

Evidence-based therapy for the ANCA-associated vasculitides: what do the trials show so far?

Anti-neutrophil cytoplasm antibody-associated vasculitides are rare multisystem inflammatory diseases including granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Previously these diseases were almost universally fatal, however, with current therapy 5-year survival for microscopic polyangiitis and granulomatosis with polyangiitis is approximately 80%. This review discusses the recent randomized controlled trials and other studies that have driven the improvement in survival and also highlights treatment-related morbidity and areas of unmet need in the management of anti-neutrophil cytoplasm antibody-associated vasculitides.

Keywords: ANCA • cyclophosphamide • eosinophilic • granulomatosis • microscopic • outcomes • rituximab • trials • vasculitis

The anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are autoimmune inflammatory conditions characterized by necrotizing inflammation of small- to medium-sized vessels, associated with the presence of ANCA. This group of diseases includes granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and its renal-limited variant and eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg–Strauss syndrome) [1].

The reported incidence of the AAV range between 10 and 20 patients per million, with GPA being more commonly seen in the North European population compared with MPA, which is more common in Southern European and Japanese populations; EGPA is the least common [2]. Cases have been reported in both pediatric and adult populations; however, the peak age of onset is 65–74 years in MPA and GPA [3]; patients with EGPA are often younger at presentation [4].

Classification of AAV

The Chapel Hill Consensus Conference (CHCC) in 1994 provided definitions for the

nomenclature of systemic vasculitides, and this was updated in 2012 [5,6]. With respect to AAV, there is little difference between the 1994 and 2012 CHCC definitions, other than the change from eponymous to non-eponymous names. The 2012 definitions for the AAV are given in Table 1. Although the CHCC definitions describe the disease phenotype there is evidence to suggest that classification based on ANCA antigen specificity may have more clinical relevance, particularly in predicting relapses, where PR3-ANCA positivity has been shown to have a strong predictive value [7].

The Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) is an ongoing international multicenter observational study, with the aim of devising diagnostic and classification criteria for AAV [8]. DCVAS is likely to finish recruitment of participants by December 2015. As yet, there exist no recognized diagnostic criteria for AAV.

ANCAs

ANCAs are directed against components of the azurophilic granules of neutrophils and monocyte lysosomes. ANCAs detected by

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Table 1. 2012 Chapel Hill Consensus Conference: definitions of anti-neutrophil cytoplasm antibody-associated vasculitis.

ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO ANCA or PR3 ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA-negative
Granulomatosis with polyangiitis (Wegener's)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present

ANCA: Anti-neutrophil cytoplasm antibody; MPO: Myeloperoxidase; PR3: Proteinase 3
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indirect immunofluorescence are categorized as either cytoplasmic (c-ANCA) or perinuclear (p-ANCA) according to the staining pattern. Confirmation of ANCA detection by ELISA provides information about the ANCA antigen specificity. ANCAs associated with AAV are usually specific for either proteinase-3 (PR3) [9] or myeloperoxidase (MPO), although other antigen specificities, including human lysosomal membrane protein 2, have been reported [10,11] and ANCA against other antigens have been reported in other inflammatory diseases. Different ANCA specificity has been associated with different AAV phenotypes, although there appears to be geographic or genetic variability in these associations as up to 60% of Chinese GPA patients were found to be MPO-ANCA-rather than PR3-ANCA-positive [12]. The utility of ANCA as a diagnostic marker depends on its detection in an appropriate clinical setting [13]. Table 2 shows the sensitivity and specificity of ANCA testing for GPA, MPA and EGPA [14]. The presence of these antibodies, although helpful, is not necessary for a diagnosis of AAV, which remains a clinical diagnosis [15,16]. Indeed, 10–30% of patients with pauci-immune crescentic glomerulonephritis lack ANCA [17], with a few studies suggesting that ANCAs may be a marker of more generalized vasculitic involvement [18,19]. There is a need for biomarkers that can reliably differentiate between active disease, infection and remission and can predict flares of disease activity before they become clinically apparent. A recent meta-analysis has demonstrated that changes in ANCA titre during follow-up are only moderately predictive of disease flares [20]. The utility of other biomarkers including circulating angiopoietin-2,

CXCL13, MMP-3 and TIMP-1 and urinary markers including MCP-1 have recently been investigated and although some show promise none have yet been validated as biomarkers of disease activity or relapse [21–23].

Pathophysiology of AAV

The last few decades have seen numerous studies investigating the pathophysiology of the AAV. Comprehensive reviews of the pathophysiology of MPA and GPA have previously been published (see [24–27]) and it is not the intention of the current authors to revisit those here, although it will be helpful to the reader to have an understanding of the basic pathophysiology as an introduction to the treatment of AAV. Although EGPA is also included in the group of AAV there is evidence that its pathogenic mechanisms differ from those observed in MPA and GPA.

Early *in vitro* experiments demonstrated ANCA were able to induce neutrophil oxidative burst and degranulation [28], although whether or not ANCAs have a pathological role in AAV has been the subject of much debate. Most authors now accept a pathological role for at least MPO-ANCA.

Xiao and colleagues provided *in vivo* evidence of the pathogenicity of MPO-ANCA in mice [29]. Following immunization with murine MPO, *MPO*^{-/-} mice developed MPO-ANCA. Transfer of splenocytes from these mice to *RAG2*^{-/-} mice or purified anti-MPO containing IgG to wild-type mice resulted in necrotizing vasculitis and glomerulonephritis. Various studies using this model have demonstrated that the disease process can be ameliorated by depleting neutrophils, blocking proinflammatory cytokines such as TNF α , inhibiting

Table 2. Sensitivity, specificity of anti-neutrophil cytoplasm antibody testing in granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (all as percentage)

	GPA			MPA			EGPA		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
c-ANCA	81.3	99.5	93.7	2.5	92.8	0.3	6.5	92.8	0.9
c-ANCA plus PR3-ANCA	69.0	99.8	97.4	0			6.5	94.2	1.1
p-ANCA	3.6	94	4.8	65.0	94.2	8.9	6.5	92.8	0.9
p-ANCA plus MPO-ANCA	1.8	99.3	17.5	47.5	99.5	47.5	4.3	99.2	5.0
ANCA positive by IFT	84.9	93.0	52.2	67.5	87.0	4.3	13.0	86.5	1.0
ANCA positive by IFT plus PR3/MPO-ANCA	70.3	99.1	87.1	47.5	93.7	6.1	10.9	93.4	1.6

ANCA: Anti-neutrophil cytoplasm antibody; c: cytoplasmic; EGPA: Eosinophilic granulomatosis with polyangiitis; GPA: Granulomatosis with polyangiitis; IFT: Indirect immunofluorescence; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; p: perinuclear; PR3: Proteinase 3
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plasma cell function and most recently by inhibiting the function of the complement component C5 [30–37].

