Conventional treatment and outcome of Wegener's granulomatosis and microscopic polyangiitis

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The systemic vasculitides are usually fatal if untreated, and immunosuppressive therapy now saves lives and salvages organ function. Combination immunosuppressive therapy has changed the outcome of vasculitis to that of a chronic disorder with accumulating morbidity and incapacity; however, current treatments are toxic and contribute to morbidity and mortality. Optimization of therapy and the introduction of new treatments has been facilitated by the antineutrophil cytoplasmic autoantibody (ANCA) test, by consensus statements on classification, by improved understanding of pathogenesis, and by the construction of collaborative trial networks.

CLASSIFICATION

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are primary systemic vasculitides predominantly affecting small blood vessels. Immune deposits are scanty or absent and circulating ANCA are usually present at diagnosis; ANCA may be negative in localized WG or after therapy. The strong similarities, particularly in renal involvement and ANCA status, between WG and MPA have prompted their collective grouping as ANCA-associated vasculitis (AASV). Renal vasculitis, or idiopathic rapidly progressive glomerulonephritis, has been regarded as an organ-limited form of AASV. Up to 50% of patients with Churg-Strauss angiitis are ANCA-positive, and their clinical phenotype often overlaps with that of WG or MPA. Polyarteritis nodosa is distinct from AASV although cases with involvement of both medium-sized muscular arteries and microscopic vessels are now classified as MPA. Despite agreed, consensus definitions of these vasculitic syndromes, diagnostic criteria have not been unified and vary between clinical trials.[1]

The European Vasculitis Study Group (EUVAS) has sub-classified AASV at presentation with the purpose of designing appropriate therapeutic protocols according to disease severity **(Table 1)**.[2] Further sub-classification, such as by age or ANCA specificity, is likely to be of importance to the treatment of vasculitis in the future.

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APPROACHES TO TREATMENT

The natural history of systemic vasculitis includes acute flares, which can be fulminant; treatment-induced remission without clinical evidence of vasculitis; partial remission with grumbling disease activity; and relapse that can be major, involving vital organs, or minor. In response to these patterns, treatment aims to induce rapid remission with high drug doses at the expense of short-term toxicity, then taper the drug doses or switch to safer agents once remission is achieved and maintain low dose therapy for a prolonged period to prevent relapse. Monitoring of vasculitic activity and the prediction of relapse is of importance during this remission phase. Those with only a partial response to induction therapy are at particular risk from ongoing vasculitis and the dangers of a high cumulative treatment exposure.

REMISSION INDUCTION

Localized disease

WG affecting the upper or lower respiratory tract alone without constitutional disturbance has been treated with prednisolone alone or with the antibiotic combination, sulfamethoxazole/trimethoprim.

Early systemic disease

This subgroup comprises localized WG with constitutional disturbance or WG or MPA which is multi-focal but without threatened organ function.[3] Cyclophos-phamide and steroids has been standard therapy, but several uncontrolled studies have reported disease remission in 60-70% with methotrexate and steroids **(Table 2)**.[4-8] Inability to reduce the steroid dose and relapsing disease have been predictive of more widespread vasculitis after methotrexate therapy.[8] Adverse effects related to methotrexate included pneumonitis, which is difficult to differentiate from pulmonary vasculitis, hepatotoxicity, and myelosuppression, but these events were reversible. The control of early renal

TABLE 1
CLINICAL SUBGROUPING ACCORDING TO DISEASE SEVERITY AT PRESENTATION FOR ANCA-ASSOCIATED VASCULITIS[3]

Clinical subgroup	Constitutional symptoms	Typical ANCA status*	Threatened vital organ function	Serum creatinine (μmol/L)	EUVAS trial[3]
Localized	No	Negative	No	<120	
Early systemic	Yes	Positive or negative	No	<120	NORAM
Generalized	Yes	Positive	Yes	<500	CYCAZAREM
Severe	Yes	Positive	Organ failure	>500 if renal; hypoxia if pulmonary	MEPEX
Refractory†	Yes	Positive or negative	Yes	any	SOLUTION

*ANCA is negative in a minority of generalized and severe renal presentations. †Refractory disease implies progressive disease despite at least six weeks treatment with an appropriate regimen; ANCA may become negative with treatment.

