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Management of ANCA-associated Vasculitis

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Abstract

Background: Antibody-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a potentially life-threatening condition. Multi-organ involvement can occur and is associated with significant morbidity, particularly if there is lung and renal disease. Aggressive and early immunosuppressant therapy is the cornerstone of management and has transformed ANCA-associated vasculitis (AAV) into a chronic relapsing condition. Remission induction therapy typically consists of high dose glucocorticoids in combination with cyclophosphamide or rituximab or both for several months. Plasma exchange is recommended for life-threatening disease, although evidence is conflicting. Remission maintenance therapy is often continued for up to two years and usually consists of glucocorticoids, azathioprine or rituximab. Methotrexate and mycophenolate mofetil (MMF) can also be used. Rituximab has been the focus of clinical trials over the previous few years and has shown to be effective therapy for both remission induction and maintenance. There has also been a focus on reduction of glucocorticoids due to the risk of infections and other debilitating side-effects. There is an ongoing need for new therapies, particularly those with better safety-profiles than current medication. Avacopan, a C5a receptor inhibitor, has recently been approved by the European Medicines Agency and U.S Food and Drug Administration as a treatment option for AAV. The COVID-19 pandemic has added another layer of complexity to the management of AAV, and immunosuppression regimes have been altered especially with regards to timing of rituximab infusions, which reduces the effectiveness of the vaccines.

Summary: This review focuses on the management of AAV (GPA and MPA) and the key clinical trials are summarised.

Key messages: Immunosuppression regimes have been revised due to emerging evidence from clinical trials. Rituximab, avacopan and reduced-dose glucocorticoid schedules have been the focus of recent studies. The COVID-19 pandemic must be considered when determining immunosuppression regimes.

Keywords: ANCA-associated vasculitis • Clinical trials • COVID-19

Introduction

The antibody-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of disorders with severe and systemic small vessel vasculitis. They are characterised by granulomatous and neutrophilic inflammation and are typically associated with autoantibodies that target neutrophil antigens [1].

Literature Review

Classification

The vasculitides can be classified using the 2021 Revised International Chapel Hill Consensus Conference Nomenclature [2] (Figure 1).

Epidemiology

AAV is a rare disease with an estimated incidence of 20 per million population per year and prevalence of 200-400 per million people in Europe and North America. However, the incidence is increasing due to improved clinical recognition, disease classification and ANCA testing. GPA and MPA typically affects those over 60 years old, whereas EGPA patients tend to be younger. There is also geographical variation – 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].

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Clinical syndromes

AAV can affect any organ, although the respiratory tract and kidneys are the most commonly and severely affected. Patients with AAV typically share general features of systemic inflammation, which include fatigue, fever, weight loss, arthralgia and myalgia. A prodromal phase of constitutional disturbance for several months often precedes clinical presentation [3] (Table 1 and Figure 2).

The Birmingham vasculitis activity score (BVAS) is a validated clinical tool that quantifies disease activity in systemic vasculitis. It consists of nine sections – eight are organ-based and the ninth section is for systemic symptoms. A numerical score between 0-68 is calculated and is used to assess disease severity and response to treatment [4].

ANCA

ANCAs are autoantibodies directed against cytoplasmic antigens expressed in the primary granules of neutrophils and the lysosomes of monocytes. The relevant antigens in AAV are proteinase 3 (PR3) and myeloperoxidase (MPO). ANCAs are usually immunoglobulin G in the active stage of the disease. Indirect immunofluorescence assay (IIF) can be used as a screening test for ANCA. Ethanol fixation leads to dissolution of primary granules and MPO attaches to the nuclear membrane resulting in a perinuclear pattern (p-ANCA), whereas PR3 remains distributed in a cytoplasmic pattern (c-ANCA). Enzyme-linked immunosorbent assay (ELISA) can then confirm whether the target antigen is PR3 or MPO, which is currently the preferred method of ANCA testing [5].

PR3-ANCA is more commonly associated with GPA, whereas MPO-ANCA is usually present in MPA or EGPA. Only half of patients with EGPA and localised forms of GPA test positive for ANCA. Patients with renal-limited vasculitis are also likely to be ANCA negative. Atypical ANCAs, which are not directed against PR3 or MPO, can be present in other inflammatory and infective illnesses. They are usually p-ANCA and the anti-MPO and anti-PR3 assays are usually negative or low titre. If a patient has both anti-MPO and anti-PR3 antibodies this suggests

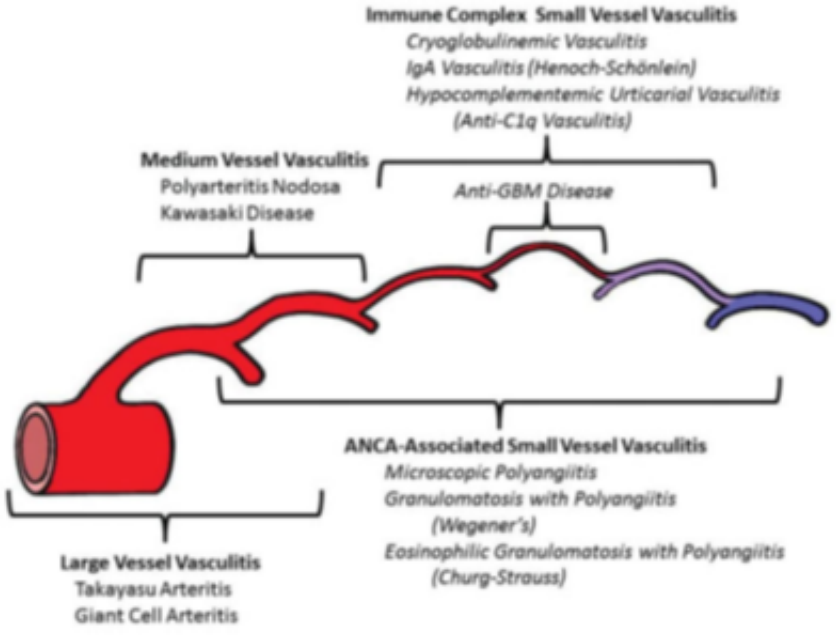

Figure 1. This diagram depicts the usual distribution of vessel involvement by the large, medium and small vessel vasculitides. Small vessel vasculitis encompasses ANCA-Associated Vasculitis (AAV) and immune complex vasculitis, and predominantly affects venules and capillaries. AAV is subdivided into Microscopic Polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Additional subgroups of the small vessel vasculitides have been identified as renal-limited ANCA-negative vasculitis and localised GPA ANCA-negative vasculitis [2].

