Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Advances in the Assessment and Treatment of Anti-Neutrophil Cytoplasmic Antibody-Associated Glomerulonephritis

Anqi Ni[1–3], Ying Xu[1–3], Jianghua Chen[1–3], Fei Han[1–3]

[1]Kidney Disease Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [2]Zhejiang Clinical Research Center of Kidney and Urinary System Disease, Zhejiang University, Hangzhou, Zhejiang, People's Republic of China; [3]Institute of Nephrology, Zhejiang University, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Fei Han, Kidney Disease Center, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, Zhejiang, 310003, People's Republic of China, Tel +86 57187236996, Email hanf8876@zju.edu.cn

Abstract: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of autoimmune diseases primarily cause inflammation of small blood vessels. Renal involvement occurs frequently and often leads to end-stage renal disease (ESRD), which significantly impacts patient health and survival. Early diagnosis and appropriate treatment are essential to improving patient outcomes. This review provides an overview of the latest advances in the assessment and treatment of ANCA-associated glomerulonephritis (AAGN). The assessment section covers diagnostic tools, disease activity assessment, and risk stratification, with the introduction of the latest ANCA kidney risk score (AKRiS), which aids in identifying high-risk patients and facilitates personalized treatment strategies. The treatment section discusses induction and maintenance therapy, including immunosuppressive agents and emerging therapies. Recent advances have moved treatment away from reliance on cytotoxic agents, focusing on targeted biological therapies to induce and maintain disease remission, while prioritizing the reduction of corticosteroid toxicity. Overall, these advancements have greatly improved patient outcomes and provided new avenues for personalized management of AAGN.

Keywords: anti-neutrophil cytoplasmic antibody, vasculitis, kidney, assessment, treatment

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of autoimmune diseases characterized by inflammation of small blood vessels. It is classified into three major subtypes as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1] Kidneys are one of the most commonly affected organs in AAV. It has been reported that approximately 38% to 70% of GPA patients and 80% to 100% of MPA patients experience kidney involvement.[2,3] Kidney damage caused by AAV typically presents as rapidly progressive glomerulonephritis, characterized by a rapid decline in kidney function, proteinuria, microscopic hematuria, and hypertension. The pathological features primarily include segmental necrosis of glomeruli with crescent formation and minimal or absent immune complex deposition, which is known as ANCA-associated glomerulonephritis (AAGN).[4]

Untreated, AAV patients have an extremely high mortality rate, with 1-year and 2-year mortality rates of about 80% and 93%, respectively, primarily due to renal and respiratory failure.[5,6] Since the introduction of glucocorticoids and immunosuppressant, there has been a significant improvement in the prognosis of AAV.[7] However, the toxic side effects associated with steroids and immunosuppressive agents have also gained widespread attention. In recent years, the anti-CD20 chimeric monoclonal antibody rituximab is recognized as a better choice for both inducing and maintaining remission when compared to conventional treatment regimens. Additionally, avacopan stands out as an effective glucocorticoid-sparing alternative. Nevertheless, ensuring a proper balance between control of disease activity and safety

Received: 5 September 2024
Accepted: 15 December 2024
Published: 31 December 2024

remains a critical issue. Thus, early and accurate assessment and appropriate therapeutic strategies are essential to achieve optimal patient and renal outcomes.

In this review, we summarized the latest developments in the assessment and treatment of patients with AAGN, focusing on clinical trial evidence for therapies such as glucocorticoids, rituximab, plasma exchange, and avacopan. We also incorporate interpretations of the 2022 European League Against Rheumatism (EULAR) treatment recommendations and the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of ANCA-associated Vasculitis. These advancements have significantly improved patient outcomes and provide new avenues for personalized management.

Assessment

The assessment of AAGN includes diagnostic tools, evaluation of disease activity, as well as risk stratification, shown in Figure 1.

Diagnostic Tools

The 2012 Chapel Hill Consensus Conference established standardized definitions for ANCA-associated vasculitis (AAV), classifying it into subtypes such as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), as outlined in Table 1.[1] Building on this foundation, the 2022

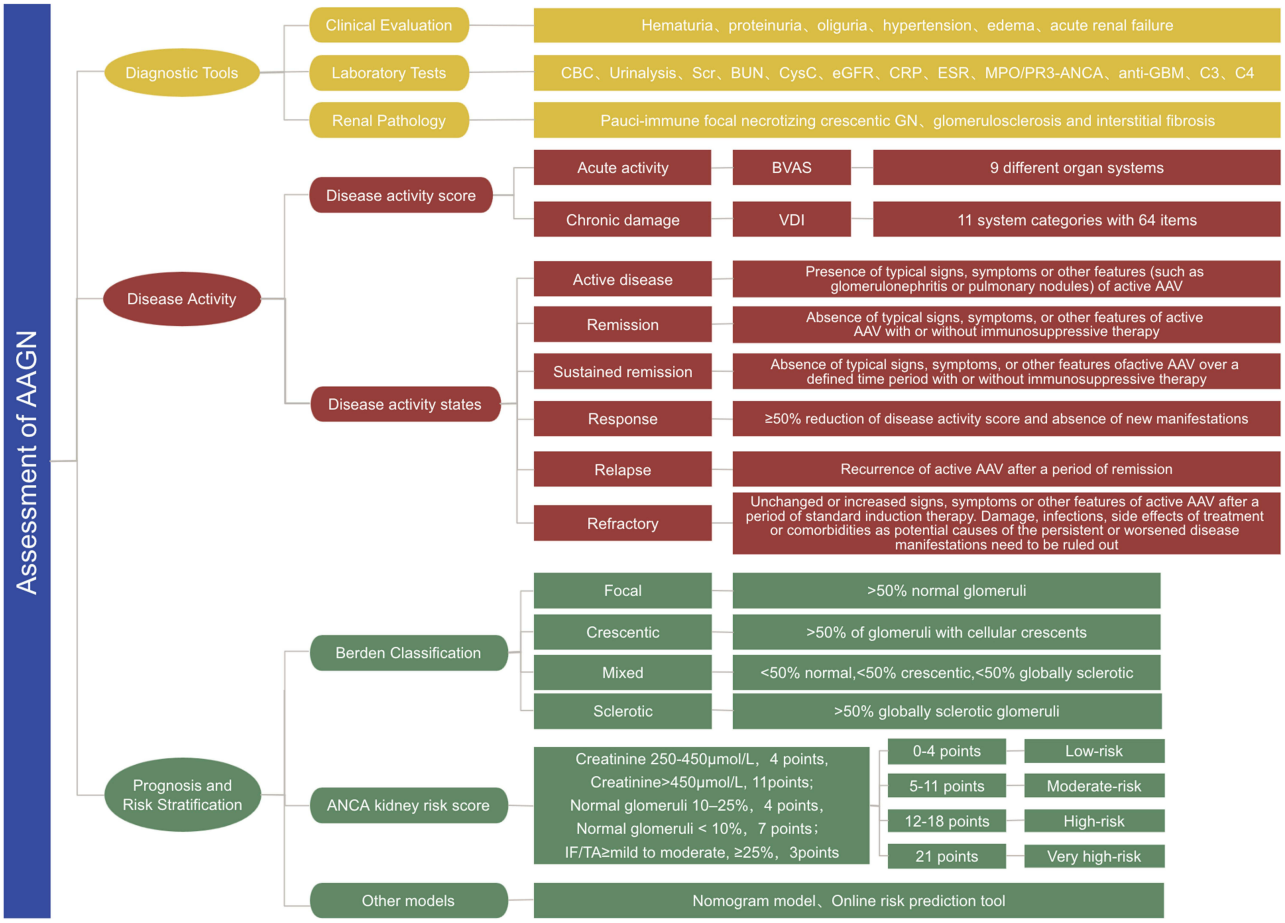

Figure 1 The assessment of AAGN.

Abbreviations: AAGN, Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis; AAV, ANCA-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; BUN, Blood Urea Nitrogen; CBC, Complete Blood Count; CRP: C-reactive protein; eGFR, estimated glomerular filtration rate; ESR: Erythrocyte Sedimentation Rate; GBM, glomerular basement membrane; GN, glomerulonephritis; IF/TA, interstitial fibrosis and tubular atrophy; MPO, myeloperoxidase; PR3, proteinase 3; Scr, serum creatinine; VDI, Vasculitis Damage Index.

Table 1 2012 Chapel Hill Consensus Conference Definition.[1]

Vasculitis Name	Definition
ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (GPA)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (eg, capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

Notes: Reproduced from Jennette JC, Falk RJ, Bacon PA, et al 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1–11. Copyright 2013, John Wiley and Sons.[1]
Abbreviation: ANCA, Anti-neutrophil cytoplasmic antibody.

ACR/EULAR classification criteria introduced a comprehensive scoring system that incorporates clinical, serological, and imaging findings to accurately classify AAV subtypes, as detailed in Table 2.[8–10]

As a renal manifestation of AAV, AAGN follows the same diagnostic framework as AAV but requires specific attention to renal involvement for effective evaluation and management. A comprehensive diagnosis of AAGN typically involves clinical evaluation, laboratory tests, and renal pathology. Clinical assessment is essential, with the most severe manifestation being a rapid decline in glomerular filtration rate (GFR) of at least 50% over a short period of time (from a few days to 3 months).[11] During active disease phases, hematuria originating from the renal glomeruli is frequently observed, often presenting as microscopic hematuria. The presence of hematuria typically reflects the activity of renal vasculitis, and it may resolve in patients during remission. Additionally, it may be accompanied by different degrees of proteinuria, primarily manifesting as non-nephrotic range proteinuria. In some cases, patients may exhibit features of nephrotic syndrome.