Recently, human anti-PR3 was also shown to induce vasculitic changes in chimeric mice with a humanized immune system [38]. At present there are no animal models that replicate the granulomatous changes seen in human GPA, leading to speculation that elements of cellular immunity are also required in addition to ANCA for the development of GPA.

The processes that lead to the development of ANCAs are not fully understood. ANCAs are class-switched IgG antibodies, suggesting a requirement for T-cell help for their production and implying a breach of self-tolerance giving rise to autoreactive T and B cells. Previous studies have demonstrated persistent activation of T cells and abnormal B-cell phenotype in patients with MPA and GPA (reviewed in [39] and [40]). There is evidence of reduced number and function of regulatory T cells in patients with AAV, which may be related to the development of the autoimmune process, and recently there has been evidence to support a role for T-helper (Th) 17 cells in AAV [41–44]. T cells may also contribute to the development of tissue injury [45,46]. Recent studies have also identified polymorphisms in genes involved in the regulation of immune function that may be associated with the development of autoimmunity, including *PTPN22* and *CTLA-4* [47–50] as well as copy number variation in the *human β-defensin 2* gene [51]. Fc receptor genetic variants may alter the susceptibility to AAV and the way that ANCAs activate neutrophils and determine disease severity [52]. Different HLA associations with AAV have been described in different populations and also with different ANCA specificities and disease phenotypes [53–56]. Recently *HLA-DRB1*0405* was reported to be an independent predictor of poor responses to therapy and end-stage renal disease in Chinese patients with AAV [57].

Several environmental influences have been implicated in the development of these diseases including molecular mimicry between pathogenic organisms and human proteins and silica exposure driving inflammatory cytokine production and T-cell activation [58–60]. The immune response to *Staphylococcus aureus* may give rise to production of antibodies that recognize a peptide encoded by the complementary DNA strand to the *PR3* gene, with subsequent production of anti-idiotypic antibodies recognizing PR3 [61]. Anti-lysosomal-associated membrane protein 2 crossreacts with proteins on fimbriated bacteria and has been identified as a potential pathogenic autoantibody in AAV patients [62]. Infection may also contribute to the development of relapses as bacterial DNA CpG motifs can drive differentiation of plasma cells and production of ANCA via TLR 9 signaling in peripheral blood B cells taken from AAV patients in remission [63].

Our current model of tissue injury in MPA and GPA involves ANCA activating cytokine-primed circulating neutrophils resulting in adhesion to activated endothelial cells with subsequent neutrophil degranulation and endothelial tissue injury. Cytokines, such as TNF and IL-18 [64], as well as chemokines and adhesion molecules have been implicated in the priming, adhesion and transmigration of neutrophils across activated endothelial cells (reviewed in [65]). Furthermore, several studies have investigated the possible signaling pathways for ANCA-mediated neutrophil activation and production of a respiratory burst. A comprehensive review of these is beyond the scope of this article; these mechanisms have been extensively reviewed elsewhere [66–68].

Recently the role of complement activation in the pathogenesis of AAV has been highlighted with evidence that the complement component C5 in particular plays an important role in murine models and in human disease [34–35,69–71].

Studies into the pathogenesis of EGPA have highlighted differences to MPA and GPA. There is evidence that EGPA is a Th2-mediated disease with the presence of Th2 cells in tissue and the dominant production of IL-4, -5 and -13. Patients with EGPA are also noted to have increased production of IgE and IgG4 antibodies, although it is not clear if these are pathogenic. Regulatory T-cell dysfunction and Th17 cell activity are thought to play a role in the late vasculitic (rather than early asthmatic) phase of the disease.

Treatment of AAV

Prior to the introduction of cyclophosphamide and corticosteroid treatment, AAV had a 2-year survival of less than 20%, whereas current 5-year survival is approximately 80% [72–74]. Although most trials report remission rates of approximately 90–95%, relapse remains a significant problem with approximately 50% of patients experiencing a relapse within 5 years [75,76]. Although survival has greatly improved, there remain significant challenges in reducing treatment-associated morbidity and mortality, particularly due to infection. Infection, not disease activity, is the leading cause of death in the first year after diagnosis and contributes to approximately a third of deaths in longer term follow-up [77]. The aim of many of the clinical trials in the last few decades has been to reduce the exposure to cyclophosphamide, which was believed to be a significant contributor to the risk of infection. More recently there has been a focus on reducing the exposure to corticosteroids as a potentially significant risk for infection in the early treatment of AAV.

Classification of AAV severity

The European Vasculitis Study Group (EUVAS) provided a framework through which disease severity could be categorized for research purposes [78]. This has guided the development of clinical trials in the treatment of AAV and hence has also informed the evidence base for treatment in clinical practice. Table 3 demonstrates the EUVAS classification of AAV disease severity.

In 1996 the French Vasculitis Study Group (FVSG) devised the Five Factor Score (FFS) in order to evaluate

prognosis at diagnosis in a cohort of patients with MPA, EGPA and polyarteritis nodosa (PAN) [79]. This was revised in 2011 with the inclusion of GPA [80]. Older age (>65 years), cardiac involvement, gastrointestinal involvement and renal insufficiency were significantly associated with higher 5-year mortality, whereas upper respiratory tract involvement was associated with a lower relative risk of death.

The recently published British Society of Rheumatology/British Health Professionals in Rheumatology guidelines suggest that “All patients with AAV should be considered to have severe, potentially life- or organ-threatening disease,” and the only distinction should be between those with or without vital organ- or life-threatening disease (or serum creatinine >500 µmol/l) [81].

