ANCA-associated vasculitis

Authors: Max Yates[1&2] and Richard Watts[2&3]

[1]Rheumatology, Norfolk & Norwich University Hospital NHS Foundation Trust, Norwich, UNITED KINGDOM

[2]Norwich Medical School, University of East Anglia, Norwich, UNITED KINGDOM.

[3]Ipswich Hospital, Heath Road, Ipswich, UNITED KINGDOM

Abstract

The vasculitides are a heterogeneous group of conditions typified by their ability to cause vessel inflammation with or without necrosis. They present with a wide variety of signs and symptoms and, if left untreated, carry a significant burden of mortality and morbidity. The ANCA-associated vasculitides (AAV) are three separate conditions - granulomatosis with polyangiitis (GPA - formerly known as Wegener's granulomatosis); microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA - previously known as Churg-Strauss Syndrome). This review examines recent developments in the pathogenesis and treatment of AAV.

Introduction

The antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a collection of relatively rare autoimmune diseases of unknown cause, characterised by inflammatory cell infiltration causing necrosis of blood vessels. The association between ANCA and vasculitis was first described in 1982, in a short report describing the clinical course of eight patients diagnosed with a segmental necrotising glomerulonephritis (1). The discovery of perinuclear and cytoplasmic patterns (P-ANCA and C-ANCA) and their specificity of myeloperoxidase (MPO) and proteinase 3 (PR3) respectively were discussed at the ANCA workshop in the Netherlands in the same year (2). The AAV comprises granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

Classification and Epidemiology

The American College of Rheumatology in 1990 developed classification criteria for GPA and EGPA. Definitions for the AAV were described at the Chapel Hill Consensus Conference in 1994 and were revised in 2012 (3). The Chapel Hill group to stress that the CHCC is a nomenclature system and not a set of classification or diagnostic criteria. The AAV are considered to be small vessel vasculitides but there is considerable overlap possible with respect to size of vessel involved. The conventional classification based on clinical phenotype has been challenged as there is now good epidemiological, genetic and clinical evidence to support a division based on ANCA subtype (4).

GPA, MPA, and EGPA have respective annual incidence rates of 2.1 – 14.4, 2.4 – 10.1, and 0.5 – 3.7 per million in Europe, and the prevalence of AAV is estimated at to be 46 – 184 per million (4). They are more common in those aged > 60 years and slightly more common in men. The 5-year survival rates for GPA, MPA, and EGPA are estimated to be 74-91%, 45-76% and 60-97% (5).

Diagnostic work-up

The relative rarity and non-specific presentation of the AAV pose diagnostic challenges and often results in a significant diagnostic delay of more than 6 months in a third of patients. A systemic approach is required in the diagnosis and follow-up of what is often a relapsing remitting disease. A detailed history and examination is required, laboratory investigations should include assessments of inflammatory markers, kidney function (U&Es, always with urine dip assessment, possibly also quantification of any protein leak and urine microscopic for red cell casts), serological testing including ANCA, ANA and anti-glomerular basement membrane antibodies (both SLE and Goodpasture's syndrome can masquerade as AAV). Infection should also be excluded and the diagnosis of bacterial endocarditis considered and excluded. Chest x-ray should be undertaken. CT or MRI may be required to assess the chest, brain, orbits and ENT structures in more detail. A biopsy should always be considered to confirm the diagnosis and exclude mimics. However, treatment should not necessarily be delayed simply to get a biopsy. Disease activity scores such as the Birmingham Vasculitis Activity Score (BVAS) can act as a useful aide memoire (6). BVAS should also be recorded to measure disease activity but training must be undertaken in order that this tool is used appropriately.

Treatment

Remission Induction

The definition of remission has been standardised by the European Vasculitis Society/European League against Rheumatism (EUVAS/EULAR) group, who recommend that the definition of remission should be one of no detectable disease activity using a recognised scoring tool such as BVAS (7).

The use of daily cyclophosphamide and glucocorticoids improved the dire prognosis of untreated AAV (>80% mortality at one year) to one of where long term remission was possible but relapses and iatrogenic side effects were common. This changed the drive in the research agenda to limit cyclophosphamide exposure and more recently reduce cumulative glucocorticoid dosage.

Induction of remission using cyclophosphamide (or rituximab) should be considered in all patients with new onset AAV. Other induction regimens using methotrexate or mycophenolate mofetil should only be considered patients with no evidence of organ or life threatening disease. This is the minority of new patients. In patients with Figure X gives an algorithm approach to the treatment of new onset AAV. In patients presenting with a creatinine of >500umol/L the addition of plasma exchange should be considered.