In addition to laboratory tests such as complete blood cell count, urine sediment analysis, renal function, C-reactive protein, and erythrocyte sedimentation rate, it is also advisable to conduct myeloperoxidase (MPO) and proteinase 3 (PR3) - ANCA testing. Patients who test positive for PR3-ANCA often exhibit acute kidney injury and tend to experience more resistant and frequent disease recurrences. On the other hand, MPO-ANCA-positive patients typically present with milder symptoms but are at a higher risk of developing chronic renal failure, leading to worse long-term renal outcomes. However, those MPO-ANCA-positive patients who respond positively to treatment have a lower risk of relapse.[4] Nonetheless, a diagnostic challenge and the potential for treatment delay may arise in clinical, as approximately 20–30% of patients exhibit atypical ANCA, and 10–20% of them are ANCA negative.[12–14] In addition, testing for anti-glomerular basement membrane (GBM) antibodies should also be performed. In some patients, both ANCA and anti-GBM antibodies are positive. These patients, often older in age with a longer duration of symptoms before a definitive diagnosis, exhibit characteristics similar to anti-GBM disease. This includes severe kidney involvement and a higher frequency of pulmonary hemorrhage, which may necessitate urgent plasmapheresis.[15] In terms of complement levels, there have been reports indicating an association between reduced C3 levels and poorer renal outcomes.[16,17] Some studies also suggest a significant elevation in complement levels in AAV patients due to the abrupt activation of the immune system.[18,19]

The pathological hallmark of AAGN is crescentic glomerulonephritis with necrosis and/or minimal immune complex deposition. Crescents result from the accumulation of inflammatory cells and proliferation of parietal epithelial cells, signifying severe glomerular injury. Segmental fibrinoid necrosis is a common early vascular change. In addition to glomerular alterations, renal arteritis and interstitial inflammation are frequently observed.[4,20] According to the latest

Table 2 The 2022 ACR/EULAR Classifcation for AAV Criteria.[8–10]

	GPA		MPA		EGPA	
Clinical	**Nasal** Bloody discharge, ulcers, crusting, congestion, blockage or septal defect/perforation	**+3**	**Nasal** Bloody discharge, ulcers, crusting, congestion, blockage or septal defect/perforation	**−3**	**Obstructive airway disease**	**+3**
	Cartilaginous Ear or nose cartilage inflammation, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity	**+2**			**Nasal polyps**	**+3**
	Conductive or sensorineural hearing loss	**+1**			**Mononeuritis multiplex**	**+1**
Laboratory, imaging, and biopsy	**Positive test for cANCA or PR3-ANCA**	**+5**	**Positive test for pANCA or MPO-ANCA**	**+6**	**Blood eosinophil count≥1×10^9/L**	**+5**
	Chest imaging Pulmonary nodules, mass, or cavitation	**+2**	**Chest imaging** Fibrosis or interstitial lung disease	**+3**	**Extravascular eosinophilic-predominant inflammation on biopsy**	**+2**
	Granuloma on biopsy	**+2**	**Pauci-immune glomerulonephritis on biopsy**	**+3**	**Positive test for cANCA or PR3-ANCA**	**-3**
	Sinus imaging Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis	**+1**	**Positive test for cANCA or PR3-ANCA**	**-1**	**Hematuria**	**-1**
	Pauci-immune glomerulonephritis on biopsy	**+1**	**Blood eosinophil count ≥ 1×10^9/L**	**-4**		
	Positive test for pANCA or MPO-ANCA	**-1**				
	Blood eosinophil count ≥ 1×10^9/L	**-4**				
Scoring	Sum scores 10 items ≥5=GPA		Sum scores 6 items ≥5=MPA		Sum scores 7 items ≥6=EGPA	

Abbreviations: AAV, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA; PR3, proteinase-3; MPO, myeloperoxidase; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis.

guidelines, a significantly positive ANCA test combined with relevant clinical symptoms may be sufficient to initiate remission induction therapy without waiting for the results of a renal biopsy.[21] However, renal biopsy is strongly recommended as it provides the "gold standard" diagnostic results, especially in cases where serological findings are inconclusive or clinical presentations are atypical. Renal biopsy, aside from playing a crucial role in disease diagnosis, also serves as an essential tool for reflecting the disease's activity and chronicity, assessing the severity of renal lesions, and holds significant value in predicting renal outcomes.[22] Several studies have shown that a high percentage of normal glomeruli is strongly correlated with a positive prognosis, while a high percentage of glomerular sclerosis is closely associated with an adverse prognosis.[23,24] For patients with ANCA-associated nephritis, renal biopsy should always be considered. When clinical manifestations are unequivocal, waiting for the biopsy should not delay the initiation of appropriate treatment. Biopsy can be performed "when feasible" at a later time.

Disease Activity Assessment

AAV exhibits chronic relapsing remission characteristics, thus requiring close monitoring of disease activity to provide appropriate treatment. Recommend using the Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) separately to assess the activity and irreversible chronic damage of AAV. The BVAS, first introduced in 1994, was subsequently revised in 1997 (2nd edition) and 2008 (3rd edition).[25–27] In order to assess the disease activity of GPA more specifically, the BVAS/WG (specific to GPA) was introduced in 2001.[28] The BVAS V3.0 score is a reliable tool for assessing disease activity and severity, examining involvement in 9 different organ systems, assessing based on the persistence or intermittency of symptoms, and weighting clinical features according to their clinical relevance.[27,29] In clinical practice, BVAS has been utilized as a measure for assessing remission or relapse.[30] Typically, remission is defined as the absence of any BVAS items for a continuous period of 2 to 6 months. Relapse can be defined by the reappearance of BVAS items (major or minor).[30,31] The VDI scale is used to assess the irreversible chronic damage in the disease and consists of 11 system categories and 64 items.[32] Injury can be caused directly by a disease or as a result of treatment, and it may persist for at least 3 months.

The 2022 EULAR guidelines propose a consensus definition for disease activity states in AAV, including active disease, remission, sustained remission, response, relapse, and refractory.[33] "Active disease" refer to presence of typical signs, symptoms or other features (such as glomerulonephritis or pulmonary nodules) of active AAV. "Remission" is used to describe absence of typical signs, symptoms, or other features of active. "Sustained remission" is defined as absence of typical signs, symptoms, or other features of active AAV over a defined time period with or without immunosuppressive therapy. "Response" is characterized as ≥50% reduction of disease activity score and absence of new manifestations. "Relapse" is considered as recurrence of active AAV after a period of remission. "Refractory" is defined as unchanged or increased signs, symptoms or other features of active AAV after a period of standard induction therapy, with potential causes of the persistent or worsened disease such as damage, infections, side effects of treatment, or comorbidities needing to be ruled out.

Prognosis Assessment and Risk Stratification

Accurate evaluation of prognosis is essential in managing treatment. Risk stratification helps identify patients at higher risk of adverse outcomes and guides treatment decisions, avoiding overly aggressive immunosuppressive therapy. In 2010, Berden et al proposed novel histopathological classification criteria for AAGN, which categorized glomerular lesions into focal (>50% normal glomeruli), crescentic (>50% of glomeruli with cellular crescents), sclerotic (>50% globally sclerotic glomeruli), and mixed types.[34] Renal survival rates at 5 years post-diagnosis were reported as 93% for patients in focal, 76% in crescentic, 61% in mixed, and 50% in sclerotic class at diagnosis. Subsequent studies have confirmed this histopathological classification, consistently showing that the focal class had the most favorable renal prognosis, while the sclerotic class had the worst.[35–37] However, there remains controversy regarding the outcomes of the crescentic and mixed classes, possibly due to variations in baseline renal function or the proportion of glomerular sclerosis among different groups. In 2018, Brix et al proposed a Renal Risk Score (RRS) model to predict renal outcomes in AAGN patients.[38] This model includes factors such as estimated glomerular filtration rate (eGFR) (G0 > 15 mL/min per 1.73 m^2, G1 ≤ 15 mL/min per 1.73 m^2), the percentage of normal glomeruli (N0 > 25%, N1 10–25%, N2 < 10%), and

the percentage of interstitial fibrosis and tubular atrophy (IF/TA) (T0 ≤ 25%, T1 > 25%). The RRS was calculated as the sum of the assigned points for each parameter (N1 = 4 points, N2 = 6 points, T1 = 2 points, G1 = 3 points). This score was developed to predict the risk of ESRD as low (0 points), medium (2 to 7 points), or high (8 to 11 points). Our center, as well as other centers, has confirmed that the RRS model demonstrates higher efficacy in predicting renal outcomes compared to the Berden's classification.[39–41] However, some research has found that it lacks predictive power for patients in the low-risk and medium-risk groups.[42,43] Moreover, although most high-risk group patients progress to ESRD, a significant proportion of patients still benefit from treatment and maintain renal function during follow-up.[44] As a result, improvements to the RRS model have been made in follow-up studies. A multicenter study by Boudhabhay et al found that incorporating the presence of concurrent renal arteritis into the ARRS model significantly improved its predictive performance.[41] Our center, in conjunction with other clinical and pathological parameters, modified the RRS model to develop a nomogram predictive model for ESRD risk in AAGN patients.[45] The C-index of the nomogram model was 0.822, which was higher than the RRS model of 0.783, with a statistically significant difference ($P < 0.05$). Wang et al developed a modified model with eGFR, normal glomerular proportion (both as continuous variables), and IF/TA (< 25%, 25–50%, > 50%) included, alongside the creation of an online risk prediction tool, which exhibited improved discrimination and calibration when compared to the RRS model.[46] Recently, a study incorporated the largest AAGN patient biopsy data cohort to date (over 1500 individuals), validating and estimating calibration errors in RRS model, and proposing revised and improved scoring tools.[47] The latest ANCA kidney risk score (AKRiS) includes the percentage of normal glomeruli (N0: >25% = 0 points, N1: 10–25% = 4 points, N2: <10% = 7 points), the percentage of IF/TA (T0: none/mild or <25% = 0 points, T1: ≥mild to moderate or ≥25% = 3 points), and the serum creatinine level at diagnosis (K0: <250 μmol/L = 0 points, K1: 250–450 μmol/L= 4 points, K2: >450 μmol/L= 11 points). The final scores are divided into four risk groups: low risk (0–4 points), moderate risk (5–11 points), high risk (12–18 points), and very high risk (21 points), with probabilities of progressing to end-stage kidney disease (ESKD) within 3 years being 4%, 11%, 46%, and 81% respectively.

