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Review Article

Current Management of Patients of ANCA-Associated Vasculitis with Glomerulonephritis

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Abstract

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) is a spectrum of diseases characterized by the inflammation of small- and medium-sized blood vessels. Its renal involvement significantly impacts patient survival and long-term prognosis. AAV-Associated Glomerulonephritis (AAV-GN) is more common in Microscopic Polyangiitis (MPA) and Granulomatous Polyangiitis (GPA). Notably, the number of cases progressing to End-Stage Kidney Disease (ESKD) is decreasing annually. However, it remains an unresolved issue in AAV treatment. Therefore, early diagnosis and treatment of renal involvement are crucial for AAV prognosis. Immunosuppressive therapies have made AAV a relapsing/remitting disease. And, several clinical trials have standardized the use of glucocorticoids, cyclophosphamide, and immunosuppressive agents, establishing a therapeutic standard of care upon which subsequent targeted therapies have been developed. Based on the European Alliance of Associations for Rheumatology (EULAR) 2022 recommendations for AAV management, this article summarizes the latest research progress on AAV-GN to provide new research ideas for diagnosis and treatment for the benefit of physicians and patients.

Keywords: ANCA-associated vasculitis; Glomerulonephritis; Rituximab; Avacopan

Introduction

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) is a group of diseases characterized by vascular inflammation resulting in tissue destruction and organ failure [1]. Renal damage is a common AAV complication and is associated with poor prognosis, and most patients develop End-Stage Kidney Disease (ESKD), which decreases their survival rate and quality of life [2,3]. Even though the survival time of patients with AAV has been prolonged in the past decades, extensive studies are still needed to find ways to improve renal function. Following recent advances, the European Alliance of Associations for Rheumatology (EULAR) provides updated guidance on AAV management to address the diagnosis and treatment of adult patients [4]. These recommendations are intended to provide clinicians, health professionals, pharmaceutical companies, and regulatory laboratory organizations with theoretical support for their work. This manuscript analyzed recent clinical studies involving AAV-GN, and summarized the guidance on its diagnosis, remission induction and maintenance, and efficacy assessment, which are crucial for treatment selection and standardized long-term management of AAV-GN patients.

The Importance of Auxiliary Examination in AAV-GN Diagnosis and Evaluation

Renal Biopsy

Chronic pathological changes in patients with AAV-GN involve renal parenchymal complications such as glomerulosclerosis, interstitial fibrosis, tubular atrophy, and atherosclerosis, which may accompany acute fibrinoid necrosis and crescent formation or develop slowly in the absence of significant acute disease [5]. Glomerulosclerosis, interstitial fibrosis, tubular atrophy, and moderate-to-severe atherosclerosis are usually irreversible and significantly impact renal function [6]. The 2016 EULAR guidelines stated renal biopsy is essential for AAV-GN diagnosis and treatment efficacy assessment [1]. The 2022 guidelines further emphasized this [4]. Therefore, identifying appropriate pathological scoring criteria when evaluating pathological changes in patients with AAV-GN is essential. In a retrospective cohort study by Moura et al., pathological changes in patients with AAV-GN were categorized using the Mayo Clinic Chronic Disease Score (MCCS) [7]. The results showed that MCCS classification correlated with patients Estimated Glomerular Filtration Rates (eGFR). Higher degrees of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and atherosclerosis were associated with lower median eGFR at baseline and an increased risk of renal failure at 12 months and 10 years. Patients with higher MCCS scores had slower renal function recovery, greater likelihood and faster onset of renal failure, and were more likely to die, suggesting that chronic changes in renal histology predict renal function, prognosis, and response to therapy in patients with AAV-GN. Furthermore, the study also severally analyzed the correlation between disease type, remission-inducing treatment, hormonal shock, plasma exchange, and MCCS score, and revealed that different renal pathological changes were insufficient to make decisions regarding treatment plan.

The Activity Index (AI) grades renal pathological changes

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as the percentage of glomerular involvement based on cellular crescent/necrotic lesions. Patients with a higher AI are more likely to develop renal failure at 12 months and do so quickly. In addition, the glomerular pathological changes can be scored according to the Berden classification. However, this score cannot be applied to renal biopsies without adequate glomeruli or with only the medulla. Therefore, the simultaneous reporting of AI and MCCS may be the best way to assess the severity of pathological changes in patients with AAV-GN. At present, AAV-GN-related studies only have focused on chronicity grading, so, further studies are required to combine these two indices meaningfully.