Table 1. Syndrome and typical organ involvement.

Syndrome	Organ Involvement
GPA	nose, sinuses, lungs, kidneys, joints, eyes
MPA	kidneys
EGPA	lungs, upper airways, heart, peripheral nerves, skin

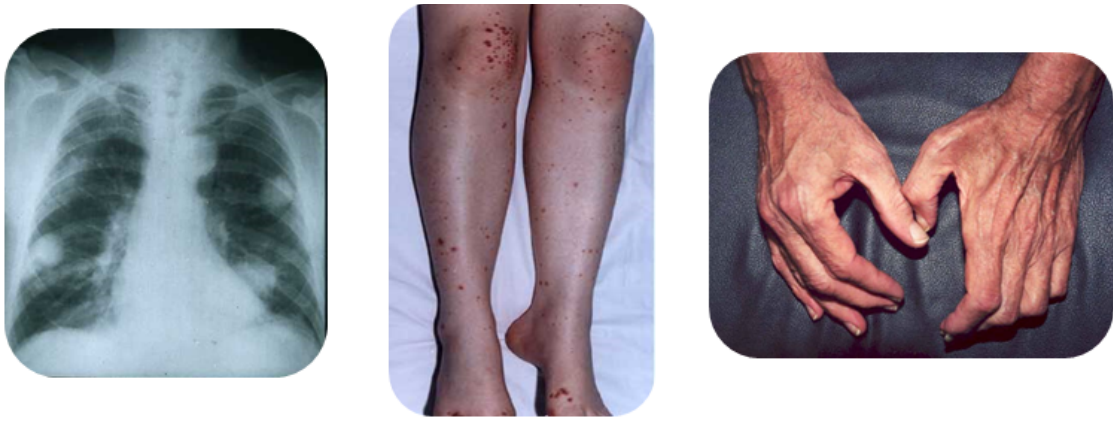

Figure 2. Images illustrating some features of AAV: Lung nodules, vasculitic rash, arthritic hand change.

drug-induced vasculitis. Cocaine adulterated with levamisole, hydralazine, propylthiouracil, minocycline and anti-tumour necrosis factor agents can cause small vessel vasculitis [5] (Table 2).

Pathogenesis

The pathogenesis of AAV is not fully understood, but genetic, environmental and infectious factors are implicated.

The majority of AAV patients have circulating ANCAs, which are thought to be pathogenic. Neutrophils are the main mediators of vessel injury and undergo a process called 'priming', displaying the target antigens MPO or PR3 on their surface membranes. ANCAs then bind to these autoantigens leading to neutrophil activation. The neutrophils bind to vascular endothelium and degranulation occurs. Neutrophil extracellular traps (NETs) are released by ANCA-stimulated neutrophils and contain PR3 and MPO, which are exposed to antigen presenting cells resulting in endothelial injury. ANCA-activated neutrophils stimulate B cells which lead to an increase in the production of ANCA. T cells, monocytes and macrophages are also involved in the pathogenesis of AAV.

Activation of the alternative complement pathway further propagates acute kidney injury. ANCA-activated neutrophils generate C5a, which binds to C5a receptors on neutrophils leading to priming. C5a also activates vascular endothelial cells leading to increased vascular permeability [3].

Renal pathology

The main pathogenic feature of AAV is necrotising inflammation and fibrinoid necrosis in the walls of small and medium vessels. Light microscopy of renal tissue typically shows a focal and segmental necrotising crescentic glomerulonephritis (GN). 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 the glomerular lesions. MPA and GPA often appear identical in the kidney by light microscopy. Granulomas are

a feature of GPA but occur in the respiratory tract and rarely in the kidney. Renal lesions in EGPA tend to be milder than those seen in GPA or MPA.

Immunofluorescence microscopy does not identify any specific immunoglobulin deposition, hence the term 'pauci-immune glomerulonephritis'. Complement components and fibrinogen may be present focally. There are no significant electron-dense deposits on electron microscopy, but fibrin deposition is often prominent [6] (Figure 3).

Early diagnosis of renal and lung disease

Early diagnosis of AAV is essential to reduce the risk of irreversible organ damage, particularly in the kidneys and lungs. Severity of renal disease correlates with the development of end-stage kidney disease (ESKD) and mortality. If the glomerular filtration rate (GFR) is <50ml/min at diagnosis there is a 50% risk of death or ESKD at 5 years [7].

The renal biopsy is the gold standard for establishing the diagnosis of ANCA-associated GN. The combination of renal histology and baseline GFR is a better predictor of renal outcome than GFR alone. The Berden classification was developed to classify ANCA-associated GN based on glomerular pathology by light microscopy. The classification consists of four categories of lesions: focal, crescentic, mixed and sclerotic. The biopsies in the focal category contain ≥50% normal glomeruli. The crescentic category contains biopsies with ≥50% of glomeruli with cellular crescents. Biopsies from the sclerotic category contain ≥50% of glomeruli with global sclerosis. The mixed category comprises biopsies that are not characterise by one predominant glomerular phenotype. The percentage of normal glomeruli is a strong predictor of short and long-term renal outcome. A high percentage of globally sclerotic glomeruli and fibrous crescents are associated with adverse renal outcomes. Tubular atrophy has also been identified as a risk factor for impaired renal function, but the relationship of vascular lesions with renal outcome is unclear [8] (Figures 4 and 5).