Treatment

The treatment of AAV typically includes a 3–6-month induction phase aimed at quickly controlling vasculitis activity to achieve complete remission. This is followed by a maintenance phase to prevent relapse, minimize treatment-related adverse reactions, and protect the function of affected organs in the long term. According to the 2024 KDIGO and 2022 EULAR guidelines, we summarize the recent management recommendations for AAGN in Figure 2.

Induction Therapy

Prompt initiation of induction therapy is essential for controlling inflammation and preventing further organ damage. Glucocorticoids combined with immunosuppressive agents, such as cyclophosphamide or rituximab, are standard treatments. The choice of agent depends on disease severity, individual patient characteristics, and comorbidities. Newer therapies like avacopan, a C5a receptor inhibitor, have shown promising results in clinical trials. The main clinical trials of induction therapy for AAV are presented in Table 3.

Glucocorticoids

Glucocorticoids are the cornerstone of treatment for AAV, with rapid onset of action and potent anti-inflammatory effects. The treatment dose and duration depend on the severity of the disease and response to treatment. Most patients with AAGN are started on glucocorticoid therapy in the form of oral prednisone (or prednisolone) at a dose of 1 mg/kg/day (with a maximum dose of 80 mg/day), followed by a gradual taper.[59] In cases of severe organ damage or life-threatening AAV, such as rapidly progressive glomerulonephritis or pulmonary hemorrhage, intravenous (IV) methylprednisolone (MP) pulses (0.5–1.0g/day) for 1–3 days are often administered at the onset of induction therapy.[60] There is currently controversy surrounding the use of high-dose glucocorticoid pulses therapy. Our center reported that high-dose IV-MP pulses therapy can reduce the mortality rate of severe AAGN and increase the recovery rate of renal function.[61] However, studies have also found that in severe AAGN patients (serum creatinine levels [SCr] > 500μmol/L or requiring dialysis), there is no difference in 1-year overall survival rate or kidney function recovery between IV-MP and non-MP

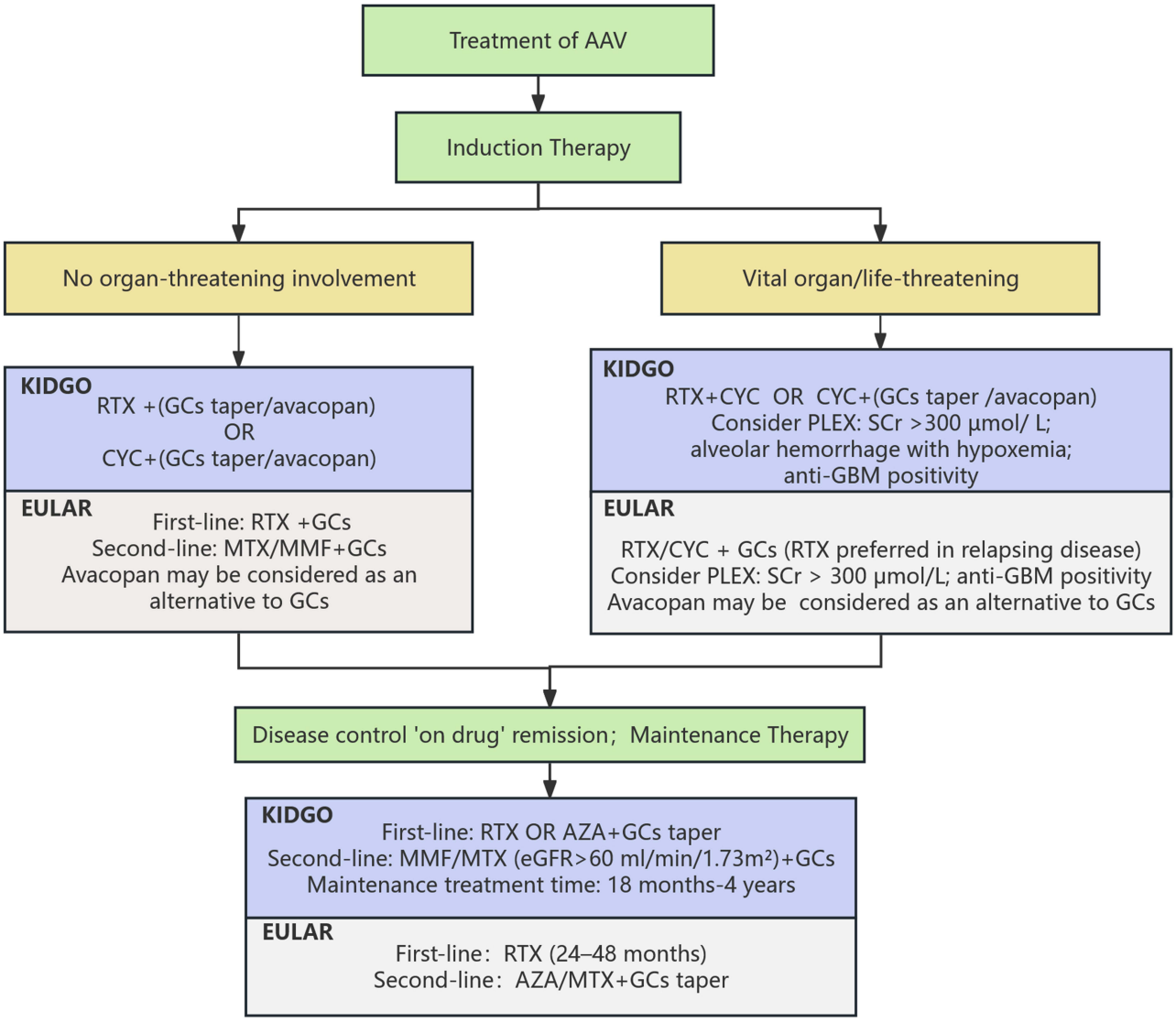

Figure 2 Recommendations for the induction and maintenance therapy of AAGN, based on the 2024 KDIGO and 2022 EULAR guidelines.
Abbreviations: AAV, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GCs, glucocorticoids; MMF, mycophenolate mofetil; MTX, methotrexate; PLEX, Plasma exchange; RTX, rituximab; SCr, serum creatinine.

patients.[62,63] Additionally, the IV-MP pulses therapy regimen increased the risk of severe infection by nearly three times at 3 months and increased the risk of new-onset diabetes by more than 6 times.[62] Therefore, the use of IV-MP pulses therapy should be approached with caution. Long-term steroid therapy significantly increases the risk of infection in patients, while the incidence of diabetes, osteoporosis, gastrointestinal reactions, weight gain, and cardiovascular adverse events also increases significantly.[64,65] In recent years, clinical experts have also been continuously exploring strategies to reduce the dosage of glucocorticoids, including initial low-dose and rapid tapering regimens. In 2021, the Low-Dose Glucocorticoid Vasculitis Induction Study (LoVAS) demonstrated that for newly diagnosed AAV patients without severe glomerulonephritis or alveolar hemorrhage, glucocorticoid reduction is feasible.[57] In this study, the regimen of rituximab (375mg/m^2 weekly, for 4 weeks) combined with reduced-dose glucocorticoids (0.5mg/kg/day) or high-dose glucocorticoids (1mg/kg/day) were equally effective in inducing disease remission. The incidence of severe adverse events was significantly reduced in the reduced-dose glucocorticoids group. The 2-year follow-up study of the LoVAS trial found that the mortality and relapse rates at 24 months were similar between the two groups and the reduced-dose glucocorticoids group experienced fewer severe adverse events.[58] Furthermore, the RITAZAREM trial indicated that the remission

https://doi.org/10.2147/JIR.S494848

https://doi.org/10.2147/JIR.S494848

Table 3 Major Clinical Trials for Induction Therapy in ANCA-Associated Vasculitis

