Kidney Diseases

Review Article

Kidney Dis 2024;10:407–420
DOI: 10.1159/000540514

Received: April 3, 2024
Accepted: July 20, 2024
Published online: August 5, 2024

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis in China: Epidemiology, Management, Prognosis, and Outlook

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Keywords
Anti-neutrophil cytoplasmic antibody · Vasculitis · Chinese patients · Treatment · Outcome

Abstract
Background: Increasing evidence indicates that clinicopathologic phenotypes and ANCA serotypes may differ ethnically and geographically. This review highlights the progress in the prevalence, pathogenesis, management, and outcomes of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in China. ***Summary:*** AAV is not rare in China. Cumulative evidence has demonstrated a significant preponderance of microscopic polyangiitis (MPA) and myeloperoxidase (MPO)-ANCA AAV in China. Even in patients with granulomatosis with polyangiitis (GPA), there is a predominance of MPO-ANCA over proteinase 3 (PR3)-ANCA, presenting a unique subset. The pathogenesis of AAV is multifactorial, with the role of complement activation being highlighted during recent years. Treatment strategies for AAV in China have also been refined recently. A rapid tapering of glucocorticoids to minimize exposure has been recommended by the Chinese guidelines. Along with a better understanding of the disease, B cell-targeted therapy and complement-targeted therapy are developing. A considerable number of patients in China received rituximab treatment and achieved remission. However, infection risk and associated mortality still remain concerns. Therefore, less rituximab exposure should be considered and evaluated in Chinese AAV patients. Prognostic factors have been reviewed. Of note, along with improved outcomes, there is an increase of cardiovascular and malignant-related death, warranting specific care. Recently, a modified renal risk score model has been validated for early risk prediction in Chinese AAV patients. Moreover, emerging biomarkers for AAV, including complement components, have been identified in Chinese patients. ***Key Messages:*** There is a preponderance of MPA and MPO-ANCA in China. Treatment strategies for Chinese AAV patients generally align with those in western countries, and to some extent, less aggressive. Prognostic factors and emerging biomarkers for AAV in China have been identified. Further challenges include optimizing

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interventions, minimizing treatment-related comorbidities, improving disease monitoring, and enhancing life qualities of AAV patients.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a cluster of systemic disorders characterized by necrotizing inflammation of small vessels, accompanied by the presence of circulating ANCA. ANCAs are the most important serological biomarkers of AAV, and the major target antigens are neutrophil cytoplasmic constituent proteinase 3 (PR3) or myeloperoxidase (MPO). According to the 2012 classification of the Chapel Hill Consensus Conference (CHCC) [1], AAV comprises granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA). GPA is predominantly associated with PR3-ANCA and its clinical features typically include sinonasal disease, lower respiratory tract involvement and respiratory granulomatous inflammation, and glomerulonephritis. MPA is usually associated with MPO-ANCA, and clinical features include more severe renal disease; granulomatous inflammation is generally absent. EGPA, characterizing by asthma, eosinophilia, and eosinophil-rich necrotizing vasculitis, is less commonly associated with ANCAs (mainly MPO-ANCA) and increasingly considered as a distinct entity.

There is increasing evidence indicating that ANCA serotypes and clinicopathologic phenotypes of AAV may differ ethnically and geographically [2–5]. In this article, we provide an updated overview of the epidemiology, treatment, and outcome of AAV in China and offer a perspective on future challenges in AAV management.

Epidemiology

The epidemiological characteristics of AAV have been investigated worldwide, revealing an estimated global prevalence of 48–184 cases per million persons, with a peak onset age of 60–70 years [6, 7]. Based on a recent systematic review and meta-analysis, the global incidence of AAV was estimated at 17.2 per million person-years (13.3–21.6). Specifically, the incidence rates were found to be 9.0, 5.9, and 1.7 for GPA, MPA, and EGPA, respectively [8]. However, there is substantial geographical variation in AAV incidence. For example, AAV is more common in white and Asian populations and less prevalent among African American populations. Moreover, notable geographical variation exists in the disease spectrum. GPA and PR3-AAV predominantly affect Caucasian populations, particularly in northern Europe, whereas MPA and MPO-AAV are more common in southern Europe and Asian regions [7]. Currently, epidemiological data on AAV in China are limited. A retrospective study using a large national inpatient database in China reported a prevalence of 0.25 cases per 1,000 inpatients, with an average age of 60.0 ± 15.6 years at diagnosis [9]. The study also revealed a significant preponderance of MPA and MPO-AAV, which accounted for about 80% of AAV cases, contrasting with the higher prevalence of GPA or PR3-AAV in Caucasian populations [10]. MPO is the major target ANCA antigen in Chinese patients, even in patients with GPA, about 60–70% of them with ANCA specificity for MPO [11, 12]. MPO-ANCA-positive GPA is a unique subset, with relatively milder renal injury at diagnosis and better renal outcome compared with PR3-ANCA positive GPA [11]. The preponderance of MPA and MPO-AAV (including a unique entity as MPO-ANCA positive GPA) is an epidemiological characteristic of Chinese patients.

