Microscopic Polyangiitis

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ABSTRACT

Microscopic polyangiitis is a systemic vasculitis affecting small- and medium-sized vessels and is characteristically associated with a focal and segmental necrotizing glomerulonephritis. It may present as a pulmonary–renal syndrome with rapidly progressive glomerulonephritis and alveolar hemorrhage, but the pattern of disease will vary according to the organ systems involved. Granulomatous disease of the upper or lower respiratory tract is not a feature, and its presence suggests the diagnosis of Wegener's granulomatosis. The etiology of the condition is unclear, but most patients have antineutrophil cytoplasm antibodies (ANCA) with specificity for either myeloperoxidase (MPO) or proteinase 3 (PR3), and there is increasing evidence that these may be pathogenic. Current treatment includes an induction phase using cyclophosphamide and steroids to attain remission, followed by a maintenance phase in which the levels of immunosuppression are gradually reduced. Azathioprine may be substituted for cyclophosphamide at 3 months. Adjunctive plasma exchange or intravenous methylprednisolone is used in the management of either or both severe renal disease and alveolar hemorrhage, and new evidence suggests that plasma exchange is more effective in recovery of renal function. Overall, 1-year survival in systemic vasculitis is around 85%, and up to 50% of patients relapse, although relapse is less common in those with MPO-ANCA. Newer therapies are being explored in an attempt to increase the efficacy and reduce the toxicity of treatment.

KEYWORDS: Systemic vasculitis, ANCA, microscopic polyangiitis

Objectives: Upon completion of this article, the reader should: (1) understand the definition of microscopic polyangiitis; (2) appreciate the pattern of organ involvement; (3) know how to make a diagnosis; and (4) understand the principles of treatment and the clinical outcome.

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DEFINITION

The term *microscopic polyangiitis* (MP) has been widely used following the 1993 International Consensus Conference in Chapel Hill,[1] which suggested a standardized nomenclature of the systemic vasculitides based chiefly on the size of vessel affected. Thus, MP was agreed to be a necrotizing vasculitis affecting primarily the small vessels, capillaries, venules, and arterioles, which presents commonly with focal necrotizing glomerulonephritis and pulmonary capillaritis. The term *microscopic polyangiitis* replaced *microscopic polyarteritis*, which was first introduced by Davson and colleagues in 1948[2] to

Pulmonary Vasculitis; Editor in Chief, Joseph P. Lynch, III, M.D.; Guest Editor, Carol A. Langford, M.D., M.H.S. *Seminars in Respiratory and Critical Care Medicine*, volume 25, number 5, 2004. Address for correspondence and reprint requests: Charles D. Pusey, F.R.C.P., Renal Section, Division of Medicine, Imperial College London, Hammersmith Hospital, Du Cane Rd., London W12 0NN, UK. E-mail: c.pusey@imperial.ac.uk. [1]Renal Section, Division of Medicine, Imperial College London, Hammersmith Hospital, London, United Kingdom. Tel: +1(212) 584-4662. 1069-3424,p;2004,25,05,523,533, ftx,en;srm00325x.

describe a form of "polyarteritis nodosa" with small-vessel involvement and crescentic glomerulonephritis. The current definition of *classic polyarteritis nodosa* allows necrotizing inflammation of small and medium arteries, but not of the smallest vessels, thus excluding glomerulonephritis. Key to the Chapel Hill definition is the requirement for few or no immune deposits, which allows its differentiation from immune complex–associated vasculitis, as seen in systemic lupus erythematosus, cryoglobulinaemia, serum sickness, or Henoch-Schönlein purpura.

ASSOCIATION WITH ANTINEUTROPHIL CYTOPLASM ANTIBODIES (ANCAs)

Antibodies directed against the constituents of the azurophilic granules of neutrophils and monocytes were first described by Davies et al in 1982.[3] Subsequently they were linked to Wegener's granulomatosis (WG)[4] and later to MP.[5,6] Those antibodies initially associated with WG were shown to have a cytoplasmic pattern of immunofluorescence staining on ethanol-fixed neutrophils,[4] known as cANCA, and the target antigen was later shown to be proteinase 3 (PR3).[7,8] It was observed, however, that the sera of many patients with vasculitis showed a perinuclear pattern of staining, pANCA, and it was found that the target antigen in these cases was predominantly myeloperoxidase (MPO).[9] These patterns of immunofluorescence are illustrated in Figure 1.[6] Although the recognition of ANCA has provided a valuable tool in the diagnosis of small vessel vasculitis, the relationship between ANCA specificity and clinical characteristics is not clear cut. Most patients with generalized WG will have PR3-ANCA (70–90%). Although the majority of patients with MP will have ANCA, they may be either MPO-ANCA or PR3-ANCA.[10] MPO-ANCA are also associated with Churg-Strauss syndrome and renal-limited vasculitis. Experience from the Hammersmith Hospital suggests that MPO-ANCA and PR3-ANCA are associated with a diagnosis of MP with approximately equal frequency, but the Chapel Hill group found a predominance of MPO-ANCA.[11] The diagnosis of MP thus rests on clinical and histological findings, as discussed later.