Trial Name (Year)	Key Inclusion/Exclusion Criteria	Therapies	Remission Rates (%) or Endpoints	Serious Side Effect Rates	Key Conclusion
NORAM[48] (2005) N=100	Newly diagnosed AAV, with Scr<150μmol/L, without critical organ manifestations of disease	Oral MTX vs oral CYC	89.8% vs 93.5%	17.6% vs 12.2%	MTX can replace CYC for initial treatment of early AAV, but it is associated with more recurrence
MEPEX[49] (2007) N=137	Newly diagnosed AAV with kidney involvement and SCr >500μmol/L, without life-threatening extra-renal manifestations	PLEX vs IV-MP	Dialysis independence 69% vs 49% at 3 Months	50% vs 48%	PLEX superior in rates of dialysis independence at 3 months and renal survival at 12 months
CYCLOPS[50] (2009) N=149	Newly diagnosed AAV (Scr >150μmol/L but < 500μmol/L)	IV-CYC vs oral CYC	88.1% vs 87.7% at 9 months	25.0% vs 42.5%	IV-CYC has similar remission rates to oral CYC, with the advantage of lower cumulative CYC doses and fewer cases of leukopenia
RAVE[31,51] (2010) N=197	Newly diagnosed or relapsing AAV with SCr <354μmol/L, exclude mechanical ventilation because of alveolar hemorrhage	RTX vs oral CYC	64% vs 53% at 6 months; 39% vs 33% at 18 months	42% vs 38%	RTX noninferior to CYC/AZA, and superior in relapsing PR3-AAV
RITUXVAS[52] (2010) N=44	Newly diagnosed AAV with kidney involvement	RTX + CYC vs IV-CYC	76% vs 82% at 12 months	42% vs 36%	RTX + CYC was not superior to IV-CYC
CORTAGE[53] (2015) N=104	≥65 years old with newly diagnosed AAV	Low-dose IV-CYC vs standard dose	89% vs 86%	60% vs 78%	In elderly patients, reduced-dose CYC are safer and equally effective compared to standard dose
MYCYC[54] (2019) N=140	Newly diagnosed aav, exclude life-threatening vasculitis, rapidly declining renal function or eGFR<15 mL/min/m^2	MMF vs IV-CYC	67% vs 61%	50% vs 40%	MMF was non-inferior to CYC for remission induction, but resulted in higher relapse rate in patients with PR3-ANCA
PEXIVAS[55] (2020) N=704	Newly diagnosed or relapsing AAV with kidney involvement and eGFR > 50 mL/min/1.73 m^2 or pulmonary haemorrhage	PLEX vs control; reduced dose GCs vs standard-dose GCs	28.4% vs 31.0%; 27.9% vs 25.5%	Infection: 39% vs 32%; 34% vs 37%	PLEX not superior compared with no PLEX; reduced-dose GCs are safe and reduce serious infections
ADVOCATE[56] (2021) N=331	Newly diagnosed or relapsing AAV, exclude alveolar haemorrhage requiring invasive ventilation	Avacopan with reduced dose GCs (20mg/day tapered off over 4 weeks) vs standard dose GCs (60mg/day starting dose)	72.3% vs 70.1% at 6 months; 65.7% vs 54.9% at 12 months	23.5% vs 25.0%	Avacopan is non-inferior to prednisone at 6 months, and superior at 12 months
LoVAS[57,58] (2021) N=134	Newly diagnosed AAV with eGFR>15mL/min/m^2, without severe glomerulonephritis or alveolar hemorrhage	Reduced-dose GCs (0.5 mg/kg/d) +RTX vs high dose GCs(1.0mg/kg/d) +RTX	Remission: 71.0% vs 69.2% at 6 months; Death: 2.8% vs 7.6% at 24 months; Relapse: 13.0% vs 7.6% at 24 months	18.8% vs 36.9% at 6 months; 27.5% vs 46.2% at 24 months	Reduced-dose GCs + RTX was noninferior to high-dose GCs + RTX in achieving remission at 6 months; mortality and recurrence rates were similar in the two groups at 24 months; the reduced-dose GCs group experienced fewer severe adverse events

Abbreviations: AAV, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GCs, glucocorticoids; IV-CYC, intravenous cyclophosphamide; IV-MP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MTX, methotrexate; PLEX, Plasma exchange; PR3, proteinase 3; RTX, rituximab; SCr, serum creatinine.

rate of combining rituximab with a low-dose glucocorticoids regimen in treating relapsing ANCA-associated vasculitis is similar to that of a high-dose glucocorticoids regimen, suggesting that for patients with relapsing AAV, the initial low dose of glucocorticoids (0.5 mg/kg/day) remains effective.[66] The PEXIVAS study assessed the non-inferiority of a glucocorticoids tapering group (with approximately 50% reduction in glucocorticoids dose starting in the second week, reaching a cumulative dose of less than 60% of the standard dose by 6 months) compared to a standard dose group (gradual reduction of glucocorticoids dose starting from the third week).[55] The results showed that in patients with severe AAV, the glucocorticoids tapering regimen was not inferior to the standard dose regimen in terms of death or ESRD, and the incidence of severe infections within the first year was significantly lower in the glucocorticoids tapering group compared to the standard dose group. Both KDIGO and EULAR guidelines recommend stepwise reduction in glucocorticoids as used in the PEXIVAS trial, as shown in Figure 3.[21,33] This approach helps minimize the risks of adverse effects associated with long-term glucocorticoid use while still maintaining control of the disease.

Cyclophosphamide

Cyclophosphamide (CYC) was initially the second drug given along with glucocorticoids, to help maintain remission, reduce the relapse rate, and improve the survival rate of AAV patients. The administration methods of cyclophosphamide include oral and intravenous pulse. The CYCLOPS trial compared the efficacy and toxicity differences between continuous oral CYC and intravenous pulse cyclophosphamide (IV-CYC).[50] Patients received either oral CYC (2 mg/kg/d; maximum oral dose 200 mg) or IV-CYC (15 mg/kg; maximum intravenous dose 1.2 g, with the first three pulses every 2 weeks and the subsequent three to six pulses every 3 weeks). The results showed that compared to oral CYC, IV-CYC reduced the total dose of CYC and had a lower incidence of leukopenia. There were no statistically significant differences between the two treatment groups in terms of remission time, renal survival rate, mortality rate, or adverse events. During a median follow-up of 4.3 years, the IV-CYC group had a higher risk of relapse compared to the oral CYC group, but there were no differences in patient survival and renal function.[67] Long-term use of CYC can pose the risk of infertility for young patients due to its gonadotoxicity, as well as the risk of hemorrhagic cystitis due to its bladder toxicity, additionally, there is an increased risk of malignant tumors and infections.[50,68] Since the toxicity of CYC is related to the cumulative dose, subsequent research aims to reduce the dosage of CYC. Especially for elderly individuals with impaired renal function, the risk of infection is higher, and their tolerance to immunosuppressive agents is reduced,

weeks	Body weight		
	<50kg	50-75kg	>75kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-18	5	5	7.5
19-52	5	5	5
>52	Individual taper		

Figure 3 Prednisolone tapering regimen for AAV according to the PEXIVAS Study.
Note: Glucocorticoids dosing in mg/d.

leading to a greater risk of early mortality.[69] Therefore, the CORTAGE study proposed that in patients with AAV (age >65 years), compared to conventional immunosuppressive therapy, an induction regimen of fixed-dose IV-CYC (500 mg × 6 times) every 2–3 weeks can reduce the incidence of serious adverse events without affecting the remission rate, but the relapse rate in patients may increase after 3 years.[53] The KDIGO guidelines provide dose reduction recommendations for elderly individuals and patients with impaired renal function regarding cyclophosphamide.[21] Generally, the recommended treatment duration for hormone combined with CYC is 3 to 6 months. In order to reduce adverse reactions related to the cumulative dose of CYC, it is advisable to switch to maintenance therapy with lower toxicity as soon as relief is achieved, as prolonging CYC treatment does not reduce the recurrence rate or improve prognosis. Therefore, the maximum treatment time for CYC should not exceed 6 months. If remission is not achieved after 6 months, treatment should be adjusted according to the refractory AAGN and the treatment plan should be changed.

Rituximab

Rituximab (RTX) is a human/mouse chimeric anti-CD20 monoclonal antibody that primarily functions by targeting and depleting B cells, thereby inhibiting antibody production for therapeutic effects. In the RAVE study in 2010, it was demonstrated that there was no statistical difference in remission rates and side effects at 6 months between RTX (375 mg/m^2 weekly for 4 weeks) plus oral CYC(2 mg/kg/d) followed by azathioprine (AZA) therapy compared to CYC/AZA treatment for induction therapy in newly diagnosed or relapsing AAV patients.[31] At 12 and 18 months, 48% and 39% of patients in the RTX group maintained complete responses, compared with 39% and 33% in the CYC/AZA-treated group, respectively, which also met the non-inferiority criteria.[51] A post-hoc analysis from the RAVE trial revealed that PR3-AAV patients treated with RTX had a higher remission rate at 6 months compared to CYC/AZA-treated patients (65% vs 48%, p=0.04).[70] Severely renal impaired patients (Scr >4 mg/dl) were excluded from the RAVE study, with only 67% of patients having renal involvement. In contrast, the RITUXVAS study focused on AAV patients with severe renal involvement and indicated that the efficacy of RTX (375 mg/m^2 weekly for 4 weeks) combined with two IV pulses of CYC was comparable to traditional IV-CYC induction followed by AZA maintenance at 3–6 months. At 12 months, the sustained remission rates were 76% in the RTX group and 82% in the CYC/AZA group (P = 0.68). Severe adverse events occurred in 42% of patients in the RTX group and 36% in the CYC/AZA group (P = 0.77), with no statistical differences between the groups.[52] At 24 months, there were no differences in the composite endpoint of death, end-stage kidney disease, and relapse between the two groups, occurring in 42% (14/33) of patients in the rituximab group and 36% (4/11) of patients in the CYC/AZA group (p=1.00).[71] Following the RITUXVAS trial, further studies explored the combination therapy of rituximab and cyclophosphamide. A retrospective study suggested that RTX (1000mg/ time, 5 times) combined with low-dose oral CYC (2.5 mg/kg/d for 1 week, then 1.5 mg/kg/d for 7 weeks) and rapid steroid withdrawal regimen effectively induced symptom remission in AAV patients.[72] Among the 129 patients, including 75 with rapidly progressive glomerulonephritis (RPGN) of whom 39 received PLEX, 84% achieved complete remission at 5 months. Another retrospective study of 64 patients with life-threatening ANCA-associated vasculitis (median eGFR of 9 mL/min/1.73 m^2, 47% requiring dialysis) demonstrated a 94% remission rate at six months, with 67% of dialysis-dependent patients recovering kidney function, using a combination of rituximab, low-dose intravenous cyclophosphamide, and plasma exchange.[73] At 36 months, 85% of patients survived, 69% avoided end-stage kidney disease, and 87% remained in remission, with a low infection rate of 0.28 infections per patient-year. These findings highlight the effectiveness of combining rituximab and reduced-dose cyclophosphamide in inducing rapid remission and improving renal outcomes in patients with severe AAV, even among those with critically impaired kidney function. In a recent retrospective study, a comparison was made between 225 severely renal-impaired patients (defined as eGFR < 30 mL/min/1.73 m^2) receiving either RTX or CYC treatment regimens, both following protocols similar to the RAVE study and combined with glucocorticoid therapy.[74] The study found that RTX and CYC monotherapy were equally effective for remission induction in AAV patients with severe renal impairment. The proportions of patients achieving remission (BVAS = 0) at 6 months, developing ESRD or death at 18 months, and progressing to ESRD at 24 months were similar between the two treatment groups. However, RTX demonstrated steroid-sparing effects, with more patients in the RTX group achieving complete remission, defined as BVAS=0 without the use of prednisone. Additionally, the RTX group showed a faster tapering rate of prednisone.

