

Anti-neutrophil cytoplasmic antibody-associated vasculitis: prevalence, treatment, and outcomes

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Received: 13 April 2017 / Accepted: 12 September 2017 / Published online: 27 September 2017
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Abstract Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a primary small-vessel vasculitis group with three distinct clinical entities, including GPA, MPA, and EGPA. The incidence of AAV has increased since the 1980s and remained stable since the early 2000s. Distinct phenotypes of AAV may also differ in various geographical regions. Elderly people are susceptible to developing AAV, and AAV is used to be a fatal disease before the introduction of glucocorticoids and immunosuppressants. Different treatment protocols should be employed for patients with different disease severity levels. Several randomized controlled trials evaluated the efficacy and safety of treatment protocols for remission induction and maintenance. Glucocorticoid and cyclophosphamide therapies remain the mainstay for treating AAV. Rituximab is non-inferior to cyclophosphamide for inducing remission, and it is more effective for relapsing and refractory disease. The combination of low-dose glucocorticoids with less toxic immunosuppressants, such as azathioprine, rituximab, and methotrexate, is suggested in place of cyclophosphamide. The prognosis of patients with AAV is another crucial issue due to the accumulating damage caused by both the disease activity and treatment toxicity. This review focused on recent progress on the prevalence, treatment, and outcomes of patients with AAV.

Keywords ANCA · Outcome · Prevalence · Treatment · Vasculitis

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of primary small-vessel vasculitis with three distinct clinical entities, including granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome) [1]. The vast majority of small-vessel vasculitis diseases have similar clinical and histopathological features. Kidneys and lungs are the most commonly involved organs in AAV. ANCA is the serological marker of AAV. By indirect immunofluorescence (IIF), two fluorescence patterns of ANCA are distinguished: the cytoplasmic staining pattern (cANCA) and perinuclear staining pattern (pANCA). Most patients with a cANCA pattern obtained by IIF have ANCA directed against proteinase-3 (PR3). Patients with pANCA mostly have ANCA directed against one of a variety of antigens, and myeloperoxidase (MPO) is the most important one.

This review focuses on the prevalence in different regions and the current therapeutic approaches for AAV. The outcomes of AAV, such as infection, relapse, treatment resistance, and renal prognosis, are also discussed.

Prevalence and incidence

AAV is a common autoimmune disease. Most epidemiology studies of AAV have been conducted in Europe, Japan, USA, and Oceania in past decades. The overall annual incidence rates of AAV in Europe are 10–20/million [2], and there is a prevalence of 46–184 cases per million [3]. A comparison study from three regions in Europe showed that the overall incidence rates of AAV are similar at approximately 19/

million [2]. The incidence rate has increased in the European population since the 1980s [4, 5] and remained stable since the early 2000s [3], which may be a consequence of the increased awareness among physicians following the introduction of routine serologic tests for ANCA. Japan has a similar overall annual incidence rate as the UK (22.6/million in Japan and 21.8/million in UK) [6], while the incidence rate in USA is estimated as 10.35/million, as reported by Zefzet et al [7].

Although AAV can affect people of all ages, elderly people are more susceptible, with a peak age of 65–74 years [8]. In most studies, the incidence of AAV was similar between males and females.

The incidence of the distinct phenotypes of AAV may differ in various geographical regions. GPA is more common in northern Europe, while MPA is more prevalent in southern Europe. The annual incidence of GPA in three regions of Europe was as follows: Tromsø (Norway, latitude 70°N), Norwich (UK, latitude 52°N), and Lugo (Spain, latitude 43°N)—10.5, 10.6, and 4.9/million, while the annual incidence of MPA in these three regions 2.7, 8.4, and 11.6/million, respectively [2]. New Zealand and Australia have similar incidence rates of GPA to northern Norway. The incidence of GPA in Australia and northern Norway was 6–7 and 8/million/year, respectively [9, 10]. The point prevalence for GPA in Canterbury, New Zealand in 2003 (93.5/million) was similar to that in northern Norway (95/million) [11]. The overall annual incidence levels

