

# Comparisons of Guidelines and Recommendations on Managing Antineutrophil Cytoplasmic Antibody – Associated Vasculitis



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Antineutrophil cytoplasmic antibodies–associated vasculitis (AAV) is associated with high morbidity or mortality, especially if not promptly diagnosed and treated. Many inroads have been made in the understanding of the pathophysiology that leads to exploration of novel therapies. Randomized controlled trials over the last 2 decades have better delineated and expanded therapeutic options and set the stage for an evidence-based approach. Since 2014, 4 scientific societies have systematically reviewed the existing data and have formulated evidence-based recommendations for the management of AAV. These recommendations cover diagnosis, remission induction and maintenance treatment, and prevention of long-term complications. This review is a comparative analysis of the recently published recommendations of the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association, the British Society of Rheumatology, the Canadian Vasculitis Research Network, and the Brazilian Society of Rheumatology, and aims to determine common ground among them and highlights the differences among the recommendations.

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Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitides (AAV) are a heterogeneous group of systemic necrotizing small vessel vasculitides. More than 90% of AAV patients have circulating ANCA. AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Several landmark trials in the last 2 decades have harmonized and optimized the treatment of AAV, which was a frequently fatal disease before the introduction of high-dose glucocorticoids (GCs) and cyclophosphamide (CYC). More recent concerns have been the cumulative toxicity of these agents and management of a chronic relapsing disease course. More effective and safer induction and maintenance therapy regimens have emerged as a result of these trials. Guidelines for management

of AAV have been published by various medical societies. This review compares 4 guidelines published in the English language, from the: (i) British Society for Rheumatology (BSR) and British Health Professionals for Rheumatology (BHPR) (2014),<sup>1</sup> updated from their 2007 guidelines<sup>2</sup>; (ii) the Canadian Vasculitis Research Network (CanVasc) (2015)<sup>3</sup> developed by members of the core committee of the CanVasc research network; (iii) the European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) (2016),<sup>4</sup> developed by an international task force representing EULAR, ERA, and the European Vasculitis Society (EUVAS), updated from their 2008 guidelines<sup>5</sup>; and (iv) the Brazilian Society of Rheumatology (SBR) (2017), which focused only on induction therapy of AAV (Table 1).<sup>6</sup> There are no guidelines published from the United States, and although the American College of Rheumatology did not endorse the recently published EULAR/ERA-EDTA guidelines, an American College of Rheumatology representative contributed to

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**Table 1.** Features of the compared guidelines

Society	Publication year	Stake holders	Geography
BSR/BHPR	2014	Vasculitis physician experts from multiple specialties and allied health care professional representatives	United Kingdom
EULAR/ERA-EDTA	2015	International task force representing EULAR, ERA, and EUVAS, and including physicians (internists, specialists, and pathologists), patients, nurses	Europe
CanVasc	2016	Vasculitis physician experts from multiple specialties	Canada
SBR	2017	Rheumatologists	Brazil

BHPR, British Health Professionals in Rheumatology; BSR, British Society for Rheumatology; CanVasc, Canadian Vasculitis research network; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Society; SBR, Brazilian Society of Rheumatology.

these guidelines. The strength of the recommendations made by BSR/BHPR, EULAR/ERA-EDTA, and CanVasc is based on the categories of evidence defined by EULAR standardized operating procedures, graded from A (highest) to D (lowest),<sup>7</sup> and the strength of recommendations made by BSR is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system<sup>8</sup> and graded from A (highest) to D (lowest). Our aim was to determine the common ground among the recommendations and highlight the differences among them.

### Diagnosis of AAV

CanVasc and EULAR/ERA-EDTA both recommend obtaining tissue biopsy at diagnosis, if possible; EULAR/ERA-EDTA also recommends biopsy at relapse. BSR/BHPR and CanVasc specifically note that ANCA testing should be performed with indirect immunofluorescence and enzyme-linked immunosorbent assay at diagnosis; BSR/BHPR also recommends testing at relapse, at change of therapy, and at every 6 months during treatment, and annually while off treatment. Indirect immunofluorescence alone is not sufficient for diagnosis for AAV due to the ability of autoantibodies against antigens other than PR3 and MPO to cause a positive staining pattern. A new international consensus statement on ANCA testing recommends initial testing for suspected AAV with immunoassays for PR3 ANCA and MPO ANCA replacing the use of indirect immunofluorescence.<sup>9</sup>

### Disease Classification

All 4 guidelines divide patients into those with life- or organ-threatening disease and those without. CanVasc specifically refers to these groups as severe versus non-severe, which is terminology also used in the EULAR guidelines. The distinction between the 2 categories varies somewhat. For example, CanVasc defines severe disease as the “presence of life- or major organ-threatening manifestations, including severe and progressive kidney involvement; severe alveolar hemorrhage; severe GI,

cardiac, CNS, and/or eye involvements; or any other manifestations considered severe enough to require induction treatment with CYC or RTX.”<sup>3,4</sup> In contrast, BSR/BHPR seems to group more patients into nonsevere disease as “those with no evidence of organ damage who may be considered for alternative induction therapy with MTX or MMF,” and all other patients should be considered to have severe disease and treated with CYC or rituximab (RTX). In addition to these categorizations, CanVasc refers to the use of the 5-factor score for prognostication of EGPA and MPA.

### Remission Induction for Severe Disease

The recommendations made by the 4 guidelines are summarized in Table 2. The protocols for the 3 landmark trials for induction therapy are depicted in Figure 1.

