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Evidence-based treatment of systemic vasculitis

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The systemic vasculitides are potentially fatal if untreated and immunosuppressive therapy now saves lives and salvages organ function. Treatment has changed the outcome of vasculitis to that of a chronic disorder with accumulating morbidity and incapacity. Current treatment is toxic and contributes to morbidity and mortality. Balancing the dangers of disease against those of treatment requires detailed knowledge of both, knowledge that has been confused by differences in classification or is lacking due to a paucity of long-term outcome studies. There have been relatively few randomized-controlled trials in vasculitis, although their number is increasing. Much of the evidence supporting therapeutic decisions derives from small prospective studies or larger, usually single centre, retrospective experiences. More recently, consensus discussions have contributed to evidence on classification and existing treatment practice.

Classification

Diagnosis

This review will focus on the primary systemic vasculitides which are distinct from those related to infection, drugs, cancer or other systemic disorders, such as rheumatoid arthritis. While international consensus on disease definitions is not complete, most current investigators use the system derived from the Chapel Hill Consensus conference in 1992 [1]. Ongoing modifications to include antineutrophil cytoplasm autoantibodies (ANCA) in the classification system will group together those conditions with a pauci-immune vasculitis predominantly affecting 'microscopic' blood vessels (Table 1) [2]. The term, 'ANCA-associated vasculitis' has been applied to this subgroup although not all patients are ANCA positive at diagnosis; in particular, the frequency of ANCA positivity is lower in milder and organ-limited presentations [3, 4]. Certain other problems with classification remain which complicate examination of the existing literature [5]. 'Polyarteritis' or 'polyarteritis nodosa' has been used to describe both polyarteritis nodosa and microscopic polyangiitis; following Chapel Hill the term polyarteritis nodosa is now restricted to disease where microscopic vessel involvement is absent [6]. The term 'Wegener's granulomatosis' is used by some writers when there is upper or lower respiratory tract involvement without the demonstration of destructive ear, nose and throat (ENT) lesions, lung cavities or granulomata in tissue biopsies, which would be regarded by others as microscopic polyangiitis. Lastly, renal vasculitis is now frequently used to describe patients with a crescentic necrotizing glomerulonephritis with few immune deposits, which has been previously termed 'idiopathic rapidly progressive glomerulonephritis' and can be regarded as a 'forme-fruste' of primary systemic vasculitis [2]. Thus, classification remains based on clinical and pathological features at presentation and not on aetiology and there are inevitable overlaps between categories.

Clinical subgrouping

Patients with more severe disease at presentation have a poorer outcome and therapeutic regimens have evolved to treat such presentations more aggressively, with, in consequence, more adverse effects. An international consensus group has formalized disease severity at presentation with the aim of designing regimens appropriate to each subgrouping (Table 2) [7, 8]. Such a system of subgrouping remains empirical and awaits the results of further studies to confirm its value. In a review of 342 patients with polyarteritis and Churg–Strauss angiitis, multiple potential prognostic factors were measured against outcome and vital organ involvement of kidneys, heart, gut, brain or lung were predictive and have been used to develop a simple 'five factor score' [9]. The same study group now classifies patients at diagnosis into 'good' and 'poor' prognostic groups and varies the intensity of treatment accordingly [10]. Other prognostic factors which have been identified are an increase in relapse rate with ANCA directed to proteinase 3 (PR3–ANCA), a diagnosis of Wegener's granulomatosis, the number of systems involved, race and serum creatinine level at diagnosis [11–14]. Increased age at diagnosis is also an important outcome predictor, with a high mortality in part due to infective complications of immunosuppression [15]. Further studies are required to identify prognostic markers, which will allow sophistication of subgrouping at diagnosis and better-targeted therapy.

Outcome

The outcome of vasculitis has been assessed by death, development of end-stage renal failure, disease relapse

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Table 1. Classification of primary systemic vasculitis according to ANCA positivity and predominant size of vessel involved

Size of predominant vessel involvement	'ANCA-associated' (usually ANCA positive)	'ANCA negative'
Small 'microscopic'	Wegener's granulomatosis Microscopic polyangiitis (renal-limited vasculitis)	Henoch–Schönlein purpura Cryoglobulinaemic vasculitis Cutaneous vasculitis
Medium (muscular arteries)	Churg–Strauss angiitis	Polyarteritis nodosa Kawasaki disease
Large		Giant cell arteritis Takayasu's arteritis

