cytes (76,77,79–82). Effector cells damage the vessel wall by degradative enzyme release, respiratory burst-induced production of toxic oxygen free radicals, perforin- or MAC-mediated cytosis, and enzyme-induced apoptosis (22,79). The cellular participants continue to express and release new cytokines that recruit new effector and regulatory immune cells to the site, promote procoagulant tendencies, and induce connective tissue reactions. Regulatory anti-inflammatory cytokines later assume a predominant role and downregulate the inflammatory process. Endothelial cell, fibroblast, and smooth muscle cell proliferation results in a thickened, scarred, and possibly thrombosed or occluded blood vessel (76, 81,83,84).

Irrespective of the exact immunopathogenesis, the expression and regulation of surface adhesion molecules on both endothelial cells and lymphocytes is crucial to the pathogenesis of all forms of vasculitis (76–82,85,86). Three large families of cellular adhesion molecules have been characterized, the selectins, integrins, and immunoglobulin superfamilies, each of which includes multiple classes of adhesion molecules that are each expressed by differing groups of inflammatory and endothelial cells. Together they account for the bulk of inflammatory cell adhesion to and migration through endothelial cells. The role of cytokines and other inflammatory mediators in the activation of both the endothelium and the circulating and adherent effector cells is equally important (75–79,83,84). Given the extreme complexity of cytokine secretion and function, their specific role in the vasculitides is still difficult to elucidate. This has been reviewed extensively elsewhere (83,84).

The principal differences in the immunopathogenic mechanisms for the vasculitides lie in the cells and molecules that initially recognize the pathogenic antigens and those cells and molecules most important in effecting the final vessel damage (22,76,77). In immune complex-mediated vasculitides, circulating antibodies recognize an endogenous or exogenous antigen, forming complexes that deposit locally along blood vessel walls. The primary effector pathway results from complement activation, formation of MAC, and the recruitment of neutrophils to the site of blood vessel wall damage from which proteolytic enzymes are locally discharged, and activation of the coagulation system occurs. The immune complex mechanism appears to be of primary importance only in vasculitides that occur in the setting of hypersensitivity vasculitis or vasculitis with some connective tissue diseases and infections (22,77,78,87).

In other antibody-mediated vasculitides, autoantibodies are directed against antigens present in microvessels and other cells rather than circulating antigens. Anti-endothelial cell antibodies have been detected in some cases of systemic vasculitis, and antibodies to neutrophil cytoplasmic antigens have been demonstrated in most patients with Wegener's granulomatosis, classic and microscopic polyarteritis, and Churg-Strauss syndrome (52,88). Anti-neutrophil cytoplasmic antibodies have a broad spectrum of activity and regulate a wide range of neutrophil functions that could result in endothelial cell damage, but their role in the pathogenesis of vasculitic neuropathy seems limited based on current evidence (22,52,89).

A primary cell-mediated process involving cytotoxic T cells now appears to be the predominant immunopathogenic mechanism for most cases of peripheral nerve vasculitis. Immunohistochemical analyses of peripheral nerve vasculitic lesions reveal that T cells and macrophages are the predominant cell types, whereas B cells and neutrophils, both important in the antibody-mediated mechanisms, are uncommon (9,73,90). Most T cells are CD8+ cytotoxic/suppressor cells, suggesting that direct cell-mediated mechanisms, possibly directed against the endothelium, are of primary pathogenic significance in this disorder (73). Similar findings have been reported in the pulmonary and temporal artery lesions of patients with Wegener's granulomatosis and temporal arteritis (91,92). The endothelial cells probably serve as antigen-presenting cells, with subsequent vascular damage mediated by degradative enzyme release, free radical production, perforin-mediated cytosis, and induced apoptosis (81).

