

Draft clinical guidelines for management of ANCA vasculitis

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Executive summary

Guidance for the clinical management of ANCA vasculitis has been provided by a 2016 EULAR document which the VINE network has adopted as a basis for clinical care for these patients in Ireland. Patients should be managed in consultation with one of the VINE centres of expertise and categorised in a protocolised fashion into organ/life-threatening and non-organ/life-threatening disease. Induction therapy should generally comprise rituximab or cyclophosphamide in conjunction with glucocorticoids, with use of other agents such as methotrexate and mycophenolate reserved for those without organ-threatening disease. Sample protocols for cyclophosphamide, rituximab and glucocorticoid are [included](#). Plasma exchange is advised for patients with a creatinine level >300uM. Most patients require maintenance therapy after induction of remission. Azathioprine is most commonly used, although an increasing number of patients are being treated with repeated doses of rituximab. Maintenance treatment duration is highly individualised, with a rough guide of two and three years for MPO-ANCA and PR3-ANCA positive patients respectively. Strong consideration should be given to pneumocystis prophylaxis, bone protection and pre-induction immunisation.

Introduction

Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Eosinophilic granulomatosis with polyangiitis (EGPA) are together termed the ANCA-associated vasculitides (AAV) (1). These are rare acquired autoimmune multi-system disorders with an annual incidence of 15/million and overall prevalence of approximately 1/5,000.

Although occurring throughout life, most cases occur in adults and present with a myriad of symptoms / signs to a wide range of specialties. The initial diagnosis of AAV frequently presents a diagnostic dilemma as many clinicians will be unfamiliar with the condition, with delays in diagnosis of 6-12 months being typical. During that time, organ destruction progresses such that 30% develop end-stage kidney disease, and intensive care unit level care is often required due to multi-organ dysfunction.

AAV are chronic relapsing conditions that require coordinated long term multi-disciplinary input. The goal of these guidelines is to assist Irish clinicians in standardising and harmonising their approach to the management of AAV. Thus, every person with AAV in Ireland should have access to the same high standard of care, with effective use of high cost immunotherapy in line with international best practice.

In the absence of treatment, AAV with renal involvement is associated with very poor outcomes. There is high quality evidence that treatment with corticosteroids and cyclophosphamide has dramatically improved the short- and long-term outcomes of AAV with systemic disease. However, despite this, 5-year mortality remains unacceptably high at 30%.

In 2009 and 2016 the European League Against Rheumatism (EULAR) published extensive peer reviewed recommendations for managing AAV¹ (1). The 2016 EULAR Guideline outlines a standardised approach to the treatment of AAV, including the use of biologic agents, the prognostic value of histopathology and management of long-term complications, integrating these into treatment algorithms.

It is proposed that the Irish Guidelines adopt the EULAR Guidelines in full. We further expand on them to provide Ireland specific guidance about the administration of immunomodulatory therapy for patients with AAV. We focus on informed consent, therapy-associated toxicities, suggested administration protocols and enrolment in the Rare Kidney Disease Registry.

¹ Yates M, et al. Ann Rheum Dis 2016;75:1583–1594 - <https://ard.bmj.com/content/75/9/1583>

Diagnosis

A diagnosis of AAV typically requires:

1. A compatible clinical syndrome (which may include, but is not limited to, any or all of the following: polyarthritis, vasculitic skin rash, glomerulonephritis, scleritis / conjunctivitis, focal neurological signs, sinusitis, deafness, nasal cartilage destruction, lung nodules, pulmonary haemorrhage, GI bleeding/perforation)
2. Positive ANCA testing by both immunofluorescence and ELISA (for anti-PR3 or anti-MPO antibodies), although some cases of renal or sinus-limited disease may be ANCA negative.
3. Consistent histological findings (which may include pauci-immune focal necrotising glomerulonephritis, granulomatous inflammation in lung or nasal tissue, or necrotising vasculitis in other sampled tissue)
4. The absence of a secondary cause of vasculitis (e.g. endocarditis).

In practice, it may not be possible to confirm all 4 diagnostic components.

Stratification of Disease Severity

In a simplification of earlier disease stratification algorithms, the 2016 EULAR Guidelines focus on a dual stratification into organ / life threatening vasculitis *versus* non-organ / life threatening vasculitis.

Therapy for Patients with ANCA Vasculitis

In line with the EULAR Guidelines the following approach is recommended for patients presenting with a diagnosis of *de novo* or relapsing AAV (summarised in Figure 1). It is important that patients with AAV are managed in close collaboration with, or at, centres of expertise. In an Irish context this includes, but is not limited to, centres participating in the Vasculitis Ireland Network (VINE). Patients should expect their treating centre to afford rapid access to specialists with expertise in AAV, immunological monitoring, the use of rituximab, specialised radiography, diagnostic histopathology, assessment of eye / ENT involvement and plasma exchange.