The geographical variation in the epidemiology of AAV is suggested to be influenced by a combination of genetic pools and certain environmental factors. There is compelling evidence supporting the presence of a genetic predisposition in AAV, as evidenced by the genetic distinction between PR3-AAV and MPO-AAV. Patients with PR3-AAV have shown a strong association with the *HLA-DP* region, in particular the *HLA-DPB1*0401* allele, while MPO-AAV is highly associated with the *HLA-DQ* region [5]. In line with that, specific susceptible alleles, such as *HLA-DQA1*0302* and *HLA-DQB1*0303*, have been identified in relation to MPO-AAV in China [13]. Accumulating evidence suggests that environmental factors participate in AAV development in China. There is a positive association between exposure to carbon monoxide and AAV frequency [9]. The role of silica is further supported by the increasing frequency of AAV observed following a severe earthquake in Yunnan Province of China in 2014 [9]. Similar observations were made after large earthquakes in Japan in 1995 and 2011 [14, 15]. There also appears to be a latitude-dependent incidence in AAV within China, with higher proportions observed in northern regions [9]. Hospitalization data observed a higher proportion of AAV cases in winter [9], which aligns with previous reports [16].

Pathophysiology

AAV is characterized by microvascular endothelial inflammation, leading to progressive vessel injury, tissue destruction, and loss of function. Autoreactivity to neutrophil constituents, MPO or PR3, is central to the pathogenesis of most cases of AAV. Genetic risk factors combine with known or unknown environmental factors, age, and potentially infection to induce a loss of T- and B-cell tolerance to neutrophil antigens, leading to the development of ANCAs [5, 13, 17, 18]. Neutrophils are the main mediators of endothelial injury. Following infection or inflammation, neutrophils are primed by inflammatory cytokines or complement C5a, leading to the translocation of MPO and PR3 from primary granules to the neutrophil surface. Subsequently, ANCAs may bind to these autoantigens on the cell surface, resulting in robust cellular activation [19, 20]. Activated neutrophils alter the expression of adhesion molecules and bind to vascular endothelium [21]. Neutrophil activation results in the release of reactive oxygen species and proteases, as well as neutrophil extracellular traps, mediating tissue injury [19, 20, 22]. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes as well as macrophages augmenting tissue injury [23, 24].

Historically, it was considered that complement played a limited role in AAV due to its pauci-immune characteristics. However, in the past decade, accumulating evidence has demonstrated that activation of complement system is crucial for the development of AAV [25–30]. In vivo evidence identified the alternative pathway as being critical to pathological interactions of C5a with C5a receptor (C5aR), which is essential for AAV development [25–27]. In particular, recent studies of humans, including those conducted in Chinese AAV patients, strongly support these findings, with the demonstration of alternative pathway activation in the circulation and tissue deposition of complement components of the alternative pathway [28–30]. Dysregulation of the alternative complement pathway has also been documented, with a decreased level of circulating complement factor H (CFH) and impaired CFH function observed in AAV patients [31, 32]. In vitro, an amplification loop has been proposed in which activated neutrophils release factors that trigger the activation of the alternative complement pathway and the generation of C5a, leading to further neutrophil priming and activation through interaction with C5a receptors [19]. Evidence from Chinese study showed that neutrophil extracellular traps released from ANCA-activated neutrophils can activate alternative complement pathways, generating C5a [33]. Moreover, two key molecules, namely, high mobility group box 1 and sphingosine-1-phosphate, were found to be important downstream effector molecules in the C5a-neutrophil interaction, augmenting neutrophil priming and activation [34, 35]. Other potential roles for complement in AAV include interactions with procoagulant molecules. As evidenced by Chen's group, treatment of C5a-primed neutrophils with ANCA resulted in the release of tissue factor, which subsequently led to thrombin generation, potentially activating platelets and triggering the coagulation system [36, 37]. Activated platelets could further amplify complement alternative pathway activation [37].

Taken together, the pathogenesis of AAV involves various factors. A loss of tolerance to neutrophil proteins, subsequent ANCA-mediated neutrophil activation, and the complement system, which plays key roles in disease initiation and progression, form a feedback amplification loop, leading to microvascular injury (shown in Fig. 1).

Treatment of AAV

Recommendations

Immunosuppressive therapy has dramatically improved the outcome of AAV patients. Therapy is generally divided into a phase aiming to induce remission and a subsequent period with the goal to maintain remission.

The recommended initial treatment approach for newly diagnosed or relapsing AAV with organ-threatening or life-threatening disease involves the use of glucocorticoids in combination with cyclophosphamide or rituximab [38, 39]. Rituximab is preferred in relapsing disease and PR3-AAV [38, 39]. For nonorgan-threatening GPA or MPA, methotrexate or mycophenolate mofetil (MMF) can be considered as alternatives [38, 39]. Oral prednisone at an initial dose of 1.0 mg/kg/day has been widely used and the PEXIVAS reduced glucocorticoid regimen with a rapid tapering schedule is recommended in recent guidelines [38–40]. Complement-targeted therapy has been emerging as another novel approach for the treatment of AAV. Avacopan, a selective C5a receptor inhibitor, demonstrated effectiveness as an alternative to glucocorticoid treatment in a phase III clinical trial of C5aR inhibition [41], facilitating it to be a new practice point to reduce exposure to glucocorticoids [42].