of GPA and MPA are reported to be 11.3 and 5.9/million in the UK, respectively [12]. In a comparative study, MPA is the predominant subtype in Japan (18.2/million, 83%), while GPA is more frequent in the UK (14.3/million, 66%) [6]. There is little, if any, epidemiological data of AAV in China yet. Data from a single-center study in China demonstrated that MPA is also more common than GPA in China, which accounts for about 70–80% of patients with AAV [13]. The annual incidence of GPA in Taiwan was 0.37/million patient-years; the ratio of the number of patients with GPA to that with MPA was 0.57 [14], which is similar to the study from the Mainland [15]. EGPA is much rarer than GPA and MPA, and it has an annual incidence of 0.5–2.0/million [16].

Treatment

The treatment for AAV includes induction and maintenance of remission. Patients with different levels of disease severity respond to different treatment protocols. The European Vasculitis Study Group (EUVAS) proposed categories to classify the clinical AAV subtypes and assign different treatment regimens (Table 1) [17]. In the past few decades, substantial progress has been made in the treatment, and patient survival has dramatically improved. Major clinical trials for AAV are listed in Table 2.

Table 1 Clinical subtype of AAV based on extent and severity of disease

Subtype	Description
Localized	One site, typically the upper respiratory tract in GPA
Early systemic	Multiple sites, except renal or imminent vital organ failure
Generalized	Imminent vital organ failure or renal involvement with creatinine < 500 µmol/L
Severe	Vital organ failure, typically renal involvement with creatinine level > 500 µmol/L
Refractory	Progressive disease despite conventional therapy

Table 2 Major clinical trials on AAV

Clinical trial	Description
CYCAZAREM [19]	Cyclophosphamide versus azathioprine for early remission phase of generalized AAV
NORAM [45]	Cyclophosphamide versus methotrexate for induction of remission in early systemic AAV
MEPEX [47]	Plasma exchange versus high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis
WEGENT [57]	Azathioprine or methotrexate maintenance for AAV
CYCLOPS [25]	Pulse versus daily oral cyclophosphamide for induction of remission in renal vasculitis
RITUXVAS [36]	Rituximab-based regimen versus a standard cyclophosphamide plus azathioprine in active generalized AAV
RAVE [37]	Rituximab versus daily oral cyclophosphamide for induction of remission
IMPROVE [63]	Mycophenolate mofetil versus azathioprine for remission maintenance in renal vasculitis
MAINRITSAN [64]	Rituximab versus azathioprine for maintenance in AAV

The basis of the trials mentioned in this table was multi-center randomized controlled trials with large sample size ($n > 100$), or those exerting major influence on the treatment of AAV despite relatively small sample size (e.g., CLEAR study, RITUXVAS study, etc.)

Induction of remission

Glucocorticoids, in combination with immunosuppressants, especially cyclophosphamide or rituximab, are the most commonly used treatment to induce remission. High-dose pulse methylprednisolone and plasma exchange are also considered for use in patients with severe disease.

Cyclophosphamide

Currently, the combination of cyclophosphamide (CYC) with corticosteroids is the standard treatment for AAV and has transformed AAV from a uniformly fatal disease to a chronic relapsing condition in recent decades [18]. This regimen is effective in 70–90% of patients with AAV [19]. In general, patients are treated with oral CYC at doses of 2 mg/kg/day, lasting for 3–6 months, with doses adjusted based on the patients' age and renal function [20, 21]. For continuous oral low-dose cyclophosphamide, the dose is reduced by 25% for > 60 years of age and by 50% for > 75 years of age, while the dose adjustment for pulsed high-dose cyclophosphamide is shown in Table 3 [17, 20]. However, adverse effects, including haemorrhagic cystitis, infertility, infection, bone marrow suppression, and malignancy, are associated with the cumulative dose of CYC.

