been sought for AAV. The desire to limit the use of CYC in AAV led to the establishment of methotrexate (MTX) as the standard therapy for remission induction in GPA that manifests with nonsevere clinical features [De Groot *et al.* 2005, 2009]. The cumulative exposure of patients to CYC has been further curtailed by the practice of converting patients to long-term maintenance therapy with MTX or azathioprine (AZA) following 3–6 months of treatment with CYC and GCS for remission induction [Sneller *et al.* 1995; Jayne *et al.* 2003].

Biologic response modifiers, which target specific immune pathways with the aim of reducing maladaptive inflammation, have provided hope that the treatment of AAV may be further improved. A variety of biologic response modifiers have been investigated in AAV, with targets including tumor necrosis factor α (TNF α), T lymphocytes, and B lymphocytes [Wegener's Granulomatosis Etanercept Trial Research Group, 2005; Walsh *et al.* 2008; Morgan *et al.* 2011]. Rituximab (RTX), a chimeric monoclonal antibody directed against the B-lymphocyte-restricted cell-surface protein CD20, has achieved the greatest success among the biologic response modifiers to be used in AAV. This review intends to provide perspective on the current knowledge about the treatment of AAV with RTX by summarizing its actions and theoretical benefits, as well as the results of clinical investigations into its use.

Rationale for treating AAV with rituximab

CD20 is thought to be involved in the activation, proliferation, and differentiation of B lymphocytes [Tedder and Engel, 1994]. The binding of RTX to CD20 induces death in the targeted cell by a variety of potential mechanisms. While the

exact mechanism of RTX-mediated B-lymphocyte killing remains unclear, there is *in vitro* evidence for antibody-dependent cellular cytotoxicity, complement-mediated cell lysis, apoptosis, and the sensitization of B cells to the effects of steroids and cytotoxic agents [Demidem *et al.* 1997; Golay *et al.* 2000; Shan *et al.* 2000; Johnson and Glennie, 2003; Uchida *et al.* 2004; Eisenberg and Looney, 2005]. Treatment with RTX induces a profound B-lymphocyte depletion such that circulating B lymphocytes remain undetectable in peripheral blood for an average of 6–12 months [Anolik *et al.* 2004; Keogh *et al.* 2006].

RTX received its initial approval from the US Food and Drug Administration (FDA) in November 1997 for the treatment of certain B-cell non-Hodgkin lymphomas. The initial experience with RTX in the US market was highly favorable, as RTX was found to be both effective and well tolerated [Gurcan *et al.* 2009]. Given this clinical success, investigational uses of RTX were soon extended to a variety of autoimmune diseases [Eisenberg, 2005].

In the case of AAV, the B-lymphocyte depletion induced by RTX was considered a particularly promising therapeutic strategy [Specks *et al.* 2001]. B lymphocytes have long been implicated in the disease pathogenesis. They are essential for the production of ANCAs and have been proposed as the key target for the therapeutic effect of CYC in AAV [Stevenson and Fauci, 1980; Cupps *et al.* 1982]. In addition, both disease activity and disease severity in patients with AAV have been associated with the frequency of activated B lymphocytes [Popa *et al.* 1999].

Early experience with rituximab for AAV

In 2001, the first reported use of RTX in a patient with AAV was described [Specks *et al.* 2001]. The patient was a 66-year-old man who had been diagnosed with GPA in 1994 and had developed a severe disease flare, with features that included a rising serum creatinine in the setting of an active urinary sediment with red blood cell casts. Treatment options for the disease flare were limited, as he had previously developed CYC toxicity, and prednisone in combination with AZA and mycophenolate mofetil had proven ineffective. Due to these limitations, treatment with RTX was initiated on a compassionate-use basis, under the hypothesis that the patient would benefit from depletion of

peripheral B lymphocytes and the consequent removal of circulating ANCAs. He was treated with a RTX course consisting of four weekly infusions of 375 mg/m², which matched the FDA-approved regimen for the treatment of non-Hodgkin lymphoma, along with a prednisone taper. The RTX course was well tolerated without any occurrence of adverse effects, and remission was quickly achieved, allowing for the discontinuation of prednisone.

Given the favorable outcome realized in this index case, the compassionate use of RTX was extended to an additional 10 patients with severe refractory AAV, of whom nine were diagnosed with GPA and one was diagnosed with MPA [Keogh *et al.* 2005]. All of these patients received the treatment regimen that had been used in the index case. The majority of patients also received intravenous methylprednisolone and three individuals underwent plasma exchange just prior to initiating RTX therapy, but no other immunosuppressive agents were used in conjunction with RTX and oral prednisone. The outcomes in this series were highly favorable, as all patients achieved clinical remission and were able to taper GCS therapy, while adverse effects were minimal.

