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Review Article

Management of antineutrophil cytoplasmic antibody-associated vasculitis: a review of recent guidelines

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune rheumatic disease consisting of three discrete diagnoses of microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. Among diseases treated in a rheumatology department, AAV has poor clinical outcomes, with high rates of mortality and progression to end-stage renal disease and frequent disease relapse. Due to the frequent negative patient outcomes, optimal therapeutic strategies are essential in the management of AAV. In the present review, four guidelines for management of AAV are summarized: British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guideline for the management of adults with AAV; European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendation for the management of AAV; 2021 American College of Rheumatology (ACR)/Vasculitis Foundation Guideline for the Management of AAV; Kidney Disease: Improving Global Outcome (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, which will aid in clinicians' medical decisions. Finally, the summary of the 2022 Update of the EULAR Recommendations on the Management of AAV, presented in the EULAR Congress 2022 is also introduced.

Keywords: Antineutrophil cytoplasmic antibody, Vasculitis, Treatment, Guideline

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune rheumatic disease composed of three discrete diagnoses of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1,2]. MPA, GPA, and EGPA are distinguished mainly based on the pattern of involved organs and the expression of ANCAs against myeloperoxidase (MPO) or proteinase 3 (PR3); however, pathologic confirmation is also important for accurate diagnosis [3]. Among various rheumatic diseases encountered in practice, AAV reportedly has a higher rate of adverse outcomes [4]. Observations from the European Vasculitis Study Group (EUVAS) reported that 12% and 22% of patients with AAV died in a 1-year and 5-year period, respectively [5]. In addition, the long-term renal outcomes of patients with AAV were unfavorable based on integrated analyses of the EUVAS inception clinical trials, in which 13% of the patients progressed to end-stage renal disease (ESRD) [6]. Furthermore, findings from the Glomerular Disease Collaborative Network inception cohort indicated that a 5-year survival and ESRD-free rate of patients with AAV with renal disease was 72% and 54%, respectively [7]. The heightened risks of mortality and ESRD in patients with AAV appear to be

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consistent in an Asian population. Outcome analysis from a Japanese AAV cohort showed that 11.0% and 10.8% of the patients experienced death and ESRD, respectively, during follow-up [8], and analysis of the national health insurance database in Republic of Korea revealed increased mortality and ESRD development in patients with AAV, with an estimated rate of 26.8% and 8.2%, respectively [9]. Furthermore, disease aggravation during the disease course was common in AAV, with a 5-year disease relapse rate reaching as high as 89%, although large variation was reported in clinical settings [10]. Especially, MPA and GPA are recognized as major AAV subtypes that have a greater risk of poor clinical outcomes of mortality and ESRD, whereas the prognoses of EGPA appears to be relatively favorable [11]. Due to the high rate of negative patient outcomes, an essential component in management of AAV is implementation of optimal therapeutic strategies. In the present review, the recent AAV

Table 1. Disease severity according to the EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis

Group	Clinical subgroup	Systemic vasculitis outside ENT tract and lung	Threatened vital organ function	Other definitions	Serum creatinine (μmol/L)
EUVAS	Localized	No	No	No constitutional symptoms, ANCA typically negative	<120
	Early systemic	Yes	No	Constitutional symptoms present, ANCA-positive or ANCA-negative	<120
	Generalized	Yes	Yes	ANCA-positive	<500
	Severe	Yes	Organ failure	ANCA-positive	>500
	Refractory	Yes	Yes	Refractory to standard therapy	Any
WGET Research Group	Limited	Allowed, but not required	No	Not severe	≤124, if haematuria, but no red blood cell casts present
	Severe	Yes	Yes	Organ- or life-threatening disease, implies need for remission induction with CYC	Any

ANCA: antineutrophil cytoplasmic antibody, CYC: cyclophosphamide, ENT: ear, nose, and throat, EULAR: European League Against Rheumatism, EUVAS: European Vasculitis Study Group, WGET: Wegener's Granulomatosis Etanercept Trial.

Table 2. Defining disease activity status in systemic vasculitis

Activity state	Definition
Remission	Absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy. The term ''active disease'' is not restricted to vasculitis only, but also includes other inflammatory features like granulomatous inflammation in WG or tissue eosinophilia in CSS.
Response	50% reduction of disease activity score and absence of new manifestations
Relapse	Re-occurrence or new onset of disease attributable to active vasculitis
Major	Re-occurrence or new onset of potentially organ- or life-threatening disease
Minor	Re-occurrence or new onset of disease which is neither potentially organ- nor life-threatening
Refractory disease	Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or
	Lack of response, defined as ≤50% reduction in the disease activity score, after 6 weeks of treatment, or
	Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score list (e.g., BVAS or BVAS/WG) after ≥12 weeks of treatment
Low-activity disease state	Persistence of minor symptoms (e.g., arthalgia, myalgia) that respond to a modest increase of the GC dose and do not warrant an escalation of therapy beyond a modest dose increase in the current medication

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis, BVAS: Birmingham Vasculitis Activity Score, CSS: Churg–Strauss syndrome, GC: glucocorticoid, WG: Wegener's granulomatosis. Reused from the article of Mukhtyar et al. (Clin Exp Rheumatol 2006;24(6 Suppl 43):S-93-8) [14].

treatment guidelines are presented to provide key guidance to physicians for managing this complicated disease.

