ANCA-Positive Vasculitis

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Inflammation and necrosis of blood vessel wall occurs in a dozen or so primary vasculitic disorders. An attempt to classify these diverse forms of vasculitis resulted in the Chapel Hill international consensus definitions, which used the vessel size as the determinant of classification (1). Wegener granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome are described as small-vessel vasculitides and are acknowledged to be commonly associated with antineutrophil cytoplasm antibodies (ANCA). These diseases share a common pathology with focal necrotizing lesions, which affect many different vessels and organs; in the lungs, a capillaritis may cause alveolar hemorrhage; within the glomerulus of the kidney, a crescentic glomerulonephritis may cause acute renal failure; in the dermis, a purpuric rash or vasculitic ulceration may occur. Wegener granulomatosis and Churg Strauss syndrome have additional granulomatous lesions (for further review, see reference 2). The incidence of these diseases is increasing, with more than 20 per million affected and occurring more often in an elderly population (peak age, 55 to 70 yr) (3).

Pathogenesis

Understanding the pathogenesis of ANCA-associated vasculitis is important for the development of novel therapeutic agents, and important advances have been made in recent years (4,5). ANCA are thought to contribute to the pathogenesis of these small-vessel vasculitides, activating cytokine-primed neutrophils and monocytes, which express the ANCA antigens, proteinase 3 and myeloperoxidase, on their surface. Neutrophils respond by developing the capability of adhering to endothelial-bound antigens, inducing endothelial cell apoptosis of these cells. Furthermore, ANCA can bind to endothelial cells; indeed endothelial cells express receptors for proteinase 3. Myeloperoxidase can induce endothelial cell detachment, whereas proteinase 3 can cause direct apoptosis of these cells. Furthermore, ANCA can bind to the endothelial-bound antigens, inducing endothelial cell cytotoxicity.

Activation of endothelial cells and neutrophils is important for the early development of vasculitic lesions, and progression of these lesions is accompanied by T cell and monocyte recruitment. T cell–mediated immunity is thought to contribute to the pathogenesis of ANCA-associated vasculitis. Several studies have documented the ability of peripheral blood T cells from patients with either active or quiescent disease to proliferate in response to proteinase 3 or myeloperoxidase. T cell activation has also been shown to persist after disease remission with reduced CD28, a costimulatory molecule for T cell activation, and increased CD69, an early marker of T cell activation. These and other studies (see reference 6 for review) suggest that T cells may contribute to the remitting/relapsing nature of ANCA-associated vasculitis and show the failure of current therapies to suppress immune disease processes and induce tolerance.

Clinical Features

Constitutional symptoms, such as fever, myalgia, anorexia, weight loss, malaise, and night sweats, are common in vasculitis. In Wegener granulomatosis, there is a predilection for the upper and lower respiratory tracts and the kidneys to be involved. Upper respiratory tract symptoms include rhinorrhea,
basis of the clinical findings, by biopsy of a relevant involved organ (typically kidney, nasal mucosa, or occasionally lung) and the presence of ANCA. Testing for ANCA using both indirect immunofluorescence and antigen-specific enzyme-linked immunosorbent assay is recommended and provides a high sensitivity (approximately 99%) and good specificity (approximately 70%) (10,11).

Treatment in ANCA-Associated Vasculitis

The prognosis of untreated ANCA-associated vasculitis is poor, with up to 90% of patients dying within 2 yr, usually due to respiratory failure (12). The introduction of cyclophosphamide and high-dose corticosteroids by Hoffman et al. (12) and Fauci et al. (13) in the 1970s markedly reduced the mortality. Cyclophosphamide alkylates DNA guanidine nucleotides, induces lymphopenia, particularly of B lymphocytes, and suppresses Ig responses. The combination of prednisolone and cyclophosphamide, now viewed as standard therapy, leads to control of disease in 80 to 90% of patients. However, these regimes are associated with treatment-related morbidity in over 50% of patients, including steroid-induced diabetes, bladder and lymphoproliferative malignancy, and infertility (12,14). There appears to be little role for prednisolone alone. When compared with combined cyclophosphamide and prednisolone, prednisolone alone is associated with a lower remission rate (56 versus 85% in one study), a higher relapse rate, and a higher mortality rate (15).

Treatment has converted this acutely fatal disease into a chronic relapsing disorder with accumulating morbidity. Current treatment is toxic and contributes to morbidity and mortality. Treatment must be tailored to the stage and severity of disease to balance the dangers of disease against those of treatment.