Intravenous methylprednisolone (MP) pulses and plasma exchange may be considered as part of therapy to induce remission in severe GPA or MPA. MP pulse therapy should be limited to the treatment of severe organ-threatening manifestations, in particular, rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage (DAH) [38, 39].

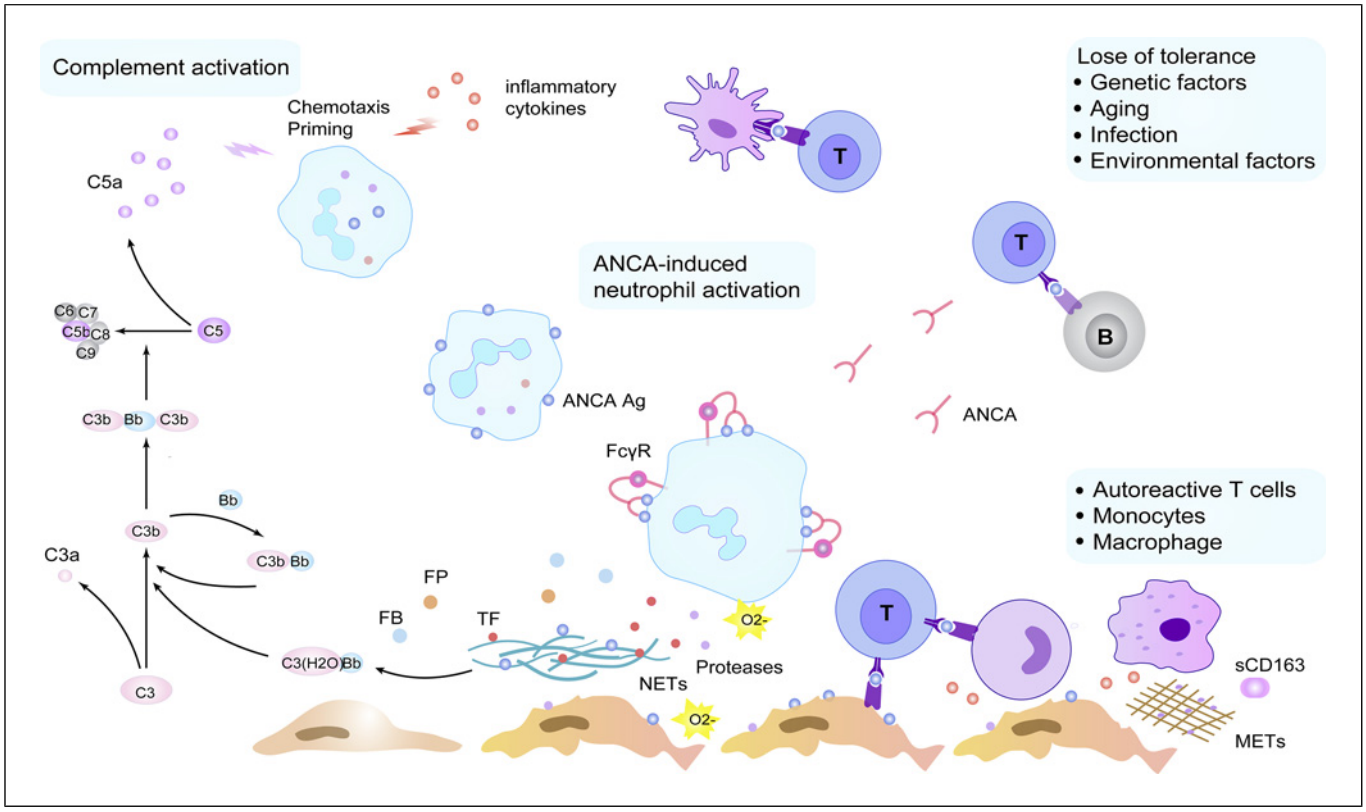

Fig. 1. Pathogenesis of ANCA-associated vasculitis. Genetic risk factors combine with environmental factors, age, and potentially infection to induce a loss of T- and B-cell tolerance to neutrophil antigens, leading to the development of ANCAs. Following infection or inflammation, neutrophils are primed by inflammatory cytokines or complement C5a, resulting in the translocation of myeloperoxidase (MPO) and proteinase 3 (PR3) from primary granules to the neutrophil surface. Subsequent binding of ANCA to these autoantigens activates neutrophils, which adhere to vascular endothelium and release reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Factors released from ANCA-activated neutrophils, including factor P and NETs, can activate the alternative complement pathways, generating C5a, which amplifies the inflammatory response by priming neutrophils for activation by ANCA. Chemokines and tissue deposition of ANCA autoantigens result in the recruitment of autoreactive T cells and monocytes as well as macrophages augmenting tissue injury. Ag, autoantigen; FB, factor B; FP, factor P; METs, macrophage extracellular traps; TF, tissue factor.

