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Newer therapies for vasculitis

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There is a clear unmet need in the therapy of vasculitis reflecting the toxicity and partial efficacy of conventional agents. Vasculitis is a complex area for the evaluation of newer therapies due to the heterogeneity between and within syndromes with multisystem manifestations. Much of the evidence supporting newer therapies comes from small, non-randomised trials and is insufficient to permit firm recommendations. Newer immunosuppressive drugs, including mycophenolic acid and leflunomide, are alternative second-line agents to methotrexate and azathioprine. Plasma exchange appears to have a role in severe renal vasculitis and vasculitis caused by circulating immune complexes, but evidence supporting other indications is weak. In contrast to most other therapies, intravenous immunoglobulin (Ig) does not affect infective risk and is an alternative agent for refractory disease where standard approaches are contraindicated. The role of tumour necrosis factor blockade remains unresolved with important negative studies, but the therapeutic rationale persists and positive non-randomised trials are also under way. Experience with more aggressive immunosuppression, such as, T-cell depletion or autologous stem cell transplantation has been limited to a few centres. B-cell depletion with rituximab is currently attracting most attention with good success rates in small studies of refractory disease. The treatment of vasculitis in the future will become more complex with a wider range of available treatments; their optimal combination, sequencing and tailoring to the individual clinical situation will place unique demands on those delivering vasculitis services.

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The different vasculitis syndromes

Much of the experience of newer therapies has been with primary vasculitis that predominantly affects small blood vessels and is associated with anti-neutrophil cytoplasmic antibodies (ANCA). The ANCA vasculitides (AAV) include Wegener's granulomatosis, microscopic polyangiitis (and its renal-limited variant) and Churg–Strauss angiitis. This experience also reflects the stronger evidence base of standard therapies for ANCA vasculitis which permits comparisons to be made with studies of newer agents. There is considerably less study of large-vessel vasculitides and of secondary vasculitis, and by their nature, rare vasculitis syndromes are difficult to study. The extent to which results in ANCA vasculitis can be extrapolated to other vasculitis syndromes is uncertain and it cannot be assumed that success in one syndrome will be reflected in another.

Vasculitis syndromes have been defined according to the nature of their pathology.

An understanding of the pathogenesis of a vasculitis syndrome, such as the role of ANCA in AAV, provides a rationale for targeted therapy, for example, B-cell depletion with rituximab aimed to reduce autoantibody production [1]; however, this understanding remains limited and the actual therapeutic mechanisms may be quite different. On the other hand, the targeted nature of monoclonal-antibody-based therapies permits exploration of pathogenesis as the activity of a specific immune or inflammatory component, for example, tumour necrosis factor (TNF), is modulated.

Vasculitis syndromes differ in their steroid responsiveness, in their demography and patterns of organ involvement, for example, between giant cell arteritis (which affects the elderly, reliably responds to glucocorticoids and spares the kidneys) and AAV (which affects a wider age group, requires an immunosuppressive agent and commonly causes renal vasculitis). Furthermore, there is considerable inter-patient variability in the severity and extent of disease. This heterogeneity between and within syndromes makes vasculitis a challenging scenario for the introduction of newer agents.

Areas of unmet need

Current therapy has dramatically changed the prognosis of vasculitis from a usually fatal condition to one that can be controlled, but is limited by both only partial efficacy and high levels of toxicity (Table 1) [2]. Despite optimal standard therapy, remission of disease is incomplete in 20–30%, and a smaller proportion progress to more severe disease. Active disease is the second most common cause of death in vasculitis patients, especially in the first year after diagnosis [3]. Remission is often slow, requiring at least 3 months of therapy, by which time irreversible damage has usually occurred. It is possible that more rapid remission induction will salvage organ function and reduce long-term organ dysfunction. By 5 years after diagnosis, 50% of patients will relapse in spite of at least 2 years of therapy, indicating a failure of current therapies to correct the underlying immunopathogenicity of vasculitis [4]. Approximately 25% will pursue a refractory course manifested by incomplete disease control or frequent relapses despite remission-maintaining therapy. The quality of life of vasculitis patients remains depressed for at least a year after diagnosis, although the causes are likely to be multifactorial,

Table 1
The areas of unmet need in vasculitis.

Induction phase (0–6 months)	Maintenance phase (beyond 6 months)
Failure to control progressive disease (5–10%) Failure to induce remission (10–20%)	Failure to prevent relapse, 50% by 5 years
Delay in achieving remission	Requirement for prolonged therapy to prevent relapse (immunosuppressive and glucocorticoid drugs)
Failure to prevent accrual of irreversible organ damage	Morbidity related to irreversible organ damage
Drug-related toxicity (>90%)	Drug-related toxicity (>90%)
Failure to tolerate therapy	Failure to tolerate therapy
Non-drug-related severe adverse events (e.g., cardiovascular events, thrombo-embolic disease)	Increased risk of cardiovascular events Increased malignancy risk Depressed quality of life