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Practical Management of ANCA-Associated Vasculitis: A Clinician's Perspective

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Keywords
ANCA-associated vasculitis · Clinical trials · Rituximab · Avacopan · Infection

Abstract
Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis can be a life-threatening condition, characterized by necrotizing inflammation of small blood vessels. Major organ involvement, most commonly kidney and lung disease, is associated with significant morbidity and mortality. Intensive early immunosuppressive therapy is the cornerstone of management and has transformed ANCA-associated vasculitis (AAV) into a chronic relapsing condition. Remission induction with tapering glucocorticoids in combination with cyclophosphamide or rituximab is the standard of care for severe disease. Avacopan, an oral C5aR1 antagonist, has been approved for remission induction and helps minimize glucocorticoid exposure. Plasma exchange should be considered for severe kidney or life-threatening disease. Lower dose glucocorticoid induction regimens can be used without compromising remission rates. Remission maintenance therapy is recommended, and rituximab is usually first line over azathioprine. Mycophenolate mofetil (MMF) or methotrexate with low-dose glucocorticoids are third-line options. Immunosuppression-associated infection risk remains a concern, both during acute presentations and in the long term, highlighted by the impact of rituximab on humoral immunity and vaccine response during the COVID-19 pandemic. There remains an ongoing need for therapies that induce rapid remission and optimize kidney recovery while minimizing infection risk. Clinical trials are evaluating newer therapeutic options. Due to increasing treatment options, management should be individualized, balancing effective immunosuppression against comorbidities and frailty.
Summary: This review focuses on the treatment decision pathways for clinicians and patients in the management of severe AAV (granulomatosis with polyangiitis and microscopic polyangiitis). Key clinical trials, predictors of outcome, novel therapeutics, and practical steps to mitigate infection risk are discussed. ***Key Messages:*** Immunosuppression regimens have been refined due to emerging evidence from clinical trials. Rituximab, avacopan, and reduced-dose glucocorticoid schedules have been the focus of recent studies. Infections and immunosuppression-induced immunodeficiency must be considered when determining individualized treatment.

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Plain Language Summary
This is a review article on the management of ANCA-associated vasculitis (AAV) aimed at clinicians. The focus is severe AAV (granulomatosis with polyangiitis and microscopic

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polyangiitis) with kidney involvement. Key clinical features and investigations are summarized, as well as data from clinical trials for remission induction and remission maintenance. In addition, novel therapeutics and management of infection risk are discussed. Our aim is to assist clinicians with an effective and safe approach to management of patients with this potentially life-threatening condition.

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Introduction

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of disorders characterized by pauci-immune perivascular neutrophilic inflammation with necrosis and thrombosis. They are associated with autoantibodies that target the neutrophil cytoplasmic proteases: proteinase 3 (PR3) or myeloperoxidase (MPO) [1]. ANCA-associated vasculitis (AAV) is the largest subgroup of small vessel vasculitis described in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature and predominantly affects small intraparenchymal arteries, arterioles, capillaries, and venules. AAV is subdivided into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [2]. EGPA is frequently considered separately due to key differences in pathogenesis, clinical phenotype, disease course, and treatment approach and is not the focus of this article.

AAV is a rare disease, although incidence is increasing due to better recognition, disease classification, and the availability of improved ANCA testing. There is an estimated incidence of 20 per million population per year and prevalence of 200–400 per million people in Europe and North America. GPA and MPA can occur at any age, but typically affect those over the age of 60 years, whereas EGPA tends to affect younger adults following a prodrome of adult-onset asthma. Geographical variation also occurs; GPA is more common in Northern Europe and Australia/New Zealand (further from the equator), whereas MPA is more common in Southern Europe and Asia. Overall, AAV is more common in Caucasians and affects males and females equally [3].

Summary of Pathogenesis

The understanding of AAV pathogenesis is continuing to evolve and predisposing genetic, epigenetic, environmental, and infectious factors have been described. B lymphocytes produce ANCAs; autoantibodies are directed against cytoplasmic antigens expressed in the primary granules of neutrophils and the lysosomes of monocytes. Neutrophils undergo "priming," displaying the target antigens PR3 or MPO on their surface membranes. ANCAs have epitope specificity for the antigens PR3 or MPO in most systemic presentations of disease and therefore bind to either PR3 or MPO leading to neutrophil activation. Together with aberrant T cell responses and complement activation, this results in a cascade of inflammation. ANCA-activated neutrophils generate C5a, which binds to C5a receptors on neutrophils leading to further priming. Neutrophil extracellular traps are released by ANCA-stimulated neutrophils and together with proinflammatory cytokines result in endothelial injury and damage to the vessel wall [3].

Clinical Syndromes

AAV can affect any organ, with kidney and lung as the most common major organs affected. Definitions of "severe disease" vary, so EULAR (European League Against Rheumatism) recently recommended defining disease as "organ/life-threatening" and "not organ/life-threatening" instead. Examples of organ/life-threatening manifestations include glomerulonephritis, pulmonary haemorrhage, and meningeal involvement. Non-organ/life-threatening manifestations include nasal and paranasal disease, skin involvement without ulceration and myositis [4]. The breadth of organ involvement is wide, and a low index of suspicion is required to make an early diagnosis. Summary of major organs systems and initial investigations are outlined in Table 1.

Extravascular granulomatous inflammation of the upper and lower respiratory tract is a characteristic of GPA. Kidney disease is frequent in both GPA and MPA (70–80%), but less common in EGPA. Patients with AAV frequently have symptoms of systemic inflammation, including fatigue, fever, weight loss, arthralgia, and myalgia. A prodromal phase of constitutional disturbance for several weeks or months often precedes clinical diagnosis [6].

Cocaine (with or without adulteration with levamisole), hydralazine, propylthiouracil, and minocycline can trigger small vessel vasculitis [7]. Both cocaine and levamisole may independently trigger the production of ANCA and mimic GPA with midline destructive nasal lesions. With increasing prevalence of cocaine use, urine toxicology should be performed on patients with midline destructive nasal lesions. In the absence of organ-threatening disease,

Table 1. Summary of key organ system features and investigations for vasculitis management key organ system features are informed by the BVAS [5]

Organ system	Features	Investigations	Indication
Constitutional	Myalgia, arthralgia, fever, weight loss	Full blood count	To assess for anaemia, thrombocythemia
		Urea and electrolytes (serum creatinine and eGFR)	To assess for kidney injury
Cutaneous	Gangrene, infarct, purpura, ulcer	Liver function tests	May be elevated with acute disease/ with treatment
		C-reactive protein	Often raised
Mucous membranes/ eyes	Mouth ulcers, proptosis, scleritis/ episcleritis, uveitis, retinal changes	ESR	Often raised
		Blood cultures	To exclude infection
		Procalcitonin	Often elevated with bacterial infection
ENT	Bloody nasal discharge, crusts, ulcers, subglottic stenosis, sensorineural/ conductive deafness, sinus disease	Autoimmune serology: ANCA, anti-GBM, Anti-dsDNA, ENA, C3, C4, rheumatoid factor	To identify "double-positive" ANCA and anti-GBM disease and exclude alternative diagnoses
		Troponin	To assess for potential cardiac involvement
Pulmonary	Pleurisy, pleural effusion, infiltrate, endobronchial involvement, alveolar haemorrhage, respiratory failure	Urinalysis	To assess for haematoproteinuria
		Urine albumin creatinine ratio/urine protein creatinine ratio	Quantify proteinuria (usually sub-nephrotic)
Cardiovascular	Ischaemic cardiac pain, cardiomyopathy, myocarditis, congestive cardiac failure	Urine toxicology	To detect cocaine use
		ECG	To assess for cardiac involvement
Abdominal	Peritonitis, bloody diarrhoea, ischaemic abdominal pain	CXR/CT chest	Patchy or diffuse alveolar shadowing, nodules, endobronchial stenoses, cavities may be present
		ECHO	To assess for cardiac dysfunction/ masses
Renal	Hypertension, proteinuria, haematuria, rise in creatinine	Cardiac MRI	To assess for myocarditis
		Bronchoscopy	Frank blood or haemosiderin-laden macrophages if pulmonary haemorrhage, to investigate for subglottic/endobronchial stenoses, to exclude infection
Nervous system	Cerebrovascular accident, meningeal disease, cranial nerve palsy, seizures, spinal cord lesion, mononeuritis multiplex, sensory peripheral neuropathy	Skin biopsy	To assess for vasculitic changes in patients with skin involvement
		Renal biopsy	For diagnosis of pauci-immune glomerulonephritis and to determine extent/chronicity of renal inflammation