Rituximab for refractory AAV

Building on these early experiences, Keogh and colleagues conducted an open-label pilot trial that investigated the use of RTX in combination with oral GCS in active, severe, refractory AAV [Keogh *et al.* 2006]. Ten patients were included in the trial, and all 10 achieved complete remission by 3 months. Adverse effects were minimal. Subsequently, at least 21 additional case series and open-label pilot trials reporting experiences with the use of RTX in three or more patients with refractory AAV have been published, as summarized in Table 1. Given similarities in both disease manifestations and treatment responses, MPA and GPA have been considered together in most clinical studies, while EGPA has been studied separately [Jayne *et al.* 2003, 2007; De Groot *et al.* 2005; Jones *et al.* 2010; Stone *et al.* 2010]. The reports summarized in Table 1 included over 200 patients with a variety of disease manifestations. Most of the studies describe treatment success, with the vast majority of patients achieving either complete or partial remission. RTX is now commonly used when more traditional therapies have failed [Guerry *et al.* 2012].

Rituximab for remission induction in severe AAV: results from randomized controlled trials

The strongest evidence for the safety and efficacy of RTX for the treatment of severe AAV is derived from two prospective, randomized controlled trials, which are summarized in Table 2 [Jones *et al.* 2010; Stone *et al.* 2010]. The 'Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis' (RAVE) study was a multicenter non-inferiority trial that compared RTX with CYC for remission induction in severe AAV using a randomized, double-blind, double placebo-controlled trial design [Stone *et al.* 2010]. The study included 197 patients with severe, ANCA-positive GPA or MPA, with 'severe' AAV defined as disease activity with at least one life- or organ-threatening manifestation classified as a major item on the Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) [Stone *et al.* 2001]. It should be noted, however, that alveolar hemorrhage requiring mechanical ventilation was an exclusion criterion. The patients were randomized 1:1 to treatment with RTX (via four weekly intravenous doses of 375 mg/m²) *versus* oral CYC (dosed at 2 mg/kg/day) followed by AZA. Treatment regimens for all patients also included GCS, consisting of intravenous methylprednisolone followed by a protocolized prednisone taper. When remission was achieved during months 3–6, patients in the CYC arm were transitioned to AZA, while patients in the RTX arm who did not receive active maintenance therapy were transitioned to an AZA placebo.

The primary endpoint in RAVE was complete remission of disease at 6 months, defined as a BVAS/WG of 0 in the absence of GCS therapy. This primary endpoint was achieved by 64% of the patients in the RTX arm *versus* 53% in the CYC arm, meaning that RTX met criteria for noninferiority ($p < 0.0001$). In addition, rates of total adverse events and serious adverse events were similar between the two groups, as were rates of disease relapse. Among treatment-naïve patients, outcomes did not differ according to treatment regimen, but among the 101 patients who were experiencing severe relapses upon study enrollment, RTX was more efficacious than CYC, with 67% of the patients in the RTX arm achieving the primary endpoint compared with 42% in the CYC arm ($p = 0.01$). On extended follow up, the rates of sustained remission remained similar between the two groups at 12 and 18 months, and

Table 1. Rituximab for treatment of refractory ANCA-associated vasculitis: review of uncontrolled studies.

Study	Study design	Number of patients with AAV treated with RTX	AAV syndromes (number of patients)	Outcome	Citation
Keogh	Retrospective case series	11	GPA (10); MPA (1)	11 CR	[Keogh <i>et al.</i> 2005]
Eriksson	Prospective case series	9	GPA (7); MPA (2)	8 CR; 1 PR	[Eriksson, 2005]
Omdal	Retrospective case series	3	GPA (3)	3 Remission (CR <i>versus</i> PR not specified)	[Omdal <i>et al.</i> 2005]
Keogh	Prospective pilot study	10	GPA (10)	10 CR	[Keogh <i>et al.</i> 2006]
Aries	Prospective pilot study	8	GPA (8)	2 CR; 1 PR; 5 TF	[Aries <i>et al.</i> 2006]
Stasi	Prospective case series	10	GPA (8); MPA (2)	9 CR; 1 PR	[Stasi <i>et al.</i> 2006]
Smith	Prospective pilot study	11	GPA (5); MPA (5); EGPA (1)	9 CR; 1 PR; 1 TF	[Smith <i>et al.</i> 2006]
Garcia Hernandez	Prospective case series	4	GPA (4)	1 CR; 3 TF	[Garcia Hernandez <i>et al.</i> 2007]
Brihaye	Retrospective case series	8	GPA (8)	3 CR; 3 PR; 2 TF	[Brihaye <i>et al.</i> 2007]
Henes	Retrospective case series	6	GPA (6)	5 CR; 1 PR	[Henes <i>et al.</i> 2007]
Sanchez-Cano	Retrospective case series	4	GPA (4)	2 CR; 2 PR	[Sanchez-Cano <i>et al.</i> 2008]
Seo	Prospective case series	8	GPA (8)	8 CR	[Seo <i>et al.</i> 2008]
Roccatello	Retrospective case series	7	GPA (2); MPA (4); EGPA (1)	7 Remission (CR <i>versus</i> PR not specified)	[Roccatello <i>et al.</i> 2008]
Taylor	Retrospective case series	10	GPA (10)	10 CR	[Taylor <i>et al.</i> 2009]
Eleftheriou	Retrospective case series	4	GPA (4)	Not specified	[Eleftheriou <i>et al.</i> 2009]
Jones	Retrospective case series	65	GPA (46); MPA (10); EGPA (5); Unclassified (4)	49 CR; 15 PR; 1 TF	[Jones <i>et al.</i> 2009]
Lovric	Retrospective case series	15	GPA (13); MPA (1); EGPA (1)	6 CR; 8 PR; 1 TF	[Lovric <i>et al.</i> 2009]
Martinez Del Pero	Retrospective case series	34	GPA (34)	21 CR; 9 PR; 4 TF	[Martinez Del Pero <i>et al.</i> 2009]
Ramos-Casals	Retrospective case series	19	GPA (17); MPA (2)	10 CR; 3 PR; 6 TF	[Ramos-Casals <i>et al.</i> 2010]
Mansfield	Prospective case series	23	GPA (13); MPA (10)	22 CR; 1 TF	[Mansfield <i>et al.</i> 2011]
Roccatello	Retrospective case series	7	GPA (5); MPA (4); EGPA (2)	11 CR	[Roccatello <i>et al.</i> 2011]