TABLE 2
THERAPEUTIC TRIALS OF METHOTREXATE FOR WEGENER'S GRANULOMATOSIS

Study	Number	Follow-up (months)	Design	Remission rate	Relapse rate	Adverse effects
Sneller 1995[6]	41	?	Prospective open	71%	34%	21, 2 deaths (infective)
de Groot 1996[7]	33	18	Prospective open	-	12%	16 in 12 patients
de Groot 1998[4]	17	25	Prospective open	59% partial 35% full	20%	2
Stone 1999[8]	19		Prospective open	89% partial 79% full	50%	2
Langford 2000[5]	42	76	Prospective open	20/21 with renal involvement	10% renal progression	

vasculitis, hematuria with normal or modest creatinine elevation, with methotrexate is more controversial. Two studies have reported stabilization of excretory function; others have found renal vasculitis to predict refractory, progressive disease after methotrexate.[5,7,8] The NORAM trial is comparing oral methotrexate (20-25 mg/week) to oral cyclophosphamide (2 mg/kg/day), both with the same steroid regimen, for this subgroup and includes patients with MPA.[3]

Generalized/renal disease

The empirical introduction of daily oral cyclophosphamide became popular during the 1970s but was only recently subjected to randomized trial.[9,10] Retrospective data from the North Carolina glomerulonephritis study group compared patients with MPA treated with cyclophosphamide to those treated with steroids alone and found improved renal survival and a lower relapse rate in those receiving cyclophosphamide.[11] Recent studies have aimed to reduce cyclophosphamide exposure by using pulse rather than continuous administration or by switching to an alternative drug once remission has been obtained.

Two open, prospective studies of pulse intravenous cyclophosphamide investigated whether this form of administration might be superior to daily oral administration for induction of sustained remission.[12,13] It did not appear more successful in this setting; those with more extensive organ involvement and high ANCA titers had a poor therapeutic response.[13] In contrast, continuing disease activity despite pulsed, intravenous cyclophosphamide has responded to conversion to a daily oral regimen.[14] Four randomized trials have investigated whether pulsed cyclophosphamide is safer and as effective as daily oral administration for the induction of remission.[15-18] None were sufficiently powered to make any conclusions about efficacy in controlling vasculitis, although one study clearly showed a higher relapse rate after intravenous pulse use.[16] All of the studies concluded that adverse effects were more frequent with daily oral cyclophosphamide although this was only the primary end-point in the study by Adu.[15] The studies by Guillevin and Haubitz were both stopped early due to more adverse effects in the daily oral arms.[16,17] The high number of adverse events has been associated with the steroid dose used in these trials and with the protocols for tapering cyclophosphamide.[19] A meta-analysis has summarized results from these trials **(Table 3)**.[20] The CYCLOPS study is currently comparing the efficacy of daily oral to pulsed cyclophosphamide for renal vasculitis in 160 patients.[2]

Severe renal disease

The delayed diagnosis of renal vasculitis increases the risk of the development of renal failure by the time of presentation. Progression to end-stage renal failure is not in-

evitable, and recovery of renal function is possible in many. The addition of pulsed methylprednisolone or plasma exchange or both to cyclophosphamide and oral prednisolone has been advocated to increase the chances of renal recovery. A pooled analysis of existing data suggests that plasma exchange may be superior in this regard but numbers are small and inclusion criteria and immunosuppressive regimens varied **(Table 4)**.