Table 2. Clinical subgrouping according to disease severity at presentation for ANCA-associated vasculitis [7]. ANCA is negative in a minority of generalized and severe renal presentations. Refractory disease implies progressive disease despite at least 6 weeks of treatment with an appropriate regimen; ANCA may become negative with treatment

Clinical subgroup	Constitutional symptoms	Typical ANCA status	Threatened vital organ function	Serum creatinine (μmol/l)
Localized	No	Negative	No	<120
Early systemic	Yes	Positive or negative	No	<120
Generalized	Yes	Positive	Yes	<500
Severe renal	Yes	Positive	Yes	>500
Refractory	Yes	Positive or negative	Yes	Any

and acquisition of irreversible damage [8]. Therapeutic trials often use remission as an end-point, but this term has not been standardized. Prior to the introduction of steroids, mortality of vasculitis with vital organ involvement was over 75%; an early Medical Research Council trial of cortisone found reduced mortality of polyarteritis at 1 yr, but after 3 yr there was no difference between treated and untreated patients due to steroid-associated mortality [16]. Leib *et al.* [17] found a reduction in 5-yr mortality to 50% with steroids in polyarteritis nodosa and a further reduction with the use of cytotoxics to 12%. Although cytotoxic drugs had been used in various forms since the mid-1950s, the reports by Fauci *et al.* [18, 19] from the National Institutes of Health confirmed the position of cyclophosphamide in induction regimens for systemic vasculitis with a remission rate of 93% in 85 patients with Wegener's granulomatosis. Retrospective studies from single centres have reported survival rates with immunosuppressive therapy varying between 75% at 12 months and 87% at 8 yr with differences in disease presentations and possibly, therapeutic protocols accounting for much of the difference [20]. Recent studies of ANCA-associated vasculitis point to a 2-yr survival of approximately 79%, with 21% of initial diagnoses progressing to end-stage renal failure; thus, at present, over 40% have a poor outcome by these two simple definitions (Table 3). Age and creatinine at presentation have been consistently associated with survival [11, 15, 23]. Similarly, the development of end-stage renal failure is closely linked to creatinine; it occurs in around 20% of patients, and is also associated with features on renal biopsy [11, 23].

Relapse rates have varied between 11 and 60% and are influenced by disease subgroup and treatment; long-term immunosuppressive therapy to prevent relapse contributes to late damage, and therapeutic regimens designed to induce disease remission also need to be judged by their subsequent disease relapse rates [13, 20, 23, 25, 26]. Inclusive scores to record accumulating 'all cause' damage have only recently been developed and are likely to play an increasing role in evaluating the medium- to long-term efficacy of treatments in the future [8].

Treatment by clinical subgrouping

Early systemic disease

This subgrouping also includes 'limited Wegener's granulomatosis', patients with organ involvement confined to the respiratory tract [7]. Historical protocols have used the combination of cyclophosphamide and steroids, but several recent studies have substituted methotrexate for cyclophosphamide (Table 4) [27–30]. Remission rates of 60–70% have been achieved, when used as a remission-maintaining agent after cyclophosphamide; relapse rates are low. Sneller *et al.* [27] and Stone *et al.* [30] observed higher relapse rates, possibly related to no previous cyclophosphamide exposure. Although most relapses were responsive to increases in the methotrexate and/or steroid doses, an inability to reduce the steroid dose and relapsing disease was predictive of more widespread vasculitis [29]. Adverse effects related to methotrexate included pneumonitis, although this can be difficult to diagnose in a patient with pulmonary Wegener's granulomatosis, hepatotoxicity and myelosuppression, but these events were reversible. The control of renal vasculitis with methotrexate is more controversial; patients with elevated serum creatinine have not typically been treated with methotrexate. In one series, those with presumed renal vasculitis had stabilization of excretory function; in another study, this subgroup were more likely to have refractory, progressive disease [27, 29]. The route of administration of methotrexate

Table 3. Outcome according to death and end-stage renal failure for ANCA-associated vasculitis. (Jayne) refers to unpublished data

	Year of publication	No.	Death median 2 yr	End-stage renal failure	Both
Gans *et al.* [21]	1993	39	11	4	15
Pettersson *et al.* [22]	1995	42	8	7	15
Hogan *et al.* [11]	1997	107	12	42	54
Westman *et al.* [23]	1998	123	38	19	57
(Jayne)	1998	66	15	9	24
Aasarod *et al.* [24]	1999	112	16	23	39
Total		489	100 (21%)	104 (21%)	204 (42%)