Other Assessment Methods

Obtaining renal pathology in all patients is quite difficult in clinical practice, and the delay in renal biopsies and case reports affects patient treatment; therefore, relevant biomarkers that can facilitate disease diagnosis are crucial. Correlation studies between B-cell activation, pathogenic autoantibodies, and disease activity provide a theoretical basis for evaluating remission and relapse in patients with AAV-GN. However, there are few studies on the correlation between clinical investigations and pathological manifestations, which should be the focus of future studies.

Pathogenic autoantibodies: ANCA binds to the respective surface antigens on activated leukocytes in vitro, leading to cell activation and degranulation, which results in vascular injury. Detecting the ANCA type guides disease prognosis [8]. ANCA conversion can indicate effective disease treatment, whereas ANCA positivity can be a specific risk factor for disease recurrence. Patients with the lowest MCCS classification had similar proportions of MPO-ANCA and PR3-ANCA positivity. However, the proportion of patients with MPO-ANCA positivity increased, and that of patients with PR3-ANCA positivity decreased with increasing chronic disease classification [7]. And the risk of recurrence reduced significantly in patients who became PR3-ANCA-negative within 18 and 24 months of diagnosis. In addition, patients who tested positive again for PR3-ANCA within 1 year of diagnosis had a significantly shorter time to recurrence than patients who had a longer period before positive PR3-ANCA recurrence. Hogan et al. showed that PR3-positive patients were more likely to experience recurrence than MPO-positive patients [9]. Proverbially, most relapses occur during immunosuppression tapering or cessation, which means that prolonging the treatment duration in patients of high risk for recurrence may prevent relapses. However, the time interval between ANCA positivity and relapse is unforeknowable, making it difficult to individualize treatment. Further prospective studies are needed to evaluate the relationship between the intervals of ANCA positive and disease recurrence.

$CD19^+/CD20^+$ B-cells: We can also assess AAV efficacy and risk of relapse by testing peripheral blood B-cells. The Rituximab (RTX) in ANCA-associated vasculitis (RAVE) trial demonstrated that after two RTX infusions, peripheral blood B-cell counts dropped to <10 cells/mm^3 in 94% of patients, and most patients maintained this level for 6 months [10]. The RTX versus Cyclophosphamide (CYC) in ANCA-Associated Vasculitis (RITUXVAS) trial demonstrated that 82% of patients in the RTX group developed B-cell depletion at 6 weeks, and this was maintained at 12 months in 75% of patients [11]. In the RITUXVAS continuation trial, all patients receiving RTX had concurrent B-cell depletion [12]. In the Rituximab plus low cyclophosphamide (RTX + low CYC) study, all patients developed circulating $CD19^+$ B-cell depletion, and 14 patients had circulating B-cells reconstructed during the follow-up period, with three of them experiencing severe relapses after B-cell reconstruction. All relapses in patients treated with RTX occurred after B-cell levels were restored, suggesting that sustained B-cell depletion is required to maintain remission, and peripheral blood B-cell counts are useful for assessing a patient's risk of relapse. However, this approach still has drawbacks, there are patients with RTX-treated lymphomas whose B-cells lose surface and cytoplasmic CD20 expression at the time of relapse. Like the use of ANCA expression for assessing patients' risk of relapse, we could not clarify the temporal relationship between B-cell reconstitution and disease relapse. In subsequent studies, the relationship between the time to relapse and B-cell reconstitution should be investigated to provide insight into patients with relapse risk assessment.

