ANCA associated vasculitis – Should we change the standard of care?

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Introduction

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic polyangiitis (EGPA) are the antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV). They are rare autoimmune conditions characterised by inflammation and sometimes necrosis of blood vessels unified by their association with antibody production towards antigens in the neutrophil cytoplasm. The two antigens of interest are proteinase 3 (PR3) and myeloperoxidase (MPO).

This review examines the evidence of the current state of play in the care of patients with this condition.

Standards of care

1. **Early diagnosis and treatment**

   There are no diagnostic criteria for the diagnosis of AAV, there are no diagnostic tests for AAV, and there are no pathognomonic signs for AAV. But like all complex and life-threatening conditions, early diagnosis and treatment must be a goal. We know that damage is accrued over time and increasing damage has adverse prognosis.(1)

a. **Pattern recognition –** Pattern recognition is still the key to making an early diagnosis of AAV.(2) Eosinophilia in asthma, urine analysis in patients with persistent upper respiratory symptoms, the presence of multiple system involvement should all lead to increased suspicion of AAV. We know that GPA is a spectral disorder much like leprosy, ranging from the indolent granulomatous pattern of involvement to acute life-threatening vasculitis.(3) Early diagnosis due to otorhinolaryngological involvement may be the reason for a more favourable prognosis in this group of patients.(4, 5) Conversely, when these 'herald' symptoms are not present, as in MPA, there is a greater chance of sclerosis being present on the renal biopsy.(6)

b. **Getting the name right –** It was not that long ago that all patients with MPA and CSS were grouped together with polyarteritis nodosa.(7) The American College of Rheumatology classified the various systemic vasculitides in 1990 but ignored microscopic polyangiitis.(8, 9) Two international consensus conferences have influenced on our practice on naming the distinct vasculitides.(10, 11) It is also recognised that these are not diagnostic criteria, and their use as diagnostic criteria is met with disappointing results.(12, 13) The authors use the European Medicines Agency algorithm to classify vasculitis in clinical practice.(14) Usually the reason for getting the name right is to inform treatment and prognosis. It could be argued, that in AAV the treatment is led by the level of organ involvement irrespective of the name provided to the condition.(15, 16) But the prognosis is related to the disease classification.(17, 18) On the flip-side, it could be argued that the prognosis may be related more to the clinical phenotype of the disease and therefore the names of the conditions as they currently stand may need revision in the future. For example, a recent review of five clinical trials identified the following clinicopathological subtypes - renal AAV with PR3-ANCA (40%), renal AAV without PR3-ANCA (32%), non-renal AAV' (12%), cardiovascular AAV' (9%), and gastrointestinal AAV' (7%).(19) The five clusters had distinct death and relapse rates. It is

desirable to validate any international consensus criteria in local population to improve acceptance and robustness of concepts that have often been formulated in populations which are genetically and environmentally very different.(20)

c. **Context of laboratory investigations –** From the experience of the authors, the internist is still guided by the presence of absence of ANCA to make a diagnosis of AAV. We know that in the appropriate clinical context, the presence of either PR3-ANCA or MPO-ANCA is highly specific for a diagnosis of small vessel vasculitis.(21) We also know that active GPA/MPA is associated with PR3/MPO ANCA positivity in about 90% of patients.(22) But ANCA are commonly generated by infections. In the Indian scenario, it is very relevant that multi-system diseases like malaria, tuberculosis and leprosy have been known to generate ANCA.(23) In one study of 70 consecutive patients with tuberculosis, 30% were ANCA positive and >75% of these demonstrated either PR3/MPO-ANCA.(24) ANCA cannot be used for diagnosis of AAV, but remain helpful in the appropriate clinical context.

   Histopathology remains the gold standard of diagnosis. It may not always be needed, and it may not always be possible. The results depend on the biopsied organ (lower yield from nasal biopsy than renal biopsy), the skill of the operator and the skill of the pathologist. If there is any doubt about the diagnosis, a histological diagnosis remains the standard of care.

d. **Specialist input –** AAV are rare conditions with an annual incidence of 10-20/million.(25, 26) The British and European societies recommend that these rare and complex patients should be treated at or in consultation with specialist centres.(15, 16) A Medline search for literature from India using the search string "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis"[Mesh] NOT "Case reports"[pt] AND "India"[all fields] provides 6 papers published in the last 5 years (search as of 31/07/2015). During the same time there were 116 papers from the UK. This may suggest that there is a dearth of

academic centres and physicians caring for patients with AAV. Specialist input cannot be provided without adequate number of specialists.