The MEPEX trial is comparing the rates of renal recovery for those with an initial creatinine over 500 μmol/l (6 mg/dl) between the addition of 3 g of intravenous methylprednisolone and seven plasma exchanges, in addition to daily oral cyclophosphamide and prednisolone.[3] Plasma exchange aims to deplete circulating pathogenic autoantibodies; other effects, such as the removal of cytokines, complement, and coagulation factors, and less well-defined immunoregulatory phenomena may also contribute to its therapeutic effects. In a randomized study of 32 patients with Wegener's granulomatosis of varying severity, plasma exchange improved outcome.[21]

Plasma exchange dosing remains empirical; factors likely to be of importance which merit further study include persisting ANCA positivity, ongoing inflammation reflected by C-reactive protein, urinary sediment and repeat renal biopsy. Renal function at presentation remains the strongest predictive factor for renal outcome; however, active lesions on biopsy confer a superior and chronic lesions an inferior prognosis.[22,23] A subgroup of renal vasculitis patients present with dual positivity for ANCA and autoantibodies to the glomerular basement membrane (GBM) with linear IgG deposition in the glomeruli on biopsy. In this setting, renal disease is more severe and renal recovery less common, and concomitant pulmonary hemorrhage is more frequent than presentation with ANCA alone. Prospective therapeutic studies have not been performed although the presence of anti-GBM has argued for the use of plasma exchange. ANCA-associated vasculitis is the most frequent cause of diffuse pulmonary hemorrhage, usually in the context of the pulmonary renal syndrome, and this presentation carries a high mortality.[24,25] No prospective therapeutic studies are available although both plasma exchange and methylprednisolone have been used in retrospective reports.[24,26]

■ REMISSION MAINTENANCE

Over 50% of patients will have a relapse of vasculitis, and this possibility has a major influence on their long-term care.[27] The efficacy of azathioprine for remission maintenance in vasculitis has been previously reported, with relapse rates of 11-30%; smaller studies have used azathioprine in remission induction protocols.[15,28-30] The CYCAZAREM trial compared azathioprine to continued cyclophosphamide for prevention of relapse, following induction of remission with oral cyclophosphamide and steroids for three to six months.[31] There was no difference in relapse rate, 16%, up to the end of the study, 18 months from treatment onset, and there was a trend to fewer serious adverse events in the azathioprine arm.[31] A surprising result of this study was the high remission rate with oral cyclophosphamide and prednisolone in this subgroup. Apart from the withdrawal of ten patients prior to the start of the remission phase, largely due to death or treatment intolerance, all patients entered clinical remission. Thus the 'standard' induction treatment with oral steroids and cyclophosphamide appears effective, but toxicity was high, with over 160 adverse events reported and a serious or life-threatening adverse-event rate of 26%. Reversible leukopenia was the most common adverse effect; azathioprine hypersensitivity was reported in 7% and has features similar to a relapse of vasculitis, which has caused difficulties in diagnosis.[32,33]

The optimal duration of maintenance therapy is undetermined. For those presenting with renal vasculitis, a current trial (REMAIN) is comparing two years to four years of azathioprine and prednisolone.[2] Other factors of potential importance to the duration of remission therapy are persistent ANCA positivity, a history of relapsing disease and the severity of presenting disease. Alternative remission-maintaining drugs include methotrexate (see above), cyclosporin, mycophenolate mofetil and leflunomide.[34, 35]

■ RELAPSE

The diagnosis of relapse requires a similar approach to investigation of the initial presentation, but clinical features may be modified by concurrent immunosuppression, and there is a complex relation between infection and relapse. Vasculitis may occur as a consequence of infection, such as endocarditis, and intercurrent infection can provoke relapse of primary vasculitis.[36-40] Alternatively, infection may be a consequence of immunosuppressive treatment or secondary to structural damage to an epithelial surface caused by previous vasculitis, where it may mimic relapse.[41] Colonization of the upper respiratory tract by *Staphylococcus aureus* in Wegener's granulomatosis increases the risk of disease relapse, and this observation has drawn attention to the possibility of an infectious etiology for this vasculitis, first suggested by Wegener.[39,42] Long-term antibiotic therapy with sulfamethoxazole/trimethoprim in Wegener's granulomatosis reduced the risk of respiratory tract relapse in a placebo-controlled study when added to conventional immunosuppression.[43] The treatment duration was two years, and the difference in relapse frequency was largest in the first six months; a high rate of drug intolerance was observed. Sulfamethoxazole/trimethoprim was less effective in controlling disease activity in Wegener's granulomatosis when used in place of immunosuppression at various stages of disease in a prospective study of 72 patients.[44] An association between ANCA titer and relapse exists but the strength of this association and the role that changes in ANCA should play in dictating treatment remain controversial.[27,45] PR3-ANCA positivity at diagnosis appears to be associated with a higher risk of relapse when compared to MPO-ANCA.[46] An early study in Wegener's granulomatosis randomized patients in remission to treatment intensification or no change in therapy on the basis of a rise in ANCA titer.[47] Subsequent relapse was frequent in the latter group and was not seen in the group treated on the basis of the ANCA titer; the cumulative exposure to immunosuppression was lower in the treatment intensifica-