MRI, magnetic resonance imaging; BVAS, Birmingham Vasculitis Activity Score.

cessation of cocaine and localized treatments are usually sufficient. However, immunosuppression may be warranted if there is evidence of ongoing ear, nose, and throat involvement or systemic vasculitis [8]. AAV induced by anti-thyroid medication is typically MPA with MPO-ANCA, but dual antibody positivity is frequent. Skin and musculoskeletal manifestations are common, and immunosuppression is often required to achieve remission [9]. Hydralazine-associated ANCA-GN usually exhibits overlapping clinical and pathological features of a mild immune complex GN resembling lupus nephritis. Most cases are MPO-ANCA positive and immunosuppression results in

similar outcomes to primary ANCA-associated glomerulonephritis (ANCA-associated GN) [10]. Minocycline-induced AAV typically presents with cutaneous features, but there may also be systemic involvement. All patients are positive for p-ANCA, and some are MPO-ANCA positive. Pathological findings are similar to polyarteritis nodosa. Symptoms usually resolve after discontinuation of minocycline, but immunosuppressive therapy may be required [11].

Diagnosis

A detailed clinical history is important to diagnose AAV. Symptoms together with ANCA status, biochemical markers, imaging, and histology should be used to determine diagnosis and disease severity and extent. The main differential diagnoses are infection and malignancy, which should be considered carefully as an incorrect diagnosis can result in inappropriate immunosuppression. Alternative or additional diagnoses and evaluation of medication adherence should be considered in cases of refractory disease. EULAR define refractory disease as unchanged or increased disease activity after 4 weeks of standard therapy, and a reduction in disease activity score of less than 50% [4]. It is important to recognize that vasculitis and infection can coexist and treating infection is vital, but concurrent treatment for vasculitis may also be required. The Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) are validated tools used in clinical trials that quantify disease activity and assess for accrued damage, respectively [5]. Early diagnosis of AAV is essential to reduce the risk of irreversible organ damage, particularly in the kidneys and lungs.

PR3-ANCA is usually associated with GPA (80%), whereas MPO-ANCA is usually present in MPA (60–70%) and EGPA (40%). Genetic polymorphisms in AAV associate more strongly with PR3/MPO ANCA subtype than with clinical phenotype, implicating ANCA in disease pathogenesis. Only half of patients with EGPA and localized forms of GPA test positive for ANCA, whereas kidney-limited vasculitis is rarely ANCA negative (<5%). ANCAs are usually immunoglobulin G (IgG). Enzyme-linked immunosorbent assay to detect the target antigen (PR3 or MPO) with high sensitivity and specificity is now the preferred method of ANCA testing. Indirect immunofluorescence is used second line, where ethanol fixation results in dissolution of primary granules and MPO attachment to the nuclear membrane resulting in a perinuclear pattern (p-ANCA), whereas PR3 remains distributed in a cytoplasmic pattern (c-ANCA). Atypical ANCAs, which are not directed against PR3 or MPO, can be present in other inflammatory and infective illnesses. In such cases, an atypical/p-ANCA indirect immunofluorescence staining pattern may occur with negative or only weakly positive PR3 and/or MPO enzyme-linked immunosorbent assay. Additional testing for anti-glomerular basement antibody (anti-GBM) is advisable, particularly in the context of pulmonary-renal syndrome. Patients who are "double positive" for both anti-GBM and ANCA display a severe lung and/or kidney phenotype with a tendency to relapse as with AAV, and a higher frequency of kidney failure and alveolar haemorrhage, as with anti-GBM disease [12].

Kidney Disease

Severity of kidney disease correlates with the development of end-stage kidney disease (ESKD) and mortality. A glomerular filtration rate (GFR) <50 mL/min/1.73 m^2 at diagnosis is associated with a 50% risk of death or ESKD at 5 years [13]. The EULAR guidelines recommend a kidney biopsy as the gold standard for establishing the diagnosis of ANCA-associated GN for both new diagnosis and suspected relapse [4]. The combination of kidney histology and baseline GFR is a better predictor of kidney outcome than GFR alone [14].

Kidney Histology

Histology shows necrotizing inflammation and fibrinoid necrosis in the walls of small and medium vessels. Light microscopy of kidney tissue typically shows an acute neutrophilic capillaritis, leading to the formation of cellular crescents from rupture of glomerular capillary loops, and accumulation of leucocytes including macrophages in Bowman's space and epithelial cell proliferation. There is a focal and segmental necrotizing crescentic GN and acute vascular lesions in vessels show neutrophils with leukocytoclastic features and vessel wall necrosis. Medullary angiitis may be present. An active tubulointerstitial nephritis frequently accompanies glomerular lesions. MPA and GPA often appear identical in the kidney by light microscopy. Granulomas are a feature of GPA although they occur in the respiratory tract and rarely in the kidney. Kidney lesions in EGPA tend to be milder than those seen in GPA or MPA. Untreated, a crescentic GN leads to glomerular sclerosis, interstitial fibrosis (IF), and tubular atrophy (TA) [15].

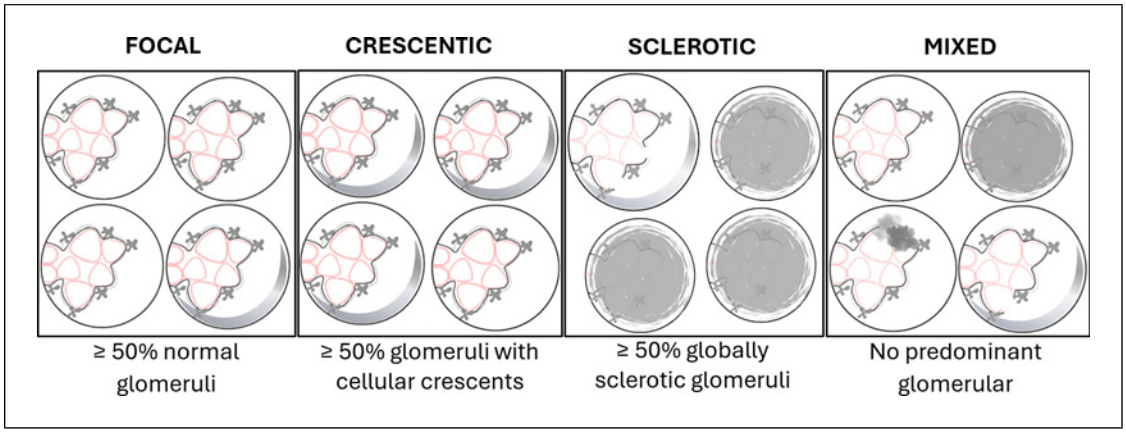


Fig. 1. Histopathologic classification of ANCA-associated glomerulonephritis. Adapted from Berden et al. [14].

Immunofluorescence microscopy does not identify any specific immunoglobulin deposition, hence the term "pauci-immune glomerulonephritis." However, complement components may be present focally and usually with crescents and are associated with poor renal outcomes. There are no significant electron-dense deposits on electron microscopy, but fibrin deposition is prominent. The "pauci-immune" feature differentiated the necrotizing crescentic GN in AAV from that seen in anti-GBM disease and subacute bacterial endocarditis, where typically immune complex deposition is observed [15].

The Berden classification was developed to classify ANCA-associated GN based on glomerular pathology by light microscopy. The Berden classification consists of four categories of lesions as demonstrated in Figure 1: focal, crescentic, sclerotic, and mixed. The percentage of normal glomeruli is a strong predictor of short- and long-term kidney outcome. A high percentage of globally sclerotic glomeruli and fibrous crescents are associated with adverse kidney outcomes. TA has also been identified as a risk factor for impaired kidney function. The degree of IF/TA suggests chronicity and indicates a poor kidney prognosis [14].

A kidney biopsy should not delay the initiation of treatment. Kidney histology may not be essential for diagnosis but can help with prognosis. Remission of kidney disease is not well-defined in the literature, but improvement and stabilization of serum creatinine with resolution of haematuria and reduction in proteinuria are key features supporting remission. Control of extrarenal disease and reduction in inflammatory markers may not correlate with ongoing kidney inflammation. Proteinuria may remain present due to chronic damage or ongoing inflammation [16]. Other pathologies and refractory disease should be considered if there is poor treatment response, and a repeat kidney biopsy may be indicated. Serum creatinine and urinalysis should be monitored to detect kidney relapse. Patients with MPO-ANCA and MPA typically have the worst kidney prognosis due to chronic damage [17].