2. **Standardized evaluation of patients with systemic vasculitis**

In the absence of biomarkers, standardized evaluation of patients with AAV using clinical activity tools is recommended for documenting the full extent of the disease and for identifying new or resolving clinical signs on follow up. The Birmingham Vasculitis Activity Score (BVAS) v3 or the BVAS/WG are most commonly used for this purpose.(27, 28) In the author's experience, the use of these tools in routine clinical practice has the following advantages –

a. Identifying sub-clinical disease activity in organs other than the presenting manifestations allowing for recognition of disease extent and differential diagnosis. For example, a 67 year old woman presenting with headache, raised inflammatory markers and monocular loss of vision was considered to have giant cell arteritis till the use of BVAS v3 in clinic identified an old nasal septal perforation leading to further investigations and a diagnosis of GPA. She was MPO-ANCA positive with MRI evidence of meningitis at the orbital apex and cavernous sinus.
b. Identifying new disease in hitherto unaffected systems on follow up. (29)
c. Quantifying the disease activity with a numerical score which can be used to evaluate the course of the disease.
d. Teaching the user the common and serious manifestations of vasculitis.

3. **Standards for choice of drugs**

a. **Remission Induction –** Combination therapy with cyclophosphamide and prednisolone made survival an achievable outcome.(30) However, relapses and iatrogenic side effects were common.(31) This changed the drive in the research agenda to limit the exposure of cyclophosphamide. Remission induction with pulsed intravenous

cyclophosphamide remains the standard of treatment. The regimen devised by the European Vasculitis Society is 15 mg/kg/pulse (max 1.2g) every 2 weeks for the first 3 pulses and then 3 weekly for the next 3 pulses. In a randomized controlled trial of 149 patients with GPA/MPA, comparing this pulsed regimen with daily oral cyclophosphamide 2 mg/kg/day, there was no difference in time to remission in both arms (median of 3 months).(32) The daily oral arm had nearly twice the cumulative cyclophosphamide dose (15.9g vs. 8.2g) and consequently higher hazard of leucopenia. Longer follow-up of this cohort (4.3 years) demonstrated that the pulsed cyclophosphamide group suffered significantly greater relapse rates (40% vs. 21%) but this did not affect mortality.(33) The authors still believe that pulsed cyclophosphamide remains the standard of therapy due to lower cumulative dose of cyclophosphamide.

Rituximab 375 mg/m^2/week for 4 weeks is non-inferior to pulsed cyclophosphamide in producing remission in GPA/MPA.(34) The risk of adverse events is the same with both drugs implying that pulsed cyclophosphamide is not particularly toxic and that most of the therapy-related toxicity may be related to the use of glucocorticoids. In patients with relapsing disease, rituximab has been shown to be superior to cyclophosphamide.(34) Rituximab has become the new standard of therapy for remission induction in patients with relapsing disease and those who have a contraindication to cyclophosphamide, e.g. young women of child-bearing age, patients with urothelial cancers.

In a RCT of 100 patients, methotrexate 20-25 mg/week was non-inferior to cyclophosphamide 2 mg/kg/day in inducing remission.(35) But long-term follow up of these patients (median 6 years) showed that patients treated with methotrexate were more likely to relapse and needed more glucocorticoid therapy.(36) The authors do not use this anymore except in patients with non-organ threatening disease with contraindication to cyclophosphamide who have no evidence of organ

dysfunction. Nasal bony destruction and olfactory dysfunction should not be considered as non-organ threatening disease for this purpose.

Mycophenolate mofetil 1-1.5 g/day can be considered in non-organ threatening AAV if there is a contraindication to methotrexate, cyclophosphamide or rituximab. (37)

EULAR and BSR guidance recommends use of plasma exchange in rapidly progressive severe renal disease (creatinine > 500 µmol/litre) (18). Use of Plasma Exchange could be considered in patients with severe renal disease or rapidly progressive renal failure as an adjunct to cyclophosphamide.(38)

Glucocorticoid therapy is an important adjunct to chemotherapy or immunotherapy. In patients with life-threatening or organ-threatening disease, it is common practice to use pulsed intravenous methylprednisolone 1 g every day for 3 days. Subsequently, oral prednisolone 1 mg/kg/day tapered to about 10-15 mg/day at 3 months is advocated. In recent years, there has been increasing recognition of the toxicity of prednisolone and this will hopefully lead to the development of prednisolone-light regimens.

b. **Remission Maintenance –** The long-term toxicity of cyclophosphamide provoked the search for alternative agents to maintain remission.(31) Azathioprine (2mg/kg/day) is well established as an effective agent for use as maintenance therapy after remission induction. In a RCT of 155 patients with AAV, azathioprine (2 mg/kg/day) was shown to be as effective as cyclophosphamide (1.5 mg/kg/day) for maintaining remission up to 18 months, but more safely.(39) It remains the standard of remission maintenance.