Table 4. Therapeutic trials of methotrexate for Wegener's granulomatosis

Study	Number	Follow-up (months)	Design	Remission rate	Relapse rate	Adverse effect events
Sneller *et al.*, 1995 [27]	41	?	Prospective open	71%	34%	21, 2 deaths (infective)
De groot *et al.*, 1996 [28]	33	18	Prospective open	–	12%	16 in 12 patients
De groot *et al.*, 1998 [29]	17	25	Prospective open	59% partial 35% full	20%	2
Stone *et al.*, 1999 [30]	19		Prospective open	89% partial 79% full	50%	2

has varied between studies, oral or subcutaneous, which may influence tolerability and efficacy.

Methotrexate is therefore an alternative component of initial therapy to cyclophosphamide for a patient with systemic vasculitis without threatened vital organ function. A proportion of patients will develop progressive disease and require conversion to cyclophosphamide and the effect of methotrexate on the control of relapse over longer time periods is unknown. None of the above studies have compared methotrexate to cyclophosphamide or studied microscopic polyangiitis, and this subject forms the focus of a current international trial (NORAM) [7].

A comparison of daily oral to pulse intravenous cyclophosphamide in polyarteritis nodosa and Churg–Strauss angiitis in a good prognosis subgrouping according to the five factor score, similar to early systemic disease, found similar remission rates of 9/12 and 10/13, respectively, which are comparable to those obtained in Wegener's granulomatosis with methotrexate [10]. Side-effects appeared more frequently, 41 events in 25 patients [10].

Generalized/renal disease

The empirical introduction of daily oral cyclophosphamide became popular during the 1970s but was only recently subjected to randomized trials. In a study of 71 patients with polyarteritis nodosa and Churg–Strauss angiitis who also received steroids and plasma exchange, cyclophosphamide led to improved disease control and fewer relapses [31]. The role of cyclophosphamide has been further confirmed by a meta-analysis of three trials, including 182 cases, from the same study group [32]. Retrospective data from the North Carolina glomerulonephritis study group compared patients with microscopic polyangiitis treated with cyclophosphamide with those treated with steroids alone and found improved renal survival and a lower relapse rate in those receiving cyclophosphamide [11]. In a consensus statement by the European Vasculitis Study Group, the combination of cyclophosphamide for 1 yr and a tapering dose of prednisolone was regarded as the standard treatment for this subgroup [7].

Efforts have focused on minimizing cyclophosphamide exposure by using pulse rather than continuous administration (see below) or switching to an alternative drug once remission has been obtained. 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 [13, 17, 26, 33]. A large, international, randomized trial comparing azathioprine with continued cyclophosphamide for prevention of relapse, has recently been reported (CYCAZAREM) [34]. One hundred and fifty-five patients were studied, and following induction of remission with oral cyclophosphamide and steroids for 3–6 months, they were randomized to continuing a lower dose of oral cyclophosphamide to 12 months or switching to oral azathioprine [34]. There was no difference in relapse rates, 17%, 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 limb (Fig. 1). A surprising result of this study was the high remission rate with oral cyclophosphamide and prednisolone in this subgroup. Apart from the withdrawal of 10 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

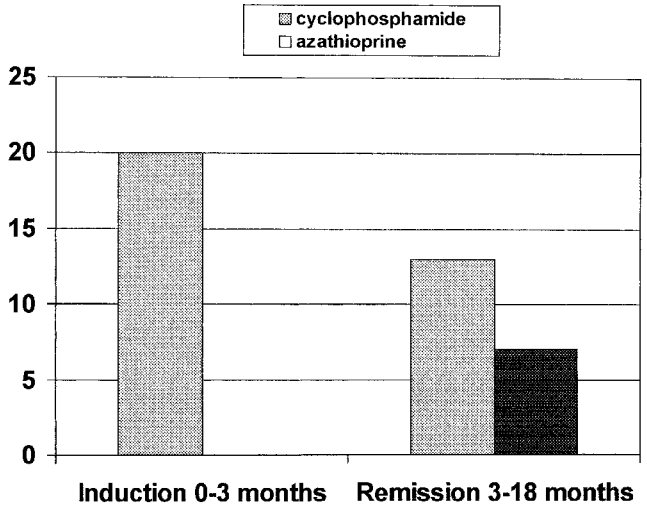

FIG. 1. Frequency of severe and life-threatening adverse effects in the CYCAZAREM trial [34].

was high with over 160 adverse events reported and a serious or life-threatening adverse event rate of 26%. Reversible leucopaenia was the most common adverse effect, azathioprine hypersensitivity was reported in 5/70 and has features similar to a relapse of vasculitis which has caused difficulties in diagnosis [35, 36].