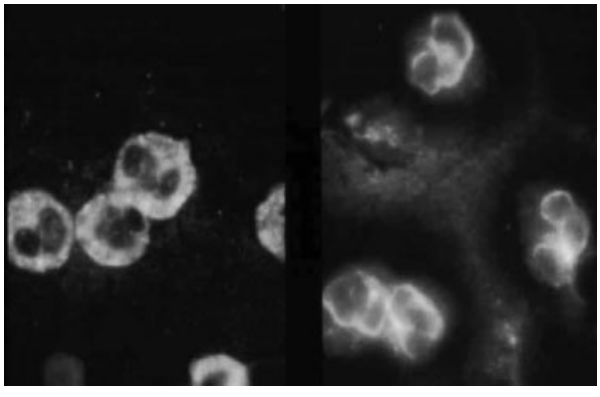

Figure 1 Indirect immunofluorescence on ethanol-fixed neutrophils showing positive cytoplasmic ANCA (left) and perinuclear ANCA (right).

EPIDEMIOLOGY

Formal classification of the vasculitides has allowed collection of previously unavailable epidemiological data. Current estimates of the incidence of all primary systemic vasculitis in several European centers range from 13 to 19 patients per million population per year, with an incidence of MP of three to nine patients per million population per year.[12,13] There are suggestions of a higher incidence of MP in southern Europe in contrast to the higher incidence of WG in northern Europe. There is a slight male preponderance, and a peak incidence in the 55- to 74-year-old age group. The incidence of MP appears to be increasing, but whether this is a reflection of improved disease recognition is unclear. Several epidemiological studies have tried to elucidate environmental factors associated with the onset of the vasculitides. Some authors have found associations with silica and solvent exposure.[14,15] The strongest evidence, however, points to a link with the treatment of thyroid disease, particularly with propylthiouracil.[16] Anti-MPO antibodies are often seen in these patients, although overt vasculitis is less common. Other drugs, such as hydralazine and penicillamine, have also been implicated. Interestingly, up to one third of patients with anti-GBM disease have also been shown to have ANCA, although whether one antibody precedes the other remains unclear.

PATHOGENESIS

The pathogenesis of the vasculitides has been discussed in depth in a previous chapter, but it now seems clear that ANCA are directly involved in the disease process.[17] Until recently, there was much in vitro evidence to suggest a pathogenic role for ANCA, but strong evidence in vivo was lacking. Xiao and colleagues have produced a mouse model in which anti-MPO antibodies, raised in MPO deficient mice, are able to induce a pauci-immune glomerulonephritis in Rag 2 deficient and wild-type recipients.[18] Similarly, we have developed a model in which autologous anti-MPO antibodies are directly induced by immunization of WKY rats with MPO, leading to a pauci-immune focal segmental glomerulonephritis and pulmonary vasculitis similar to MP in humans.[19]

CLINICAL FEATURES

According to the Chapel Hill definitions, both MP and WG are defined as necrotizing vasculitis predominantly

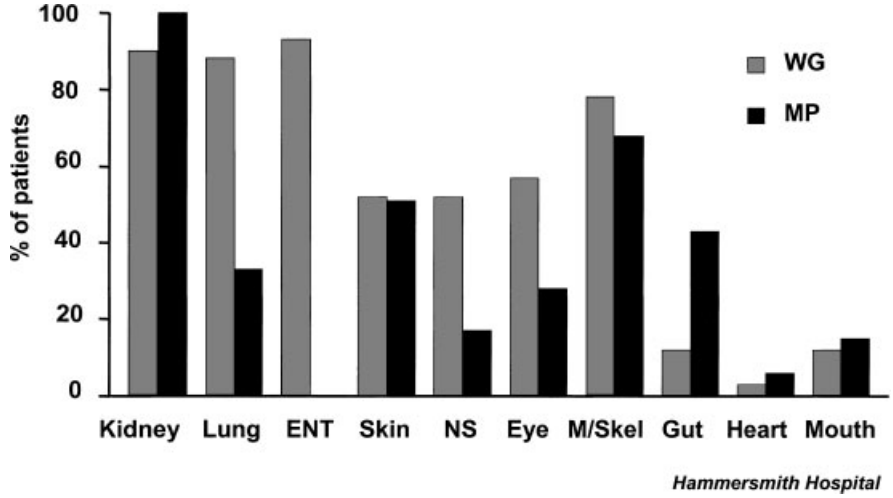

Figure 2 Organ involvement in patients with microscopic polyangiitis and Wegener's granulomatosis treated at the Hammersmith Hospital.