All vasculitic processes invariably result in narrowing or occlusion of affected vessels, with reduced blood flow and ischemic damage to the affected organs. Because of its rich anastomotic blood supply, the peripheral nerve is injured only after extensive involvement of the vasculature and then frequently in the “watershed” zones of relatively poor perfusion (93). In the upper limb, the median and ulnar nerves frequently receive no nutrient arteries between the axilla and elbow, whereas in the lower limb, the sciatic nerve has few collateral feeding vessels between the inferior gluteal and popliteal arteries (71). The clinical relevance of these anatomic features has never been formally studied. However, large-vessel vasculitis might render these territories more susceptible to ischemic nerve damage.

TREATMENT

The remarkable achievements of the past 15 years in the immunopathogenic mechanisms of systemic and peripheral nerve vasculitis have not yet translated into an equally diverse array of therapeutic options. Current treatment of vasculitic neuropathy is far from satisfactory and reflects the intrinsic difficulties encountered in treating vasculitis in general. Most patients are treated with relatively nonspecific immunosuppressive agents such as prednisone that result in global immunosuppression. Treatment decisions are still based largely on anecdotal evidence, because there are few prospective double-blind trials (94–96). Therapy has also been complicated by the difficulty involved in treating multiple organ systems in a given patient and the differing approaches by subspecialists.
The cornerstone of therapy for vasculitic neuropathy involves the removal of the inciting antigen, if it can be identified, and the prompt institution of aggressive immunosuppressive therapy for a duration sufficient to ensure that the inflammatory processes have been suppressed. Antigen removal is possible for relatively few of the vasculitides, particularly those related to drugs and infections. For example, there are several reports of a 70 to 80% response to antiviral therapy with vidarabine or interferon-α2, with or without concurrent plasma exchange, in patients with neuropathy and either hepatitis B-associated polyarteritis nodosa or hepatitis C-associated cryoglobulinemia (28,49,97,98).

In most patients with vasculitic neuropathy, however, the pathogenic antigen is not known; even in those patients where an inciting antigen can be identified, general immunosuppressive therapy is usually given (96). Many different regimens and agents have been used with varying success; however, the most consistently effective one for patients with systemic necrotizing vasculitis (group 1, Table 1) involves the combination of oral prednisone or intravenous methylprednisolone and cyclophosphamide (24,94,95). Patients with nonsystemic vasculitic neuropathy (group 4, Table 1) can be treated with prednisone alone if the clinical involvement is relatively mild. However, it has been our experience that more mistakes are made by undertreating vasculitic neuropathy than by overtreating it with combination therapy.

The standard regimen of prednisone 1.5 mg/kg/day and cyclophosphamide 1.5 to 2.5 mg/kg/day can each be taken in a single morning dose. In fulminant cases, there is a theoretical advantage in commencing with 1 g of intravenous methylprednisolone daily or on alternate days for five or six doses to control the inflammatory process more quickly (69,96,99). After 3 to 4 weeks of daily oral therapy, the prednisone can be switched to an alternate-day regimen at the same dose. The combination regimen is then maintained for 3 to 12 months or more, depending on the clinical response.

Several modifications of the above protocol have been described with varying degrees of success. Oral pulse therapy with doses of cyclophosphamide of up to 5 mg/kg/day for 2 to 5 days was used in patients with severe Wegener's granulomatosis (33), and intravenous pulsing has also been used in dose ranges of 350 to 1,000 mg/m² at 1- to 4-week intervals (94,99-101). These regimens appear to have fewer long-term side effects than daily oral therapy, including less hemorrhagic cystitis and bladder carcinoma, but their comparative efficacy is uncertain.

The primary goals of treatment are to stop progression of neurologic deficits, reduce pain related to ischemia, and restore an appropriate microenvironment to the nerve so that axonal regeneration can take place. Because this may be an extremely slow process, particularly if extensive and proximal axonal damage has occurred, actual clinical improvement in strength or sensation may not be evident for months after initiation of therapy. A common mistake in treatment is to assume that the immunosuppressive regimen is "not working" because the patient has noticed no clinical improvement and to switch to alternative agents. The first signs of improvement may only be reduced pain and a mild increase in proximal strength. Once the clinical status is stable and improvement maximized, the prednisone can be slowly tapered, as for example, by 5 mg every 2 to 3 weeks to avert disease exacerbation. If it does relapse, the patient can be pulsed with prednisone or methylprednisolone at doses equivalent to the initial therapy until control of the disease is again attained, and tapering is then resumed. Cyclophosphamide is continued for at least 1 year after disease stabilization and then tapered off over 4 to 8 weeks.