Other remission drugs. Alternative remission-maintaining drugs include cyclosporin, for which a randomized trial found a higher relapse rate in the patients switched to cyclosporin as compared with continued cyclophosphamide, but many patients remained under good control [37]. One observational study including seven patients with ANCA-associated vasculitis also found good remission control in all with cyclosporin and prednisolone [38]. Mycophenolate mofetil is an immunosuppressive which blocks purine metabolism and is superior to azathioprine in the prevention of solid organ allograft rejection with equivalent toxicity. A prospective study with a similar induction regimen to the CYCAZAREM trial (see above) used mycophenolate mofetil in place of azathioprine and one relapse was observed in 12 patients studied [39].

Plasma exchange. A rationale for plasma exchange in vasculitis was based on a presumed immune complex aetiology even though immune deposits in most primary systemic vasculitides are typically scanty or absent. Further support for plasma exchange came from its success in antiglomerular basement membrane disease where the renal histology is similar to that in renal vasculitis apart from the pattern of immune deposits. The addition of plasma exchange to steroids alone was assessed in 78 patients with polyarteritis nodosa and Churg–Strauss angiitis. No difference in therapeutic efficacy was observed [40]. A further study from the same group using a similar patient subgroup compared the addition of plasma exchange to steroids and cyclophosphamide in 62 patients and again found no additional therapeutic effect of plasma exchange [41]. The discovery of ANCA and arguments for the pathogenicity of these autoantibodies has now provided a new rationale for plasma exchange in ANCA-associated disease. In a randomized study of 32 patients with Wegener's granulomatosis of varying severity, plasma exchange appeared to improve outcome, but this study is yet to be fully reported [37]. The addition of plasma exchange to immunosuppression for rapidly progressive glomerulonephritis was not found to help those presenting with a creatinine level below 500 μmol/l in a prospective, randomized study which stratified entries according to renal function [42]. A conclusion of this study was that this subgroup had a generally good outcome and plasma exchange was more likely to benefit those presenting with renal failure [42].

Intravenous pulse cyclophosphamide. Two open, prospective studies of pulse intravenous cyclophosphamide investigated whether this form of administration might be superior to daily oral for the induction of sustained remission [12, 43]. It did not appear more successful in this setting; those with more extensive organ involvement and high ANCA titres had a poor therapeutic response [12, 43]. In contrast, continuing disease activity despite pulsed, intravenous cyclophosphamide has responded to conversion to a daily oral regimen [44].

Four randomized trials have addressed the question as to whether pulsed cyclophosphamide is safer and as effective as daily oral administration for the induction of remission (Table 5) [10, 33, 45, 46]. None was sufficiently powered to make any conclusions about efficacy in controlling vasculitis, although one study clearly showed a higher relapse rate after intravenous pulse use [45]. All the studies concluded that adverse effects were more frequent in continuous oral cyclophosphamide limbs, although this was only the primary endpoint in the study by Adu *et al.* [33]. In this study, azathioprine was substituted for cyclophosphamide once remission had been achieved and the difference in adverse effects events was not significant [33]. The studies by Guillevin *et al.* [45] and Haubitz *et al.* [46] were both stopped early due to more adverse effects in the continuous limb. The high number of adverse events has been associated with the steroid dose used in these trials and with the cyclophosphamide tapering protocol in the Haubitz *et al.* study, which may have increased the incidence of leucopenia [47]. Further studies are required before conclusions can be drawn between the two routes of cyclophosphamide administration [4]. With the demonstration that shorter courses of cyclophosphamide are effective, some of the concern over cumulative cyclophosphamide exposure will be reduced [34].

Severe renal disease

Many patients with vasculitis present in renal failure with an imminent requirement for dialysis. Early intervention to reverse renal inflammation is likely to minimize damage and this theory is supported by the observation that the recovery level of serum creatinine, reflecting surviving nephrons, is related to long-term renal survival [48]. Such cases have received more

TABLE 5. Studies of intravenous 'pulsed' cyclophosphamide in primary systemic vasculitis.

