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ANCA-associated systemic vasculitis (AASV)

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ABSTRACT Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis is a multi-system disease that can present to a number of medical specialties, and where early identification and treatment improves outcome. The vasculitides are commonly divided into WG, MPA, and CSS. This review will revise the common clinical presentations of these diseases and initial investigations. Anti-neutrophil cytoplasmic antibodies have provided a valuable test to aid in diagnosis and there is increasing clinical and experimental evidence that suggests they have an important role in the pathogenesis of disease. Anti-neutrophil cytoplasmic antibodies are directed at either MPO or PR3 which are present in the granules and on the cell surface of neutrophils. They can be detected by indirect immunofluoresence and ELISA-based assay, and both are essential when vasculitis is suspected. The antibodies are able to activate neutrophils and promote injury, and recent data have shown they can directly cause glomerulonephritis and systemic vasculitis in animal models.

Diagnosis of AASV is made using clinical features, ANCA test, and relevant tissue biopsy. Treatment with cytotoxics has transformed the prognosis but until recently there has been limited trial evidence to determine which regime is best. This article will review a range of studies published over the last five years and preliminary evidence from ongoing studies to give an outline of current practice for immunosuppression and monitoring of disease. There is also now a range of biological therapies available including anti-TNF and anti-B-cell antibodies, which may have an increasing role as either adjunctive therapy or new regimes to induce remission.

KEYWORDS Anti-neutrophil cytoplasmic antibody, glomerulonephritis, neutrophil, vasculitis

LIST OF ABBREVIATIONS ANCA-associated systemic vasculitis (AASV), anti-neutrophil cytoplasmic antibody (ANCA), anti-thymocyte globulin (ATG), C-reactive protein (CRP), central nervous system (CNS), Churg–Strauss syndrome (CSS), cyclophosphamide (CYP), cytoplasmic ANCA (cANCA), ear, nose and throat (ENT), enzyme-linked immunosorbent assay (ELISA), European Vasculitis Study Group (EUVAS), immunofluorescence (IF), interleukin-1β (IL-1β), interleukin-8 (IL-8), methotrexate (MTX), microscopic polyangiitis (MPA), monocyte chemotactic protein-1 (MCP-1), myeloperoxidase (MPO), perinuclear ANCA (pANCA), proteinase-3 (PR3), tumour necrosis factor (TNF), Wegener's granulomatosis (WG)

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Wegener's granulomatosis, MPA, and CSS are small to medium vessel vasculitides that can present in a wide range of clinical contexts. Their identification has been aided by their frequent association with ANCA, but diagnosis is often delayed, and treatment, although in large part successful, is associated with significant side-effects and risk of relapse.

DEFINITIONS

Although there is no agreed definition, the Chapel Hill Consensus Conference definitions provide a reasonable starting point to divide these conditions (www.vasculitis.org/nomenclature.htm), and there are certain clinical characteristics that favour individual diagnoses (see Table 1).

CLINICAL FEATURES

There is considerable overlap between these vasculitides in terms of clinical presentations.

Upper respiratory tract

Ear, nose and throat disease occurs most commonly in WG. Features include nasal discharge and crusting, epistaxis, and destruction of nasal cartilage leading to a saddle-nose deformity. Deafness may occur as a result of middle ear disease, blockage of the eustachian tube due to nasopharyngeal disease, and inner ear damage. When disease affects the upper airways, tracheal subglottic stenosis or blockage of major bronchi may