Plasma exchange is recommended as an additional treatment for AAV patients with certain indications, such as severe renal injury (serum creatinine >300 μmol/L) or DAH with hypoxemia, or coexistence of anti-glomerular basement membrane antibody [39, 42, 43].

For AAV patients receiving cyclophosphamide, rituximab, and/or high doses of glucocorticoids, low-dose trimethoprim/sulfamethoxazole (TMP-SMX), or alternative, is advised for pneumocystis pneumonia prophylaxis [38, 39]. After the induction of remission, less toxic drugs instead of cyclophosphamide should be used for maintenance of remission, such as rituximab, azathioprine, or MMF. Among these medications in maintenance therapy, rituximab or azathioprine is suggested as the first choice [38, 39].

Strategies for Chinese AAV Patients

The treatment for AAV in China is consistent with the above recommendations from western countries. Cyclophosphamide in combination with glucocorticoids is still the most widely used first-line therapy for induction remission. The cumulative dosage for intravenous cyclophosphamide ranged from 6 to 9 g, while for oral cyclophosphamide, it ranged from 9 to 12 g [4, 10, 44–50]. In older patients and those with renal insufficiency, a reduction in the cyclophosphamide dose was implemented. These cumulative dosages are relatively smaller than those reported in RCTs conducted in European countries [51]. There was no significant difference in remission rates between oral cyclophosphamide group and intravenous cyclophosphamide group, according to a

large cohort study in China [4]. This finding is consistent with RCTs conducted worldwide, which showed similar rates of complete remission with induction therapy using either intravenous or oral cyclophosphamide [51–53]. Although the CYCLOPS study reported a higher relapse rate with intravenous pulse cyclophosphamide [51], the above Chinese study found no significant difference in relapse risk between these two arms [4]. Regarding adverse events, no significant difference in the risk of infection was observed [50]. However, since intravenous cyclophosphamide allows for a reduction in the total dosage compared to oral cyclophosphamide and is associated with less leukopenia [51], it is considered much safer.

Rituximab in initial treatment is relatively new in China and is increasingly being preferred as the induction agent for various patient subgroups, such as those who prioritize fertility preservation, PR3-AAV patients, patients with relapsing disease, and those with urgent need of glucocorticoid-sparing. However, there are limited comparative data on the use of cyclophosphamide versus rituximab in Chinese AAV patients yet. A retrospective study conducted at a single Chinese center reported that 22 out of 27 patients (81.5%) who received rituximab (mean rituximab dose 1,270.4 mg) achieved complete or partial remission [54]. The remission rate was similar to that of patients receiving cyclophosphamide as induction therapy in the same center [4]. In terms of adverse events, in the abovementioned study, 10 cases of severe infection were observed in 27 patients (37.0%) receiving rituximab during a median follow-up period of 16 months, corresponding to an incidence of 20.9 per 100 person-years [54]. However, in a meta-analysis comprising studies mainly from western countries, the overall prevalence and incidence of severe infections were 15.4% and 6.5 per 100 person-years, with a mean rituximab dose of 2,040 mg [55]. It suggests that despite less rituximab exposure, the incidence of severe infections seems higher in Chinese AAV patients, which requires close monitoring and effective prevention. As previously described, in China there is a striking preponderance of MPO-AAV, in which older age and chronic lesions are more frequent. We speculate that this might partially explain the reason for the difference in safety of rituximab administration between China and western countries. Another Chinese case series showed that low-dose rituximab (100 mg per week for 4 weeks) was as effective as cyclophosphamide in improving renal function, with a significantly lower incidence of adverse events, including infections [56]. Further large-scale clinical trials are warranted to evaluate the efficacy and safety of rituximab-based therapy, together with the optimal dose and duration of rituximab for Chinese AAV patients.

Intravenous MP is widely used for more severe presentations, although without an evidence base. In China, intravenous MP pulses are mainly used for AAV patients with acute renal failure or DAH, with a dosage of 7–15 mg/kg/day (500–1,000 mg/day) for 3 days. A retrospective study conducted in Chinese AAV patients with severe renal injury evaluated the impact of intravenous MP pulses on renal survival. The study found that intravenous MP pulses at a dosage of 500 mg/day for 3 days improved long-term outcomes in terms of dialysis independence, with no significant difference in mortality and adverse events [57].

Retrospective studies from China have reported that approximately 10–15% of AAV patients received plasma exchanges [4, 49, 50]. However, there is a paucity of research investigating the effects of plasma exchange. One preliminary study encompassing a cohort of 15 patients with severe renal failure (median initial serum creatinine of 495 μmol/L) showed that the implementation of double filtration plasmapheresis, in combination with immunosuppressive treatment, yielded an augmented renal recovery rate. Notably, 73.3% of patients achieved dialysis independence within 3 months, while the 1-year renal survival rate reached 62.9% [58]. Further studies are required to evaluate the efficacy and long-term impact of plasma exchange in Chinese AAV patients.