MAIN SUBJECTS

Important considerations when selecting therapeutic agents for AAV

Administration of appropriate immunosuppressive agents is important in management of AAV. Two key issues should be considered prior to selection of treatment for AAV.

1) Assessment of disease stages

An essential component in treating AAV is assessing the stage and activity of underlying disease. In the European League Against Rheumatism (EULAR) recommendation for conducting clinical studies and/or clinical trials in systemic vasculitis (Table 1), the EUVAS group categorized clinical subgroups into "Localized," "Early systemic," "Generalized," "Severe," and "Refractory" according to the presence of systemic vasculitis outside ears, nose, throat and lungs, threatened vital organ function, other definitions, and serum creatinine [12]. Conversely, Wegener's Granulomatosis Etanercept Trial (WGET) Research Group separated clinical subgroups into limited and severe disease. The definition for limited disease provided by the WGET research group refers to a patient who fulfills the American College of Rheumatology (ACR) criteria for GPA diagnosis, but in the absence of disease that has a potential to threat either a critical individual organ or to the patient's life [13]. Detailed descriptions for this are (1) no red blood cell casts in the urine; (2) serum creatinine ≤1.4 mg/dL and no evidence of serum creatinine rise of more than 25% above the baseline levels; (3) Circumscribed pulmonary involvement of room air partial pressure of oxygen >70 mmHg or room air oxygen saturation by pulse oximetry >92%; (4) and no disease in critical organs such as the gastrointestinal tract, eyes, and central nervous system, without the immediate requirement of maximal therapy that may compromise organ function and/or patient life. Severe disease, which is not classified as limited disease by definition, is a stage that is particularly important to note because it indicates the need to start intensified remission induction therapy. Therefore, for management of AAV, a thorough systematic evaluation via physical examination, imaging study, and laboratory testing is necessary to guide treatment decisions.

2) Defining disease activity status

Next, the activity state of AAV should be evaluated. The EULAR defines activity states as remission, response, relapse, refractory disease, or low-activity disease state (Table 2) [14]. Remission is defined as the absence of disease activity attributable to active disease qualified by need for ongoing stable maintenance immunosuppressive therapy. In addition, relapse (recurrence or new onset of disease attributable to active vasculitis) can be divided into major or minor based on the potential threat to organs or life. Refractory disease is an unsatisfactory response to a sustained duration of appropriate therapy. Accurate determination of disease status is crucial in AAV because the goal of treatment is clinical remission, and disease relapse should be managed effectively using glucocorticoids (GCs) and/or immunosuppressive agents per treatment recommendations.

Available guidelines for management of AAV

The pharmacologic agent-specific recommendations proposed by the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guideline for the management of adults with AAV, EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendation for the management of AAV, 2021 ACR/Vasculitis Foundation Guideline for the Management of AAV, and Kidney Disease: Improving Global Outcome (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases are summarized and presented in Tables 3~5. Furthermore, recommendations for medication dosage, if described in the guidelines, and other recommendations are outlined in Tables 6 and 7.

1) BSR and BHPR guideline for management of adults with AAV

In the BSR and BHPR guideline released in 2014, selection of treatment regimens is based on a purpose of remission induction, maintain remission, in relapsing or refractory diseases during follow-up [15]. In addition, five principles of management are emphasized: rapid diagnosis; rapid initiation of treatment; early induction of remission to prevent organ damage; maintenance of remission with the aim of eventual drug cessation; and prevention of drug toxicity. In the BSR and BHPR guideline, the use of GCs and intravenous (IV) cyclophosphamide (CYC) or rituximab (RTX) should be considered in newly diagnosed AAV patients. Methotrexate (MTX) and mycophenolate mofetil

Table 3. Recommendation comparison of pharmacologic agents RTX, CYC, and GC according to guidelines

Pharmacologic agents	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
RTX				
Remission induction	- Effective as CYC in previously untreated patients and CYC intolerance - Preferred when CYC avoidance is desired (infertility, risk of infection)	- New-onset organ- or life-threatening AAV	- Conditionally recommended over CYC in active, severe GPA/MPA - May be prescribed in active, severe EGPA - Conditionally recommended over MEP in active, severe EGPA	- Initial treatment for new-onset AAV - Combination of RTX/CYC can be considered when creatinine >354 μmol/L
Maintenance	- May be considered	- Maintenance	- Conditionally recommended over MTX or AZA after achieving remission with CYC or RTX in severe GPA/MPA - Scheduled re-dosing conditionally recommended over using ANCA titer or CD19+ B cells based approach	- Preferred option in relapsing and PR3-ANCA positive disease, frail elderly, for glucocorticoid sparing, AZA allergy - Either on a fixed schedule or following reappearance of CD19+ B cells and/or ANCA
Relapsing disease	- In the case of major relapse	- In the case of major relapse	- Conditionally recommended over CYC in severe GPA/MPA relapse not receiving RTX maintenance - RTX conditionally recommended over CYC in severe EGPA relapse previously reached remission with CYC or RTX	- Preferred than CYC in life- or organ-threatening relapse
Refractory disease	- More effective than CYC, and initial choice when previously RTX untreated	- CYC refractory	- Switching to RTX conditionally recommended over RTX/CYC combination in CYC refractory severe GPA/MPA	- If CYC used previously
CYC				
Remission induction	- Remission induction	- New-onset organ- or life-threatening AAV	- May be used in RTX avoidance or active disease with RTX treatment in active, severe GPA/MPA - May be prescribed in active, severe EGPA - Conditionally recommended over MEP in active, severe EGPA	- Initial treatment for new-onset AAV - Preferred in severe renal impairment (creatinine >354 μmol/l) - Combination of two pulses of IV RTX/CYC can be considered when creatinine >354 μmol/l
Relapsing disease	- In the case of major relapse	- In the case of major relapse	- Conditionally recommended over additional RTX in severe GPA/MPA relapse while receiving RTX maintenance	- In life- or organ- threatening relapse setting
Refractory disease		- If RTX refractory	- Switching to CYC conditionally recommended over RTX/CYC combination in RTX refractory severe GPA/MPA	- If RTX used previously