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CR, complete remission; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PR, partial remission; RTX, rituximab; TF, treatment failure.

Table 2. Comparison of two major randomized controlled trials that investigated the use of rituximab for remission induction in ANCA-associated vasculitis.

	RAVE [Stone <i>et al.</i> 2010]	RITUXVAS [Jones <i>et al.</i> 2010]
Trial design	Double-blind, double-dummy, randomized noninferiority trial	Open-label, two-group, randomized parallel trial
Total number of patients	197	44
AAV syndromes (number of patients)	GPA (148); MPA (48); unclassified (1)	GPA (22); MPA (16); renal-limited vasculitis (6)
Percent ANCA positive at enrollment	100	100
Percent with severe AAV at enrollment	100	100
Percent with renal involvement at enrollment	66	100
Therapy in RTX arm	Induction: RTX + GCS Maintenance: placebo	Induction: RTX + CYC + GCS Maintenance: GCS
Therapy in CYC arm	Induction: CYC + GCS Maintenance: AZA	Induction: CYC + GCS Maintenance: AZA + GCS
Remission outcomes	Complete remission achieved in 64% in RTX group and 53% in CYC group (RTX noninferior, $p < 0.0001$)	Sustained remission achieved in 76% of RTX group and 82% of control group (RTX not superior, $p = 0.68$)
Frequency of relapse	Reported per patient-month, according to severity: (1) Severe flares: 0.011 in RTX group and 0.018 in CYC group ($p = 0.30$) (2) Limited flares: 0.023 in RTX group and 0.027 in CYC group ($p = 0.81$)	Reported as incident rate during the study period: 15% in the RTX group and 10% in the control group ($p = 0.70$)
AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; GCS, glucocorticosteroids; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RAVE, Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis; RITUXVAS, Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis; RTX, rituximab.		

no unexpected safety issues were detected [Stone *et al.* 2011].

Another randomized controlled trial was called 'Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis' (RITUXVAS) [Jones *et al.* 2010]. RITUXVAS studied 44 patients with newly diagnosed AAV and evidence of renal involvement using a randomized, open-label, parallel, two-group trial design. The patients were randomized 3:1, with 33 patients receiving a RTX-based regimen and 11 patients receiving standard therapy. One-quarter of the patients underwent plasma exchange prior to enrolling in the study, and all of the patients received a standard glucocorticoid regimen, including intravenous methylprednisolone, after enrollment. The patients in the RTX arm received four weekly infusions of RTX 375 mg/m², as well as two intravenous CYC

pulses that were given in conjunction with the first and third RTX doses. The patients randomized to the control group received intravenous CYC pulses for 3–6 months followed by AZA.

RITUXVAS had two primary outcomes: sustained remission (defined as BVAS of 0 for 6 months) and the rate of severe adverse events at 12 months. For both primary outcomes, results were similar between the two treatment arms. Sustained remission was achieved by 76% of patients in the RTX group *versus* 82% in the control group ($p = 0.68$), while the rate of severe adverse events was 1.00 per patient year in the RTX group *versus* 1.10 per patient-year in the control group ($p = 0.77$). In both groups, 18% of the patients died during the study period, and similar rates of disease relapse were observed among patients in the two treatment arms. On

extended follow up of the RITUXVAS cohort over 2 years, rates of death, relapse, and end-stage renal disease remained similar in both groups [Jones *et al.* 2011].

The favorable results of RAVE and RITUXVAS have established RTX as an effective and safe alternative to CYC for the treatment of severe AAV. Based on the data from the RAVE trial, RTX in combination with GCS was approved for remission induction in newly diagnosed and relapsing severe GPA and MPA by the FDA in April 2011, and subsequently by many other regulatory agencies across the globe. In addition, given the superior outcomes realized with RTX compared with CYC in patients who enrolled in the RAVE trial with severe relapses, RTX is now considered the preferred agent for such patients [Guerry *et al.* 2012].

Rituximab for maintenance therapy in AAV

For patients with AAV who have achieved remission following treatment with RTX, there is not yet consensus as to the preferred therapy for remission maintenance. In fact, for newly diagnosed patients who achieve a first-ever remission with RTX, it remains unclear whether any maintenance therapy is needed at all. In those patients for whom a maintenance regimen is necessary, it is yet to be determined what role RTX itself should play as a maintenance agent. In recent years, several retrospective studies and one prospective randomized controlled trial have investigated the utility of RTX for remission maintenance in AAV [Jones *et al.* 2009; Rhee *et al.* 2010; Cartin-Ceba *et al.* 2012; Guillevin *et al.* 2012; Roubaud-Baudron *et al.* 2012; Smith *et al.* 2012]. The findings of these studies are summarized in Table 3.

