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Rational therapy in systemic necrotising vasculitis

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The systemic necrotising vasculitides (SNV) are a rare group of diseases that present considerable diagnostic and therapeutic challenges. The identification of antineutrophil cytoplasmic antibodies (ANCA) in the serum of patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) has advanced research and physician awareness of these conditions. As a result, it is becoming increasingly recognised that therapy for SNV needs to be tailored to the specific diagnosis and phase of disease in the individual patient. To achieve this, an understanding of the natural history of the specific conditions is required, together with a thorough assessment of the patient to identify the extent and activity of disease.

Progression and prognosis of systemic necrotising vasculitides

Classification of the vasculitides is most often based on the size of vessel involved (Table 1)[1]. In some instances, the initial and predominant inflammatory process is granulomatous, with the vasculitic phase of the illness presenting later. This may delay the commencement of effective therapy, adding to the morbidity and mortality of these diseases. This is particularly true of WG where constitutional and upper respiratory symptoms may be present for several years prior to diagnosis.

The vasculitides are characteristically relapsing diseases, but the rate of relapse depends on the specific underlying diagnosis. The risk of relapse in polyarteritis nodosa (PAN) is low, in contrast to the ANCA-associated vasculitides where relapse is as high as 50%[2]. The five-year survival of SNV before the introduction of effective therapy was only 15%. This was improved to 48% with the introduction of steroids, with a further significant improvement in five-year survival to 80% by the use of a combination of corticosteroids and cyclophosphamide (CP). However, this improved survival comes at a cost. Recurrent flares of disease activity lead to the accumulation of organ damage, with appreciable morbidity also related to drug toxicity.

Table 1. Classification of primary systemic vasculitis.

Large vessel	Takayasu arteritis giant cell arteritis
Medium vessel	polyarteritis nodosa Kawasaki disease
Small vessel	*Wegener's granulomatosis *microscopic polyangiitis *Churg-Strauss syndrome Henoch-Schönlein purpura leucocytoclastic vasculitis

* antineutrophil cytoplasmic antibody-associated vasculitis.

Aim of therapy

The aim of therapy in SNV must be rapid and effective suppression of disease activity so that organ damage is limited. The key issue at presentation is to recognise that some sort of vasculitis is present and, if critical organ involvement exists, to start appropriate therapy before the specific diagnosis is obtained. In other cases, more information may be necessary before a diagnosis of vasculitis is reached and potentially toxic treatment commenced. The need to suppress disease activity must be balanced against the potential short- and long-term risks of immunosuppressive therapy. One way is to adopt a phased approach to treatment, with a short course of intensive induction therapy to achieve remission followed by milder, long-term maintenance therapy to prevent relapse and limit drug toxicity.

Assessment

Accurate clinical and laboratory assessment is necessary to allow targeting of therapy for the phase of disease.

Clinical assessment

Clinical tools to assess disease activity and damage have been developed to aid the physician in the diagnosis and management of these complex diseases. These scoring systems can have predictive value for severe disease where patients are at higher risk of dying. In addition, when used routinely they can aid the clinician unfamiliar with these conditions in diagnosis and recognition of disease activity. Organ damage has been shown to accumulate most rapidly after the first flare in disease activity and is not just a late effect. This highlights the need for

prompt recognition of disease activity, with the institution of effective therapy before irreversible damage develops.

- The *Birmingham Vasculitis Activity Score* provides a weighted numerical score based on the specific organ involved and the severity of involvement. A high score reflects either critical organ involvement or multisystem disease and predicts a higher mortality[3].
- The *Vasculitis Damage Index* (VDI) is a cumulative score where items of organ damage must be present for a period of at least three months and be attributable to effects of the disease, its therapy or any other cause. A high VDI score identifies a subgroup of patients with more severe or fatal disease[4].
- The *Five Factor Score*, developed by Guillevin[5], can be used to identify the subgroup of patients with PAN or Churg-Strauss syndrome with a worse prognosis. This scoring system can be used to direct therapy, with a more aggressive approach being taken in patients with a higher score.

Laboratory tests

Thorough assessment to differentiate vasculitis localised to a single organ (eg bowel vasculitis) from more systemic disease is important as the former group may not require systemic immunosuppression, particularly if surgical intervention has completely removed the affected segment of bowel[6]. Laboratory tests may provide supportive evidence of active disease. A rise in C-reactive protein or changes in ANCA titre may be associated with a flare in activity, but should not on their own prompt a change in therapy without appropriate clinical features[7]. More invasive procedures may be needed to provide tissue samples for histopathological examination so that alternative diagnoses, such as infection or malignancy, can be excluded[8]. More widespread involvement of the vascular tree than clinically apparent is suggested in a recent study demonstrating endothelial dysfunction in patients with SNV[9]. This abnormal vascular response, which is associated with an increased risk of atherosclerosis, appears reversible in SNV after immunosuppression.