	Chapel Hill Consensus Conference criteria	Typical clinical features
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract and necrotising vasculitis affecting small- to medium-sized vessels (i.e. capillaries, venules, or arterioles). Necrotising glomerulonephritis is common.	**ENT disease:** often presents with nasal and/or upper airway disease. Nasal discharge, epistaxis and stridor occur. Deafness common. **Lung:** pulmonary granulomas and alveolitis may present with lung haemorrhage. **Kidney:** glomerulonephritis common. **ANCA:** typically cANCA- and PR3-positive. Disease has a higher rate of relapse.
Microscopic polyangiitis	Necrotising vasculitis with few or no immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles). Necrotising arteritis involving small- and medium-sized arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs.	**Lung:** pulmonary capillaritis occurs leading to alveolitis, lung haemorrhage, and fibrosis. **Kidney:** most common organ involvement with focal necrotising glomerulonephritis. **ANCA:** majority pANCA- and MPO-positive, but significant number are PR3-positive. Relapse frequency lower when MPO-positive.
Churg–Strauss syndrome	Eosinophil-rich granulomatous inflammation involving the respiratory tract and necrotising vasculitis affecting small- to medium-sized vessels associated with asthma and eosinophilia.	**ENT disease:** nasal polyps and rhinitis. **Lung:** asthma and granulomatous inflammation. **Nervous system:** Mononeuritis multiplex.

TABLE 1 Clinical features of different forms of AASV.

cause inspiratory stridor (see Figure 1). Most of these conditions require direct visualisation for diagnosis, which also allows for tissue biopsy. In CSS, allergic rhinitis with a history of nasal polyps are common features and usually occur many years before the full-blown disease.

Eyes

Ocular inflammation may occur in all AASV. Scleritis is typical, and, if left untreated, can lead to scleral perforation and blindness. Other features of WG include retro-orbital granulomatous masses, causing pain, diplopia and proptosis, and blockage of the nasolacrimal duct.

Lungs

Both pulmonary nodules and diffuse alveolitis can occur. Acutely, these may present with pulmonary haemorrhage, which is a life-threatening complication. Subsequently, patients may develop pulmonary fibrosis, a more common feature of MPA. Patients with CSS often present with a preceding history of asthma and more transient alveolar infiltrates.

Nervous system

Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis can lead to sensorimotor neuropathy, typically a mononeuritis multiplex. This is most commonly seen in CSS. Rarely, WG can produce CNS lesions, usually presenting as cranial nerve palsies, but cerebral involvement is rare.

Skin

Purpuric rashes are typical of AASV. Additionally, cutaneous nodules and papules can occur in WG and CSS. A skin biopsy will most frequently show a leukocytoclastic vasculitis.

Renal disease

The most common serious manifestation of AASV is the development of glomerulonephritis. This presents with significant proteinuria and haematuria (usually 3–4+ of both on urinalysis) and variable degrees of renal impairment. Renal biopsy shows a segmental necrotising glomerulonephritis, and progression of this injury leads to inflammatory cells surrounding the glomerulus giving the characteristic 'crescent' formation (see Figure 2). Immunofluoresence is typically negative giving rise to the term 'pauci-immune' glomerulonephritis. Histology often shows glomeruli at different stages of injury, some with acute 'fresh' crescents and others showing fibrotic 'old' crescents, highlighting the sub-acute nature of the disease.

Systemic features

Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis usually has a sub-acute course and patients will have generally been unwell for 2–3 months before presentation. Weight loss, anorexia, fever, night sweats, arthralgia, and lethargy are common presenting complaints.

DIAGNOSIS

Owing to the multiple systems that can be affected in vasculitis, diagnosis is often delayed and requires a high

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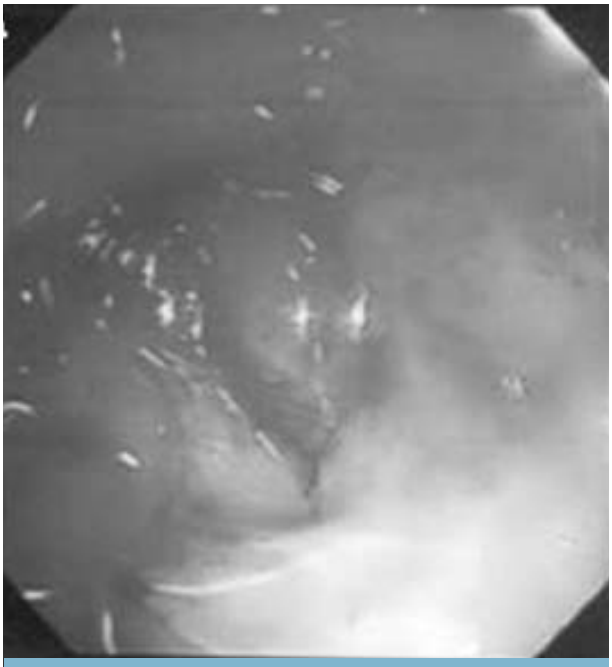