As part of a larger retrospective survey of the use of RTX in AAV, Jones and colleagues described 15 patients who were treated preemptively with RTX 1 g every 6 months for remission maintenance [Jones *et al.* 2009]. No relapses occurred among these 15 patients over a median follow-up period of 11 months. In the first report to focus on the use of RTX for remission maintenance, Rhee and colleagues described a retrospective cohort of 39 consecutive patients with AAV in complete or partial remission who were treated with RTX 1 g every 4 months for at least 1 year [Rhee *et al.* 2010]. All patients maintained disease control, without any instances of organ- or life-threatening flares. In another recent report, Smith and

colleagues described a single-center experience with RTX for remission maintenance in refractory or relapsing AAV [Smith *et al.* 2012]. Patients were divided into two main study groups. In group A, 28 patients received RTX for induction therapy (either four weekly doses of 375 mg/m² or two biweekly doses of 1 g) and then further RTX dosing only at the time of clinical relapse. Conversely, in group B, 45 patients received RTX on a protocolized, fixed-interval schedule, with an induction course of two biweekly doses of 1 g followed by maintenance dosing of 1 g every 6 months for 2 years. At the end of 2 years, relapses had occurred in 73% of patients in group A, but only 12% of patients in group B ($p < 0.001$). Severe adverse events were similar between the two groups. The Mayo Clinic experience has been described in a retrospective report of 53 patients with refractory GPA treated with RTX for long-term remission maintenance [Cartin-Ceba *et al.* 2012]. Repeated RTX-mediated depletion of B lymphocytes appeared safe and only a low rate of infections was observed. All relapses in the patient cohort occurred after reconstitution of B lymphocytes and relapses were accompanied or preceded by an increase in serum ANCA levels, with the exception of a single patient with ANCA-negative disease. Finally, Roubaud-Baudron and colleagues described 28 patients with AAV who received at least two RTX maintenance infusions between 2003 and 2010 [Roubaud-Baudron *et al.* 2012]. The maintenance regimens varied among the studied patients, but RTX was well tolerated and prevented relapse in the majority of patients in the series.

Consistent with the encouraging results of these four retrospective studies, the initial results from MAINRITSAN, the first randomized controlled trial to investigate RTX as a maintenance therapy in AAV, have also been promising [Guillevin *et al.* 2012]. In MAINRITSAN, 114 patients with AAV who had achieved remission with conventional therapies were randomized to receive either RTX or AZA for disease maintenance. Patients in the RTX arm received a total of five 500 mg infusions over 18 months, dosed on days 1 and 15, then 5.5 months later, and again every 6 months. Patients in the AZA arm received daily AZA for 22 months at an initial dose of 2 mg/kg/day. The primary endpoint was major relapse at 28 months. Based on initial results, RTX was superior to AZA, with a major relapse rate of 3.6% in the RTX arm *versus* 27.1% in the AZA arm [Guillevin *et al.* 2012].

Table 3. Rituximab for remission maintenance in ANCA-associated vasculitis: review of published studies.

Study	Study design	Number of patients	Rituximab dosing regimen for remission maintenance	Duration of follow up	Outcomes	Citation
Jones	Retrospective review	15	1000 mg every 6 months	5–23 months	Remission successfully maintained in all 15 patients	[Jones <i>et al.</i> 2009]
Rhee	Retrospective review	39	1000 mg every 4 months	12–24 months	3/39 patients experienced nonsevere clinical flares, all beyond 20 months of follow up	[Rhee <i>et al.</i> 2010]
Smith	Retrospective review	73 (45 received maintenance RTX; 28 received no maintenance)	1000 mg every 6 months for 24 months	24–66 months	At 24 months, relapses had occurred in 12% of patients receiving RTX maintenance <i>versus</i> 73% of patients receiving no maintenance	[Smith <i>et al.</i> 2012]
Cartin-Ceba	Retrospective review	53	Four weekly doses of 375 mg/m ² (90%) or two biweekly doses of 1000 mg (10%), given on the basis of laboratory parameters	Median of 4.4 years (interquartile range 2.7–6.2 years)	Remission successfully maintained in all patients who were preemptively treated with RTX (148 courses)	[Cartin-Ceba <i>et al.</i> 2012]
Roubaud-Baudron	Retrospective review	28	375 mg/m ² every 6 months (<i>n</i> = 13) 1000 mg every 6 months (<i>n</i> = 4) 1000 mg every 12 months (<i>n</i> = 3) Other (<i>n</i> = 8)	21–97 months	2/28 patients experienced clinical flares, at 12 and 48 months after induction treatment	[Roubaud-Baudron <i>et al.</i> 2012]
Guillevin (MAINRITSAN)	Prospective, randomized controlled trial comparing RTX versus AZA	114 (55 randomized to receive RTX; 59 randomized to receive AZA)	500 mg on days 1 and 15, then 5.5 months later, and again every 6 months for a total of 5 doses over 18 months	28 months	Preliminary data: major relapse rate is 3.6% in the RTX arm <i>versus</i> 27.1% in the AZA arm	[Guillevin <i>et al.</i> 2012]
ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; RTX, rituximab.						