A renal biopsy should not delay the initiation of treatment, which will aim to preserve renal function regardless of GFR at presentation. Remission of kidney disease results in stabilisation or improvement of serum creatinine or resolution of haematuria. Proteinuria may remain present due to chronic damage. Serum creatinine and urinalysis should be monitored to detect renal relapse. Patients with MPO-ANCA and MPA typically have the worst renal prognosis due to chronic damage (glomerulosclerosis, interstitial fibrosis and tubular atrophy) [9].

Early recognition and treatment of AAV is also paramount to prevent chronic lung disease. The five main types are: necrotising granulomatous inflammation, tracheobronchial inflammation, pulmonary capillaritis manifesting as diffuse alveolar haemorrhage, interstitial lung disease (ILD) and asthma. Necrotising granulomatous inflammation and tracheobronchial inflammation are defining features of GPA, whereas ILD is primarily seen in patients with MPO-ANCA and MPA. Asthma is characteristic of EGPA. The presence of pulmonary involvement is a risk factor for mortality in AAV. Alveolar haemorrhage and interstitial lung disease have the worst prognosis [10] (Figure 6).

Table 2. Syndrome and association with ANCA.

Syndrome	PR3-ANCA (%)	MPO-ANCA (%)
GPA	80	10
MPA	30	60
EGPA	5	40

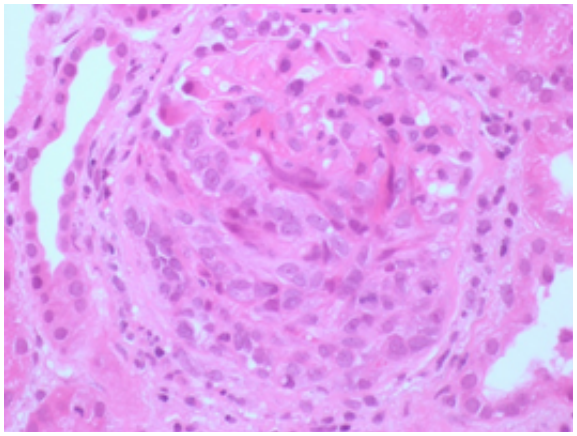

Figure 3. Light microscopy demonstrating a cellular crescent.

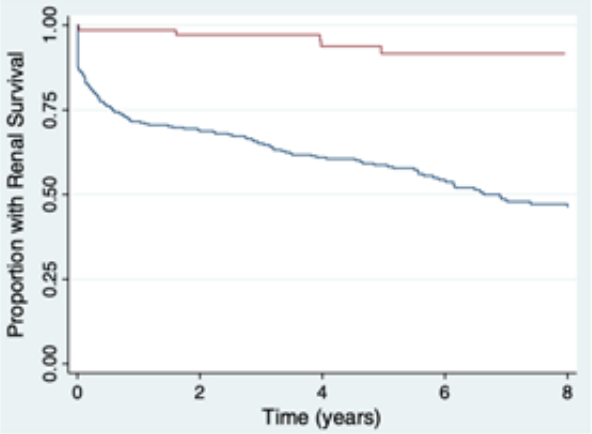

Figure 4. Graph illustrating renal survival depending on GFR at presentation.

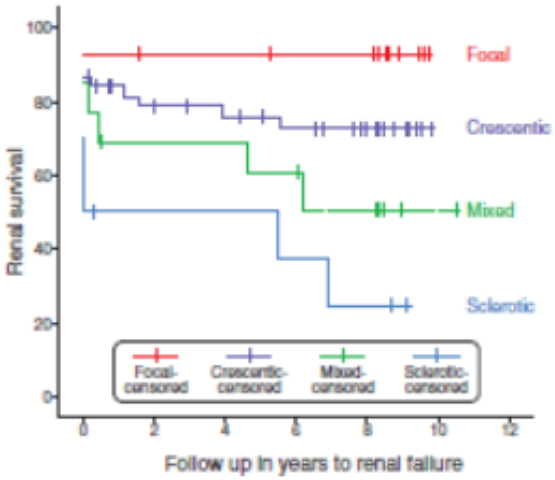

Figure 5. Graph illustrating renal survival based on Berden classification.

Treatment strategy

The management of AAV is determined by disease severity. Severe AAV encompasses organ or life-threatening disease, therefore patients with ANCA-associated GN are classified as having severe disease. The management of ANCA-associated GN consists of two treatment phases. An induction phase which aims to reduce inflammation and decrease renal scarring. Once the acute phase of the disease is in remission then treatment is transitioned to a maintenance phase to prevent disease relapses. Treatment should be offered to all patients with ANCA-associated GN regardless of the degree of renal injury as a significant proportion of patients recover renal function. Stabilisation or improvement in renal function has been shown to occur in approximately 70% of patients with a GFR <20ml/min and those requiring dialysis at presentation have over a 50% chance of becoming dialysis independent [11] (Figure 7).

Remission induction for severe disease

Glucocorticoids, cyclophosphamide and rituximab are the mainstay therapies that are used to induce remission for severe AAV. Rituximab is a newer addition and can be used in conjunction with or as an alternative to cyclophosphamide.