Patients who are not candidates for cyclophosphamide because of unacceptable or anticipated side effects or who progress while on it require alternative therapy (Table 8). In these instances, azathioprine or methotrexate are the suitable alternatives, but there is no clear evidence favoring one over the other (94,102,103). Cyclosporine has been used in resistant patients and should be considered in those refractory to all other agents or with tenuous bone marrow function (104).

Controlled trials of plasma exchange with standard immunosuppression in polyarteritis nodosa and Churg-Strauss syndrome showed no benefit (99), although it has been used with some success in combination with antiviral therapy for patients with hepatitis B-associated polyarteritis and cryoglobulinemia (96,98). Intravenous immunoglobulin has been tried in several different types of vasculitis. The initial results are encouraging, but controlled trials have not yet been reported, and no information exits regarding its effect on vasculitic neuropathy (105).

Comprehensive management of the patient with vasculitic neuropathy requires more than immunosuppressive treatment. A program of supportive measures is crucial in optimizing recovery. The most important of these include limiting the side effects of the immunosuppressive drugs by careful monitoring, pain management, controlling other conditions that may be contributing to ischemia, and providing optimal physical and occupational therapy.

Patients treated with prednisone must be carefully monitored for hypertension, weight gain, glucose intolerance, electrolyte imbalance, cataracts, glaucoma, osteoporosis, superimposed myopathy, and avascular necrosis of the hip (106). A tuberculin skin test should be placed before treatment, and antituberculosis prophylaxis should be given to positive responders. A low-sodium, low-simple-sugar, calorie-restricted diet limits weight gain in most patients. Calcium, vitamin D or calcitriol, biphosphonates, and estrogen supplements in postmenopausal women limit osteoporosis (107). Bone mineral density measurements should be obtained at baseline and repeated at 6- to 12-month intervals in appropriate
### TABLE 8. Alternative immunosuppressive agents in treatment of vasculitic neuropathies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms</th>
<th>Dose</th>
<th>Side effects</th>
<th>Laboratory monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Inhibits purine metabolism</td>
<td>2–3 mg/kg/day</td>
<td>Marrow suppression, Hepatotoxicity, GI intolerance</td>
<td></td>
</tr>
<tr>
<td>DNA/RNA synthesis</td>
<td></td>
<td></td>
<td>Systemic hypersensitivity</td>
<td>CBC, LFTs, CXR</td>
</tr>
<tr>
<td></td>
<td>Inhibits T, B, NK cell function</td>
<td></td>
<td>Susceptibility to infection, Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folate antagonist</td>
<td>7.5–20 mg/wk (oral)</td>
<td>Marrow suppression, GI intolerance</td>
<td>CBC, LFTs, CXR, creatinine</td>
</tr>
<tr>
<td></td>
<td>↓ DNA/RNA synthesis</td>
<td>25–50 mg/wk (IM or IV)</td>
<td>Mucositis, hepatotoxicity, Alopecia</td>
<td>Hep B and C</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Suppression of T-cell activation and proliferation</td>
<td>3–5 mg/kg/day (oral)</td>
<td>Susceptibility to infection</td>
<td>CBC, LFTs, BUN, creatinine</td>
</tr>
<tr>
<td>IVlg</td>
<td>Blocks Fc receptors on effector cells</td>
<td>0.4 mg/kg/day for 5 days</td>
<td>Neutropenia/hypertension, HypoK, HypoMg, Gingival hyperplasia, GI intolerance,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibits complement deposition</td>
<td></td>
<td>Tremor, paresthesias, edema, Encephalopathy/seizures, Fever, chills, myalgias,</td>
<td>CBC, BUN, creatinine</td>
</tr>
<tr>
<td></td>
<td>Idiotypic/anti-idiotypic interactions</td>
<td></td>
<td>Headache, aseptic meningitis, Nausea, rash, Leukopenia</td>
<td>Quantitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>immunoglobulins, Urinalysis, hepatitis C transmission</td>
</tr>
</tbody>
</table>