While the proper role for RTX for the maintenance of remission in AAV remains undetermined, the initial results of these studies have all suggested that RTX may prove safe and effective when used for prevention of disease flares. The issue will be reexamined in the forthcoming RITAZAREM trial, which will investigate RTX *versus* AZA for remission maintenance in relapsing AAV [ClinicalTrials.gov identifier: NCT01697267].

Rituximab in combination with other therapies for AAV

For remission induction in severe AAV, the concomitant use of GCS with RTX is now a well established therapeutic combination [Jones *et al.* 2010; Stone *et al.* 2010]. However, the utility of other adjunctive therapies in combination with RTX for AAV is not clear. This lack of clarity contrasts with uses of RTX alongside alternate immunosuppressive agents in other autoimmune diseases. For example, in rheumatoid arthritis the use of methotrexate in combination with RTX is well established [Edwards *et al.* 2004; Cohen *et al.* 2006; Emery *et al.* 2006; Greenwald *et al.* 2011]. Nonetheless, when RTX is used for AAV, there is no evidence that the use of additional immunosuppressive agents beyond GCS improves outcomes. In a retrospective review of 65 consecutive patients who received RTX for refractory AAV at four centers in the UK, Jones and colleagues found no difference in the time to relapse among those who received additional immunosuppressive agents (which included methotrexate, azathioprine, mycophenolate mofetil, and intravenous immunoglobulin) and those who stopped all such adjunctive medications [Jones *et al.* 2009]. The addition of CYC to a RTX-based regimen is also of unclear benefit. In the RITUXVAS trial, patients who received RTX were also treated with two to three infusions of CYC, dosed at 15 mg/kg [Jones *et al.* 2010]. By contrast, the patients in the control arm received six to eight infusions of CYC, also at 15 mg/kg. Rates of sustained remission were similar between the two groups. This outcome, whereby the success rate of a RTX-based therapy was similar to a standard-dose CYC-based regimen, was also seen in the RAVE trial [Stone *et al.* 2010]. However, in the RAVE trial, patients who received RTX were not treated with CYC, or any other immunosuppressive medications except GCS. It is therefore not clear whether the application of intravenous CYC pulses in combination with RTX and GCS

provides any therapeutic benefit beyond the effects of RTX and GCS alone, but it may add toxicity. In what may be considered a window into common practice, three recent retrospective studies that described the use of multiple courses of RTX for AAV all reported that the vast majority of patients were taken off other immunosuppressive agents (with the exception of GCS) either upon initiating RTX or soon thereafter [Rhee *et al.* 2010; Cartin-Ceba *et al.* 2012; Smith *et al.* 2012]. Simply put, the routine use of alternative immunosuppressive agents in combination with RTX is not supported on the basis of current evidence.

Another area of uncertainty with respect to combination therapy in AAV concerns the use of plasma exchange in conjunction with RTX for remission induction. The appropriate indications for plasma exchange for AAV are not well established, though there is some evidence for benefit in patients who present with severe renal involvement, and based on the experience with antglomerular basement membrane disease, there may be theoretical benefit for patients with pulmonary–renal syndrome [Szpirer *et al.* 2011; Walsh *et al.* 2011, 2013]. When plasma exchange is combined with RTX for remission induction in AAV, the timing of the first RTX infusion in relation to plasma exchange deserves consideration, as plasma exchange will remove unbound RTX from the circulation. While the optimal time for RTX administration is not certain, our practice is to wait until the completion of the full course of plasma exchange (which we typically perform in seven sessions). Alternatively, one can apply the first RTX infusion 48–72 h prior to the first plasma exchange session.

Rituximab for EGPA

In comparison to the accumulated knowledge regarding the use of RTX in GPA and MPA, the experience with RTX for the treatment of EGPA remains far more limited. Beyond the cases of EGPA that have been reported as parts of series examining RTX for refractory AAV generally [Smith *et al.* 2006; Roccatello *et al.* 2008, 2011; Jones *et al.* 2009; Lovric *et al.* 2009], several additional case reports have specifically described the successful use of RTX for EGPA that was refractory to conventional immunosuppressant medications, as summarized in Table 4 [Kaushik *et al.* 2006; Koukoulaki *et al.* 2006; Pepper *et al.* 2008; Saech *et al.* 2010; Donvik and Omdal, 2011]. The first prospective,

Table 4. Rituximab for eosinophilic granulomatosis with polyangiitis: review of published case series.