#### Cyclophosphamide

CYC use for remission induction received a grade A recommendation across all 4 guidelines. The preference for i.v. CYC by BSR/BHPR is based on the results of CYCLOPS (Cyclophosphamide Oral versus Pulsed)<sup>10</sup> trial, which demonstrated lower cumulative exposure in the i.v. CYC arm and in earlier randomized controlled trials.<sup>11</sup> EULAR/ERA-EDTA also favored i.v. CYC for this reason, as well as due to a reduced risk of CYC-related bladder complications. SBR and CanVasc recommend either oral or i.v. pulsed CYC. CanVasc also notes the potential lower rate of relapse on longer term follow-up with oral CYC. The standard dosing for oral CYC is 2 mg/kg per day (maximum 200 mg/d), and dosing for i.v. CYC is 15 mg/kg (maximum 1.2 g/pulse), given 3 times 2 weeks apart, and then once every 3 weeks for 3 to 6 months (CYCLOPS).

#### Rituximab

RTX is generally recommended as an alternative to CYC for remission induction of AAV. BSR/BHPR (grade B recommendation) and EULAR/ERA-EDTA (grade A recommendation) recommend it as a first-line alternative without particular restrictions, although EULAR notes that the data remain weakest among patients with EGPA. SBR also recommends it as an alternative, highlighting a particular role in patients in whom CYC is contraindicated or not preferred due to fertility or other concerns, or in those with relapsing disease. CanVasc is the most restrictive, specifying RTX as a first-line remission induction in patients with severe GPA/MPA disease in whom CYC is contraindicated and/or not preferred. None of the guidelines recommend against RTX as first-line induction treatment. The main drawbacks cited are access and/or cost barriers.

#### Glucocorticoids

GCs are an ubiquitous part of front-line induction therapy. Patients with severe disease may be administered i.v. pulse methylprednisolone initially. All

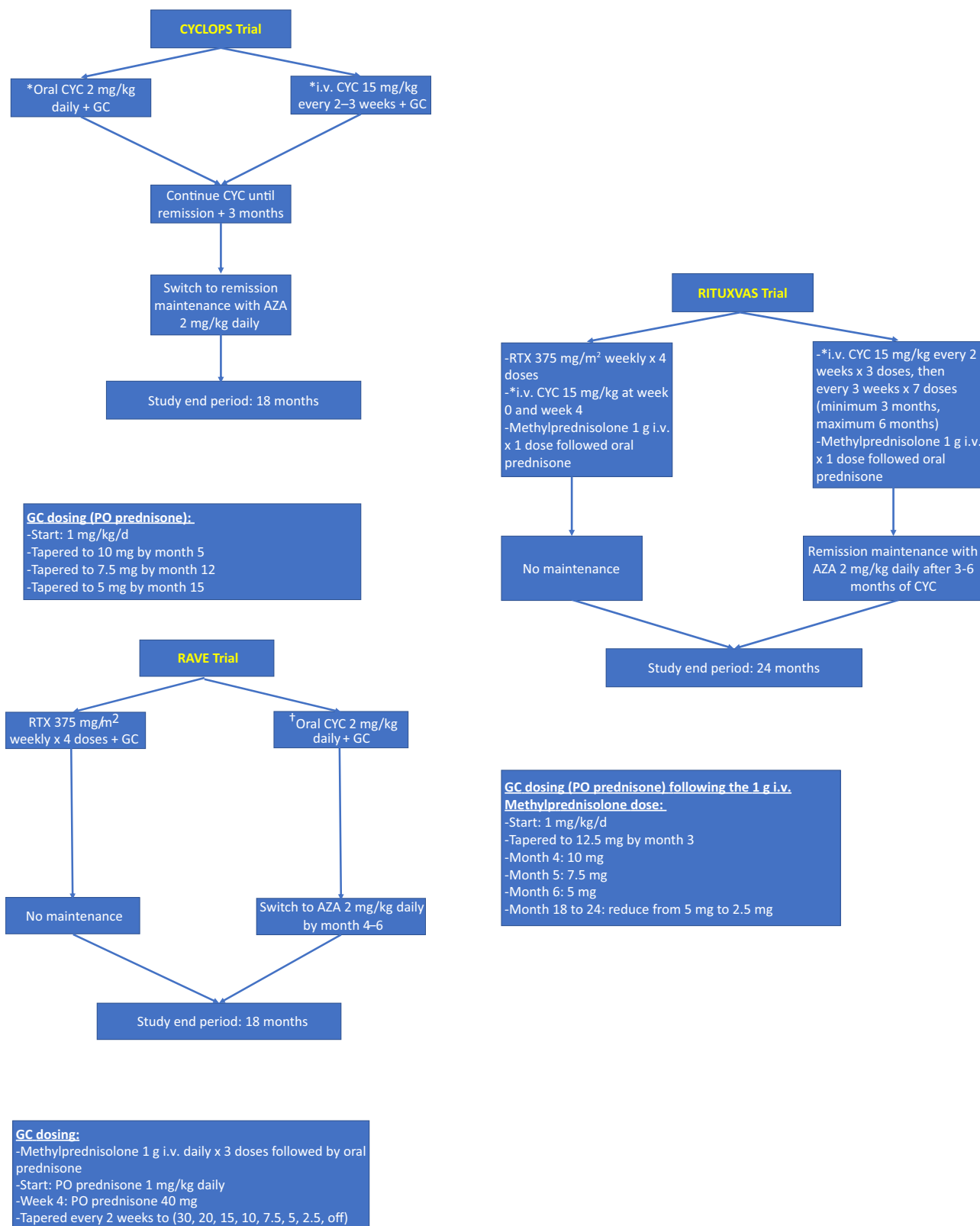
**Table 2.** Induction therapy in severe disease and refractory disease