The ANCA Renal Risk Score (ARRS) is a novel tool to predict ESKD in ANCA-associated kidney vasculitis. Histopathologic features were analysed in over 200 patients. As with other studies, the percentage of normal glomeruli was an independent inverse predictor for ESKD. Points were also given for the percentage of IF/TA and GFR at the time of diagnosis. The risk score was subdivided into three groups, low risk, intermediate risk, and high risk, and was found to predict the risk of ESKD with improved accuracy [18].

Lung Disease and Other Organ Involvement

Early recognition and treatment of AAV are paramount to prevent chronic lung disease. Computed tomography imaging of the chest is more sensitive than chest radiographs at differentiating AAV from infection. Pulmonary manifestations associated with GPA are necrotizing granulomatous inflammation (lung nodules and cavities) and tracheobronchial inflammation, whereas interstitial lung disease in a usual interstitial pneumonia pattern can occur in association with MPO-ANCA or MPA, and more often in patients who have a smoking history. Pulmonary capillaritis manifesting as diffuse alveolar haemorrhage can occur across the spectrum of AAV. In EGPA, adult-onset asthma and flitting pulmonary infiltrates occur [19]. The presence of

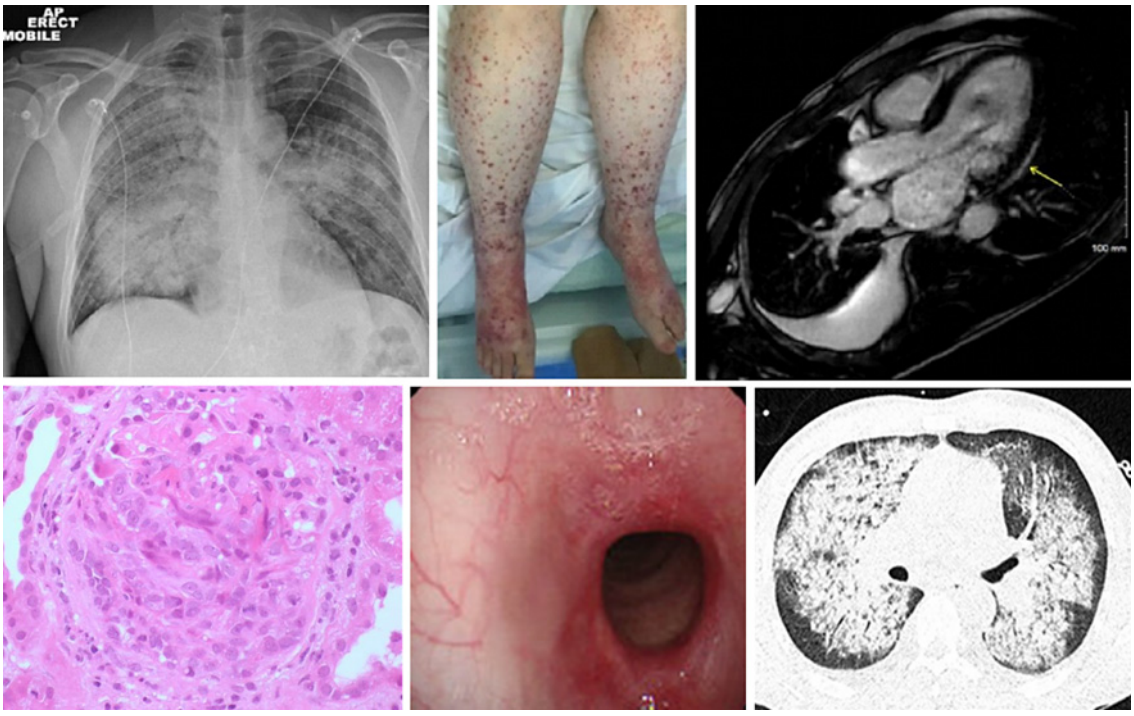


Fig. 2. Images illustrating features of AAV: alveolar haemorrhage on chest X-ray, non-blanching retiform purpuric rash, myocarditis with late gadolinium enhancement on cardiac MRI, cellular crescent on light microscopy of a kidney biopsy, subglottic stenosis on bronchoscopy, and alveolar haemorrhage with peripheral sparing on CT chest. CT, computed tomography; MRI, magnetic resonance imaging.

pulmonary involvement is a risk factor for mortality in AAV [20]. Alveolar haemorrhage and interstitial lung disease have the worst prognosis. Bronchoscopy with bronchoalveolar lavage is helpful for the diagnosis of alveolar haemorrhage and exclusion of infection. Repeated bronchoscopies with dilatation may be needed to treat subglottic or endobronchial stenoses [19].

AAV can also cause cardiac manifestations including myocarditis, pericarditis, inflammatory masses, and coronary artery disease (arteritis, thrombosis, dissection), which although rare can be life-threatening. Cardiac involvement appears to be more common in EGPA than other forms of AAV [21]. The prevalence of cardiac involvement is underestimated as symptoms are often attributed to atheromatous disease, and patients may be asymptomatic. All patients with acute severe AAV should have troponin tests. Electrocardiogram and echocardiogram are also required if cardiac involvement is suspected. Cardiac magnetic resonance imaging is the gold standard for detecting myocardial inflammation and risk stratification [22, 23].

Cutaneous and ear, nose, and throat manifestations are common, with features outlined in Table 1. Brain magnetic resonance imaging with contrast can detect pachymeningitis and retro-orbital lesions in GPA. Endoscopies are indicated if vasculitis of the gastrointestinal tract is suspected. F-18-Fluorodeoxyglucose positron emission tomography with computed tomography is not a diagnostic test for AAV but may detect occult sites of significant tissue inflammation in addition to excluding malignancy and infection. Figure 2 illustrates a variety of features that may be present in AAV.

Approach to Management

The treatment of AAV is based on the presence of non-organ threatening or organ/life-threatening disease. Two treatment phases characterize the management of ANCA-associated GN. An induction phase initially aims to rapidly reduce inflammation and decrease permanent damage including kidney scarring. Glucocorticoids or avacopan, with cyclophosphamide or rituximab are the main therapies used to induce remission in kidney AAV. Once the acute phase of the disease is in remission, then treatment is transitioned to a maintenance phase to

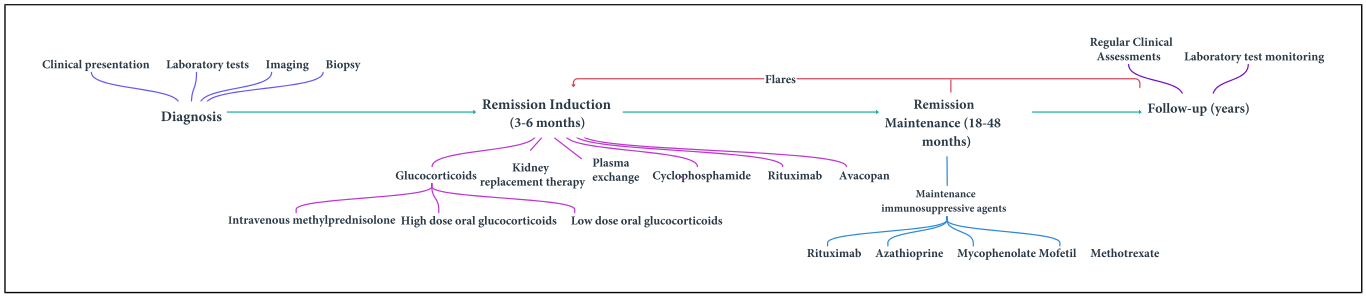


Fig. 3. The patient journey during the management of AAV.

prevent disease relapse, with rituximab usually first line over azathioprine. Most patients will recover some kidney function. Improvement and/or stabilization in kidney function has been shown to occur in approximately 70% of patients with an estimated GFR (eGFR) <20 mL/min/1.73 m^2 and those requiring dialysis at presentation have over a 50% chance of becoming dialysis independent within 6–12 months [24]. There are no definitive baseline clinical or histological criteria for treatment futility. Figure 3 outlines the patient journey during the management of AAV.