TABLE 3
CRITICAL ANALYSIS OF TRIALS COMPARING 'PULSE' TO DAILY ORAL CYCLOPHOSPHAMIDE[20]

	Daily oral	Pulse	Comparison
Remission rate	77%	93%	Odds ratio 0.3
Relapse rate	29%	42%	Odds ratio 2.2
Infection	58%	39%	Odds ratio 0.24
Death	22%	20%	No difference
End-stage renal failure	15%	17%	No difference
Cyclophosphamide dose	34 g	17 g	$P < 0.001$

TABLE 4
RENAL SURVIVAL IN PROSPECTIVE TRIALS INCLUDING PATIENTS PRESENTING WITH RENAL FAILURE DUE TO RENAL VASCULITIS. TREATMENT WITH OR WITHOUT PLASMA EXCHANGE

	No. pts	Plasma exchange	No plasma exchange
Glockner[65]	12	5/8	3/4
Pusey[66]	19	10/11	3/8
Cole[67]	11	3/4	2/7
Levy[68]	20	9/11	5/9
Guillevin[16]	8	4/6	1/2
Haubitz[17]	22	6/12	2/10
(Jayne)†	26	9/16	4/10
Total	88	46/68 (67%)*	20/50 (40%)

*$P < 0.05$; †(Jayne) refers to unpublished data

tion group.[47] Other studies have consistently reported a high frequency of ANCA positivity at the time of relapse, and an increased relapse risk in those with persistent ANCA positivity during remission or in those whose ANCA becomes positive during remission.[28,29,48] While further interventional studies based on ANCA specificity and persistence are anticipated, a common response to the increased risk of relapse is to reduce the period between clinic reviews in order to diagnose relapse as early as possible.

■ ADVERSE EFFECTS

The toxicity of treatment contributes to the chronic morbidity and mortality of vasculitis. The National Institutes of Health experience with Wegener's granulomatosis reported a contribution of treatment toxicity to permanent damage in over 50% of their patients.[49] The CYCAZAREM trial revealed an adverse-effect frequency of 1.1 episode per patient with 26% having severe or life-threatening adverse effects within the first 18 months.[31] Infectious adverse effects are the most common cause of death or severe morbidity and their frequency is associated with age and concomitant steroid dosage.[50] *Pneumocystis carinii* pneumonia rates of up to 20% have been found, which have prompted advice for routine prophylaxis with low-dose sulfamethoxazole/trimethoprim in centers where this infection is common.[3,16,51] Urothelial toxicity of cyclophosphamide metabolites is known to cause cystitis and bladder cancer. In the largest cohort to be studied to date, 73/145 developed non-glomerular hematuria and seven (5%) bladder cancer.[52] These patients were collected over a time period when prolonged daily oral cyclophosphamide was standard therapy. The frequency of hematuria was related to the duration or total dose of cyclophosphamide with a 50% rate after 40 months or 120 g.[52] None of the 72 patients without hematuria developed bladder cancer. Of particular concern is the rise in bladder cancer risk with longer follow-up, which was estimated in this study to be 5% at 10 years and 16% at fifteen years.[52] Hemorrhagic cystitis is rare in pulse cyclophosphamide-treated patients, being reported in only one case from the reviewed studies. A Swedish study found an 11-fold increase in bladder cancer rates in patients receiving oral cyclophosphamide for more than one year, and an increase in dermatological malignancy related to azathioprine and steroid exposure.[53] Gonadal failure is associated with the total cyclophosphamide dose and is therefore likely to be more frequent in daily oral regimens. This toxicity has been assessed in Lewis rats when comparable oral regimens led to significantly greater changes in testis histology and reduced conception rates.[54] The human corollary was reflected in male FSH levels that were higher with oral regimens, indicating greater gonadal suppression.[54]

