Diagnosis and latest treatment strategies of ANCA-associated glomerulonephritis (Review)

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Abstract. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a spectrum of conditions characterized by inflammation of the small- and medium-sized vasculature. Glomerulonephritis associated with AAV (AAV-GN) exerts a profound effect on patient survival and long-term prognosis, with renal impairment resulting in end-stage renal disease in ~20% of cases within a 5-year period. Therefore, the early detection of renal involvement is of pivotal significance. The present review aimed to summarize the diagnostic utility of serological and urinary assays, coupled with renal biopsy, in the context of AAV-GN, thus promoting the early diagnosis of the disease. Furthermore, standardized protocols for glucocorticoid and immunosuppressive therapy have been established in the last decade, with the development of subsequent targeted treatment regimens. The current review also summarized the current research developments associated with AAV-GN, thus providing more references for clinical practice and benefiting a greater number of patients.

Contents

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1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) can manifest at any age. However, its incidence peaks among individuals aged between 50 and 60 years. In southeast Asia, the prevalence of AAV is estimated to be between 10 and 20 cases per million individuals, whereas in Europe and North America, it varies from 10 to 30 cases per million. The primary pathogenesis of AAV involves ANCA, an autoantibody, which triggers the activation of neutrophils within the immune system (1). In turn, the aforementioned activated neutrophils generate free radicals, thus leading to the destruction of endothelial cells in several vascular beds, and an increase in the secretion of inflammatory mediators, such as proteolytic enzymes and reactive oxygen species, and consequently, vasculitis (2). The kidney, a highly vascularized organ, is the most commonly affected organ in vasculitis. Renal involvement is observed in >75% of patients with AAV (3), with the likelihood of renal involvement differing based on disease subtype. Therefore, ~90% of patients with microscopic polyangiitis (MPA), 70% of patients with granulomatosis with polyangiitis (GPA), and 25% of those with eosinophilic granulomatosis with polyangiitis can experience kidney injury. Furthermore, it has been reported that >20% of patients with AAV-associated glomerulonephritis (AAV-GN) progress to end-stage kidney disease (ESKD) within 5 years (4,5). The etiology of AAV is incompletely understood. It may be associated with infections, as well as abnormalities in both the innate and acquired immune systems (6). Despite the extension of survival time for patients with AAV over the past decades, extensive research is still required for the development of novel techniques to improve renal function (7). In light of the recent advancements, the European Alliance of Associations for Rheumatology (EULAR) has provided updated guidance on AAV management, addressing the diagnosis and treatment of adult patients (8). These recommendations are aimed at clinicians, healthcare professionals, pharmaceutical companies, and regulatory laboratory organizations, offering theoretical support for their work. The current review article aimed to summarize recent clinical studies on AAV-GN, as well as the guidelines for diagnosis, induction of remission, maintenance and evaluation of the efficacy of therapies, which are crucial

for the standardized long-term management of patients with AAV-GN.

2. Significance of auxiliary examination in AAV-GN diagnosis and evaluation

Renal biopsy. The chronic pathological alterations in patients with AAV-GN include renal parenchymal complications, such as glomerulosclerosis, interstitial fibrosis, tubular atrophy and atherosclerosis. The aforementioned complications can be accompanied by acute fibrinoid necrosis and crescent formation or can evolve gradually in the absence of significant acute disease (9). Glomerulosclerosis, interstitial fibrosis, tubular atrophy, and moderate-to-severe atherosclerosis are commonly irreversible and can severely affect renal function (10). According to the 2016 EULAR guidelines, renal biopsy is essential for the diagnosis of AAV-GN and treatment assessment (1). This was further emphasized in the 2022 guidelines (8). Consequently, the identification of appropriate pathological scoring criteria when evaluating pathological changes in patients with AAV-GN could be of paramount importance. In a retrospective cohort study conducted by Moura *et al* (11), the pathological changes in patients with AAV-GN were categorized using the Mayo Clinic Chronic Disease Score (MCCS). The results revealed an association between MCCS classification and the estimated glomerular filtration rates (eGFR) of patients. A high degree of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and atherosclerosis were associated with a low median eGFR at baseline and an increased risk of renal failure at 10 years. Patients with higher MCCS scores exhibited slower renal function recovery, a greater likelihood and more rapid onset of renal failure and were more likely to succumb to disease compared with patients with lower MCCS scores. The aforementioned findings suggested that chronic changes in renal histology could predict renal function, prognosis, and response to therapy in patients with AAV-GN. Furthermore, the aformentioned study separately analyzed the association between disease type, remission-inducing therapy, hormonal shock, plasma exchange and MCCS score, thus indicating that different renal pathological changes have no guiding significance for disease treatment.