For nonsevere disease, MMF can be considered as alternatives [38, 39, 59]. In China, two single-center RCTs compared the efficacy and safety of MMF and intravenous cyclophosphamide as induction treatments in nonorgan-threatening AAV [46, 47]. MMF was given orally at 1.0–2.0 g/day, and the results showed that MMF was comparable to intravenous cyclophosphamide in terms of remission rate and renal recovery rate at 6 months. No significant difference in adverse events, including serious infections, was observed [46, 47]. In addition, a retrospective study in a Chinese cohort showed that the combination of glucocorticoids and MMF as induction therapy achieved a high remission rate of 91.2% in MPA patients with mild to moderate renal involvement [60]. These findings support MMF as an alternative therapy for patients with nonsevere AAV in China. Information of key clinical investigations of induction therapies for AAV in China is summarized in Table 1.

Regarding maintenance therapy, oral azathioprine (at a dose of 2.0 mg/kg/day) is the most common choice as reported in retrospective studies conducted in China [4,

Table 1. Key clinical investigations of induction therapies for AAV in China

Study design	Population	Intervention	Key result	Other findings	Refs
Multicenter RCT	Newly diagnosed or relapsed GPA or MPA	BDB-001 and reduced GCs or no GCs versus GCs All received CYC	Phase II trial in progress (NCT05197842)		[61]
Retrospective study	27 AAV patients	Rituximab (maximum 375 mg/m^2 per week for 4 weeks) plus GCs	Remission rate of 81.5% Relapse rate of 13.6% Severe infections were common (37%)	Older age and renal dysfunction increased the risk of infection	Li et al. [54] (2021)
Case series	22 AAV patients	Low-dose RTX (100 mg per week for 4 weeks) versus CYC	Equally effective in improving renal function	Fewer adverse events with low-dose RTX	Liu et al. [56] (2023)
Retrospective study	439 AAV patients	IV-CYC versus oral CYC	Similar remission rates	Similar relapse rates	Li et al. [4] (2014)
Single center RCT	41 MPA patients	MMF (1.0–1.5 g/day) versus IV-CYC	MMF was non-inferior for remission induction	Similar adverse events	Han et al. [46] (2011)
Single center RCT	35 AAV patients with moderate renal injury[1]	MMF (1.5–2 g/day) versus IV-CYC	MMF was non-inferior for remission induction	Similar adverse events	Hu et al. [47] (2008)
Retrospective study	111 AAV patients with severe renal injury[2]	Intravenous MP (500 mg/day for 3 days) as add-on to standard treatment	Intravenous MP improved renal outcome[3]	Patients with more severe renal injury serum[4] may have worse responses	Ma et al. [57] (2017)

AAV, ANCA-associated vasculitis; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GCs, glucocorticoids; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, microscopic polyangiitis; RCT, randomized clinical trial; RTX, rituximab. [1]Serum creatinine <500 μmol/L. [2]eGFR ≤10 mL/min/1.73 m^2. [3]Dialysis dependent. [4]Creatinine ≥855 μmol/L and urine protein ≥3.7 g/24 h.

44, 50]. In recent years, the application of rituximab for maintenance therapy is increasing in China. A retrospective study reported a relapse rate of 13.6% in 22 cases treated with individually tailored rituximab regimens during a follow-up of 23.6 ± 14.0 months [54]. The relapse rate was comparable to that previously reported in patients receiving traditional immunosuppressant in the same center [4]. As for MMF, a retrospective study showed that glucocorticoids plus MMF as both induction and maintenance therapy achieved favorable long-term renal survival in patients with nonsevere MPA, with a relapse rate of 22.6% during a median follow-up of 86 months [60]. In the IMPROVE study carried out in European countries, relapses were more common (55.3%) in the MMF group [62]. The discrepancy in relapse rates may be attributed to the variations in the enrolled population, with more than half of the patients in the IMPROVE study being PR3-ANCA positive, whereas the Chinese population mentioned above consisted mostly of MPO-ANCA-positive patients.

TMP-SMX prophylaxis has been proved to be effective and recommended by a number of guidelines [38, 39, 63–65]. In China, a recent retrospective study including 415 new-onset AAV patients (92 of them received TMP-SMX prophylaxis) showed a lower 1-year mortality rate associated with TMP-SMX prophylaxis compared to patients without prophylaxis. But regarding infection, this study failed to demonstrate the protection effect of TMP-SMX [66]. In Chinese AAV patients, the use of TMP-SMX prophylaxis has increased, but is still not systematic and relied on the decision of the clinician.