Study	Subgroup	No.	Follow-up (months)	Design	Prednisolone dose in 6 months	Remission rate	Relapse rate	Deaths	Adverse effect events/patient
Gayraud *et al.* 1997 [10]	PAN, CSA good prognosis	25	60	Randomized	6.5	75% oral 77% i.v.	18% oral 18% i.v.	0 oral 1 (8%)	2.25 oral 1.1 i.v.
Adu *et al.* 1997 [33]	PAN, MPA, WG	54	40	Randomized	4.1 oral 5.4 i.v.	73% oral 63% i.v.	36% oral 47% i.v.	4 (13%) oral 5 (21%) i.v.	1.86 oral 1.66 i.v.
Guillevin *et al.* 1997 [45]	WG	50	60	Randomized	9.2	78% oral 89% i.v.	18% oral 52% i.v.	10 (44%) oral 9 (33%) i.v.	Oral 0.7 i.v.
Haubitz *et al.* 1998 [46]	MPA, WG	47	40	Randomized	5.9	84% oral 100% i.v.	29% oral 40% i.v.	4 (16%) oral 3 (18%) i.v.	0.75 oral 0.25 i.v.

PAN, polyarteritis nodosa; CSA, Churg–Strauss angiitis; MPA, microscopic polyangiitis; WG, Wegener's granulomatosis.

intensive therapy with high-dose steroids or plasma exchange to try to 'rescue' renal function. Both interventions have been reported to increase the chance of renal recovery but only plasma exchange has been subjected to controlled trial. In the randomized study by Pusey *et al.* [42], those with a creatinine over 500 μmol/l or already established on dialysis appeared to benefit from plasma exchange with 9/10 recovering independent renal function as compared with 3/8 not treated with plasma exchange. Other studies have included a wider range of presentations, but when patients with renal failure are selected there appears to be an improved outcome with plasma exchange (Table 6). Other mechanisms for the effect of plasma exchange include the removal of cytokines and coagulation factors, and anticoagulation with heparin has been used in the past for this indication [53]. The European Vasculitis Study Group has regarded both 'pulsed' methyl prednisolone and plasma exchange as widely used additions to oral steroids and cyclophosphamide for this indication, and is comparing the two interventions in a current study (MEPEX) [7].

ANCA-associated vasculitis is the most frequent cause of diffuse pulmonary haemorrhage, usually in the context of the pulmonary renal syndrome, and this presentation carries a high mortality. No prospective therapeutic studies are available although both plasma exchange and methyl prednisolone have been used in retrospective reports [54, 55].

Refractory and relapsing disease

Several alternative treatments have been studied for progressive disease resistant to standard therapy or where standard therapy is not tolerated. Lymphocyte depletion using antithymocyte globulin or monoclonal anti-T-cell antibodies with or without anti-CD4 antibodies, has led to remission in small open studies; some of these remissions have been long lasting [56–58]. While the role of this approach awaits larger studies, these results have indicated the importance of the T cell to the pathogenesis of vasculitis and they are the first drugs since cyclophosphamide to induce sustained remission of aggressive disease. Pooled, intravenous immunoglobulin (IgIV) has several modes of action of potential importance in vasculitis: it contains antibodies which inhibit ANCA, has regulatory effects at both B- and T-cell levels and interacts with inflammatory factors

TABLE 6. Renal survival in randomized trials including patients presenting with renal failure due to renal vasculitis. Treatment with or without plasma exchange. (Jayne) refers to unpublished data

	No.	Plasma exchange	No plasma exchange
Glockner *et al.* [49]	12	5/8	3/4
Pusey *et al.* [42]	19	10/11	3/8
Cole *et al.* [50]	11	3/4	2/7
Levy and Winearls [51]	20	9/11	5/9
Guillevin *et al.* [52]	8	4/6	1/2
Haubitz *et al.* [46]	22	6/12	2/10
(Jayne)	26	9/16	4/10
Total	88	46/68 (67%)	20/50 (40%)