Other assessment methods. Procuring renal pathology specimens from all patients represents a significant challenge in clinical practice. Therefore, delays in renal biopsies and case reporting could affect patient treatment. Consequently, the identification of relevant biomarkers that can facilitate disease diagnosis is of critical importance.

Laboratory tests. In patients with AAV, increased erythrocyte sedimentation rate and C-reactive protein (CRP) levels are indicative of active disease and potential renal involvement, thus warranting vigilant attention (12,13). The presence of hematuria, proteinuria, tubular casts, increased serum creatinine and decreased eGFR are all associated with renal injury and necessitate prompt and active treatment to prevent further renal function deterioration (14). A previous study demonstrated that the combined detection of homocysteine and cystatin C displayed high sensitivity and specificity for the diagnosis of AAV-GN (15). Furthermore, urinary soluble CD163, a biomarker of active renal vasculitis, was identified as a promising target for predicting renal vasculitis flares (16). It has been also reported that elevated serum potassium and decreased complement 3 levels can serve as independent risk factors for renal injury in patients with AAV (17). In another study, the expression levels of serum and urinary neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein 1 and dickkopf-related protein 3 were increased in patients with AAV presenting with acute kidney injury (18). Furthermore, bioinformatics analysis predicted that interferon-γ response, and the IL-6 and TNF-α signaling pathways were closely associated with AAV-GN. The expression levels of arachidonate 5-lipoxygenase, CD44 and tumor protein 53 (TP53) in patients with AAV-GN were closely associated with renal function, thus supporting their potential as prognostic biomarkers (19).

Pathogenic autoantibodies. *In vitro*, ANCA binds to the respective surface antigens on activated leukocytes, thus inducing cell activation and degranulation, which in turn results in vascular injury. The detection of ANCA type is instrumental in guiding disease prognosis (20). Emerging evidence has indicated that conversion of ANCA can serve as an indicator of treatment effectiveness, while ANCA positivity is considered as a particular risk factor for disease relapse (21). A previous study revealed that patients with the lowest MCCS classification displayed similar positivity for myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. However, the proportion of patients positive for MPO-ANCA was increased, while that for PR3-ANCA was decreased with increasing chronic disease classification (11). Furthermore, the risk of relapse was significantly reduced in patients who became PR3-ANCA-negative within 18 and 24 months after diagnosis. Additionally, patients who tested positive for PR3-ANCA again within 1 year after diagnosis exhibited a significantly shorter time to relapse compared with those with a longer interval prior to positive PR3-ANCA recurrence. A study by Pagnoux *et al* (22) demonstrated that patients positive for PR3 were more likely to relapse compared with those who were positive for MPO. Proverbially, most relapses occur during the tapering or cessation of immunosuppression, thus implying that extending the treatment duration in patients at high risk of relapse can prevent such occurrences. However, the time interval between ANCA positivity and relapse is unpredictable, thus posing challenges to the individualization of therapy. Nevertheless, further prospective studies are warranted to evaluate the association between the time intervals of ANCA positivity and disease recurrence.