Prognosis

Mortality

Immunosuppressive treatment has substantially improved the survival of AAV patients. Over the past decades, the 5-year survival for AAV worldwide has steadily

increased to around 70–80% [67]. In China, a previous study involving 426 AAV patients reported 1-year and 5-year death rates of 13.1% and 22.4%, respectively [10]. Consistently, recent studies in Chinese patients found that early mortality within 6 months for AAV patients ranged from 8.2% to 11.4% [48, 49], and the cumulative mortality rates at 1-year and 3-year survival rates were 87.5% and 79.2%, respectively [49]. Several risk factors have been identified. Based on our previous study, secondary infection, pulmonary involvement, poor initial renal function, and older age were independent predictors of death in Chinese AAV patients [50, 68]. Consistently, recent study showed that alveolar hemorrhage, interstitial lung disease, and low initial estimated glomerular filtration rate (eGFR) were independently associated with all-cause mortality [49]. Other risk factors for mortality in AAV, such as high leukocyte counts, high Birmingham Vasculitis Activity Score (BVAS), and low serum albumin, have also been reported [48]. These findings align with previous long-term observations of AAV patients in Europe [67].

Of note, although death due to infection remains prevalent within the first year, it seems that cardiovascular events and malignancy become leading causes of death during a longer follow-up [67]. Data from Chinese patients also demonstrated that cardiovascular diseases are major causes of death after 12 months from diagnosis [50] and further identified that besides traditional risk factors including age, systolic blood pressure, smoking, and high-density lipoprotein level, BVAS is an independent predictor for cardiovascular events and cardiovascular disease-related mortality [69]. These findings highlight the importance of implementing measures to reduce the risk of cardiovascular disease as an integral part of AAV management. Consistent with the findings in AAV patients in Europe [67, 70], an increase in mortality attributed to malignancy has also been observed over a prolonged follow-up in Chinese AAV patients [50]. Our preliminary data also showed that AAV patients have a higher malignancy risk than the general population. Previous studies found that malignancy risk was associated with the duration and cumulative dose of cyclophosphamide [70, 71]. Besides, it has been suggested that an increased risk of malignancy may arise from chronic stimulation of the immune system due to vasculitis [72]. Since both AAV and malignancy affect mainly older people, the aging immune system, i.e., immunosenescence and immune dysfunction, might be another contributor. AAV is associated with the loss of immune tolerance, while the loss of immune surveillance may contribute to malignancy [73]. Risk factors for developing malignancy in Chinese AAV patients need to be further evaluated. Ongoing efforts are warranted to reduce malignancy risk and improve patients' outcome, especially by safer targeted therapies and more precise treatment approach.

Renal Outcome

The kidney is one of the most commonly affected organs in AAV. Although immunosuppressive therapy has dramatically improved patient outcomes, a significant proportion of patients still progress to end-stage renal disease (ESRD). According to our previous study, the percentage of patients progressing to ESRD at 1 and 5 years was 15.9% and 27.1%, respectively [10]. Similarly, recent studies in Chinese AAV patients reported renal survival rates of 72.9–75.5% at 6 months [48, 49], with 1-year and 4-year renal survival rates of 74.3% and 59.1%, respectively [49]. Risk factors including poor initial renal function, high daily urinary protein, and high initial BVAS have been identified [48, 49]. Moreover, the prognostic value of renal histopathology has been widely recognized, and several studies in China evaluated the predictive value of the histopathological classification of ANCA-associated glomerulonephritis proposed by Berden et al. [74]. Analyses conducted by different centers in China found that patients with the focal class have the best renal outcomes, while those with the sclerotic class do the worst [75–77]. Brix et al. [78] proposed a renal risk score (RRS) including baseline eGFR, proportion of normal glomeruli, and proportion of interstitial fibrosis and tubular atrophy to predict renal outcomes in ANCA-associated glomerulonephritis. The RRS has been validated worldwide [79–85], including three studies conducted in Chinese AAV cohorts, and has proven to be applicable in predicting renal survival [83–85]. The validation study conducted by our group showed that a modified RRS model including baseline eGFR, proportion of normal glomeruli (both as continuous variables), and interstitial fibrosis and tubular atrophy (<25%, 25–50%, >50%) predicts ESRD and acts out with improved discrimination and calibration in Chinese AAV patients [85]. These findings highlight the prognostic value of the RRS model in early risk prediction, which may be helpful in guiding individualized therapy in clinical practice.

Relapse and Treatment Resistance

Previous reports found that approximately 10–25% of AAV patients in European and American centers were resistant to immunosuppressive treatment [86, 87].

Similarly, treatment resistance was also observed in a considerable proportion of Chinese AAV patients, ranging from 10.7% to 34.9% [4, 44, 45]. The severity of renal disease at presentation, lung involvement, and female sex were identified as risk factors [4, 44, 45]. These findings are consistent with previous observations from European or American centers [86, 87]. Interestingly, Huang et al. [45] reported a significant association between lower serum C3 levels and a higher risk of treatment resistance. It is in line with the recent evidence that reduced serum C3 levels are associated with worse renal prognosis and patient outcomes [88, 89], highlighting the rationale for complement-targeted therapies in AAV.