Category		Common view	Differences
Severe disease	CYC	CYC with high-dose steroids for first-line induction is universally recommended. GC + CYC therapy should be continued for 3–6 mo, then switched to a less toxic maintenance therapy when remission is achieved. Dosing adjustments should be made for age and renal function (BSR, CanVasc, SBR)	Formulation SBR and CanVasc: Either oral or i.v. pulsed CYC. BSR and EULAR: Favor i.v. pulsed CYC Dosing BSR, SBR: Standard 15 mg/kg, max 1.2 g (SBR) 1.5 g (BSR) per pulse, first 3 pulses at 2-wk intervals, then every 3 wks for total of 3–6 mos EULAR: not specified, but refers to CYCLOPS trial, which is same as the preceding
	RTX	All 4 guidelines recommend RTX with high-dose steroids for first-line induction in patients in whom CYC is contraindicated or not preferred	First line RTX: BSR and EULAR: recommend RTX first-line in general for all AAV patients; EULAR notes that the data are weakest among patients with EGPA. SBR: recommends RTX as an alternative in patients in whom CYC is contraindicated or not preferred CanVasc: recommends GC + RTX as first-line remission induction in patients with severe GPA or MPA in whom CYC is contraindicated or not preferred Dosing: SBR: rituximab should be given at 375 mg/m <sup>2</sup> weekly for 4 wks, or in 2 infusions 2 wks apart at a dose of 1 g. BSR and CanVasc: recommend 375 mg/m <sup>2</sup> weekly for 4 wks
	GC dosing	Every patient should receive systemic GCs. In severe disease, patient may be started first on i.v. pulse methylprednisolone	Oral GC dosing and schedule: BSR: start oral prednisolone at 1.0 mg/kg per day (max, 60 mg/d), tapered to 15 mg per day at 12 wks. SBR: start prednisone at 0.5–1.0 mg/kg per day (max, 80 mg/d) for 1–4 wks, taper by 10 mg for 2–4 wks until 20 mg/d, then reduce by 2.5–5.0 mg every 2–4 wks until full withdrawal. CanVasc: start prednisone equivalent at 1.0 mg/kg per day (max, 60–80 mg/d) for 1 mo, then gradually tapered EULAR: 1.0 mg/kg per day (max, 80 mg/d) i.v. pulse methylprednisolone dosing: BSR: 200–500 mg/d before or with first 2 doses of CYC CanVasc: 500–1000 mg/d for 1–3 days SBR: 500–1000 mg/d or 15 mg/kg per day for 1–3 days EULAR: not specified
	i.v. Ig		SBR: patients with infection and persistent disease, with disease refractory to GC + CYC, or contraindications to CYC or RTX should be given i.v. Ig CanVasc: there is insufficient evidence for any specific recommendation of i.v. Ig, but it could have a role in certain subgroups such as adjunct in refractory disease, pregnant women in whom other immunosuppressants are contraindicated, and those with current severe infection or recurrent severe infections EULAR: i.v. Ig can be given as an adjunct therapy in the refractory setting.
	Other agents	Etanercept should not be used to treat AAV; other TNF- $\alpha$ inhibitors have limited evidence (BSR, CanVasc, SBR)	SBR: recommends against azathioprine in the remission induction setting BSR, CanVasc: Possible experimental options for refractory disease include mepolizumab for patients with EGPA, alemtuzumab (anti-CD52). SBR: other experimental options include guselkumab and leflunomide.
Refractory disease		All refractory patients should be referred to a vasculitis center (BSR, CanVasc, EULAR)	Patients who received CYC: BSR and EULAR: all refractory patients with severe disease who have failed CYC should receive RTX. CanVasc: Severe GPA/MPA patients in whom CYC failed should receive RTX. Patients who received RTX: EULAR: refractory patients who received RTX should now receive CYC. These patients can be considered for more experimental treatments at a vasculitis referral center (BSR, CanVasc). Other strategies include adjunct i.v. Ig and switching from pulsed to oral CYC (when RTX is unavailable/cannot be administered). (EULAR).

BSR, British Society for Rheumatology; CanVasc, Canadian Vasculitis research network; CYC, cyclophosphamide; EULAR, European League Against Rheumatism; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RTX, rituximab; SBR, Brazilian Society of Rheumatology.

guidelines acknowledge that the data on the benefits of i.v. methylprednisolone are limited. BSR/BHPR recommends 250 to 500 mg pulse before or with the first 2 CYC infusions. CanVasc and SBR recommend using i.v. methylprednisone 500 to 1000 mg/d for 3 days preceding oral prednisone in life-threatening and/or organ-threatening AAV. CanVasc gives a grade B recommendation, and SBR gives a grade C recommendation for use of i.v. methylprednisone. EULAR does not provide specific recommendations on the use of i.v.