The treatment aims for AAV are to induce and then maintain disease remission using the minimum necessary immunosuppression appropriate to the severity of the disease.

Evidence-based treatment for MPA and GPA

The results of completed randomized controlled trials in AAV are summarized in Tables 4 & 5.

Although EUVAS defined localized disease as separate from early systemic disease recent guidelines suggest that all patients with localized disease be considered for treatment with methotrexate or cyclophosphamide in combination with corticosteroids [81].

Induction therapy in early systemic disease

Non-Renal Wegener's Alternatively Treated with Methotrexate (NORAM) was a randomized controlled non-inferiority trial comparing oral cyclophosphamide to methotrexate in early systemic disease. All patients received oral corticosteroids and were randomised to receive either cyclophosphamide or methotrexate. Treatment was for 12 months at which point all drugs were discontinued and follow-up continued for a further 6 months. The primary endpoint was remission induction within 6 months. Secondary endpoints were disease relapse and adverse events. NORAM demonstrated that methotrexate was as effective in inducing

Table 3. European Vasculitis Study Group Disease Severity Categories

Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any system, without organ-threatening or life threatening disease
Generalized	Renal or other organ-threatening disease, serum creatinine <500 µmol/l (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine >500 µmol/l (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

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Table 4. Completed randomized controlled trials in anti-neutrophil cytoplasm antibody-associated vasculitides – induction.

Treatment phase	Disease	Trial name	Protocol	Trial endpoints	Trial outcomes
Induction	Early systemic GPA and MPA	NORAM	Oral corticosteroid and randomized to cyclophosphamide or methotrexate for 12 months	Remission induction	89.8% of the methotrexate group achieved remission compared with 93.5% in the cyclophosphamide group at 6 months ($p = 0.041$)
Induction	Generalized MPA or GPA	CYCLOPS	Corticosteroid and randomized to daily oral or pulsed intravenous cyclophosphamide until 3 months after remission	Time to remission, cumulative cyclophosphamide dose	No difference in achieving remission (Hazard ratio: 1.098 [95% CI: 0.78 to 1.55]; $p = 0.59$). Cumulative dose of cyclophosphamide in daily oral group was 15.9 g versus 8.2 g in pulsed group ($p < 0.001$)
Induction	Generalized or severe MPA or GPA	RITUXVAS	Corticosteroids and randomized to intravenous cyclophosphamide followed by azathioprine or rituximab (with two cyclophosphamide pulses)	Sustained remission at 12 months, severe adverse events	76% of the rituximab arm achieved remission compared with 82% in the cyclophosphamide group ($p = 0.68$). 42% of the rituximab group compared with 36% in the control arm suffered adverse events ($p = 0.77$)
Induction	Generalized or severe (see exclusions) MPA or GPA	RAVE	Corticosteroids and randomized to oral cyclophosphamide followed by azathioprine or rituximab	Remission of disease achieved without further steroid therapy after 6 months of induction therapy	67% of the patients treated with rituximab compared with 42% in the daily oral cyclophosphamide group ($p = 0.01$) achieved remission of disease not requiring steroid therapy at 6 months
Induction	Severe MPA or GPA	MEPEX	Oral corticosteroids and cyclophosphamide and randomized to methylprednisolone or plasma exchange	Dialysis independence at 3 months	69% of those who received plasma exchange were dialysis-independent at 3 months compared with 49% in the methylprednisolone arm ($p = 0.02$)
Induction	Refractory MPA or GPA	Intravenous Immunoglobulin	Current immunosuppression (corticosteroids with either cyclophosphamide or azathioprine) and randomized to intravenous immunoglobulin or placebo	50% reduction of disease activity by assessment of Birmingham Vasculitis Score at 3 months	6 out of 17 in the placebo group compared with 14 out of 17 patients in the IVIG group achieved a reduction in disease activity at month 3 ($p = 0.015$). However, this response was not maintained beyond 3 months

GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis.

remission as cyclophosphamide. Methotrexate was associated with a longer time to remission in patients with lower respiratory tract disease or with a Disease Extent Index [82] score >10 and a significantly higher risk of relapse. Leukopenia was more common in patients treated with cyclophosphamide and liver dysfunction more common in patients treated with methotrexate. There was no difference in mortality between the trial limbs [83]. The long-term follow-up of this

trial was recently reported at a median of 6 years follow-up. This demonstrated that patients treated with methotrexate relapsed more quickly after discontinuing therapy than patients receiving cyclophosphamide; received corticosteroid treatment for longer; and, were more likely to receive other immunosuppressants, including azathioprine or mycophenolate mofetil, during follow-up. There were no significant differences in the rates of malignancy, organ failure and serious

infection between the two treatment groups [84].

Induction therapy in generalized disease

Until recently it was accepted that patients with generalized and more severe forms of MPA and GPA needed to receive cyclophosphamide as part of their remission induction regime. Originally given as an oral daily dose, cyclophosphamide can also be administered as an intermittent (pulsed) intravenous infusion regime, which is associated with a lower cumulative exposure to the drug. A meta-analysis of 11 retrospective non-randomized studies and three randomized controlled trials suggested that pulsed cyclophosphamide may be better at inducing disease remission and be associated with fewer infections but a possibly higher relapse rate than daily oral cyclophosphamide [85]. The Cyclophosphamide Daily Oral versus Pulsed (CYCLOPS) Trial, hypothesized that pulsed intravenous cyclophosphamide was not inferior to daily oral cyclophosphamide for remission induction in MPA and GPA with generalized systemic disease group. All patients received oral corticosteroids and were randomized to receive either daily oral or pulsed intravenous cyclophosphamide until 3 months after they achieved remission. All patients subsequently received azathioprine maintenance therapy. Patients who did not achieve remission within 9 months were considered treatment failures. There was no difference between the treatment arms in the time to achieve remission. Patients in the pulsed

cyclophosphamide arm received approximately half the cumulative dose of cyclophosphamide and had fewer episodes of leucopenia, but there were no significant differences in episodes of infection or other adverse events [86]. Long-term follow-up of CYCLOPS demonstrated that reduced exposure to cyclophosphamide was associated with an increased risk of relapse for patients treated with a pulsed regime, although there was no increased risk of renal failure or mortality [87].