affecting the small vessels, commonly associated with glomerulonephritis. The diagnosis of WG also involves the presence of granulomatous inflammation of the respiratory tract. In practice, however, histological evidence of granulomas is not always available, and the presence clinically of destructive inflammatory disease of the upper respiratory tract points toward a diagnosis of WG. Thus the diagnosis of MP depends on clinical, histological, and serological evidence of a systemic small-vessel vasculitis in the absence of marked upper respiratory tract disease.

There is debate as to whether the clinical definition or the ANCA specificity is more important in determining the spectrum and outcome of the disease. Data from our series at the Hammersmith Hospital suggest a different pattern of organ involvement between patients with MP and those with a diagnosis of WG (Fig. 2). However, evidence is emerging that ANCA specificity does affect the histological pattern of disease seen on renal biopsy, and the subsequent course and outcome of the disease.

Systemic Features

Most patients describe a prodromal illness of fever (45%), weight loss (35–60%), myalgia (40%), and arthralgia (30–60%), which may precede diagnosis by up to 2 years.[5,20] Several groups have reported that the onset of renal involvement follows a more indolent course in disease associated with MPO-ANCA than in that associated with PR3-ANCA. This is borne out by histological evidence showing a higher incidence of chronic lesions on renal biopsy in patients with MPO-ANCA at the time of diagnosis.[10,21]

CUTANEOUS INVOLVEMENT

A purpuric rash is seen in ~30% at the time of diagnosis (Fig. 3). This is typically a pauci-immune necrotizing leucocytoclastic vasculitis on skin biopsy. Nail bed infarcts and splinter hemorrhages may be seen and, rarely, digital ischemia occurs.

RENAL INVOLVEMENT

Renal disease is seen in around 90% of patients with MP, irrespective of ANCA specificity. This is classically a focal and segmental glomerulonephritis with fibrinoid necrosis of the glomerular capillary wall leading to the formation of crescents (Fig. 4). Immunofluorescence staining reveals absent or scanty immune deposits, hence the term *pauci-immune*. As well as being focal, the glomerular lesions are characteristically of varying ages. Although the underlying histopathology is similar in MP and WG, it is now recognized that biopsies of patients with MPO-ANCA associated vasculitis tend to show features consistent with a more chronic pattern of

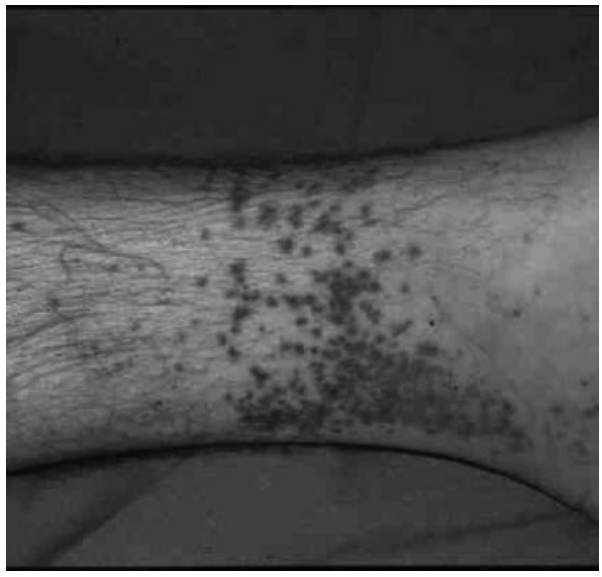

Figure 3 Vasculitic skin rash in a patient with microscopic polyangiitis.