- For **remission-induction** of new-onset organ/life-threatening AAV we recommend treatment with a combination of glucocorticoids and either **cyclophosphamide** OR **rituximab**
 - We favour pulsed intravenous over oral cyclophosphamide due to the reduced cumulative dose of cyclophosphamide overall, a reduced risk of bladder-related complications and similar long term renal outcomes, albeit at the cost of a higher long term relapse rate in those at high risk (e.g. anti-PR3 antibody specificity, large granuloma burden).
- Strongly consider use of **plasma exchange** for AAV patients presenting with a serum creatinine level of ≥ 300 $\mu\text{mol/L}$ due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Factors that should be considered in this shared decision with the patient include the acuity of the presentation, the presence of pre-existing chronic kidney disease and

the appearance of the renal histopathology: evidence of slowly developing or longstanding chronic tissue injury mitigates against use of plasma exchange. We do not recommend general use of plasma exchange for treatment of isolated pulmonary haemorrhage; if this occurs in conjunction with kidney involvement, the decision should be guided primarily by the degree of kidney damage.

- For remission-induction of non-organ / life threatening AAV treatment options also include a combination of glucocorticoids and either methotrexate or mycophenolate mofetil (MMF). Methotrexate is reserved for those without renal impairment. The use of methotrexate or mycophenolate mofetil should not be used for remission induction in the following scenarios:
 - Meningeal involvement
 - Retro-orbital disease
 - Cardiac involvement
 - Mesenteric involvement
 - Acute-onset mononeuritis multiplex
 - Pulmonary haemorrhage of any severity
- For remission maintenance of AAV we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil. The factors that guide choice of regimen include:
 - *ANCA specificity*: accumulating evidence favours use of rituximab for maintenance therapy in PR3 ANCA vasculitis.
 - *Thiopurine S-methyltransferase (TPMT) status*: if TPMT level low consider avoiding use of azathioprine.
 - *Immunoglobulin levels*: in the setting of secondary hypoglobulinemia rituximab should be used only if other options not available or ineffective.
 - *Renal impairment*: if sGFR <30ml/min methotrexate should be avoided unless other options not available.
 - *Choice of induction agent*: this does not have a strong impact on choice of maintenance therapy as randomised trial data exist to support use of rituximab maintenance therapy after both cyclophosphamide and rituximab induction therapy
 - *Mycophenolate*: This agent should be reserved for those who cannot receive other.
 - *Rituximab*: Either six-monthly programmed doses or dosing to maintain peripheral B-cell depletion can be used. The latter strategy employs less rituximab overall without an increase in clinically significant relapses, although it does require more intensive monitoring.
- For a major AAV relapse with organ-threatening or life-threatening disease we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR Rituximab. Consideration should be given to the cumulative cyclophosphamide burden and the potential for reversibility of end organ injury.
- Treatment resistant OR relapsing disease despite adequate standard therapy should be managed in a centre of expertise.
- We support the use of a [protocol-based assessment](#) in the initial management of patients diagnosed with AAV.

- All patients should be considered for inclusion in the [RKD Registry](#).