To minimize the drug toxicity, pulsed intravenous CYC (IV-CYC) was designed and tested in several randomized trials [22–24]. In the CYCLOPS (randomized trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis) study, newly diagnosed AAV cases with renal involvement and without life-threatening disease were treated with prednisolone in combination with either oral CYC (2 mg/kg/day, a maximum of 200 mg/day) or IV-CYC (15 mg/kg, a maximum of 1200 mg/pulse, every 2–3 weeks). The results showed that IV-CYC therapy was non-inferior to oral CYC for inducing AAV remission in the time to remission (HR, 1.098; $P = 0.59$) and remission

rates (88.1% in the pulse group versus 87.7% in the daily oral group), decreasing the cumulative CYC doses by half and treatment-related leukopenia by one-third [25].

However, a lower cumulative CYC dose seems to be associated with a higher relapse rate. A long-term follow-up study (median 4.3 years) showed that continuous oral CYC for induction has a lower subsequent relapse rate compared with a pulsed IV-CYC regimen (20 and 40%, respectively) [26]. Nevertheless, some patients who do not respond well and/or rapidly to IV-CYC induction could also achieve remission when switched to oral CYC [25]. Physicians need to balance the possibly higher relapse rates in IV-CYC with higher rates of side effects in daily oral regimens [27] and establish individually tailored treatment approaches based on the disease stage and activity.

All patients treated with CYC are encouraged to be well hydrated during treatment, and patients with the IV-CYC regimen are encouraged to take oral or intravenous Mesna (2-mercaptoethane sulfonate sodium) to reduce the bladder toxicity. Cortimoxazole is also recommended as a prophylaxis against *Pneumocystis jirovecii* infection for all patients during treatment if there are no intolerance reactions or contraindications. Strict monitoring of complete blood count tests should be routinely performed for leukopenia and lymphocytopenia, especially for patients with oral CYC regimen (usually twice a week). In both administration modalities, dose changes or discontinuation of CYC may be necessary in the event of acute leukopenia or a gradual decrease over time [28].

Rituximab

Rituximab (RTX), a chimeric anti-CD20 IgG monoclonal antibody, was reported as effective for patients with severe, refractory relapsing AAV in the previous case reports, and retrospective and prospective clinical trials [29–35]. Furthermore, two randomized controlled trials were conducted to evaluate its efficacy and safety in introducing remission for AAV. The RITUXVAS study (Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis) [36] recruited 44 patients with newly diagnosed GPA or MPA and renal involvement (including patients requiring dialysis and undergoing plasma exchange). The rituximab group ($n = 33$) received high-dose oral corticosteroids (with the initial dose of 1 mg/kg/day, tapering to 5 mg/day at the end of 6 months) plus 4 consecutive infusions of rituximab (375 mg/m² weekly) and 2 infusions of intravenous cyclophosphamide (15 mg/kg, with the first and third rituximab infusions), while the cyclophosphamide arm received high-dose oral corticosteroids plus intravenous cyclophosphamide (15 mg/kg) for 3–6 months, which was followed by maintenance by azathioprine (AZA). The primary endpoint, sustained remission, was achieved by 76% in the rituximab arm compared to

Table 3 Dose modification of pulsed cyclophosphamide as used in a randomized controlled trial comparing the efficacy of daily oral versus pulsed cyclophosphamide for renal vasculitis

Age, years	Serum creatinine ($\mu\text{mol/L}$)	
	< 300 (mg/kg/pulse)	300–500 (mg/kg/pulse)
Pulsed CYC dose reductions for renal function and age		
<60	15	12.5
60–70	12.5	10
>70	10	7.5

The trial did not include a separate regimen for patients with a creatinine of < 150 $\mu\text{mol/L}$

CYC cyclophosphamide

82% in the CYC arm at 12 months, indicating that rituximab is as efficient as cyclophosphamide for inducing remission in AAV [36].

