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Treatment of vasculitis

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Introduction

Inflammation of blood vessels leading to necrosis and, in some conditions, to granuloma formation is the pathological feature of the systemic vasculitic syndromes. The protean clinical manifestations depend on the size and distribution of affected vessels, and range from minor purpuric lesions on the legs to rapidly progressive multi-organ necrosis and failure. The aetiological uncertainty, clinical overlap and difficulties in investigation make classification of these syndromes difficult (Alarcon-Segovia, 1977; Hunder & Lie, 1983; Zeek, 1952). We prefer the classification of Fauci *et al.* (1978) because it is useful to the clinician in making diagnostic and therapeutic decisions. A simplifed version of this classification is presented in Table 1. The American College of Rheumatology has recently published classification criteria (Hunder *et al.*, 1990) and this and the subsequent articles provide an up to date view of the seven major systemic vasculitic syndromes.

In polyarteritis nodosa small and medium sized arteries are involved by inflammation affecting the entire vessel wall, eventually leading to aneurysm formation. Conditions grouped under the heading hypersensitivity vasculitis are characterised by inflammation of small arteries, arterioles and venules. Demonstration of aneurysms by angiography of appropriate biopsy may be required to differentiate between these two groups of conditions. Many of the hypersensitivity vasculitides will respond to simple removal of the initiating agent, frequently a drug.

Table 1 Clinical classification of vasculitis (after Fauci *et al.* (1978))

Polyarteritis nodosa
Idiopathic
Virus associated
Rheumatic disease associated
Malignancy associated
Hypersensitivity vasculitis (small vessel vasculitis)
Serum sickness
Henoch-Schonlein purpura
Cryoglobulinaemia
Associated with connective tissue disease or malignancy
Churg-Strauss vasculitis
Wegener's granulomatosis
Lymphomatoid granulomatosis
Large vessel vasculitis
Giant cell arteritis
Takayasu's arteritis
Kawasaki's disease

Both Churg-Strauss vasculitis and Wegener's granulomatosis are associated with granuloma formation but asthma and, often, peripheral eosinophilia are features of Churg-Strauss vasculitis, while many of the features of Wegener's granulomatosis are a result of small vessel vasculitis and glomerulonephritis. Lymphomatoid granulomatosis is a rare condition characterised by vascular infiltration with atypical lymphocytoid and plasmacytoid cells causing very destructive lesions particularly in the lungs and interstitium of the kidneys (Liebow *et al.*, 1972). A proportion of patients progress to a recognizable T-cell lymphoma (Fauci *et al.*, 1982).

Large and medium sized arteries are involved in giant cell arteritis and Takayasu's arteritis which are similar pathologically, and may both be associated with a polymyalgia rheumatica like illness. Takayasu's arteritis is distinguished by affecting predominantly young women and having its major impact on the aorta and its primary branches, rather than the cranial arteries. Kawasaki's disease or mucocutaneous lymph node syndrome is a disease of childhood with an abrupt onset of fever, rash, conjunctivitis, arthritis and lymphadenopathy. The arteritis affects particularly the coronary vessels leading to aneurysm formation and possible sudden death as a result of aneurysm thrombosis.

Because of the life and organ threatening nature of many of the major vasculitides there are ethical difficulties in not giving the treatment currently thought to be most beneficial to the patient. There are, therefore, relatively few well controlled trials in the treatment of necrotizing vasculitis, many studies making use of historical controls or established natural history for comparison (Conn, 1991). Other problems in the comparison of treatment regimes include the rarity of many of these conditions and the wide range of disease manifestations within each syndrome. This means that a number of departments (e.g. rheumatology, dermatology, nephrology) will each see relatively few patients and that genuine comparison between different centres requires stratification. Given these difficulties we will review those agents whose place in the treatment of systemic necrotizing vasculitis is well established as well as those which seem most promising for the future or which may have an expanding role.