Recently the monoclonal anti-CD20 antibody rituximab has been considered as an alternative to cyclophosphamide for disease remission induction for patients with generalized or severe disease. Following the publication of several encouraging case reports and series describing its use in MPA and GPA, two prospective randomized controlled trials were performed; An International, Randomized, Open-label Trial Comparing a Rituximab Based Regimen with a Standard Cyclophosphamide/Azathioprine Regimen in the Treatment of Active, "Generalized" AAV (RITUXIVAS) and Rituximab in ANCA-Associated Vasculitis (RAVE).

RITUXIVAS looked at the effectiveness of rituximab as a remission induction agent. Patients were eligible for inclusion with generalized or severe disease and could have 2 weeks of corticosteroid therapy, cyclophosphamide and plasma exchange before randomization. All patients received corticosteroids and were randomized to either pulsed intravenous cyclo-

Table 5. Completed randomised controlled trials in anti-neutrophil cytoplasm antibody-associated vasculitides – maintenance.

Treatment phase	Disease	Trial name	Protocol	Trial endpoints	Trial outcomes
Maintenance	Generalized MPA or GPA	CYCAZAREM	Corticosteroids with oral cyclophosphamide until remission then randomized to reduced-dose oral cyclophosphamide or azathioprine. After month 12 all receive azathioprine	Rate of relapse	The observed relapse rates were 15.5% in the azathioprine arm versus 13.7% in the long (12 months) course of cyclophosphamide arm ($p = 0.65$)
Maintenance	Generalized or severe GPA	WGET	Corticosteroids with cyclophosphamide or methotrexate and randomized to etanercept or placebo	Disease remission for at least 6 months	Sustained remission in 69.7% in the etanercept group vs 75.3% in the placebo arm ($p = 0.39$)
Maintenance	Generalized or severe MPA or GPA	WEGENT	Corticosteroids with pulsed cyclophosphamide then randomized to either azathioprine or methotrexate	Adverse event rate requiring cessation of study drug	7 patients in the azathioprine compared with 12 patients who received methotrexate achieved the primary endpoint ($p = 0.21$)
Maintenance	Generalized MPA or GPA	IMPROVE	Corticosteroids and cyclophosphamide then randomized to azathioprine or mycophenolate mofetil	Relapse-free survival	Mycophenolate was inferior to azathioprine as maintenance therapy, with an increased risk of relapse (hazard ratio of 1.69; 95% CI 1.06–2.70; $p = 0.03$)

GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis.

phosphamide for 6 months followed by azathioprine as maintenance therapy, or two initial pulses of cyclophosphamide and four weekly infusions of rituximab. The rituximab group did not receive any additional maintenance therapy except prednisolone. The primary endpoint was sustained remission for 6 months. Secondary outcomes included adverse events. There was no significant difference in the sustained remission rate between the two arms of the trial, indicating non-inferiority of rituximab (with two cyclophosphamide infusions) compared with pulsed intravenous cyclophosphamide. Interestingly, despite the significantly reduced exposure to cyclophosphamide there was no difference between the trial arms in the episodes of infection, suggesting that other factors, including the use of corticosteroids, may be primarily responsible for the high infection rates seen in vasculitis trials [88].

RAVE was a randomized double-blind, double-dummy placebo-controlled trial. Patients with new or relapsed, generalized or severe, MPA or GPA were eligible for inclusion but patients with pulmonary hemorrhage requiring mechanical ventilation or new-onset renal impairment with serum creatinine $>4\text{mg/dl}$ ($354\text{ }\mu\text{mol/l}$) were excluded. All patients received corticosteroids and were randomized to either daily oral cyclophosphamide for 3–6 months followed by azathioprine or four weekly infusions of rituximab. The primary outcome was clinical remission with withdrawal of prednisolone by 6 months. There was no significant difference in the primary outcome between the two treatment arms, indicating non-inferiority of rituximab compared with cyclophosphamide. As with the RITUXVAS trial there were no significant differences between the treatment groups in the incidence of adverse events, including infection [89]. At 18 months follow-up there was no difference between the treatment arms in the risk of relapse, infection or mortality although there were more episodes of leucopenia and pneumonia seen in patients receiving cyclophosphamide followed by azathioprine [90].

Mycophenolate mofetil is a relatively lymphocyte-specific immunosuppressant and has been considered as an alternative to cyclophosphamide for patients with AAV. A total of 35 patients with MPA or GPA and renal involvement with serum creatinine $<500\text{ }\mu\text{mol/l}$ were randomized to receive either mycophenolate mofetil or monthly pulsed intravenous cyclophosphamide in conjunction with corticosteroids. There was no significant difference between treatment arms in the primary outcome of remission rate at 6 months. The interpretation of the results of this trial is limited by the absence of a power calculation in the protocol and that nearly 25% (4/17) of the patients treated with cyclophosphamide were lost to follow-up before 6 months.

There was no difference between treatment arms in the adverse event rate [91].

As TNF was shown to have an important role in ANCA activation of neutrophils in human *in vitro* studies and in the development of glomerulonephritis in murine *in vivo* studies, there has been interest in the possibility of using TNF-blocking drugs to induce remission in AAV. To date, the utility of anti-TNF agents in disease remission induction has only been investigated in small open-label, uncontrolled or non-randomized studies. A small open-label prospective trial of 32 patients reported some benefit in the use of infliximab in remission induction and reduction of steroid requirements [92]. However, a further cohort study looking at the addition of infliximab to the standard therapy of corticosteroid and cyclophosphamide did not show any added benefit [93]. Adalimumab given in combination with corticosteroids and pulsed intravenous cyclophosphamide for patients with new or relapsed MPA or GPA with glomerulonephritis demonstrated improvement in disease activity scores and renal function consistent with previous trial outcomes with reduced corticosteroid exposure [94]. Etanercept given in combination with standard therapy was investigated for patients with relapsed or persistently active GPA in an open-label uncontrolled trial. There was a significant improvement in disease activity scores at 6 months and a non-significant reduction in prednisolone dose [95].