In the RAVE study (Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis) [37], in addition to tapering the corticosteroid dose, 197 ANCA-positive GPA or MPA patients, including newly diagnosed and relapsing AAV patients, were randomly assigned in a 1:1 ratio according to clinical site and ANCA type, to receive 4 infusions of rituximab (375 mg/m² weekly plus daily placebo-cyclophosphamide, *n* = 99) without maintenance therapy, or oral cyclophosphamide (2 mg/kg per day adjusted for renal insufficiency plus placebo-rituximab infusions, *n* = 98), which was followed by maintaining remission with AZA (2 mg/kg/day). The complete remission rates at 6 months, in the absence of corticosteroids, were not significantly different between the two arms (64% in the rituximab group and 53% in cyclophosphamide group, *P* < 0.001) [37]. This study also demonstrated that rituximab is comparable to oral cyclophosphamide for remission induction. In the subset of patients with relapsing disease (*n* = 101), rituximab showed superior efficacy compared to cyclophosphamide, with remission rates of 67% in the rituximab group versus 42% in the cyclophosphamide group [37]. Furthermore, patients with PR3-ANCA were more likely to achieve disease remission than those with MPO-ANCA in the RTX arm (50% patients in the RTX arm became negative for PR3-ANCA, as compared with 40% for MPO-ANCA) [37]. Regarding remission on long-term follow-up, rituximab was likely to be more effective than cyclophosphamide at 12 months (48 versus 39%), which was not the case at 18 months (39 versus 33%) [37].

Adverse events were similar for both the rituximab and cyclophosphamide regimens in the two trials, indicating that those side effects were probably caused by high-dose glucocorticoids and the disease itself and current cyclophosphamide regimen would be reasonably safe.

These studies suggest that rituximab is non-inferior to cyclophosphamide for AAV remission induction and is more effective than cyclophosphamide in patients with relapsing disease. However, rituximab treatment does not result in earlier remission or a lower incidence of severe adverse events. As there was no maintenance following the RTX regimen in both trials, further refinement and evaluation of treatment strategies following RTX-based induction therapy are still required.

Methotrexate

Methotrexate (MTX) may be an option for remission induction when dosed at 20–25 mg weekly (oral or parenteral) for patients with non-organ-threatening and normal renal function [38–44]. A randomized controlled

trial compared methotrexate with cyclophosphamide in patients without critical organ manifestations, termed the NORAM study [45]. At 6 months, methotrexate was as effective as cyclophosphamide in disease control; 90% of patients in the MTX group achieved remission, and 94% in the CYC group achieved remission [45]. However, long-term (median 6 years) follow-up demonstrated that MTX-treated patients were more likely to relapse and needed to be treated with glucocorticoids and further immunosuppression for a longer time compared with CYC-treated patients [46]. Furthermore, MTX was shown to be less effective in induction remission in patients with more extensive disease (*P* = 0.04) or pulmonary disease (*P* = 0.03) as remission was delayed among these patients [45]. Therefore, MTX should be considered as an alternative to cyclophosphamide for non-organ-threatening disease according to the EULAR/ERA-EDTA recommendations [28]. The recommendations also listed the types of patients for whom MTX could be considered: nasal and paranasal disease without bony involvement (erosion), cartilage collapse, olfactory dysfunction or deafness; skin involvement without ulceration; myositis (skeletal muscle only); non-cavitating pulmonary nodules/infiltrate without haemoptysis or when cyclophosphamide or rituximab were not available, contraindicated or undesirable for the patient [28]. Folic acid supplement is suggested during MTX treatment.