Principles of AAV-GN management

Remission-Induction Treatment

RTX and CYC are widely used in AAV-GN induction remission therapy. CYC is the recommended agent for AAV with major organ involvement. However, the adverse effects always come with CYC, such as infections, cancers, and infertility. Treatment regimens have been optimized to minimize CYC toxicity by switching to other agents or pulsed dosing. RTX offers an opportunity to reduce CYC exposure. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for inducing a remission regimen for patients with AAV-GN recommend that the initial treatment of new-onset AAV includes CYC or RTX with Glucocorticoid (GC) [13]. RTX is recommended for children and adolescents, premenopausal women, men concerned about fertility, frail older adults, patients with GC-sparing disease, disease relapse, and PR3-ANCA disease. CYC can be used in patients with severe glomerulonephritis (creatinine >354 μmol/L) and when RTX is difficult to obtain. For disease recurrence, KDIGO and EULAR recommend the choice of RTX, considering that malignancy is significantly increased when the cumulative dose of CYC is more than 36 g.

The RAVE trial compared RTX with CYC in inducing 6-month complete remissions in patients with severe AAV [10]. Even though, they had the same therapeutic efficacy in inducing remission and reducing kidney injury, patients who received RTX had a higher remission rate than those who received CYC, and CYC toxicities were more severe than those of RTX. The study still has limitations in that patient with Diffuse Alveolar Hemorrhage (DAH) and with advanced renal dysfunction (serum creatinine levels >4.0 mg/dL [354 μmol/L]) were excluded. A recent study, PEXIVAS, included patients with severe kidney disease and/or DAH treated with RTX or CYC, and the results mentioned that no difference was observed in the treatment efficacy between the two groups [14]. RTX is an effective remission induction therapy for AAV treatment based on the 12-month observations of the RITUXVAS and the 6-month observations of the RAVE [11]. To assess the long-term efficacy of the different treatment regimens for patients in the RITUXVAS study, the investigators followed up for 24 months. They showed that the frequency of the composite outcomes of death, ESKD, and relapse were similar between RTX and CYC plus

azathioprine (AZA) maintenance therapy [12]. Considering the drug's long-term safety, impact on fertility, and the incidence of malignant tumors, RTX was favored over CYC, and RTX reduces CYC exposure and decreases the risk of malignancy in patients.

For patients with AAV-GN, combinations are increasingly used 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 and subsequent maintenance therapy with AZA resulted in clinical remission within 6 weeks. The steroid avoidance method, in which induction therapy included two RTX doses, 3 months of low-dose CYC, and a short course of oral GC, resulted in reductions in creatinine, proteinuria, C-reactive protein, and ANCA levels [15]. Therefore, the RTX-based low-dose CYC regimen effectively induced long-term disease-free remission, providing a therapeutic regimen with significant efficacy and an acceptable safety profile [15]. At the same time, this regimen minimized steroid use in older adults at a high risk of renal impairment.

The standard AAV induction therapy is currently high-dose GC combined with CYC or RTX. Despite the 80–90% remission rates of these therapies, the 5-year mortality rate remains high at 10–20%, with treatment-induced infections and cardiovascular disease being the leading causes of death in patients with AAV. Two randomized clinical trials (RAVE and RITUXVAS) have shown that RTX and CYC combined with high-dose GC have similar remission rates and incidences of adverse effects. Data from these two trials suggested that high-dose GC is the main causative agent of adverse events in the current standard of care. A retrospective study showed that low-dose GC and RTX adequately induced AAV remission [16]. The PEXIVAS study demonstrated that a low-dose GC resulted in reduction of serious infections during the first year [14]. In the low-dose glucocorticoid vasculitis induction study [17], patients were randomized to receive low-dose prednisolone (0.5 mg/kg/day) and RTX (375 mg/m2/week, four times) or high-dose prednisolone (1mg/kg/day) and RTX. After 6 months, 71% and 69.2% of patients in the low-dose and high-dose groups were in remission. In total, 21 serious adverse events occurred in 18.8% of patients in the low-dose group, and 41 serious adverse events occurred in 36.9% of patients in the high-dose group. Furthermore, seven serious infections occurred in 7.2% of patients in the low-dose group, compared with 20 serious infections in 20% of patients in the high-dose group. The RITAZAREM trial, a prospective study of patients with recurrent Microscopic Polyangiitis (MPA) or Granulomatosis with Polyangiitis (GPA), showed that the combination of RTX and low-dose GC was highly effective in relieving patients with relapsed AAV with a similar or better safety profile than those reported in previous studies [18]. The 2022 EULAR guidelines 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 tapered down, subsequently to 5 mg prednisone daily at 4-5 months [4]. 114 consecutive patients from five European and U.S. centers were retrospectively studied. They received standard therapy (plasma exchange, CYC, and high-dose oral GC) to induce remission with or without pulsed methylprednisolone. The results of this study suggest that pulsed intravenous GC combined with standard therapy to induce remission in patients with severe AAV may not be clinically beneficial and may lead to more infectious episodes and a higher incidence of diabetes [19]. Therefore, the 2022 EULAR guidelines stated that there is no compelling evidence for applying hormonal shock therapy [4].