   In those patients who have had methotrexate used for remission induction, there is evidence for its continuing use to maintain remission. In a RCT involving 126 patients with GPA/MPA, methotrexate 25 mg/week was no more toxic than azathioprine 2 mg/kg/day.(40)

Rituximab in varying doses have been used to maintain remission in AAV. In one RCT, it has been shown to be superior to azathioprine.(41) In the UK, rituximab (1 g pulse every 6 months for 2 years – then observe) is recommended for maintaining remission in patients with refractory disease post-cyclophosphamide or relapsing disease post-rituximab. A clinical trial examining its efficacy against standard maintenance of azathioprine 2 mg/kg/day is underway and may become the new standard of therapy.

Currently, all patients must continue immunosuppression for at least 2 years. Patients with persistent PR3-ANCA may need longer immunosuppression.

Prednisolone is commonly used as an adjunct. Every effort should be made to get patients off glucocorticoid therapy. Relapses should not be treated with just prednisolone increments, but should be accompanied with a change in the chemotherapy/immunotherapy as well.

4. **Recognition and management of co-morbidities**
    a. **Infections –** Infection is the main cause of early mortality in patients with AAV.(18) Prophylaxis against Pneumocystis jirovecii is commonly provided with trimethoprim/sulfamethoxazole (800/160 mg three times a week) for the duration of cyclophosphamide treatment. In patients who cannot tolerate this drug, we do not regularly administer pentamidine. Blood count monitoring, education of patients to seek early help for infection related symptoms and open access to a vasculitis unit may help minimise the mortality in this group of patients.
    b. **Cardiovascular risk –** Patients with AAV are at a higher risk of cardiovascular events and hypertension than the general population.(42) While it is imperative to address the traditional Framingham risk factors, control of blood pressure, especially in MPO-ANCA positive patients is important.(43)
    c. **Urothelial risk –** Cyclophosphamide is associated with urothelial cancers and bladder injury.(44) It should be a standard of care to refer

patients for a cystoscopy if there is persistent non-glomerular dipstick haematuria.

d. **Monitoring damage –** Diabetes mellitus, osteoporosis and other long-term risks of glucocorticoid use should be screened for on a regular basis.

5. **Patient education –** Patients with AAV want information about their health, prognosis and therapy. They prefer to get their information from health-care professionals who deal with vasculitis as opposed to from patient support groups.(45) But, it is important to develop different kinds of educational material so that they can take things away and digest the information in their own time.(46)

Discussion

Over the past 25 years, collaborative clinical trials in vasculitis have changed the face of vasculitis therapeutics. Patients with vasculitis have a reasonable expectation of surviving a decade after diagnosis and leading a meaningful and economically productive life. With greater evidence there has been an evolution of clinical standards. But, as with everything else, the evolution of standards has not been uniform across the globe. Like-minded vasculitis clinicians have driven the formation of the European Vasculitis Society and the Vasculitis Clinical Research Consortium in Europe and USA respectively. Several clinicians in other parts of the world have participated in the collaborative clinical trials, but these remain predominantly European and North American initiatives.

Over the past 5 years, rituximab has become the standard of care for remission induction in young women, relapsing patients and those with urothelial cancers. The availability of this expensive drug has led to initiatives in the UK to recognise specialist centres which can supervise the use of this drug but more importantly advice on the care of the patients who need this drug. Methotrexate is falling out of favour. In clinical trial as well as in personal experience, it did not fulfil its early promise and we fear the same for mycophenolate mofetil – but time will tell!

Using a piece of paper – BVAS v3 or BVAS/WG seems to be an archaic way of assessing disease activity, but for those of us who do it regularly, it is proving invaluable. It is a simple but effective way of making sure that all activity is accounted for and forces the clinician to make a judgement on every symptom and its relationship to the disease – activity, damage or coincidental. It needs training for its use to ensure that it is used appropriately.

We are making people live longer with complex drug regimens. This is now allowing us to see the havoc that the disease and its treatment can sometimes cause the body. It should not be a surprise that patients with a vascular problem have greater risk of cardiovascular complications, especially when we use high-dose glucocorticoids to treat it. We need to be more vigilant about monitoring those patients when remission has been achieved.

EGPA has become an orphan amongst orphans. There is very little data to say anything meaningful about this disease. Most of what we have said above is based on data from GPA and MPA. It is time that the vasculitis community brought this condition into focus.

The remit of this paper was to address the need for a change in standards of care for AAV. The short answer to that question would be 'yes'. There is always need to change and evolve with increasing availability of evidence and we anticipate that this will continue to evolve rapidly – get on board and enjoy the ride.

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