The 2021 ACR guidelines conditionally recommend the use of rituximab over cyclophosphamide for inducing remission in active, severe GPA/MPA patients.[75] Despite the lower cumulative doses of cyclophosphamide in current use compared to previous regimens, rituximab remains the preferred choice due to its perceived lower toxicity. Cyclophosphamide may be considered when rituximab is contraindicated or for patients with ongoing disease activity following rituximab treatment. For certain severe conditions such as acute renal failure (SCr>4.0 mg/dl), there is still debate over whether cyclophosphamide should be the preferred choice. The 2022 EULAR guidelines recommend glucocorticoids combined with RTX or CYC therapy for new or relapsing GPA or MPA patients with organ-threatening or life-threatening diseases.[33] The 2024 KDIGO guidelines suggest glucocorticoids combined with either rituximab or cyclophosphamide as initial treatment for newly diagnosed AAV.[21] In cases of significantly decreased eGFR or rapidly declining renal function, or in severe kidney disease patients with SCr >4 mg/dl (354 μmol/l), data on rituximab induction therapy are limited, and in such instances, a combination of cyclophosphamide and glucocorticoids, as well as rituximab and cyclophosphamide, may be considered. While autoantibodies typically decrease rapidly after rituximab treatment, clinical efficacy may be delayed compared to cyclophosphamide, necessitating a longer time for onset of action. For patients with severe vasculitis, rapid and effective treatment is crucial for early disease control, making the combination of rituximab with reduced cyclophosphamide dosing a novel approach to achieve quicker remission and potentially reduce steroid doses promptly.

Mycophenolate Mofetil

When treating patients with vasculitis associated with mild to moderate renal impairment, the efficacy of steroid combined with mycophenolate mofetil (MMF) induction of remission is similar to that of IV-CYC. In the MYCYC study, 140 newly diagnosed AAV patients (81% with ANCA-associated glomerulonephritis, eGFR≥15 mL/min/1.73m^2) were treated with either glucocorticoids combined with MMF or IV-CYC.[54] The rates of treatment remission and severe infections were comparable between the two groups, while the overall relapse rate was higher in the MMF group compared to the IV-CYC group. However, subgroup analysis revealed that only in PR3-AAV patients did the MMF treatment show a higher relapse rate than IV-CYC, whereas for MPO-AAV patients, the relapse rates were similar for both treatments. A prospective study compared the efficacy of oral MMF or IV-CYC combined with glucocorticoids for induction therapy over 6 months in MPA patients with kidney involvement.[76] The results indicated no statistical difference in remission rates and renal function recovery rates between the two treatment regimens. Therefore, for patients with mild to moderate renal damage with MPO-ANCA positivity in AAV, MMF may serve as an alternative to cyclophosphamide while avoiding the urogenital toxicity associated with cyclophosphamide.

Methotrexate

Non-severe vasculitis patients can also be treated with glucocorticoids combined with methotrexate (MTX). The NORAM trial compared the efficacy of MTX and CYC in inducing remission in non-severe AAV patients.[48] The study showed that at 6 months, the remission rate in the MTX group was not inferior to the CYC group (89.8% vs 93.5%). However, for patients with more extensive lesions or lung involvement, MTX treatment took longer to achieve remission. Although at 18 months, the relapse rate was higher in the MTX treatment group (69.5% vs 46.5%), the authors believe that in early-stage AAV patients without severe organ damage, MTX can be used instead of CYC. Long-term follow-up of patients participating in the NORAM clinical trial for a median time of 6 years showed that patients initially treated with MTX had a lower relapse-free survival rate and received immunosuppressive treatment for a longer time than the CYC group.[77] The EULAR guidelines recommend initiating remission in GPA or MPA with non-organ-threatening or non-life-threatening disease by first suggesting the combination of glucocorticoids and rituximab, with MTX or MMF being considered as alternatives to rituximab.[33]

Plasma Exchange

Plasma exchange (PLEX) is a method for rapidly removing potentially pathogenic ANCA and other inflammatory mediators from the circulation. However, it may increase the risk of hemorrhage by eliminating coagulation factors, and the risk of infection by eliminating antibodies. Therefore, its use requires rigorous indications. In the first randomized controlled trial for patients with severe kidney damage and dialysis dependence, PLEX combined with standard treatment

improved short-term renal function in AAV,[49] but long-term results failed to demonstrate the benefit of PLEX in ESRD or death.[78] The PEXIVAS trial included 704 AAV patients (eGFR <50 mL/min/1.73m^2 and/or diffuse alveolar hemorrhage) and studied the efficacy of PLEX beyond immunosuppression and glucocorticoid therapy.[55] The incidence of the primary endpoint events (death or ESRD) in the PLEX group was 28.4%, while it was 31% in the control group (HR=0.86, 95% CI 0.65–1.13, P=0.27), indicating that adding PLEX to standard treatment did not improve patient survival rate or prevent ESRD. A recent meta-analysis confirmed a reduced risk of renal failure at 12 months with plasma exchange, but also an increased risk of severe infection.[79] The relative risk of renal failure reduction at 12 months was comparable between the subgroup with SCr <5.7 mg/dl (500 μmol/l) and the subgroup with SCr >5.7 mg/dl (500 μmol/l) or on dialysis. Patients with SCr between 3.4 mg/dl (300 μmol/l) and 5.7 mg/dl (500 μmol/l) had an absolute risk reduction of 4.6% (95% CI: 1.2% 6.8%) for renal failure at 12 months, and patients with SCr exceeding 5.7 mg/dl (500 μmol/l) had a 6% absolute risk reduction. Therefore, the addition of plasma exchange to standard treatment is a controversial issue, and different guidelines provide differing recommendations. The latest KDIGO guidelines suggest that plasma exchange should be considered in patients with SCr >3.4 mg/dl (300 μmol/ L), or in patients with high early mortality from alveolar hemorrhage and hypoxemia, or in patients with an overlap syndrome of AAV and anti-GBM antibody.[21] However, the EULAR guidelines do not recommend routine use of plasma exchange for treating pulmonary hemorrhage in GPA and MPA, and for patients with active glomerulonephritis and SCr ≥300μmol/L, plasma exchange may be part of the induction therapy for remission in GPA or MPA.[33] The ACR guidelines also oppose routine addition of plasma exchange for patients with severe active GPA/MPA combined with glomerulonephritis, and plasma exchange may only be considered in patients at high risk of ESRD or with positive anti-GBM antibodies.[75]

Avacopan

Avacopan is a selective C5a receptor inhibitor that can block the action of C5a, mitigate inflammation-related cellular damage, and does not directly affect the formation of the terminal complement complex or membrane attack complex C5b-9.[80] C5a and its receptor play a pivotal role in the pathogenesis of AAV.[81] The ADVOCATE trial demonstrates that avacopan is effective in treating newly diagnosed or relapsing vasculitis as a substitute for glucocorticoids.[56] The remission rate in the avacopan group at week 26 was non-inferior to the prednisone group, and the sustained remission rate at week 52 was superior to the prednisone group. Additionally, in patients with renal disease, the average increase in eGFR was 7.3mL/min/1.73 m² in the avacopan group compared to 4.1 mL/min/1.73 m² in the prednisone group (p=0.029). It is worth noting that the avacopan group also used steroids during the induction phase (total dose one-third of the prednisone group), and the rates of severe adverse events (excluding worsening vasculitis) were similar between the avacopan and prednisone groups (37.3% vs 39.0%), with a lower rate of steroid-related adverse events in the avacopan group (66.3% vs 80.5%). A recent study by Cortazar et al showed that in patients with baseline eGFR ≤20 mL/min/1.73 m² in the ADVOCATE trial, at week 52, the average eGFR increase was 16.1 and 7.7 mL/min/1.73 m² in the avacopan and prednisone groups, respectively (P = 0.003).[82] Geetha D et al performed in a subset analysis of AAV patients treated with rituximab in the ADVOCATE trial, demonstrated the effectiveness and safety of avacopan in patients undergoing rituximab-induced remission therapy.[83] The latest KDIGO and EULAR guidelines recommend using avacopan as an alternative to glucocorticoids in the induction treatment of AAV, with patients at increased risk of glucocorticoid toxicity potentially benefiting the most from avacopan, and those with lower eGFR potentially benefiting from greater GFR recovery.[21,33] Currently, there is no data on the use of avacopan beyond 1 year, and future studies are needed to assess the efficacy of avacopan for over 1 year and in patients with refractory diseases.

Maintenance Therapy

After induction therapy, lower levels of immunosuppression are required to maintain achieved remission and prevent relapse. Common maintenance therapies include glucocorticoids, AZA, RTX, MMF, and MTX. The duration and intensity of maintenance therapy depend on the patient's risk of relapse, cumulative drug dose and toxicities. The main challenge currently is to tailor remission-maintenance regimens according to the individual needs of patients and determine the optimal treatment duration. A summary of the major trials for maintenance of remission in AAV can be found in Table 4.