$CD19^+/CD20^+$ B cells. The efficacy of AAV treatment and the risk of relapse can also be assessed via examining peripheral blood B cells. The ANCA-associated vasculitis RAVE trial demonstrated that following two infusions of rituximab (RTX), the peripheral blood B-cell counts fell to <10 cells/mm^3 in 94% of patients, with the majority of them maintaining this level for 6 months (23). In addition, the ANCA-associated vasculitis RITUXVAS trial comparing RTX vs. cyclophosphamide (CYC), revealed that 82% of patients in the RTX group achieved B-cell depletion at 6 weeks, which was sustained

until 12 months in 75% of patients (24). In the RITUXVAS continuation trial, all patients who were treated with RTX exhibited concurrent B-cell depletion (25). Furthermore, in the RTX + low-dose CYC study (26), all patients developed circulating $CD19^+$ B-cell depletion, during the follow-up period, 14 patients experienced restoration of B-cells, with 3 of them suffering from severe relapses. All relapses in patients treated with RTX occurred after B-cell levels were restored, thus suggesting that sustained B-cell depletion was necessary to maintain remission, while peripheral blood B-cell counts were considered a useful indicator for assessing a patient's risk of relapse. However, this approach revealed several limitations. Consequently, there were cases of patients with RTX-treated lymphomas where B cells lost surface and cytoplasmic CD20 expression at the time of relapse (25). Similar to the use of ANCA expression for assessing the risk of relapse, the temporal association between B-cell reconstitution and disease relapse could not be clarified. In future studies, the association between the time to relapse and B-cell restoration should be further investigated to provide novel insight into the assessment of relapse risk in patients.

3. Principles of AAV-GN management

Remission-induction treatment. RTX and CYC are extensively utilized in the remission induction therapy for AAV-GN. CYC is the recommended agent for AAV with major organ involvement. However, CYC is commonly accompanied by adverse effects, such as infections, cancer and infertility. Treatment regimens have been optimized to minimize CYC toxicity through the substitution with alternative agents or the implementation of pulsed dosing (25). RTX represents an opportunity to reduce exposure to CYC. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for inducing remission in patients with AAV-GN recommend an initial treatment regimen composed of CYC or RTX in conjunction with a glucocorticoid (GC) (27). RTX is recommended for children and adolescents, premenopausal women, men concerned about fertility, frail older adults, patients with GC-sparing disease, those experiencing disease relapse and those with PR3-ANCA disease. CYC can be employed in patients with severe glomerulonephritis (creatinine >354 μmol/l) and when RTX is not readily available (25). For disease recurrence, both KDIGO and EULAR advocate the use of RTX, considering that the risk of malignancy could be significantly increased when the cumulative dose of CYC exceeds 36 g (25,27).

The RAVE trial compared RTX with CYC in inducing 6-month complete remissions in patients with severe AAV (23). Although both agents showed equivalent therapeutic efficacy in inducing remission and reducing kidney injury, patients receiving RTX exhibited a higher remission rate compared with those treated with CYC. In addition, the CYC-related toxicities were more severe compared with those recorded in patients who received RTX. The study did not include patients with diffuse alveolar hemorrhage (DAH) and those with advanced renal dysfunction (creatinine >354 μmol/l). In a previous trial, namely Plasma Exchange in Vasculitis (PEXIVAS), patients with severe kidney disease and/or DAH treated with RTX or CYC were included. The results indicated no variation in treatment effectiveness between the two groups (28). Based on the 12- and 6-month observations of the RITUXVAS (24) and RAVE (23) trials, respectively, RTX is now considered as an effective remission induction therapy for patients with AAV. To evaluate the long-term efficacy of different treatment regimens, a 24-month follow-up was performed in the RITUXVAS study. This trial demonstrated that the frequency of the composite outcomes of death, ESKD, and relapse were similar between patients treated with RTX and those who received CYC plus azathioprine (AZA) maintenance therapy (25). Considering the long-term safety of the drug, impact on fertility and the incidence of malignant tumors, RTX is favored over CYC, as it reduces CYC exposure and decreases the risk of malignancy.