CBC, complete blood count; BUN, blood urea nitrogen; LFTs, liver function tests; CXR, chest x-ray; IVlg, intravenous immunoglobulin; NK, natural killer.

patients (107). The potential toxicity of cyclophosphamide, includes hemorrhagic cystitis in up to 40% of patients and bladder cancer in 5%, which can be minimized by aggressive oral hydration and frequent urination (108). The risk of *Pneumocystis carinii* pneumonia can be reduced with trimethoprim/sulfamethoxazole prophylaxis given three times weekly in patients taking daily glucocorticoids and a cytotoxic agent (108). The principal side effects of the other medications are given in Table 8.

Effective pain management is an important, and often neglected, aspect to the care of these patients. Aside from the obvious benefit to the patient’s overall well-being, it permits more aggressive physical therapy to be performed and also allows the treating physician to more accurately assess changes in muscle strength by manual muscle testing. Agents such as the tricyclic antidepressants, carbamazepine, gabapentin, mexiletine, clonazepam, and topical lidocaine cream have all been used with varying degrees of success (109). Opioid therapy is often necessary to achieve adequate pain control.

Strenuous efforts should be made to limit the possible ischemia-enhancing effects of other conditions. Smoking should be discontinued, and diabetes should be controlled as tightly as possible. This is frequently a difficult task because prednisone therapy exacerbates glucose intolerance. Hyperlipidemia and hypertension should also be treated. Antiplatelet agents should be considered in patients with signs of progressive neurologic injury despite aggressive immunosuppression (95).

Physical therapy is important for patients with significant motor impairments, not only to maintain range of motion and strength but also to improve functional status. There is convincing data that exercise that involves compressive force both reduces osteoporosis and minimizes the risk of steroid myopathy (110). Judicious bracing and the use of ambulatory aids in conjunction with physical therapy can be crucial in maintaining ambulation, although bracing can be extremely difficult in patients with joint deformities due to superimposed collagen-vascular disease. Occupational therapy can assist patients in their recovery of upper limb function and reacquisition of daily living skills.

### PROGNOSIS

The value of combination immunosuppression therapy in patients with certain vasculitides is unquestionable. In Wegener's granulomatosis, a remission rate of 75% is now achievable, compared with a mean survival of only 5 months before the introduction of immunosuppressive agents (31). Similar results have been reported for polyarteritis nodosa and isolated central nervous system angiitis (95,102).
Although the prognosis is less well defined for patients with vasculitic neuropathy, three retrospective series have examined long-term outcome (7,10,14). These studies clearly demonstrate that patients with nonsystemic vasculitic neuropathy have a more benign prognosis than those with a systemic necrotizing vasculitis. Mortality, in particular, is much higher in the systemic group, with a 60% mortality within 5 years in one study (10). In contrast, patients with nonsystemic vasculitic neuropathy had an 85% survival after a mean follow-up of 11 years in one study and a 96% survival after 3 to 4 years in other series (7,14). The neurologic status of the patients with nonsystemic vasculitic neuropathy was also more likely to improve than the status of those with systemic disease.

Although there is strong support for the use of aggressive immunosuppression in vasculitic neuropathy patients, several long-term studies have identified disturbing aspects to the standard regimen that have a serious impact on prognosis (31,111). For example, about 50% of patients with Wegener's granulomatosis on chronic combination therapy suffer a disease relapse and 40% experience serious drug-induced side effects, with a 50% rate of significant infection. Even more ominously, there was a 2.4-fold increase in malignancy, a 30-fold increased risk of bladder cancer, and an 11-fold increase in lymphoma compared with a control population (31). These findings indicate that more effective and less toxic treatments are urgently needed for this group of diseases.

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PERIPHERAL NERVE VASCULITIS / 255