Induction therapy in severe disease

In the Methylprednisolone Versus Plasma Exchange as Additional Therapy for Severe ANCA-Associated Glomerulonephritis (MEPEX) trial patients with serum creatinine $>500\text{ }\mu\text{mol/l}$ (5.8 mg/dl) were randomized to either three 1 g methylprednisolone infusions on consecutive days or seven 60 ml/kg plasma exchange treatments within 14 days. All patients received daily oral cyclophosphamide for 6 months followed by azathioprine and a tapering dose of prednisolone. The primary outcome was dialysis independence at 3 months with a serum creatinine $<500\text{ }\mu\text{mol/l}$ (5.8 mg/dl). Plasma exchange was associated with significantly better renal recovery at 3 months (69 vs 49%) than methyl prednisolone and the difference was maintained at 12 months [96]. Recently published long-term outcome data from this trial have shown no difference between the trial limbs in survival, renal function or a composite outcome of death or dialysis dependence at a median of 3.95 years [97].

A recent retrospective non-controlled study showed that pulsed cyclophosphamide, plasma exchange and corticosteroids in severe life-threatening AAV are also associated with a favorable outcome (65% of patients alive with independent renal function at 1 year) when

compared with the MEPEX arm of oral cyclophosphamide, plasma exchange and corticosteroids (51%). Therefore, pulsed cyclophosphamide may be an effective and potentially preferable alternative to oral cyclophosphamide in severe disease [98].

A meta-analysis of nine trials involving 387 patients suggested a possible benefit of plasma exchange in reducing progression to end-stage renal disease; however, this conclusion is limited by its low study power (the combined study power required 1478 patients). The recommendation from the authors was for further trials to be conducted in this area [99].

Plasma Exchange and Glucocorticoid Dosing in the Treatment of AAV: an International Randomized Controlled Trial (PEXIVAS; ClinicalTrials.gov Identifier: NCT00987389) is an actively recruiting large, multicenter, randomized clinical trial. PEXIVAS is designed to answer two questions. Firstly, is plasma exchange associated with improved renal outcomes for patients with glomerulonephritis and secondly whether a reduced dose of prednisolone is associated with similar efficacy to standard dose prednisolone but with an improved adverse event rate.

Maintenance therapy

When cyclophosphamide was initially introduced for the treatment of AAV it was often given in high doses and for prolonged periods of time to induce and then maintain remission and was associated with high rates of infection, infertility and bladder cancer in long-term follow-up.

The Cyclophosphamide Versus Azathioprine for Early Remission Phase of Vasculitis (CYCAZAREM) trial investigated the efficacy of switching to azathioprine for maintenance therapy after inducing remission with a combination of oral prednisolone and cyclophosphamide in patients with a new diagnosis of generalized MPA or GPA who achieved remission within 6 months. All patients received oral cyclophosphamide and prednisolone until remission was achieved (minimum 3 months therapy, maximum 6 months) were then randomized to either continue a lower dose of oral cyclophosphamide or switch to oral azathioprine until month 12. From 12 months all patients were treated with oral prednisolone and azathioprine. The primary outcome was time to relapse following achieving remission. There was no difference between the trial limbs in the relapse rate or the adverse event rate indicating that azathioprine could be safely substituted for cyclophosphamide once remission has been achieved [100].

The FVSG tested the hypothesis that methotrexate is associated with fewer adverse events than azathioprine in the Wegener's Granulomatosis–Entretien

(WEGENT) trial [101]. Patients with newly diagnosed MPA or GPA had induction therapy with intravenous pulsed cyclophosphamide and prednisolone, and subsequently randomized to 12 months of methotrexate or azathioprine. The primary outcome was an adverse event that necessitated stopping the trial medications or caused death. There were no statistically significant differences in terms of safety between the methotrexate and azathioprine group. Approximately a third of patients experienced a relapse with the majority of these occurring after the discontinuation of the maintenance therapy. Relapse rates were similar in both groups.

Two open-label studies have investigated the relapse rates of patients with GPA receiving methotrexate with or without prednisolone for maintenance therapy following remission induction with oral cyclophosphamide and prednisolone [102,103]. In one study, more than 50% of patients suffered a relapse, including severe glomerulonephritis with fatal outcome. The majority of relapses occurred after discontinuing prednisolone [103]. In the second study, approximately 30% of patients relapsed at a median of 15 months after starting methotrexate and all had discontinued glucocorticoids prior to their relapse. The relapse rate was not different to historic control patients who had continued cyclophosphamide for 12 months after achieving remission [102].

The German Network of Rheumatic Diseases Methotrexate hypothesised that leflunomide would be as effective as methotrexate at maintaining remission in GPA patients but with fewer adverse events. This was based on observations from an open-label uncontrolled study of 20 patients [104]. Patients with GPA who had achieved remission following treatment with oral cyclophosphamide and prednisolone were randomized to receive maintenance therapy with either methotrexate or leflunomide. The primary outcome was major or minor relapse. Patients were eligible for inclusion with either complete or stable partial remission. The starting dose of methotrexate was relatively low at 7.5 mg per week only increasing to 20 mg per week after week 8. The trial safety board recommended discontinuing the trial early due to an unexpectedly high major relapse rate in the methotrexate-treated patients. The very high relapse rate in the methotrexate group, incomplete recruitment (only 54 out of a planned 145 patients recruited) and early termination severely limit any conclusions that can be drawn from the trial. The study authors concluded that further investigation into the potential efficacy of leflunomide in GPA was warranted as only six out of 26 patients treated with leflunomide suffered a relapse [105].

The EUVAS group tested the hypothesis that mycophenolate mofetil would be more effective than aza-

thioprine in preventing disease relapses in patients with GPA or MPA in the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in AAV (IMPROVE) trial. Following induction with cyclophosphamide and prednisolone for 6 months, with addition of methylprednisolone or plasma exchange for severe disease, participants were randomized to either azathioprine or mycophenolate mofetil for 36 months with oral prednisolone. Relapse-free survival was used as the primary endpoint. IMPROVE demonstrated that mycophenolate mofetil was not as effective as azathioprine at maintaining remission with a significantly higher risk of relapse seen in the group treated with mycophenolate mofetil (hazard ratio of 1.69 [95% CI: 1.06–2.70; $p = 0.03$]) [106]. Nevertheless, mycophenolate mofetil remains an option for patients who are unable to tolerate azathioprine.

