Research Review
EDUCATIONAL SERIES

Management of ANCA-associated Vasculitis

About the Reviewer

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Ravi Suppiah is an Auckland-based Rheumatologist with an academic interest in systemic vasculitis. Ravi has published peer-reviewed papers and book chapters in this area. He remains involved with database projects and clinical trials with the European Vasculitis Society (EUVAS) and is on the steering committee of the DCVAS project to develop new diagnostic and classification criteria for systemic vasculitis.

This review is intended as an educational resource for specialists. It presents a concise overview of anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis, including its disease burden and multiple manifestations. In terms of treatment, the review highlights the emergence of rituximab, and its inclusion in the most recent published evidence-based guidelines on the management of ANCA-associated vasculitis.

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Disease Background

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) represents a group of heterogeneous, multisystem disorders characterized by the presence of circulating autoantibodies to neutrophil cytoplasmic antigens and neutrophil infiltration of blood vessel walls, resulting in inflammation, fibrinoid necrosis, and vascular damage. The AAV are usually classified into one of the three following subtypes:

1. granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis)
2. microscopic polyangiitis (MPA)
3. eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome).[1,2]

In all three forms of AAV, small-to-medium-sized blood vessels are affected, most commonly those of the kidneys, lungs and peripheral nervous system.[1] The cause of AAV is not known but a role for genetic susceptibility, with links between environmental factors and induction, has been demonstrated in the multifactorial pathogenesis of the condition.[3]

Burden of Disease

The AAV are rare diseases, requiring a large population to estimate their incidence and prevalence. Epidemiological data accumulated over the past 20 years suggest an overall annual incidence of 10-20 per million in Caucasian populations (with GPA accounting for about half of the cases, MPA a third, and EPGA the remainder) and peak age of onset occurring in those aged 65-74 years.[4,5]

In New Zealand, a 2006 epidemiological study identified 73 cases of GPA and 28 cases of MPA in the Canterbury region.[6] This translated to a 5-year period prevalence of 152 GPA cases per million and 58 MPA cases per million and a point prevalence of 93.5 per million for GPA and 37 per million for MPA. At the time of publication, the authors considered these prevalence rates to be the highest reported for these diseases.[6] The study also identified high rates of significant renal disease and death associated with MPA (82% and 34%, respectively) and GPA (36% and 26%).[6] Hence, although it is a relatively uncommon condition, AAV is a cause of substantial morbidity and substantial mortality in New Zealand.

AAV progresses to a fatal outcome due to organ failure if left untreated. In a study of the natural course of GPA, for example, the average duration of patient survival was about five months, with 82% of patients not surviving the first year and 90% of patients dying within two years. The primary causes of death were renal and respiratory failure.[7] According to observational studies, 20-40% of patients with AAV require renal transplantation due to onset of endstage renal disease.[8]

The considerable morbidity associated with AAV is reflected in quality-of-life studies. Patients with AAV experience marked impairment of daily living relative to the general population, with fatigue and reduced physical functioning being major contributors to quality of life deficits.[9-11]

Clinical Manifestations and Diagnosis

AAV manifests in multiple ways (**Figure 1**), and there is considerable symptom overlap across the associated vasculitides.[8] Ear, nose, and throat problems, including hearing loss, rhinorrhoea, sinusitis, and otitis media, are common with GPA and occur in one-third of patients with MPA.[12,13] The airways and lung parenchyma are commonly affected as are the kidneys, eyes, and nervous system. In addition, skin manifestations, including urticarial rash and skin nodules occur in half of patients.[12,14,15] EGPA is often associated with asthma and eosinophilia and nasal polyps are a common feature.[2]

Blood tests, including ESR and C-reactive protein, urinalysis, chest x-rays, and ANCA testing are the main baseline investigations.[12] Anti-neutrophil cytoplasmic antibodies are an important diagnostic marker for GPA and MPA, and, to a lesser extent, EGPA. AAV is associated with ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA).[2] Current guidelines suggest that combining indirect immunofluorescence and proteinase 3 and myeloperoxidase antigen-specific immunometric assays provides optimal diagnostic specificity.[12,16,17] The main differentiating features of the three different forms of AAV are summarized in **Table 1**.

