Treatment of antineutrophil cytoplasmic antibody-associated vasculitis

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Purpose of review
The primary idiopathic small-vessel vasculitis syndromes include granulomatosis with polyangiitis, Churg–Strauss syndrome, and microscopic polyangiitis. These disorders are commonly referred to as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides and prominently affect the pulmonary vasculature. Although significant progress has been made in the management of these disorders, they continue to carry substantial morbidity and mortality as a result of both the underlying vasculitis as well as complications of its immunosuppressive therapy. This review will focus on the recent advances in the management and longitudinal monitoring of ANCA-associated vasculitis.

Recent findings
Cyclophosphamide and glucocorticoids are standard therapy, but carry measureable risk of treatment-related toxicity. The search for alternative therapies that are less toxic but similarly efficacious is continuing. Recent investigations suggest rituximab may be a well tolerated alternative to cyclophosphamide for the induction of remission, treatment of disease relapse, and as maintenance therapy.

Summary
The ANCA-associated vasculitides are a group of disorders that commonly affect the pulmonary vasculature and represent a diagnostic and therapeutic challenge to the pulmonary clinician. Recent findings have expanded our ability to diagnose and treat these disorders with a focus on limiting treatment-related toxicity while inducing and maintaining remission.

Keywords
antineutrophil cytoplasmic antibody, Churg–Strauss syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, rituximab, vasculitis

INTRODUCTION

The pulmonary vasculitides represent a group of rare disorders that specifically target the vasculature of the lung, and are characterized by inflammatory cell infiltration and destruction of the small-sized and medium-sized blood vessels with resultant tissue damage. These diseases can be divided into primary (idiopathic and immune-complex associated) or secondary disorders (Table 1). Primary pulmonary vasculitis is thought to be autoimmune-mediated, and can be classified based on the size of involved vessels (small, medium, or large), whereas secondary vasculitis results from a myriad of causes including infection, malignancy, drug reactions, or connective tissue disease. The diagnosis of vasculitis remains a challenge, even to the most experienced physician, given the significant overlap with other multisystem disorders that have similar radiographic, clinical, and laboratory features.

The primary idiopathic small-vessel vasculitis syndromes prominently affect the pulmonary vasculature and are often referred to as antineutrophil cytoplasmic antibody-associated (ANCA) vasculitides (AAV). This group of disorders includes granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis [4]), Churg–Strauss syndrome (CSS), and microscopic polyangiitis (MPA). A number of recent investigations have evaluated therapeutic alternatives to standard cyclophosphamide therapy for the induction and

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KEY POINTS

- The primary idiopathic small-vessel vasculitis syndromes commonly present with respiratory manifestations and must be differentiated from clinical entities with similar manifestations including infections, drug reactions, and autoimmune disorders.
- In ANCA-associated vasculitis, the choice of initial treatment should be guided by disease severity, with the risk of therapy-associated complications being balanced by the risk for further organ damage.
- Rituximab appears to be a well tolerated alternative to cyclophosphamide for the induction of remission and treatment of disease relapse.
- Despite recent advances, infection, active vasculitis, malignancy, and cardiovascular complications continue to cause substantial morbidity and mortality.

Table 1. Causes of pulmonary vasculitis

Primary vasculitis	Small-vessel vasculitis/ANCA-associated
	Granulomatosis with polyangiitis (GPA)
	Churg–Strauss syndrome (CSS)
	Microscopic polyangiitis (MPA)
	Idiopathic pauci-immune pulmonary capillaritis (IPIPC)
	Medium-vessel vasculitis
	Polyarteritis nodosa
	Kawasaki disease
	Large-vessel vasculitis
	Takayasu arteritis
	Giant cell arteritis
Immune-complex-mediated vasculitis	Goodpasture's syndrome
	Behçhet's disease
	IgA nephropathy
	Essential cryoglobulinemia
	Henoch-Schönlein purpura
Secondary vasculitis	Antiphospholipid antibody syndrome
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Dermatomyositis/polymyositis
	Inflammatory bowel disease
	Drug-induced
	Hypocomplementemic urticarial vasculitis
	Paraneoplastic
	Infection