methylprednisolone. Patients should be started on oral prednisone equivalent to 0.5 to 1 mg/kg per day with a maximum of 60 to 80 mg/d, and then tapered. The CanVasc discusses prednisone-tapering protocols in the RAVE (rituximab for ANCA-associated vasculitis)<sup>12</sup> and RITUXVAS (rituximab versus cyclophosphamide in ANCA-associated vasculitis)<sup>13</sup> trials in the supplement<sup>13</sup> and recommends that a prednisone dose of 1 mg/kg per day be continued for a maximum of 1 month, with a gradual taper and dose adjustment based on the clinical



**Figure 1.** Treatment Protocols in CYCLOPS, RAVE, and RITUXVAS Trials. \*CYC dose adjusted for renal function and age. †CYC dose adjusted for renal function. AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoids; PO, oral; RITUXVAS, rituximab versus cyclophosphamide in ANCA-associated vasculitis; RTX, rituximab.

course of the patient (recommendation C). The EULAR/ERA-EDTA recommends a target dose of 10 to 15 mg of prednisone daily after 12 weeks of treatment. BSR recommends rapid tapering for prednisone 15 mg/d at 12

weeks. SBR recommends a slow prednisone-tapering regimen, with an initial daily dose of 0.5 to 1.0 mg/kg per day (maximum 80 mg/d) for 1 to 4 weeks, followed by tapering 10 mg every 2 to 4 weeks until 20 mg/d.

**Table 3.** Recommendations for use of plasma exchange in induction therapy of antineutrophil cytoplasmic antibodies–associated vasculitides

Disease manifestation		Common view	Differences
Plasmapheresis	Rapidly progressive glomerulonephritis		CanVasc states there is insufficient evidence to recommend plasmapheresis for patients with severe renal or pulmonary involvement, but it may be a reasonable adjuvant if a patient is refractory to high dose GC + CYC/RTX. BSR, SBR, and EULAR recommend consideration of plasma exchange for RPGN with serum Cr greater than ~500 $\mu\text{mol/l}$ (5.7 mg/dl).
Plasmapheresis	Diffuse alveolar hemorrhage	There is insufficient evidence, but may be considered/possibly of benefit as an adjuvant when patients are in this setting and refractory to standard GC + CYC/RTX (all 4 guidelines)	

BSR, British Society for Rheumatology; CanVasc, Canadian Vasculitis research network; CYC, cyclophosphamide; EULAR, European League Against Rheumatism; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; RTX, rituximab; SBR, Brazilian Society of Rheumatology.

Afterward, they suggest that dose reduction should be 2.5 to 5.0 mg every 2 to 4 weeks until complete withdrawal. The initial starting dose of prednisone received a grade B recommendation across all guidelines, whereas the tapering regimen received a grade C from CanVasc and BSR/BHPR and grade D from SBR.

Regarding the duration of GC therapy, there are differences across the guidelines. CanVasc states low-dose GCs should be part of the initial maintenance therapy and notes that there is not enough evidence yet to support the optimal duration of low-dose GCs. EULAR does not provide recommendations on GC duration. SBR recommends that the duration of GC therapy should be at least 6 months, and, in some instances, it may be up to 1 or 2 years. Longer duration of GCs may be necessary in relapsing patients (recommendation A by BSR/BHPR and recommendation B by BSR).

### Recommendations Regarding Use of Plasma Exchange

CanVasc states that plasma exchange may be a reasonable adjuvant therapy for patients who deteriorate due to active vasculitis despite ongoing remission induction therapy with high-dose GCs plus CYC or RTX. However, there is insufficient evidence to recommend plasma exchange as first-line therapy in any patient with AAV (grade D recommendation). BSR/BHPR and EULAR/ERA-EDTA recommend that plasma exchange should be used along with CYC and GCs in patients presenting with severe renal failure with serum creatinine  $>500 \mu\text{mol/l}$  (grade B recommendation) or life-threatening manifestations, such as pulmonary hemorrhage (grade C recommendation). SBR recommends use of plasma exchange along with GCs and CYC in patients with serum creatinine  $>5.8 \text{ mg/dl}$  (grade A recommendation) and notes there is insufficient evidence to support plasma exchange to treat AAV patients who present with alveolar hemorrhage (Table 3).

CanVasc and EULAR/ERA-EDTA state that the ongoing PEXIVAS (Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm

Antibody Associated Vasculitis) trial may provide more definitive answers regarding efficacy and safety of plasma exchange in AAV.

### Remission Induction for Nonsevere Disease *Methotrexate and Mycophenolate Mofetil*

Generally, patients with nonsevere and nonorgan-threatening disease are recommended a milder regimen than CYC or RTX. BSR/BHPR and EULAR guidelines recommend systemic GCs with either methotrexate (MTX) or mycophenolate mofetil (MMF) (grade B recommendation for MTX and grade C recommendation for MMF), whereas CanVasc and SBR only recommend GCs with MTX (grade A recommendation). The EULAR/ERA-EDTA guidelines emphasize that nonsevere and nonorgan-threatening had different meanings and listed organ-specific scenarios when MTX use was inappropriate. All guidelines recommend dose adjustment of MTX for renal function. EULAR/ERA-EDTA states that MTX can be used in the absence of renal involvement and BSR/BHPR states that MTX should not be used in patients with moderate or severe renal involvement (grade B recommendation). CanVasc recommends dose adjustment when the glomerular filtration rate (GFR) is between 50 and 80 ml/min per square meter, to consider alternative therapy when GFR is  $<50 \text{ ml/min}$  per square meter, and to avoid use when GFR is  $<10 \text{ ml/min}$  per square meter. SBR recommends that the MTX dose should be decreased by 50% in patients with GFRs of 10 and 50 ml/min per square meter and to avoid use when GFR is  $<10 \text{ ml/min}$  per square meter (grade D recommendation).