A positive ANCA assay result alone, however, is not diagnostic for AAV. Clinical evidence and, where possible, histological confirmation are also required. Importantly, because AAV without detectable ANCA exist, a negative ANCA assay result does not exclude a diagnosis of AAV.[17]

Computed tomography is useful in identifying lung and sinus disease. Kidney biopsies have high diagnostic yield when there is renal involvement. In controlled trials, a histopathological diagnosis of ANCA-associated glomerulonephritis was established in 80-100% of biopsies.[18-20]

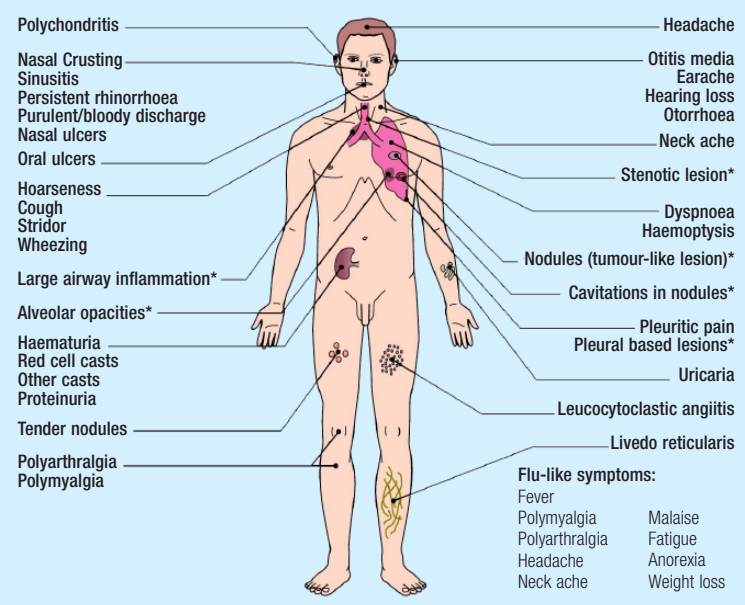

Figure 1. The multiple manifestations of anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV).[8]

*Lesions that can be seen on chest radiography and computed tomography

	Main Features
Granulomatosis with polyangiitis (GPA)	• Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract. • Necrotizing vasculitis affecting predominantly capillaries, venules, arterioles, arteries and veins. • Necrotizing glomerulonephritis is common. • Ocular vasculitis and pulmonary capillaritis with haemorrhage are frequent. • Granulomatous and non-granulomatous extravascular inflammation are common.
Microscopic polyangiitis (MPA)	• Necrotizing vasculitis, with few or no immune deposits, predominantly affecting 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 (EGPA)	• Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract. • Necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. • Nasal polyps are common. • ANCA is more frequent when glomerulonephritis is present.

Table 1. Differentiating features of the three main vasculitides that comprise ANCA-associated vasculitis (AAV) according to the 2012 Chapel Hill consensus definitions.[2]

Need for New Treatments

First used empirically in the treatment of AAV over 40 years ago, immunosuppressive therapy with a combination of high-dose glucocorticoids and cyclophosphamide transformed what is an otherwise fatal condition into a chronically relapsing disease. Despite becoming the standard therapy for induction of remission in patients with AAV, achieving remission in 75% of patients,[8] these treatments are associated with cumulative toxicity and do not produce long-lasting remission in the majority of cases. Indeed, the severe short- and long-term adverse effects of cyclophosphamide, including infection and secondary malignancies, can contribute to morbidity and mortality.[21,22] Patients with AAV treated with conventional regimens have been shown to be at increased risk of death compared with an age- and sex-matched population.[23]

In the search for more effective therapies with less toxicity, especially with respect to maintenance of remission, biological response modifiers that target specific immune pathways have been the focus of the development of potentially superior treatments. In addition to the blockade of complement, pro-inflammatory cytokines, and T-cell co-stimulation, specific targets for AAV therapy also include B-cell depletion.[24] B lymphocytes are responsible for the production of autoantibodies, including ANCA, and the efficacy of cyclophosphamide in the treatment of AAV has been attributed to its potent effects on B lymphocytes.[22,25] With B lymphocytes implicated in the pathogenesis of AAV, investigational use of the monoclonal antibody, rituximab, was extended to the treatment of AAV on the premise of its profound B lymphocyte-depleting effects.[26]

Rationale for Rituximab

The strongest support for the use of rituximab in the treatment of AAV is provided by two randomized controlled clinical trials: the 6-month Rituximab in ANCA-Associated Vasculitis (RAVE) and the 12-month Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) studies.[27,28] The favourable results demonstrated in these two trials established rituximab, in combination with glucocorticoids, as an effective alternative to cyclophosphamide and corticosteroids followed by azathioprine in the treatment of severe AAV (GPA or MPA), and that rituximab was superior in patients who had relapsing disease at 6 months (**Table 2**).[22]