Remission-Maintenance Treatment

The KDIGO guidelines stated that after remission induction, immunosuppression must be maintained owing to the high likelihood of recurrence in patients with AAV [13]. The most recent regimens for maintaining remission include RTX, AZA, and low-dose GC [20]. According to EULAR recommendations, RTX is the choice for patients with severe AAV-GN. The RITAZAREM trial demonstrated that AZA, Methotrexate (MTX), and Mycophenolate Mofetil (MMF) are viable alternatives for patients who cannot receive RTX or those with non-severe GPA/MPA [18]. A meta-analysis has shown that longer courses of GC are associated with fewer relapses; however, all expert panels agreed that GC tapering should be performed as early as possible and accepted that a few patients should be on low-dose GC for a long period.

Drug choice is one aspect, but the timing of discontinuation also needs to be explored. Thepersistence of ANCA positivity after treatment, rise in ANCA titer, and conversion of ANCA-negative to ANCA-positive status are only moderately predictive of future relapses. Therefore, discontinuing maintenance therapy remains a clinical decision rather than a biomarker-driven one. In the KDIGO guidelines, the optimal duration of AZA plus a low-dose GC is 18-48 months after the induction of remission and 18 months after remission induced by RTX [13]. EULAR recommends that maintenance therapy should be continued for at least 24 months. In patients who relapse or are at increased risk of relapse, a longer duration of maintenance therapy (approximately 48 months) should be considered [21]. However, there should be a balance between the risk of continued immunosuppression and patient preference. The MAINRITSAN3 trial of RTX or placebo infusions every 6 months for 18 months (four infusions) showed that an additional 2 years of RTX therapy resulted in a reduction in the rate of relapse (48 months) in patients who received RTX maintenance therapy and remained in remission for 2 years (24 months). So far, data on the optimal duration of remission maintenance, specifically for patients with AAV-GN, are lacking.

Targeted Drugs

Avacopan is a novel small oral molecule that selectively inhibits the action of the complement 5a (C5a) by blocking the C5a receptor (C5aR) on neutrophil surfaces, which promotes neutrophil chemoattraction and ultimately attenuates endothelial cell damage and inflammation [22,23]. Prospective studies published between 2017 and 2021 have shown that Avacopan is an effective and safe steroid replacement for inducing AAV remission [24]. The KDIGO guidelines recognized complement-targeted therapy as another strategy that may reduce GC exposure [13].

The CLEAR study, a 12-week stepwise, two-phase randomized controlled trial, enrolled 67 patients who were with newly diagnosed or relapsed GPA or MPA for remission induction therapy with CYC or RTX [25]. They were then randomized in 4 groups, high-dose GC (starting dose of 60 mg prednisone) without Avacopan (control group), oral Avacopan (30 mg twice daily) plus low-dose GC (starting at 20 mg prednisone), and Avacopan without GC. A 50% reduction in baseline BVAS score and no deterioration of any system was achieved

in 70% of patients in the control group, 86.4% in the Avacopan plus reduced GC group, and 81% in the Avacopan without reduced GC group, demonstrating that the incidence and severity of adverse events were similar across all treatment groups. The CLASSIC study evaluated the efficacy of Avacopan for remission induction in patients with AAV, with the SOC (GC plus RTX or CYC). In total, 42 newly diagnosed patients were randomized to oral Avacopan therapy (10 mg or 30 mg twice daily) plus SOC or SOC only. At 12 weeks, the incidence of severe adverse events was similar (15% in the SOC group and 17% in the Avacopan plus SOC group). Clinical responses were high in all groups (85% in the SOC group, 92% in the Avacopan 10 mg group, and 80% in the Avacopan 30 mg group). The EULAR guidelines stated that Avacopan can be combined with RTX or CYC to substantially reduce GC exposure.