FIGURE 1A Wegener's granulomatosis causing occlusion of the left main bronchus. This image shows the bronchoscopic appearances of the patient's left main bronchus. The lumen is completely occluded by granulomatous inflammation. He presented with stridor and this was a recurrence of disease. Previously this had been stented but disease recurred whilst on CYP and prednisolone.

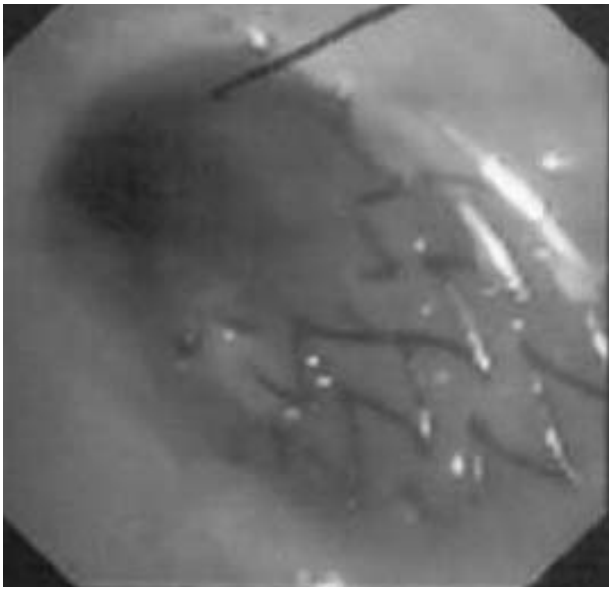

FIGURE 1B Wegener's granulomatosis causing occlusion of the left main bronchus. The patient was treated with infliximab and inflammation resolved. The previously inserted stent can now be seen and, although the airway is still narrowed, there was marked symptomatic improvement.

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degree of suspicion. Measurement of ANCA helps focus diagnostic attention and a number of tests should also be performed as baseline (see Table 2).

Diagnosis should be confirmed where possible by histological assessment of affected organs. This may include biopsy of kidney, lung (usually a thorascopic lung biopsy), nasal or upper airway disease, skin, or sural nerve.

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY

Anti-neutrophil cytoplasmic antibodies have provided a useful serological test both in diagnosis and monitoring treatment response. Anti-neutrophil cytoplasmic antibodies are IgG antibodies directed at antigens in the primary granules of neutrophils and lysosomes of macrophage/monocytes. The presence of auto-antibodies in patients' serum is identified by indirect IF on neutrophils and gives either a perinuclear (pANCA) or cytoplasmic (cANCA) pattern of staining. The target antigens appear to be MPO for pANCA and PR3 for cANCA. Enzyme-linked immunosorbent assays are available to test and quantify specific antibodies. Most laboratories provide both of these assays, and, where vasculitis is suspected, both should be looked for. Immunofluorescence is more sensitive, whilst ELISA is more specific. Combining positive ANCA results from IF and ELISA gives a specificity for AASV of 99%. Furthermore, where clinical suspicion of AASV is high, the presence of ANCA antibody has a positive predictive value of around 95%.