Table 4 Major Clinical Trials for Maintenance Therapy in ANCA-Associated Vasculitis

Trial Name (Year)	Key Inclusion/Exclusion Criteria	Therapies	Relapse Rates (%)	Serious Side Effect Rates	Key Conclusions
IMPROVE[84] (2010) N=156	Newly diagnosed AAV and attained remission with oral CYC and GCs	AZA vs MMF	37.5% vs 55.3%	16.3% vs 7.5%	MMF was less effective than AZA for maintaining disease remission
MAINRITSAN[85] (2014) N=115	Newly diagnosed or relapsing AAV with remission after IV-CYC and GCs	RTX (5 doses) vs AZA	Major relapses 5% vs 29%; minor relapses 11% vs 16%	43.9% vs 43.1%	RTX had sustained remission than AZA at 28 months
REMAIN[86] (2017) N=110	AAV in remission 18–24 months after CYC induction	AZA continuation (48 months) or withdrawal (24 months)	22% vs 63%	15% vs 6%	Prolonged AZA/GCs treatment reduced relapse risk
MAINRITSAN 2[87] (2018) N=162	Newly diagnosed or relapsing AAV with remission after GCs and CTC, RTX or MTX	RTX fixed dosing vs RTX tailored dosing	9.9% vs 17.3%	38.3% vs 32.1%	AAV relapse rates were similar for individually tailored and fixed schedule RTX regimens, individually tailored patients received fewer RTX infusions
MAINRITSAN 3[88] (2020) N=97	MAINRITSAN2 patients without major relapse	RTX (4 doses) vs placebo	Minor relapses 4% vs 26%; major relapses 0% vs 13%	24% vs 30%	Extended therapy with biannual IV-RTX over 18 months was associated with a lower frequency of relapses
RITAZAREM[89] (2023) N=170	Relapsed AAV, reinduction with RTX + GCs	RTX (5 doses) vs AZA	15% vs 38%	22% vs 36%	After induction of remission with RTX, fixed- interval, repeat- dose RTX was superior to AZA for preventing disease relapse in patients with a prior history of relapse

Abbreviations: AAV, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; GCs, glucocorticoids; IV-CYC, intravenous cyclophosphamide; IV-RTX, intravenous rituximab; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab.

https://doi.org/10.2147/JIR.S494848

Immunosuppressant

In the past, the combination of low-dose glucocorticoids and CYC was an effective maintenance therapy for AAV patients. However, the long-term use of CYC has significant toxicities and side effects. In 2003, the CYCAZAREM trial demonstrated that AZA could replace CYC for maintenance therapy, being both safe and effective.[90] Compared to AZA, MMF maintenance therapy is less effective in preventing relapse. The IMPROVE study showed that at a median follow-up of 39 months, the relapse rate with MMF treatment was higher than with AZA (55.2% vs 37.5%, with a hazard ratio of 1.69), but the incidence of adverse events did not differ significantly between the two groups.[84] Therefore, MMF is not a first-line treatment for AAV maintenance therapy, but can be chosen for maintenance therapy when patients are allergic or intolerant to other immunosuppressive drugs. A multicenter randomized controlled study compared MTX and AZA for maintenance therapy, and found similar rates of adverse events and relapse in both groups.[91] It should be noted that MTX has a lower clearance rate in patients with renal impairment. When patients cannot tolerate AZA and MMF, MTX can be used for maintenance therapy in AAV patients with eGFR > 60 mL/min/1.73m^2.

Rituximab

After finding that rituximab is effective in the induction treatment of AAV, several studies have tested it as a maintenance therapy. In the MAINRITSAN trial, 115 newly diagnosed AAV patients in remission induced by steroids/CTX were randomized to receive either RTX or AZA maintenance therapy and followed up for 28 months.[85] The relapse rate in the RTX group was lower than the AZA group (5% vs 29%, p=0.002). In the long-term follow-up of this cohort, the RTX group had a higher relapse-free survival at 60 months compared to the AZA group (57.9% vs 37.2%, p=0.012), and overall survival was also higher (100% vs 93%, p=0.045), indicating that RTX is superior to AZA in maintaining remission and preventing relapse.[92] The results of the recent RITAZAREM trial have shown that for AAV relapsing patients, after achieving remission with rituximab induction, repeated doses of rituximab are more effective than azathioprine in preventing disease relapse.[89]

The dosing interval of RTX has been a hot topic in recent years. Currently, there is debate on whether the optimal dosing interval for RTX should be a fixed time interval or adjusted based on ANCA titers/CD19+ B cell counts, as relapses have been observed even in cases with ANCA negativity and B cell depletion.[93] The MAINRITSAN2 study compared relapse rates between two different dosing regimens, involving 162 AAV patients in remission who were randomized to receive individualized tapering (re-administration when ANCA reappears/titers increase/B cells rebuild, up to 18 months) or fixed-time dosing (re-administration at day 14, months 6, 12, 18 after initial 500mg RTX treatment), followed up for 28 months.[87] There was no statistically significant difference in relapse rates between the two groups (9.9% vs 17.3%, P=0.22), but the individualized dosing regimen resulted in significantly fewer administrations and reduced cumulative RTX dose. Compared to the MAINRITSAN trial, the MAINRITSAN 2 trial suggests that maintaining remission with lower RTX doses is feasible.

The MAINRITSAN 3 trial indicates that extending RTX treatment after the initial 18-month maintenance regimen (injections of 500mg every 6 months for an additional 18 months) is effective in maintaining remission.[88] The relapse-free survival rate at 28 months was 96% in the RTX group compared to 74% in the placebo group (HR=7.5, 95% CI 1.67–33.7, p=0.008). Twelve patients (24%) in the RTX group and 14 patients (30%) in the placebo group experienced at least one severe adverse event. In the RTX group, 2 out of 50 patients relapsed, while in the placebo group, 12 out of 47 patients relapsed. Among the 12 relapsed patients in the placebo group, 10 (83%) had GPA, 2 (17%) had MPA, and 6 were experiencing their first relapse, all being ANCA-positive (10 PR3-ANCA positive, 2 MPO-ANCA positive). In MAINRITSAN 3, the relapse rate was higher in PR3-AAV patients compared to MPO-AAV patients, highlighting the potential benefits of long-term RTX use in this subgroup.

A recent study conducted long-term outcome analysis on 277 patients from the MAINRITSAN trial, comparing the long-term efficacy and safety of AZA, 18-month fixed schedule RTX, 18-month individualized RTX, and 36-month RTX for preventing relapse in AAV patients.[94] The study found that the 84-month remission rate of the 18-month fixed RTX regimen appeared to be higher than AZA and the 18-month individualized RTX regimen. Additionally, extending RTX to 36 months did not seem to reduce the long-term relapse rate compared to the 18-month fixed RTX regimen (HR 0.69, 95% CI 0.38–1.25).

In light of these findings, low cumulative doses of RTX during maintenance therapy offer several significant advantages. Firstly, it has been associated with reduced toxicity, minimizing risks such as infections, malignancies, and cardiovascular complications, which are more common with high-dose regimens. Moreover, low-dose RTX allows for sustained B-cell depletion, essential for maintaining remission, while ensuring that the immune system is not overly suppressed. This dosing approach is also more cost-effective, requiring fewer infusions and lower drug usage, making it a viable long-term treatment option for AAGN patients.

KDIGO guidelines recommend using either rituximab or AZA and low-dose glucocorticoids for maintenance therapy after induction of remission, with a preference for rituximab as the primary maintenance therapy, especially for patients with known relapsing disease, PR3-AAV, frail elderly patients, those needing to minimize glucocorticoid use, and patients allergic to AZA.[21] EULAR guidelines suggest using rituximab after RTX or CYC induction of remission, with AZA or MTX as alternatives.[33] Table 5 summarizes the recent treatment trends compared to previous ones.

Maintenance Treatment Time

The maintenance treatment duration for AAV patients remains controversial. Ceasing treatment prematurely can increase the risk of relapse, while long-term immunosuppression is associated with greater toxicity. In the REMAIN trial, 117 AAV patients receiving steroid combined with CTX induction and AZA maintenance therapy were included.[86] Patients receiving 4 years of treatment had a lower relapse rate than those receiving 2 years of treatment (22% vs 63%, $p<0.0001$), and the proportion of patients progressing to ESRD was also lower (0 cases vs 4 cases). Among patients receiving maintenance treatment for 24 months, the rate of severe relapse was 35%, suggesting that approximately two-thirds of patients may not require prolonged maintenance therapy. The KDIGO guidelines recommend a duration of 18 months to 4 years for maintenance therapy after induction of remission, while the EULAR guidelines suggest maintenance therapy should be continued for 24–48 months following induction of remission in newly diagnosed cases, and longer treatment should be considered for patients at increased risk of relapse or with recurrent disease.[21,33]

Relapse in AAGN is influenced by several mechanisms, including persistent immune activation, pharmacological resistance, and genetic factors. Immune activation is a central mechanism, particularly in PR3-ANCA-positive patients, where persistent ANCA production leads to continuous immune system activation, enhancing neutrophil activation and the release of inflammatory cytokines, thereby increasing the risk of relapse.[95] Pharmacological resistance, particularly with glucocorticoids and rituximab, plays a significant role in relapse. Glucocorticoid resistance is primarily driven by alterations in

Table 5 Comparison of Treatment Trends for ANCA-Associated Vasculitis

Aspect	Past Treatment Trends	Recent Treatment Trends
Induction Therapy	**Cyclophosphamide**: Mainstay for induction therapy, often combined with glucocorticoids. **Glucocorticoids**: High doses to rapidly control disease activity.	**Rituximab**: Proven to be non-inferior to cyclophosphamide, particularly effective in PR3-ANCA-positive patients. **Avacopan**: A C5a receptor inhibitor that reduces glucocorticoid use, recommended as adjunct therapy for remission induction.
Maintenance Therapy	**Azathioprine or Methotrexate**: Commonly used for maintenance but associated with higher relapse rates.	**Rituximab**: Recommended as the first-line maintenance therapy due to lower relapse rates.
Glucocorticoid Usage	**High-dose, prolonged use**: Effective but associated with significant side effects such as increased infection risk and osteoporosis.	**Reduced glucocorticoid use**: New drugs like Avacopan allow for reduced glucocorticoid dependency and associated side effects.
Plasma Exchange	**Widely used in severe cases**: Particularly in patients with rapid serum creatinine increase and diffuse alveolar hemorrhage.	**More selective use**: Applied for severe renal impairment (Scr > 300 μmol/L), life-threatening pulmonary hemorrhage, and anti-GBM overlap syndrome; routine use is discouraged.
Treatment Goals	**Acute symptom control**: Focused on rapid suppression of disease activity and preventing acute flares.	**Long-term management and relapse prevention**: Emphasis on sustained remission, reduced relapse rates, and managing long-term treatment side effects.

