

## Current concepts in Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated Vasculitis

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### ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is an uncommon inflammatory disease of small to medium-sized vessels that may present with constitutional symptoms, unexplained hemoptysis, pulmonary infiltrates & glomerulonephritis, though it can affect any organ system. Evidence from clinical studies supports a pathogenic role for ANCAs in the development of AAV. Whenever possible histologic confirmation of vasculitic process should be sought from involved organ, With respect to treatment of AAV, glucocorticoids, cyclophosphamide and other conventional therapies are commonly used to induce remission in generalized disease. Pulse intravenous cyclophosphamide is equivalent in efficacy to oral cyclophosphamide but seems to be associated with less adverse effects. Nevertheless, alternatives to cyclophosphamide therapy have been investigated. Furthermore, rituximab is equally as effective as cyclophosphamide for induction of remission in AAV. If untreated, the vast majority of patients will die within a year usually due to complications such as diffuse alveolar hemorrhage or renal failure. Current treatments improve prognosis but affected patients remain at a substantially higher risk of death and adverse outcomes. This article aims to review the classification of the disease, our understanding of the pathogenesis & also to update on the current established treatment regimens.

### Introduction :

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a disease process characterized by necrotizing inflammation of small vessels, the relative paucity of immune deposits and an association with detectable circulating ANCAs. The three types of vasculitis associated with ANCA are

1. **Granulomatosis with Polyangiitis - GPA.** (Formerly Wegener's granulomatosis)
2. **Microscopic Polyangiitis MPA.**
3. **Eosinophilic Granulomatosis with Polyangiitis EGPA.** (Formerly Churg Strauss syndrome) Collectively, these disorders account for a considerable burden of death and disability worldwide and are of great clinical importance owing to the vast improvement in prognosis with treatment. As a result, AAV has been studied extensively in recent years<sup>1</sup>. Most of the data come from White populations of European

descent, and the overall annual incidence is estimated at approximately 1020 / million with a peak age of onset in those aged 65 to 74 years<sup>2</sup>.

**Indian perspective** - the primary vasculitic disorders account for < 1% of all vasculitic diseases diagnosed in rheumatology clinics; the lung is involved in 84% to 94% cases. GPA is most frequently diagnosed in India, EGPA have been reported in negligible numbers. Pulmonary vasculitis is misdiagnosed as tuberculosis (TB), at least initially; in 40% to 50% of the cases pulmonary involvement with haemoptysis and radiologic appearances (justifiably) lead to suspicion of tuberculosis. While this is acceptable, it is pointed out that a diagnosis of vasculitis should be considered in any case of 'unproven' tuberculosis that fails to respond to standard therapy in 1-2 months. If diagnosis of AAV is delayed, precious time is lost and patients often present when significant organ damage is already present. Hence early diagnosis of AAV is of paramount importance.<sup>3,4</sup> In recent years lot of changes have occurred in the field of ANCA Associated Vasculitis (AAV) with new nomenclature & advances in therapy including the use of Biologic agents such as Rituximab<sup>1</sup>. They have been classified together in

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the majority of Systemic Vasculitis classification systems published since the introduction of ANCA, including the most recent 2012 Chapel Hill classification system<sup>5</sup>. ANCA should be tested in patients with chronic destructive upper airway disease, pulmonary nodules, renal and pulmonary inflammatory disease, rapidly progressive glomerulonephritis, skin vasculitis with systemic illness, mononeuritis multiplex, subglottic stenosis of the trachea, and retro-orbital mass. More than 90% of GPA and MPA patients are ANCA positive.