PATHOGENESIS

Increasing evidence points to a role for ANCA in the pathogenesis of vasculitis. Both PR3 and MPO can be expressed on the surface of TNF-α-activated neutrophils and thus they become a target for ANCA. *In vitro*, ANCA treatment of isolated TNF-α-stimulated neutrophils leads to enhanced degranulation; release of pro-inflammatory cytokines, including TNF-α and IL-1β; chemokines, including IL-8 and MCP-1; and augmented respiratory burst, all features consistent with an inflammatory response. Anti-neutrophil cytoplasmic antibody is able to bind to the neutrophil surface via both the F(ab) domain and Fc portion and both are required for maximal neutrophil activation. Anti-neutrophil cytoplasmic antibody-treated neutrophils also show enhanced adhesion to activated endothelium which promotes transmigration. Furthermore, ANCA can also bind to endothelial cells and induce adhesion molecule expression, which in turn increases leukocyte adhesion. Thus, a model may be envisaged whereby neutrophils binding ANCA are activated, adhere to endothelium, and release cytokines including TNF-α, which leads to further neutrophil and endothelial activation and ANCA binding. There is also increased release of proteolytic enzymes and generation of reactive oxygen species which further damage endothelium and propagate injury (see Figure 3).

Recent evidence from animal models also supports a pathogenic role for ANCA. Knockout mice were generated for MPO. Anti-MPO IgG and anti-MPO lymphocytes were produced by immunising the mice with MPO. Injection of anti-MPO IgG into naive mice resulted

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Investigation	Comment
Blood tests	
C-reactive protein	Elevated in systemic vasculitis. A useful marker to follow response of disease. Not elevated in limited disease.
Full blood count	Anaemia often present (Hb 9–12 g/l) and significant thrombocytosis is characteristic (often >> 500 x 10^9/l). As with CRP, platelet count should fall in response to treatment.
Urea and electrolytes, creatinine	Severity of renal disease affects prognosis. Patients may be dialysis-dependent at presentation.
Arterial blood gases	Perform if patient has oxygen saturation <92% on air. May help in detection of lung haemorrhage or fluid overload.
ANCA	Both indirect immunofluorescent microscopy and ELISA for MPO and PR3 should be performed on serum.
Auto-antibodies	Antiglomerular basement membrane antibodies can occur in AASV. Check for double-stranded DNA antibodies and complement levels to exclude other vasculitic conditions including systemic lupus erythematosus.
Urine tests	
Urine dipstick and microscopy	Characteristically will have 3–4+ of blood and protein on urine dipstick. Microscopy will confirm red blood cells and red blood cell casts.
24-hour urine collection	Will quantify glomerular filtration rate and proteinuria. Proteinuria usually around 1–3 g/24 hours. Nephrotic range uncommon.
Pulmonary tests	
Chest X-ray	Evidence of pulmonary fibrosis or granulomatous disease.
Pulmonary function tests	Functional assessment of pulmonary fibrosis and alveolitis. Transfer factor increased in lung haemorrhage.

TABLE 2 Initial investigations in suspected vasculitis.

in a focal necrotising crescentic glomerulonephritis. Similarly, transfer of splenocytes from MPO-immunised mice (which contain mostly T and B lymphocytes) into Rag2-deficient mice (which have no functioning T and B cells) resulted in a crescentic glomerulonephritis in association with the development of anti-MPO antibodies. Many of these mice also developed evidence of a systemic vasculitis with arteritis and granulomatous inflammation in lung, spleen, and lymph nodes. These studies and clinical data suggest that ANCA are particularly important in the pathogenesis of glomerulonephritis. It should be remembered, however, that disease can occur in the absence of detectable ANCA, particularly localised pulmonary disease.

Generation of ANCA requires competent T and B lymphocytes. Myeloperoxidase- and PR3-reactive T cells can be detected in patients with active vasculitis and increased T-cell proliferation is found during relapses of disease. In addition, large numbers of T cells can be identified in renal biopsies and correlate with disease severity. Finally, B cells, on development into plasma cells, are responsible for production of ANCA and, as discussed later, there is increasing interest in the use of anti-B-cell therapy in treatment of vasculitis.