Table 3. Continued

Pharmacologic agents	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
GC				
Remission induction	- Combination with CYC or RTX - High dosage (1 mg/kg, up to 60 mg), usually in PO prednisolone, IV can be used	- Combination with CYC or RTX in new-onset organ- or life-threatening AAV - Combination with MTX or MMF in non-organ-threatening AAV	- Reduced dose GC conditionally recommended over a standard dose GC regimen in active, severe GPA/MPA - Initial therapy of active, severe EGPA	- Combination with CYC or RTX - No evidence for IV GC administration
Maintenance	- Maintenance	- Low dose GC with AZA, RTX, MTX, or MMF	- Maintenance	- Following CYC induction, rapid dose reduction into 5 mg/day by 6 months - May be withdrawn following RTX induction - Continue 5~7.5 mg/day for 2 years and slowly reduced by 1 mg every 2 months
Relapsing disease	- Dose adjustment (IV may be considered in major relapse)	- Combination with CYC or RTX - In the case of major relapse	- Relapsing disease	- Dose adjustment (PO or IV)
Refractory disease				- Dose adjustment (PO or IV)

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, ACR: American College of Rheumatology, ANCA: antineutrophil cytoplasmic antibody, AZA: azathioprine, BHPR: British Health Professionals in Rheumatology, BSR: British Society for Rheumatology, CYC: cyclophosphamide, EGPA: eosinophilic granulomatosis with polyangiitis, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GC: glucocorticoid GPA: granulomatosis with polyangiitis, IV: intravenous, KDIGO: Kidney Disease: Improving Global Outcome, MEP: mepolizumab, MMF: mycophenolate mofetil, MPA: microscopic polyangiitis, MTX: methotrexate, PO: per oral, PR3: proteinase 3, RTX: rituximab.

Table 4. Recommendation comparison of pharmacologic agents MTX, AZA, and MMF according to guidelines

Pharmacologic agents	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
MTX				
Remission induction	- Evidence of low disease activity and not at risk of organ damage by the BVAS	- Non-organ-threatening AAV (nasal and paranasal disease without erosion, cartilage collapse, olfactory dysfunction, deafness, skin involvement without ulcer, myositis, non-cavitating pulmonary nodule/infiltrate in the absence of haemoptysis) with normal kidney function - Not for meningeal involvement, retro-orbital disease, cardiac and mesenteric involvement, acute mononeuritis multiplex, pulmonary haemorrhage	- MTX conditionally recommended over CYC or RTX for active, non-severe GPA - GC+MTX conditionally recommended over GC alone in active, non-severe GPA - GC+MTX conditionally recommended over GC+AZA or GC+MMF in active, non-severe GPA - GC+MTX conditionally recommended over GC+TMP/SMX in active, non-severe GPA - GC+MTX conditionally recommended over GC alone in active, non-severe EGPA	- In the absence of irreversible tissue damage
Maintenance	- Maintenance	- Maintenance	- Conditionally recommended over MMF/LEF after achieving remission with CYC or RTX in severe GPA/MPA - Conditionally recommended over TMP/SMX in GPA entering remission - GC+MTX conditionally recommended over GC alone or GC+CYC or RTX in active, non-severe EGPA - Conditionally recommended over RTX in severe EGPA entering remission with CYC - Conditionally recommended over MEP in severe EGPA that entered remission	- Upon MTX based remission induction - Intolerant to AZA and MMF - Not if GFR <60 mL/min/1.73 m^2
AZA				
Remission induction			- GC+AZA conditionally recommended over GC alone or GC+CYC or RTX in active, non-severe EGPA	
Maintenance	- Maintenance	- Maintenance	- Conditionally recommended over MMF/LEF after achieving remission with CYC or RTX in severe GPA/MPA - Conditionally recommended over TMP/SMX in GPA entering remission - Conditionally recommended over RTX in severe EGPA entering remission with CYC - Conditionally recommended over MEP in severe EGPA that entered remission	- Preferred in baseline IgG <300 mg/dL, HBsAg positive, and limited access to RTX

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Table 4. Continued

Pharmacologic agents	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
MMF				
Remission induction	- May be an alternative to MTX	- Non-organ-threatening AAV - Not for meningeal involvement, retro-orbital disease, cardiac and mesenteric involvement, acute mononeuritis multiplex, pulmonary haemorrhage	- GC+MMF conditionally recommended over GC alone or GC+CYC or RTX in active, non-severe EGPA	- Remission induction
Maintenance	- Alternative for intolerance or lack of efficacy to AZA or MTX	- Maintenance	- Intolerable or contraindications to MTX, AZA, or RTX - Conditionally recommended over RTX in severe EGPA entering remission with CYC - Conditionally recommended over MEP in severe EGPA that entered remission	- Maintenance
Relapse				- Non-severe relapse