Abbreviations: ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; PR3, proteinase-3; Scr, serum creatinine.

receptor expression on immune cells, which reduces their sensitivity to the drug, thereby allowing persistent inflammation and increasing the likelihood of relapse.[96] Rituximab resistance is associated with the survival of long-lived plasma cells and memory B cells, which are not effectively targeted by the drug, leading to continued ANCA production and relapse.[97] Genetic factors, including variants in the PRTN3 gene, HLA genotypes, Fcγ receptor polymorphisms, and CTLA-4 genes, can increase the risk of relapse by modulating immune activation, ANCA production, and inflammatory responses.[98–100]

Several risk factors for relapse have been identified. For example, patients who are PR3-ANCA positive have a significantly higher risk of relapse compared to MPO-ANCA positive patients, which is related to the higher inflammatory activity associated with PR3-ANCA-related diseases.[101] Additionally, persistent ANCA positivity or elevated ANCA titers have been identified as important independent predictors of relapse.[102] Other clinical risk factors for relapse include ear, nose, and throat involvement, chronic Staphylococcus aureus nasal carriage, and a history of previous relapses.[103] Treatment factors, such as rapid corticosteroid tapering or inadequate maintenance therapy (eg, premature discontinuation of immunosuppressants), have also been clearly linked to an increased risk of relapse.[104] Therefore, for high-risk relapse populations, it is important to consider extending the maintenance therapy duration appropriately, enhancing monitoring, and making necessary adjustments to the treatment plan to reduce the risk of relapse.

Conclusions

In general, there have been significant advances in the treatment of AAV in recent years, with improvements in both mortality and remission rates. Despite these achievements, the early and accurate assessment of the condition, along with the implementation of appropriate treatment strategies, remains crucial for optimizing patient and renal outcomes. A delicate balance is required between minimizing disease relapse and mitigating the adverse effects of immunosuppressive therapy, particularly the risk of severe infections. Looking ahead, the development of targeted therapies aimed at reducing reliance on corticosteroids and traditional immunosuppressants has emerged as a key area of focus. Future efforts should also prioritize the advancement of personalized treatment approaches, incorporating precision medicine to further enhance patient outcomes and long-term prognosis.

Data Sharing Statement

Data sharing is not applicable to the review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The work was supported by the National Natural Science Fund (82270706) and the Primary Research and Development Plan of Zhejiang Province (2020C03034) to Fei Han.

Disclosure

The authors declare that there are no competing interests.

References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65:1–11.
2. Holle JU, Laudien M, Gross WL. Clinical manifestations and treatment of Wegener's granulomatosis. *Rheum Dis Clin North Am*. 2010;36:507–526. doi:10.1016/j.rdc.2010.05.008
3. Chung SA, Seo P. Microscopic polyangiitis. *Rheum Dis Clin North Am*. 2010;36:545–558. doi:10.1016/j.rdc.2010.04.003
4. Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis*. 2020;75:124–137. doi:10.1053/j.ajkd.2019.04.031
5. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J*. 1958;2:265–270. doi:10.1136/bmj.2.5091.265

6. Frohnert PP, Sheps SG. Long-term follow-up study of periarteritis nodosa. *Am J Med*. 1967;43:8–14. doi:10.1016/0002-9343(67)90144-1
7. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League against rheumatism systemic vasculitis task force. *Ann Rheum Dis*. 2008;67:1004–1010. doi:10.1136/ard.2007.071936
8. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Arthritis Rheumatol*. 2022;74:393–399. doi:10.1002/art.41986
9. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for microscopic polyangiitis. *Arthritis Rheumatol*. 2022;74:400–406. doi:10.1002/art.41983
10. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Arthritis Rheumatol*. 2022;74:386–392. doi:10.1002/art.41982
11. Sinico RA, Di Toma L, Radice A. Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis. *Autoimmun Rev*. 2013;12:477–482. doi:10.1016/j.autrev.2012.08.006
12. Eisenberger U, Fakhouri F, Vanhille P, et al. ANCA-negative pauci-immune renal vasculitis: histology and outcome. *Nephrol Dial Transplant*. 2005;20:1392–1399. doi:10.1093/ndt/gfh830
13. Jayne D. Vasculitis-when can biopsy be avoided? *Nephrol Dial Transplant*. 2017;32:1454–1456. doi:10.1093/ndt/gfx248
14. Mollaeian A, Chan N, Aloor R, et al. ANCA-negative microscopic polyangiitis with diffuse alveolar hemorrhage masquerading as congestive heart failure. *Auto Immun Highlights*. 2021;12:1. doi:10.1186/s13317-020-00143-z
15. McAdoo SP, Tanna A, Hruskova Z, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. *Kidney Int*. 2017;92:693–702. doi:10.1016/j.kint.2017.03.014
16. Manenti L, Vaglio A, Gnappi E, et al. Association of Serum C3 concentration and histologic signs of thrombotic microangiopathy with outcomes among patients with ANCA-associated renal vasculitis. *Clin J Am Soc Nephrol*. 2015;10:2143–2151. doi:10.2215/CJN.00120115
17. Crnogorac M, Horvatic I, Kacinari P, Ljubanovic DG, Galesic K. Serum C3 complement levels in ANCA associated vasculitis at diagnosis is a predictor of patient and renal outcome. *J Nephrol*. 2017;31:257–262. doi:10.1007/s40620-017-0445-3
18. Kronbichler A, Lee KH, Denicolo S, et al. Immunopathogenesis of ANCA-associated vasculitis. *Int J Mol Sci*. 2020;22:21. doi:10.3390/ijms22010021
19. Moiseev S, Lee JM, Zykova A, et al. The alternative complement pathway in ANCA-associated vasculitis: further evidence and a meta-analysis. *Clin Exp Immunol*. 2020;202:394–402. doi:10.1111/cei.13498
20. Jennette JC, Nachman PH. ANCA Glomerulonephritis and Vasculitis. *Clin J Am Soc Nephrol*. 2017;12:1680–1691. doi:10.2215/CJN.02500317
21. Kidney Disease: Improving Global Outcomes ANCA-Associated Vasculitis Work Group (AVWG). *Kidney Int*. 2024;105:S71–S116. doi:10.1016/j.kint.2023.10.008
22. Haas M, Rastaldi MP, Fervenza FC. Histologic classification of glomerular diseases: clinicopathologic correlations, limitations exposed by validation studies, and suggestions for modification. *Kidney Int*. 2014;85:779–793. doi:10.1038/ki.2013.375
23. Bajema IM, Hagen EC, Hermans J, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int*. 1999;56:1751–1758. doi:10.1046/j.1523-1755.1999.00758.x
24. Tanna A, Guarino L, Tam FW, et al. Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. *Nephrol Dial Transplant*. 2015;30:1185–1192. doi:10.1093/ndt/gfu237
25. Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Qjm*. 1994;87:671–678.
26. Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. *Baillieres Clin Rheumatol*. 1997;11:423–446. doi:10.1016/S0950-3579(97)80052-0
27. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis*. 2009;68:1827–1832. doi:10.1136/ard.2008.101279
28. Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). *Arthritis Rheum*. 2001;44:912–920. doi:10.1002/1529-0131(200104)44:4<912::AID-ANR148>3.0.CO;2-5
29. Luqmani RA. Disease assessment in systemic vasculitis. *Nephrol Dial Transplant*. 2015. doi:10.1093/ndt/gfv002
30. Ponte C, Sznajd J, O'Neill L, Luqmani RA. Optimisation of vasculitis disease assessments in clinical trials, clinical care and long-term databases. *Clin Exp Rheumatol*. 2014;32:S–118–25.
31. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221–232. doi:10.1056/NEJMoa0909905
32. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum*. 1997;40:371–380. doi:10.1002/art.1780400222
33. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. 2024;83:30–47. doi:10.1136/ard-2022-223764
34. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic Classification of ANCA-Associated Glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628–1636. doi:10.1681/ASN.2010050477
35. Quintana LF, Perez NS, De Sousa E, et al. ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis. *Nephrol Dial Transplant*. 2014;29:1764–1769. doi:10.1093/ndt/gfu084
36. Ge Y, Yang G, Yu X, et al. Outcome predictors of biopsy-proven myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. *Front Immunol*. 2021;11.
37. Chen Y, Bao H, Liu Z, et al. Risk factors for renal survival in chinese patients with myeloperoxidase-ANCA–associated GN. *Clin J Am Soc Nephrol*. 2017;12:417–425. doi:10.2215/CJN.06200616
38. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int*. 2018;94:1177–1188. doi:10.1016/j.kint.2018.07.020