TREATMENT

Before the introduction of immunosuppressive treatment, systemic vasculitis had a poor prognosis with around 80–90% mortality at one year. With such a devastating disease it is not surprising that treatment with cytotoxic agents became accepted without any controlled studies. However, the last five years have seen the publication of a number of such studies particularly by the EUVAS, and these have provided a firmer evidence base for our treatment regimes. Current therapies have improved one-year patient survival in renal vasculitis to around 85%, and five-year survival to 75%.

Induction of remission

Standard treatment for systemic vasculitis is the combination of prednisolone 1 mg/kg and CYP 2 mg/kg. Intravenous hydrocortisone (5 mg/kg in divided doses) can be substituted for oral prednisolone in fulminant presentations. In the elderly, a lower dose of CYP (1·5 mg/kg) is frequently used. Cyclophosphamide is continued for 12 weeks, or until remission is achieved, whilst the steroid dose is steadily reduced to 20 mg by week 5 and to 10 mg by week 12; although dose reduction should be tailored to clinical response. In uncontrolled studies this regime gave remission rates of around 85%. Once in remission, at three months, patients are switched from CYP to azathioprine.

An alternative regime has been intravenous pulsed CYP therapy. Pulsed therapy can reduce the total dose of CYP given, which is related to long-term side effects such as infertility and malignancy (particularly bladder carcinoma and haematological malignancies). Meta-analysis of the available studies has shown that pulsed therapy gives similar remission rates to oral treatment and is associated with a lower incidence of infections. However, there is a trend towards a higher relapse rate. A randomised controlled comparison between oral daily and pulsed CYP has been performed in the CYCLOPS study (protocol found on EUVAS website www.vasculitis.org) and the results are awaited.

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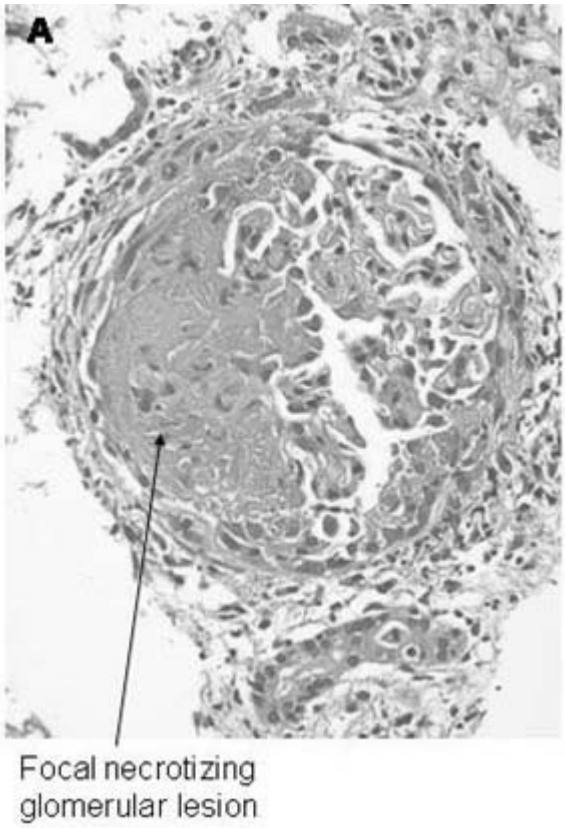

FIGURE 2A Renal biopsy in AASV. A glomerulus is shown with a focal area which has been destroyed by inflammation leading to necrosis of this segment.