### *Patients With Nonsevere EGPA or MPA Without Renal Involvement*

CanVasc states that it is acceptable to treat patients with nonsevere EGPA or MPA without renal involvement with GCs alone. It cites 2 studies from the French Vasculitis Study Group, which showed that GCs alone induced remission in a significant portion of patients—93% of patients with EGPA<sup>14</sup> and 79% of patients with MPA or polyarteritis nodosa<sup>15</sup>—although there were with significant relapse rates. In these studies, patients



**Table 4.** Maintenance therapy and management of relapse

Category	Common view	Differences
Maintenance	Patients with severe AAV in remission after GC + CYC should receive maintenance therapy with GC + an immunosuppressant drug, among which AZA and MTX are most universally recommended.	<p>Population who should receive maintenance therapy: BSR, CanVasc: severe AAV in remission after GC + CYC CanVasc: there is no clear evidence/consensus to guide decisions for maintenance after RTX EULAR: not specified</p> <p>Agent: BSR: AZA or MTX in combination with GC. LEF or MMF may be alternatives. RTX is also an option. CanVasc: AZA or MTX, initially in combination with low-dose GC. LEF and MMF are second-line alternatives. RTX is also an option particularly in PR3-ANCA-positive GPA. TMP/SMX can be considered as adjuvant maintenance therapy after normal maintenance with an immunosuppressant in patients with GPA. EULAR: Patients with GPA/MPA should receive low-dose GC and AZA, RTX, MTX, or MMF (greatest consensus for AZA); those with EGPA should receive AZA. LEF is a second-line option. TMP/SMX can be considered as adjuvant therapy but is not recommended alone.</p> <p>Duration of immunosuppressant agent in general: BSR, EULAR: 24 mos after duration. CanVasc: 18 mos, but no clear evidence.</p> <p>Duration of immunosuppressant agent for PR3-ANCA+ patients: BSR: up to 5 yrs EULAR: evidence still pending, but 36 mos</p> <p>Duration of GCs: BSR: patients in remission after 1 yr can begin to taper GCs. After GCs are withdrawn, the other immunosuppressive agent can be tapered after 6 mos. - CanVasc: no clear evidence for GC duration</p>
Relapse	<p>Patients who have a severe relapse should receive GC + CYC or RTX (BSR, CanVasc, EULAR).</p> <p>Nonsevere relapse may be managed with increasing the dosage of GC in addition to optimizing current immunosuppressant agent (BSR, CanVasc, EULAR).</p>	<p>Severe relapse BSR: Severe relapse should be treated with GC + CYC or RTX. If the patient is trying a second round of GC + CYC, the dose of GC should be increased; addition of i.v. methylprednisolone and PLEX can be considered. Also, drivers for relapse should be identified. CanVasc: Patients who already tried GC + CYC should receive RTX. EULAR: In general, due to the cumulative toxicity of CYC, RTX is recommended over CYC in relapsing disease.</p>

AAV, antineutrophil cytoplasmic antibodies (ANCA)—associated vasculitides; AZA, azathioprine; BSR, British Society for Rheumatology; CanVasc, Canadian Vasculitis research network; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; EULAR, European League Against Rheumatism; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; LEF, leflunomide; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab; SBR, Brazilian Society of Rheumatology; TMP/SMX, trimethoprim/sulfamethoxazole.

in whom GCs failed or patients who relapsed would then receive azathioprine (AZA) or CYC, both of which were effective in that setting.<sup>14,15</sup> None of the other guidelines advocate use of GCs alone.

### Maintenance Treatment

Table 4 provides an overview of the common view and differences across these guidelines.

#### Patient Population

For patients with severe AAV who are in remission after successful induction therapy with GCs + CYC, maintenance therapy is universally recommended across all guidelines, except for SBR, which focuses on induction therapy only. CanVasc is the only guideline that specifically discusses patients who receive GCs + RTX as induction therapy, stating that there is no adequate evidence yet for recommending any specific approach.

#### Maintenance Therapy Selection Among Conventional Immunosuppressants

Remission is defined by EULAR/EUVAS as the complete absence of clinical disease activity, including vasculitis and granulomatous manifestations, whether patients are receiving immunosuppressive therapy or not. EULAR/ERA-EDTA recommends use of low-dose GCs in combination with azathioprine, RTX, MTX, or MMF (in this

order of preference) for remission maintenance. The use of these agents for remission maintenance received a grade A recommendation for GPA and MPA and a grade C recommendation for EGPA. Leflunomide was recommended as a second-line treatment due to adverse effects mentioned by EULAR/ERA-EDTA.

BSR/BHPR and CanVasc recommend use of low-dose GCs combined with AZA or MTX as first-line therapy for remission maintenance (grade A recommendation) and use of MMF (recommendation C by BSR/BHPR and recommendation B by CanVasc) or leflunomide (grade B recommendation for both) as alternatives when patients are intolerant or refractory to AZA and MTX, or in whom these agents are contraindicated. RTX is also recommended as an alternative maintenance agent by BSR/BHPR with a grade C recommendation. The CanVasc guideline has clarified that there is no definitive evidence to guide decisions for maintenance therapy after remission induction with RTX. They recommend use of RTX as an alternative to AZA for remission maintenance therapy, especially in PR3 ANCA-positive patients (grade A recommendation).