For successful treatment vasculitis must be recognized and treated early before permanent scarring occurs. Disease monitoring tools have been developed to aid distinction of tissue damage by active disease that would be amenable to treatment from that caused by healing scars or treatment. For example, the Birmingham Vasculitis Activity Score (BVAS) and vasculitis damage index (VDI) score active disease and chronic damage respectively (for review, see reference 16). These tools have been particularly useful in clinical studies, contributing to definitions of clinical remission and relapse, which are necessary end points of therapeutic trials.

Induction Therapy

Initial therapy requires high-dose cyclophosphamide and corticosteroids, with additional therapy in those with life-threatening or organ-threatening disease. In those with non-organ-threatening renal involvement (creatinine <5.6 mg/100 ml; 500 μmol/L), a commonly used approach is prednisolone (1 mg/kg per d to a maximum of 80 mg, with reducing doses over time to 12.5 to 15 mg by 3 mo) and cyclophosphamide (2 mg/kg, adjusted for age, renal function, and the prevailing white cell count), in which the cyclophosphamide is maintained for 3 mo. A recently reported multicenter randomized controlled trial (CYCAZAREM) comparing 3-mo or 12-mo therapy with cyclophosphamide followed by conversion to...
azathioprine for remission therapy supported this approach (17); the patients converted to azathioprine at 3 mo entered remission as readily as those receiving more protracted cyclophosphamide therapy.

Encouraged by the success of pulsed cyclophosphamide in the treatment of systemic lupus erythematosus, several studies have addressed the question of efficacy of a pulsed regime in ANCA-associated vasculitis (for review, see reference 18). A recent meta-analysis suggested that pulsed cyclophosphamide is less toxic with fewer adverse effects than continuous oral cyclophosphamide and that it is at least as potent an inducer of remission, but possibly at the expense of a higher relapse rate (18). The existing studies were, however, flawed, and there is a need for a large multicenter randomized controlled trial.

The most important indicators of prognosis are pulmonary hemorrhage and severity of renal failure at diagnosis. Patients who present with fulminant disease require intensification of induction therapy with the addition of methylprednisolone or plasma exchange. In one study, plasma exchange that removes ANCA IgG and other inflammatory mediators from the circulation conferred additional benefit when patients were dialysis-dependent (19). Neutrophils from patients with ANCA-associated vasculitis have a greater inflammatory potential compared with healthy controls, producing more oxygen free radicals (20). Methylprednisolone may improve inflammation by increasing the production of the antioxidant, superoxide dismutase, normalizing superoxide anion production and reducing damage by neutrophils (21). Plasma exchange has theoretic advantages over methylprednisolone in reducing morbidity; at least one study (22) suggests that a high total steroid dose increases the likelihood of intercurrent infection. A comparative study of plasma exchange (7 × 3 to 4 L exchanges within 14 d) versus intravenous methylprednisolone (1 g daily for 3 d) in severe disease (creatinine >5.7 mg/100 ml; 500 μmol/L) is in progress; the MEPEX trial has been organized by the European Vasculitis Study Group (EUVAS) and has completed recruitment. Intravenous Ig has also been used as adjuvant therapy, but a randomized placebo-controlled trial of 34 patients suggested only a transient improvement (23). Intravenous Ig is associated with significant side effects, including acute renal failure, and further studies are required to prove efficacy.

Cyclophosphamide may induce neutropenia that can be severe and protracted. A small study (24) suggested that the use of granulocyte colony-stimulating factor, a neutrophil-activating agent, does not carry a high risk of inducing a flare of vasculitis.

**Maintenance Therapy**

The risks of maintenance therapy have to be balanced against the risks of disease relapse, which varies from 25 to 50% over 3 to 5 yr. Azathioprine has been extensively used for maintenance. It blocks synthesis of inosinic acid, a precursor of the purines, adenylic and guanylic acid, in the S phase of the cell cycle, reducing T and B cell proliferation. In the recently reported CYCAZAREM study, which compared azathioprine and cyclophosphamide as maintenance treatments, azathioprine was as effective as continued cyclophosphamide in the maintenance of remission (17). Prednisolone was maintained at low levels in both limbs. Adverse events were frequent in both limbs, although with a nonsignificant trend toward less severe adverse events with azathioprine. It is unclear whether continuation of immunosuppression beyond 18 to 24 mo improves relapse rates. There is evidence that Wegener granulomatosis is more likely to relapse than microscopic polyangiitis (17) and, if confirmed, may imply the need for a different approach to therapy in those with Wegener granulomatosis.