The results of RAVE were subsequently confirmed in a longer term follow-up analysis.[29] It showed that the efficacy outcomes with rituximab were consistently as good as those with cyclophosphamide over the course of 18 months, even though patients in the rituximab group who had achieved complete remission by 6 months did not receive additional immunosuppression for more than one year.[29]

In terms of tolerability, the frequency and severity of adverse effects were similar in AAV patients treated with rituximab versus cyclophosphamide-based regimens in the RAVE and RITUXVAS trials,[27-29] indicating that rituximab is generally well tolerated. Certain potential adverse effects with rituximab should, however, be considered when contemplating its use in AAV patients. They include infusion-related reactions, reactivation of latent viral infections, opportunistic infections, and pulmonary toxicity.[30]

Largely on the basis of the favourable results of the RAVE, rituximab was approved for remission induction therapy in newly diagnosed and relapsing severe GPA and MPA by the US FDA in 2011, and subsequently by regulatory agencies in many other countries.[26] In New Zealand, rituximab in combination with glucocorticoids is indicated for the induction of remission in patients with severely active GPA and MPA. PHARMAC announced widening of funding restrictions for rituximab use in DHB hospitals for induction therapy in patients with AAV, effective from 1st March 2014.

Current Treatment Guidelines

With the emergence of new evidence in the field of AAV, the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) have published the most current evidence-based guidelines for the management of AAV in adults (**Figure 2**).[31] The primary principles of treatment according to the BSR-BHPR guidelines are:

1. AAV is a potentially life- or organ-threatening disease
2. Rapid diagnosis and rapid initiation of treatment
3. Early induction of remission to prevent organ damage
4. Maintenance of remission, with the objective of eventual drug withdrawal
5. Minimization of drug toxicity.[31]

Primary Remission Induction

Although glucocorticoids have been used in the standard treatment of vasculitis over the past 40 years, there is no randomized controlled trial evidence supporting their use for remission induction.[22] Nevertheless, the latest BSR-BHPR guidelines recommend that glucocorticoids (usually prednisolone), initially at relatively high doses then rapidly tapered, in combination with IV pulse cyclophosphamide or rituximab should be considered for patients with newly diagnosed AAV.[31] Rituximab should be preferred to cyclophosphamide in patients intolerant to cyclophosphamide or in whom its avoidance is desirable, e.g. those at risk of infertility.[31]

Methotrexate and mycophenolate mofetil are alternative agents for induction of remission in patients with low disease activity and not at risk of organ damage. In patients presenting with severe renal failure (creatinine >500 µmol/L), the combination regimen of cyclophosphamide and a glucocorticoid should be used with adjuvant plasma exchange. Plasma exchange should also be considered in patients with other life-threatening manifestations of disease, e.g. pulmonary haemorrhage.[31]

	RITUXVAS trial	RAVE trial
Patients (n)	44–33 RTX, 11 CYC	197–99 RTX, 98 CYC
New diagnosis (%)	100	49
Wegner's granulomatosis: microscopic polyangiitis	1:1	3:1
PR3/MPO antibodies	58:42	67:33
Median age (years), RTX:CYC	68:67	54:51.5
Renal function at entry, RTX:CYC	20:12 (GFR)	54:69 (creatinine clearance)
Rituximab dose	375 mg/m^2×4 + two i.v. CYC pulses	375 mg/m^2×4
CYC dose	15 mg/kg i.v., six to 10 cycles	2 mg/kg/day per orally
Plasma exchange	Yes	No
Steroid dose	1g i.v. methylprednisolone	1 to 3g i.v. methylprednisolone
	1 mg/kg/day prednisolone per orally	1 mg/kg/day prednisolone per orally
	Decrease to 5 mg/day by 6/12	Decrease to 40 mg/day by 1/12
		Stop prednisolone by 6/12
Maintenance therapy	CYC → AZA at 3 to 6 months	CYC → AZA at 3 to 6 months
	RTX → none	RTX → none
Primary endpoints	12 months	6 months
Remission (%), RTX:CYC	76:82	64:53 (no prednisolone)
		71:62 (<10mg prednisolone)
Median time to remission (days), RTX:CYC	90:94	NR
Serious adverse events (%), RTX:CYC	42:36	22:33
Deaths, RTX:CYC	6:1	1:2
GFR at end of study, RTX:CYC	39:27	NR

Table 2. Key features and outcomes in the two pivotal randomized controlled clinical trials that evaluated the use of rituximab for remission induction in patients with AAV.[22]
Abbreviations: CYC=cyclophosphamide; GFR=glomerular filtration rate; i.v.=intravenous; NR=not recorded; RTX=rituximab.