For patients with AAV-GN, combination therapies are increasingly employed to maximize efficacy and minimize drug toxicity. A study named RTX + low CYC demonstrated that this low-dose induction therapy, based on CYC and RTX, followed by maintenance therapy with AZA, resulted in clinical remission within 6 weeks. The steroid avoidance method, combining induction therapy with two doses of RTX, 3 months of low-dose CYC and a short course of an oral GC, significantly reduced creatinine, proteinuria, CRP and ANCA levels (29). Consequently, the RTX-based low-dose CYC regimen effectively induced long-term disease-free remission, thus providing a therapeutic regimen with significant efficacy and an acceptable safety profile (29). This regimen also limited the use of steroids in older adults at high risk of renal dysfunction.

Currently, the standard induction therapy for patients with AAV consists of a high dose of a GC combined with CYC or RTX. Although these therapies can achieve remission rates of 80-90%, the 5-year mortality rate remains high at 10-20%, with treatment-induced infections and cardiovascular diseases being the leading causes of mortality in these patients (30). Two randomized clinical trials, namely RAVE (23) and RITUXVAS (24), showed that RTX and CYC, when combined with a high dose of a GC, displayed similar remission rates and incidence of adverse effects. The results of these trials suggested that a high dose of a GC could be the primary causative agent of adverse events in the current treatment strategy for AAV. A retrospective study demonstrated that a low dose of a GC combined with RTX could adequately promote AAV remission (31). The PEXIVAS study revealed that a low dose of a GC could reduce the incidence of serious infections during the first year following diagnosis and treatment (28). In the low-dose glucocorticoid vasculitis induction study (32), patients were randomized to receive low-dose prednisolone (0.5 mg/kg/day) and RTX (375 mg/m^2/week, four times) or high-dose prednisolone (1 mg/kg/day) combined with RTX. After 6 months, 71 and 69.2% of patients in the low-dose and high-dose groups, respectively, were in remission. A total of 21 serious adverse events were recorded in 18.8% of patients in the low-dose group, while 41 serious adverse events occurred in 36.9% of patients in the high-dose group. Furthermore, seven and 20 serious infections were recorded in 7.2 and 20% of patients in the low-dose and high-dose groups, respectively. Additionally, in the RITAZAREM trial (33), a prospective study of patients with recurrent MPA or GPA, demonstrated that the combination of RTX with a low dose of a GC was

significantly effective in relieving patients with relapsed AAV, showing a similar or better safety profile compared with that reported in previous research (34). According to the 2022 EULAR guidelines, it is stated that for the treatment component of GPA or MPA-induced remission, oral hormones are recommended at a starting dose of 50-75 mg/day (based on body weight) and with an imminent reduction to 5 mg prednisone daily for 4-5 months (8). A retrospective study of 114 consecutive patients from five European and U.S. centers, who received standard therapy, namely plasma exchange, CYC and a high dose of an oral GC, to induce remission with or without pulsed methylprednisolone, suggested that a pulsed intravenous GC combined with standard therapy could not be clinically beneficial for patients with severe AAV and could lead to more infectious episodes and a higher incidence of diabetes (35). Therefore, the 2022 EULAR guidelines stated that there was no compelling evidence to support the application of hormonal shock therapy (8).

Remission-maintenance treatment. According to the KDIGO guidelines, following the induction of remission in patients with AAV, it is imperative to maintain immunosuppression due to the high likelihood of recurrence in patients with AAV (27). The most recent regimens for sustaining remission include RTX, AZA and a low dose of a GC (36). The EULAR recommendations advocate RTX as the preferred option for patients with severe AAV-GN (8). The RITAZAREM trial suggested that AZA, methotrexate, and mycophenolate mofetil could be considered as viable alternatives for patients who could not receive RTX or those with non-severe GPA or MPA (33). Moreover, all expert panels concurred that GC tapering should be performed as early as possible, acknowledging that a minority of patients may require long-term administration of a low dose of a GC.