The addition of etanercept, a TNF inhibitor, to standard therapy for maintenance of remission in GPA was tested in the Wegener's Granulomatosis Etanercept Trial (WGET). The primary endpoint was disease-free remission sustained for 6 months. Patients with either new or relapsed disease were treated with oral prednisolone with either oral cyclophosphamide or methotrexate depending on disease severity for 3–6 months to induce remission. They then received methotrexate or azathioprine with prednisolone, depending on renal function, for maintenance therapy. Patients were randomized to receive either etanercept or placebo in addition to their standard therapy throughout. Prednisolone was tapered and withdrawn 6 months after randomization and methotrexate and azathioprine were tapered and withdrawn from 12 months after achieving remission. The addition of etanercept to standard therapy was not associated with a significant reduction in the risk of relapse (69.7% in the etanercept group vs 75.3% in the placebo arm) [107]. Furthermore, solid malignancies were seen more frequently in the etanercept-treated group than the placebo-treated group, although this was also associated with prior cyclophosphamide use and indeed all patients that developed cancer had been exposed to cyclophosphamide at some point during their treatment [108].

The association between *S. aureus* carriage and disease activity resulted in two prospective randomized placebo controlled trials investigating the effectiveness of co-trimoxazole in preventing disease relapse in patients with GPA. Co-trimoxazole 960 mg twice daily for 24 months in addition to standard maintenance therapy effectively reduced the risk of relapse and the risk of infection compared with control in a trial that enrolled 81 patients in remission. Of the patients receiving co-trimoxazole, 20% experienced adverse events that necessitated stopping the drug [109].

More recently a randomized placebo controlled trial of co-trimoxazole 960 mg thrice weekly for 18 months in 31 patients GPA in remission also reported reduced risks of relapse and infection in patients treated with co-trimoxazole compared with placebo. The study protocol does not make clear whether patients continued usual remission maintenance therapy during the trial [110].

Successful use of rituximab as a remission maintenance agent has been described in several large case series but so far has not been formally tested in a randomized controlled trial against any of the usual oral agents [111–115]. Although the drug was reported to be generally well tolerated serious infectious adverse events were not uncommon, although many of the patients had large cumulative doses of cyclophosphamide before administration of rituximab.

Managing refractory & relapsing disease

Refractory AAV, unresponsive to standard therapy with cyclophosphamide and prednisolone, remains an area of difficulty, and has remained largely under-investigated with robust clinical trials. There is only one prospective randomized controlled trial for refractory disease in AAV. A total of 34 patients with active disease requiring further treatment following at least 2 months treatment with prednisolone and either cyclophosphamide or azathioprine were randomized 1:1 to receive either placebo or 400 mg/kg/day intravenous immunoglobulin (IVIG) for 5 days. The primary outcome was a >50% reduction in BVAS score three months after study entry. Patients receiving IVIG were significantly more likely to achieve the primary outcome than patients receiving placebo; however, beyond 3 months there was no difference between the groups in disease activity [116]. In longer term follow-up five patients required open-label IVIG to help maintain disease remission.

The FVSG have reported on the use of IVIG 500 mg/kg/day 4 days per month for 6 months in addition to the patient's usual immunosuppression to control disease in 22 patients with refractory or relapsing MPA or GPA. In this open-label uncontrolled study 18 patients achieved complete or partial remission at 6 months and 17 were in complete remission at 2 years. No deaths or severe infections were reported during follow-up [117].

EUVAS investigated the use of rabbit anti-human thymocyte globulin given over 10 days to 15 patients with refractory GPA (SOLUTION). All immunosuppression other than corticosteroids was stopped prior to treatment. Complete remission was achieved in four and partial remission in nine patients. One patient died during the treatment period of uncontrolled disease and one patient from bacterial pneumonia.

Corticosteroid doses were able to be reduced in all surviving patients. Seven patients relapsed at a mean of 8.4 months. Five additional episodes of severe infection were noted during follow-up [118].

The lymphocyte-depleting antibody alemtuzumab (anti-CD52) has also been reported to successfully induce remission in patients with refractory AAV in an open-label non-controlled study of 71 patients with refractory life-threatening disease or multiple relapses despite adequate therapy. All immunosuppression other than prednisolone was discontinued prior to alemtuzumab administration. Complete remission was achieved in 65% of patients and partial remission in a further 20%. Multiple treatment courses were required in 42% of patients and it was noted that giving more than two courses was not associated with an increased remission rate. A total of 31 patients died during follow-up at a median of 106 months. Deaths were mainly due to infection, active disease, cancer or vascular events. In total, 21 episodes of severe infection were noted during follow up [119].

The immunosuppressant 5-deoxyspergualin in conjunction with oral corticosteroids has shown some promise in the treatment of refractory and relapsing AAV in three uncontrolled open-label studies [120–122]. The majority of patients showed an improvement in disease activity with a minority achieving complete remission. All three studies reported significant adverse events, including serious infections, although it should be noted that the patients participating in these studies had a large cumulative immunosuppressant burden prior to receiving 5-deoxyspergualin. The Clinical Study Comparing the New Immunosuppressive Drug Gusperimus with the Conventional Treatment in Wegener's Granulomatosis (SPARROW; ClinicalTrials.gov Identifier: NCT01446211) is an actively recruiting clinical trial of gusperimus in refractory GPA.

The use of infliximab in the refractory disease group has been shown to be effective in a small study of seven GPA patients with partial and complete remission, as assessed by BVAS, achieved in all patients with no serious adverse events reported [123]. Efficacy for infliximab has also been reported in persistently active GPA and MPA with 88% of patients achieving complete remission following 14 weeks of infliximab in addition to their usual immunosuppression, although 21% experienced a relapse during subsequent follow-up [124]. Four patients in this group experienced serious infections, including an episode of nocardia endophthalmitis requiring enucleation.

The Infliximab Versus Rituximab in Systemic Necrotizing Vasculitides (RATTRAP; ClinicalTrials.gov Identifier: NCT00307593) trial by the French Vascu-

litis Group has completed recruitment to compare the use of rituximab with infliximab in refractory vasculitis. The outcomes of RATTRAP have yet to be published.