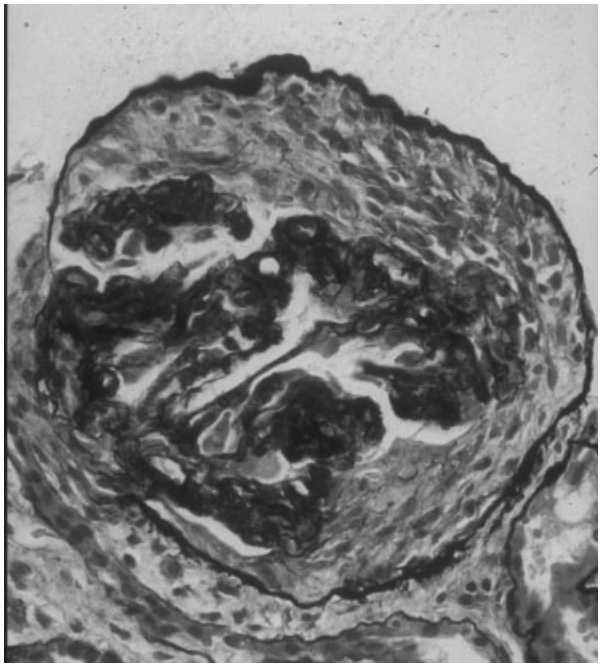

Figure 4 Silver stain of a glomerulus showing a cellular crescent.

disease. Thus there is more interstitial fibrosis, tubular atrophy, and glomerulosclerosis.[21] This reflects the more insidious onset of symptoms and longer time to diagnosis seen in these patients, and could also indicate a difference in the pathogenicity of the ANCA types involved.

Renal involvement in MP may present with urinary abnormalities such as microscopic hematuria, proteinuria, and red cell or granular casts, detected during investigation of other features of the illness. However, many patients have a rapidly progressive glomerulonephritis and several studies have shown that, at the time of diagnosis, 50 to 100% have renal impairment leading to acute, or subacute, renal failure, and that 11 to 22% require dialysis.[5,20,22] The mean creatinine at presentation in different series was found to be between 220 and 574 μmol/L. Patients with MPO-ANCA may have a less rapid decline of their renal function prior to treatment than those with PR3-ANCA[23] Although nephrotic syndrome is uncommon, up to 40% of patients have a urinary protein excretion of more than 3 g per 24 hours, and this has been suggested as a poor prognostic feature for renal outcome.[24]

PULMONARY INVOLVEMENT

Pulmonary involvement in MP most often presents as alveolar hemorrhage, although pleurisy, pleural effusions, and pulmonary fibrosis may be seen. Alveolar hemorrhage is seen in up to 30% of patients[5] and is associated with a worse prognosis.[25] Patients present with either or both breathlessness and hemoptysis, and a chest radiograph characteristically shows patchy alveolar shadowing (Fig. 5). Nodular or cavitating lesions on the chest film tend to indicate granulomatous disease more suggestive of WG. The presence of alveolar hemorrhage can be confirmed by an elevated K_{CO} on pulmonary function studies, and blood or hemosiderin-laden macrophages on bronchoalveolar lavage. Lung biopsy is rarely performed, but the histological lesion seen is pulmonary capillaritis.

Pulmonary fibrosis is an increasingly recognized feature of MP, predominantly associated with MPO-ANCA. We originally observed pulmonary fibrosis in eight of 90 patients and noted the poor prognosis. All were associated with previous alveolar hemorrhage.[26] Several reports have now confirmed this link.[27,28]