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, ACR: American College of Rheumatology, AZA: azathioprine, BHPR: British Health Professionals in Rheumatology, BSR: British Society for Rheumatology, BVAS: Birmingham Vasculitis Activity Score, CYC: cyclophosphamide, EGPA: eosinophilic granulomatosis with polyangiitis, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GC: glucocorticoid, GFR: glomerular filtration rate, GPA: granulomatosis with polyangiitis, KDIGO: Kidney Disease: Improving Global Outcome, LEF: leflunomide, MEP: mepolizumab, MMF: mycophenolate mofetil, MTX: methotrexate, RTX: rituximab, TMP/SMX: trimethoprim/sulfamethoxazole.

Table 5. Comparison of therapeutic options of LEF, MEP, and PLEX according to guidelines

Therapeutic options	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
LEF				
Maintenance	- Alternative for intolerance or lack of efficacy to AZA or MTX	- When intolerance to AZA, MTX, MMF, or RTX present		
MEP				
Remission induction			- GC+MEP conditionally recommended over MTX, AZA, or MMF combined GC in active, non-severe EGPA	
Relapsing disease			- Adding MEP conditionally recommended over switching to other agent in non-severe EGPA relapse under MTX, AZA, or MMF therapy - Adding MEP conditionally recommended over adding MTX, AZA, or MMF in non-severe EGPA relapse under low-dose GC monotherapy - Conditionally recommended over omalizumab in non-severe EGPA relapse under MTX, AZA, or MMF in those with high serum IgE levels	
PLEX				
Remission induction	- Adjunct with GC+CYC in severe renal failure (creatinine >500 μmol/L) - Considered in the presence of life-threatening manifestation (i.e., pulmonary hemorrhage)	- Considered in patients with creatinine >500 μmol/L due to rapidly progressive glomerulonephritis - Considered in severe diffuse alveolar haemorrhage	- Routine addition conditionally recommended against in GPA/MPA with active glomerulonephritis - Advisable in GPA/MPA having anti-GBM disease - Conditionally recommend against adding PLEX in active, severe GPA/MPA with alveolar hemorrhage	- In combination with induction regimen ● Patients with creatinine >500 μmol/L requiring dialysis ● Patients with diffuse alveolar hemorrhage with hypoxemia ● Overlap of AAV and anti-GBM antibody
Relapsing disease	- Addition may be considered in the case of major relapse with GC+RTX or CYC	- Considered in patients with creatinine >500 μmol/L due to rapidly progressive glomerulonephritis - Considered in severe diffuse alveolar haemorrhage		- Can be considered
Refractory disease				- Can be considered

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, ACR: American College of Rheumatology, AZA: azathioprine, BHPR: British Health Professionals in Rheumatology, BSR: British Society for Rheumatology, CYC: cyclophosphamide, EGPA: eosinophilic granulomatosis with polyangiitis, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GBM: glomerular basement membrane, GC: glucocorticoid, GPA: granulomatosis with polyangiitis, IgE: immunoglobulin E, KDIGO: Kidney Disease: Improving Global Outcome, LEF: leflunomide, MEP: mepolizumab, MMF: mycophenolate mofetil, MPA: microscopic polyangiitis, MTX: methotrexate, PLEX: plasma exchange, RTX: rituximab.

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Table 6. Specific recommendations of medication dosage in the guidelines

	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
RTX	- 375 mg/m^2/week for 4 weeks; 1 g at week 0 and 2 shows equal efficacy - 1 g every 4~6 months as maintenance therapy for two years, either as a fixed-interval regimen or evidence of relapse		- 375 mg/m^2/week for 4 weeks or 1 g at week 0 and 2 in adults - 575 mg/m^2 for patients with body surface area ≤1.5 m^2 or 750 mg/m^2 for patients with body surface area >1.5 m^2 (maximum of 1 gm/infusion, at week 0 and 2) in children - 1 g every 4~6 months as maintenance therapy for two years, either as a fixed-interval regimen or evidence of relapse	- Remission induction ● 375 mg/m^2/week for 4 weeks or 1 g at week 0 and 2 ● CYC/RTX combination: RTX 375 mg/m^2/week for 4 weeks with IV CYC 15 mg/kg at week 0 and 2 or RTX 1 g at week 0 and 2 with CYC 500 mg/biweekly ×6 - Maintenance ● 500 mg twice on complete remission and 500 mg at month 6, 12, and 18 or 1 g after remission induction, followed by infusion at month 4, 8, 12, and 16 - Special consideration ● Limited data for severe renal impairment remission induction (creatinine >354 μmol/L) ● Preferred in young aged and frail elderly patients, considering fertility issues, glucocorticoid sparing, relapsing, and PR3-ANCA positivity
CYC	- IV preferred owing to low toxicity, 2-week interval and in a 3-week interval subsequently following the CYCLOPS trial regimen - 15 mg/kg standard dosage, reduced in the elderly and decreased renal function - Administered for 3~6 months - Lifelong exposure should be ≤25 g - Monitoring of leukopenia/cytopenia		- Dose of up to PO 2 mg/kg/day for 3~6 months or IV 15 mg/kg every 2 week for 3 dosage, followed by every 3 weeks for at least 3 doses	- Remission induction ● PO 2 mg/kg/day for 3 months to a maximum of 6 months (dose reduction by age 60 and 70, and GFR <30 mL/min/1.73 m^2) ● IV 15 mg/kg at week 0, 2, 4, 7, 10, 13 (extended until 16, 19, 21, 24, if necessary; dose adjustment according to age 60 and 70, GFR <30 mL/min/1.73 m^2) ● CYC/RTX combination: RTX 375 mg/m^2/week for 4 weeks with IV CYC 15 mg/kg at week 0 and 2 or RTX 1 g at week 0 and 2 with CYC 500 mg/biweekly ×6