Based on data from China [4, 44, 45], approximately 24%–45% AAV patients achieving remission experienced relapse, which is similar to the relapse rate of 11%–57% in western countries [86, 87, 90–93]. Risk factors for relapse in Chinese AAV patients include PR3-ANCA, lung involvement, and cardiovascular involvement [4, 44, 45], which strengthen these factors as predictors of relapse identified in previous studies [86, 87, 93]. Interestingly, Li et al. [4] observed a significant association between higher serum creatinine levels and a lower risk of relapse, which is consistent with findings from a large EUVAS cohort study [93]. It suggests that patients with severe renal dysfunction may benefit from relatively less intense immunosuppressive therapy after an initial response to treatment, considering that these patients are at a lower risk of relapse but at a higher risk of therapy-related adverse events [93]. Information on predictors for different outcomes is listed in Table 2.

Disease Monitoring

As AAV involves multiple organs and relapses are frequent, a structured clinical assessment during the follow-up at regular intervals is recommended [38, 39]. Being unique markers of AAV, patients with a reappearance of ANCA or an increase in ANCA levels have an increased likelihood of relapse [94, 95]. However, the value of ANCA monitoring in predicting relapse is controversial, and treatment decisions based on ANCA alone are not recommended [38, 39]. Close monitoring for renal function and urinalysis remains an integral component of long-term management of patients with AAV [96]. Additionally, assessing disease activity using tools like the BVAS and monitoring inflammatory markers such as C-reactive protein concentrations and erythrocyte sedimentation rate are beneficial. Specific biomarkers indicating active disease may aid in the identification and management of relapse. These biomarkers include circulating B-cell subtypes such as CD20+ B cells [97, 98] and CD5+ B cells [99, 100] and markers of T-cell activity like CD8+ T-cell transcription signatures [101]. Other emerging biomarkers include urinary levels of soluble CD163 (sCD163) [102, 103] and soluble CD25 (sCD25) [104], which have shown potential in assessing disease activity and predicting renal relapse.

In Chinese AAV patients, novel biomarkers reflecting disease activity have been explored in recent years. Considering the central role of complement in AAV, the potential of complement activation products as effective biomarkers has been evaluated. Circulating and urinary levels of complement fragment Bb [29] and circulating CFH levels [31] were found to be associated with disease activity of patients with AAV in China. Moreover, plasma levels of CFH were associated with composite outcome of ESRD or death [31]. Other potential complement biomarkers are undergoing evaluation. In addition, circulating and urinary levels of high mobility group box 1 and serum levels of sphingosine-1-phosphate, both of which being important in C5a-mediated neutrophil activation, were also found to be correlated with disease activity [105–107]. Other biomarkers include urinary levels of epidermal growth factor [108] and mitochondrial DNA [109]. Particularly, lower uEGF/Cr levels were demonstrated to be associated with more severe renal disease, renal resistance to treatment, and higher risk of CKD progression in patients with AAV [108]. Given the pathogenic role of B cells, downregulation of FcγRIIB/CD32B expression on B cells and increased frequency of IgD-CD27hiCD38hi B cells were recently found to be associated with active disease and renal injury in Chinese AAV patients [110, 111]. Potential biomarkers of AAV in Chinese studies are listed in Table 3. Overall, a comprehensive approach involving clinical assessments and monitoring of conventional and novel biomarkers is essential for effectively managing patients with AAV, preventing relapses and achieving better outcomes.

Outlook

Substantial progress has been made in the treatment of AAV over the past 2 decades, transforming it from a life-threatening disease to a chronic one with relapsing course that requires lifelong specialist management. However, AAV still leads to substantial morbidity and mortality, both from the disease per se and from the treatment. Developing more effective management strategies to reduce disease relapses and treatment-related comorbidities, as well as improve health-related qualities of life, remains major challenges.

Table 2. Predictors of different outcomes of AAV in Chinese studies

Outcome	Predictor	Refs
Death	Alveolar hemorrhage, interstitial lung disease, lower initial, eGFR	Guo et al. [49] (2023)
	Age ≥65 years, high leukocyte counts, high BVAS, infection, low serum albumin	Ni et al. [48] (2021)
	Secondary infection, older age, pulmonary involvement, poorer initial renal function	Lai et al. [50] (2014)
	Older age, lower initial eGFR, preexisting cardiovascular disease[1]	Bai et al. [69] (2018)
	Older age, pulmonary hemorrhage[2]	Li et al. [68] (2013)
CVE	BVAS, age, systolic blood pressure, eGFR, high-density lipoprotein level	Bai et al. [69] (2018)
Treatment resistance	Lung involvement, higher serum creatinine, lower platelet, lower serum C3 levels	Huang et al. [45] (2020)
	Higher serum creatinine	Li et al. [4] (2014)
	Female, severity of renal disease	Cao et al. [44] (2014)
Relapse	Lung involvement, cardiovascular involvement, lower serum globulin	Huang et al. [45] (2020)
	Lung involvement, lower serum creatinine level	Li et al. [4] (2014)
	PR3-ANCA, lung involvement	Cao et al. [44] (2014)
ESRD	Modified RRS model for Chinese AAV patients	Wang et al. [85] (2023)
	RRS model of Brix et al. [78]	Wang et al. [85] (2023); You et al. [84] (2021); An et al. [83] (2021)
	High BVAS, high initial serum creatinine, the need for dialysis	Guo et al. [49] (2023)
	High BVAS, high daily urine protein, lower eGFR	Ni et al. [48] (2021)
	Histopathological classification of Berden et al. [74]	Chen et al. [76] (2017); Chen et al. [77] (2017); Chang et al. [75] (2012)
	Lower percentages of normal glomeruli, severity of IF/TA[2]	Li et al. [68] (2013)

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CVE, cardiovascular events; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IF/TA, interstitial fibrosis and tubular atrophy; PR3, proteinase 3; RRS, renal risk score. [1]For cardiovascular disease-related mortality. [2]In patients who had rapid renal function deterioration requiring dialysis.