Cyclophosphamide

The CYCAZAREM trial showed that oral daily cyclophosphamide (2mg/kg/day) for 3-6 months with glucocorticoids achieved remission in more than 90% of patients (8). Subsequently the CYCLOPS trial showed that pulsed IV cyclophosphamide (10-15mg/kg) was as effective at inducing remission as daily oral cyclophosphamide but with a lower cumulative dose of the drug, causing fewer side effects (9). Long-term follow-up of the trial participants revealed an increased risk of relapse in those participants who had received pulsed cyclophosphamide, but importantly no differences in renal function or survival (10). However, due to the reduced total dose of cyclophosphamide associated with pulsed regimens, these are favoured by national guideline groups (11).

Rituximab

Rituximab in AAV has been tested in two RCTs (RAVE and RITUXVAS) (12, 13). In both studies participants initially received high-dose glucocorticoids with subsequent dose tapering. The rituximab dose in both studies was 375 mg/m^2 of body surface area, once a week for four infusions. In both trials, rituximab was non-inferior to cyclophosphamide and appeared more effective for relapsing disease in RAVE. In the RAVE trial a better response was seen in PR3 +ve patients (14).

An alternative regimen of 1gm given on two occasions two weeks apart has been widely used and shown to be as effective (15). The UK guidelines recommend the use of rituximab in AAV for primary induction in the following circumstances:

1. For remission induction in newly-diagnosed patients when avoiding cyclophosphamide is desirable due to relative contraindications such as previous uroepithelial malignancy, pre-menopausal women who have not completed their family, previous cyclophosphamide treatment or inability to complete a planned treatment course of cyclophosphamide due to allergy or intolerance.

2. When cyclophosphamide has not worked (after three to six months of treatment), either failed to control active disease or new items of disease have occurred during the treatment course.
3. For treatment of first relapse
4. For remission maintenance when rituximab has been used to induce remission or when alternative remission maintenance agents (azathioprine, methotrexate or mycophenolate mofetil) have been ineffective, or have not been tolerated due to toxicity.

Remission Maintenance

After successful remission induction guidelines recommend a withdrawal of the initial immunosuppressive agent and commencing a maintenance regimen with either azathioprine or methotrexate (11). However, data are lacking on the precise duration of the maintenance regimen and recommendations have been made based on expert consensus. Early cessation of therapy (< 1 year) is associated with an increased risk of relapse (16). It is generally advised that maintenance therapy is continued for at least 18-24 months before being gradually withdrawn. In general, attempts at reduction of glucocorticoids should be made prior to tapering of the immunosuppressive remission maintenance agent. The risk of relapse is greater in patients who are PR3-ANCA positive at presentation and in those who remain PR3-ANCA when switched from induction to maintenance immunosuppression.

The optimum use of rituximab for remission maintenance remains to be established, a strategy of fixed interval retreatment for up to 2 years appears to be better than retreatment based on other clinical relapse, return of peripheral B cells or ANCA status (17). The MAINRITSAN study reported that rituximab 500mg given at days 0, 14 and at months 6, 12 and 18 was more effective in remission maintenance than a withdrawing azathioprine regimen (18).

Treatment intent is now long term and therefore attention should be paid to the morbidity associated with treatment. All patients should be screened for cardiovascular disease and appropriate treatment given to reduce risk factors, osteoporosis prevention should be given, immunisation against pneumococcus (preferably before immunosuppression is given) and annual influenza vaccination. Patients need specific education about their condition and their treatment, they may find it difficult to obtain the necessary information (19). The increasing complexity of disease management means that a multi-disciplinary approach is essential for optimal management and networks of interested clinicians need to be developed.

Prognosis

Patients with AAV are at risk of complications, both from their disease and its treatment (5). Mortality in the first year is mainly due to active vasculitis or infection, late mortality is due to infection, cardiovascular disease and malignancy. Five year survival is around 75%. Morbidity accumulates with time due to the consequences of active disease and therapies. Around one-third of patients have ≥five items of damage at a mean of seven years post diagnosis (5).

Conclusions

The conditions which comprise AAV are challenging to diagnose but improved treatment regimens with the introduction of rituximab have improved the outlook for patients. These conditions need to

be considered as chronic diseases and care needs to be organised into regional networks in order that all patients benefit from access to appropriate and timely advice without necessarily having to travel to a specialist centre.

Key messages

The AAV a rare multisystem autoimmune diseases, more common in the elderly and in men.