The Rituximab *vs.* Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial evaluated the use of rituximab for induction remission. This was a double blind, non-inferiority trial that enrolled 197 patients with newly diagnosed or relapsing severe ANCA positive GPA or MPA; 102 of these patients had kidney involvement. However, patients with a serum creatinine greater than 4.0mg/dL (354μmol/L) and those with diffuse alveolar haemorrhage requiring ventilatory support were excluded. Patients were randomised to receive either rituximab (four weekly 375mg/m² doses) or oral daily cyclophosphamide (2mg/kg/d – adjusted for renal function) for 3-6 months followed by azathioprine (2mg/kg/d). All patients received pulsed IV methylprednisolone followed by a 5.5 month steroid taper. The primary endpoint was complete remission (BVAS=0) and to be off steroids by 6

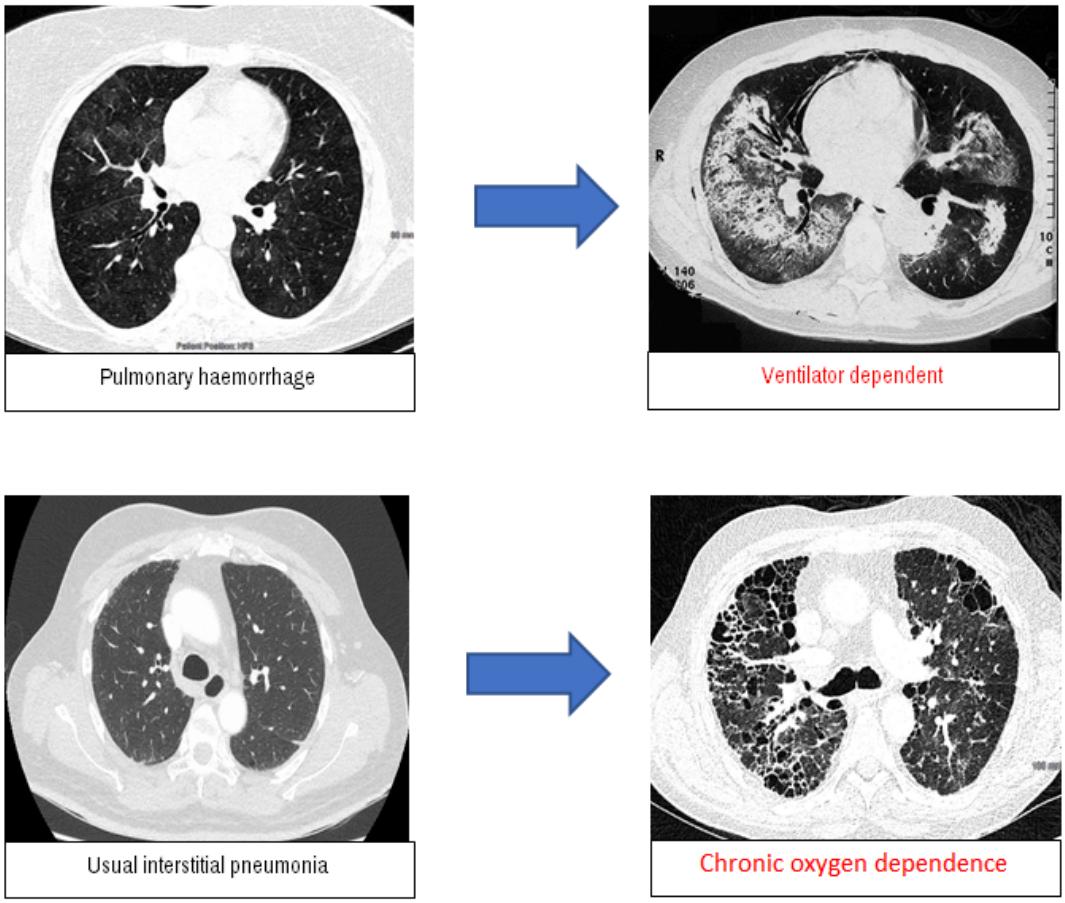

Figure 6. CT images showing progression of lung disease in AAV.

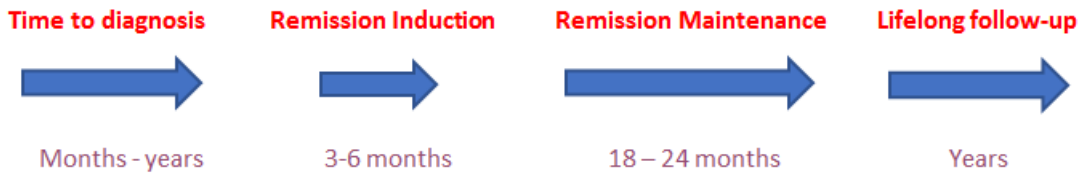

Figure 7. Timeline illustrating the different phases of AAV.

months. The primary outcome was reached by 64% of patients randomised to rituximab and 53% of those randomised to cyclophosphamide. Overall rituximab was non-inferior to cyclophosphamide at achieving the primary endpoint [12].

The Rituximab *vs.* Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trial evaluated combination therapy with cyclophosphamide and rituximab. A total of 44 patients, with newly diagnosed AAV, were randomly assigned in a 3:1 ratio to a standard glucocorticoid regime plus rituximab (four weekly 375mg/m² doses) and cyclophosphamide (15mg/kg for 2 doses), or intravenous cyclophosphamide for 3-6 months followed by azathioprine. Patients in the combination group did not receive any maintenance immunosuppression. In contrast to the RAVE trial, patients with severe renal involvement were included, but those with relapsing disease weren't. The primary endpoints were sustained remission at 12 months (BVAS=0 for 6 months) and severe adverse events. Severe adverse events included life-threatening events, events that required hospitalisation, cancer or death. 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 renal function based on eGFR [13].

Remission induction for life threatening disease

Plasma exchange (PLEX) is used in conjunction with rituximab, cyclophosphamide and steroids in patients with rapidly progressive GN, diffuse alveolar haemorrhage or both. It is postulated that the rapid removal of ANCAs by PLEX leads to earlier reversal of the immunological response and reduces organ damage.