#### **Clinical manifestations of ANCA - Associated Vasculitis (AAV)**

<i>System</i>	<i>Manifestations</i>
Constitutional	Fever, weight loss, anorexia, general malaise
Musculoskeletal	Myalgia, arthralgia
Skin	Palpable purpura, urticaria
Kidney	Proteinuria, hematuria, renal insufficiency, renal failure, necrotizing glomerulonephritis
Respiratory tract	Dyspnea, cough, hemoptysis; lung infiltrate, interstitial lung disease, pulmonary hemorrhage, sinusitis, nasal crusting.
Nervous system	Peripheral neuropathy, especially mononeuritis.
Gastrointestinal Tract	Fecal blood, elevated liver enzymes; diarrhea, nausea, vomiting, abdominal pain

#### **Granulomatosis with Polyangiitis (GPA)**

GPA commonly has the classic triad of involvement of the upper respiratory tract, lungs, and kidneys<sup>6</sup>. Upper respiratory tract signs and symptoms like sinusitis, nasal ulcers, otitis media, or hearing loss are seen in 70 percent of patients and pulmonary infiltrates or nodules that may cavitate develop in 85 percent of patients. Serum anti-proteinase 3 or PR3 (c-ANCA) is positive in 75 to 90%, although 20 percent may have positive p-ANCA. Open lung biopsy is the most definitive diagnostic test. Sinus biopsy is diagnostic in only 30 percent of cases because inflammatory findings are often

nonspecific and renal biopsy is also relatively nonspecific. GPA can affect patients at any age, with the peak incidence during the fourth decade of life and is slightly more common in men.

#### **Microscopic Polyangiitis (MPA)**

MPA is the most common ANCA - Associated small-vessel vasculitis, and is characterized by the presence of ANCA and few or no immune deposits in the involved vessels. The kidneys are the most commonly affected organs in 90 percent of patients who have this type of vasculitis. Patients present with variable combinations of renal manifestations, palpable purpura, abdominal pain, cough, and hemoptysis. Most patients have positive MPO-ANCA (p-ANCA), although PR3-ANCA (c-ANCA) may be also present in 40 percent of patients. The most common age of onset is 40 to 60 years and is more common in men.

#### **Eosinophilic Granulomatosis with Polyangiitis (EGPA)**

EGPA (formerly Churg-Strauss syndrome) is a rare disease and has three phases: allergic rhinitis and asthma, eosinophilic infiltrative disease resembling pneumonia, and systemic small vessel vasculitis with granulomatous inflammation. The vasculitic phase usually develops within three years of the onset of asthma. Almost all patients have more than 10 percent eosinophils in the blood. Coronary arteritis and myocarditis are the principal causes of morbidity and mortality. The age of onset varies from 15 to 70 years and is more common in men. French vasculitis study group has devised a scoring system Five-factor score (FFS) to quantify disease activity<sup>7</sup>. 1 point was given for presence of each of 5 factors namely cardiac involvement, GI ischemia, renal insufficiency, proteinuria & CNS disease. Score of 1 is moderate disease & score of 2 or more indicates severe disease with poor prognosis.

#### **Classification & Nomenclature**

Classification of the ANCA-associated vasculitides remains controversial. Existing systems have many deficiencies, especially when applied to unselected patients<sup>8</sup>. Following classification is widely used nowadays.

### Chapel Hill Consensus Conference - 2012, Revised criteria for classification of ANCA vasculitis<sup>5</sup>

ANCA-associated Vasculitis	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. PR3-ANCA, MPO-ANCA and ANCA negative.
Microscopic Polyangiitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules or arterioles). Necrotizing arteritis involving small - and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (Wegener's)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tracts, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels (e.g. capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.
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-sized vessels, and associated with asthma and eosinophilia. ANCA is most frequent when glomerulonephritis is present.