Factors that influence disease management include disease severity, frailty, comorbidities, and chronic disease-related damage. AAV is more frequently diagnosed in those over the age of 65 years. The Clinical Frailty Score (CFS) is a tool used to assess frailty, validated in those >65 years of age. A single centre cohort of patients over the age of 65 years with AAV demonstrated that age, frailty score, and CRP at presentation were independently associated with mortality [25]. Another cohort study of patients with AAV ≥65 years old showed that patients ≥75 years old had a higher incidence of death/ESKD and severe infections [26]. However, a meta-analysis has shown that patients ≥75 years old with AAV who receive induction immunosuppression had a significant survival benefit, indicating that age alone should not be a discriminating factor when considering treatment and a holistic patient approach is required when assessing a patient for treatment [27].

Immunosuppression, in particular glucocorticoids, is a significant risk factor for infectious complications as well as other adverse effects. Patients with comorbidities such as diabetes, hypertension, cataracts, and osteoporosis are more susceptible to glucocorticoid-related damage. A reduced-dose glucocorticoid regimen with a rapid taper or avacopan should be considered in these patients [28]. High cumulative doses of cyclophosphamide are associated with reduced fertility, in addition to an increased risk of malignancy (particularly bladder cancer) and bone marrow failure [29]. Rituximab can be used instead of cyclophosphamide or with low-dose cyclophosphamide, which significantly reduces cyclophosphamide toxicity. Patients with predominantly kidney-limited disease and a high proportion of IF/TA are unlikely to benefit from aggressive and prolonged immunosuppression and if they remain dialysis dependent. Therefore, individualized management of patients with AAV and shared decision-making between the patient and the physician is encouraged. Figure 4 summarizes the considerations for the management of AAV.

Remission Induction for Severe Disease

Rituximab and Cyclophosphamide

Rituximab, a B cell-depleting anti-CD20 monoclonal antibody, can be used in conjunction with or as an alternative to cyclophosphamide. Rituximab was compared to cyclophosphamide in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial, which enrolled patients with newly diagnosed or relapsing severe GPA or MPA; just over half had kidney involvement. Patients with severe lung haemorrhage and creatinine >4 mg/dL were excluded. Patients were randomized to receive either rituximab induction (4 × 375 mg/m^2 weekly) or oral daily cyclophosphamide for 3–6 months followed by azathioprine, and all patients received pulsed IV methylprednisolone followed by a high-dose glucocorticoid taper. Rituximab was non-inferior to cyclophosphamide for the primary endpoint of glucocorticoid free remission at 6 months and sustained remission at 18 months. Rituximab was more effective than cyclophosphamide for remission induction in the subgroups of patients with relapsing disease or PR3 ANCA positivity at trial entry. In patients with kidney involvement, improvement in GFR was similar between groups. Adverse events were similar

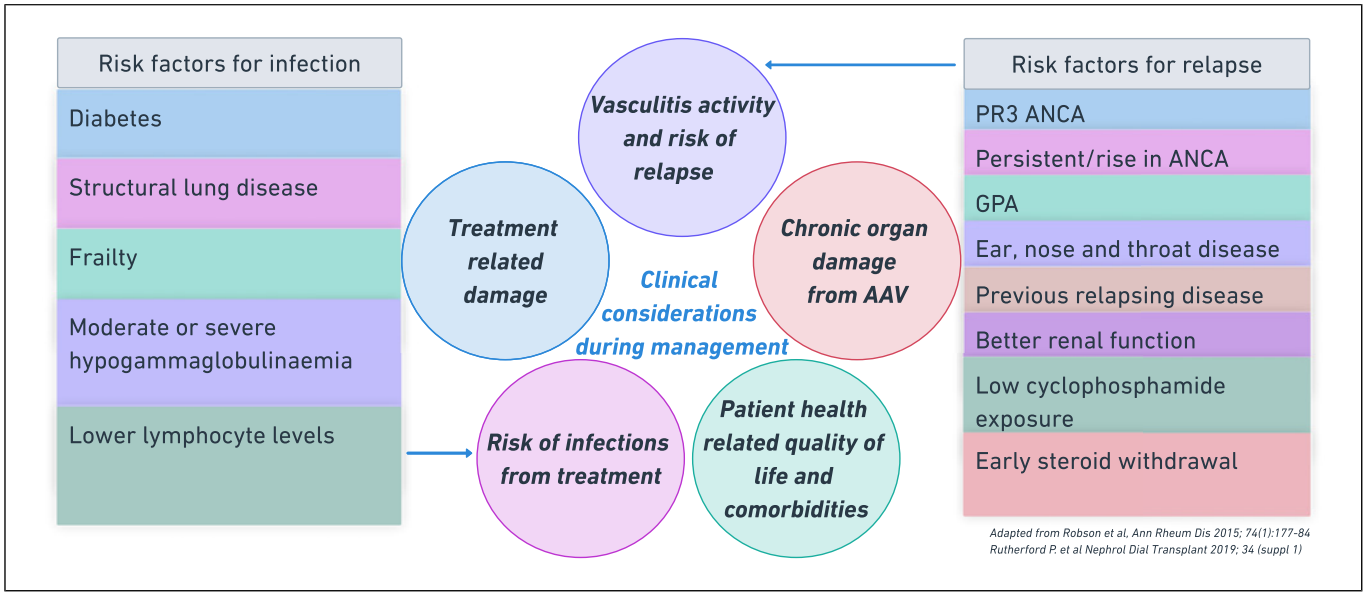


Fig. 4. Considerations during the management of AAV.

between the rituximab and cyclophosphamide groups [30].

Combination therapy with rituximab (4 × 375 mg/m^2) and low-dose cyclophosphamide (2–3 × IV doses) was associated with similar remission rates to a 6–10 IV dose cyclophosphamide course in the Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) trial. Patients with newly diagnosed severe kidney AAV (including dialysis dependence) received a high-dose glucocorticoid regimen plus rituximab (4 × 375 mg/m^2 weekly) with two intravenous pulses of cyclophosphamide for induction, or IV cyclophosphamide for 3–6 months followed by azathioprine. There was no difference in the rate of severe adverse events, infections, or relapses at 12 months, and both groups had a similar improvement in kidney function [31].

A cohort study comprising a treatment protocol (CycLowVas) consisting of rituximab, low-dose IV cyclophosphamide followed by maintenance azathioprine with tapering glucocorticoids has been studied over a median follow-up of 56 weeks in 66 patients. All patients achieved clinical remission within 6 weeks. In this study with median creatinine 205 μmol/L (creatinine >500 μmol/L or requirement for dialysis at initial presentation, and pulmonary haemorrhage were excluded) at 5 years' patient survival was 84%, and 95% of these patients were dialysis independent. Relapse rates were lower compared to previously published cohorts treated with only cyclophosphamide. Rituximab and cyclophosphamide may have a synergistic effect in enhancing tissue B-cell depletion [32].

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis has recommended that the combination of cyclophosphamide and rituximab can be considered if there is markedly reduced or rapidly declining GFR (serum creatinine > 354 μmol/L or 4g/dL). This combination may be associated with a lower glucocorticoid requirement which is desirable [17].

Remission Induction for Life-Threatening Disease

Plasma Exchange

Plasma exchange (PLEX) can be considered in severe presentations of AAV in combination with rituximab and/or cyclophosphamide and glucocorticoids. It is postulated that the rapid removal of ANCA by PLEX leads to earlier control of immunological activity. The use of PLEX in severe AAV remains controversial due to associated infection risk and only modest efficacy. Patients with a creatinine >500 μmol/L or severe alveolar haemorrhage with an oxygen requirement may gain the greatest benefit. PLEX can also be considered in patients with creatinine 300–500 μmol/L. There is a strong indication for PLEX in anti-GBM disease.

The Plasma Exchange for Renal Vasculitis (MEPEX) trial compared seven PLEXs to high-dose (3 × 1 g) methylprednisolone as adjunctive therapy for severe kidney vasculitis, creatinine >500 μmol/L. All patients received oral cyclophosphamide and a glucocorticoid taper. Patients who received PLEX were less likely to have ESKD at 3 months. However, there was no difference in survival at 1 year and a long-term analysis at 4 years after randomization found that there was no difference in the rates of ESKD or death between the two groups [33]. A post hoc analysis of dialysis-dependent patients treated with PLEX showed that the chance of dying from treatment was higher than dialysis independence, if severe TA and <2% normal glomeruli were present. This indicates that serum creatinine should not be the sole factor when deciding if PLEX is warranted [34].