Data from [1–3].

maintenance of disease remission (no evidence of disease activity) with a goal of limiting therapy-related toxicity. This review will focus on the recent advances in the field.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

The AAV often present with respiratory manifestations including upper airway involvement, cavitary or nodular lung disease, and diffuse alveolar hemorrhage (DAH). The presence of one or more of these respiratory manifestations combined with abnormalities in other organs such as neurologic signs or symptoms, cutaneous changes (e.g., palpable purpura), and renal disease [e.g., rapidly progressive glomerulonephritis (RPGN)] should prompt the consideration of a vasculitis (Table 2).

The 1990 American College of Rheumatology (ACR) and the 1994 Chapel Hill Consensus Conference classification systems have been used to define the primary vasculitides in both clinical practice and research [1]. However, both systems have significant limitations, and a coordinated international effort between the European League Against Rheumatism (EULAR) and ACR is currently underway to develop a single classification system, termed Diagnosis and Classification of Vasculitis (DCVAS) [8▪,9]. The goal of this effort is to create criteria that distinguish primary vasculitis from similar but distinct clinical entities.

MANAGEMENT OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

Since Fauci *et al.* [10] published their seminal paper in the early 1980s, standard therapy for AAV involves immunosuppression with corticosteroids and cyclophosphamide. However, although cyclophosphamide is highly effective in achieving disease remission, it has significant potential for toxicity and adverse effects. The goal of initial therapy is to induce disease remission, balancing the risk of ongoing organ damage with the risk of therapy-related complications. In order to help quantify these risks, the European Vasculitis Study Group (EUVAS) has categorized disease severity into five groups which assist in guiding initial therapy: limited, early generalized, active generalized, severe, and refractory (Table 3).

Induction therapy

With limited disease, patients with AAV have disease activity localized to the upper airway, have

Table 2. Manifestations of ANCA-associated vasculitis

	GPA	CSS	MPA
Constitutional symptoms	50–90%	50–90%	>90%, commonly manifests weeks to months prior to RPGN
Upper airway	70–90%; destructive and ulcerative lesions common	Nondestructive sinusitis in 50–80%	Sinus disease in 5–30%
Pulmonary	Abnormal imaging (mixed opacities, commonly nodular with or without cavitary) in >80%. DAH in 5–10%. Endobronchial and tracheobronchial disease in 10–50%	Asthma nearly universal, often steroid dependent. Ground glass with or without consolidation in 90% by HRCT	Cough and dyspnea common. 30% with DAH
Renal	40% of patients will have GN at presentation. 80–90% will develop GN during disease course	25–60%	RPGN nearly universal
Gastrointestinal	Rare	30–60% of patients with colitis, pain, hemorrhage, perforation and contributes significantly to morbidity/mortality	30–50% of patients. Hemorrhage, ischemia, perforation, aneurysms
Cardiac	Reports of coronary vasculitis and pericarditis (5–15%)	30–50% of patients with conduction abnormalities, coronary vasculitis, heart failure. Disproportionately contributes to mortality	10–20%
Neurologic	Peripheral abnormalities (10–30%) more common than central abnormalities	Mononeuritis multiplex 50–70%. Central involvement less common	Mononeuritis multiplex 15–58%
ANCA	c-ANCA/PR3 positivity in the appropriate clinical setting is highly specific and sensitive for the diagnosis of active systemic GPA (sensitivity 85–90%, specificity 90–95%)	ANCA positive in 40–70% of patients, most commonly p-ANCA/MPO positive. ANCA-positive patients have more frequent renal involvement, whereas ANCA-negative patients may have more significant eosinophilia, pulmonary, and cardiac disease	45–80% ANCA positive, most commonly p-ANCA/MPO

Data from Refs [3,5,6▪▪,7]. CSS, Churg–Strauss syndrome; DAH, diffuse alveolar hemorrhage; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; HRCT, high-resolution computed tomography; MPA, microscopic polyangiitis; MPO, antimyeloperoxidase antibody; PR3, antiproteinase 3 antibody; RPGN, rapidly progressive glomerulonephritis.

normal renal function (creatinine <1.4 mg/dl), and do not have constitutional symptoms. Treatment recommendations are generally limited to expert opinion, given the paucity of randomized studies, and suggest topical or systemic corticosteroids, azathioprine, or methotrexate.