Induction treatment for most patients with AAV should be with cyclophosphamide or rituximab and glucocorticoids

AAV should be considered to be a chronic disease needing long term immunosuppressive therapy

Rituximab should be considered as an alternative induction agent for those at high risk of infertility and infection.

The mortality remains high, and late death is due to cardiovascular disease, infection (secondary to treatment) and malignancy

Self Assessment Questions

1. Which of the following is a risk factor for increased relapse rate in AAV

    a. ANCA negative status after completion of induction therapy

    b. Higher cumulative dose of cyclophosphamide

    c. Higher serum creatinine at presentation

    d. Microscopic polyangiitis

    e. PR3 +ve at presentation

2. A 76 year old man is admitted with painful unilateral proptosis. He has been feeling unwell for the last few weeks with arthralgia, weight loss and cough. On close questioning he admits to nasal crusting and discharge. Examination reveals proptosis associated with lateral gaze diplopia. CT scanning reveals a pseudo-tumour of the orbit and proteinase 3 ANCA is positive. He has normal renal function. Which of the following would be the most appropriate initial treatment?

    a. IV rituximab 1g given now and another 1g two weeks later

    b. Methotrexate 20mg oral once per week

    c. Plasma exchange

    d. Pulsed cyclophosphamide 10-15mg/kg given at two weekly intervals along with an oral glucocorticoid regimen

    e. Pulsed IV methyl-prednisolone (500mg to 1g) alone

    Answers

    1 e. Patients who are PR3 positive at presentation are at higher risk of relapse, primarily because retro-orbital and ENT disease appear to be relatively resistant to therapy with cyclophosphamide. PR3-AAV patients typically GPA patients have lower creatinine at presentation that MPA (or MPO-ANCA +ve) patients and hence a lower serum creatinine at presentation is associated with increased chance of relapse. Conversely, patients who are MPO +ve have an increased risk of death or ESRD within the first 1 year but a lower risk for relapse.

    2 d. This patient has active GPA, which is potentially threatening his sight. He needs induction immunosuppression with pulsed IV cyclophosphamide combined with high dose glucocorticoids

References

1. Davies DJ, Moran JE, Niall JF, Ryan GB. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? British Medical Journal (Clinical research ed). 1982;285(6342):606-.
2. Jennette JC, Hoidal JR, Falk RJ. Specificity of anti-neutrophil cytoplasmic autoantibodies for proteinase 3. Blood. 1990 Jun 1;75(11):2263-4.
3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatism. 2013;65(1):1-11.
4. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suarez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015 Apr;30 Suppl 1:i14-22.
5. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2015 Jan;74(1):177-84.
6. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009 Dec;68(12):1827-32.
7. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Annals of the Rheumatic Diseases. 2007 66(5):605-17.
8. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JWC, Dadonienė J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. New England Journal of Medicine. 2003;349(1):36-44.
9. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009 May 19;150(10):670-80.
10. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012 Jun;71(6):955-60.
11. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford). 2014 Dec;53(12):2306-9.
12. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010 Jul 15;363(3):211-20.
13. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010 Jul 15;363(3):221-32.
14. Unizony S, Villarreal M, Miloslavsky EM, Lu N, Merkel PA, Spiera R, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis. 2016 Jun;75(6):1166-9.
15. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009 Jul;60(7):2156-68.
16. De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis and Rheumatism. 2005;52(8):2461-9.
17. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012 Nov;64(11):3760-9.

18. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014 Nov 6;371(19):1771-80.
19. Mooney J, Spalding N, Poland F, Grayson P, Leduc R, McAlear CA, et al. The informational needs of patients with ANCA-associated vasculitis-development of an informational needs questionnaire. Rheumatology (Oxford). 2014 Aug;53(8):1414-21.

Table 1 Chapel Hill Consensus definitions (2012) for ANCA-associated vasculitis.

Definitions for ANCA associated vasculitis	
ANCA Associated Vasculitis (AAV)	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, ANCA-negative.
Granulomatosis with Polyangiitis (Wegener's) (GPA)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., 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.

From Jennette et al, 2013

Table 2 Factors increasing the risk of relapse

Factors increasing relapse risk		
Clinical presentation	**Serology**	**Treatment related**
GPA	PR3-ANCA at presentation	Steroid withdrawal
ENT involvement	ANCA positive after induction	Immunosuppressive withdrawal
Better renal function (creatinine < 200μmol/L)	Rise in ANCA during treatment	Lower cumulative CYC exposure

Figure 1 Algorithm for treating ANCA associated vasculitis (Ntatsaki et al, 2014)