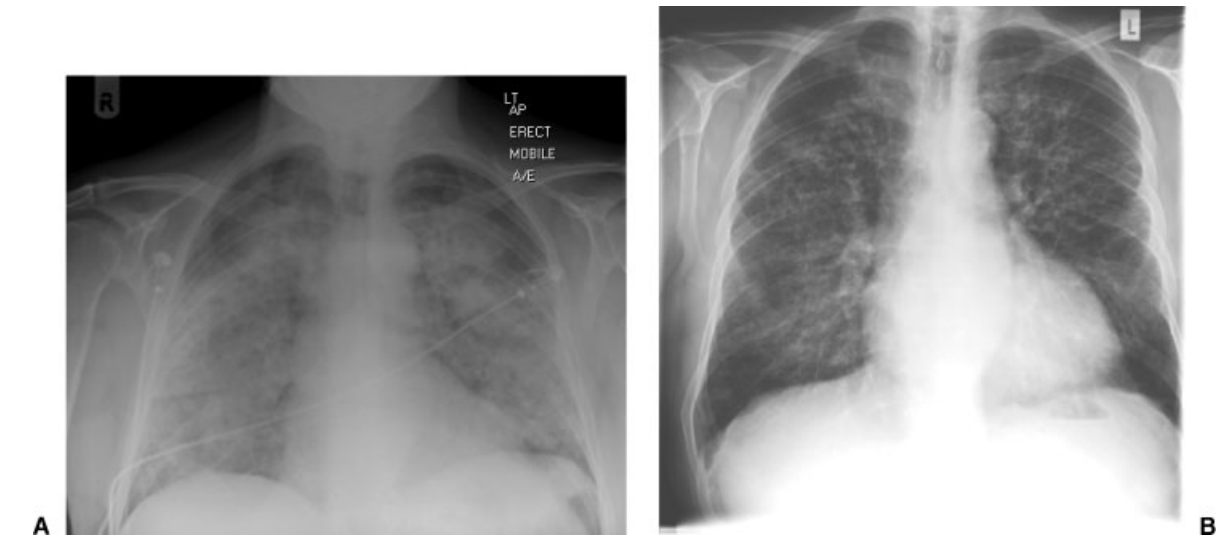

Figure 5 Chest radiographs of a patient presenting with alveolar hemorrhage, taken (A) at day 1, (B) at day 3, following immunosuppression and plasma exchange.

GASTROINTESTINAL INVOLVEMENT

Gastrointestinal symptoms, such as abdominal pain, diarrhea, and gastrointestinal bleeding occur in 30 to 40% of patients with vasculitis and are reported to be more common in MP than in WG in some series. Histologically, necrotizing vasculitic lesions are described, which may lead to bleeding or perforation. Oral ulceration is seen in some patients, but the gingivitis characteristic of WG has not been reported

NEUROLOGICAL INVOLVEMENT

Neurological involvement is seen in up to 30% and most commonly presents as a mononeuritis multiplex affecting either peripheral or cranial nerves, although sensory neuropathy is also seen. Cerebral vasculitis may be manifest as cerebral hemorrhage, infarction, seizures, or headache. MRI of the brain is helpful in diagnosis. Some authors have suggested that neurological disease is less common in MP than in WG.

CARDIAC INVOLVEMENT

Cardiac involvement is rare, but pericarditis and cardiac failure have been reported. This is in contrast to Churg-Strauss syndrome, also associated with MPO-ANCA, in which cardiac disease is a prominent feature.

EYE INVOLVEMENT

Episcleritis is seen in up to 20% of patients with MP, but the more florid features of uveitis, retinal vasculitis, optic neuropathy, and orbital granulomatous disease generally indicate a diagnosis of WG.

EAR, NOSE, AND THROAT INVOLVEMENT

Mild symptoms of rhinitis, epistaxis, and sinusitis are compatible with a diagnosis of MP, but severe destructive or infiltrative disease of the upper respiratory tract is not seen, and its presence is suggestive of WG.

DIAGNOSIS

Because the initial prodromal symptoms of fever, myalgia, and arthralgia are so nonspecific, patients typically come to specialist attention with renal impairment, often with alveolar hemorrhage (so-called pulmonary–renal syndrome). There are several important differential diagnoses to consider, and these are listed in Table 1. Clinical workup should include a history and examination of all the organ systems already described here, and a suggested list of investigations that may be required is outlined in Table 2.

Standardized tests for ANCA now include immunofluorescence and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence on ethanol-fixed neutrophils reveals either the cytoplasmic staining pattern of cANCA or the perinuclear pattern of pANCA. The presence of antibodies specific for the major autoantigens PR3 or MPO is then determined using solid-phase ELISA. This is particularly important for pANCA because other antigen specificities and disease associations are more common than with cANCA. Taken together, a large European study showed these assays to have a specificity of 99%, with a sensitivity of around 75%, for diagnosis of systemic vasculitis[29]

Table 1 Important Differential Diagnoses of Microscopic Polyangiitis

Diagnosis	Clinical Signs in Addition to Renal Impairment	Positive Investigations
Anti-GBM disease	Alveolar hemorrhage	Anti-GBM antibodies
		Linear IgG on GBM on renal biopsy
Systemic lupus erythematosus	Fever	ANA, anti-dsDNA positive
	Arthralgia	Decreased serum C4 ± C3
	Rash	Widespread granular immune deposits on renal biopsy
	Neurological involvement	
Mixed essential cryoglobulinemia (type 2)	Arthralgia	Rheumatoid factor positive
	Vasculitic rash	Circulating cryoglobulins
	Mononeuritis multiplex	Paraprotein (often IgMκ)
		Decreased serum C4, normal C3
		Subendothelial IgG/IgM on renal biopsy
Henoch-Schönlein purpura	Purpuric rash	Raised serum IgA
	Abdominal pain	Mesangial IgA/IgG on renal biopsy
Infective endocarditis	Fever	Valvular vegetations on TOE
	Vasculitic rash	Decreased serum C3 ± C4
	Splinter hemorrhages	Granular immune deposits on renal biopsy
Cholesterol emboli	Vasculitic rash	Decreased serum complement
	Evidence of atherosclerosis	Eosinophilia
		Cholesterol clefts on skin or renal biopsy

ANA, anti-nuclear antibodies; dsDNA, double stranded DNA; GBM, glomerular basement membrane; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IgMκ, immunoglobulin M kappa; TOE, trans-oesophageal echocardiogram.