Plasma exchange

The main indications for plasma exchange (PLEX) as an adjunctive therapy with standard remission induction are AAV with anti-glomerular basement membrane (GBM) antibody, diffuse alveolar haemorrhage and severe renal impairment. The randomized MEPEX study (Methylprednisolone versus Plasma Exchange) [47] enrolled 137 new diagnoses of severe renal vasculitis (serum creatinine level > 500 μmol/L or dependent on dialysis). In addition to oral prednisolone and cyclophosphamide, patients were randomly treated with seven sessions of plasma exchange (PLEX, *n* = 70) or three infusions of 1 g of pulse methylprednisolone daily (MP, *n* = 67). PLEX was superior in terms of patient survival and renal recovery, with 69 and 43% of those treated with PLEX who were alive and dialysis independent at 6 and 12 months, respectively, compared to 49 and 19% of those treated with MP, respectively [47]. However, there were no significant differences in end-stage renal disease (ESRD) and mobility in the subsequent observation (median 3.95 years), indicating that the long-term prognosis and overall benefit of plasma exchange for severe AAV remain uncertain [48].

CCX 168

As AAV pathogenesis therapies continue to evolve, complement activation through alternative pathways has been demonstrated to be associated with the progression of AAV [49, 50]. The common pathway component C5a is demonstrated to play a significant role in ANCA-mediated neutrophil activation [51, 52]. Several trials were designed to evaluate the efficacy and safety of CCX168, a C5a-receptor inhibitor since 2011. Recently, the result from CLEAR study (C5aR inhibitor on Leukocytes Exploratory ANCA-associated Renal Vasculitis) showed that C5a receptor inhibition with avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis [53]. In this study, 67 newly diagnosed or relapsing vasculitis were randomly assigned to receive avacopan (30 mg, twice daily) plus reduced-dose prednisone (20 mg daily, $n = 22$), avacopan (30 mg, twice daily, $n = 22$) without prednisone, or placebo plus prednisone starting at 60 mg daily (control group, $n = 23$). All patients received cyclophosphamide or rituximab. At 12 weeks, 86, 81, and 70% of the avacopan with reduced prednisone, avacopan with no prednisone groups, and high-dose glucocorticoid group achieved clinical response, respectively, while the incidence of adverse events in three groups was similar (86, 96, and 91%, respectively) [53]. This study showed that both avacopan groups were non-inferior to high-dose glucocorticoid for remission induction.

Maintenance of remission

Despite the significant benefit of corticosteroid plus cyclophosphamide for AAV patients, relapse and drug toxicity are related to this approach. Relapse remains a major challenge, although most patients achieved remission under proper treatment [19, 45]. The relapse rate is higher after discontinuation of immunosuppression or glucocorticoids [19, 54]. Therefore, long-term maintenance of remission is necessary to reduce relapse, and the optimal duration is 24 months according to the 2016 recommendations [28]. Considering the adverse effects caused by long-term exposure to cyclophosphamide, the most commonly used medication in maintenance therapy, there are less toxic immunosuppressive agents, such as azathioprine, methotrexate, rituximab, leflunomide, and mycophenolate mofetil, that can be combined with or without low-dose glucocorticoids.

Azathioprine

Azathioprine (AZA) is the first-line medication for remission maintenance. In the CYCAZAREM study [19] (Cyclophosphamide versus Azathioprine for Early Remission Phase of Vasculitis), following induction of remission

with prednisolone plus oral CYC, 144 newly diagnosed AAV patients were randomized to receive either AZA (2 mg/kg/day) or CYC (1.5 mg/kg/day). At 18 months, no significant difference was observed in the relapse rates in both arms (15.5% in the AZA-treated group and 13.7% in the CYC-treated group), demonstrating that AZA and CYC appear to be comparably efficacious in preventing relapse in maintenance therapy. This study has demonstrated that converting from CYC to AZA once patients achieve remission is an effective way to maintain treatment efficacy while reducing adverse events from the cumulative dose of long-term CYC use. White blood cells in peripheral blood should be monitored during AZA treatment.