An alternative to azathioprine is methotrexate weekly. Methotrexate inhibits the enzyme, dihydrofolate reductase, which is essential for the synthesis of purines and pyrimidines. Methotrexate has been used as induction/remission therapy in Wegener granulomatosis without threatened vital organ function (25,26). Its use to control renal vasculitis is more controversial; of 21 patients who had active glomerulonephritis in the original study by Sneller et al. (27), those who had normal or near normal serum creatinines showed no long-term decline in renal function. However, in another study, a third of patients relapsed, with more than 50% of relapses affecting the kidney (28). Methotrexate is contraindicated when the serum creatinine is >2 mg/100 ml (>177 mmol/L), at which time there is a major risk of hepatic and bone marrow toxicity.

More recently, mycophenolate mofetil (MMF) has been used as an alternative to azathioprine. MMF is an immunosuppressant drug with high lymphocyte specificity. Lymphocyte proliferation after stimulation requires the de novo purine synthesis pathway almost exclusively. MMF reversibly inhibits inosin-monophosphate-dehydrogenase, a key enzyme of the de novo pathway (29). MMF has antiproliferative effects on mesangial and smooth muscle cells and inhibits leukocyte recruitment by inhibition of glycosylation and expression of endothelial adhesion molecules (30). A pilot study of 11 patients receiving MMF following standard induction therapy, showed that it was well tolerated. Only one patient relapsed in the 14th month, with all patients followed for 15 mo. MMF was able to reduce continuing disease activity and proteinuria that had been present at the end of induction therapy (31). Two other studies published in abstract form also support the use of MMF in ANCA-associated vasculitis. In these two studies, 17 patients who had persistent or recurrent disease were treated with MMF: 15 improved, 2 failed, and 1 was intolerant of treatment (32,33). Patients who are intolerant of cyclophosphamide and who relapse on azathioprine may also respond well to treatment with MMF (34). A large multicenter trial of MMF as maintenance therapy has been launched by EUVAS. Active metabolites of MMF are excreted by the kidneys (35), so pharmokinetic/dynamic properties may have an important impact on the drug’s therapeutic efficacy in acute renal failure. In any event, there is large variability of plasma concentrations of the drug between individuals; monitoring of plasma concentrations of MMF should therefore be considered.

The use of cyclosporin as an alternative agent was suggested after the use in two patients who had sustained remission and improved renal function. However, a randomized trial found a higher relapse rate in patients switched to cyclosporin com-
pared with those maintained on cyclophosphamide (36). Furthermore, recurrence of Wegener in transplanted patients receiving cyclosporin whose disease responds to discontinuation of cyclosporin and commencement of cyclophosphamide is further evidence of the limited efficacy of cyclosporin in acute vasculitis.

Colonization of the upper respiratory tract by *Staphylococcus aureus* may increase the risk of disease relapse, and use of sulfamethoxazole/trimethoprim reduced the risk of respiratory relapse compared with placebo when added to conventional therapy. There is, however, a high rate of drug intolerance (37), and it is not known whether efficacy of the drug relates to eradication of Staphylococcal carriage. Sulfamethoxazole/trimethoprim is not recommended for use at the expense of conventional immunosuppression (38).

**Rescue Therapy for Refractory and Relapsing Disease**

Standard induction therapy fails to induce remission in approximately 10% of patients. A further difficult patient group comprises those who frequently relapse, necessitating recurrent use of cyclophosphamide. Both these groups have a high risk of side effects from cyclophosphamide, due to the high cumulative dose of cyclophosphamide that is accrued. Alternative strategies have involved the use tumor necrosis factor (TNF) blockade, polyclonal antithymocyte globulin (ATG), or monoclonal anti–T cell antibodies.

The success of TNF blockade in rheumatoid arthritis has paved the way for the use of similar exciting therapeutic strategies in patients with ANCA-associated vasculitis. There are strong reasons for believing that TNF may be pivotal in sustaining the ongoing inflammation in systemic vasculitis that is associated with ANCA. Increased circulating TNF levels have been detected during active vasculitis (39), and TNFα mRNA and protein are markedly increased at vasculitic sites (39). The secretion of TNF by T cells from patients with active Wegener granulomatosis is increased when T cells are stimulated with lipopolysaccharide or anti-CD2/anti-CD28 in vitro (40). Enhanced TNF gene expression in peripheral blood mononuclear cells in patients with systemic vasculitis (41) and elevated serum levels of soluble receptors, TNF-R55 and TNF-R75, have been found also (42). Important targets for this TNF include neutrophils and endothelial cells. Thus, TNF priming of neutrophils increases the surface expression of antigenic targets (43), and neutrophils isolated from patients with ANCA-associated vasculitis are more likely to have high proteinase 3 expression on the neutrophil surface (20,44). Neutrophils in systemic vasculitis have been shown to be primed intravascularly (20,44). Further evidence of circulating primed, but not activated, neutrophils was shown by the upregulation of the activation markers CD66b, CD64, and CD63 but no increase in adhesion molecule expression; with CD63 and CD66b correlating with disease (45) and increased basal secretion of superoxide (20). Such priming is also required for an effective ANCA-induced respiratory burst with superoxide release (46). Furthermore, TNFα-primed neutrophils can undergo accelerated and dysregulated apoptosis after activation by ANCA, which may lead to the disintegration of the apoptotic neutrophil through secondary necrosis (47).