Table 2 Investigations Suggested to Aid Diagnosis of Microscopic Polyangiitis

Investigation	Results Compatible with Microscopic Polyangiitis
Urinalysis	Dipstick haematuria
	Proteinuria
	Red cell and granular casts
Full blood count	Normocytic or microcytic anemia
	Raised white cell count
	Raised platelets
Biochemistry	Elevated urea, creatinine
	Acute phase response (↑CRP, ↑ALP, ↓albumin)
ANCA immunofluorescence and ELISA	Perinuclear or cytoplasmic pattern
	Raised anti-MPO or anti-PR3 antibody titers
ANA, dsDNA rheumatoid factor cryoglobulins anti-GBM antibody	Usually negative
	pANCA can give false positive ANA
	5% have positive anti-GBM antibodies
Blood gases	Hypoxia
	Acidosis
Chest radiograph	Patchy infiltrates suggest alveolar hemorrhage
	Pulmonary edema if renal failure
	Rarely pulmonary fibrosis
Renal ultrasound	Normal-sized kidneys, increased echogenicity
Pulmonary function tests	Raised Kco if lung hemorrhage
	Rarely restriction/diffusion abnormalities if fibrosis
Renal biopsy	Focal segmental glomerulonephritis
	Fibrinoid necrosis
	Crescents
	Absent or scanty immune deposits
Skin biopsy	Leucocytoclastic vasculitis
	Absent or scanty immune deposits
Bronchoalveolar lavage	Fresh blood or hemosiderin laden macrophages

ANA, anti-nuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CRP, C-reactive protein; dsDNA, ; ELISA, enzyme-linked immunosorbent assay; GBM, glomerular basement membrane; MPO, myeloperoxidase; PR3, proteinase 3; pANCA, perinuclear ANCA.

TREATMENT

It is now widely recognized that the use of cyclophosphamide, in addition to steroids, improves survival in patients with vital organ involvement.[30] However, the induction and maintenance regimens used have varied widely between different centers, as has the use of adjunctive therapies such as plasma exchange and intravenous methylprednisolone pulses. The potential toxicity of treatment is also recognized. Over the last few years, collaboration across European centers [European Vasculitis Study Group (EUVAS)] has allowed prospective randomized, controlled trials of different treatments for vasculitis. These trials have included patients with both MP and WG, so their results are relevant to both disorders. Overall, there is no apparent difference in the initial response to treatment, but WG tends to relapse more frequently than MP.

Standard Immunosuppressive Regimen

The standard treatment regimen used in our center is outlined in Table 3. Treatment is divided into an early aggressive induction phase, lasting 3 months or until remission is achieved, and a later maintenance phase, in which the level of immunosuppression is reduced. For maintenance treatment it is our practice to switch from cyclophosphamide to azathioprine at 3 months, which differs from the standard National Institutes of Health (NIH) regime in which cyclophosphamide is continued for 1 year after remission and then tapered thereafter. The CYCAZAREM trial has shown that an early change to azathioprine is equally effective, with no increased risk of relapse in up to 18 months of follow-up, thus allowing a reduced exposure to cyclophosphamide.[31] It is standard practice to taper oral steroids, and we suggest a rapid reduction every 1 to 2 weeks until a dose of 20 mg/day is achieved at 6 weeks, then a slower reduction to a dose of 10 mg/day at 6 months, and 5 to 7.5 mg/day at 12 months.

Prophylaxis against the side effects of the immunosuppressive agents should also be used. To reduce infective complications, co-trimoxazole, amphoteracin lozenges, and isoniazid/pyridoxine (if previous infection with, or at risk of, tuberculosis) are used while the

Table 3 Standard Treatment Regimen, as Used at the Hammersmith Hospital

Induction	0–3 months	Cyclophosphamide	2–2.5 mg/kg/day orally Dose reduced in elderly or in renal failure
		Prednisolone	1 mg/kg/day Tapering to 20 mg/day
Adjunctive	0–2 weeks	Plasma exchange	7–10 exchanges of 60 mL/kg over 2 weeks
		Methylprednisolone	10–15 mg/kg IV × 3 doses over 3 days
Maintenance	From 3 months if in remission	Azathioprine	2 mg/kg/day Tapering slowly
		Prednisolone	20 mg/day Tapering slowly

patient is taking cyclophosphamide. A proton pump inhibitor is used for the duration of high-dose steroid treatment. Bone protection with calcium/vitamin D and a bisphosphonate is suggested.