Rituximab has also been reported to be effective in refractory or relapsing disease [125]. A subgroup analysis of patients with relapsing disease in the RAVE study showed that rituximab was more effective than control medication at inducing remission [89]. The Rituximab Vasculitis Maintenance Study (RITAZAREM; ClinicalTrials.gov Identifier: NCT01697267) is an open-label randomized controlled trial looking at rituximab compared with azathioprine in relapsing AAV with time to relapse as its primary endpoint. Alemtuzumab for ANCA Associated Refractory Vasculitis (ALEVI-ATE; ClinicalTrials.gov Identifier: NCT01405807) is a similar trial investigating the effectiveness of different doses of alemtuzumab in patient with refractory disease. The proportion of patient achieving remission at 6 months and the adverse event rate are the two primary endpoints.

Abatacept is a fusion protein of CTLA-4 and the IgG Fc portion that inhibits CD80 and CD86 costimulation during T-cell activation. A recent open-label uncontrolled trial of 20 patients with non-severe relapsing GPA demonstrated that 80% of patients receiving abatacept in conjunction with steroids and their usual additional immunosuppression achieved complete remission. Nine serious adverse events and 92 additional adverse events, almost all infection, were reported during follow-up [126].

Management of EGPA

EGPA is a much less common disease than either MPA or GPA and consequently there are fewer clinical trials and the evidence base for therapy is less secure. The FVSG has had an interest in trying to establish evidence-based treatment for EGPA for several decades, although interpreting some of their early trials is difficult because patients with several different forms of vasculitis were often recruited to the same trial.

Recruitment to FVSG trials has usually been based on the presence or absence of the poor prognostic indicators described in the FFS.

The group have published long-term follow-up of patients from four early trials that included patients with EGPA (n = 64) along with patients with MPA and patients with PAN with or without associated hepatitis B virus infection. The report does not differentiate between the different diseases but identified that survival of patients with FFS ≥ 2 at a mean follow up of 88.3 ± 51.9 months was better for patients who received cyclophosphamide in conjunction with corticosteroids rather than corticosteroids alone. For patients with FFS < 2 the addition of cyclophosphamide

to corticosteroids did not affect overall survival [127].

In a more recent trial of EGPA patients with an FFS score of zero, successful remission induction with corticosteroids alone was reported in 93% of 72 patients recruited to an open-label non-controlled study [128]. A total of 19 patients who either did not achieve remission, relapsed or were unable to reduce oral prednisolone below 20 mg per day were subsequently randomized to either oral azathioprine ($n = 10$) or pulsed intravenous cyclophosphamide ($n = 9$) as second-line therapy. Five patients who received azathioprine and seven patients who received pulsed cyclophosphamide subsequently achieved remission and the majority continued to require oral prednisolone at 5-years follow-up.

The FVSG have also compared a six or 12 dose pulsed intravenous cyclophosphamide regime for EGPA patients with at least one poor prognostic factor (FFS ≥ 1). All patients received a tapering dose of oral prednisolone and 3 x 1g methylprednisolone. It was planned to recruit 110 patients (55 per limb) to the trial, however, it was stopped early when 48 patients had been recruited because of an increased minor relapse rate seen in the patients who received six pulses of cyclophosphamide. The majority of relapses occurred following discontinuation of cyclophosphamide and there was no difference between the limbs in the time between stopping cyclophosphamide and the relapse. There was no difference between treatment arms in the major relapse rate, adverse events or survival [129].

The combined long-term follow-up data from the two FVSG EGPA trials was recently reported. At a mean follow-up of 81.3 ± 39.6 months, overall survival at 1, 3 and 5 years was 98, 94 and 92%, respectively with no significant difference in survival between the patients with or without poor prognosis factors at diagnosis. A total of 41% of patients experienced a relapse during follow up and there was no significant difference in the relapse rates between the two groups [76].

A small open-label uncontrolled study investigated the role of IVIG in treating 15 EGPA patients with continued evidence of peripheral nerve disease activity and additional myocardial involvement in five patients following treatment with corticosteroids with or without cyclophosphamide. IVIG at 400 mg/kg was administered daily for 5 days and was associated with improved cardiac and muscle function. Patients were followed for 12 months [130].

There are several case reports describing remission induction with rituximab in EGPA patients with disease resistant to standard therapy and one case series describing its successful first line use in conjunction with corticosteroids in three EGPA patients with renal involvement [131–135].

The results of an open label prospective trial investigating the role of an interleukin-5 antibody, mepolizumab, in maintaining remission for 52 weeks in EGPA is awaited (ClinicalTrials.gov Identifier: NCT00716651).

Other current trials

In addition to the ongoing clinical trials already discussed the following are active clinical trials registered on ClinicalTrials.gov, the clinical trials register maintained by the National Institute of Health.

The Clinical Trial of Mycophenolate versus Cyclophosphamide in ANCA Vasculitis (MYCYC, ClinicalTrials.gov Identifier: NCT00414128) trial by the EUVAS group is a non-inferiority trial comparing mycophenolate to current standard therapy with cyclophosphamide. MYCYC was completed in December 2013, and publications of the results are awaited. The Randomised Trial of Prolonged Remission-Maintenance Therapy in Systemic Vasculitis (EUVAS REMAIN) is another study looking at the relapse rate in combined therapy with low dose prednisolone and azathioprine compared with withdrawal of therapy at 2 years following remission.

The efficacy of two anti-B lymphocyte stimulator (also known as B-cell activating factor) monoclonal antibodies are currently being investigated; The BIANCA-SC trial (ClinicalTrials.gov Identifier: NCT01598857; A Study of the Efficacy, Safety, and Tolerability of Blisibimod in Addition to Methotrexate During Induction of Remission in Subjects With ANCA-Associated Small Vessel Vasculitis) and the BREVAS trial (Belimumab in Remission of Vasculitis) comparing belimumab with placebo in combination with azathioprine in remission maintenance (ClinicalTrials.gov Identifier: NCT01663623).

C5a receptor inhibition is a novel therapeutic target in AAV and a clinical trial of a novel C5a receptor inhibitor is already underway investigating safety as well as the potential to reduce toxicity of induction therapy in AAV with mild to moderate renal involvement by reducing the exposure to corticosteroids during induction regimes (ClinicalTrials.gov Identifier: NCT01363388).