The Plasma Exchange and Glucocorticoids for Treatment of Antineutrophil Cytoplasmic Antibody Associated Vasculitis (PEXIVAS) trial factorial design allowed comparisons of PLEX versus no PLEX as well as standard-dose versus reduced-dose oral glucocorticoid regimens. Patients with new or relapsing GPA or MPA, GFR <50 mL/min/1.73 m^2, or alveolar haemorrhage were included. All patients received induction therapy with cyclophosphamide or rituximab and IV methylprednisolone, with or without PLEX. Patients were followed for 7 years. PEXIVAS demonstrated that PLEX did not lower death or ESKD as a composite endpoint. PLEX is postulated to have an acute effect on the disease; therefore, a long-term follow-up may not be accurate when assessing efficacy [35]. A subsequent meta-analysis of nine randomized controlled trials showed that PLEX had no effect on all-cause mortality but was associated with reduction in the risk of ESKD at 12 months. In the PEXIVAS trial, PLEX was associated with an increased risk of serious infection, which should be considered when planning treatment for individual patients [36].

Glucocorticoids

The PEXIVAS study also showed that a reduced-dose oral glucocorticoid regimen was non-inferior to a standard-dose regimen with respect to both risk of death and ESKD but was associated with a lower risk of serious infections in the first year of treatment. However, a retrospective multicentre study comparing the reduced-dose glucocorticoid regimen with a standard regimen for severe flares showed that the reduced-dose had worse outcomes in patients with creatinine >300 μmol/L and with rituximab compared with cyclophosphamide in terms of risk of death, ESKD, and disease progression or relapse [37]. Methylprednisolone is commonly used but has not been formally tested in a randomized controlled trial.

The recently published Low-dose Glucocorticoid Vasculitis Induction Study (LoVAS) supports the use of a reduced-dose glucocorticoid regimen. Patients with newly diagnosed AAV, but without severe kidney disease or alveolar haemorrhage, were included. Patients were randomized to receive reduced-dose glucocorticoid plus rituximab or high-dose glucocorticoid plus rituximab. The reduced-dose glucocorticoid group was non-inferior for achieving remission at 6 months and there was a reduced rate of infections and serious adverse events in this group [38]. Figure 5 summarizes glucocorticoid dosing in the PEXIVAS and LoVAS trials.

Avacopan

Avacopan is a C5aR1 antagonist, administered orally, and is the first therapy to be developed with AAV as the primary indication. Two-phase two trials (CLEAR and CLASSIC) and one-phase three trials (ADVOCATE) demonstrated their efficacy as an alternative to glucocorticoids for remission induction [39–41]. A practice point in the KDIGO 2024 Clinical Practice Guideline has stated that avacopan can be used as an alternative to glucocorticoids for remission induction in combination with either rituximab or cyclophosphamide. Avacopan is effective at controlling disease and improving quality of life compared to glucocorticoids [17]. Avacopan is a high-cost therapy that is not yet available in all countries.

The ADVOCATE trial included patients with new or relapsing AAV and was assigned to receive avacopan or tapering oral prednisolone. All the patients received cyclophosphamide (followed by azathioprine) or rituximab induction. Key exclusion criteria were an eGFR <15 mL/min/1.73 m^2, alveolar haemorrhage requiring invasive ventilation, use of PLEX, and dual therapy with cyclophosphamide and rituximab. Avacopan was non-inferior to prednisolone in inducing clinical remission at 26 weeks, but superior in inducing sustained remission at 52 weeks. There was a greater and continued improvement in kidney function and albuminuria up to 12 months in the avacopan group. The differential effect on kidney function was greatest in those with the lowest baseline eGFR. There was also a decreased rate of glucocorticoid-related adverse effects; however, serious infection rates were similar [41]. There are no safety data beyond 1 year. AVACOSTAR is a phase 4 safety study,

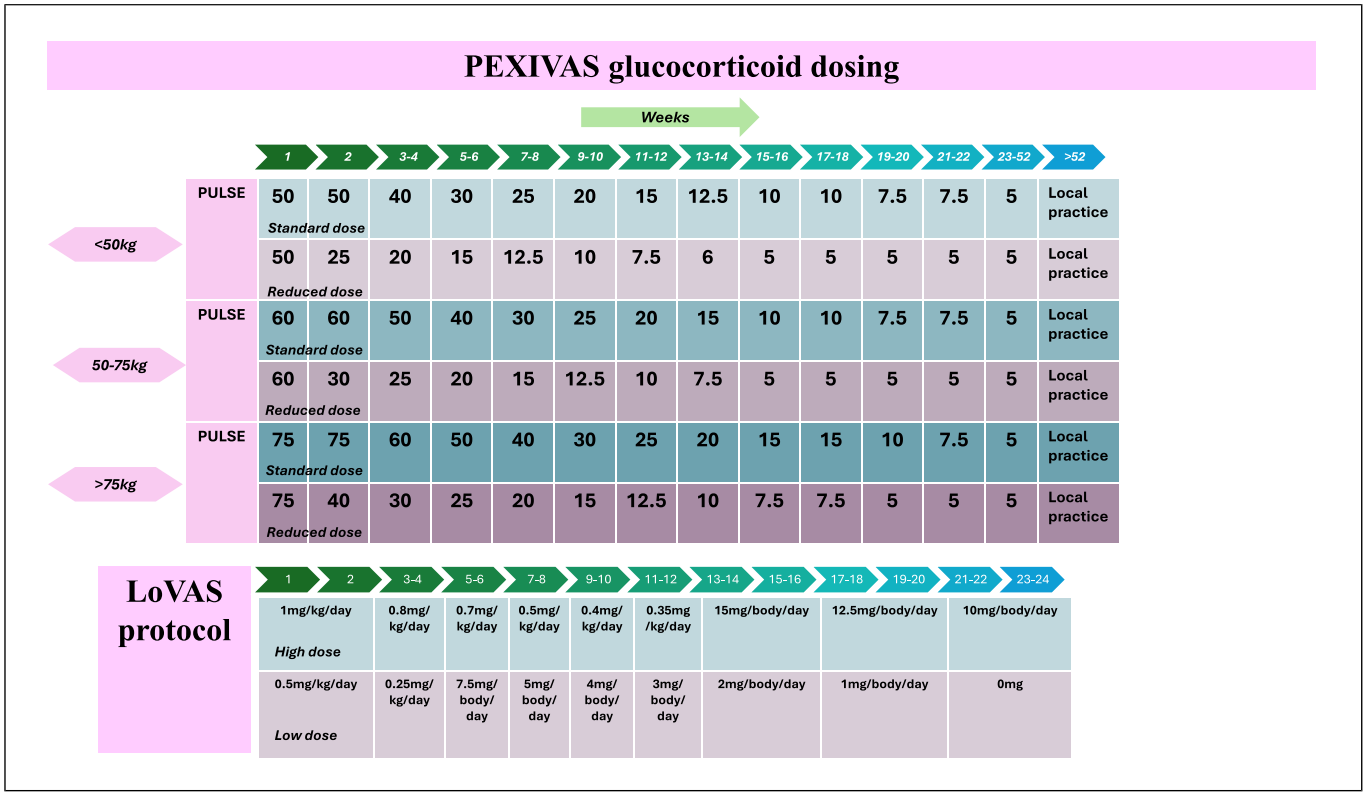


Fig. 5. Glucocorticoid dosing in the PEXIVAS and LoVAS trials [35, 38].

currently evaluating the long-term safety and efficacy of avocopan (NCT05897684). Based on the ADVOCATE trial data, the 2024 KDIGO AAV guidelines state that patients likely to gain greatest benefit from avacopan are those at high risk of glucocorticoid toxicity, or those with low GFR.