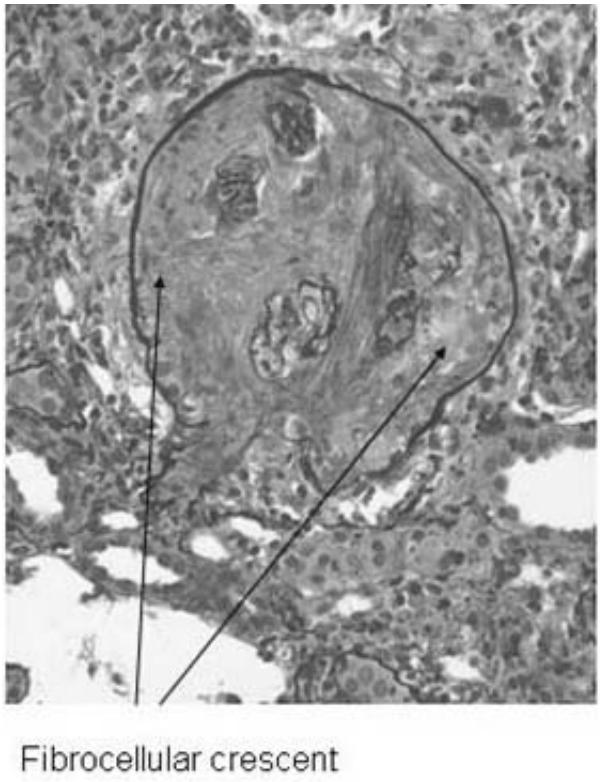

FIGURE 2B Renal biopsy in AASV. Shows a glomerulus which has been surrounded by inflammatory cells and subsequent fibrotic reaction such that the normal glomerular architecture has been destroyed. The glomerulus will subsequently sclerose.

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An alternative to CYP for induction of remission is oral weekly MTX. This was initially used in non-life-threatening systemic WG and showed remission rates of around 70%. Methotrexate has recently been tested in a study in patients with systemic AASV, without life-threatening organ involvement and a serum creatinine <150 µmol. They were randomised to either daily oral CYP or MTX (20–25 mg per week) for 12 months. Induction of remission was similar in both groups (~90%), although MTX was slower to induce remission when disease was more extensive or where there was pulmonary involvement. Immunosuppression was stopped at 12 months, and by 18 months the relapse rate was significantly higher in the MTX arm of the study (70% vs 46%). Thus, MTX has similar effectiveness to CYP in reducing remission but should be continued for longer than one year.

Induction treatment in severe disease

Severe renal failure and pulmonary haemorrhage are associated with a significant early mortality. It is thus standard practice to give additional immunosuppression in this context. The MEPEX study compared methylprednisolone (three daily injections of 1 g) with plasma exchange (seven times over 14 days) in patients with severe renal disease (serum creatinine >500 µmol or dialysis-dependent). Initial results showed a significant benefit of plasma exchange, with 69% of these patients alive and dialysis-independent at three months, vs 49% of the methylprednisolone group, an improvement that was maintained at one-year follow-up.

Maintenance treatment

Relapse of disease remains a significant clinical problem, as is toxicity of the immunosuppressive agents used. Current practice switches from CYP to azathioprine (2 mg/kg) at three months, or when remission is achieved. This regime was compared with one year of treatment with oral CYP followed by azathioprine in the CYCAZAREM trial. Relapse rates were similar in both groups over 18 months from study entry (~14%) without any additional adverse events. In this and other studies there was a higher relapse rate in WG compared with MPA. The length of maintenance therapy remains uncertain, but current practice would advocate treatment for at least two years and probably longer in those with WG or persistent PR3-positive serum.

Adjunctive therapy

Early studies showed the benefit of adjunctive therapy with co-trimoxazole prophylaxis in WG in reducing disease relapse rates. Relapse has been associated with staphylococcal nasal carriage and it is thought that co-