Adjunctive Therapies

The use of additional treatments in addition to oral steroids and cyclophosphamide in patients with severe disease has been debated at length. Several studies have examined the use of either plasma exchange[32–34] or pulses of intravenous methylprednisolone[35,36] in ANCA-associated vasculitis. The results have been difficult to compare due to the different treatment regimens used.[37] There does, however, appear to be a benefit of plasma exchange in those patients presenting with severe renal disease. Recently, EUVAS has directly compared plasma exchange with pulse methylprednisolone in this group of patients in a randomized controlled trial (MEPEX). The results show a significant advantage of plasma exchange in maintaining independent renal function in those patients presenting with a creatinine of 500 μmol/L or over.[38] Many centers, including ours, also use plasma exchange for patients with alveolar hemorrhage. Although there is no controlled evidence, retrospective data from the Chapel Hill group suggest a prompt resolution of alveolar hemorrhage in patients treated with plasma exchange in addition to immunosuppression, compared with several deaths before this approach was introduced.[39] Recent in vivo data suggesting a pathogenic role of ANCA in vasculitis provide a rationale for the use of plasma exchange to rapidly remove circulating autoantibodies.[18,19] It is our practice to carry out seven to 10 plasma exchanges over a 2-week period, aiming to exchange 60 mL/kg per session (usually 3–4 L). The replacement fluid used is 4% human albumin, with the addition of fresh-frozen plasma toward the end of the procedure if there is active alveolar bleeding or in the first 5 days post renal biopsy or surgical procedure.

Alternative Agents

There is currently much discussion about the use of alternative agents in the treatment of vasculitis. This partly stems from a desire to find newer agents with greater efficacy or fewer side effects, and partly to try and tailor treatments to the individual. At present, alternative agents are generally used in patients with particularly refractive or relapsing disease, or to minimize exposure to the toxicity of standard agents, particularly cyclophosphamide.

Intravenous Pulsed Cyclophosphamide may reduce the cumulative dose of the drug, and hence potential toxicity. A meta-analysis of several small trials did not show increased efficacy of intravenous over oral cyclophosphamide, and the rate of relapse was higher, although the number of adverse events was lower.[40] EUVAS is currently running a randomized, controlled trial comparing daily oral with pulse administration, using an accelerated regimen of IV dosing, to examine remission and relapse rates and adverse effects (CYCLOPS).

Mycophenylate Mofetil (MMF) may be an effective alternative to azathioprine in the maintenance treatment of vasculitis.[41] A EUVAS randomized controlled trial is currently in progress (IMPROVE). We often use MMF in maintenance if the patient tends to relapse on azathioprine. Some authors suggest that MMF may also be used for induction therapy in patients without life-threatening disease.

Intravenous Immunoglobulin (IVIG) may have a role in the treatment of refractory or relapsing disease as an addition to continued immunosuppression.[42,43] The mode of action is unclear, and results are variable. However, one trial did show a significant benefit lasting for 3 months.[42] There is potential nephrotoxicity of IVIG in patients with underlying renal impairment.

Methotrexate appears to be effective in the maintenance treatment of respiratory tract disease in WG.[44] EUVAS has recently completed a trial of methotrexate versus cyclophosphamide in induction of remission in "nonrenal" WG, and the results suggest that remission rates are similar (NORAM).[45] However, its role in MP is unclear, and renal impairment is a contraindication to its use.

T Cell Depletion with polyclonal and monoclonal antibodies may be effective in refractory disease. A recent open-label study of anti-thymocyte globulin (ATG) reported benefit in 13 of 15 patients with refractory WG.[46] The use of anti-CD52 antibody (CAMPATH-IH) in vasculitis has been reported to induce long-lasting remission, but with frequent infective complications.[47]

B Cell Depletion with the anti-CD20 monoclonal antibody rituximab has recently been shown to be effective in individual patients,[48] but data are limited at present.

Anti-Tumor Necrosis Factor (TNF) Therapies, including both anti-TNF monoclonal antibodies and soluble TNF receptor fusion proteins, are undergoing trials in vasculitis. Although the preliminary data pertain mainly to patients with persistent or relapsing WG,[49] there is evidence that these therapies may also be effective in relapsing MP.[50]

Leflunomide has been shown to be effective in maintenance of remission of WG, but there have been no trials of its use in MP.