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Corticosteroids

Corticosteroids are widely used in vasculitic conditions, either alone or in combination. Their vast array of effects, both beneficial and detrimental, are beyond the scope of this article. The desired effects in vasculitis are those on the local inflammatory response and on lymphoid tissue. Corticosteroids inhibit the chemotactic response of neutrophils and monocyte-macrophages (Parillo & Fauci, 1979) and may also inhibit their binding to vascular endothelium at sites of inflammation (MacGregor, 1977). They also induce the synthesis of lipocortin which inhibits phospholipase A_2 (Blackwell *et al.*, 1980; Hirata *et al.*, 1980). The activity of phospholipase A_2 is, in turn, the rate limiting step in the production of arachidonic acid for metabolism to prostaglandins and leukotrienes (Irvine, 1982). In addition corticosteroids have important effects on monocyte/macrophages, T lymphocytes and B lymphocytes. Circulating lymphocytes are reduced by 70% and monocytes by 90% after a single dose of hydrocortisone (Fauci & Dale, 1974). This is due to redistribution to other compartments, particularly the bone marrow, rather than cell death or lysis (Fauci, 1976), as occurs in rats and mice (Claman, 1972). Monocyte Fc and C3 receptor expression and function *in vitro* and the monocyte phagocyte clearance system *in vitro* are inhibited by corticosteroids (Fries *et al.*, 1983; Schriber *et al.*, 1975), as is bacterial killing by monocytes (Rinehart *et al.*, 1975). Pharmacologic doses of corticosteroids suppress IL-1 production by monocytes by inhibiting translation of IL-1 beta mRNA and inhibiting release of IL-1 beta into the extracellular fluid (Kern *et al.*, 1988). Interleukin-1 (IL-1) serves a permissive role in T and B cell function and is thought to play a key part in enhancing lymphocyte function (Boumpas *et al.*, 1991).

T cell proliferation is inhibited by corticosteroids (Gillis *et al.*, 1979; Smith, 1980). The production of interleukin-2 (IL-2), vital for T cell growth and the normal immune response, is suppressed. This is mediated both by reduced transcription of the IL-2 gene and increased degradation of IL-2 mRNA (Boumpas *et al.*, 1991). Transcription of other interleukin genes, including those of gamma interferon (IFN) and interleukin-6 (IL-6), are also inhibited by steroids (Boumpas *et al.*, 1991). Corticosteroids appear to suppress early activation events in B cells (Dennis *et al.*, 1987), but once activated, these cells are relatively steroid resistant (Cupps *et al.*, 1984). This and the steroid induced loss of suppressor influences in some systems (Paavonen, 1985) may explain the variable effects of steroids on immunoglobulin production in different experimental systems (Butler & Rossen, 1973; Cupps *et al.*, 1984; Goodwin & Atluru, 1986).

Corticosteroids alone remain the treatment of choice in giant cell arteritis. While many physicians still use a starting dose of 60 mg prednisolone daily (Calamia & Hunder, 1989), a recent study has shown a 40 mg dose to be sufficient in the vast majority of cases (Kyle & Hazleman, 1989). Those with visual symptoms should be started on at least 60 mg prednisolone daily. An initial 250 mg hydrocortisone intravenously as well as 80 mg prednisolone daily has been suggested for this group of patients (Graham *et al.*, 1981). The frequency of steroid side effects correlates with both the initial and the cumulative dose (Kyle & Hazleman, 1989b). However dose reduction to 20 mg prednisolone day^{-1} or less by the second month leads to a higher relapse rate (Kyle & Hazleman, 1989a). We therefore recommend a starting dose of 40 mg prednisolone day^{-1} in uncomplicated giant cell arteritis, reducing by 10 mg day^{-1} each month for 3 months and then from 20 mg day^{-1} to 10 mg day^{-1} over a further 3 months. Further reduction will be gradual (in 1 mg day^{-1} decrements) and dictated by an assessment of the patient's symptoms as well as the sedimentation rate or C-reactive protein level. Kyle & Hazleman (1989a) also showed that a starting dose of 15 to 20 mg prednisolone day^{-1} is required for the related, and commoner, condition polymyalgia rheumatica. Here the dose should be reduced to 10 mg prednisolone day^{-1} by 3 months. This study also showed that a slow reduction in dose resulted in fewer relapses. Biopsy of clinically involved arteries are positive in 82% of cases of giant cell arteritis prior to treatment but this drops to 60% with up to 7 days treatment and 10% thereafter (Allison & Gallagher, 1984). Up to a third of patients develop steroid related side effects (Kyle & Hazleman, 1989b) and there is a rapid increase in the rate of osteoporosis (Andersson *et al.*, 1990). Treatment is usually required for more than 2 years (Fernandez-Herlihy, 1980) and management of side effects often becomes the most difficult aspect of treating patients with this disease.

Retrospective studies of Takayasu's arteritis have shown a steroid response rate of between 20% and 100% (Fraga *et al.*, 1972; Lupi-Herrera *et al.*, 1977). In a prospective study of 16 patients with a 5 year follow up, 50% responded to prednisone at an initial dose of 1 mg kg^{-1} with gradual tapering (Shelhamer *et al.*, 1985). Patients with persistently active disease had cyclophosphamide 2 mg kg^{-1} added. This was successful in achieving long-term disease suppression in four out of the six patients (Shelhamer *et al.*, 1985). Takayasu's arteritis has a very prolonged course and patients should be converted to alternate day steroid therapy after suppression of disease activity. The addition of cyclophosphamide appears useful if suppression is not attainable within 3 months.