Study	Study design	Number of patients	Rituximab dosing regimen for EGPA	Outcome	Citation
Koukoulaki	Retrospective report	2	(1) Four weekly doses of 375 mg/m ² (2) Two doses of 1000 mg, separated by 2 weeks	Remission achieved in both patients	[Koukoulaki <i>et al.</i> 2006]
Kaushik	Retrospective report	1	Three weekly doses of 375 mg/m ²	Remission achieved	[Kaushik <i>et al.</i> 2006]
Pepper	Retrospective report	2	Two doses of 1000 mg, separated by 2 weeks	Remission achieved in both patients	[Pepper <i>et al.</i> 2008]
Saech	Retrospective report	1	Two doses of 1000 mg, separated by 2 weeks	Remission achieved	[Saech <i>et al.</i> 2010]
Donvik	Retrospective report	2	Two doses of 1000 mg, separated by 2 weeks	Remission achieved in both patients	[Donvik and Omdal, 2011]
Cartin-Ceba	Prospective, open-label pilot study	3	Four weekly doses of 375 mg/m ²	Remission achieved in all three patients	[Cartin-Ceba <i>et al.</i> 2011]

EGPA, eosinophilic granulomatosis with polyangiitis.

open-label pilot study designed to evaluate the safety and efficacy of RTX in EGPA was reported in 2011 [Cartin-Ceba *et al.* 2011]. This small study investigated the use of RTX in three patients with EGPA with active renal disease. Following treatment with RTX, the renal disease activity was successfully controlled in all three patients, and no significant adverse events occurred. These promising results provide a rationale for future investigations into the safety and efficacy of RTX in EGPA.

Rituximab following kidney transplantation in patients with AAV

Kidney transplantation is the treatment of choice for patients with end-stage renal disease secondary to AAV. Post transplantation, the rates of subsequent AAV disease flares in these patients are reduced due to the use of potent antirejection immunosuppression [Gera *et al.* 2007; Geetha *et al.* 2011]. However, relapses of AAV do occur and may adversely impact the renal allograft. Traditionally, such relapses have been treated with CYC and GCS, but CYC carries substantial risk of toxicity for patients following transplantation. Preliminary evidence suggests that RTX may be a suitable alternative for the treatment of AAV flares following kidney transplantation [Geetha *et al.* 2007; Hermle *et al.* 2007].

Unanswered questions regarding the use of rituximab in AAV

In addition to questions surrounding the use of RTX for remission induction in EGPA and for remission maintenance in GPA and MPA, several other questions remain regarding the use of RTX in AAV. First, given that all of the patients studied in RAVE and RITUXVAS were ANCA positive, it remains unclear whether RTX is also effective in ANCA-negative patients. Second, it is not yet established whether RTX has a clear role in the treatment of limited GPA and MPA, as both RAVE and RITUXVAS included only patients with severe disease. To this point, only anecdotal reports describe the experience with RTX for patients with limited disease [Seo *et al.* 2008]. Finally, the optimal dosing regimen for a treatment cycle of RTX for AAV has not clearly been determined. Most published reports describing the use of RTX for remission induction in AAV, including both RAVE and RITUXVAS, utilize a RTX regimen consisting of four weekly doses of 375 mg/m², in line with the FDA approved regimen for non-Hodgkin lymphoma. However, a few observational studies have reported good results with respect to remission induction with the RTX regimen that was FDA approved for use in patients with rheumatoid arthritis: two 1 g doses of RTX separated by 14 days [Jones *et al.* 2009; Taylor *et al.* 2009; Mansfield

et al. 2011]. Whether this simplified two-dose RTX regimen is as effective as the traditional four-dose regimen remains to be tested.

Safety considerations when using rituximab for AAV

Based on the experience to date, RTX appears to be well tolerated in the vast majority of patients with AAV in whom it is used. In both the RAVE and RITUXVAS trials, the frequency and severity of adverse events were similar among patients who received RTX- and CYC-based treatment regimens [Jones *et al.* 2010; Stone *et al.* 2010]. Furthermore, on extended follow up of each trial, adverse event rates remained similar in the two treatment arms [Jones *et al.* 2011; Stone *et al.* 2011]. Nonetheless, there are important potential side effects to be considered when contemplating initiating RTX in a patient with AAV. These potential side effects include infusion reactions, opportunistic infections, reactivation of latent viral infections, late-onset neutropenia, hypogammaglobulinemia, and pulmonary toxicity. Special consideration should also be given to women of childbearing years as to potential effects on future pregnancies.

Infusion-related adverse events are the most common side effects associated with RTX therapy. These infusion reactions, which are usually mild, but have rarely manifested as angioedema, bronchospasm, and blood pressure perturbations, occur in 2–17% of patients, typically only with the first infusion [Larsen and Jacobsen, 2013]. To reduce the rate of infusion-related adverse events, we recommend treatment with an antihistamine, acetaminophen, and methylprednisolone prior to RTX infusion [Gottenberg *et al.* 2005; Larsen and Jacobsen, 2013].

Patients who have undergone treatment with RTX are susceptible to opportunistic infections as long as they remain B-lymphocyte depleted. Potential opportunistic infections include *Pneumocystis* pneumonia, despite the traditional association between *Pneumocystis* defense and T-cell immunity [Hugle *et al.* 2010; Martin-Garrido *et al.* 2013]. Adequate prophylaxis against *Pneumocystis* should be provided to all patients who are treated with RTX until B-lymphocyte populations are reconstituted.