### Anti-Neutrophil Cytoplasmic Antibody (ANCA)

ANCA are specific antibodies for antigens in cytoplasmic granules of neutrophils and monocyte lysosomes. These antibodies can be detected with indirect immunofluorescence microscopy. Two major patterns of staining are present : cytoplasmic ANCA (c-ANCA) and peri-nuclear ANCA (p-ANCA). Specific immunochemical assays demonstrate that c-ANCA is mainly antibodies to proteinase 3, and p-ANCA is antibodies to myeloperoxidase. Using antigen-specific immunochemical assay to characterize ANCA (rather than the pattern of immunofluorescence microscopy) is more specific and more clinically relevant; therefore, the terms proteinase 3-ANCA (PR3-ANCA) and myeloperoxidase - ANCA (MPO-ANCA) are now in use<sup>9</sup>. There are prognostic differences between PR-3 & MPO positivity. PR-3 positivity is an independent predictor of disease relapse & is associated with higher mortality, as compared to MPO. Patients with PR3-ANCA & renal disease may have a faster decline in renal function as compared to MPO-ANCA. Although ANCA detection has diagnostic & prognostic importance in ANCA associated vasculitis, various studies have proven that ANCAs are insufficiently sensitive or specific for monitoring disease activity, predicting relapse or guiding therapy. However at an individual level, in patients in whom relationship between ANCA level & disease activity has been established, serial ANCA testing may have a role in disease monitoring & therapeutic decision making<sup>10</sup>.

### Role of B cells in AAV

The role of B cells in AAV extends way beyond their role in ANCA production. B cells are excellent antigen-presenting cells for antigens delivered via their B-cell receptor for antigen. When costimulated through their innate receptors (eg, Toll-like receptors), B cells can upregulate costimulatory molecules of the B7 family, with T-cell activation. They can also secrete pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF), that can downregulate the function of regulatory T cells and boost the differentiation of

effector T cells. Indeed, the complex and delicate interplay between T cells - including circulating follicular helper T cells and regulatory T cells - and B cells has been observed in GPA patients treated with Rituximab, which is Anti-B cell therapy. Treatment with Rituximab, but not conventional therapy, resulted in restored balance between follicular helper T cells and regulatory T cells.

### Tissue Biopsy for diagnosis of AAVs

Guided tissue biopsies are important in defining the character & extent of the inflammatory process in the diagnosis of AAVs. Histologic confirmation of AAVs should be attempted whenever possible, but treatment should not be delayed in critically ill patients with high suspicion for disease in which the tissue is not readily or safely accessible. Individual clinical presentation should dictate the biopsy location with overall aim of performing safest procedure with highest potential yield. Diagnostic yield depends on organ system biopsied, especially because inflammatory changes may be patchy and examination of large amount of tissue may be required to make histopathologic diagnosis.

### Criteria for diagnosis of AAV

For diagnosis of ANCA associated vasculitis (AAV), the following criteria must be fulfilled

- A) Symptoms and signs characteristic of systemic vasculitis.
- B) At least one of the following :
  1. Histological evidence of vasculitis and / or granuloma formation,
  2. Positive serology for ANCA (either c-ANCA /PR3 or p-ANCA/MPO),
  3. Specific indirect evidence of vasculitis.
- C) No other diagnosis to account for symptoms or signs.

### Definition of disease states

1. Remission : well-controlled disease.
  - i. On drug remission : prednisolone dose  $\leq 10$  mg / day **and** A Birmingham Vasculitis Activity Score (BVAS) of  $\leq 1$  for  $\geq 6$  months.

- ii. Drug-free remission :  $\geq 6$  months off all treatment for vasculitis.
2. Relapse : disease that has been previously well controlled and has become active.
3. Minor relapse : increase of one or more new or worse minor items and no major BVAS items.
4. Major relapse : increase of one or more major BVAS item.
5. Refractory : progressive disease unresponsive to current therapy, i.e. remission is not achieved.

### Treatment guidelines for ANC-Aassociated vasculitis (AAV)<sup>11</sup>

All patients with AAV should be considered to have severe, potentially life - or organ-threatening disease. Treatment regimens are divided into induction, maintenance and long-term follow-up. Patients who relapse may require a further course of induction therapy (secondary).