Early studies provided evidence that steroid therapy improved both morbidity and mortality in polyarteritis nodosa (PAN), although these studies used historical controls (Frohnert & Scheps, 1967; Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel, 1960). A later study showed that the outcome of PAN patients treated with steroids alone was similar to those treated with a combination of steroids and cytotoxics (Cohen *et al.*, 1980). The mean follow up in this study was however, only 3.3 years and other studies with longer follow up have shown benefit from the addition of a cytotoxic drug and gradual withdrawal of steroids (Fauci *et al.*, 1979; Scott *et al.*, 1982). This may reflect the increasing impact of steroid side effects with time. There has been one prospective randomised trial of corticosteroids *vs* cytotoxics (cyclophosphamide) in systemic vasculitis. Guillevin *et al.* (1991) found no significant differences in the outcome of 71 patients with PAN or Churg-Strauss

angiitis with a minimum 3 years follow up randomized to either steroids and plasma exchange or cyclophosphamide, steroids and plasma exchange. They did however find significantly fewer relapses in the cyclophosphamide group. Of the 10 withdrawals for inefficacy 9 were in the steroid group while 8 of the 9 withdrawals because of side effects were in the cyclophosphamide group. There are criticisms of this trial however, not least because both groups received plasmapheresis, which has its own immunosuppressive effect (Conn, 1991).

Pulse methylprednisolone (usually 1 g intravenously over 60 min repeated at intervals of 24 to 72 h according to severity and response) is being increasingly used at the initiation of therapy in severe systemic vasculitis because of its rapid action and relative safety (Leavitt & Fauci, 1986; MacFayden *et al.*, 1987). Whereas B cells are relatively resistant to moderate doses of corticosteroids (David *et al.*, 1970) the higher doses achieved by pulse therapy will increase Ig catabolism and suppress Ig production (Butler & Rossen, 1973). The resulting fall in Ig levels will be particularly beneficial in vasculitic conditions. Adverse effects of pulse steroid therapy include temporary glucose intolerance (16%), facial flushing (14%), headache (12%), a bitter taste (10%), significant rise in blood pressure (4%) and rarely gastro-intestinal bleeding and avascular necrosis of the hip (Weusten *et al.*, 1992).

Conn *et al.* (1988) have proposed that corticosteroids may in fact exacerbate the coagulopathy found in some vasculitic diseases. Normally, at sites of vascular injury, the action of the platelet derived procoagulant thromboxane A_2 is limited by prostacyclin, produced by endothelial cells. Theoretically, steroids should inhibit both, by their effect on phospholipase A_2 (Blackwell *et al.*, 1980; Hirata *et al.*, 1980). But, since this depends on inducing the nucleus to produce lipocortin mRNA, inhibition will occur in the endothelium but not in the anucleate platelets. Unopposed platelet products could then enhance platelet activation, thrombus deposition, vasoconstriction and platelet derived growth factor release (Conn *et al.*, 1988). These proposals require confirmation, particularly with regard to pulse methylprednisolone. It may however, in the present state of knowledge, be prudent to add low dose aspirin when treating vasculitis with steroids.

Cyclophosphamide and chlorambucil

Although the success of nitrogen mustard (Fahey *et al.*, 1954) first opened the way for the use of alkylating agents in the treatment of vasculitis, this drug has largely been superseded by cyclophosphamide, the latter having the advantages of oral as well as intravenous administration and a greater margin of safety. Cyclophosphamide has a high apparent volume of distribution and a plasma half-life of 6 to 7 h (Bagley *et al.*, 1973). The parent molecule is not cytotoxic itself but is metabolised, chiefly in the liver, to active and inactive metabolites (Friedman *et al.*, 1979). Of these, phosphoramide mustard is responsible for most of its activity, and acrolein for the bladder toxicity (Friedman *et al.*, 1979). Approximately 65% of elimination is by renal excretion of metabolites. This may be significantly reduced by concomitant allopurinol therapy (Bagley *et al.*, 1973) or renal failure (Mouridsen & Jacobsen, 1975). Alteration of the rate of metabolism by enzyme induction is clinically unimportant (Sladek, 1972).