The ADVOCATE trial compared the use of Avacopan (30 mg twice daily) as a standard induction regimen (RTX or CYC) as against GC (taper from 1 mg/kg/day to 0 mg/kg/day over 21 weeks) [26]. The cumulative GC dose was reduced by 2.3 g over 1 year in the Avacopan group compared with the prednisone group, and the incidence of adverse events, serious adverse events, and infections did not differ 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 recovered better with Avacopan. Avacopan appears to be a promising option for reducing GC in patients with AAV. However, uncertainties remain regarding the optimal duration of treatment (when combined with RTX maintenance therapy), residual need for GC, long-term follow-up, and efficacy in patients with an eGFR <15 mL/min/1.73 m2. There is no data on using Avacopan for longer than 1 year, therefore, its long-term use is not recommended.

In addition to Avacopan, many new drugs have been developed to target the various signaling pathways involved in AAV development. The main pathogenesis is activating neutrophils stimulated by inflammatory factors to produce Neutrophil Extracellular Traps (NETs), which persist in patients with low NET degradation activity and whose prolonged exposure to their contents disrupts tolerance to specific autoantigens, especially MPO and PR3 [27-29]. These antigens are presented through dendritic cells to $CD4^+$ T cells, further stimulating B cells and producing ANCA [30]. An essential strategy to prevent NET formation is identifying new peptidyl arginase deiminase inhibitors, a key enzyme in NET generation. Another approach may be to investigate potential neutrophil elastase inhibitors, which may act synergistically with Gasdermin D to disrupt the nuclear and cellular membranes during NET generation. In addition, deoxyribonucleases (DNases), particularly DNase I, may be a crucial approach to facilitate the disruption of already formed NETs for AAV treatment [30,31]. However, this deserves further exploration. Furthermore, Mepolizumab (an anti-IL-5 antibody) has recently been approved for vasculitis treatment and is recommended for patients with relapsed or refractory GPA. Alemtuzumab, an anti-CD52 antibody, was investigated for its lymphocyte-killing effect in patients with refractory vasculitis in a phase 3 study (ALEVIATE). Further in-depth studies on AAV pathogenesis are required to provide more insights for drug development.

Plasma Exchange

Patients with AAV-GN are at a high risk of progression to ESKD, which develops in 14-25% of patients at the 5-year follow-up, suggesting suboptimal renal survival in patients with AAV [32]. The addition of plasma exchange therapy (PLEX) to standard remission-inducing therapies has become the SOC, especially for patients with severe renal disease. However, there is controversy regarding patients who may benefit from PLEX [33]. A meta-analysis concluded that adding PLEX to standard AAV remission induction therapy reduces the risk of ESKD at 12 months [34]. These findings have been interpreted to support the provision of PLEX to patients with AAV and to those at high risk of developing ESKD or requiring dialysis. However, the recently reported PEXIVAS trial did not show the benefits of PLEX presenting with an eGFR ≥50 mL/min/1.73 m2 or alveolar hemorrhage [14,35]. The relative risk of ESKD is reduced by at least 20%, but the relative risk of severe infection is increased by at least 20%. Therefore, the latest EULAR guidelines recommend that plasma exchange should not be routinely used in patients with AAV.

Conclusion

Early diagnosis of AAV-GN is essential for improving the short- and long-term prognoses of patients at risk of renal impairment. In our daily clinical work, individualized treatment

plans should be developed for different patients, from adopting new classification criteria to adopting new therapeutic recommendations and using newly approved drugs for AAV treatment. Through the progress of more clinical trials, the treatment of AAV-GN is more systematic, standardized, and it is a critical factor in achieving remission for more patients, reducing the risk of progression to critical illness, and reducing the risk of adverse drug effects. In the future, more comprehensive research on the mechanisms underlying AAV will lead to the discovery of novel drugs. Simultaneously, there is a need for continued interaction between basic research and clinical studies to fully understand the etiology and pathogenesis of AAV and ultimately develop safe and effective treatments.

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