The Plasma Exchange for Renal Vasculitis (MEPEX) study was a randomised trial of plasma exchange or high dose methylprednisolone as adjunctive therapy for severe renal vasculitis. MEPEX randomised 137 patients with severe renal disease (serum creatinine >5.7 mg/dL or on dialysis) to oral cyclophosphamide and a glucocorticoid taper with either 7 plasma exchanges or 3 days of pulsed methylprednisolone. Patients who received PLEX had lower mortality and were less likely to have end-stage renal disease (ESRD) at 3 months, but there was no difference in survival at 1 year. However, a post-hoc analysis 4 years after randomisation found that there was no difference in the rates of ESRD or death between the two groups [14].

The Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody – Associated Vasculitis (PEXIVAS) trial assessed both the efficacy of PLEX and a reduced-dose regimen of oral glucocorticoids in the management of severe AAV. This was a randomised trial with a 2-by-2 factorial design, which allowed separate evaluations of initial treatment with plasma exchange *vs.* no plasma exchange and of two different regimens of oral glucocorticoids. A total of 704 patients were randomised with new or relapsing GPA or MPA, GFR <50mL/min or diffuse alveolar haemorrhage. All patients received induction therapy with cyclophosphamide or rituximab, and IV methylprednisolone for 1 to 3 days. The primary endpoint was death from any cause or ESRD and patients were followed for up to 7 years [15].

This trial showed that PLEX did not result in a lower incidence of death or ESRD. However, a trend towards lower mortality was observed for the limited number of patients with severe alveolar haemorrhage (Figure 8).

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Figure 8. Glucocorticoid dosing in the PEXIVAS trial.

It is advised that PLEX should be used in severe presentations of AAV; if serum creatinine >500µmol/L or severe pulmonary haemorrhage, and should be considered for patients with serum creatinine 300-500µmol/L.

The PEXIVAS study also showed that reduced exposure to oral glucocorticoids was non-inferior to a standard-dose regimen with respect to both risk of death and ESRD. There was also a lower risk of serious infections in the first year of treatment. However, the reduced-dose glucocorticoid regimen had worse outcomes with rituximab compared with cyclophosphamide (Figure 9).

The recently published Low-dose Glucocorticoid Vasculitis Induction Study (LoVAS) study has also supported the use of a reduced-dose glucocorticoid regimen. This was phase 4, multicentre, open-label, randomised non-inferiority trial, which enrolled 140 patients with newly diagnosed AAV without severe renal disease (eGFR<15 ml/min/1,73m²) or alveolar haemorrhage. Patients were randomised to receive reduced-dose prednisolone (0.5mg/kg/d) plus rituximab (375mg/m²/wk, 4 doses) or high-dose prednisolone (1 mg/kg/d) plus rituximab. Reduced-dose glucocorticoid plus rituximab was non-inferior to a high-dose glucocorticoid plus rituximab regimen with regards to remission induction at 6 months, which was the primary end-point. There was also a reduced rate of infections and serious adverse events in this group [16].

Remission induction for non-severe disease

Mycophenolate mofetil (MMF) can be used for remission induction in AAV but is typically used in patients with non-severe disease. Methotrexate is comparable to cyclophosphamide for remission induction for non-severe AAV but its toxicity prevents use in renal impairment.

The Mycophenolate *vs.* Cyclophosphamide in ANCA Vasculitis (MYCYC) was the largest randomised controlled trial that investigated whether MMF was non-inferior to cyclophosphamide for remission induction in AAV. 140 patients with newly diagnosed GPA or MPA were randomly assigned to MMF (2g/d) or pulsed cyclophosphamide. All patients received the same oral glucocorticoid regime and were switched to azathioprine following remission. Patients were excluded if they had life-threatening disease, rapidly declining renal function or eGFR <15ml/min. The primary outcome was remission at 6 months. A similar proportion of patients in the MMF and cyclophosphamide groups achieved remission at 6 months, showing that MMF was non inferior to cyclophosphamide. However, following remission more relapses occurred in the MMF group and this was more pronounced in those who were PR3-ANCA positive. Serious infections were similar between groups. Based on this study, it is advised that MMF can be used to induce remission in those without severe disease and is probably more effective in those who are MPO-ANCA positive [17].

Steroid sparing combination approaches

Avacopan (CCX168) is a C5a receptor inhibitor, administered orally, and it

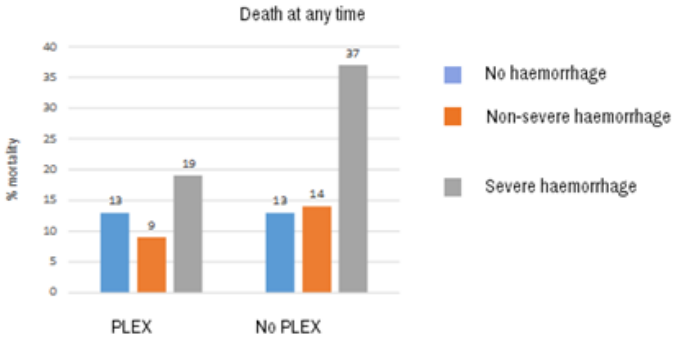

Figure 9. Graph illustrating reduced mortality with PLEX in severe pulmonary haemorrhage.

has been shown to be effective in the treatment of AAV alongside rituximab or cyclophosphamide and as an alternative to steroids.

The Study to Evaluate the Safety and Efficacy of CCX168 in Subjects With ANCA-Associated Vasculitis (CLEAR) was a phase 2 randomised placebo-controlled trial, which enrolled 67 patients with newly diagnosed or relapsing AAV (non-severe renal involvement) into 3 groups; receive placebo plus prednisolone starting at 60 mg daily (control group), avacopan (30mg twice daily) plus reduced-dose prednisolone (20 mg daily), or avacopan (30 mg twice daily) without prednisolone. All patients received rituximab or cyclophosphamide. Avacopan was non-inferior to the control group in achieving >50% decrease in BVAS and remission was achieved more quickly (BVAS=0). Additionally, albuminuria reduced earlier in both avacopan groups, and quality of life was improved compared with the control group [18].