Methotrexate

Methotrexate has been effectively used for maintenance therapy after inducing remission [55, 56]. A prospective, open-label trial, termed WEGENT, by the French Vasculitis Group was conducted in 126 patients and randomly treated them with AZA (2 mg/kg/day) or MTX (starting at 0.3 mg/kg/week and reaching 25 mg/kg/week) for 12 months [57]. Adverse events occurred in 29 AZA recipients and 35 MTX recipients ($P = 0.29$), and seven patients (11%) in the AZA arm reached the primary end point (adverse events requiring therapy discontinuation), as compared to 12 patients (19%) in the MTX arm ($P = 0.21$). Furthermore, relapse rates in the follow-up observation (29 ± 13 months) were similar in both groups (36 and 33%, respectively) [57]. This study showed that AZA and MTX were comparable in both safety and efficacy for maintenance therapy. However, the use of MTX is limited in AAV remission due to its renal clearance. MTX should not be used in patients with renal insufficiency ($\text{Scr} < 177 \mu\text{mol/L}$), and folic acid supplementation is helpful during MTX treatment.

Leflunomide

Metzler et al. reported a randomized controlled trial evaluating the efficacy and safety in a comparison of leflunomide (30 mg/day) and MTX (starting at 7.5 mg/week and reaching 20 mg/week after 8 weeks) for 2 years in 54 patients who achieved remission with CYC and prednisolone [58]. Leflunomide was more effective than MTX in remission maintenance, but it caused a high rate of adverse events, including hypertension and infection. Therefore, leflunomide is not routinely used as the first-line maintenance therapy and would be an option in the event of intolerance to AZA or MTX.

Mycophenolate mofetil (MMF)

MMF was indicated to represent an alternative to CYC for induction and maintenance of remission in MPO–ANCA-associated MPA with mild-to-moderate renal disease in some uncontrolled studies [59–62]. However, a randomized controlled trial, IMPROVE, that recruited 154 newly diagnosed AAV patients (after CYC induction) from 42 centers in 11 European countries demonstrated that at a median follow-up of 36 months, MMF (starting at 2 g/day) was less effective than AZA (starting at 2 mg/kg/day) without significant difference in adverse events [63]. Therefore, MMF may be considered for use in patients with intolerance to other agents.

Rituximab

As mentioned above, no maintenance treatment was conducted in either the RAVE or RITUXVAS trial. The MAIN-RITSAN study (Maintenance of Remission using Rituximab in Systemic ANCA-associated vasculitis) is the first randomized controlled trial to compare RTX (low dose at 500 mg every 6 months) to AZA (dosed at 2 mg/kg/day and tapered until 22 months) for maintenance therapy. It was conducted in 115 AAV patients following standard remission with CYC plus glucocorticoids [64]. At 28 months, 5% (3/57) of patients in the RTX arm suffered major relapse compared to 29% (17/58) of patients in the AZA arm, and there was not a significant difference in the adverse event rates [64]. Although RTX seemed to be more effective than AZA for maintenance in this trial, the result is limited, because the dose of AZA was tapered from 12 months (starting at 2 mg/kg/day for 12 months, and then 1.5 mg/kg/day for 6 months, and 1 mg/kg/day for 4 months) [64]. Further evaluation of the efficacy and optimal dose of RTX in maintenance remission is still needed.

Treatment of relapsing and refractory disease

Relapse was defined as re-occurrence, new onset of disease attributable to active vasculitis, or worsened disease activity. “Major relapse” is defined as “recurrence or new onset of potentially organ- or life-threatening disease attributable to active vasculitis”. “Minor relapse” is defined as “recurrence or new onset of disease attributable to active vasculitis that is neither potentially organ- nor life-threatening” [65]. Relapse in AAV is a well-recognized, independent risk factor for subsequent progression to end-stage renal disease (ESRD) [66]. Major relapse of organ-threatening or life-threatening disease is suggested to be treated as a new disease, with the combination of glucocorticoids and either cyclophosphamide or rituximab to induce remission [28].