Table 6. Continued

	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
GC	- Either PO or IV - Longer use may increase infection, but with fewer relapses - Rapid dose reduction to 15 mg prednisolone at week 12 on remission induction - Consider GC tapering when sustained remission for at least 1 year on maintenance therapy	- Rapid dose reduction to 7.5~10 mg prednisolone (or equivalent) at week 12	- Either PO or IV - IV pulse GC: Methylprednisolone 500-100 mg/day or 30 mg/kg/day for adults and children or equivalent for 3~5 days - High-dose oral GC: Prednisone 1 mg/kg/day in adults and 1~2 mg/kg/day for children (up to 80 mg in adults and 60 mg in children) or equivalent	- 1 mg/kg/day at week 1, and sequential tapering
PLEX				- In severe kidney disease: 7 treatments in a maximum of 14 days, with volume and albumin replacement - In diffuse pulmonary hemorrhage: Daily until hemorrhage cessation, with fresh frozen plasma - Anti-GBM antibody positive: Daily for 14 days or anti-GBM antibody negative conversion
MTX	- Dose of up to 25~30 mg/week - Prohibited in moderate-severe renal impairment		- Dose of up to 25 mg/week (SC or PO) - Should be administered in caution or avoided in those with moderate-several renal impairment	
AZA	- Maintenance	- Maintenance	- Dose of up to 2 mg/kg/day	- 1.5~2 mg/kg/day at complete remission until one year, decrease by 25 mg every 3 months - Continuation until four years after complete remission: dose of 1.5~2 mg/kg/day for 18~24 month, 1 mg/kg/day until 4 years, and taper by 25 mg every 3 month
MMF	- Dose up to 3 g/day		- Dose of up to 3 g/day	- Remission induction ● 2 g/day, dose of up to 3 g/day in poor response - Maintenance ● 2 g/day for 2 years at complete remission
LEF				
MEP			- SC every 4 weeks	

ACR: American College of Rheumatology, ANCA: antineutrophil cytoplasmic antibody, AZA: azathioprine, BHPR: British Health Professionals in Rheumatology, BSR: British Society for Rheumatology, CYC: cyclophosphamide, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GBM: glomerular basement membrane, GC: glucocorticoid, GFR: glomerular filtration rate, IV: intravenous, KDIGO: Kidney Disease: Improving Global Outcome, LEF: leflunomide, MEP: mepolizumab, MMF: mycophenolate mofetil, MTX: methotrexate, PLEX: plasma exchange, PO: per oral, PR3: proteinase 3, RTX: rituximab, SC: subcutaneous.