The Clinical ANCA Vasculitis Safety and Efficacy Study of Inhibitor of C5aR (CLASSIC) trial was a randomised phase 2 double-blind, placebo-controlled three-arm study, which evaluated twice daily avacopan (10 mg or 30 mg) plus standard of care (rituximab or cyclophosphamide with high dose tapering glucocorticoids) with standard of care only. The study enrolled 42 patients with relapsing or newly diagnosed AAV. The primary end-point was the incidence of adverse events and the proportion of patients achieving disease response at day 85 (defined as a 50% or greater reduction of BVAS from baseline). The study found that the addition of avacopan at both doses appeared to be well tolerated and did not increase the rate of adverse events. There was no difference between the arms in disease response rates. Interestingly, the addition of avacopan (particularly 30mg) was associated with earlier remission, quicker improvement in eGFR and reduction in albuminuria, and improvement in quality of life, which is consistent with the CLEAR study [19].

Avacopan was also studied in a larger phase 3 randomised controlled trial; CCX168 in Patients with ANCA-Associated Vasculitis (ADVOCATE). A total of 331 patients with new or relapsing AAV were assigned to receive avacopan (30mg twice daily) or tapering oral prednisolone. All the patients received cyclophosphamide (followed by azathioprine) or rituximab. The first primary end point was remission (BVAS=0) at week 26 and no glucocorticoid use in the previous 4 weeks. The second primary end point was sustained remission, defined as remission at both weeks 26 and 52. Avacopan was non-inferior to prednisolone in inducing clinical remission at 26 weeks, but was superior in inducing sustained remission. There was a better improvement in eGFR at 26 and 52 weeks, with a reduction in albuminuria, in the avacopan group. There was also a decreased rate of glucocorticoid-related adverse effects, but the number of serious infections was similar in both groups [20].

Belimumab is a human monoclonal antibody against BLyS (B lymphocyte stimulator protein). BLyS is expressed by neutrophils, which are the key mediators of injury in AAV and elevated levels of circulating BLyS have been reported. Therefore, belimumab may be a potential therapy for AAV.

The ongoing Rituximab and Belimumab Combination Therapy in PR3 Vasculitis (COMBIVAS) trial (unpublished data) is a randomised, double-blind, controlled study of rituximab and belimumab combination therapy in PR3 AAV. Although B cell depletion with rituximab and treatment with glucocorticoids is effective at inducing remission in AAV, patients who are PR3-ANCA positive and those with the GPA subtype have a lower remission rate after this induction therapy. 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 subsequent relapse. This study will assess B cell depletion in both lymph node biopsies and blood. Patients will receive rituximab (2g) at days 8 and 22, 3 months of glucocorticoids and belimumab or placebo for 12 months. Patients who have a diagnosis of AAV (GPA or MPA), and only those who are PR3-ANCA positive will be included. Time to ANCA negativity will be measured.

Remission maintenance regimes

Relapse is common and approximately a third of patients will relapse by 18 months. Therefore, the use of maintenance immunosuppression is required to prevent relapses. Azathioprine was typically the standard of care for maintenance therapy, but more recently rituximab was found to be a superior. Methotrexate and mycophenolate mofetil can also be used.

Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN), an unblinded randomised controlled trial, enrolled 115 patients with newly diagnosed or relapsing GPA, MPA or renal-limited AAV in complete remission after a cyclophosphamide-glucocorticoid induction regime. Patients were assigned to receive either 500mg rituximab twice over 14 days followed by infusions every 6 months until month 18 or daily azathioprine for 22 months (tapering schedule of 2mg/kg initially, 1.5mg/kg at 12 months and 1mg/kg at 18 months). The primary end point was the rate of major relapse at month 28 (worsening disease reappearance or activity with BVAS>0, and involvement of ≥ 1 major organs disease-related life-threatening events or both). The conclusion was that more patients had sustained remission with rituximab than azathioprine at month 28 (only 5% had relapses compared to 29% in the azathioprine group). At 5 years, rituximab remained superior to azathioprine but relapse-free survival was reduced in both groups. The frequency of adverse events was similar in the two groups. A flaw in this study was that the dose of azathioprine was decreased whereas the rituximab dose remained unchanged throughout [21].

The Belimumab in Remission of VASculitis (BREVAS) trial was a double-blind placebo-controlled study which randomised 105 AAV patients to receive azathioprine (2mg/kg/d), low dose glucocorticoids (≤10mg/d) and either intravenous belimumab (10mg/kg) or placebo, following remission induction with cyclophosphamide or rituximab with glucocorticoids. The conclusion was that belimumab plus azathioprine and glucocorticoids for the maintenance of remission in AAV did not reduce the risk of relapse. Interestingly, all relapses in the belimumab group occurred in those who were PR3-ANCA positive and had received cyclophosphamide for disease remission [22].

The Wegener's Granulomatosis-Entretien (WEGENT) trial directly compared azathioprine and methotrexate as maintenance therapy. This was a prospective, open-label, multicentre trial. 126 patients with GPA or MPA who entered remission with IV cyclophosphamide and glucocorticoids were randomly assigned to oral azathioprine (2mg/kg/d) or methotrexate (0.3mg/kg/week, increased to 25mg/week) for 12 months. The primary end-point was an adverse event requiring discontinuation of the study drug or causing death. Both agents were found to be effective at maintaining remission, but severe adverse events surprisingly occurred more frequently in the methotrexate group [23].

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. This was an open-label randomised controlled trial, which enrolled 156 patients with newly diagnosed GPA or MPA, who had induction of remission with cyclophosphamide and prednisolone. Patients received either azathioprine (2mg/kg/d) or MMF (starting at 2000mg/d). Patients were followed up for a median of 39 months. Relapses were more common in the MMF group and severe adverse events did not differ significantly between groups [24].