Deoxyspergualin has been effective in treatment of relapsing WG in an open-label trial, and controlled trials are being undertaken.[51]

Supportive Treatment

Renal replacement therapy is required in about half of patients presenting with MP, and up to a third of patients may go on to require long-term dialysis.[22] Acutely, intermittent haemodialysisis is usually used, although continuous therapies may be required if the patient is hemodynamically unstable. Long-term patients may be managed by either hemodialysis or peritoneal dialysis, although immunosuppressive treatment may increase the infectious complications in both modalities.

The outcome of renal transplantation in patients with MP has generally been shown to be good. The rate of relapse of vasculitis in our unit has been shown to be 0.02 per patient per year,[52] possibly reflecting the continued high level of immunosuppression. Relapse may affect the graft[53] or other organ systems.[54] It appears that positive ANCA titers at the time of transplantation do not affect the outcome,[55] although we would be cautious if ANCA titers were rising.

Ventilatory support may be required in around 50% of patients with alveolar hemorrhage,[39,56] and possibly for other complications such as pneumonia or pulmonary edema.

Side-Effects of Treatment

Leukopenia is particularly common with cyclophosphamide, and to a lesser extent with azathioprine. It is our practice to discontinue the drug temporarily if the total white cell count falls below 4×10^9/L, and to reintroduce it at a lower dose once the count has recovered.

Infections are common, especially in those heavily immunosuppressed with steroids and/or with leukopenia. Sepsis is clearly associated with decreased survival.[22] In the early stages of treatment, opportunistic infections may include *Pneumocystis,* bacterial and fungal infections, and the reactivation of tuberculosis. Intravenous catheter–related sepsis is also common. *Nocardia* and *Aspergillus* are among infectious agents seen in the long-term immunosuppressed patient.

Malignancy is associated with long-term immunosuppression, particularly with cyclophosphamide, as reported from the NIH.[57,58] Cyclophosphamide most often causes bladder cancer and hematological malignancies, whereas azathioprine increases the risk of skin malignancies.

OUTCOME

Current treatment regimens have greatly improved the outcome of this previously fatal condition.[11,59] A recent multicenter retrospective study of 264 patients with a new diagnosis of ANCA-associated vasculitis, 49% of whom had MP, showed a 1-year survival rate of 84%, with a 5-year survival rate of 76%. However, survival was lower in those patients with end-stage renal failure, being 64% and 53% at 1 and 5 years, respectively. Of those patients presenting with a creatinine of >500 μmol/L, 45% went on to end-stage renal failure, a total of 28% of the cohort.[22] Thus, over half of the patients with severe renal failure recovered independent renal function. Results from our unit, in 73 patients presenting with a creatinine $>$ 500 μmol/L (55 on dialysis) treated with plasma exchange in addition to drugs, show that 74% have independent renal function at 2 months, and that the long-term renal prognosis is good in responding cases.

There is evidence that certain features of the renal biopsy may predict a good outcome, in particular the

number of normal glomeruli, and the less interstitial scarring seen.[60,61] ANCA specificity has not been shown to affect early survival or renal outcome in most studies. Alveolar hemorrhage has been shown to be the worst single predictor of poor outcome, with an eightfold greater relative risk of death.[25]

Relapse

Relapse rates in several studies of vasculitis are very similar, at around 35 to 50% by 5 years.[20,22,62,63] However, relapse is generally less common in MP than in WG. In the CYCAZAREM trial, by 18 months the relapse rate was 18% for WG but only 8% for MP. There is also evidence that the rate of relapse is higher in those patients with persistently high ANCA titers, particularly in those with PR3-ANCA rather than MPO-ANCA,[10] and it is our practice to consider long-term maintenance immunosuppressive treatment in the former group. There has been much debate about the use of ANCA testing to predict relapse in vasculitis. Certainly, rising ANCA titers often precede a relapse, but relapses may occur without an ANCA rise, and indeed titers may fluctuate without clinical evidence of relapse.[64] There is evidence from two studies that increased immunosuppression based on rising ANCA titers may reduce the rate of clinical relapse[65,66]; however, there is a risk that some patients may be treated unnecessarily. It is our current practice to view a rise in ANCA titer as an indication for increased vigilance, and as a factor in determining whether to reduce treatment. Relapses may occur in the same or different organ systems as the initial presentation, and regular follow-up in a specialist center is suggested.

Treatment of relapse will depend on the clinical features and history of the disease process in the individual patient: in particular, the organ systems involved, the severity of the relapse, the previous treatments used, and the patient's response to treatment. Escalation of treatment may involve increasing the dose of current maintenance therapy, reintroducing a standard induction regimen, or a trial of alternative agents.

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