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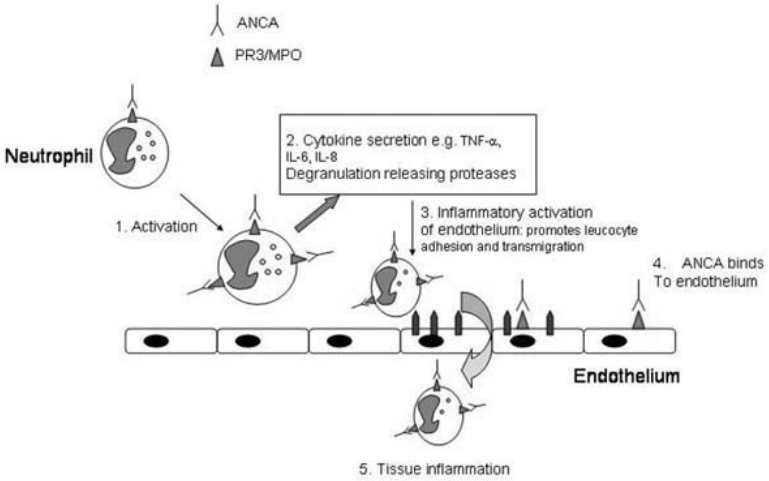

FIGURE 3 Pathogenic role of ANCA. (1) ANCA binding to neutrophils leads to their activation causing. (2) Pro-inflammatory cytokine secretion and release of proteases from granules which cause further activation of neutrophils, increase PR3 and MPO cell surface expression, and activate endothelium. (3) This in turn promotes adhesion and transmigration of neutrophils and, (4) Leads to PR3 and MPO expression on endothelial cells allowing ANCA binding and further endothelial activation. (5) The activation and infiltration by inflammatory cells leads to tissue damage and further leukocyte activation.

trimoxazole may reduce such colonisation. It is our current practice to give patients co-trimoxazole (960 mg once daily) for the first 3–6 months of treatment and a study is also assessing the effects of nasal mupirocin in patients with WG in remission.

Newer therapeutic approaches

Despite the effectiveness of standard immunosuppression, a number of patients have disease which does not respond or remains active. In this group, increasing interest has been shown in the use of biological agents.

Anti-TNF therapies

As discussed earlier, TNF-α is an important pro-inflammatory cytokine which may have important effects in propagating injury. Anti-TNF-α therapy is of value in a number of autoimmune diseases including rheumatoid arthritis and Crohn's disease. Current drugs available are infliximab, an anti-TNF antibody, and etanercept, a soluble p75 TNF receptor. A recent prospective study looked at the addition of infliximab (5 mg/kg at 0, 2, 6, and 10 weeks) at both the initial presentation of AASV and in those with continuing disease activity. In both groups remission was induced in around 90% of patients, with a trend to earlier remission with infliximab treatment resulting in lower steroid dosing. Adverse events, particularly infection, occurred in about one-fifth of patients.

Etanercept has also been assessed in a randomised, placebo-controlled study in patients with WG. Remission rates were about 70% in both treatment groups over a similar time course. Flares of disease were common in both etanercept- and placebo-treated patients. This study also noted the development of solid cancers in six patients in the etanercept-treated group vs none in the placebo arm. Thus the data does not currently support the routine use of anti-TNF treatment but our current practice is to consider infliximab where there is ongoing disease activity despite standard immunosuppression. This is given at a dose of 5 mg/kg on weeks 0, 2, 6, and 10, and as monthly injections where there is evidence of response, until remission is sustained. Continued vigilance for infectious complications is essential with particular concern over the occurrence of tuberculosis.

Anti B-cell therapy

B-cells are responsible for generation of antibodies thus their depletion is an attractive therapeutic strategy in AASV. In addition, B-cells may be involved in other aspects of immune regulation in autoimmunity, including antigen presentation and cytokine production such as TNF-α. Rituximab is a chimeric monoclonal antibody for CD20 (which is expressed exclusively on human B-cells), and has been developed for the treatment of lymphomas. It has been used extensively in this setting without any reported significant increase in infections. A number of small studies have been carried out in patients with refractory AASV, and collectively these give around 80% remission rates but with considerable variability in the additional immunosuppression used. B-cell numbers are depleted rapidly (measured by anti-CD19 FACS analysis on blood), and remain low for around 6–9 months. Reduction in ANCA titres occurs in some patients but does not appear to predict remission. There has not been a significant increase in infection rates with rituximab and plasma levels of IgG are maintained, probably because plasma cells are not depleted by this treatment. The early promise of this agent has lead to design of randomised controlled studies comparing CYP with rituximab for induction treatment. An alternative approach to resistant disease has been to treat with anti-T cell antibodies including campath-1H and ATG. Data are limited to small numbers of patients from individual centres; however

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encouraging results have been obtained. Our current treatment strategy is shown in Figure 4.