Patients with early generalized disease have clinically active vasculitis with constitutional symptoms, but lack a specific threat to organ function. Recommended therapy for these patients has traditionally been corticosteroids and cyclophosphamide. However, the Nonrenal Alternative with Methotrexate (NORAM) trial compared methotrexate with cyclophosphamide for remission induction and found that methotrexate was better tolerated, but had a longer time to remission (5 vs. 3 months) and higher relapse rate (74 vs. 42%) [11]. On the basis of this study, methotrexate can be considered an alternative to cyclophosphamide. A new EUVAS sponsored randomized clinical trial comparing mycophenolate mofetil (MMF) to cyclophosphamide for remission induction (MYCYC) is currently enrolling patients.

Patients with active generalized disease have clinically active vasculitis with constitutional symptoms and threatened organ function (e.g., renal dysfunction, abnormal serum creatinine <5.7 mg/dl). Standard treatment with corticosteroids and cyclophosphamide to induce remission is indicated as the first-line therapy. Since the widespread use of cyclophosphamide for AAV began in the 1980s, concerns have been raised about cumulative drug-related toxicity, leading investigators to search for alternative remission induction therapies with a lower risk of treatment-related complications. The Daily Oral Versus Pulse Cyclophosphamide for

Table 3. Treatment of ANCA-associated vasculitis

Disease severity	Organ function threatened?	Updated five factor score	Clinical features and renal function	Therapeutic options
Limited	No	0	Limited to upper airway abnormalities Serum creatinine <1.4 mg/dl	Corticosteroids or methotrexate or azathioprine
Early generalized	No	0–1	Constitutional symptoms, mild respiratory and systemic symptoms Serum creatinine <1.4 mg/dl	Cyclophosphamide + corticosteroids or methotrexate + corticosteroids
Active generalized	Yes	1–2	Constitutional symptoms, limiting respiratory symptoms, parenchymal pulmonary disease, subglottic stenosis, gastrointestinal or cardiac involvement. Serum creatinine <5.7 mg/dl	Cyclophosphamide plus corticosteroids or rituximab plus corticosteroids
Severe	Yes	≥2	Organ dysfunction with immediate threat of death including alveolar hemorrhage and cardiac failure. Serum creatinine >5.7 mg/dl	Plasmapheresis + corticosteroids + rituximab or cyclophosphamide
Refractory	Yes	N/A	Any creatinine	Rituximab or investigational therapies
Maintenance of remission	No	N/A	N/A	Azathioprine or methotrexate with or without corticosteroids (low-dose) If induced with rituximab, no additional therapy or azathioprine or scheduled rituximab infusions (trials ongoing)

Data from [10–13,14▪▪,15].

Renal Vasculitis (CYCLOPS) trial significantly changed how clinicians dose cyclophosphamide in AAV [16]. Patients were randomized to pulse intravenous cyclophosphamide with prednisolone or daily oral cyclophosphamide with prednisolone, and no difference was found in the proportion of patients that achieved remission or the time to remission. Of particular importance is that the pulse cyclophosphamide group received a lower total cumulative cyclophosphamide dose and had less leukopenia. However, long-term follow-up (median 4.3 years) of these patients revealed significantly higher rates of relapse in the pulse regimen group (hazard ratio = 0.5; $P = 0.029$), with no associated difference in mortality or long-term morbidity between the two groups [17▪▪].