Reactivation of latent viral infections also occurs rarely following treatment with RTX. All patients

should undergo serologic screening for viral hepatitis prior to initiating RTX therapy, as reactivation of hepatitis B following treatment with RTX has been reported, including instances of progression to fatal fulminant hepatic failure [Sarrecchia *et al.* 2005; Perceau *et al.* 2006]. If RTX therapy is being considered in an occult carrier of the hepatitis B virus (that is, a patient whose serologic studies come back negative for hepatitis B surface antigen, but positive for hepatitis B core antibody), lamivudine prophylaxis is recommended [Cooper and Arnold, 2010]. Significant attention has also been paid to the potential of RTX therapy to increase the risk of progressive multifocal leukoencephalopathy (PML), a devastating demyelinating disease of the central nervous system caused by reactivation of the John Cunningham virus. In 2007, following reports of fatal PML in patients treated with RTX, the FDA added a black box warning regarding PML to RTX's product labeling. PML has been reported in patients with systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and cryoglobulinemic vasculitis who received RTX [Carson *et al.* 2009; Clifford *et al.* 2011; Molloy and Calabrese, 2012]. However, the risk of PML attributable to RTX is unclear, as PML also occurs in patients with autoimmune diseases who have never been exposed to RTX, including patients with AAV [Choy *et al.* 1992; Calabrese and Molloy, 2009]. In the case of rheumatoid arthritis, the increased risk of PML has been estimated at about one case per 25,000 RTX-treated individuals [Clifford *et al.* 2011]. While the risk of developing PML due to RTX exposure is small, it should always be discussed with a patient before initiating treatment [Calabrese and Molloy, 2009].

Late-onset neutropenia is another adverse effect that has been associated with RTX, occurring in approximately 5% of patients who have received RTX for the treatment of autoimmune diseases, and perhaps more commonly in patients with AAV [Tesfa *et al.* 2011; Besada *et al.* 2012]. By definition, late-onset neutropenia occurs at least 4 weeks after completion of a cycle of RTX, and most cases appear several months after RTX administration [Tesfa *et al.* 2011; Besada *et al.* 2012]. Often, RTX-associated late-onset neutropenia is clinically silent and self-limited, and therefore surveillance of neutrophil counts in asymptomatic patients is likely unnecessary. However, the neutropenia can be complicated by neutropenic fever or infection, in which case

administration of granulocyte macrophage colony-stimulating factor can be considered [Tesfa *et al.* 2011; Besada *et al.* 2012].

Sustained hypogammaglobulinemia has also been reported in patients with AAV who have been treated with RTX [Roubaud-Baudron *et al.* 2012; Venhoff *et al.* 2012; Besada *et al.* 2013]. The risk of sustained hypogammaglobulinemia may be increased among those who receive repeated RTX courses (as with remission maintenance therapy) or who receive RTX following CYC. However, the clinically relevant question as to whether the reduced immunoglobulin levels that are associated with RTX exposure lead to increased infection rates remains unanswered [Specks *et al.* 2011; Cartin-Ceba *et al.* 2012]. Consequently, it is unclear whether surveying asymptomatic patients for hypogammaglobulinemia is warranted. Certainly, patients who develop recurrent infections following RTX therapy should be evaluated for hypogammaglobulinemia, and those who are found to have depressed immunoglobulin levels should be treated according to standard practices concerning acquired hypogammaglobulinemias.

Pulmonary parenchymal toxicity manifesting as interstitial pneumonitis has also been associated with RTX therapy [Burton *et al.* 2003; Ennishi *et al.* 2008; Liu *et al.* 2008]. The frequency of pulmonary toxicity due to RTX remains undetermined, but a recent retrospective survey found only one case among 831 patients treated with RTX at a single center over the course of 9 years [Yannick, 2013]. Most cases of RTX-associated lung injury resolve with discontinuation of RTX and initiation of GCS, but some cases have been fatal [Bitzan *et al.* 2009]. When evaluating a possible instance of RTX-associated lung injury, it is imperative that an infectious etiology be considered and ruled out.

An additional consideration regarding the safety of RTX concerns its use in women during or in advance of pregnancy. RTX crosses the placenta, and when administered in the second or third trimesters, maternal and fetal serum drug levels are similar [Ostensen and Forger, 2011]. Chakravarty and colleagues performed an analysis of the RTX global drug safety database and identified 153 pregnancies with known outcome that were associated with maternal RTX exposure [Chakravarty *et al.* 2011]. Ninety (59%) of these pregnancies resulted in live birth, while 33 pregnancies (21%) ended in first-trimester miscarriage, one fetal loss

