



## **Evolving Trends and Changing Perspectives in ANCA Associated Vasculitis– A Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. 'All authors read and approved the final manuscript.*

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### **ABSTRACT**

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a group of conditions characterized by inflammation and destruction affecting small to medium vessels accompanied by excess morbidity and mortality. These diseases present as multisystem diseases with variety of signs and symptoms. Earlier AAV were considered fatal diseases, however recent advances have changed them to chronic illnesses associated with morbidity & relapses. This review analyses recent developments in the pathogenesis, treatment and follow up of ANCA associated vasculitis.

**Keywords:** *Anti-neutrophil cytoplasmic antibody (ANCA); Vasculitis; Microscopic polyangiitis (MPA); Granulomatosis with polyangiitis (GPA).*

## 1. INTRODUCTION

ANCA associated vasculitis encompasses group of multisystem autoimmune disorders which are categorised by inflammation and damage of small- and medium-sized blood vessels along with presence of circulating ANCA. It was first time in 1980 that perinuclear and cytoplasmic patterns were discovered on indirect immunofluorescence and also myeloperoxidase and proteinase 3. Then in 1982, a short report recounting the clinical course of eight patients diagnosed with a segmental necrotising glomerulonephritis first time labelled the connection between ANCA and vasculitis [1]. The AAV comprises granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome).

## 2. CLASSIFICATION

The American College of Rheumatology in 1990 developed classification criteria for GPA and EGPA. Chapel Hill Consensus Conference (CHCC) in 1994 termed definitions for AAV and these were revised in 2012 [2]. Currently there are two broad categories which include classification based on phenotypes and serotypes. Conventional classification based on phenotypes has significant overlap of clinical features [3]. ANCA-associated vasculitis (AAV) by definition involves necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, arterioles and small arteries) and is accompanied by MPO-ANCA or PR3-ANCA [4]. Some patients may not have ANCA, hence a prefix is added indicating ANCA reactivity, eg PR3-ANCA, MPO-ANCA, ANCA-negative. Granulomatosis with polyangiitis (GPA) is characterised by necrotising granulomatous inflammation mostly associated with upper and lower respiratory tract involvement and necrotising vasculitis affecting chiefly small to medium vessels (eg capillaries, venules, arterioles, arteries and veins). Eosinophilic granulomatosis with polyangiitis (EGPA) is characterised by eosinophil-rich and necrotising granulomatous inflammation often involving the respiratory tract, and necrotising vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. Microscopic polyangiitis (MPA) is associated with necrotising vasculitis predominantly affecting small vessels (ie

capillaries, venules or arterioles). It is frequently associated with glomerulonephritis and pulmonary capillaritis often occurs. Granulomatous inflammation is characteristically absent. Second classification based on serotypes, according to ANCA specificity includes PR3-ANCA disease and MPO-ANCA disease. Relapse rates are higher in PR3-ANCA whereas mortality is higher in MPO-ANCA [5].

## 3. EPIDEMIOLOGY OF AAV

AAV diseases are rare with an incidence of about 20 per million populations per year in Europe and North America. It is slightly more common in males than females and is a disease of elderly population with peak at age between 60 and 70 years. It is more common in white and Asian population [6]. Geographically there is variation in occurrence with GPA more common in Northern Europe and Australia/New Zealand, while MPA is more common in Southern Europe and Asia. There are certain factors identified to elicit AAV which includes *Staphylococcus aureus* infection. Other environmental factors include silica exposure, hydrocarbon exposure, and pesticides. Also, there are many medications linked with AAV which include hydralazine, propylthiouracil [7], cefotaxime [8], minocycline [9], vancomycin [10], cocaine adulterated with levamisole [11] anti-tumor necrosis factor agents [12] and, infliximab [13].

**Genetics:** A genome wide association study has shown both major-histocompatibility-complex (MHC) and non-MHC associations with ANCA-associated vasculitis. The strongest genetic associations have been found with the antigenic specificity of ANCA, not with the clinical syndrome [14]. Anti-PR3ANCA was associated with HLA-DP and the genes encoding  $\alpha$  (1)-antitrypsin (SERPINA1) and proteinase 3 (PRTN3). Anti-MPOANCA was associated with HLA-DQ [15].

**Clinical presentation:** The clinical features of the AAV are wide-ranging and hence the presentation can be quite diverse, stretching between mere skin rashes to fulminant multisystem involvement. Distinctive features of GPA include nasal crusting, stuffiness and epistaxis, uveitis, upper respiratory tract involvement and often, when in the context of an active urinary sediment, renal involvement. Presentation of patients with MPA is typically at older age and with more severe renal disease than GPA together with rash and neuropathy.

EGPA characteristically presents as a multisystem disease with asthma, nasal polyposis and peripheral blood eosinophilia

**Activity assessment:** There are some consistent authenticated clinical methods to quantify disease activity and damage in systemic vasculitis patients. Their inclusion in patient management will provide a lucid basis for clinical evaluation and deciding therapy, by providing reproducible definitions of relapse, remission and response to therapy. These include the Birmingham Vasculitis Activity Score (BVAS) [16], Five factor score (FFS) [17] and Vasculitis damage index (VDI) [18] and combined damage assessment index (CDA) [19].

**Investigations:** AAV are rare diseases with wide ranging presentation, hence high index of suspicion is required for the diagnosis especially in life threatening situation when there is urgent need to institute the therapy. Detailed history and examination is of crucial importance along with laboratory tests. Laboratory investigations include urine examination with dipstick, microscopy and quantification of 24 hours urine proteins, kidney function test. Serological tests include antinuclear antibody (ANA), PR3 and MPO ANCA (cANCA and pANCA respectively) and anti-glomerular basement antibody (anti GBM Ab) [20]. Other tests include chest X ray and cardiac evaluation (especially to rule out bacterial endocarditis). Additional investigations may be required include CT scan or MRI of chest, brain, spine, orbit or ear, nose and throat as per the organ involvement. Tissue diagnosis is always required; however treatment needs to be started immediately and should not be delayed just to get a biopsy.