Patients with severe disease have clinically active vasculitis with severe organ dysfunction, frequently manifested as advanced renal disease (creatinine >5.7 mg/dl). Additional manifestations of severe organ dysfunction may include DAH, cardiac involvement with life-threatening arrhythmias, or gastrointestinal hemorrhage. These patients require aggressive therapy to induce remission because of the significant threat to organ function and the high risk of death without therapy. Aggressive therapy is recommended with high-dose corticosteroids and intravenous cyclophosphamide or rituximab.

In patients with RPGN and DAH, plasma exchange therapy (PLEX) should be considered. Randomized controlled trials to support PLEX as standard therapy are limited, while only case series in DAH exist [18▪▪,19▪▪]. The most encouraging data comes from the Methylprednisolone or Plasma Exchange for Severe Renal Vasculitis, study which randomized 137 patients with a new diagnosis of AAV and a serum creatinine greater than 5.8 mg/dl to seven rounds of PLEX or 3000 mg of methylprednisolone (all patients received oral cyclophosphamide and prednisolone). Significantly, more of the PLEX-treated patients were dialysis independent at 3 months (49 vs. 69%) and 12 months (19 vs. 43%) [20]. The current ongoing Plasma Exchange and Glucocorticoid Dosing in the Treatment of ANCA-associated Vasculitis trial should provide further guidance with regard to the role for PLEX in patients with alveolar hemorrhage and renal disease. This randomized controlled trial is enrolling patients with severe, new, or relapsing AAV to determine whether PLEX is effective in reducing death and end-stage renal disease. The role for PLEX in less severe disease is even less clear. Recently, Szpirt *et al.* [21▪] have shown intriguing evidence for improved renal survival in patients with GPA and less severe renal dysfunction (creatinine >2.85 mg/dl), but further studies are required to define the role for PLEX in less severe disease.

Alternative therapies

Recent clinical trials in AAV have focused on the alternatives to cyclophosphamide in patients with severe, refractory, or relapsing disease. The most promising agent is rituximab, a monoclonal anti-CD20 antibody that selectively depletes B-lymphocytes.

Two randomized controlled trials provide the most definitive data to date for the use of rituximab as an alternative to cyclophosphamide for remission induction. The Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis (RAVE) trial was a randomized controlled noninferiority study in newly diagnosed or relapsing severe AAV [12]. Patients with GPA or MPA and positive PR3-ANCA or MPO-ANCA were randomized to rituximab or cyclophosphamide. Glucocorticoids were tapered off over 5 months in both groups. The cyclophosphamide group was transitioned to azathioprine maintenance therapy, whereas the rituximab group was transitioned to placebo. The primary endpoint was disease remission without the use of glucocorticoids at 6 months. This endpoint was achieved in 64% of the rituximab group and 53% of the cyclophosphamide group, confirming the noninferiority of rituximab. Importantly, in the subgroup of patients with relapsing disease, rituximab appeared superior to cyclophosphamide (67 vs. 42%, $P = 0.01$). These results led to FDA approval for the use of rituximab in remission induction for severe GPA and MPA. The frequency of relapse was similar between the two groups at 6 and 18 months, even in the absence of maintenance immunosuppression in the rituximab group.

A second trial, Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS), randomized 44 patients with newly diagnosed GPA or MPA with clinically apparent renal involvement to rituximab (375 mg/m^2 i.v. weekly four times) versus pulsed cyclophosphamide for 3–6 months followed by maintenance azathioprine [13]. It is important to note that the rituximab group was given pulse cyclophosphamide with the first and third rituximab infusion. All patients were given maintenance low-dose glucocorticoids. There was no difference in the rate of sustained remission at 12 months (rituximab 42% and control 36%) or mortality.

Rituximab can be recommended as a suitable alternative to cyclophosphamide for induction therapy with the potential advantage of less risk of treatment-related toxicity, and may be superior to cyclophosphamide in the treatment of relapsing disease [14▪▪,22▪▪].

Maintenance therapy

Maintenance of disease remission involves continued immunosuppression but with a transition to therapies with a lower risk of treatment-related toxicity. Controversies exist in the timing of the transition, the choice of agent, and the duration of maintenance therapy.