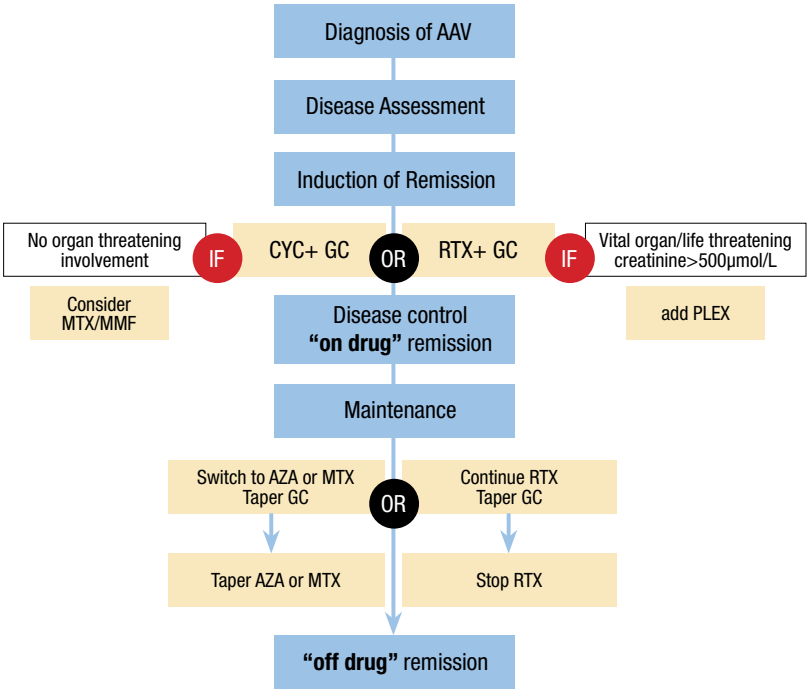

Figure 2. Treatment algorithm for anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), as recommended by the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) Standards, Guidelines, and Audit Working Group.[31] Abbreviations: AZA=azathioprine; CYC=cyclophosphamide; GC=glucocorticoid; MMF=mycophenolate mofetil; MTX=methotrexate; PLEX=plasma exchange; RTX=rituximab.

Maintenance of Remission

AAV is a relapsing condition, with the risk of relapse influenced by both disease and treatment factors.[22] Successful disease remission should be managed with the withdrawal of cyclophosphamide and substitution with either azathioprine or methotrexate, according to the BSR-BHPR guidelines.[31] They suggest mycophenolate mofetil or leflunomide as alternatives in situations of intolerance to or ineffectiveness of azathioprine or methotrexate. Maintenance therapy should be continued for ≥24 months following successful remission.[31]

The BSR-BHPR guidelines include rituximab as another option for maintenance therapy, and re-treatment can be can be decided based on fixed-interval regimens or evidence of relapse.[31] Note, however, that AAV maintenance therapy is not a registered indication for rituximab in New Zealand.

The efficacy of rituximab as maintenance therapy has been evaluated in the Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN).[32] Preliminary results from this randomized trial show that the risk of major relapse was significantly ($p<0.0001$) lower with rituximab (12.7%) than with azathioprine (48.1%) at 39 months after starting maintenance therapy in AAV patients who had achieved remission with conventional therapies.[32]

Relapsing and Refractory Disease

Approximately 50% of treated patients experience one or more relapses by five years according to a large observational study.[33] The BSR-BHPR guidelines recommend increased immunosuppression in response to relapsing disease.[31] An increase in prednisolone dosage and optimization of concurrent immunosuppression is recommended for minor relapses and use of either rituximab or cyclophosphamide with an increase in prednisolone dosage is recommended for major relapses. Also worthy of consideration is the addition of IV methylprednisolone or plasma exchange.[31]

Approximately 5% of patients fail to attain remission after induction therapy.[34,35] In a retrospective analysis of data from the German Registry of Autoimmune Diseases, rituximab achieved complete and partial responses of 40% and 52%, respectively, in patients with refractory AAV and was well tolerated.[36] The BSR-BHPR guidelines consider rituximab to be more effective than cyclophosphamide for refractory disease, and recommend it as the first choice in rituximab-naïve patients.[31]

Expert's Case Study

A 57-year-old Caucasian woman presented in 2007 with 5kg weight loss and fevers, and imaging of her chest at the time revealed cavitating lung nodules. Blood tests showed that she was cANCA positive on immunofluorescence and PR3-ANCA positive at high titre. A diagnosis of GPA (Wegener's granulomatosis) was made. Her co-morbidities included type 2 diabetes and hypertension. She was treated initially with pulse IV cyclophosphamide and oral glucocorticoids for 6 months, with a good clinical response (total of 7g cyclophosphamide). Her ANCA tests were negative at the time she was switched to maintenance therapy. She was maintained in remission with methotrexate 20 mg/week due to intolerance to azathioprine.