#### 4. ANCA TESTING

Type of testing: Many laboratories use indirect immune fluorescence assay (IIF) as a screening test for ANCA. A 2017 international consensus statement on ANCA testing recommended initial testing for suspected AAV with immunoassays for PR3-ANCA and MPO-ANCA, rather than IIF. Role of serial ANCA levels for determining remission is controversial. Treatment needs to be titrated based upon overall assessment of the patient rather than ANCA measurement alone [21].

**Treatment:** As per definition, remission of disease is when there is no detectable disease activity using a recognised tool like BVAS.

Recent advances in management, early detection and timely intervention has changed the AAV prognostically from potentially fatal disease to a chronic, relapsing disease. Glucocorticoids and cyclophosphamide are agents well established for use in induction of remission. Newer therapies consider Rituximab with lesser toxicity of cyclophosphamide and where cyclophosphamide is contraindicated. Other agents include methotrexate, and mycophenolate mofetil in less severe disease [21]. Patients presenting with severe renal impairment need plasma exchange, high dose corticosteroids and cyclophosphamide.

**Cyclophosphamide [22,23]:** Two major trials studied oral versus pulsed cyclophosphamide CYCAZAREM (cyclophosphamide versus azathioprine for early remission phase of vasculitis) and CYCLOPS (Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis).

**Rituximab:** Two RCTs have tested Rituximab, RAVE (Rituximab versus cyclophosphamide for ANCA-associated vasculitis) and RITUXVAS. In both RCTs patients received high-dose glucocorticoids with subsequent dose tapering and rituximab in dose of 375 mg/m<sup>2</sup> of body surface area, once a week for four infusions. Both trials concluded response with Rituximab to be almost equivalent to cyclophosphamide. RAVE trial showed Rituximab better for relapsing disease and better response in PR3 positive patients. Another extensively used regimen of Rituximab 1 gm given twice 2 weeks apart has been found to be effective as well. Rituximab administration in those patients undergoing plasmapheresis needs consider significant drug removal by plasmapheresis. Regarding ideal timing of dosing in this situation, there is no consensus although, PEXIVAS trial had suspended plasma exchange for 48 hours post initial Rituximab dose [24-25].

**Mycophenolate Mofetil:** MYCYC, a randomized controlled trial, assessed the use of Mycophenolate Mofetil (MMF) for remission induction in AAV. MMF was found to be non-inferior to cyclophosphamide for remission induction in AAV, however it resulted in higher relapse rate. Dose of MMF used was 2-3 g/d orally. This study concludes that in MPO-ANCA patients with mild to moderate renal involvement and without life-threatening extra renal vasculitis MMF and glucocorticoids can be used as a first-line induction [26-27].

**Table 1. Activity assessment**

Score Name	Birmingham Vasculitis Activity Score (BVAS)	Five factor score (FFS)	Vasculitis damage index (VDI)	Combined Damage Assessment Index (CDA)
Prediction by score	Activity Survival	Survival Prognosis	Measures damage Predicts Outcome	Measures damage
Factors included	9 sections & 56 items	4 positive & 1 negative	64 items grouped into 11 categories	135 individual items in 17 categories
Latest version available	BVAS 3	FFS version 2009	-	-

**Table 2. Trial of Cycazarem and Cyclops**

Sr. No.	Name of trial	CYCAZAREM	CYCLOPS
1.	Dose of Cyclophosphamide	Oral daily 2 mg/kg/day with glucocorticoids for 3–6 months	Pulsed intravenous cyclophosphamide (10–15 mg/kg)
2.	Remission	>90%	>90%
3.	Cumulative dose of the drug & side effects	More	Less
4.	Risk of relapse	Less	More
5.	Inclusion in recent guidelines	No	Yes

**5. KEY POINTS ABOUT TREATMENT**

1. For remission-induction.
  - a. New-onset organ-threatening AAV: Combination of glucocorticoids and either cyclophosphamide OR rituximab.
  - b. Non-organ-threatening AAV: Combination of glucocorticoids and either Methotrexate or Mycophenolate Mofetil.
2. For a major relapse of organ-threatening or life-threatening disease: Treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.
3. Indications for Plasma exchange: Serum creatinine level of >500 µmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis (RPGN) in the setting of new or relapsing disease and severe diffuse alveolar haemorrhage.
4. For remission maintenance: Combination of low-dose Glucocorticoids and either Azathioprine, Rituximab, Methotrexate or Mycophenolate Mofetil.
5. Duration of remission-maintenance therapy for at least 24 months following induction of sustained remission.
6. For AAV refractory to remission-induction therapy: Shift from cyclophosphamide to rituximab or from rituximab to cyclophosphamide.

7. Organised clinical assessment rather than ANCA testing for decisions on changes in treatment for AAV.
8. Immunisations against infectious disease according to local policy.

**6. CONCLUSION**

In AAV immuno suppression therapies have evolved and have improved survival significantly. Otherwise without treatment, prognosis is grave. There are significant side effects of long term immuno suppression. Presently, we need therapies with maximum benefit in terms of improved disease activity measures, least risk of relapses and with minimum side effects. Advantage of plasma exchange is still not well recognized; also role of complement C5a receptor inhibitor avacopan as a safer alternative is yet not established. Further research and trials will guide in personalizing AAV care of individuals.

**CONSENT**

It is not applicable.

**ETHICAL APPROVAL**

Ethical Approval taken from institutional ethics committee

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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