Traditionally, patients were treated with cyclophosphamide and glucocorticoids for 12 months prior to transitioning to azathioprine or methotrexate [23]. This changed significantly after the publication of the Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis (CYCAZAREM) trial [24]. This trial showed that a transition of cyclophosphamide to azathioprine soon after a clinical remission has been induced (between 3 and 6 months) was associated with no difference in the rate of relapse or loss of renal function when compared to the longer duration of cyclophosphamide. The International MMF Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) provided additional evidence for the safety of early (within 6 months) transition to maintenance therapy after remission induction [15]. A total of 156 patients were followed for a median of 39 months after randomization to either MMF or azathioprine for the maintenance of disease remission. Relapses were more common in the MMF group, with an unadjusted hazard ratio of 1.69 (1.06–2.7; $P = 0.03$). There were no significant differences in serious adverse events or Vasculitis Damage Index between the two groups. Therefore, current evidence supports the initiation of azathioprine maintenance therapy soon after clinical disease remission has been obtained.

The optimal glucocorticoid dosing and tapering regimen is unknown and differing protocols have been used in treatment trials. The 2009 EULAR guidelines recommend treatment with high-dose (1 mg/kg/day) glucocorticoids for the first month of induction therapy followed by a gradual taper [25]. In 2007, the British Society of Rheumatology (BSR) reported an alternative weekly tapering regimen, which has been employed in some recent randomized controlled trials including IMPROVE. No definitive studies have compared the monthly versus weekly reduction methods, but the IMPROVE trial results, along with a retrospective review of both regimens in a Japanese cohort of AAV patients, suggest similar rates of relapse with a possible reduction in infectious complications and hyperglycemia in the weekly reduction method [26▪]. Additional information comes from a recent meta-analysis of 13 randomized controlled trials in AAV

that included a predefined glucocorticoid treatment plan published by Walsh *et al.* [27▪]. This data showed that compared to patients with a target glucocorticoid dose of zero, there was a lower disease relapse rate when patients continued receiving some dose of glucocorticoid during the trial period; only 14% of patients on glucocorticoids suffered a relapse compared with 43% in the zero glucocorticoid group. In fact, the glucocorticoid treatment plan was the most significant variable explaining the proportion of patients suffering a relapse. On the basis of these data, a longer duration of glucocorticoid therapy may decrease the risk of relapse.

Although the data is limited, if cyclophosphamide induction therapy is initiated, a weekly glucocorticoid reduction method is recommended with consideration given to a longer duration of low-dose therapy. When rituximab is used for induction therapy, glucocorticoid use as directed by the RAVE trial, pulse methylprednisolone for 1–3 doses, followed by prednisone 1 mg/kg/day for 2–4 weeks, and subsequent taper every 2 weeks with discontinuation of glucocorticoids by 5 months can be recommended.

To date, no randomized trial has been published for the use of rituximab as maintenance therapy or re-induction therapy in disease relapse. However, several studies suggest that maintenance therapy with rituximab may decrease the risk of relapse [28,29]. The French Vasculitis Study Group conducted a retrospective review of 28 patients who received a median of four rituximab maintenance infusions. In this group of patients, rituximab was well tolerated and only two patients experienced relapses shortly before a planned infusion [30▪]. The optimal dosing regimen and duration for rituximab as maintenance therapy is unclear, but the ongoing Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial should provide additional guidance. This randomized trial compares maintenance rituximab to azathioprine. The primary outcome is the number of major relapses over 28 months (18 months treatment and 10 months follow-up).

Longitudinal monitoring

Longitudinal follow-up of patients with AAV requires ongoing, routine evaluation for disease relapse and complications of medication therapy. Although the clinical manifestations of the relapse may mimic the initial presentation of the AAV, new organ involvement as part of the relapse is common and a systematic survey of potential sites of disease activity is generally necessary. And just as the clinical features of the initial presentation overlap with other conditions, the differential of a disease relapse always includes infection and drug toxicity as well as unrelated conditions.