Rituximab is preferred for use in relapse of organ-threatening or life-threatening disease considering the clinical data in the relapse subgroup of the RAVE study and the cumulative toxicity caused by long-term cyclophosphamide use. To treat non-severe relapse in AAV (so-called “minor relapse”), the intensification of immunosuppressive agents, such as an increased dose of glucocorticoids or AZA, is suggested. Modification of the immunosuppressive remission maintenance regimen was recommended by the EULAR/ERA-EDTA recommendation in 2016 [28] based on a study that demonstrated a higher severe relapse rate caused by increasing the glucocorticoid dose in patients with minor relapse [67]. It remains important to avoid excessive exposure to cyclophosphamide, because most malignancies occur at a cumulative dose of cyclophosphamide over 36 g [68].

Patients with refractory disease include those who have unchanged or increased activity after 4 weeks of treatment or an inadequate response (less than 50% reduction in the disease activity score in 6 weeks) and those who have chronic persistent disease (at least one major or three minor items on the disease activity score after 12 weeks of treatment) [65]. A switch from cyclophosphamide to rituximab or from rituximab to cyclophosphamide is suggested for such patients. For patients who inadequately respond to pulsed cyclophosphamide or rituximab or when rituximab is unavailable, a switch to oral cyclophosphamide can be considered [69]. Intravenous immunoglobulins (0.4 g/kg for 5 days, 2 g per cycle) may also benefit patients who fail to achieve remission and have persistent low activity [70–72].

Outcomes of AAV

As mentioned above, AAV is usually fatal before the introduction of standard immunosuppressive treatment, and it has a 1-year mortality rate of approximately 80% [73]. Patients with generalized AAV have a very poor prognosis if the disease is not properly diagnosed and treated [74]. The use of glucocorticoids and cyclophosphamide has dramatically improved the outcomes of AAV patients and could increase the 5-year survival rate to 69–91% in patients with GPA and 45–76% in patients with MPA [75]. Advanced age, secondary infection, especially pulmonary involvement, and initial renal function are independent predictors of mortality [73]. Despite the effective control of disease activity, treatment-related adverse effects, such as infections, urothelial malignancy, and infertility, have received closer attention [76, 77]. Of note, infection has become the leading cause of patient death. In a 5-year follow-up cohort study by EUVAS ($n = 535$, median age 61 years, 53% of GPA), infections contributed to 48% of deaths in the first year, which was followed by active vasculitis (19%), while mortality after the first year was mainly related to cardiovascular disease,

malignancy, and infection (26, 22, and 20%, respectively) [18]. Most infections are associated with *Staphylococcus aureus* and *P. jirovecii*, and prophylaxis and effective treatment against any infections play a significant role during remission. Furthermore, it was found that patients with older age, renal dysfunction, a lower lymphocyte count, or pulmonary involvement are more likely to suffer from infection [78]. A recent study revealed that the CD4 lymphocyte count had a higher predictive value than the total lymphocyte count for overall infections [79]. Therefore, strict monitoring of the lymphocyte count in the peripheral blood (no less than $600/\text{mm}^3$), especially the CD4+ lymphocyte count (no less than $200/\text{mm}^3$), is useful for decreasing treatment-related adverse effects and improving prognosis.