DISEASE MONITORING

Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis remains a treatment challenge, and although remission is achieved in the majority, relapse remains a major concern with around 50% relapsing over five years. The presence of a positive ANCA titre at the time of switch from CYP to azathioprine increases chances of recurrent disease, particularly in those who are PR3-positive. However, a remaining challenge is whether ANCA can be used to predict relapse of disease, allowing immunosuppression to be augmented before organ damage occurs. A number of studies have shown a correlation between a rising ANCA titre and subsequent disease relapse. A recent small study found that a fourfold increase in ANCA titres was associated with significant increase in risk of disease relapse and that pre-emptively increasing immunosuppression reduced the incidence of relapse by 80%. However, cumulative analysis of a number of studies shows that a rise in ANCA titres is not associated with clinical relapse in 25–40% of patients. Thus, currently, a rising ANCA titre should increase vigilance for relapse with closer clinic follow-up but on its own should not direct treatment.

KEYPOINTS

- Anti-neutrophil cytoplasmic antibodies are associated with systemic vasculitis of small- to medium-sized vessels which predominantly affects the kidneys, large airways and lungs, and peripheral nervous system.
- Anti-neutrophil cytoplasmic antibodies should be tested by both indirect immunofluoresence and PR3/MPO ELISA on cases where the diagnosis is suspected. Tissue diagnosis should be obtained where possible.

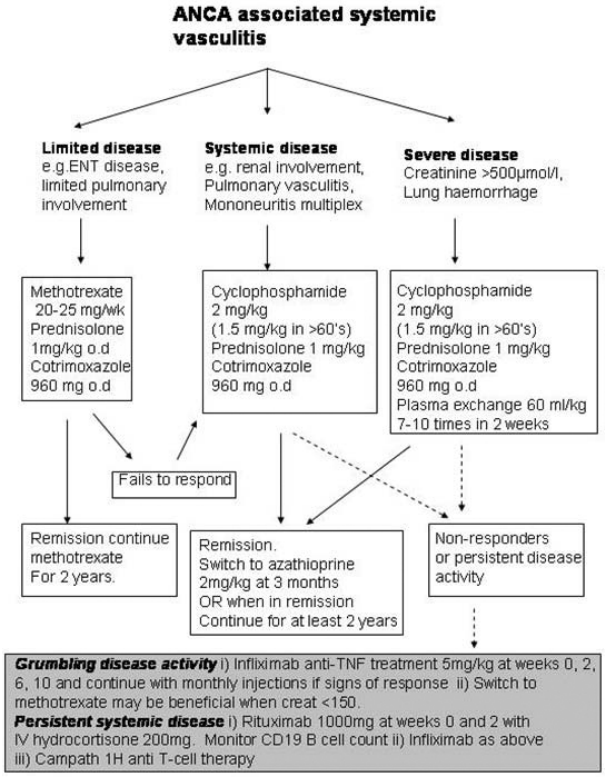

FIGURE 4 Treatment of AASV.

- Increasing evidence points to the role of ANCA in the pathogenesis of disease, rather than as a simple marker. Anti-neutrophil cytoplasmic antibodies are able to bind to and activate neutrophils and endothelium.
- In systemic disease, initial immunosuppression is with prednisolone (1 mg/kg) and CYP (2 mg/kg) which is switched to azathioprine at three months. This regime gives an 80–90% remission rate.
- When disease persists despite standard immunosuppression biological agents with anti-TNF therapy (infliximab) or anti-B-cell therapy (rituximab) show promise.

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