Cyclophosphamide achieves its cytotoxic effects by alkylating DNA. This in itself may not be harmful but it interferes with mitosis and cell division (Calabresi & Parks, 1985). Thus, although not cell cycle specific its cytotoxicity is dependent on cell proliferation and tissues with a high mitotic rate will be primarily affected. It causes a marked depletion of lymphoid tissue (Turk & Poulter, 1972). In comparison to other alkylating agents cyclophosphamide has a relatively greater effect on lymphocytes and lesser effect on granulocytes, platelets and nervous tissue (Calabresi & Parks, 1985). B cells appear more susceptible than T cells (Hurd & Guiliano, 1975; Turk & Poulter, 1972) and both cellular function and immunoglobulin production are inhibited at relatively low doses (Cupps *et al.*, 1982; Zhu *et al.*, 1987). Lymphocytopaenia is evident within 24 h of a single dose and becomes more severe over 1 week. Granulocytopaenia becomes apparent within a few days, persisting for 10 to 21 days. Haematological recovery is achieved in 4 to 6 weeks (Calabresi & Parks, 1985). These events are particularly important in planning pulse therapy. In the vasculitides cyclophosphamide is usually used in low dose as a daily oral medication. Low dose has conventionally been taken as 2 mg kg^{-1} day^{-1} or less and doses as low as 50 mg on alternate days have been successfully used for maintenance (Fauci *et al.*, 1979). More recently intravenous pulse cyclophosphamide has been used in these diseases (Cupps, 1990).

Low dose oral cyclophosphamide has dramatically improved the prognosis in Wegener's granulomatosis, remission being achieved in over 90% of cases with a 5 year survival rate of 80% (Fauci *et al.*, 1983; Novack & Pearson, 1971; Wolff *et al.*, 1974). This compared with a mean survival of 5 months for untreated Wegener's (Walton, 1958) and 12.5 months with corticosteroid therapy (Hollander & Manning, 1967) in earlier studies. In the NIH series 23 of their 85 cyclophosphamide treated patients were in remission off all treatment for a mean 35.3 months (Fauci *et al.*, 1983). These patients received cyclophosphamide 2 mg kg^{-1} day^{-1} and prednisone 1 mg kg^{-1} day^{-1} to induce remission. This was successful in 79 out of 85 patients. The prednisone was then converted to an alternate day regime and the dose tapered to 20 mg on alterate days by 6 to 12 months. Once the patient had been in complete remission for 1 year the cyclophosphamide was reduced by 25 or 50 mg decrements every 2 or 3 months until it could be stopped or the patients disease became active again (Fauci *et al.*, 1982).

Although several studies provide evidence that the long term outcome in PAN is improved by the addition of cytotoxics to steroid therapy (Fauci *et al.*, 1979; Scott *et al.*, 1982) this remains unproven in controlled trials (Conn, 1991; Guillevin *et al.*, 1991). Most of the mortality in steroid treated patients is due to active vasculitis or disease complications such as hypertension, while overwhelming infection is the major

problem in cyclophosphamide treated patients (Luqmani *et al.*, 1990). Cyclophosphamide has been successfully used in Churg-Strauss vasculitis but the evidence to show that it is superior to steroids alone is lacking (Chumbley *et al.*, 1977; Guillevin *et al.*, 1991; Luqmani *et al.*, 1990). Lymphomatoid granulomatosis frequently progresses to lymphoma and has a high mortality rate. In a prospective NIH study Fauci *et al.* (1982) treated 13 of 15 patients with oral cyclophosphamide and prednisone, seven patients having a complete remission with a mean follow up of 5.2 years. Since 7 of the 8 patients who died developed lymphoma, the authors suggest that earlier treatment with cyclophosphamide might prevent this development.

Cyclophosphamide proved more effective than steroids alone or in combination with azathioprine in the treatment of lupus nephritis (Carette *et al.*, 1983) but at the cost of considerable toxicity, and this has led to the successful use of intermittent intravenous cyclophosphamide pulses (Austin *et al.*, 1986; Balow *et al.*, 1984). This method of administration is now being increasingly used in the systemic necrotizing vasculitides. Pulse cyclophosphamide therapy allows a lower cumulative dose to be given and exposes the patient to potential toxicity for shorter periods. Induction doses used vary from 0.5 g to 2.5 g at intervals of 1 week to 1 month, and up to 3 months for maintenance therapy. However, a recent study showed that, although it was very effective in inducing remission in 14 patients with Wegener's granulomatosis, nine relapsed and two stopped treatment because of toxicity (Hoffman *et al.*, 1990). These patients all received prednisone 1 mg kg^{-1} day^{-1} for 1 month before being converted to alternate day therapy and then tapered and discontinued. Cyclophosphamide was given as 1 g intravenous infusions every month for 6 months, then reduced to one infusion every 2 months for a further 6 months if the disease was inactive. If control was maintained cyclophosphamide was given at 3 monthly intervals and then stopped after 18 months. Toxicity included haemorrhagic cystitis and severe infection (Hoffman *et al.*, 1990). This highlights the importance of establishing effective treatment regimes for different conditions and suggests the possibility of using different induction and maintenance regimes. At present low dose oral cyclophosphamide is the preferred long-term treatment in Wegener's granulomatosis although intravenous pulses may be used for inducing remission. Successful use of pulse cyclophosphamide has been reported in systemic rheumatoid vasculitis where it may be the treatment of choice (Scott & Bacon, 1984), Churg-Strauss syndrome (Chow *et al.*, 1989), PAN and Wegener's granulomatosis resistant to conventional treatment (Fort & Abruzzo, 1988; Locht & Lindstrom, 1989) and Behcet's disease, although results in the latter disease have not all been favourable (De Vita *et al.*, 1991).