While the choice of medication is crucial, the timing of discontinuation also warrants careful consideration. The persistence of ANCA positivity post-treatment, the elevation of ANCA titers and conversion from ANCA-negative to ANCA-positive status are only moderately predictive of subsequent relapses. Consequently, the decision to discontinue maintenance therapy remains a clinical judgement and not one driven by biomarkers. According to the KDIGO guidelines, the recommended optimal duration of AZA combined with a low dose of a GC is 18-48 months following the induction of remission and 18 months post-remission induction through RTX (27). The EULAR guidelines suggested that maintenance therapy should be upheld for a minimum of 24 months (8). For patients who experience relapse or who are at an elevated risk of relapse, a longer duration of maintenance therapy, ~48 months, should be contemplated (37). However, it is essential to strike a balance between the risk of ongoing immunosuppression and patient preferences. The MAINRITSAN3 trial which evaluated the therapeutic efficacy of RTX vs. placebo infusions every 6 months for 18 months (a total of four infusions), demonstrated that an additional therapy with RTX for 2 years resulted in a lower relapse rate (48 months) for patients treated with RTX maintenance therapy and who remained in remission for 2 years (38). Thus far, data regarding the optimal duration of remission maintenance, particularly for patients with AAV-GN, remain limited.

Targeted drugs. Avacopan is a novel small oral molecule that selectively inhibits the function of the complement 5a (C5a) via blocking the C5a receptor (C5aR) on neutrophil surfaces. This mechanism can promote neutrophil chemoattraction, thus ultimately mitigating endothelial cell damage and inflammation (39,40). Prospective studies published between 2017 and 2021 demonstrated that Avacopan was an effective and safe alternative to steroids for inducing remission in patients with AAV (41). The KDIGO guidelines acknowledge complement-targeted therapy as a strategy that can reduce GC exposure (27).

The CLEAR study, a 12-week stepwise, two-phase randomized controlled trial, enrolled 67 patients with newly diagnosed or relapsed GPA or MPA treated with remission induction therapy with CYC or RTX (42). The participants were randomized into the following four groups: The control group, which consisted of patients who received a high dose of a GC (starting dose of 60 mg prednisone) without Avacopan; an oral Avacopan group (30 mg twice daily) plus a low dose of a GC (starting at 20 mg prednisone); and a group of patients who received Avacopan without a GC. A 50% reduction in baseline Birmingham Vasculitis Activity Score and no deterioration of any system were observed in 70% of patients in the control group, 86.4% in the Avacopan plus low-dose GC group and 81% in the Avacopan without low-dose GC group. These findings indicated that the incidence and severity of adverse events were similar across all treatment groups (42). Additionally, the CLASSIC study investigated the efficacy of Avacopan for remission induction in patients with AAV, comparing it against standard of care (SOC), which included GC plus RTX or CYC. A total of 42 newly diagnosed patients were randomized to receive oral Avacopan therapy (10 mg or 30 mg twice daily) in addition to SOC or SOC alone. At 12 weeks, the incidence of severe adverse events was comparable, 15% in the SOC group vs. 17% in the Avacopan plus SOC group. Clinical responses were robust across all groups, with an 85% response rate in the SOC group, 92% in the 10-mg Avacopan group, and 80% in the 30-mg Avacopan group. According to the EULAR guidelines, Avacopan can be combined with RTX or CYC to substantially reduce GC exposure (8). The ADVOCATE trial compared the use of Avacopan (30 mg twice daily) as part of a standard induction regimen (RTX or CYC) against a GC; tapering from 1 to 0 mg/kg/day over 21 weeks (43). The results showed that the cumulative GC dose was reduced by 2.3 g over 1 year in the Avacopan group compared with the prednisone group. No significant differences were recorded in the incidence of adverse events, serious adverse events, or infections between the groups. Patients at risk of developing or exacerbating GC-related adverse events and complications, or those with active glomerulonephritis and rapidly deteriorating renal function, showed improved recovery with Avacopan (43). Therefore, the aforementioned findings indicated that Avacopan could serve as a promising option for reducing GC use in patients with AAV. However, uncertainties regarding the optimal duration of treatment, when combined with RTX maintenance therapy, the residual need for a GC, long-term follow-up and treatment efficacy in patients with an eGFR <15 ml/min/1.73 m^2, still remain. Currently, there are no data on the use of Avacopan beyond 1 year and therefore its long-term administration is not recommended.