### The essential principles of management

Rapid diagnosis, rapid initiation of treatment, early induction of remission to prevent organ damage, maintenance of remission with the aim of eventual drug withdrawal and Prevention of drug toxicity

### Primary induction of remission

All patients with newly diagnosed AAV should be assessed for treatment with Glucocorticoids (GCs) and I.V. pulse Cyclophosphamide (CYC) or Rituximab (RTX)<sup>12,13</sup>

**Cyclophosphamide (CYC) :** I.V. pulses of CYC should be given initially at 2-week intervals and then at 3-week intervals foll. The standard dose is 15 mg / kg, reduced for age and renal function. Because of the lower toxicity, the I.V regimen is preferred over oral<sup>14</sup>. Each individual course of CYC should be  $\geq 3$  months and  $\leq 6$  months. Lifetime exposure to CYC should be  $\leq 25$  g since the long-term toxicity of CYC is determined by cumulative dose. Patients on CYC should be monitored regularly and the dose should be reduced if there is CYC-induced leucopenia / neutropenia. Patients intolerant or not suitable to CYC can be effectively treated with Rituximab.

**Mesna** : is used to prevent hemorrhagic cystitis caused by acrolein, a metabolite of cyclophosphamide. Mesna binds to acrolein to form a non-toxic compound and is administered in three doses before and then two and six hours after intravenous cyclophosphamide. The dose of mesna administered is a percentage of the cyclophosphamide dose : 20% if given intravenously or 40% if given orally.

**Rituximab (RTX)** : Rituximab is a genetically engineered chimeric (mousehuman) anti-CD20 monoclonal antibody that depletes B-lymphocytes, thereby reducing the production of antibodies. It was licensed for induction of remission in GPA and MPA in 2013 by the European Medicines Agency for use in the European Union. The RAVE<sup>15</sup> and RITUXVAS<sup>16</sup> trials found that Rituximab was non-inferior to Cyclophosphamide. The British Society for Rheumatology suggests that Rituximab is preferable in situations where the use of Cyclophosphamide is undesirable. RTX is as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable, such as in young people at risk of infertility and those at high risk of infection. The licensed RTX dosing protocol is 375 mg / m<sup>2</sup> / week for 4 weeks, however, 1 g repeated after 2 weeks is equally effective.

**Methotrexate (MTX) and Mycophenolatemofetil (MMF)** : MTX (up to 25-30 mg/week) and MMF (up to 3 g/day) are alternative remission induction agents for patients with evidence of low disease activity, and not at risk of suffering organ damage as assessed by the BVAS. MTX should not be used in patients with moderate or severe renal impairment. MMF may be an alternative to MTX. Regular monitoring with CBC, LFT & KFT, to look for drug side effects.

**Plasma exchange (PLEX)** : Plasma exchange is frequently used in AAV patients, particularly in those presenting with severe renal involvement resulting in rapidly deteriorating renal function. The rationale for plasma exchange is to rapidly remove ANCA and other inflammatory mediators, before the effect of immunosuppressive / anti-

inflammatory agents comes into play. Patients with AAV presenting with severe renal failure should be treated with pulsed CYC and GCs, with adjuvant plasma exchange<sup>17</sup>. Treatment with plasma exchange should also be considered in those with other life-threatening manifestations of disease, such as pulmonary haemorrhage.

**Glucocorticoids (GC)** : Induction therapy for AAV includes treatment with high-dose GCs in combination with another immunosuppressive agent (CYC, RTX). GCs are usually given as daily oral prednisolone 1 mg/kg up to 60 mg with the dose rapidly reduced to 15 mg prednisolone at 12 weeks. GC Intravenous infusions 500 mg to 1 g of methylprednisolone are given initially for severe disease

**Maintenance therapy** : After successful remission, CYC should be withdrawn and substituted with either Azathioprine (AZA) or Methotrexate (MTX). Mycophenolate (MMF) or Leflunomide (LEF) may be used as an alternative. Patients should continue maintenance therapy for at least 24 months following successful disease remission. Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years. Rituximab (RTX) may also be used as maintenance therapy, and re-treatment can be decided based on fixed-interval regimens or evidence of relapse<sup>18</sup>. The recommended RTX regimen uses 1 g every 4 - 6 months for 2 years.

**Withdrawal of treatment** : Patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment. Following GC withdrawal, other immunosuppressive therapy may be withdrawn after 6 months.