#### Duration of Maintenance Therapy

BSR/BHPR and EULAR recommend at least 24 months of immunosuppressive therapy following successful remission induction (recommendation B by BSR/BHPR

and recommendation D by EULAR), whereas CanVasc recommends at least 18 months of maintenance therapy, after which treatment is discontinued at the discretion of the physician according to the individual characteristics, treatment tolerance, and understanding of subsequent relapse risk of the patients (recommendation C). However, patients with PR3 ANCA disease are more likely to relapse and are generally recommended a longer course of maintenance therapy (EULAR, 36 months; BSR/BHPR, up to 5 years). BSR/BHPR is the only guideline that provides guidance on duration of RTX for maintenance therapy: every 4 to 6 months for 2 years (recommendation B). CanVasc is the only guideline to note that there is insufficient evidence to guide optimal GC duration. CanVasc also addresses the use of trimethoprim/sulfamethoxazole (TMP/SMX) as an adjuvant to immunosuppressants or after cessation of immunosuppressive therapy in GPA patients (recommendation C).

### Withdrawal of Treatment

BSR/BHPR recommends that patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment. After GC withdrawal, other immunosuppressive therapy may be tapered after 6 months (recommendation D). No recommendations regarding withdrawal of immunosuppressive treatment are made by the EULAR, CanVasc, and SBR guidelines.

### Treatment of Refractory Disease

BSR/BHPR, EULAR, and CanVasc provide recommendations or statements for treatment of refractory disease, whereas SBR does not specifically address refractory disease. All guidelines underscore that refractory patients should be managed in collaboration with or at a vasculitis referral center. The definition of refractory disease differs across the guidelines. EULAR defines refractory disease as unchanged or increased disease activity after 4 weeks of an appropriate dose of CYC with GCs; lack of response, defined as  $\leq 50\%$  reduction in disease activity score and/or lack of improvement in at least 1 major item after 4 to 6 weeks of treatment; or chronic persistent disease, defined as the presence of at least 1 major or 3 minor items on the Birmingham Vasculitis Activity Score (BVAS) list despite 8 weeks of treatment. CanVasc defines refractory disease as unchanged or worsening disease despite 6 weeks of appropriate remission induction therapy or the presence of persistent disease activity after 3 months of appropriate remission induction therapy. BSR/BHPR defines refractory disease as progressive disease that is unresponsive to current therapy and recommends that drivers for refractory disease should be sought, and clinicians should consider revision of the clinical

diagnosis. EULAR and CanVasc recommend that it is important to ensure that the diagnosis is correct, alternate infectious and/or neoplastic diagnoses have been excluded, and that the treatment, including drug choice, dosage and duration, was appropriate in all cases of apparent refractory disease.

### Rituximab and Cyclophosphamide

Patients with severe AAV in whom remission induction with first-line CYC + GCs has failed should receive RTX (recommendation A by BSR/BHPR and recommendation C by EULAR and CanVasc). CanVasc specifies this for patients with severe GPA and MPA, noting that the management of EGPA patients is less clear-cut. Because more patients are receiving RTX as a first-line therapy, EULAR also notes that those who received first-line RTX but in whom it failed should receive CYC (recommendation C).

### Other Treatments in the Refractory Setting

A variety of other experimental treatments have been used in the setting of refractory disease. I.v. Ig is recommended as an adjunct therapy in refractory AAV by BSR/BHPR, EULAR, and CanVasc (grade C recommendation). BSR/BHPR and CanVasc refer to the use of alemtuzumab for refractory disease (grade D recommendation). Other agents suggested for use in refractory AAV by BSR/BHPR include guselimumab and leflunomide. BSR/BHPR and CanVasc recommend against use of etanercept, an antitumor necrosis factor medication, due to increased risk of infection and malignancy (grade A recommendation). CanVasc and BSR/BHPR refer to use of mepolizumab for refractory EGPA.

### Treatment of Disease Relapse

#### Severe Relapse

The treatment of major and/or severe disease relapse is similar to initial induction treatment and generally consists of high-dose GCs + RTX or CYC (grade A recommendation by BSR/BHPR, EULAR/ERA-EDTA, and CanVasc), with RTX being the more recommended agent. In the RAVE study, among the subgroup of patients who relapsed, RTX was superior to CYC at 6 and 12 months, but the difference was not significant at 18 months. CanVasc recommends use of RTX preferentially for patients who received CYC for initial disease remission induction or a previous disease flare. EULAR/ERA-EDTA favored use of RTX for relapsing disease because of the toxicity associated with cumulative CYC use. BSR/BHPR recommends addition of i.v. methylprednisolone or plasma exchange for severe and/or major relapses (grade C recommendation), and CanVasc notes that there is insufficient evidence to support a recommendation to use plasma exchange as first-line therapy, but suggests that plasma exchange

may be a reasonable adjunct therapy for relapsing patients who deteriorate clinically despite ongoing treatment with GCs plus CYC or RTX (grade D recommendation). For patients who do not receive a second course of CYC, BSR/BHPR recommends that the GC dose be increased. CYC may also be appropriate for patients who received RTX as first-line therapy or who cannot receive RTX because of contraindications.