In a retrospective evaluation of 535 patients with 1804 patient-years, the most significant risk factors for AAV relapse include positive ANCA/PR3 antibodies and cardiovascular involvement. Interestingly, patients with a creatinine level greater than 200 μmol/l at the time of diagnosis have a lower risk of relapse [31▪]. Controversy exists regarding the utility of serial measurements of ANCA in patients with AAV to predict disease relapse. A recent meta-analysis evaluating this question suggests that a rise in ANCA during clinical remission is at best moderately predictive of relapse. A rise in ANCA during remission has a positive likelihood ratio of 2.84 and negative likelihood ratio of 0.49 for subsequent relapse of disease. Persistently positive ANCA during remission has a positive likelihood ratio of 1.97 and negative likelihood ratio of 0.73 for subsequent relapse of disease [32▪]. Therefore, serial ANCA measurements provide limited guidance for predicting relapse and careful integration of this information with the clinical history, physical examination, and laboratory studies required as part of therapeutic decision-making.

PROGNOSIS AND COMPLICATIONS

Since the wide adoption of aggressive immunosuppressive therapy, the mortality rate for patients with AAV has improved significantly over the past 20 years. Therapy not only improves survival, but also appears to have a positive effect on health-related quality of life [33▪]. However, compared with age-matched and sex-matched controls in the general population, there is still an elevated mortality ratio of 2.6 [34▪▪]. Morbidity and mortality is related not only to active vasculitis, but also to complications related to immunosuppressive therapy.

Flossman and colleagues [34▪▪] reported the clinical outcomes for 535 patients from 4 randomized clinical trials. During the first year, infection was the main cause of death (48%) followed by active vasculitis (19%). In subsequent years, the cause of death shifts to cardiovascular disease (26%), malignancy (22%), and infection (20%). Mortality from cardiac involvement in CSS is well documented, occurring in 10–50% of patients and accounting for a disproportionate number of deaths. More recently, cardiovascular mortality has also been appreciated as a significant contributor to

the 5-year mortality in GPA and MPA. A retrospective review of four EUVAS randomized controlled trials found that 13.8% of patients had at least one cardiovascular event in the 5 years of follow-up [35▪]. Risk factors included older age and diastolic hypertension, while positive ANCA-PR3 antibody status is associated with a reduced cardiovascular risk compared to ANCA-MPO or a negative ANCA. A recent overview of thromboembolic disease in vasculitis also highlights the increased occurrence of venous thromboembloic events in patients with AAV and the close relationship between the events and vasculitis disease activity [36].

Recent changes in the management of AAV designed to decrease the cumulative dose of cyclophosphamide and thereby limit cyclophosphamide-associated morbidity have been investigated. One of the major morbidity concerns is the risk of malignancy. In fact, the risk of malignancy with current cyclophosphamide therapy may not be as high as previously thought. In this review (93% treated with cyclophosphamide for mean 11.8 months, 2650 person-years), only 50 cancers were diagnosed in 46 patients. Although the cancer rates for AAV patients were elevated [standardized incidence ratio (SIR) 1.58] for cancers at all sites, it was driven mostly by nonmelanoma skin cancer [37▪▪].

CONCLUSION

Pulmonary vasculitis is most commonly due to the AAV. Management is directed at initial induction of disease remission followed by maintenance therapy to prevent disease relapse. Recent advances in the field have mainly focused on the alternative therapies to cyclophosphamide to limit treatment-related morbidity and mortality. Rituximab is a well tolerated alternative to cyclophosphamide for the induction of remission and treatment of disease relapse. Early transition from remission induction therapy to maintenance therapy is appropriate to lower the risk of treatment-related adverse effects. In the short term, infection remains a major cause of mortality, while over the long term, infection, malignancy, and cardiovascular complications account for the majority of deaths. Ongoing studies will inform our therapy for remission induction, maintenance, and disease monitoring.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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