Relapse and treatment resistance are also crucial issues for AAV outcomes. Although most patients could achieve remission after induction therapy, relapse remains common for patients with AAV, even while receiving maintenance treatment. For example, in the CYCAZAREM study, the relapse rates were 13.7% in the CYC group and 15.5% in the AZA group at 18 months [19], and in the NORAM study, relapse rates were 46.5% in MTX arm and 69.5% in CYC arm at 18 months, respectively [45]. Severe relapse, such as pulmonary haemorrhage, may be life-threatening. In the long-term follow-up of patients in four EUVAS trials, i.e., MEPEX, CYCAZAREM, NORM, and CYCLOPS studies, a total of 201 patients (38%) experienced at least one relapse between 44 and 62 months, and renal insufficiency at enrolment (creatinine level $> 200 \mu\text{mol/L}$) was strongly associated with a reduced risk of relapse [80]. The relapse rate increases with time [81] and patients with GPA are more likely to relapse than those with MPA (18 versus 4%, respectively) [19]. PR3-ANCA and cardiovascular involvement at presentation were independent factors associated with a higher risk of relapse [80] [80], whereas PR3-ANCA and pulmonary and/or ENT involvement were observed in two cohort studies from USA and France [82]. Cyclophosphamide-sparing strategies with pulsed intravenous cyclophosphamide or methotrexate, instead of oral cyclophosphamide, seem to increase the risk of relapse [26, 83, 84]. Some patients insufficiently respond to glucocorticoids and cyclophosphamide therapy. Treatment resistance occurs in 23% of 334 treated patients, particularly females, black patients, and those with severe kidney disease [66]. Another study documented that older age and MPO-ANCA may be predictors of treatment resistance [82].

As one of the most commonly involved organs in AAV, renal involvement is another key issue in AAV patients. Renal survival was documented to be 57% at 30 months and 82% at 57 months [85, 86]. In addition, 38% of MPO-ANCA patients and 15% of PR3-ANCA patients progressed to end-stage renal disease (ESRD) [87]. Patients with poor renal function have worse renal survival outcomes. The higher the

serum creatinine at the time of diagnosis is, the poorer the renal survival [88]. In the follow-up of patients in the above-mentioned MEPEX trial ($n = 137$, median 3.95 years), 51% ($n = 70$) of patients died, and 41% ($n = 56$) developed ESRD [47]. A study from The Netherlands described similar results, where 23% patients on dialysis at the time of diagnosis died within 6 months of follow-up and another 29% continued to depend on dialysis [89]. Relapse was reported to be a factor that increased the risk of progression to ESRD by 4.7 times [66]; in addition, it is an independent predictor of ESRD. The age, percentage of normal glomeruli, tubular atrophy, and intraepithelial infiltrates in the renal biopsy were found to be predictors of renal function in patients with severe renal dysfunction caused by ANCA glomerulonephritis [19]. In 2010, Berden et al. proposed a histopathological classification of ANCA-associated glomerulonephritis, i.e., focal, crescentic, mixed and sclerotic categories, and renal survival rates in their cohort for these four categories were 93, 76, 61, and 50%, respectively [90]. Another study from Europe had similar findings [91] and revealed that this classification system could predict renal outcomes. However, a study by Chang et al. investigated Chinese patients with AAV and found that the probability of progressing to ESRD was increased with ascending categories of focal, mixed, crescentic, and sclerotic glomerulonephritis [92]. Such difference between the Chinese and European cohorts might be attributed to the following reasons. First, in the Chinese cohort, most patients have MPO-ANCA and thus had more chronic lesions. Second, plasma exchange was not sufficiently employed in the Chinese cohort [92].

Summary

Ethnicity, geographical factors, age, and distinct phenotypes of AAV may contribute to the different occurrence rates of AAV. Considerable strides have been made in the treatment of AAV in past decades. To induce remission, glucocorticoids in combination with cyclophosphamide remain the standard therapy for generalized AAV, while methotrexate can be used as an alternative to cyclophosphamide in patients with non-organ-threatening disease. Rituximab is non-inferior to cyclophosphamide for AAV remission induction and is more effective in patients with relapsing disease. For maintenance therapy, azathioprine, rituximab, and methotrexate are well-accepted options. The C5a receptor may be an important treatment target. Infection has become the leading cause of death instead of active AAV per se. The intensity of immune suppression should be properly adjusted to control disease manifestations and prevent relapse, as well as to avoid adverse events related to the standard immunosuppressive treatment.

Compliance with ethical standards

Conflict of interest Author Lei Shi declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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