Remission Induction for Non-Severe Disease

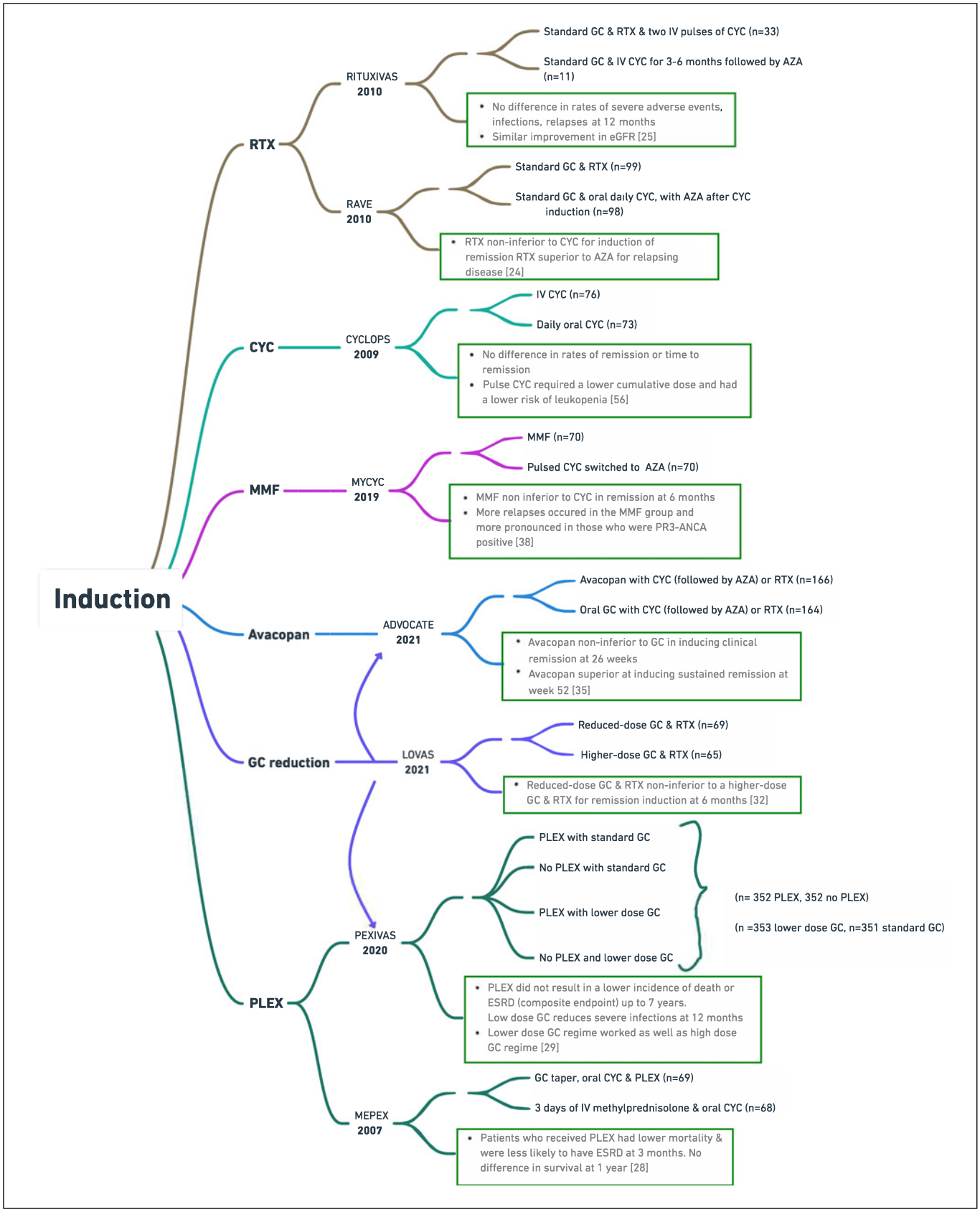
Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an alternative option for remission induction in non-severe AAV in combination with a high-dose glucocorticoid tapering regimen. MMF is associated with a high relapse risk so should only be considered for non-severe MPO-ANCA patients with low relapse risk [42]. Methotrexate is comparable to cyclophosphamide for remission induction for non-severe AAV, but again is associated with a high subsequent relapse risk and its toxicity prevents use in kidney impairment [43].

The Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC) study compared MMF to pulsed IV cyclophosphamide for remission induction in newly diagnosed GPA or MPA. All patients received the same high-dose glucocorticoid regimen and were switched to azathioprine following remission. Patients were excluded if they had life-threatening disease, rapidly declining kidney function or eGFR <15 mL/min/1.73 m^2. MMF was non-inferior to cyclophosphamide for remission induction at 6 months. However, following remission more relapses occurred in those who received MMF and were most frequent in those who were PR3-ANCA positive. Rates of serious infections were similar between groups [44].

Remission Maintenance

Maintenance immunosuppression is required to prevent relapses. Relapse is common and approximately 50% of patients will relapse by 5 years. The RAVE and RITUXVAS trials did not use remission maintenance therapy following rituximab induction. The relapse rates observed suggest that maintenance therapy after rituximab induction is required. In the RAVE trial, after a



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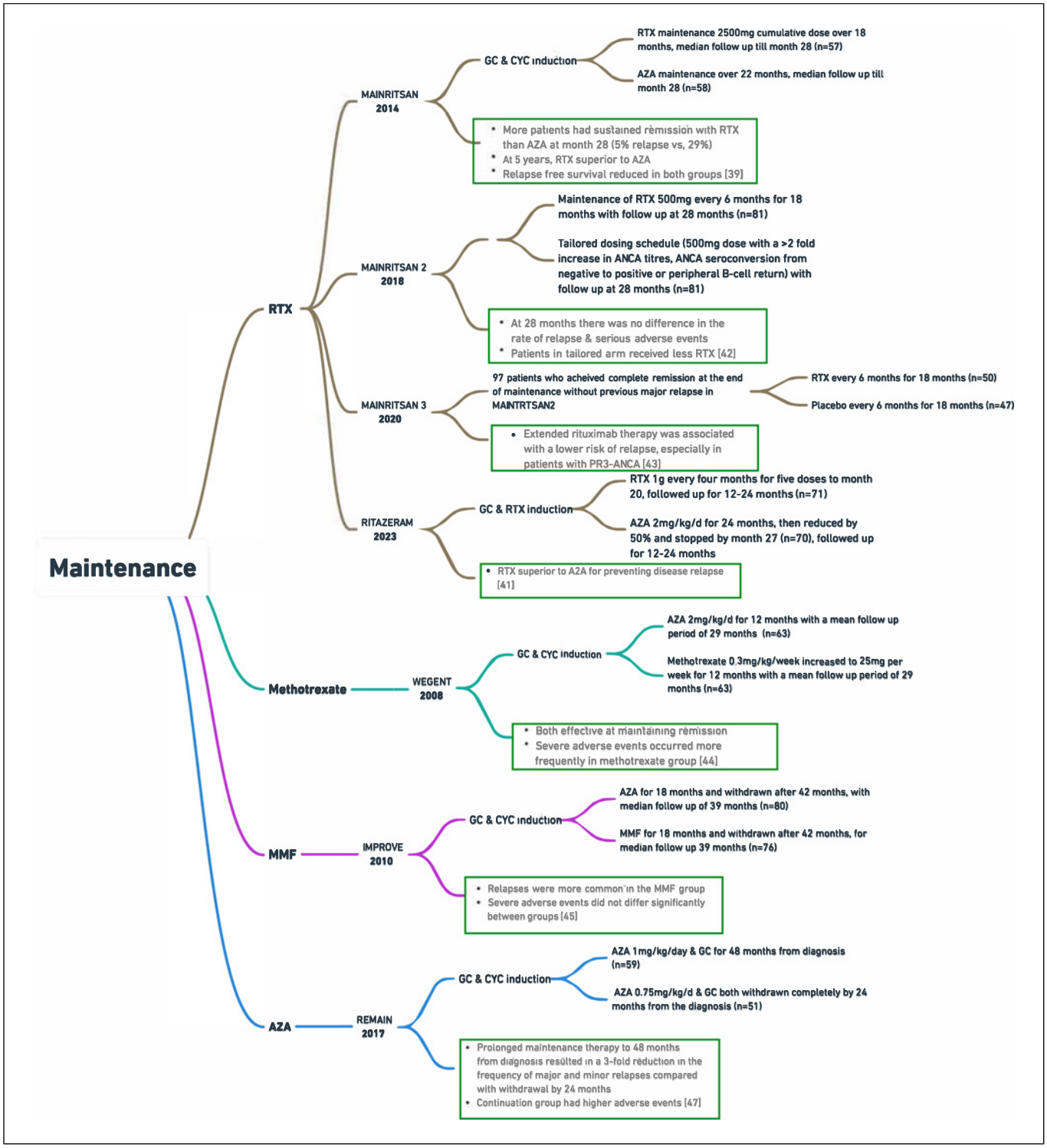

Fig. 6. Summary of main trials for remission induction and maintenance of AAV. CYC, cyclophosphamide; GC, glucocorticoids; ESRD, end-stage renal disease; PLEX, plasma exchange; MMF, mycophenolate mofetil; IV, intravenous; AZA, azathioprine; RTX, rituximab.

single course of rituximab, only 39% of patients were in remission at 18 months and in the RITUXVAS trial 21% of the rituximab group relapsed by 24 months [30, 31]. Patients with PR3-ANCA are at higher risk of relapse than those with MPO-ANCA. Persistent ANCA positivity, despite clinical remission, is associated with an increased relapse risk [45]. Fixed interval rituximab dosing is now recommended as maintenance treatment over azathioprine [46].