Summary

Survival of patients with AAV has significantly improved over the last few decades. In MPA and GPA randomized controlled trials have demonstrated that cyclophosphamide exposure can be effectively reduced by using methotrexate as an alternative agent in patients with early systemic disease. In generalized and severe disease the cumulative exposure of cyclophosphamide can be reduced by converting to maintenance

nance therapy once remission is achieved and by using pulsed intravenous cyclophosphamide rather than oral regimes. Rituximab is an effective alternative for patients with generalized or severe disease. In severe disease with creatinine > 500 µmol/l the addition of plasma exchange to corticosteroids and cyclophosphamide may improve renal recovery, but more evidence is needed. For patients with active relapsed disease rituximab appears to be superior to cyclophosphamide at inducing remission.

Following remission induction azathioprine and methotrexate both appear to be effective at reducing relapse rates, although methotrexate is not suitable for use in patients with renal impairment. Relapse rates remain high in both GPA and MPA, particularly if immunosuppression is withdrawn. The optimal regime for preventing relapse following induction therapy with rituximab is not yet established and the role of rituximab as a remission maintenance agent has not yet been formally tested.

In EGPA patients corticosteroids alone appear to be effective in some patients with FFS ≤ 1 although cyclophosphamide improves survival in patients with more severe disease. The optimal remission maintenance regime in EGPA is not established.

The evidence base for treating refractory disease and frequently relapsing disease for all the AAV is mainly limited to uncontrolled studies and case series, although a number of agents including IVIG, TNF inhibitors and B- and T-cell-depleting therapies have all been reported.

Future perspective

Although the last couple of decades have seen a rapid increase in the number, size and quality of clinical trials in AAV there remain many unanswered questions and areas of unmet need.

Hopefully as we continue to improve our understanding of the pathogenic mechanisms of AAV we will come to understand the processes that drive the autoimmune process in a way that will allow us to develop treatments that would 'reset' this process restoring tolerance to the autoantigens and preventing the risk of future relapse without the need for ongoing immunosuppression. The AVATARS study (ClinicalTrials.gov Identifier: NCT01934504) being led by Alan Salama in the UK may be a step along this path as it attempts to define an immunological phenotype associated with the reinstitution of tolerance to autoantigens in AAV patients.

In the mean time, the majority of patients currently achieve remission using corticosteroids and conventional immunosuppressants; however, the relapse rates remain high, overall approximately 50% over 5

years. This means that many patients are dependent on corticosteroids and additional immunosuppressants to maintain disease control, which is associated with risks of infection, malignancy, weight gain, osteoporosis and diabetes amongst others. The alternative is to discontinue immunosuppression and monitor for the occurrence of a relapse, which entails the risk of serious organ injury or life-threatening disease activity. Although previous studies have identified some factors that identify patients at risk of disease relapse (PR3-ANCA, persistent ANCA positivity and ENT disease), at present there is no evidence that supports the use of these markers to stratify patients for the safe withdrawal or necessary continuation of immunosuppressive medication. There is a pressing need for biomarkers that either identify patients who remain at risk of relapse, which may determine the need for continued immunosuppression, or biomarkers that would identify the very early stages of relapse before organ injury occurs, which would allow reinstitution of immunosuppression appropriately.

In the absence of biomarkers able to identify those at continued risk of relapse or in the earliest stage of relapse there is a need to continue to improve our current treatment strategies. Establishing the most effective ways of using the agents we currently have remains a priority and will require adequately powered double-blinded placebo-controlled trials. One of the problems with many recently published trials is the lack of uniformity in the treatment regimes, outcome measures and trial reporting. Some of this has been addressed by the consensus statement from the European League Against Rheumatism (EULAR) recommendations for conducting clinical studies and trials in AAV [136], but to be able to answer these questions adequately will require the type of international collaboration demonstrated by the PEXIVAS trial. This trial is funded by multiple funding agencies in Europe and North America and is recruiting patients from centers worldwide to deliver a trial that is adequately powered to answer important questions about the use of corticosteroids and plasma exchange in AAV.

The developments in our understanding of the pathogenesis of AAV are leading to the investigation of new drugs and novel targets. The identification of IL-5 as a probable key cytokine in EGPA has led to industry-sponsored and -funded clinical trials of the anti-IL-5 antibody mepolizumab, which are still ongoing (ClinicalTrials.gov Identifier: NCT02020889). The discovery of the role of complement component C5 in ANCA-induced neutrophil activation and the development of glomerulonephritis in AAV has led to the development of clinical trials of a novel C5a receptor inhibitor to induce disease remission in AAV with

renal involvement and reduce the need for corticosteroids (ClinicalTrials.gov Identifier: NCT01363388).

The increasing understanding of the pathogenesis of these diseases and collaborative working in delivering high-quality clinical trials and increasing interest from industry in identifying and testing new drug targets means that this is an exciting time to be involved in vasculitis research and in providing treatment for patients with these challenging diseases.

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Executive summary

- Survival for patients with anti-neutrophil cytoplasm antibody-associated vasculitides has significantly improved over the last few decades.
- Randomized controlled trials in microscopic polyangiitis and granulomatosis with polyangiitis have changed treatment to reduce adverse effects by minimising cyclophosphamide exposure.
- Methotrexate is an alternative for cyclophosphamide in early systemic disease.
- Pulsed cyclophosphamide safely halves the exposure compared with oral cyclophosphamide.
- Rituximab is an alternative to cyclophosphamide for generalized and severe microscopic polyangiitis and granulomatosis with polyangiitis.
- Plasma exchange may improve renal recovery in severe disease.
- Cyclophosphamide can be switched to other immunosuppressants once remission is achieved in microscopic polyangiitis and granulomatosis with polyangiitis.
- Azathioprine is superior to mycophenolate mofetil for remission maintenance.
- Methotrexate is equivalent to azathioprine for remission maintenance.
- In eosinophilic granulomatosis with polyangiitis corticosteroids alone may be adequate in the absence of poor prognostic factors.
- In eosinophilic granulomatosis with polyangiitis cyclophosphamide improves survival in the presence of two or more poor prognostic factors.
- New agents in current clinical trials target novel pathological processes identified in observational and translational studies

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