### Nonsevere Relapse

Patients with nonsevere relapse may be managed by optimizing the immunosuppressive regimen and/or increasing the GC dose. BSR/BHPR, EULAR/ERA-EDTA, and CanVasc recommend treatment of nonsevere relapses with an increase in the GC dose in addition to intensification or modification of the remission maintenance regimen (grade C recommendation) without making specific recommendations on the choice or change of immunosuppressant and duration of therapy after a nonsevere relapse.

### Management of Specific Disease Manifestations Ear, Nose, and Throat Disease and Subglottic Stenosis

Patients with GPA and ear, nose, and throat involvement may require additional local therapy for ear, nose, and throat disease. The treatment of topical mupirocin may be used in patients who have *Staphylococcus aureus* according to the BSR/BHPR and EULAR/ERA-EDTA guidelines. BSR specifically recommends performing a bacterial swab at baseline and at every 6 to 12 months to detect *S. aureus* colonization, which is associated with an increased risk of relapse. However, CanVasc concludes that this is of limited benefit and has not been shown to lower the risk of relapse or progression from a limited ear, nose, and throat to a more systemic form of the disease in GPA patients. SBR discusses subglottic stenosis in particular, recommending that patients with concurrent systemic disease receive systemic therapy, whereas those with subglottic stenosis should only receive local therapy, such as first-line mechanical dilation with long-acting GC injection (grade C recommendation).

### Prophylaxis Against *Pneumocystis jirovecii*

All 4 guidelines recommend prophylaxis for *Pneumocystis jirovecii* in AAV patients receiving induction therapy with CYC or RTX. SBR specifies that all patients with a total lymphocyte count of  $<300$  cells/mm<sup>3</sup> should receive prophylaxis, regardless of immunosuppression therapy. The recommended first-line prophylaxis by all guidelines in the absence of allergy is TMP/SMX at a dose of 400/80 mg daily or 800/160 mg 3 times a week. Dose adjustment for renal impairment is recommended in the SBR guideline. CanVasc recommends continuing *P*

*jirovecii* prophylaxis 3 months after stopping CYC. CanVasc notes that the optimal duration of *P jirovecii* prophylaxis after the RTX-based induction regimen is unknown. CanVasc highlights that there is no consensus on *P jirovecii* prophylaxis for AAV patients who receive monotherapy with high-dose GCs. Except for patients on MTX (with which TMP/SMX interacts), BSR and CanVasc specify that TMP/SMX is generally safe at the prophylaxis dose. BSR recommends that if using TMP/SMX in patients who are on MTX, that it not be given on the same day as MTX. SBR recommends that these patients receive inhaled pentamidine instead of TMP/SMX.

Alternative therapy varies slightly among the guidelines. BSR/BHPR recommends either inhaled pentamidine or dapsone. CanVasc and EULAR/ERA-EDTA both recommend dapsone or atovaquone more than inhaled pentamidine. CanVasc cites a 2008 study that found aerosolized pentamidine to be less effective than TMP/SMX at preventing *P jirovecii*<sup>16</sup>; EULAR states that inhaled pentamidine is less cost-effective and not routinely indicated. SBR recommends inhaled pentamidine only.

### Monitoring and Management of Treatment Side Effects

#### Patients Receiving CYC

BSR/BHPR, CanVasc, and EULAR/ERA-EDTA discuss a number of precautions for patients receiving CYC. During CYC treatment, patients should undergo routine monitoring of blood counts, particularly for leukopenia and/or neutropenia. Patients should also be monitored for renal and liver function with possible therapy adjustments as needed. Patients who receive i.v. CYC should receive adequate hydration and antiemetics during administration. BSR and EULAR/ERA-EDTA notes that the use of Mesna may be considered for possible benefit in preventing cystitis in patients who receive pulse i.v. and oral CYC. Patients who have been exposed to CYC and who have persistent hematuria should be referred for consideration of cystoscopy. BSR and CanVasc also specifically recommend that patients exposed to CYC receive lifelong urinalysis every 3 to 6 months to monitor for hematuria. With respect to fertility, all 4 guidelines discuss the impact on patients of reproductive age, noting the importance of counseling and consideration of substituting RTX when appropriate. BSR more specifically recommends offering patients fertility preservation, such as sperm and oocyte cryopreservation, hormonal ovarian stimulation, use of gonadotropin-releasing hormone analogues during CYC therapy, and so on.

#### Patients Receiving RTX

BSR/BHPR, EULAR/ERA-EDTA, and SBR discuss the importance of measuring serum Ig levels at baseline



and before each course of RTX, with possible therapy modification or replacement therapy as needed. BSR/BHPR and SBR specifically make vaccination recommendations, including hepatitis B, pneumococcal, and annual influenza vaccinations. BSR/BHPR recommends that the vaccine be administered at least 2 weeks before therapy but ideally at 4 to 6 weeks, whereas SBR recommends 3 weeks. SBR also specifies measurement of HIV, hepatitis B virus (HBV), and syphilis serology before infusion, and possible concurrent antiviral treatment for HBV/HIV patients in collaboration with an infectious disease specialist.

#### *Other Adverse Effect Concerns Associated With Immunosuppression*

BSR/BHPR and CanVasc both specify that patients with AAV should have periodic systematic assessment of osteoporosis risk factors with appropriate prophylaxis and treatment. BSR/BHPR lists several other concerns, such as screenings (and appropriate management) for oral candidiasis, cervical invasive neoplasia and/or human papillomavirus among female patients, tuberculosis, thromboembolic risk, and varicella zoster titers.