Rituximab has cemented its role as an agent for both induction and maintenance of remission in AAV. Rituximab can be used for remission maintenance in patients who have received either cyclophosphamide or rituximab for induction therapy. Methotrexate, MMF, and azathioprine are alternative options. Glucocorticoid tapering should occur as early as possible. The Assessment of Prednisolone in Remission Trial (TAPIR) randomized patients with GPA in remission to either 5 mg prednisolone daily or no prednisolone. There were more relapses (nearly all minor) in the group taking no prednisolone [NCT01933724]. Rituximab is also recommended for remission induction in relapsing disease, followed by rituximab re-dosing (500–1,000 mg) in fixed intervals for a period of 24–48 months.

Rituximab versus Azathioprine

The rituximab versus azathioprine for maintenance in ANCA-associated vasculitis study (MAINRITSAN) enrolled patients with newly diagnosed or relapsing GPA, MPA, or kidney-limited AAV in complete remission after a cyclophosphamide-glucocorticoid induction regimen. Patients received two 500 mg rituximab infusions followed by 500 mg infusions every 6 months until month 18 (cumulative dose 2,500 mg) or a tapering schedule of azathioprine for 22 months. There were fewer severe relapses with rituximab than azathioprine at month 28. Rituximab remained superior to azathioprine at 5 years, but relapse-free survival declined over this period in both groups. The frequency of adverse events was similar. This study concluded that rituximab was superior to azathioprine for remission maintenance; however, all the trial participants had received cyclophosphamide, rather than rituximab, for induction therapy [47].

Based on a retrospect cohort study indicating that 6 monthly dosing of rituximab in patients with relapsing and refractory AAV for a period of 24 months reduced relapses rates, the Rituximab Vasculitis Maintenance (RITAZAREM) study was designed. This approach also enabled early withdrawal of immunosuppression and reduction or cessation of glucocorticoids. Because initial relapsing AAV cohort data found that some patients receiving 6 monthly rituximab relapsed early at 4–5 months, a fixed interval 4 monthly rituximab regimen was selected for the RITAZAREM trial [48].

RITAZAREM randomized patients with relapsing GPA or MPA, who all received rituximab and glucocorticoids for induction, to receive rituximab maintenance (cumulative dose 5,000 mg) or azathioprine. Rituximab was superior to azathioprine for preventing disease relapse [49].

The comparison study of two rituximab regimens in the Maintaining Remission of ANCA-Associated Vasculitis (MAINRITSAN 2) trial compared individually tailored or fixed-schedule rituximab re-infusion for remission maintenance. Patients with newly diagnosed or relapsing GPA or MPA were randomized to receive a fixed dose of rituximab or a tailored dosing schedule (500 mg dose with either a >2-fold increase in ANCA titres, ANCA seroconversion from negative to positive, or peripheral B-cell return). Rituximab was given until 18 months after randomization. At 28 months, there was no difference in the rate of relapse or serious adverse events, but patients in the tailored arm received less rituximab [46]. However, pooled data from MAINRITSAN 1 and 2 trials revealed that an 18-month fixed-schedule rituximab regimen was more effective at maintaining remission for up to 7 years than the tailored-schedule rituximab regimen [50] and is more feasible in clinical practice when frequent blood monitoring is not always reliably performed.

Methotrexate

The Wegener's Granulomatosis-Entretien (WEGENT) trial found that both methotrexate and azathioprine are effective at maintaining remission, but severe adverse events occurred more frequently in the methotrexate group [51].

Mycophenolate Mofetil

The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial compared MMF with azathioprine on the prevention of relapses in patients with AAV. Relapses were more common in the MMF group and severe adverse events did not differ significantly [52].

Immunosuppression Withdrawal

The optimal duration of maintenance immunosuppression is unknown, but current guidelines recommend therapy for between 18 months and 4 years after induction of remission [17].

Table 2. Summary of novel therapeutic agents under investigation for the treatment of AAV, detailing their mechanisms of action, associated clinical trials, planned enrolment, primary endpoints, and current outcomes

Therapeutic agent	Mechanism of action	Clinical trial	Planned enrolment	Primary endpoint	Outcome
Obinutuzumab	Type-II glycoengineered monoclonal antibody with increased CD20 binding affinity, promoting enhanced direct B-cell death	OBIVAS phase II (NCT05376319)	26	$CD19^+$ B cell depletion in nasal-associated lymphoid tissue (NALT) from baseline to week 26	Ongoing
Belimumab	Monoclonal antibody targeting BLyS (B lymphocyte stimulator), which is involved in promoting B-cell survival and inflammation in AAV	BREVAS phase III (NCT01663623)	105	Time to first protocol-specified event with belimumab + azathioprine maintenance remission vs. azathioprine alone	Did not reduce the risk of relapse
Rituximab + Belimumab	Combination therapy providing B-cell depletion with rituximab and BLyS inhibition with belimumab for dual-targeted immunotherapy	COMBIVAS phase II (NCT03967925)	36	Time to PR3 ANCA negativity in patients receiving combination therapy	Ongoing
Abatacept	Fusion protein that inhibits T-cell activation by binding to CD80/86 on antigen-presenting cells, blocking T-cell co-stimulation	ABROGATE phase III (NCT02108860)	20	Proportion of patients achieving sustained GC-free remission in relapsing non-severe GPA	Did not reduce the risk of relapses
Lixudebart (formerly ALE.F02)	Anti-Claudin 1 (CLDN1) monoclonal antibody targeting non-junctional CLDN1 overexpression associated with kidney fibrosis	RENAL-F02 phase II (NCT06047171)	80	Safety and tolerability of Lixudebart (formerly ALE.F02)	Ongoing
Sparsentan	Dual endothelin receptor (ETA) and angiotensin II receptor (AT1) antagonist	SPARVASC phase II (NCT05630612)	32	Change in proteinuria	Ongoing
Hydroxychloroquine	Immunomodulatory agent that reduces inflammation and inhibits immune cell activation through lysosomal and Toll-like receptor inhibition	HAVEN phase IV (NCT04316494)	76	Change in BVAS in low-activity AAV	Ongoing
Telitacicept + RTX	Combination therapy of BAFF/APRIL dual-target inhibition and B-cell depletion to enhance suppression of autoreactive B-cell activity	Phase II (NCT05962840)	40	Time to first relapse	Ongoing
Vilobelimab	Anti-C5a monoclonal antibody that reduces inflammation and aims to lower glucocorticoid requirements by blocking C5a-driven immune activation	IXCHANGE phase II (NCT03895801)	57	Proportion of subjects achieving clinical response	Induced remission with RTX or CYC while significantly reducing the required dose of GCs

RTX, rituximab; CYC, cyclophosphamide; BAFF, B cell activating factor; APRIL, a proliferation-inducing ligand; BVAS, Birmingham Vasculitis Activity Score; GC, glucocorticoid.

The Comparison Between a Long Term and a Conventional Maintenance Treatment with Rituximab (MAINRITSAN 3) trial evaluated the efficacy of prolonged rituximab therapy in preventing AAV relapses in patients who were in remission after 18 months of maintenance rituximab infusions. Patients were randomized to receive rituximab or placebo infusion every 6 months for 18 months (four infusions). Extended rituximab therapy was associated with a lower risk of relapse, especially in patients with PR3-ANCA [53].

The Prolonged Remission-Maintenance therapy in systemic vasculitis study (REMAIN) compared two different durations of maintenance immunosuppression to prevent relapses in AAV. Patients with AAV who were in remission 18–24 months after diagnosis and had received cyclophosphamide/prednisolone induction treatment followed by azathioprine/prednisolone maintenance treatment were included. They either received azathioprine/prednisolone for 48 months from the diagnosis (continuation group) or withdrew azathioprine/prednisolone by 24 months from the diagnosis. The trial concluded that prolonged maintenance therapy with azathioprine and low-dose glucocorticoids resulted in a 3-fold reduction in the frequency of relapses compared with the withdrawal of treatment by 24 months. The continuation group had improved kidney survival and a reduced incidence of ESKD. ANCA positivity at randomization was associated with relapse risk. There was no difference in patient survival, but the continuation group had a higher frequency of adverse events [54]. Figure 6 is a summary of the main trials for remission induction and maintenance of AAV.