39. Kong W, Ni A, Wang M, et al. The predictive value of Berden's classification versus renal risk score for renal survival of Chinese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. *Clin Exp Rheumatol*. 2023;41:893–901. doi:10.55563/clinexprheumatol/ozkrr0
40. Brilland B, Boud'hors C, Copin M-C, et al. Assessment of renal risk score and histopathological classification for prediction of end-stage kidney disease and factors associated with change in eGFR after ANCA-glomerulonephritis diagnosis. *Front Immunol*. 2022;13.
41. Boudhabhay I, Delestre F, Coutance G, et al. Reappraisal of renal arteritis in ANCA-associated vasculitis: clinical characteristics, pathology, and outcome. *J Am Soc Nephrol*. 2021;32:2362–2374. doi:10.1681/ASN.2020071074
42. Tan PG, O'Brien J, Pusey CD, McAdoo SP. Validation of the ANCA renal risk score in a London cohort: potential impact of treatment on prediction outcome. *Kidney Int*. 2021;99:488–489. doi:10.1016/j.kint.2020.04.061
43. Gercik O, Bilgin E, Solmaz D, et al. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. *Ann Rheum Dis*. 2020;79:675–676. doi:10.1136/annrheumdis-2019-216742
44. Mejía-Vilet JM, Martín-Nares E, Cano-Verduzco ML, Pérez-Arias AA, Sedano-Montoya MA, Hinojosa-Azaola A. Validation of a renal risk score in a cohort of ANCA-associated vasculitis patients with severe kidney damage. *Clin Rheumatol*. 2020;39:1935–1943. doi:10.1007/s10067-020-04936-5
45. Ni A, Chen L, Lan L, et al. Validation of the antineutrophil cytoplasmic antibody renal risk score and modification of the score in a Chinese cohort with a majority of myeloperoxidase-positive patients. *J Rheumatol*. 2023;50:662–670. doi:10.3899/jrheum.220818
46. Wang R-X, Wang J-W, Li Z-Y, et al. A modified renal risk score for Chinese patients with antineutrophil cytoplasmic antibody-associated vasculitis. *BMC Med*. 2023;21.
47. Bate S, McGovern D, Costigliolo F, et al. The improved kidney risk score in ANCA-associated vasculitis for clinical practice and trials. *J Am Soc Nephrol*. 2024;35:335–346. doi:10.1681/ASN.0000000000000274
48. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Rheum*. 2005;52:2461–2469. doi:10.1002/art.21142
49. Jayne DRW, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007;18:2180–2188. doi:10.1681/ASN.2007010090
50. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2009;150:670–680. doi:10.7326/0003-4819-150-10-200905190-00004
51. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. 2013;369:417–427. doi:10.1056/NEJMoa1213277
52. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363:211–220. doi:10.1056/NEJMoa0909169
53. Pagnoux C, Quemeneur T, Ninet J, et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis Rheumatol*. 2015;67:1117–1127. doi:10.1002/art.39011
54. Jones RB, Hiemstra TF, Ballarin J, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. *Ann Rheumatic Dis*. 2019;78:399–405. doi:10.1136/annrheumdis-2018-214245
55. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. 2020;382:622–631. doi:10.1056/NEJMoa1803537
56. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384:599–609. doi:10.1056/NEJMoa2023386
57. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA*. 2021;325:2178–2187. doi:10.1001/jama.2021.6615
58. Furuta S, Nakagomi D, Kobayashi Y, et al. Reduced-dose versus high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: predefined 2-year follow-up study. *Ann Rheumatic Dis*. 2024;83:96–102. doi:10.1136/ard-2023-224343
59. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016;75:1583–1594. doi:10.1136/annrheumdis-2016-209133
60. Mendel A, Ennis D, Go E, et al. CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update. *J Rheumatol*. 2021;48:555–566. doi:10.3899/jrheum.200721
61. Ma Y, Han F, Chen L, et al. The impact of intravenous methylprednisolone pulses on renal survival in anti-neutrophil cytoplasmic antibody associated vasculitis with severe renal injury patients: a retrospective study. *BMC Nephrol*. 2017;18:381. doi:10.1186/s12882-017-0782-4
62. Chanouzas D, McGregor JAG, Nightingale P, et al. Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated vasculitis: a multi-center retrospective cohort study. *BMC Nephrol*. 2019;20:58. doi:10.1186/s12882-019-1226-0
63. Huang L, Zhong Y, Ooi JD, et al. The effect of pulse methylprednisolone induction therapy in Chinese patients with dialysis-dependent MPO-ANCA associated vasculitis. *Int Immunopharmacol*. 2019;76:105883. doi:10.1016/j.intimp.2019.105883
64. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. *Clin J Am Soc Nephrol*. 2012;7:240–247. doi:10.2215/CJN.05610611
65. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf*. 2016;15:457–465. doi:10.1517/14740338.2016.1140743
66. Smith RM, Jones RB, Specks U, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis*. 2020;79:1243–1249. doi:10.1136/annrheumdis-2019-216863
67. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis*. 2012;71:955–960. doi:10.1136/annrheumdis-2011-200477
68. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992;116:488–498. doi:10.7326/0003-4819-116-6-488
69. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis*. 2010;69:1036–1043. doi:10.1136/ard.2009.109389

70. Unizony S, Villarreal M, Miloslavsky EM, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann Rheumatic Dis*. 2016;75:1166–1169. doi:10.1136/annrheumdis-2015-208073
71. Jones RB, Furuta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis*. 2015;74:1178–1182. doi:10.1136/annrheumdis-2014-206404
72. Cortazar FB, Muhsin SA, Pendergraft WF, et al. Combination therapy with rituximab and cyclophosphamide for remission induction in ANCA vasculitis. *Kidney Int Rep*. 2018;3:394–402. doi:10.1016/j.ekir.2017.11.004
73. Gulati K, Edwards H, Prendecki M, et al. Combination treatment with rituximab, low-dose cyclophosphamide and plasma exchange for severe antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int*. 2021;100:1316–1324. doi:10.1016/j.kint.2021.08.025
74. Casal Moura M, Irazabal MV, Eirin A, et al. Efficacy of rituximab and plasma exchange in antineutrophil cytoplasmic antibody–associated vasculitis with severe kidney disease. *J Am Soc Nephrol*. 2020;31:2688–2704. doi:10.1681/ASN.2019111197
75. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Rheumatol*. 2021;73:1366–1383. doi:10.1002/art.41773
76. Han F, Liu G, Zhang X, et al. Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. *Am J Nephrol*. 2011;33:185–192. doi:10.1159/000324364
77. Faurschou M, Westman K, Rasmussen N, et al. Brief report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Rheum*. 2012;64:3472–3477. doi:10.1002/art.34547
78. Walsh M, Casian A, Flossmann O, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int*. 2013;84:397–402. doi:10.1038/ki.2013.131
79. Walsh M, Collister D, Zeng L, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ*;2022. e064604. doi:10.1136/bmj-2021-064604
80. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991;4:359–395. doi:10.1128/CMR.4.3.359
81. Xiao H, Dairaghi DJ, Powers JP, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol*. 2014;25:225–231. doi:10.1681/ASN.2013020143
82. Cortazar FB, Niles JL, Jayne DRW, et al. Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of Avacopan. *Kidney Int Rep*. 2023;8:860–870. doi:10.1016/j.ekir.2023.01.039
83. Geetha D, Dua A, Yue H, et al. Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. *Ann Rheumatic Dis*. 2024;83:223–232. doi:10.1136/ard-2023-224816
84. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010;304:2381–2388.
85. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014;371:1771–1780. doi:10.1056/NEJMoa1404231
86. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis*. 2017;76:1662–1668. doi:10.1136/annrheumdis-2017-211123
87. Charles P, Terrier B, Perrodeau É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, Phase III trial (MAINRITSAN2). *Ann Rheum Dis*. 2018;77:1143–1149. doi:10.1136/annrheumdis-2017-212878
88. Charles P, Perrodeau É, Samson M, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2020;173:179–187. doi:10.7326/M19-3827
89. Smith RM, Jones RB, Specks U, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. *Ann Rheumatic Dis*. 2023;82:937–944. doi:10.1136/ard-2022-223559
90. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med*. 2003;349:36–44. doi:10.1056/NEJMoa020286
91. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med*. 2008;359:2790–2803. doi:10.1056/NEJMoa0802311
92. Terrier B, Pagnoux C, Perrodeau É, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheumatic Dis*. 2018;77:1150–1156. doi:10.1136/annrheumdis-2017-212768
93. Tieu J, Smith R, Basu N, et al. Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. *Rheumatology*. 2020;59:e24–e32. doi:10.1093/rheumatology/kez640
94. Delestre F, Charles P, Karras A, et al. Rituximab as maintenance therapy for ANCA-associated vasculitides: pooled analysis and long-term outcome of 277 patients included in the MAINRITSAN trials. *Ann Rheumatic Dis*. 2024;83:233–241. doi:10.1136/ard-2023-224623
95. Chen M, Kallenberg CG. ANCA-associated vasculitides–advances in pathogenesis and treatment. *Nat Rev Rheumatol*. 2010;6:653–664. doi:10.1038/nrrheum.2010.158
96. Lin DW, Chang CC, Hsu YC, Lin CL. New insights into the treatment of glomerular diseases: when mechanisms become vivid. *Int J Mol Sci*. 2022;23. doi:10.3390/ijms23073525
97. Crickx E, Weill J-C, Reynaud C-A, Mahévas M. Anti-CD20–mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. *Kidney Int*. 2020;97:885–893. doi:10.1016/j.kint.2019.12.025
98. Chen DP, Aiello CP, McCoy D, et al. PRTN3 variant correlates with increased autoantigen levels and relapse risk in PR3-ANCA versus MPO-ANCA disease. *JCI Insight*. 2023;8.
99. Hilhorst M, Arndt F, Joseph Kemna M, et al. HLA-DPB1 as a risk factor for relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a cohort study. *Arthritis Rheumatol*. 2016;68:1721–1730. doi:10.1002/art.39620
100. Sanders JS, Stassen PM, van Rossum AP, Kallenberg CG, Stegeman CA. Risk factors for relapse in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: tools for treatment decisions? *Clin Exp Rheumatol*. 2004;22:S94–101.

101. Hong Y, Shi P, Liu X, et al. Distinction between MPO-ANCA and PR3-ANCA-associated glomerulonephritis in Chinese patients: a retrospective single-center study. *Clin Rheumatol*. 2019;38:1665–1673.
102. Samoreau C, Piccoli GB, Martin C, et al. Association between kinetic of anti-neutrophil cytoplasmic antibody (ANCA), renal survival and relapse risk in ANCA glomerulonephritis. *Nephrol Dial Transplant*. 2023;38:1192–1203. doi:10.1093/ndt/gfac240
103. McClure M, Jones RB. Treatment of relapses in ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. 2019;14:967–969. doi:10.2215/CJN.06250519
104. Neumann I. Immunosuppressive and glucocorticoid therapy for the treatment of ANCA-asssociated vasculitis. *Rheumatology*. 2020;59:iii60–iii7.