**Relapsing disease** : Relapsing disease should be treated with an increase in immunosuppression. A minor relapse may be treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression. A major relapse may be treated with RTX<sup>18</sup> or CYC with an increase in prednisolone. The addition of I.V methylprednisolone or plasma exchange may also be considered. Drivers for relapse need to be

identified and addressed and may include infection, malignancy and change of drug therapy<sup>19</sup>.

**Refractory disease :** RTX is more effective than CYC in refractory AAV<sup>21</sup>. If the patient has not had previous treatment with RTX, then the first choice is RTX. Drivers for refractory disease should be sought and clinicians should consider revision of the clinical diagnosis

**Assessment and monitoring of disease status :** Validated tools such as the Birmingham Vasculitis Activity Score (BVAS) & Vasculitis Damage Index (VDI) should be used to assess disease activity, extent of damage and quality of life. ANCA should be detected using IIF with ELISA to confirm PR3 or MPO specificity and checked at diagnosis, relapse, change of therapy, every 6 months while on treatment and annually while off treatment. Treatment should not be escalated solely on the basis of an increase in ANCA.

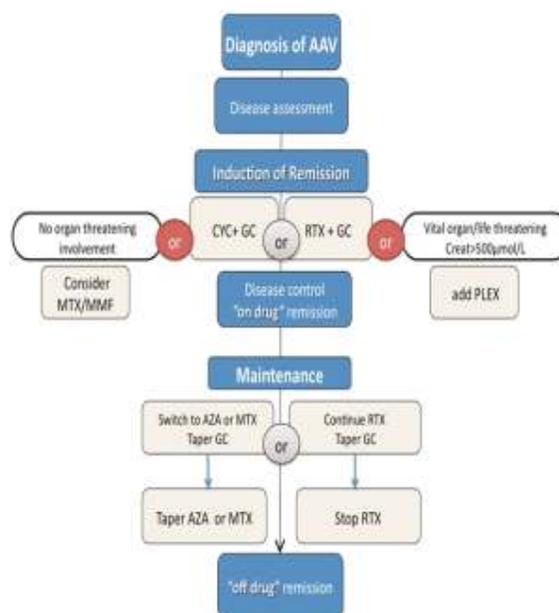
#### Detection and prevention of potential adverse effects of immunosuppressive therapy

The following recommendations should be considered for patients with AAV on immunosuppressive therapy :

- Routine CBC, KFT & LFT - initially every 4 weeks, then every 6-8 weeks.
- Regular urinalysis and Mesna for protection against CYC-induced urothelial toxicity
- Serum immunoglobulin measurement before each cycle of RTX therapy
- Trimethoprim / sulfamethoxazole as prophylaxis against *Pneumocystis jiroveci*
- Antifungal prophylaxis
- Staphylococcal aureus treatment with long-term nasal mupirocin
- Screening for cervical intraepithelial neoplasia in female patients
- Counselling about the possibility of infertility following CYC treatment
- Prophylaxis against osteoporosis where appropriate (GC use > 5 mg/day for > 6 weeks)
- Tuberculosis screening (specially before Rituximab)

- Vaccination against pneumococcal infection, influenza and hepatitis B.
- Cardiovascular and thrombo-embolic risk assessment

#### Flowchart of ANCA associated vasculitis (AAV) treatment<sup>11</sup>



CYC - Cyclophosphamide, GC - Glucocorticoid, RTX - Rituximab, AZA - Azathioprine, MTX - Methotrexate, MMF - Mycophenolatemofetil, PLEX - Plasma exchange Creat > 500 µmol/L = Creatinine > 5.8mg/dl

#### Conclusion

Despite major therapeutic advances in AAVs, there remains a need for therapies that are less toxic to prevent treatment related damage & those that are effective in maintaining remission & preventing relapse. Modern therapy has converted these from fatal conditions to ones with a relapsing and remitting course. Since the advent of Rituximab, the outcome of AAVs is much better with improved survival rates. Histologic confirmation of vasculitis is gold standard rather than relying on ANCA alone. Prevention of opportunistic infections, osteoporosis & bladder toxicity is essential. Fertility issues need to be discussed in young females before immunosuppression. Comorbidities need to be managed properly as they might worsen the organ damage

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