Refractory Disease

Current therapies have minimized the prevalence of refractory disease. Treatment options include increasing the dose of glucocorticoids and adding rituximab if cyclophosphamide induction had been used, and vice versa. PLEX and intravenous immunoglobulin therapy can also be considered. More evidence is needed to establish a treatment strategy for resistant disease [55].

Novel Therapeutics

Rituximab treatment depletes peripheral blood anti-CD20 B cells. However, tissue B-cell depletion with rituximab may be incomplete. Persistence of tissue B-cells may predispose to earlier relapse and strategies that enhance tissue B-cell depletion may be advantageous for early and sustained disease control.

Obinutuzumab is a type-II glycoengineered monoclonal antibody, which has a higher affinity for CD20 antigen binding and has increased direct cell death. ObiVas is a phase 2 experimental medicine study evaluating whether obinutuzumab can more effectively achieve tissue B-cell depletion that rituximab in PR3-positive patients (NCT05376319).

Belimumab is a human monoclonal antibody that targets BLyS (B lymphocyte stimulator protein), which is expressed by neutrophils. The Belimumab in Remission of Vasculitis (BREVAS) trial randomized AAV patients to receive azathioprine, low-dose glucocorticoids, and either intravenous belimumab or placebo, following remission induction with cyclophosphamide or rituximab with glucocorticoids. The conclusion was that belimumab plus azathioprine and glucocorticoids did not reduce the risk of relapse. All relapses in the belimumab group occurred in those who were PR3-ANCA positive and had received cyclophosphamide for induction of disease remission [57].

The Rituximab and Belimumab Combination Therapy in PR3 Vasculitis (COMBIVAS) trial is assessing rituximab and belimumab combination induction therapy in PR3 AAV. Dual B-cell targeted immunotherapy with B-cell depletion and BLyS blockade may be more efficacious than targeting either mechanism alone. BLyS levels rise after treatment with rituximab, and this may lead to autoreactive B-cell re-emergence and relapse. This study will assess B-cell depletion in lymph node biopsies and blood. Patients will receive rituximab and 3 months of glucocorticoids and belimumab or placebo for 12 months (NCT03967925).

T-cells interact with B-cells to enable the production of antibodies and are a potential therapeutic target. Abatacept is a fusion protein that inhibits T-cell co-stimulation by binding to CD80/86 on antigen-presenting cells. The Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis with Polyangiitis (ABROGATE) trial compared abatacept to placebo as add on therapy with a tapering prednisolone regime for minor GPA relapses. The addition of abatacept did not reduce the risk of relapses (NCT02108860).

Claudin-1 is a tetraspan-transmembrane protein, which is a component of tight junction complexes in parietal epithelial cells and endothelial cells. Non-junctional CLDN1 overexpression in crescents may drive the evolution of rapidly progressive glomerulonephritis [58]. The RENAL-F02 trial will assess if targeting CLDN1 with lixudebart, an anti-Claudin 1 (CLDN1) monoclonal

antibody, can halt the fibrotic process. Participants will receive lixudebart along with standard therapy for 6 months. The study will assess the change in eGFR and proteinuria, time to stable haematuria, incidence of kidney replacement therapy, and total glucocorticoid and immunosuppressive exposure (NCT06047171).

Other potential treatments being evaluated include sparsentan (NCT05630612) and hydroxychloroquine (NCT04316494) in those with low-level disease activity and there is an ongoing study on the combination of telitacicept (a BAFF/APRIL dual-target inhibitor) with rituximab (NCT05962840). A phase II study of vilobelimab, an anti-C5a monoclonal antibody, has demonstrated similar results to the standard of care for AAV, while reducing glucocorticoid use [59].

The range of potential novel therapeutics is promising; however, there is uncertainty about how to use them in combination with current treatments and outside clinical trial populations. Table 2 summarizes the novel therapeutics currently under investigation for the treatment of AAV.

Infection

Severe infections, largely due to immunosuppressive therapy, are the leading cause of death within the first year of diagnosis [60]. A post hoc analysis of the RAVE trial found that 68% of infections occurred within 6 months of treatment and over half of infections were respiratory in origin. In this study, low-dose co-trimoxazole resulted in a reduced risk of severe infections in patients treated with glucocorticoids with either rituximab or cyclophosphamide and azathioprine [61]. As evidenced by the PEXIVAS and LoVAS trials, a lower dose glucocorticoid protocol reduces severe infection risk [35, 38].

Repeated dosing with rituximab can cause hypogammaglobulinaemia, which increases the risk of infections. This is in part due to prolonged depletion of plasma cell precursors, which reduce replenishment of mature plasma cells. It is advised that serum immunoglobulin concentrations should be measured prior to each course of rituximab to detect secondary immunodeficiency. There is no universal IgG threshold for hypogammaglobulinaemia, but nadir IgG subgroups of 5 to <7g/L can be considered mild, 3 to <5g/L moderate, and <3g/L severe [62]. Discontinuation of further rituximab may be necessary in patients with IgG <5 g/L with a downward IgG trajectory and recurrent infections, while also considering disease severity and relapse risk. Immunoglobulin replacement may be required with moderate-to-severe hypogammaglobulinaemia if recurrent infection is present and can permit the ongoing use of rituximab for disease control if required. IgG replacement decreases the frequency and severity of infections, although prolonged IgG replacement is required in most patients. However, intravenous immunoglobulin may not mitigate disease-related airways damage and colonization of the respiratory tract that commonly contribute to chronic and recurrent infections in this patient population [63].

For individuals receiving induction immunosuppression, low-dose co-trimoxazole is advised for pneumocystis pneumonia prophylaxis. Influenza, pneumococcal, and SARS-CoV-2 vaccines are recommended in immunosuppressed patients, but vaccine response is blunted, which increases their risk of infection. Rituximab reduces the immune response following the influenza and pneumococcal vaccines [64]. The OCTAVE trial assessed SARS-CoV-2 vaccine responses in patients with chronic immune-mediated disease including those with AAV on rituximab. Vaccine failure rates (no generation of anti-spike antibodies) were high in this group, and they were more likely to have severe COVID-19 infection. Reduced seropositivity occurs if rituximab has been administered within 6 months prior to the vaccine [65]. Other studies have also confirmed severely reduced antibody titres in those receiving B-cell-depleting therapies. Glucocorticoids and MMF have also been associated with reduced antibody titres [66]. However, measurement of neutralizing antibodies is more accurate than absolute antibody titres to demonstrate functionality, along with T-cell response for protection.

Pre-exposure prophylactic therapies, over and above vaccination, are needed for patients on immunosuppression who have poor vaccine responses. The PROTECT-V trial is an international platform trial, testing multiple prophylactic agents against SARS-CoV-2 infection in vulnerable populations, including those with AAV. The results from the intranasal niclosamide arm have recently been published, and it does not reduce the risk of COVID-19 infection. High-dose sotrovimab (2,000 mg) is currently being evaluated (NCT04870333) [67].

Summary

AAV is a life-threatening condition with multi-organ involvement. Early diagnosis and prompt treatment are paramount to protect organ function and prevent long-term damage particularly in those with lung and kidney involvement.

For remission induction, cyclophosphamide or rituximab is the first line along with either a glucocorticoid-tapering regimen or more recently avacopan. In severe kidney disease, PLEX can be considered, in addition to combining rituximab with low-dose cyclophosphamide. The PEXIVAS reduced-dose glucocorticoid regimen is recommended for major organ disease and the low-dose (LoVAS) glucocorticoid regimen allows further glucocorticoid reductions for non-organ-threatening disease.

For remission maintenance, rituximab is recommended over azathioprine, particularly for PR3-ANCA vasculitis, but relapses occur after cessation of therapy, so ongoing monitoring is warranted. Rituximab is effective to induce remission in relapsing disease, but relapse prevention and early detection are key.

Infection risk poses a challenge to the management of patients with AAV. Rituximab causes hypogammaglobulinaemia, which increases the risk of infections. Strategies to optimize protection from infection while avoiding relapse risk from undertreating patients are important.

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