Haemorrhagic cystitis and carcinoma of the bladder are worrying complications of cyclophosphamide therapy. Mesna (sodium-2-mercaptoethanesulphonate) is a thiol compound which combines directly with the urotoxic acrolein and 4-hydroxyoxazaphosphorine metabolites of cyclophosphamide to form stable and non-toxic compounds (Shaw & Graham, 1987). Mesna and its oxidation product dimesna are rapidly cleared from the circulation ($t_{½}$ = 1.2 h) and concentrated in the urine (Dechant *et al.*, 1991). Mesna has been shown to decrease the incidence of cyclophosphamide induced bladder tumours in rats (Petru & Schmahl, 1987) and it is hoped that it will do the same in humans. Because of the difference in half-lives repeated doses of mesna are required. We give mesna as 20% of the cyclophosphamide dose (w/w) intravenously with the cyclophosphamide followed by two oral doses of 40% in fruit juice 4 and 8 h after the infusion.

Chlorambucil, like cyclophosphamide an alkylating agent, has similar actions but with a slower onset. It is less effective than cyclophosphamide in the treatment of Wegener's granulomatosis (Israel & Patchevsky, 1975) and its use is largely limited to the treatment of Behcet's disease (O'Duffy *et al.*, 1984; Tabbara, 1983).

Azathioprine

Azathioprine is a purine analogue which is well absorbed and converted to 6-mercaptopurine (6-MP) in erythrocytes and the liver (Bertino, 1973; Clements & Davis, 1986). The plasma half-life of 3 h (Huskisson, 1984) may be prolonged by both renal and liver disease (Maddocks, 1978; Ware *et al.*, 1979). Metabolism of azathioprine is blocked by allopurinol which should be avoided or, if essential, accompanied by a 75% reduction in the dose of azathioprine (Bertino, 1973). Azathioprine cytotoxicity is associated with the intracellular formation of its nucleotide metabolite 6-thioinosinic acid (Brock, 1963) which is metabolised to 6-thioguanine and then incorporated into DNA (Tidd & Paterson, 1974). Cytotoxicity, however, is not necessary for immunosuppression and it has been shown that azathioprine is superior to 6-MP in inhibiting the mixed lymphocyte reaction (Al-Safi & Maddocks, 1983). This inhibition is achieved by a different mechanism to 6-MP (Al-Safi & Maddocks, 1984). Azathioprine and 6-MP cause a lymphocytopaenia of both T and B cells (Yu *et al.*, 1974) and suppress Ig production (Levy *et al.*, 1972). In addition azathioprine has potent anti-inflammatory effects, probably by inhibiting monocyte migration into inflammatory sites (Gassman & van Furth, 1975).

First used in autoimmune disease in 1960 (Damesheck & Schwartz, 1960), azathioprine is still widely used in lupus nephritis (Cameron *et al.*, 1979). However, this is seldom due to a vasculitic process, and even the chief proponents of azathioprine in lupus nephritis now regard cyclophosphamide as superior in renal vasculitis (Cameron, 1988). Likewise, although benefit from azathioprine has been reported in Wegener's granulomatosis (Brandwein *et al.*, 1983), PAN (Lieb *et al.*, 1979), Churg-Strauss syndrome (Lanham *et al.*, 1984) and Takayasu's arteritis (Hall *et al.*, 1985), it has largely been superseded by cyclophosphamide in these conditions. It is not effective in rheumatoid vasculitis (Nicholls *et al.*, 1973).

Behcet's disease is a condition notable for the lack of controlled therapeutic trials. Recently, in a large placebo controlled trial, azathioprine has been shown to significantly reduce the frequency and severity of

inflammatory episodes in Behcet's disease (Yazici *et al.*, 1990). There are two other roles in which azathioprine is likely to continue to be used in the management of systemic vasculitis. It is commonly used in combination with steroids to allow reduction of the steroid dose, and has been shown to be effective in doing this in polymyalgia/giant cell arteritis in a double-blind placebo-controlled study (De Silva & Hazleman, 1981). In this study of 31 patients the mean 12 month prednisolone dosage in the azathioprine group was 1.9 mg day^{-1} and in the placebo group, 4.2 mg day^{-1} ($P < 0.05$). It is also used as maintenance therapy after an initial period of cyclophosphamide therapy in a number of vasculitic conditions including Wegener's granulomatosis and microscopic polyarteritis because of its lower toxicity (Cameron *et al.*, 1988; Luqmani *et al.*, 1990).