A high incidence of steroid-induced bone disease has been an inevitable consequence of the prolonged exposure to high-dose steroids.[49] Steroid-induced bone disease is common due to the high cumulative exposure and age of the patient population. No protective effect with salmon calcitonin was found in a relatively small randomized trial of steroid-induced bone disease.[55] Patients with chronic inflammatory disease have increased incidence of cardiovascular disease, which is likely to be further exacerbated by steroids, due to effects on blood pressure, glucose and lipid metabolism and possibly other mechanisms.[56] This problem remains to be quantified in vasculitis.

■ OUTCOME

The outcome of vasculitis has been assessed by death, development of end-stage renal failure, disease relapse and the acquisition of irreversible damage.[57] In a retrospective review of 55 cases of Wegener's granulomatosis, Walton reported a mortality of 80%, largely due to renal failure.[58] Leib found a reduction in five-year mortality to 50% with steroids in polyarteritis nodosa and a further reduction with the use of cytotoxics to 12%.[30] Retrospective studies from single centers have reported survival rates with immunosuppressive therapy varying between 75% at 12 months to 87% at eight years, with heterogeneity in disease presentations and therapeutic protocols accounting for much of the difference.[11,49] A large recent review of 155 WG patients highlighted age, renal and pulmonary

involvement as adverse prognostic factors, and the value of a treatment approach adapted to the stage and extent of disease.[59] A retrospective audit of 246 patients with AASV and renal involvement diagnosed in London, UK, between 1995 and 2000 found a standardized mortality rate of 242%. Survival was significantly worse in those presenting with a creatinine over 200 µmol/l, aged over 60, with renal limited vasculitis or those who were dialysis dependent. These results reflect single center experience from the 1990s which reported two-year survivals of 80%, with 20% progressing to end-stage renal failure.[22,53,60-62] Age and creatinine at presentation have also been consistently associated with survival.[22,50,53] The London audit found an end-stage renal failure rate of 27% by two years. Thus, at present, over 40% have a poor outcome by these two simple definitions. Survival in the three initial EUVAS trials has reflected severity of disease (NORAM, 98%; CYCAZAREM, 93%; and MEPEX, 78%).

An inclusive score to record accumulating 'all-cause' damage, the vasculitis damage index (VDI) provides a semi-objective score of incapacity.[63] Vasculitis is the major contributor to VDI in the first six months from onset of disease; subsequently, treatment toxicities, such as diabetes, fractures and infertility, become more important.[57] In the CYCAZAREM study, by 18 months patients had aquired a mean of at least two items of permanent damage. Patient function, as assessed by the generic short-form 36 questionnaire, revealed low perceptions of general health and vitality during remission despite normalization of disease activity scores, with direct consequences on physical and social activity.[31,64] It is unclear whether these continuing symptoms result from subclinical disease activity, ongoing treatment toxicity or the effects of irreversible damage.

CONCLUSIONS

Agreement of diagnostic terminology and the introduction of ANCA testing have stimulated clinical and therapeutic research in WG and MPA. Prospective outcome data from multi-center trials is emerging of direct value in clinical decision making. Current outcomes of vasculitis show a high mortality and renal failure rate, especially in the elderly and in those with renal involvement. Diagnostic delay has a major impact on outcome, and strategies to encourage early suspicion of vasculitis should be encouraged. Survivors suffer relapsing disease and chronic morbidity due to vasculitic damage and the long-term consequences of immunosuppression. Such outcomes provide considerable scope for improvements in therapy in the future.

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