### **Special Populations**

#### *Pregnancy*

Pregnancy is only specifically discussed in the CanVasc guidelines, which recommends no pregnancy earlier than 6 months after remission and referral to an obstetrician specializing in high-risk pregnancies.

#### *Pediatric Population*

Pediatric patients are also only specifically discussed in the CanVasc guidelines. Referral is recommended to a pediatric specialist at an academic center, with management under or in collaboration with a vasculitis specialist. At diagnosis, pediatric patients should be classified by severity based on EULAR/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society criteria to tailor treatment.<sup>17</sup> Otherwise, they can be treated like adults with appropriate dosing adjustments for age and/or size.

### **General Care Approach and Follow-up**

#### *Setting of Care*

Most of the guidelines (BSR/BHPR, CanVasc, and EULAR) recommend that all patients with AAV be referred to or treated in collaboration with a vasculitis referral center and/or center of excellence, especially if the disease is challenging and in the refractory and/or relapse settings. BSR/BHPR notes that there should be collaboration with a primary care physician to improve monitoring and compliance, although the actual assessment of vasculitic disease should still be by specialists.

#### *Disease Assessment Tools*

BSR/BHPR recommends use of validated tools to assess disease activity and extent of disease. BVAS version 3<sup>18</sup> was recommended for disease activity assessment, and the Vasculitis Damage Index (VDI)<sup>19</sup> was recommended for determining the extent of the irreversible damage resulting from both disease and treatment-related damage. It is also recommended that BVAS and VDI be used by staff trained in their use. Quality of life assessment using SF-36 is recommended by BSR/BHPR. Although these tools are used in clinical trials, BSR/BHPR recommends using these tools in routine practice to facilitate good quality of care and enable auditing of disease outcomes. EULAR, CanVasc, and SBR do not mention use of these disease activity tools.

#### *Frequency of Disease Assessment*

BSR/BHPR recommends disease assessment should occur monthly during remission induction, every 3 months during initial remission maintenance treatment, thereafter every 6 months, and then annually. CanVasc recommends patients receiving remission induction and maintenance therapy to have regular clinical assessment to monitor their treatment response, disease course, and adverse events. Monitoring frequency suggested by CanVasc is monthly during remission induction and every 3 months for 2 years while on remission maintenance therapy, and annually thereafter. No recommendation on frequency of disease assessment is made by EULAR or SBR.

#### *Cardiovascular Risk Factors*

Most of the guidelines (BSR/BHPR, CanVasc, EULAR) specify that patients with AAV should receive periodic systematic assessment of cardiovascular risk factors.

#### *Patient-Centered Care*

Patients with AAV should receive clear education on their disease, management options, side effects, and prognosis. They should be assessed for social and biological impacts, and provided with therapies and support (BSR, EULAR). BSR delves further, recommending using validated tools to assess not only disease activity and/or extent, but also quality of life. It recommends annual holistic reviews of these areas with appropriate resulting action plans, with a specific emphasis on optimizing the patient's chance of maintaining employment. It also discusses complementary and/or alternative medicine, which, although not substantiated by evidence, should be kept accessible to patients for symptomatic management.

### **Conclusions**

This review reveals numerous areas of consensus in the management of AAV, but also highlights fundamental differences among the 4 compared guidelines. These

distinctions exist largely due to a lack of controlled trials in the topic in question, with differing expert opinions, despite an increase in clinical trial activity over the past 2 decades. Some of the differences noted across the guidelines may be attributed to different perspectives for the access and/or cost of treatments. Great strides have been made in refining induction therapy for AAV. In this context, we must acknowledge that the GC regimen, which is 1 of the 2 central pillars of induction therapy, is associated with major toxicity, is not evidence-based, and varies across the guidelines. There are other areas where evidence is lacking, including management of pediatric vasculitis and treatment of severe AAV because these patients are largely excluded from clinical trials, identifying AAV phenotypes where treatment is futile, AAV management in the setting of infection, and management of EGPA. Because the use of RTX for remission induction and maintenance therapy is expanding, more guidance is needed to assess infection risk and recommend infection prophylaxis. In addition, the most important outcome is follow-up beyond 10 years, including quality of life and risk of end-stage renal disease and cardiovascular mortality; the data are scarce in this regard.

Guidelines are necessarily based on published evidence and are therefore retrospective in nature, covering evidence accrued over a long period of time. This is a particular problem for a disease whose management is subject to a rapid pace of change. Furthermore, for example, the initial design of the trial and the drug regimen that occurred years before the published result determines much of the detail of the recommendation. There is then a potential conflict between the opinions of currently active, “expert” physicians, and the more historic evidence. This balance is hard to explore among recommendation statements but may account for some of the variance; it also supports the routine recommendation that patients should be managed in experienced centers, and that physicians managing AAV cannot simply rely on a set of published guidelines. Finally, we should be aware that each patient is unique, and although these guidelines can assist physicians in decision making, they do not replace the insight of the experienced physician in crafting a therapeutic regimen tailored to the individual patient.

## DISCLOSURE

DG is consultant to ChemoCentryx and Kyowa Hakko Kirin Co Ltd. DJ has received research grants from GlaxoSmithKline, Roche, and Sanofi, and has been a consultant for AstraZeneca, ChemoCentryx, GlaxoSmithKline, InflaRx, and Vifor. CP has been a consultant and has received Speaker’s fees from Roche, and has been a consultant and

a member of the Advisory board for ChemoCentryx. All the other authors declared no competing interests.

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