such as complement and cytokines. Several randomized trials have confirmed a place for IgIV in the treatment of Kawasaki disease, a vasculitis of young children related to bacterial superantigen exposure. The optimal dose for Kawasaki disease is 2 g/kg infused over 2–4 days and this regimen has been used in addition to cytotoxics and steroids for ANCA-associated vasculitis [59]. Small prospective studies in persistent ANCA-associated vasculitis have found treatment responses in 45–75% of patients after IgIV [60–63]. Evaluation of the contribution of IgIV is complicated by continuing immunosuppressive therapy; when administered as sole therapy to six new patients, four entered remission for up to 1 yr [64]. Subsequently, a placebo-controlled trial of relapsing or persistent ANCA-associated vasculitis found improved disease control in IgIV-treated patients [65]. This effect was only observed up to 3 months, suggesting that repeated dosing, possibly at 3-month intervals, would be necessary for a sustained effect [65]. Treatment responses have also been seen after IgIV in other forms of refractory vasculitis, including childhood polyarteritis nodosa and Churg–Strauss angiitis [66, 67]. Different therapeutic mechanisms may be relevant to the clinical response to IgIV seen in Henoch–Schönlein purpura [68]. This systemic vasculitis is characterized by dysregulation of IgA production and deposition of IgA-containing immune complexes; IgIV increases the removal of circulating immune complexes and solubilization of deposited complexes. Adverse effects of IgIV therapy are frequent and include inflammatory manifestations and renal failure, as well as vasculitis [65, 69, 70].

Infection and relapse. Vasculitis may occur as a consequence of infection, such as endocarditis, and intercurrent infection can provoke relapse of primary vasculitis [71, 72]. 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 aetiology for this vasculitis, first suggested by Wegener [73, 74]. Long-term antibiotic therapy with sulphamethoxazole/trimethoprim in Wegener's granulomatosis reduced the risk of respiratory tract relapse in a placebo-controlled study when added to conventional immunosuppression [75]. The study duration was 2 yr and the difference in relapse frequency was largest in the first 6 months; a high rate of drug intolerance was observed [75].

Sulphamethoxazole/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 [76]. These factors have prompted an alternative approach using cyclical application of the topical antibiotic mupirocin, which is undergoing clinical investigation [4].

ANCA and relapse. An association between ANCA titre and relapse exists but the strength of this association and the role changes in ANCA should play in dictating treatment remain controversial [77]. PR3–ANCA-positive patients are at higher risk of relapse than those with myeloperoxidase (MPO)–ANCA and series with largely renal vasculitis patients had lower relapse rates than those where Wegener's granulomatosis with respiratory tract involvement predominated [13]. An early study in Wegener's granulomatosis during remission randomized patients whose ANCA titre rose to treatment intensification or no change in therapy [25]. Subsequent relapse was frequent in the latter group and was not seen in the group treated on the basis of the ANCA titre; the cumulative exposure to immunosuppression was lower in the early intervention group [25]. 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 [13, 26]. 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. Both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are of value in sequential monitoring, but lack prognostic value for vasculitis relapse [26].

Newer approaches to treatment

Other drugs for which preliminary observations have been made include etoposide in Wegener's and interferon-α for Churg–Strauss angiitis [78–81]. Newer immunosuppressives, developed for other clinical indications, such as leflunomide, deoxyspergualin and the tumour necrosis factor (TNF) antagonists infliximab and ENBREL, are also attracting interest in vasculitis. Colchicine was not shown to be an effective treatment in cutaneous skin vasculitis, although certain individuals have responded well [82]. Developments of plasma exchange including semi-specific immunoabsorption with L-tryptophan or protein-A columns to remove ANCA without depletion of non-immunoglobulin plasma proteins and appear of comparable efficacy to plasma exchange [83, 84]. The production of recombinant ANCA autoantigens will permit the development of ANCA-specific extra-corporeal immunoabsorption which has the theoretical advantage of removing pathogenetic factors without depleting regulatory antibodies or unrelated immunoglobulins [85].

Immunoablation using high-dose cytotoxic medication followed by stem cell rescue has led to prolonged remission in a few cases of refractory vasculitis [86]. Bone marrow allografting has also corrected vasculitis in a genetically prone mouse [87]. The further development of this technology in vasculitis depends on the safety of the procedure and the identification of suitable patients before organ damage has taken place.

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 [20]. The CYCAZAREM trial revealed an adverse effect frequency of 1.1 episodes per patient with 26% having severe or life-threatening adverse effects within the first 18 months [34]. Infectious adverse effects are the most common cause of death or severe morbidity and their frequency is associated with age and concomitant steroid dosage [15]. *Pneumocystis carinii* pneumonia rates of up to 20% have been found which have prompted advice for routine prophylaxis with low-dose sulphamethoxazole/trimethoprim in centres where this infection is common [4, 45].