A combination of clinical tools and laboratory investigations can help differentiate disease activity, for which immunosuppressive therapy may be required, from irreversible organ damage where more therapy may be harmful.

Staged approach to treatment

Induction stage

Cyclophosphamide (CP) is the drug of choice for remission induction, but the best way to give it is unclear. In two recent trials[10,11], there was a median time of three months to induce remission with continuous oral CP (2 mg/kg/day) in conjunction with oral prednisolone (1 mg/kg reducing to 10 mg daily by three months). Remission induction takes longer in some patients, increasing the risk of drug-related toxicity. Intermittent pulse CP is as effective, but the pulse interval is an important and frequently forgotten factor (Table 2)[12]. This mode of administration may be associated with fewer side effects but a higher relapse rate has been reported[13]. A reducing dose of daily steroid is frequently needed, particularly when there is renal involvement or serositis. Where PAN is associated with hepatitis B infection, the combination of plasma exchange with antiviral therapy (interferon-α2b or vidarabine) has been successful[14], though a short course of immunosuppressive therapy may be necessary where there is critical organ involvement by the vasculitis.

Maintenance stage

When remission has been induced, CP should be switched to milder maintenance therapy. Azathioprine (2 mg/kg/day) is as effective as CP at maintaining remission in WG and MPA[10]. Methotrexate is an alternative maintenance agent, particularly in WG when there is grumbling disease activity in the upper or lower airways[15]. These immunosuppressive agents allow the daily dose of steroid to be reduced. Septrin also lowers the relapse rate in WG, possibly by eliminating nasal carriage of *Staphylococcus aureus*. Other maintenance agents that have been used in small series include cyclosporin A, leflunamide and mycophenolate mofetil. It is not clear for how long maintenance therapy should be continued, but in diseases where the relapse rate is high therapy should probably be continued for 3–5 years.

Adjuvant therapy

Adjuvant treatment modalities can be used in addition to standard therapy when disease control proves difficult. In the presence of severe organ involvement, pulses of methylprednisolone (1,000 mg on three consecutive days) may be used, but this should not delay the commencement of CP. Plasma exchange has a place in the treatment of pulmonary haemorrhage and also when there is a rapid deterioration in renal

Key Points

- **Systemic necrotising vasculitides are relapsing diseases with high morbidity and mortality**
- **Clinical scoring tools are useful for management decisions**
- **Thorough clinical and laboratory assessment allows identification of disease activity**
- **Treatment should be aimed at the current phase of the disease**
- **A short induction regimen with cyclophosphamide (pulse or oral) should be followed by milder long-term maintenance therapy**

Table 2. Pulse cyclophosphamide induction regimen.

Drug doses	methylprednisolone (10 mg/kg) *plus* cyclophosphamide (15 mg/kg)
Dose interval	0, 2 ,4, 7, 10, 13 weeks after 6 pulses switch to methotrexate or azathioprine if in remission
Dose reductions	age (>70 years) renal impairment infection neutropenia
Toxicity	nausea alopecia neutropenia infertility haemorrhagic cystitis

function or a serum creatinine level above 500 µmol/l at presentation. Intravenous immunoglobulin may have a role in severe active vasculitis when infection is also present, causing a delay in the commencement of immunosuppressive therapy.

Treatment of relapse

Flares in disease activity are often recognised earlier by patient and physician after relapse than at first presentation, with less damage accumulating[4]. One approach for major relapses is a short course of CP (six pulses), with an early transfer to maintenance methotrexate, azathioprine or cyclosporin. Patients with recurrent relapses may be exposed to several courses of CP, increasing the risk of drug-related toxicity. Methotrexate may be used as an alternative to CP for less severe relapse or where the use of further CP is limited by previous side effects.

Alternative approaches to therapy

A short course of higher dose pulse CP may induce an early remission when used in a more structured regimen (induction, consolidation and maintenance phases), but at an increased risk of neutropenia and infection. Successful autologous stem cell transplantation after intensive immunosuppression has been carried out in a few patients with severe unremitting disease. Anti-T cell monoclonal antibodies (Campath-1H and anti-CD4) have produced dramatic responses in some patients. Inhibition of the pro-inflammatory cytokine tumour necrosis factor-α by monoclonal antibody may theoretically lead to a faster remission induction, but clinical studies are awaited.

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