Table 7. Other considerations described in the guidelines

Other treatment considerations	BSR and BHPR guideline [15]	EULAR/ERA-EDTA recommendations [18]	2021 ACR/Vasculitis Foundation Guideline [21]	KDIGO 2021 Clinical Practice Guideline [27]
Maintenance duration	- At least 24 months following remission - Up to 5 years in patients with GPA or PR3-ANCA serology positive	- At least 24 months after sustained remission induction - 36 months therapy in PR3-ANCA positive patients	- Guided by disease and patient factors	- Between 18 months and 4 years after induction with AZA+GC - Unknown in RTX, evaluated up to 18 months
Treatment withdrawal	- Immunosuppressive agent withdrawal after GC withdrawal			- Treatment discontinuation after 3 months in dialysis and in the absence of extrarenal manifestation
Disease status assessment	- Using BVAS, VDI, SF-36, ANCA testing			
Treatment adverse effect monitoring/ adjunct measures	- Investigation of drivers in refractory disease - Blood test and urinalysis monitoring - Mesna for protection against CYC toxicity and CYC-related infertility consultation - Immunoglobulin testing prior to each RTX cycle - Antifungal prophylaxis and TMP/SMX for *Pneumocystis jiroveci* prophylaxis - Nasal mupirocin for *Staphylococcal aureus* treatment - Cervical intraepithelial neoplasia screening for females - Osteoporosis prophylaxis - Tuberculosis screening - Pnuemococcal, influenza, and hepatitis B vaccination - Assessment of cardiovascular and thromboembolic risk	- Structured clinical assessment for clinical decisions rather than ANCA testing - Utilizing clinical tools for systematic clinical assessment - Perform regular blood test and urinalysis - Hematuria work up in patients treated with CYC and administration of anti-emetics and mesna upon IV CYC treatment - Serum immunoglobulin testing prior to each cycle of RTX and those with recurrent infection, as well as when considering the use of IV immunoglobulin - Cardiovascular risk regular monitoring - Comorbidity assessment - TMP/SMX prophylaxis for CYC treated patients - Topical mupirocin may be considered in chronic carriage of *Staphylococcal aureus* nasal disease - Re-evaluation of the specific cause in refractory disease - Recommend active immunization against infections (herpes zoster, pneumococcus and influenza), while avoiding live attenuated vaccines	- TMP/SMX for *Pneumocystis jiroveci* prophylaxis conditionally recommended when receiving RTX or CYC, and in moderate-dose GC using and immunosuppressive agent combination setting - Adding TMP/SMX to other therapies for GPA maintenance conditionally recommended against - Immunoglobulin supplementation in IgG <3 gm/L and recurrent severe infection under RTX maintenance - GC toxicity monitoring - Addition of IV immunoglobulin conditionally recommended in remission induction refractory GPA/MPA or active GPA/MPA that is unable to receive other immunomodulatory therapy - Nasal rinses and topical nasal therapies may be beneficial in sinonasal GPA and EGPA - Reconstructive surgery conditionally recommended in GPA under remission upon patient desire - Immunosuppression conditionally recommended over surgical dilation in actively inflamed subglottic and/or endobronchial tissue with stenosis or surgical removal in the presence of mass lesions - Dosing immunosuppression conditionally recommended against based on merely ANCA titer results - Consider renal transplantation in GPA/MPA with stage 5 CKD in remission - Echocardiogram evaluation at disease diagnosis and Five-Factor Score guided therapy conditionally recommended in EGPA - Continuation of leukotriene inhibitor conditionally recommended over discontinuation in newly diagnosed EGPA	- No changes in treatment decision based on ANCA serology changes solely - Potential of an oral C5a receptor antagonist, avacopan, for reducing GC exposure - TMP/SMX advised for *Pneumocystis jiroveci* prophylaxis during CYC or RTX treatment, longer-term use in those with structural lung disease, ongoing immunosuppressive or GC therapy - Use of validated scoring system, such as BVAS to evaluate clinically active disease - Structured assessment in parallel with laboratory testing - Transplantation consideration after complete clinical remission of ≥6 months - Cause evaluation for refractory disease

ACR: American College of Rheumatology, ANCA: antineutrophil cytoplasmic antibody, AZA: azathioprine, BHPR: British Health Professionals in Rheumatology, BSR: British Society for Rheumatology, BVAS: Birmingham Vasculitis Activity Score, CKD: chronic kidney disease, CYC: cyclophosphamide, EGPA: eosinophilic granulomatosis with polyangiitis, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GC: glucocorticoid, GPA: granulomatosis with polyangiitis, IV: intravenous, KDIGO: Kidney Disease: Improving Global Outcome, MPA: microscopic polyangiitis, PR3: proteinase 3, RTX: rituximab, SF-36: short form-36, TMP/SMX: trimethoprim/sulfamethoxazole, VDI: Vasculitis Damage Index.

(MMF) are alternative drugs for disease remission induction in patients with evidence of low disease activity and no risk of organ damage based on the Birmingham Vasculitis Activity Score (BVAS). However, the use of MMF is considered as an alternative for MTX [16,17]. In contrast, in the presence of severe renal failure or other life-threatening conditions, the guideline recommends that plasma exchange (PLEX) should be considered. High-dose GC, used in combination with CYC or RTX, is also required in the induction phase, although rapid tapering is necessary.

For maintenance therapy, azathioprine (AZA) or MTX is typically considered, although MMF or leflunomide (LEF) as well as RTX also are options. The duration of maintenance is not specified but is recommended to continue for at least 24 months after achieving disease remission and may be lengthened in patients with GPA or with continuously positive PR3-ANCA. In addition, when remission is successfully maintained for at least one year on maintenance therapy, GC can be tapered, and when GC is successfully withdrawn, other immunosuppressive agents may be stopped after six months. Furthermore, for relapsing diseases, the degree of relapse should be considered. For example, minor relapse is recommended to be treated with increased GC dosage and optimization of immunosuppression. However, major relapse may require RTX or CYC treatment with GC dose increment, and PLEX could be considered as adjunct therapy. Finally, in the case of refractory diseases, RTX is more effective than CYC and should be the first choice for a patient not previously treated with RTX. In both relapsing and refractory diseases, the cause should be investigated.

Other general recommendations in the BSR and BHPR guideline include regular assessment and monitoring of disease status using instruments such as the BVAS, Vasculitis Damage Index, 36-item short form, laboratory testing of ANCAs, and detection and prevention of potential adverse effects following treatment. In addition, active patient involvement, education, and a collaboration of specialists is also underscored.