Plasmapheresis

Plasmapheresis has been used in a large number of conditions of diverse aetiology and pathogenesis (AMA Panel on Therapeutic Plasmapheresis, 1985). The rationale is to remove pathogenic material from the circulation. Its use, therefore, can readily be justified in conditions such as Goodpasture's syndrome (anti-glomerular basement membrane antibody) or lupus nephritis (DNA:anti-DNA antibody complexes), but less easily in diseases like psoriasis or amyotrophic lateral sclerosis. Its use in vasculitis depends at least in part on the belief that circulating factors are important in disease pathogenesis, and can be removed by plasmapheresis, although it should be remembered that plasmapheresis also has a more general immunosuppressive effect.

Of particular interest in this regard is the demonstration of autoantibodies directed against endothelial cells in patients with vasculitis (Baguley & Hughes, 1989). This has been well shown in Kawasaki syndrome (Leung *et al.*, 1986) but also in other forms of vasculitis (Baguley & Hughes, 1988). These antibodies appear to be absent in polyarteritis nodosa and Wegener's granulomatosis (Baguley & Hughes, 1989). IgE containing immune complexes with evidence of complement activation have been identified in patients with Churg-Strauss syndrome and not in patients with allergic conditions and raised IgE levels (Manger *et al.*, 1985). Defective clearing of immune complexes is thought to be aetiologically important in lupus erythematosus, and plasmapheresis significantly accelerates clearance of microaggregated human serum albumin in patients with lupus and other immune complex mediated vasculitides, with a parallel clinical improvement (Low *et al.*, 1985). Its effectiveness depends both on the ease with which the pathogenic material can be removed via the circulation and the rate at which it is replaced (Clough & Calabrese, 1981). The effect is therefore transitory and indeed it has been postulated that a drop in antibody concentration results in a rebound increase in its rate of synthesis (Schlansky *et al.*, 1981). While this may make the antibody producing cells more susceptible to immunosuppressive drugs the use of these drugs negates one of the main attractions of plasmapheresis, that of its relative safety. Other problems include its expense, the necessity for multiple procedures and the complications of central venous access including pneumothorax, sepsis and thrombosis.

The use of plasmapheresis, either alone (Delaney *et al.*, 1984) or in combination with immunosuppressive agents (Geltner, 1988; Geltner *et al.*, 1981; Petersen, 1985), for the vasculitis associated with essential mixed cryoglobulinaemia is effective and well established. It has been reported to be successful in other vasculitides associated with circulating immune complexes including leukocytoclastic vasculitis (Wysenbeek *et al.*, 1982), Henoch-Schonlein purpura (Joseph *et al.*, 1987; Kauffman & Houwest, 1981) and rheumatoid vasculitis (Sakamoto *et al.*, 1985; Wiklestein *et al.*, 1984; Schneider *et al.*, 1985). Following its success in treating Goodpasture's syndrome, plasmapheresis was used in nine patients with severe crescentic glomerulonephritis of heterogenous aetiology (Lockwood *et al.*, 1977). Although these patients were also treated with steroids and immunosuppressive drugs, the prompt improvement in six of them together with a fall in C1q binding lead the authors to suggest that plasmapheresis had an important role in the initial treatment of these patients. It continues to be used in renal vasculitis, particularly in rapidly progressive cases and those with pulmonary haemorrhage (Fuiano *et al.*, 1988; O'Meara *et al.*, 1989). Despite the availability of good technology for this technique since the 1960s and its widespread use, we are not aware of any controlled trials of plasmapheresis in treating vasculitis in the English language journals. It is more frequently used in continental Europe and in the former Soviet Union. Indeed, in the French trial of corticosteroids *vs* cyclophosphamide for systemic vasculitis (Guillevin *et al.*, 1991) both groups received plasmapheresis.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) is prepared from large plasma pools of over 20,000 healthy donors (Kaveri *et al.*, 1991). They contain polyspecific IgG with a subclass distribution corresponding to that of normal serum, and minimal IgA and IgM. There are a number of proposed mechanisms of action including, reversible blockade of Fc receptors, Fc dependant inhibition of antibody synthesis, interference with complement mediated damage, modulation of cytokine secretion and modulation of the autoimmune process by anti-idiotype antibodies (Kaveri *et al.*, 1991). There is evidence for the presence and functional importance of anti-idiotypic antibodies to anti-factor VIIIc autoantibodies in antifactor VIII disease (Sultan *et al.*, 1984). Clearly multiple mechanisms may be involved.