Three years later she presented with increasing myalgia, a hoarse voice, nasal crusting and bleeding, and dark urine. Her PR3-ANCA titre was high positive. Urine analysis showed 3 g/d of protein and microscopic haematuria with red cell casts. Creatine was raised at 230 µmol/L, CRP 131, Hb 101, and white cell count was 12 x 10^9/L. A kidney biopsy confirmed cresentic glomerulonephritis consistent with AAV. Upper airway endoscopy demonstrated inflammatory tissue around the sub-glottic region with biopsy showing non-specific inflammation only.

This woman has obviously had a flare of her AAV and needs further induction therapy to get her back into remission. The two options are either rituximab or further cyclophosphamide. In an ideal world

the best option is probably rituximab (which is more effective in relapsing disease), but in a cost-constrained treatment environment she received more IV cyclophosphamide (total of 6g) and went back into remission. She has now had a total of 13g of cyclophosphamide. If she flares in the future she should receive rituximab as more cyclophosphamide would push her above the 15g threshold agreed with PHARMAC due to the rising risk of malignancy.

Expert's Concluding Remarks

The AAV are serious life- and organ-threatening disorders where accurate diagnosis and early treatment are important. Conventional therapy over the last few decades has involved treatment with cyclophosphamide and a glucocorticoid. Initially, therapy was with cyclophosphamide long-term. However, the recognition of toxicity (infection, infertility, and malignancy) directly related to the total cumulative dose led to studies in the late 90s and early 2000s looking at limiting the dose of cyclophosphamide. The results of these studies informed our current treatment paradigm of using cyclophosphamide to induce remission over the first 3-6 months and then using less toxic medications such as azathioprine to maintain remission. Rituximab has now been shown to be a reasonable alternative to cyclophosphamide for induction therapy in AAV – a 4-week induction course is as effective at inducing and maintaining remission for 18 months as cyclophosphamide given for 3-6 months followed by azathioprine for 15 months (RAVE trial long-term follow-up). Rituximab was better in the RAVE trial in inducing remission in patients having a flare of disease compared with cyclophosphamide. The perceived benefits of rituximab are reduced risk of infertility and lower risk of long-term malignancy (although both of these benefits have yet to be proven as follow-up is still too short from the current trials in rituximab for AAV). Rituximab has also been shown to be superior to azathioprine at maintaining remission (MAINTRITSAN trial and other observational studies). The optimal re-treatment frequency to maintain remission is being studied in the RITAZAREM trial.

In New Zealand, PHARMAC has recently funded the use of rituximab in DHB hospitals for induction therapy in AAV for specific indications. Rituximab can be used in patients who have failed induction therapy with cyclophosphamide, had a previous high cumulative dose of cyclophosphamide or where a further course of cyclophosphamide would take the cumulative dose above 15g, or who have some contraindication to cyclophosphamide and methotrexate. Rituximab can also be used in women of child bearing age who want to preserve their fertility and in patients who have had haemorrhagic cystitis, bladder malignancy or haematological malignancy.

A notable exception for its use is in MPO-ANCA-positive patients (this usually means a MPA phenotype) where there is an additional requirement to trial mycophenolate mofetil (MMF) prior to considering rituximab. There is very limited published randomised controlled data on the use of MMF, but an abstract presentation of the MYCYC trial (a non-inferiority trial of MMF vs cyclophosphamide for induction therapy in AAV powered to show that there would be <12% fewer patients who achieved remission with MMF compared to cyclophosphamide) demonstrated that the remission rates were numerically similar. However, due to lower remission rates than anticipated in both groups when powering the study, the confidence intervals where wider than the 12% criteria to show non-inferiority. Despite the lack of hard evidence, the preliminary results of the MYCYC trial and other observational data would suggest that a treatment trial with MMF is a reasonable option in this group of patients.

PHARMAC has at this stage not funded routine re-treatment with rituximab to maintain remission. However, if a patient flares, rituximab can be used again as induction therapy.

Take-Home Messages

- AAV is a relatively uncommon condition; however, its disease burden is considerable.
- Left untreated, AAV progresses to a fatal outcome due to vital organ failure.
- High-dose glucocorticoids in combination with either cyclophosphamide or rituximab induces remission in most patients.
- Successful remission should be followed by remission maintenance treatment with azathioprine or methotrexate.
- Relapses and drug toxicity are common so long-term follow-up is required.

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