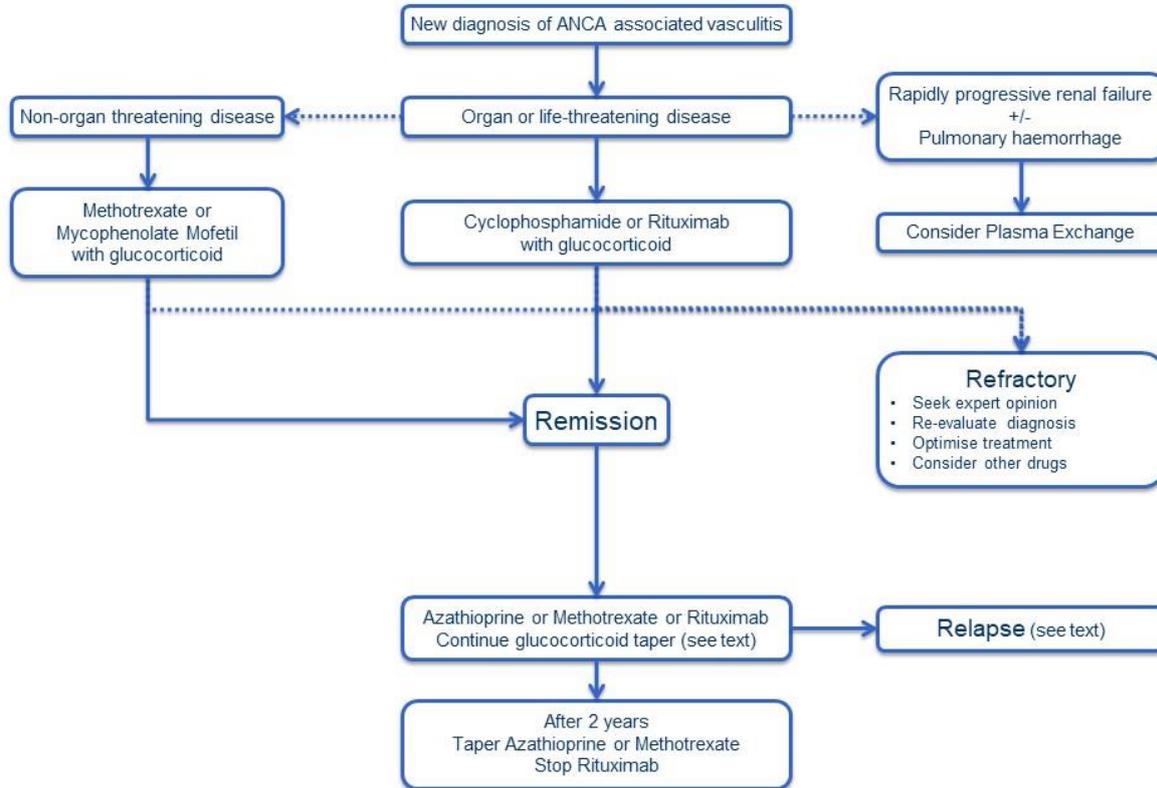


Figure 1. Suggested algorithm for management of AAV.

Patient Information

All patients with AAV should be given a clear verbal explanation of the nature of their disease and proposed treatment plan. This should be supplemented by written information (sample VINE Patient Information Document provided on [the VINE website](#) and [here](#)). We recognise that the internet can provide immediate, easy access to reliable and up-to-date information and advice, and to patient support groups which provide the reassurance of peer support and the ability to share knowledge and experience. However, patients should be counselled that the internet can also provide incorrect, unproven and even dangerous information. A patient who understands and is educated about the disease is frequently better able to recognise the early signs and symptoms of relapse.

Informed Consent

Informed written consent should be obtained before prescribing cyclophosphamide and rituximab due to the frequency and severity of the potential side effects. All patients receiving rituximab should receive a Patient Information Leaflet about the potential risk of progressive multifocal leucoencephalopathy and an [alert card](#) at each infusion in line with HPRA Guidelines.

Corticosteroid Administration in AAV

For severe, organ and/or life-threatening acute disease, up to 3 pulses of 0.5-1g methylprednisolone may be considered. High dose intravenous methylprednisolone should not be **routinely** administered to all patients with a new diagnosis of AAV.

A proposed corticosteroid dosing schedule for patients receiving induction therapy with cyclophosphamide OR rituximab is provided [on the VINE website](#). A target prednisolone dose of 5-7.5mg is desirable by 3-6 months.

It is considered useful to give patients an explicit written dosing schedule for their prednisolone taper and written explicit instructions not to stop their corticosteroids without consulting their treating physician.

Cyclophosphamide Administration in AAV

Cyclophosphamide is an alkylating agent used to treat some types of cancer and is a potent immunosuppressive agent. The dosage must be [individualized](#). The prescribed dose will depend on the patient's age, weight, level of renal function and the results of laboratory monitoring (in particular, blood cell monitoring).

All patients receiving cyclophosphamide should be counselled prior to written informed consent with regard to the following potential side effects:

1. Risk of infection (possibly life threatening)
2. Risk of loss of fertility (males and females)
3. Hair loss(rare)/thinning (common)
4. Haemorrhagic cystitis (rare (<5%) with iv administration, more common with oral)
5. Increased risk of bladder cancer (approx 1% at 10 years, increased risk of lymphoma and non-melanomatous skin cancer)
6. Teratogenicity (males and females of child bearing age only).

Cyclophosphamide is contra-indicated in patients with:

1. Hypersensitivity to cyclophosphamide or to any of its metabolites.
2. Acute severe infection
3. Acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy
4. Urinary outflow obstruction

5. Patients with severely depressed bone marrow function
6. Patients with a history of bladder cancer or haemorrhagic cystitis
7. Pregnancy / Breastfeeding

Patients of both sexes in the reproductive age should take contraceptives during therapy and for 3 months post-therapy.

Other considerations

Immunisation. Consideration should be given to immunisation with inactivated vaccines including: pneumovax, Haemophilus influenzae B and influenza. Unless vaccination can occur at least 2 weeks before starting immunosuppression, patients should be re-vaccinated 6 months after completing therapy as the initial immune response is likely to be sub-optimal.