2) EULAR/ERA-EDTA recommendation for management of AAV

The 2016 EULAR/ERA-EDTA recommendations [18] are an update of the 2009 EULAR recommendations for management of primary small- and medium-vessel vasculitis [19] proposed the overarching principle of shared decision making between the patient and their specialist, as well as presenting 15 recommendations based on level of evidence. The recommendation stresses the importance of patient care with close collaboration with or at centers of expertise and of pathologic confirmation. In the EULAR/ERA-EDTA guideline, new-onset organ- or life-threatening AAV is recommended to be treated with a combination of GCs and either CYC or RTX; non-organ-threatening disease can be treated using a combination of GCs with MTX or MMF treatment. Major relapses that are either organ- or life-threatening are recommended to be treated as new-onset organ- or life- threatening AAV, and PLEX should be considered in AAV with serum creatinine ≥500 μmol/L as a result of rapidly progressive glomerulonephritis and can be considered in severe diffuse alveolar hemorrhage. For remission-maintenance, a combination of low-dose GCs with AZA, RTX, MTX, or MMF is recommended for at least 24 months of sustained remission. In disease refractory to remission-induction therapy, it is recommended to switch CYC to RTX or RTX to CYC.

Other statements in the recommendation include a structured clinical assessment instead of ANCA testing and investigation of hematuria in patients exposed to CYC, testing for immunoglobulin levels prior to each cycle of RTX and in patients with recurrent infection, assessment of cardiovascular risk and comorbidities, and consultation with the patient concerning the disease nature, treatment, and outcomes.

3) 2021 ACR/Vasculitis Foundation Guideline for the Management of AAV

Although EGPA is included as a disease subtype of AAV, it usually confers a good prognosis compared with GPA/MPA, has a distinct pathogenetic mechanism, and may respond differently to immunosuppressive therapy [20]. Thus, the ACR/Vasculitis Foundation Guideline, published in 2021, provides recommendations for AAV management after subtyping AAV as GPA/MPA and EGPA [21,22]. Unfortunately, lack of randomized control trials restrict the recommendations; therefore, there are conditional and ungraded position statements in the guideline. Notably, in the ACR/Vasculitis Foundation Guideline, RTX is conditionally recommended over CYC for remission induction in active, severe GPA/MPA considering efficacy, safety, and patient preference. In addition, reduced GC dose is conditionally recommended over a standard GC dose regimen in active, severe GPA/MPA. Furthermore, using RTX instead of MTX or AZA for maintenance is conditionally recommended in patients with severe GPA/MPA in remission after CYC or RTX treat-

ment, and IV immunoglobulin therapy is conditionally recommended in patients with GPA/MPA refractory to remission induction treatment. In the ACR/Vasculitis Foundation Guideline, simultaneous use of GC and MTX is conditionally recommended over GC+RTX, GC+CYC, GC+AZA, GC+MMF, or GC alone for active non-severe GPA. Regarding active, severe EGPA, either IV pulse GC or high-dose oral GC as well as CYC or RTX may be prescribed as initial therapy or for remission induction. Especially for EGPA patients, the therapeutic option of mepolizumab (MEP), a humanized monoclonal antibody against interleukin-5 [23], has been included in remission induction for active, non-severe disease as well as for maintenance and relapsing disease. These significant changes likely represent the results of clinical studies published in recent years, indicating that selection of immunosuppressive agents could be outlined in more detail for patients with AAV in the following years. Furthermore, for patients with EGPA, treatment based on the Five-Factor Score is conditionally recommended in the guideline [24,25]. However, no promising results have been achieved for the oral C5a receptor inhibitor avacopan because the ACR/Vasculitis Foundation Guideline encompasses only therapeutic agents approved by the U.S. Food and Drug Administration (FDA) [26].

4) KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

Although the KDIGO guidelines primarily focus on management of AAV that results in kidney inflammation manifesting as necrotizing and crescenticglomerulonephritis, general management strategies for AAV not limited to the kidney are also described and summarized as practice points [27]. For induction of remission, GC+CYC or RTX could be used, which is similar to other guidelines. MMF and MTX, in the absence of irreversible tissue damage, could be considered if there is no organ-threatening involvement. PLEX combined with an induction regimen is recommended for patients with creatinine >500 μmol/L requiring dialysis, diffuse alveolar hemorrhage with hypoxemia, and an overlap of AAV and anti-GBM antibodies. Several noticeable practices introduced include immediate initiation of active treatment in active deteriorating kidney disease, the recommendation to consider combined RTX and CYC in markedly reduced or rapidly declining kidney function (typically serum creatinine >354 μmol/L), proposal of a protocol-based reduction of GC dosage in accordance with the PEXIVAS trial [28], and a specific description of immunosuppressive dosing.

5) 2022 Update of the EULAR Recommendations on the Management of AAV

The 2022 update of the EULAR recommendations on the management of AAV presented at the EULAR Congress 2022 in Copenhagen, proposed four overarching principles and 17 recommendations (Table 8). In addition to the main overarching principles that highlighted holistic and multidisciplinary approach in patient care, noticeable changes in these recommendations compared to the former recommendations included testing for both PR3- and MPO-ANCA using high-quality antigen-specific assay as a primary method under the suspicion of AAV, an emphasis on RTX in remission maintenance for GPA/MPA, and remission induction of non-organ- or life-threatening GPA/MPA using RTX. Furthermore, a specific dose defined upon GC initiation (starting at a dose of 50~75 mg prednisolone/day according to body weight) with a stepwise reduction into a prespecified target was proposed. On the other hand, PLEX was suggested to be considered in those with serum creatinine >300 μmol/L and active glomerulonephritis, and a routine application in alveolar haemorrhage were no longer recommended. In addition, treatment for both GPA/MPA and EGPA are separately provided - with an emphasis on using MEP in EGPA - consistent with the recent ACR/Vasculitis Foundation Guideline; however, consideration of avacopan combination with RTX or CYC for GC dose reduction in GPA/MPA was included, which was absent in the 2021 ACR/Vasculitis Foundation Guideline (Table 8).