Great efforts have been made to explore safer therapies targeting specific cellular and molecular pathways involved in the autoimmune response of AAV. The efficacy and safety of B cell-targeted therapy (rituximab, monoclonal anti-CD20 antibody) and complement-targeted therapy (avacopan, C5a receptor inhibitor) have been proved. These new regimens may reduce the requirement for glucocorticoids, thus minimizing their toxic effects. It is foreseeable that, in the near future, rituximab will be used in more Chinese AAV patients. However, the risk of infection and the associated mortality still remain great concerns with rituximab-based treatment. Further large-scale studies are warranted to evaluate the efficacy and safety of rituximab administration, together with the optimal cumulative dose of rituximab for Chinese AAV patients. Although complement-targeted therapy has not yet been approved for AAV in China, a clinical trial is currently being conducted to evaluate the efficacy and safety of a monoclonal antibody targeting C5a (BDB-001) in patients with AAV in China [61]. We also anticipate clinical trials to evaluate the efficacy and safety of avacopan, as well as other complement-targeted therapies including antifactor B therapy, in Chinese AAV patients.

Table 3. Potential biomarker of AAV in Chinese studies

Biomarkers	Key finding	Refs
*HLA-DQA1*0302* *HLA-DQB1*0303*	*HLA-DQA1*0302* and *HLA-DQB1*0303* were strongly linked to the risk of MPO-AAV	Wang et al. [13] (2019)
Bb	Circulating and urinary levels of complement fragment Bb were associated with disease activity and the severity of renal injury	Gou et al. [29] (2013) Gou et al. [30] (2013)
CFH	Circulating levels of CFH were associated with disease activity and a composite outcome of ESRD or death	Chen et al. [31] (2015)
S1P	Circulating levels of S1P were associated with disease activity and the severity of renal injury	Sun et al. [107] (2017)
EGF	Urinary levels of EGF/Cr were associated with renal injury, renal resistance to treatment, and renal outcome[1]	Wu et al. [108] (2018)
Mitochondrial DNA	Urinary mtDNA levels correlated with the severity of kidney injury	Wu et al. [109] (2020)
HMGB1	Circulating HMGB1 levels and urinary levels of HMGB1/Cr were associated with disease activity	Wang et al. [105] (2023) Ma et al. [106] (2015)
FcγRIIB/CD32B	Downregulation of FcγRIIB/CD32B expression on B cells was associated with the disease activity of AAV	Wang et al. [111] (2023)
IgD-CD27hiCD38hi B cells	The frequency of IgD-CD27hiCD38hi B cells correlated with the severity of renal injury	Wang et al. [110] (2022)

AAV, ANCA-associated vasculitis; CFH, complement factor H; Cr, creatinine; EGF, epidermal growth factor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; HMGB1, high mobility group box 1; MPO, myeloperoxidase; mtDNA, mitochondrial DNA; S1P, sphingosine-1-phosphate. [1]ESRD or 30% reduction of eGFR.

Of note, the improvement of AAV management will rely on more effective therapeutic intervention together with the development of effective biomarkers to better define disease activity and predict relapse. The identification and validation of biomarkers for AAV management are indispensable for facilitating a more precise and personalized treatment approach and achieving better outcomes, which requires great efforts in the future.

Conclusions

AAV is a group of multisystem autoimmune diseases and it is not rare in China, with a preponderance of MPA and MPO-ANCA. Treatment strategies for Chinese AAV patients generally align with those in western countries, and to some extent, less aggressive. Prognostic factors and emerging biomarkers for AAV in China have been identified. Further challenges for the management of AAV in China include optimizing interventions, minimizing treatment-related comorbidities, improving disease monitoring, and improving life qualities.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

This study is supported by the National Key Research and Development Program (Grant Nos. 2022YFC2502500 and 2022YFC2502502), National Natural Science Fund (Grant No. 82270754, 82090020, 81900640, and 81870477), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-046), Peking University Clinical Scientist Training Program, supported by "the Fundamental Research Funds for the Central Universities" (BMU2024PYJH009), Beijing Physician Scientist Training Project (BJPSTP-2024-15), and Peking University Medicine Sailing Program for Young Scholars' Scientific & Technological Innovation (BMU2023YFJHMX006).

Author Contributions

S.F. Chen and Z.Y. Li wrote the main manuscript text and prepared the tables. S.F. Chen prepared the figure. S.F. Chen, Z.Y. Li, M.H. Zhao, and M. Chen reviewed the manuscript.

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