IVIg was first suggested as an effective treatment for Kawasaki syndrome in 1984 (Furusho *et al.*, 1984). Since then, a multi-centre randomised placebo controlled trial has shown it to be highly effective in reducing fever, lowering laboratory indicators of the acute phase response and, most importantly, in preventing the development of coronary artery aneurysms

(Newberger *et al.*, 1986). A further study showed that a single large dose (2 g kg^{-1} body weight) was more effective than the commonly used 400 mg kg^{-1} daily for 4 days (Newberger *et al.*, 1991). In this multicentre, randomised, controlled trial involving 549 children the single dose group had significantly lower mean temperatures, shorter duration of fever, more rapid reduction in acute phase reactants and fewer coronary artery lesions at the 2 week review. Coronary artery lesions were fewer but not significantly so at the 7 week review. Aspirin, the traditional treatment for Kawasaki syndrome, is used simultaneously. It seems likely that IVIg will be tried in other vasculitic syndromes, especially those in which autoantibody formation is thought to be important. In a recent report a course of IVIg resulted in clinical improvement and significant reduction of ANCA levels in seven patients with systemic vasculitis, five of whom were resistant to immunosuppressive therapy (Jayne *et al.*, 1991). Further controlled trials are required in the non-Kawasaki vasculitides.

Cotrimoxazole

A number of reports have suggested that cotrimoxazole may be effective in the treatment of Wegener's granulomatosis (Axelson *et al.*, 1987; De Remee *et al.*, 1985; West *et al.*, 1987; Yuasa *et al.*, 1988). There are several possible modes of action although none is proven. If Wegener's granulomatosis is initiated by an as yet unidentified bacterial infection, cotrimoxazole could work by eradicating the antigenic stimulus. Secondly, relapses have been thought to be precipitated by a range of infections (Pinching *et al.*, 1980) and cotrimixazole could therefore be acting as a prophylactic agent. The third possibility is that patients with Wegener's granulomatosis are particularly susceptible to upper and lower respiratory tract infections, which may be difficult to differentiate from mild flares of limited Wegener's (Fauci *et al.*, 1983), and it is merely these infections that cotrimoxazole is treating.

De Remee has, on the basis of his experience at the Mayo Clinic, recommended the use of cotrimoxazole in disease limited to the nose and/or lungs in the absence of a rapidly progressive vasculitis (De Remee, 1988). The published data has, however, been criticized on a number of counts and the urgent need for a controlled trial stressed (Leavitt *et al.*, 1988). Our own anecdotal experience with three patients has not been encouraging.

Monoclonal antibody therapy

As advances in the understanding of immune events occur the idea of targetting intervention at specific cells or molecules becomes increasingly attractive. Monoclonal antibodies can be prepared which block receptors, adhesion molecules, growth factors or cause cell lysis by activating effector mechanisms such as the complement system. Apart from the problems of antigenic specificity and physiological activity, use of xenogeneic antibodies induces an antibody response which may result either in neutralization or a serum sickness reaction (Reichmann *et al.*, 1988). For this reason a 'humanized' antibody has been prepared by attaching rat hypervariable regions recognizing an antigen on virtually all human lymphocytes and monocytes to human variable regions and constant domains of IgG1 type (Reichmann *et al.*, 1988). This antibody, CAMPATH-1H, was used in a patient with systemic vasculitis previously unsuccessfully treated with steroids, dapsone, azathioprine and cyclophosphamide (Mathieson *et al.*, 1990). This resulted in a dramatic improvement but only for about 10 days. It was then given daily for 3 days (2 mg daily) followed by a rat IgG1 anti-CD4 antibody (20 mg daily) for 12 days. This has produced an excellent clinical response for up to 12 months despite the reappearance of CD4 lymphocytes after 1 month (Mathieson *et al.*, 1990).

Antilymphocyte monoclonal antibodies have also been successfully used in rheumatoid arthritis without vasculitis (Horneff *et al.*, 1991), murine lupus with vasculitis (Wofsy *et al.*, 1988) and in both the treatment and prophylaxis of organ rejection, a largely vasculitic process (Costanzo-Nordin *et al.*, 1989; Delaney *et al.*, 1988). Monoclonal antibodies against Gram-negative endotoxin are effective (Ziegler *et al.*, 1991) and antibodies to specific cytokines are being prepared (Exley *et al.*, 1990). There is much to be learnt about specific manipulation of the immune system but these therapies will undoubtably be increasingly used in the future.