6) Novel therapeutic agents for AAV

Although significant advances have been achieved in management of AAV, due to the heterogeneous manifestations and rarity of disease [29], evidence is insufficient to support certain treatments as more effective than others [30]. In addition, although observations from clinical trials of patients with AAV increased the understanding of the therapeutic benefits/limitations of immunosuppression, the outcomes in AAV patients, especially for GPA/MPA, remained unfavorable. Moreover, there are also substantial toxic effects of current immunosuppressive treatments. Therefore, there is a continuous need for novel therapeutic agents for disease management [31]. In this context, the recently demonstrated therapeutic efficacy of avacopan in GPA/MPA is encouraging. Combination of avacopan in a background

Table 8. Key changes described in the 2022 EULAR recommendations for the management of AAV compared to the former recommendations

Category	2016 EULAR/ERA-EDTA recommendations for the management of AAV	2022 Update of the EULAR Recommendations on the Management of AAV
RTX maintenance	- Recommended for remission maintenance of AAV, along with AZA, MTX, or MMF	- In GPA/MPA, RTX maintenance recommended after remission induction with either RTX or CYC
Remission induction for non-severe AAV	- Recommend treatment with combination of GC and either MTX or MMF	- Treatment with a combination of GC and RTX recommended for induction of remission of non-organ- or non-life-threatening GPA/MPA
GC dosing		- For remission induction in GPA/MPA, oral GC treatment starting from a dose of 50~75 mg prednisolone/day. A stepwise dose reduction recommended and to achieve 5 mg prednisolone/day dosage by 4~5 months
PLEX	- Should be considered for patients with AAV and a serum creatinine level of ≥500 mmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in new or relapsing AAV - Can be also considered for the treatment of severe diffuse alveolar haemorrhage	- May be considered for remission induction in GPA/MPA for patients with serum creatinine > 300 μmol/L and active glomerulonephritis - Routine use not recommended to treat alveolar haemorrhage in GPA/MPA
MEP		- Recommended in patients with relapsing or refractory EGPA without active organ- or life threatening disease - Recommended at the time of relapse for maintenance remission of relapsing EGPA after induction remission for non-organ- or life threatening manifestations
Avacopan		- Combination with RTX or CYC may be considered for induction of remission in GPA/MPA, for GC exposure reduction
EGPA		- High-dose GC and CYC combination recommended for remission induction of new-onset or relapsing EGPA with organ- or life-threatening manifestations - GC recommended for remission induction in new-onset or relapsing EGPA without organ-or life threatening manifestations
Assays for ANCA testing		- Testing for both PR3-and MPO-ANCA using high-quality antigen-specific assay as a primary test recommended
Pneumocystis jirovecii prophylaxis	- Encourage prophylaxis against infection with *Pneumocystis jirovecii* using TMP/SMX in all patients being treated with CYC	- Recommend the use of TMP/SMX as prophylaxis against *Pneumocystis jirovecii* pneumonia in patients with AAV receiving RTX, CYC, and/or high doses of GC

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, AZA: azathioprine, CYC: cyclophosphamide, EGPA: eosinophilic granulomatosis with polyangiitis, ERA-EDTA: European Renal Association-European Dialysis and Transplant Association, EULAR: European League Against Rheumatism, GC: glucococticoid, GPA: granulomatosis with polyangiitis, MEP: mepolizumab, MMF: mycophenolate mofetil, MPA: microscopic polyangiitis, MPO: myeloperoxidase, MTX: methotrexate, PLEX: plasma exchange, PR3: proteinase 3, RTX: rituximab, TMP/SMX: trimethoprim/sulfamethoxazole.

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treatment of CYC (followed by AZA) or RTX regimen resulted in a higher rate of sustained remission at week 52 compared with prednisone tapering with an acceptable safety profile [26]. Because GC use is associated with significant toxic effects and minimizing the use of GC is of increased interest in rheumatology, the role of avacopan in the treatment of patients with AAV remains unclear. Next, omalizumab, a recombinant, humanized, monoclonal antibody against human immunoglobulin E (IgE) approved for treatment of various allergic diseases [32], could have benefit in the management of EGPA [33]. However, no specific recommendations supporting the use of omalizumab in EGPA are present in the ACR/Vasculitis Foundation Guideline, even in subjects with high serum IgE level. Data from future large, randomized, control trials are warranted.

CONCLUSION

AAV is a potentially lethal disorder associated with significantly increased rate of adverse clinical outcomes. Because appropriate treatment is essential to improve patient outcomes, the updated information provided in the guidelines for AAV will contribute to clinicians' medical decisions. Furthermore, novel therapeutic guidelines are expected to be released continuously based on the results from clinical trials. Finally, research investigating the pathogenesis of AAV will also enhance the understanding of disease and aid in development of optimal management recommendations for patients with AAV.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study conception and design: S.S.A. and S.W.L. Acquisition of data: S.S.A. Data analysis and/or interpretation: S.S.A. and S.W.L. Drafting the manuscript: S.S.A. and S.W.L. Manuscript revision for important intellectual content: S.S.A. and S.W.L.

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