Sperm banking. This should be considered if it can be arranged without delaying therapy irrespective of proposed induction therapy.

Ovarian protection. Case-control studies and rodent experiments have suggested that suppressing ovarian activity during cytotoxic therapy using GnRH agonists can preserve fertility. This premise has not been formally tested and its utility is debated. The protocol involves giving Goserelin 3.6mg monthly. The first dose should be given as soon as possible. In the outpatient setting, the best time to give this is at the clinic appointment. This may cause menopausal symptoms. It is generally not possible to arrange oocyte collection prior to induction therapy.

Dialysis. Cyclophosphamide is removed very efficiently by dialysis. All cyclophosphamide doses should be administered after dialysis.

Plasma Exchange in AAV

Plasma exchange is advised for patients with AAV and a serum creatine level of >300 µmol/L due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage, especially if occurring in conjunction with glomerulonephritis.

General protocol: 3-4L/exchange x 7 exchanges over 7-10 days. Replace final litre with Fresh Frozen Plasma if active bleeding is present (eg pulmonary) or if a renal biopsy has been performed within 48hours.

Rituximab Administration in AAV

Rituximab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes and activates complement-dependent cytotoxicity. It may be used in the treatment of de novo and relapsing ANCA vasculitis. However, we recognise that there are significant costs associated with its use and there are no compelling data suggesting superiority of Rituximab over cyclophosphamide in de novo ANCA vasculitis. Therefore, we recommend limiting the use of Rituximab to the following situations in consultation with a specialist centre:

- AAV that has remained active despite a course of cyclophosphamide lasting 3–6 months;
- Major relapse in the face of a previous complete cyclophosphamide course (or >22g cumulative exposure), or evidence of fragile marrow/myelodysplasia.
- Cyclophosphamide is contraindicated or not tolerated.
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility.
- The person has had uroepithelial malignancy.

All patients receiving rituximab should be counselled prior to written informed consent with regard to the following potential side effects:

1. Risk of infection (possibly life threatening)
2. Risk of progressive multifocal leukoencephalopathy (PML).
3. Reactivation of Hepatitis B & C

Rituximab is contraindicated in patients with:

1. Hypersensitivity to the active substance or to murine proteins.
2. Active, severe infections e.g. tuberculosis, sepsis and opportunistic infections
3. Patients in a severely immunocompromised state e.g. where levels of CD4 or CD8 are very low.
4. Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease.

The recommended dosage of rituximab for induction of remission therapy of AAV is 375 mg/m² body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total). However, rituximab can also be given as two doses of 1g separated by 2 weeks, although this dosing regimen has not been tested in AAV clinical trials. There is evidence that a single dose of 375mg/m², with confirmation of B cell depletion, is effective in non-organ threatening disease. Complete ablation of peripheral CD19+ cells (<0.005/ml) at 2 weeks after the final infusion is the goal. An administration Protocol is provided [on the VINE website](#).

Other considerations:

Progressive multifocal leukoencephalopathy

All AAV patients treated with rituximab must be given written information regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).

Infections

Serious, potentially fatal, infections can occur during therapy with rituximab. Rituximab should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Prophylaxis against *Pneumocystis Jiroveci* pneumonia must be considered in all patients receiving Rituximab.

Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g. hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with Rituximab, at one month and monitored at 3 monthly intervals thereafter.

Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab treatment, patients should be re-evaluated for any potential risk for infections.

Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in patients receiving rituximab. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. This should include HBsAg- and HBcAb-status.

Immunization

Physicians should review the patient's vaccination status and follow current immunization guidelines prior to rituximab therapy. Vaccination should be completed at least 4 weeks prior to first administration of rituximab.

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Therefore, vaccination with live virus vaccines is not recommended whilst on rituximab or whilst peripherally B cell depleted.

Patients treated with rituximab may receive non-live vaccinations. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.

Contraception in males and females

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab. Rituximab should be discontinued if possible at least six months before planned conception.

Bone Protection

Glucocorticoid therapy is associated with a significant risk of bone loss, which is most pronounced in the first few months of use. All patients should take between 600-800iu of Vitamin D daily and

maintain a calcium intake of 1000-1200mg day through diet/or supplements. Glucocorticoid-induced bone loss should be actively managed with oral bisphosphonate therapy as a first line intervention, in those already at high risk for fracture (older age, post-menopausal, prior fragility fracture). In lower risk individuals, clinical risk factor and bone density assessment may help guide therapy. The Fracture Risk Assessment Tool (FRAX) can help guide which individuals require bisphosphonate therapy.