Other therapies

By inhibiting tetrahydrofolate reductase, methotrexate blocks the conversion of dihydrofolate to tetrahydrofolate, an essential cofactor in the synthesis of thymidylate and purines. It is widely used in the treatment of uncomplicated rheumatoid arthritis and there are several uncontrolled reports of its efficacy in cutaneous vasculitis associated with rheumatoid arthritis (Espinoza *et al.*, 1986; Upchurch *et al.*, 1987; Williams & Pembroke, 1989). Interestingly, its use in rheumatoid arthritis has been complicated by the abrupt development of nodulosis and other vasculitic manifestations (Fondevila-Carlos *et al.*, 1989; Jeurissen *et al.*, 1989; Navarro *et al.*, 1986; Segal *et al.*, 1988). There are no comparative trials of its use in systemic vasculitis.

Dapsone is used predominantly in vasculitic conditions characterised by a leukocytoclastic picture on histology. It has been reported to be effective in urticarial vasculitis (Fortson *et al.*, 1986), cutaneous vasculitis of rheumatoid arthritis (Bernard *et al.*, 1988), complement deficiency associated vasculitis (Holtman *et al.*, 1990) and uncomplicated leukocytoclastic vasculitides (Fredenberg & Malkinson, 1987). Its use in Henoch-Schonlein purpura has been well reviewed and the need for a controlled trial stressed (Hoffbrand, 1991). The mode of action of dapsone in vasculitis is unknown.

Colchicine is a potent inhibitor of granulocyte migra-

tion and has therefore been used in situations where these cells play an important role. There are anecdotal reports of its efficacy in leukoctyoclastic vasculitis (Asherson *et al.*, 1991; Callen & af Ekenstrom, 1987; Plotnick *et al.*, 1989; Werni *et al.*, 1986) and equally, of its lack of efficacy (Boom *et al.*, 1988; Spann *et al.*, 1986). Colchicine is extensively used in Behcet's syndrome. The one controlled trial in this condition showed that it was superior to placebo in controlling arthralgias and erythema nodosum but not eye disease (Aktulga *et al.*, 1980).

Radiotherapy has been reported to be effective in isolated vasculitis of the central nervous system (de Toledo Codina *et al.*, 1991) but there are limitations to its use and it may also cause vasculitis (Galland & Spencer, 1987; Groothuis & Mikhael, 1986).

Conclusion

Corticosteroids and cyclophosphamide are still the primary therapeutic agents in treating systemic necrotizing vasculitis. Although the addition of a cytotoxic agent to steroids in PAN is not of proven value, many physicians do so in order to circumvent the problems of long term steroid therapy. Cyclophosphamide is the drug of choice for Wegener's granulomatosis. Corticosteroids will adequately treat giant cell arteritis but the addition of azathioprine may reduce the steroid side effects. Pulse cyclophosphamide appears highly effective in rheumatoid vasculitis although some steroids are usually used concomitantly. Cyclophosphamide also improves outcome in most forms of renal vasculitis. Kawasaki's disease is definitively treated with aspirin and IVIg. Plasmapheresis may be of value in the vasculitis of cryoglobulinaemia.

Much of the improvement in outcome of vasculitis in recent decades has been the result of modification of established drug regimes and better management of complications, including those of the treatment itself, such as overwhelming infection. Further advances in this direction may well be possible. Cyclophosphamide toxicity may be reduced by intermittent dosage schedules (Hoffman *et al.*, 1990), although effective regimes remain to be established. The routine use of mesna may reduce the subsequent development of bladder carcinoma and potent new antibiotics may improve the outcome of life-threatening infections. Increasing experience with growth factors such as erythropoietin (Oster *et al.*, 1990) and granulocyte-macrophage colony-stimulating factor (Herrman *et al.*, 1990) may allow larger doses of cytotoxic agents to be used. The role and side effect profile of intermittent pulse methylprednisolone therapy and that of concomitant anticoagulant therapy (Conn *et al.*, 1988) is not yet established, and it remains to be seen whether the newer steroid preparations will fulfil their promise of lesser metabolic side effects (Gray *et al.*, 1991).

However, newer, and potentially more specific therapies are being developed. IVIg has had a dramatic impact on the outcome of Kawasaki's disease and may prove useful in other vasculitides. Monoclonal antibody therapy is an area of active research and has already been successfully used in a patient with systemic vasculitis (Mathieson *et al.*, 1990). Further advances may result in more specific targeting of cytotoxicity, blocking antibodies and/or cytokine modulation. Because of the rarity and clinical heterogeneity of these conditions many questions concerning their treatment can only be answered by well designed multicentre trials.

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