Cyclophosphamide toxicity

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 haematuria and seven (5%) bladder cancer [20]. These patients were collected over a long time period when prolonged daily oral cyclophosphamide was standard therapy. The frequency of haematuria was related to the duration or total dose of cyclophosphamide with a 50% rate after 40 months or 120 g [88]. None of the 72 patients without haematuria 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 yr and 16% at 15 yr [88].

Haemorrhagic cystitis is rare in pulse cyclophosphamide-treated patients, being reported in only one case from the reviewed studies (Table 5). A Swedish study found an 11-fold increase in bladder cancer rates in patients receiving oral cyclophosphamide for more than 1 yr, and an increase in dermatological malignancy related to azathioprine and steroid exposure [23].

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 [89]. The human corollary was reflected in male follicle stimulating hormone levels that were higher with oral regimens, indicating greater gonadal suppression [89]. Data from the use of cyclophosphamide in 39 women with lupus nephritis have shown that the risk of infertility is related to age and duration of treatment with an incidence of 12% in those under 25 yr and 60% in those over 30 yr [90]. Luteinizing hormone releasing hormone antagonists protect rats from cyclophosphamide-induced infertility and merit investigation for this indication in human studies [91].

Glucocorticoid toxicity

A high incidence of steroid related irreversible damage has been reported in retrospective series [20]. Steroid-induced bone disease is common due to the high cumulative exposure and the age of the patient population. No protective effect with salmon calcitonin was found in a relatively small randomized trial [92]. Consensus documents have recommended monitoring bone density and a recent randomized trial found a significant protective effect of cyclical etidronate on steroid-induced bone loss [93, 94]. Patients with chronic inflammatory disease have an 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 [95]. This problem remains to be quantified in vasculitis.

Other vasculitides

Polyarteritis nodosa associated with markers of hepatitis B virus replication has responded favourably to short-term steroids, the antiviral drugs vidaribine and interferon-α, and plasma exchange in over 80% with loss of HbeAg in 50% [96]. Hepatitis C has also been associated with polyarteritis nodosa and microscopic polyangiitis, but is more commonly related to cryoglobulinaemic vasculitis [97]. Two randomized trials have demonstrated improvement of vasculitis with interferon-α in combination with steroids for this indication, although disease relapse often followed drug withdrawal. More recent studies have reduced relapse rates with higher doses and prolonged treatment periods [98–100]. A small randomized study found no benefit with cyclosporin A in addition to prednisolone for giant cell arteritis [101]. No steroid sparing effect was noted with methotrexate 7.5 mg weekly in a placebo-controlled trial including 40 patients with polymyalgia rheumatica or giant cell arteritis [102].

Conclusions

The heterogeneity of vasculitis and differing approaches to classification have hindered the accumulation of evidence to direct therapy. Most clinical trials have had sample sizes too small to allow conclusions to be made and treatment protocols have developed along empirical and, more recently, consensus lines.

The extent to which primary systemic vasculitis syndromes need different approaches to treatment is unclear. Vasculitis occurring in the context of Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss angiitis and polyarteritis nodosa appears to respond in a similar way to therapy and it is probable that disease severity should determine the protocol rather than diagnostic subgroup. When threatened vital organ damage is present, early effective treatment will improve long-term outcome, as has been demonstrated for renal vasculitis, where renal function at remission determines long-term renal survival. In this regard, early diagnosis, before organ damage is sustained, is more important than therapeutic protocol.

The importance of balancing treatment efficacy with toxicity recurs in the existing literature and has inspired the use of protocols of graded intensity for progressively severe vasculitis. The CYCAZAREM protocols also appear to favour efficacy over toxicity, because the

remission rate was very high yet treatment toxicity contributed to deaths in six and caused serious adverse effects in over one quarter [34]. As well as the need for less toxic therapies overall, there is a more urgent requirement for the elderly to be regarded as a separate subgroup and appropriate protocols designed to offer a more favourable balance with less toxicity.

The advent of newer immunosuppressives and biological agents targeting specific immune components offers exciting possibilities for the vasculitis specialist. Unfortunately, experience with these drugs in vasculitis is usually delayed until they are licensed for a particular indication, typically transplantation or rheumatoid arthritis. If proven effective and safe, the expense of these agents will also require the design of cost–benefit strategies in vasculitis before they can be routinely recommended.

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