occurred at 20 weeks' gestation due to an umbilical cord knot, and one maternal death occurred due to complications of the underlying disease. The remaining 28 pregnancies (18%) were electively terminated. Of the 90 live births, 22 infants (24%) were born prematurely and one infant died at 6 weeks. Two infants (2%) were born with congenital malformations, 11 (12%) were reported to have hematologic abnormalities at birth, and 4 (4%) had neonatal infections. However, these data must be considered in the context of significant confounding factors that almost certainly affected pregnancy outcomes. Only limited information was available regarding concomitant medication exposures or maternal disease severity. In a subset of 70 pregnancies that occurred in the setting of clinical trials, concomitant exposure to potentially teratogenic medications, including MTX, mycophenolate mofetil, and combination chemotherapy, was noted in over half of the pregnancies. Recently, Pendergraft and colleagues reported more favorable experiences with respect to gestational RTX exposure in a small retrospective case series [Pendergraft *et al.* 2013]. Eight pregnancies were observed in six women receiving RTX treatment for vasculitis. Seven of these pregnancies (88%) resulted in live birth, while one ended in first-trimester miscarriage. Only one of the seven live births (14%) occurred prematurely. Interestingly, fetal cord blood was obtained at delivery in three instances in which maternal peripheral B lymphocytes were undetectable, and in all three cases B cells were at normal levels in fetal cord blood. Based on the experience to date, the safety of RTX during and prior to pregnancy remains uncertain. Some have recommended that women be counseled to avoid pregnancy for 6–12 months after RTX exposure [Chakravarty *et al.* 2011; Ostensen and Forger, 2011]. Given the uncertainties, clinicians are encouraged to report pregnancies with RTX exposure to regulatory authorities.

One further consideration with the use of RTX in AAV is the potential development of human antichimeric antibodies (HACAs). HACAs can be induced by the administration of any monoclonal antibody chimera, including RTX, and their formation during treatment with the anti-TNF α chimeric monoclonal antibody infliximab is particularly well documented [Afif *et al.* 2010]. Based primarily on experiences in patients undergoing treatment for lymphoma and rheumatoid arthritis, HACAs have been thought to form only rarely in response to RTX [Davis *et al.* 2000; Edwards

et al. 2004]. However, HACAs have been observed more frequently in patients treated with RTX for other disease processes [Looney *et al.* 2004; Albert *et al.* 2008; Fervenza *et al.* 2008]. It is unclear whether the underlying disease affects the formation of HACAs during RTX treatment, or whether differences in their occurrence are attributable to different dosing regimens, with increased RTX doses preventing the formation of HACAs more effectively than lower doses [Fervenza *et al.* 2010]. In the case of RTX for AAV, neither the rate nor the significance of HACAs is known. A high titer of HACA has rarely been associated with the development of a RTX-associated serum sickness [Goto *et al.* 2009]. In addition, theoretically, the presence of HACAs may result in reduced efficacy of future courses of RTX, but this possibility is unproven. Currently, routine assessment for the presence of RTX-associated HACAs is not recommended.

Finally, when considering that a major rationale for the use of RTX in AAV is the desire to avoid the toxicities associated with CYC, it may be surprising to note that in both the RAVE and RITUXVAS trials, the rates and severity of adverse events were similar among patients receiving RTX- and CYC-based treatment regimens, and RTX did not have an obviously more favorable safety profile [Jones *et al.* 2010; Stone *et al.* 2010]. There are several possible explanations for the observed equivalence of overall adverse effects in the treatment arms of these studies. First, in both studies all adverse events were recorded, including those related to the disease itself, those related to GCS use and those attributed to the study medication, and the majority of recorded adverse events occurred within the first 3 months after enrollment. Nevertheless, the frequency of leukopenia as well as of pneumonia was higher in the CYC arm of the RAVE trial than in the RTX arm [Stone *et al.* 2010; Specks *et al.* 2013]. Second, the studies were not designed to detect two of the most feared complications of CYC therapy: malignancy and infertility. High rates of leukemia and bladder cancer have been associated with cumulative doses of CYC in excess of 36 g, which may be observed in patients requiring multiple courses of remission induction in the setting of relapsing disease [Faurschou *et al.* 2008]. The risk of malignancy is a late complication of CYC therapy, and would not be expected to be captured in the limited timeframe of the RAVE and RITUXVAS trials [Jones *et al.* 2010; Stone *et al.*

2010]. Similarly, gonadal toxicity attributable to CYC would not be captured in the RAVE or RITUXVAS trials, as neither was designed to detect effects on fertility. Nonetheless, gonadal toxicity is well established in association with CYC, even with the short CYC courses used for remission induction in AAV [Boumpas *et al.* 1993; Huong *et al.* 2002; Clowse *et al.* 2011]. In short, in an individual patient, a desire to avoid the potential toxicities of CYC may inform a decision to use RTX for remission induction in AAV, despite the similar toxicity profiles observed between RTX- and CYC-based therapies in the RAVE and RITUXVAS trials. However, practitioners and patients should bear in mind that the full long-term effects of RTX remain unknown, especially with prolonged, repetitive use.

Conclusion

Just over a decade since its first reported use in a patient with GPA, RTX has emerged as an important addition to the armamentarium of treatment options for AAV. RTX in combination with GCS is now well established as a safe and effective alternative to CYC for remission induction in severe GPA and MPA that has been approved by regulatory agencies across the globe. RTX is now also widely considered to be the preferred agent for the treatment of severe relapses of these diseases. Moreover, RTX has become the first-line remission induction agent for patients who failed to respond satisfactorily to CYC or who have contraindications for use of CYC. In addition, several retrospective studies have found encouraging results with the use of RTX for remission maintenance in GPA and MPA and have led to forthcoming randomized controlled trials. The utility of RTX for the treatment of EGPA remains unproven, but initial reports of its efficacy have provided a rationale for further study. Overall, the experience with RTX in the treatment of AAV has been extremely positive, and RTX is now firmly established as a key therapeutic agent for the management of AAV syndromes.

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