In addition to Avacopan, a number of new drugs have been developed to target various signaling pathways involved in the pathogenesis of AAV. The primary mechanism underlying the development of AAV commonly involves the activation of neutrophils by inflammatory factors, thus leading to the formation of neutrophil extracellular traps (NETs). Such NETs persist in patients with low NET degradation activity, while the prolonged exposure to their contents can inhibit tolerance to particular autoantigens, particularly MPO and PR3 (2,44,45). These antigens are presented by dendritic cells to $CD4^+$ T cells, thus further stimulating B cells and the production of ANCA (46). Identifying new peptidylarginase deiminase inhibitors, crucial enzymes in NET generation, is considered as an essential strategy for preventing NET formation. Another potential approach involves investigating neutrophil elastase inhibitors, which can act synergistically with gasdermin D to disrupt nuclear and cellular membranes during NET formation. Additionally, deoxyribonucleases (DNases), particularly DNase I, serve as a crucial strategy for facilitating the disruption of pre-formed NETs during the treatment of AAV (46,47). However, this area warrants further investigation. In addition, mepolizumab, an anti-IL-5 antibody, has recently been approved for the treatment of vasculitis and is recommended for patients with relapsed or refractory GPA (48). Additionally, alemtuzumab, an anti-CD52 antibody, was explored for its lymphocyte-depleting effects in patients with refractory vasculitis in a phase III study (ALEVIATE) (49). However, further in-depth studies on the pathogenesis of AAV are required to provide additional insights into drug development.

Plasma exchange. It has been reported that patients with AAV-GN are at a significant risk of progression to ESKD (50). The incorporation of plasma exchange therapy (PLEX) into standard remission-inducing treatments has become the standard of care, particularly for patients presenting with severe renal impairment. However, controversy regarding which patients can derive the most benefit from PLEX still remain (51). A meta-analysis suggested that the addition of PLEX to standard AAV remission-induction therapy may be associated with a reduced risk of ESKD at 12 months (52). These findings have been interpreted to advocate for the use of PLEX in patients with AAV who were at high risk of developing ESKD or requiring dialysis. Nonetheless, the recently published PEXIVAS trial did not report any advantages of PLEX in patients with an eGFR ≥50 ml/min/1.73 m^2 or those experiencing alveolar hemorrhage (28,53). While the relative risk of developing ESKD was reduced by at least 20%, the trial also noted a concomitant increase of ~20% in the relative risk of severe infections (51). Consequently, the latest EULAR guidelines recommend that plasma exchange should not be routinely applied in patients with AAV (8).

4. Conclusion

The early diagnosis of AAV-GN is crucial for improving both short- and long-term prognoses in patients susceptible to renal impairment. In the clinical practice, the development of individualized treatment plans tailored to the individual needs of different patients, including the adoption of new classification criteria, updated treatment recommendations and the utilization of recently approved drugs for the treatment of AAV, is imperative. The advancement of clinical trials has enabled a more systematic and standardized approach to the management of AAV-GN, thus promoting the achievement of remission for a greater number of patients, reducing the risk of progression to severe illness and minimizing the risk of adverse effects. Looking ahead, comprehensive research into the underlying mechanisms of AAV is essential for the discovery of novel therapeutic agents. Furthermore, sustained interaction between basic research and clinical studies is needed to enhance our understanding of AAV etiology and pathogenesis, ultimately leading to the development of safe and effective therapeutic approaches.

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YR designed and wrote the manuscript. YZ performed the literature search and participated in discussions and improvements related to the manuscript. Both authors read and approved the final submitted manuscript.

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Competing interests

The authors declare that they have no competing interests.

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