A recent systematic review and meta-analysis of phase 2 and 3 trials assessed the use of MMF in for both remission induction and maintenance in GPA and MPA. Five phase 3 and five phase 2 trials; four assessing induction with MMF, three remission maintenance and three both. They concluded that MMF is significantly associated with higher sustained remission rates in trials enrolling only patients with kidney involvement. However, 92% proportion of remission maintenance in AAV patients with only kidney involvement was on the basis of two small single-arm trials with 28 patients in total [25].

Relapses after rituximab induction therapy

Studies have shown that rituximab-based induction regimens are effective at inducing sustained remission for up to 5 years.

The RAVE trial showed that rituximab remained non-inferior to cyclophosphamide followed by azathioprine maintenance therapy at 18 months at achieving sustained remission. Rituximab was more effective in those with relapsing disease and those who were PR3-ANCA positive. There was more B-cell depletion and a higher rate of ANCA seroconversion in the rituximab group, particularly those who were PR3-ANCA positive. In patients with renal involvement, there were similar rates of remission and improvement in GFR between the two groups at 6, 12 and 18 months. There was no significant difference in the rates of adverse events between the rituximab and cyclophosphamide groups [12].

A treatment protocol (CycLowVas) was adopted at West London Renal and Transplant Centre which consisted of rituximab (1g at day 0 and 14), low dose IV cyclophosphamide (6 pulses, no greater than 3.5g per patient episode) and maintenance azathioprine with tapering glucocorticoids (60mg prednisolone weaned to 10mg at week 13). An initial report of 23 patients showed that all had achieved clinical remission within 6 weeks. A cohort study of 66 patients (median Cr 205μmol/L, excluded severe renal disease and pulmonary haemorrhage) treated with this regime showed patient and renal survival were 84% and 95% respectively at 5 years. A total of 84% became ANCA negative and 57% remained B cell deplete at 2 years, which was associated with low rates of major relapse. Relapse rates were lower compared to previously published cohorts treated with only cyclophosphamide. Rituximab and cyclophosphamide could have a synergistic effect which enhances B cell elimination [26].

Immunosuppression withdrawal and relapse risk

The optimal duration of maintenance immunosuppression is unknown, but azathioprine and prednisolone treatment for more than 2 years from diagnosis results in a lower risk of relapse.

The Prolonged Remission-Maintenance therapy in systemic vasculitis study (REMAIN) was a prospective randomised trial, which compared two different durations of maintenance immunosuppression to prevent relapses in AAV. A total of 117 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 in the study. They either received azathioprine/prednisolone for 48 months from the diagnosis (continuation group) or withdrew azathioprine/prednisolone by 24 months from the diagnosis (withdrawal group). The primary end point was the relapse risk from randomisation to 48 months from diagnosis. The median creatinine was 116μmol/L. The trial concluded that prolonged maintenance therapy with azathioprine and low dose glucocorticoids to 48 months from diagnosis resulted in a 3-fold reduction in the frequency of major and minor relapses compared with withdrawal of azathioprine and glucocorticoids by 24 months. The continuation group had improved renal survival and a reduced incidence of ESRD. ANCA positivity at randomisation was associated with relapse risk. There was no difference in patient survival, but the continuation group had a higher frequency of adverse events [27] (Table 3).

Relapse management

Early diagnosis and management of AAV relapse is essential. Patients in remission require long term follow-up.

Non-severe GPA relapse

T cells interact with B cells to enable production of antibodies and are a potential therapeutic target in AAV. Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1). It inhibits T cell co-stimulation by binding to CD80/86 on antigen presenting cells. Abatacept is currently being studied as a steroid-sparing agent in non-severe relapsing GPA [3].

Table 3. AAV relapse risk factors.

Relapse Risk Factors
PR3 ANCA
Persistent/rise in ANCA
GPA
Ear, nose and throat disease
Relapsing disease
Better renal function
Low cyclophosphamide exposure
Early steroid withdrawal

The Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis with Polyangiitis (ABROGATE) trial is a multi-centre, randomised, double-blind, placebo-controlled trial, which will randomise patients with non-severe relapsing GPA to receive either abatacept 125 mg or placebo by subcutaneous injection weekly for a minimum of 12 months (unpublished data). Patients will be maintained on a stable dose of their maintenance immunosuppression, which could be methotrexate, MMF or azathioprine. They will also a receive prednisolone 30mg daily which will be tapered to zero. The primary outcome is the ability of abatacept to reduce the treatment failure rate – defined as relapse, disease worsening or failure to achieve BVAS ≤ 1 at 6 months.

Rituximab for severe relapse

The MAINRITSAN 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.

The Rituximab Vasculitis Maintenance Study (RITAZAREM) randomised 170 patients with relapsing GPA or MPA, who had received rituximab and glucocorticoids for induction, to receive rituximab 1g every four months or azathioprine (2mg/kg/d) as maintenance therapy. Rituximab was superior to azathioprine for preventing disease relapse [28].

This further supports the use of rituximab for remission maintenance, in patients who have received either cyclophosphamide or rituximab for induction therapy.

Rituximab maintenance strategies

Rituximab has cemented its role as an effective agent for both induction and maintenance of remission in AAV. However, the optimal dosing regime is unknown.

A retrospective study at a single centre analysed data from 73 patients receiving rituximab for refractory or relapsing AAV. Patients were divided into 3 groups: Group A received rituximab induction therapy (4 infusions of 375 mg/m² or 2 infusions of 1g) and further rituximab at the time of relapse. Group B patients received routine rituximab treatment for 2 years: 2 infusions of 1g for remission induction, then 1g every 6 months. Group C patients consisted of group A patients who relapsed and began routine re-treatment for 2 years. The study concluded that routine rituximab re-treatment was associated with a reduction in relapse rates compared to single doses of rituximab both during the 2-year treatment period and early following rituximab withdrawal. This regime also enabled early withdrawal of immunosuppression and reduction or cessation of glucocorticoids. ANCA or B counts were not found to be reliable in guiding repeat rituximab dosing. Six-monthly interval dosing for rituximab was used, as the average time to relapse post-rituximab is 6-12 months. After 24 months relapses occurred following rituximab withdrawal, but at lower rates and with a longer time to relapse than with group A patients. The proportion of severe infections was similar between groups [29].

The Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN 2) trial compared individually tailored or fixed-schedule rituximab re-infusion for remission maintenance. 162 patients with newly diagnosed or relapsing GPA or MPA were randomised to receive a fixed dose of rituximab (500mg every 6 months) or a tailored dosing schedule (500mg dose with 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 randomisation. 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 [30].

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. 68 patients were randomised 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 [31].

Relapse and infection after rituximab

A retrospective cohort study followed-up 69 AAV patients who had received fixed-interval repeat-dose rituximab maintenance therapy. Rituximab was also given at induction (2 infusions of 1g, or 4 infusions of 375mg/m²) followed by 1g every 6 months for 24 months. However, patients who were at high risk of relapse or severe flares had their maintenance therapy extended. Prednisolone dose was tapered during follow up, aiming for complete withdrawal or <5mg/day. The median follow-up period was 59.3 months. During the treatment protocol 9 patients relapsed but all patients were in remission at the end of the maintenance period and on a median prednisolone dose of 2.5mg/day. 28 patients relapsed after the last rituximab infusion at a median time interval of 34.4 months. The relapse rate was lower than after a single rituximab induction course. Risk factors for relapse were PR3-ANCA disease, return of B cells within 12 months of the last rituximab infusion and switching from ANCA negative to positive. This study concluded that fixed-interval repeat-dose rituximab for 2 years was an effective maintenance strategy. The majority of patients who relapsed were successfully re-treated with rituximab [32].

A study of 147 patients aimed to develop relapse and infection risk prediction models to help decide which patients require extended maintenance rituximab therapy beyond 2 years. Patients with a diagnosis of AAV who had received 4-8g rituximab between 2002-2018 were included in this study. The median follow-up period was 63 months after the last rituximab dose. Risk factors for relapse were ear, nose and throat involvement, ANCA positivity 12 months after rituximab, prior relapse, lower creatinine and lower prednisolone dose. B cell return within 12 months of rituximab was not associated with relapse. The presence of structural lung disease, diabetes, infections during rituximab treatment and hypogammaglobulinaemia at the end of rituximab were significantly associated with infection. However, this study recognises that due to the heterogeneity of AAV, relapse risk cannot often be accurately predicted [33].

Hypogammaglobulinaemia after rituximab

Rituximab commonly causes hypogammaglobulinaemia, which increases the risk of infections and therefore necessitates Immunoglobulin G (IgG) replacement. Low baseline immunoglobulin level, prior cyclophosphamide exposure and glucocorticoids are thought to be risk factors.

A retrospective single-centre study of 288 patients with autoimmune diseases, analysed the patients who were prescribed IgG infusions following rituximab. Over half of the patients (56%) had hypogammaglobulinaemia; it was non-sustained in 50% and moderate-severe in 25%. Twelve patients (4.2%) required IgG replacement due to recurrent infections. IgG replacement decreased the frequency and severity of infections. Normalisation of IgG concentrations occurred in two patients, but the duration of IgG replacement was prolonged in most of the patients [34].

AAV and Covid-19

Patients with AAV are thought to be more susceptible to severe Covid-19 (SARS-CoV-2) infection largely due to immunosuppression therapy. Vaccine response is also hindered in immunosuppressed patients further increasing their risk of infection.

The OCTAVE trial is a large multi-centre prospective study, which is assessing SARS-CoV-2 vaccine responses in patients with chronic immune-mediated disease including those with AAV (unpublished data). Preliminary data has revealed that 72% of patients with AAV (30 patients) who had received rituximab did not generate any antibodies. Reduced antibody response occurs if rituximab has been administered within 6 months prior to the vaccine. Other studies have also confirmed no antibody production or severely reduced titres in those receiving B-cell depleting therapies. Glucocorticoids have also been associated with reduced antibody titres.

Another prospective cohort study assessed SARS-Cov-2 antibody responses in those receiving immunosuppression for multisystem autoimmune disease (unpublished data). This study included over 100 patients who had received rituximab and confirmed that antibody titres were significantly lower in those who had received rituximab within 6 months prior to vaccination, compared to administration more than 12 months prior to vaccination. This study demonstrated a time dependent effect of rituximab on vaccine response.

Current advice is that the vaccine should be given 4 weeks or more before rituximab and maintenance rituximab therapy should be deferred beyond 6 months and ideally 12 months.

Prophylactic therapies are needed for patients on immunosuppression who have poor vaccine responses. The PROTECT-V trial is an ongoing double-blind placebo-controlled trial of prophylactic treatments against SARS-CoV-2 infection in vulnerable populations, including those with AAV. Prophylactic therapies that will be evaluated include niclosamide, ciclesonide and sotrovimab.

Summary

AAV is a life-threatening condition with multi-organ involvement. Early diagnosis and prompt treatment is paramount to protect organ function, particularly regarding the lungs and kidneys, which are most severely affected.

Remission induction

Cyclophosphamide or rituximab are first line along with high dose glucocorticoids. PLEX should be used for life-threatening disease. A combination of rituximab and cyclophosphamide with a quick steroid tapering regime can be considered.

Remission maintenance

Rituximab is superior to azathioprine, particularly for PR3-ANCA vasculitis, but relapses occur after cessation of therapy.

Relapse management

Rituximab is effective for severe relapsing disease, but prevention and early detection are key.

The Covid-19 pandemic has posed a challenge to the management of patients with AAV. Strategies are required to optimise protection from infection, whilst avoiding undertreating patients, which increases relapse risk.

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Conflict of Interest

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