TNF is also a potent endothelial cell activator, inducing increased adhesion molecule expression and promoting a proadhesive state for neutrophils and other leukocytes. Indeed, in ANCA-associated vasculitis, upregulation of intercellular adhesion molecule–1 (ICAM-1) (48) and vascular cell adhesion molecule–1 (VCAM-1) on endothelial cells correlates with disease activity (49). Trials with anti–TNF-specific antibody in patients with rheumatoid arthritis showed significant reduction in cytokine-induced vascular adhesion molecules (E selectin, ICAM-1, and VCAM-1) (50). There was a reduction in the cellularity and inflammatory score of synovial tissues with a reduction in CD3+ lymphocytes and CD68+ cells derived from the monocyte lineage (51). These studies concluded that anti-TNF monoclonal antibody therapy leads to a reduction in the trafficking of leukocytes (50). In ANCA-associated vasculitis, we believe that initial lesions are neutrophil-dependent and that subsequent T cell recruitment and infiltration occurs as a secondary event (4). In a similar manner to that shown in rheumatoid patients, treatment of patients suffering from ANCA-associated systemic vasculitis with anti-TNF monoclonal antibody may result in deactivation of the endothelium, reducing interactions between endothelial adhesion molecules and the counter ligands expressed on leukocytes, consequently reducing retention of circulating leukocytes in inflamed tissues. Recent evidence has shown benefit of TNF blockade in an animal model of acute crescentic glomerulonephritis, a model of human renal vasculitis (52).

Two anti-TNF treatments are approved for clinical use in rheumatoid arthritis and Crohn disease: etanercept, a recombinant fusion protein consisting of two p75 TNF receptors linked to the Fc portion of human IgG1; and infliximab, a chimeric monoclonal antibody. D2E7 is a fully humanized monoclonal antibody and is currently undergoing clinical testing.

An open-label study of 20 patients with Wegener granulomatosis was performed to evaluate the safety of etanercept in combination with standard therapy, which included cyclophosphamide (53). All patients had resistant disease, four of which had active glomerulonephritis. The mean time from original diagnosis was 64 mo. Using BVAS/WG, a disease activity measurement specific for Wegener granulomatosis (54), the mean activity was 3.6. Fourteen patients had never achieved remissions allowing the withdrawal of corticosteroids. Nineteen of the 20 patients improved, and 80% achieved BVAS/WG scores of 0, although intermittently active disease was seen in 15 patients. The mean daily prednisolone was reduced from 12.9 mg to 6.4 mg after 6 mo. Adverse reactions were mild, with injection site reactions being common. Two patients required hospitalization (five events), but in neither patient was it solely due to etanercept. One patient with severe subglottic stenosis developed tracheobronchitis and a subsequent herpes zoster infection. A randomized double-blind placebo-controlled study has been started in the United States to assess etanercept efficacy under the auspices of The International Network for the Study of Systemic Vasculitis (INSSYS).
Infliximab has also been used in the treatment of vasculitis, although there are as yet no reported trials. We have treated four patients with infliximab; three patients had severe lung or renal involvement, and the fourth patient had relapsing limited disease (Table 1). All patients responded to treatment within 6 wk. The three patients with generalized disease had achieved full remission by 6 wk, and patient 4, who had limited disease, achieved full remission by week 12. All remained disease-free during follow-up (median, 9 mo; range, 4 to 16 mo). Patient 3 became dialysis-dependent despite treatment; however, renal biopsy showed significant chronic damage. Two patients suffered opportunistic infections (patient 1 had a candida pneumonia, and patient 3 developed staphylococcal line sepsis and herpes zoster), but both were severely immunocompromised by previous treatments. No patients suffered infusion reactions.

Taken together with the recently published successful use of etanercept in patients with limited Wegener granulomatosis, our findings support the view that TNF is a pivotal cytokine-promoting inflammation in ANCA-associated vasculitis. TNF blockade appears to be an effective novel therapy for life-threatening disease or for those intolerant of conventional therapies.

T cells play a central role in the pathogenesis of vasculitis. ATG is directed against surface antigens of activated lymphocytes and results in lymphocyte depletion. Polyclonal ATG has been effectively used for prophylaxis and treatment of renal allograft rejection. ATG has been used as compassionate therapy for five patients with Wegener granulomatosis untreatable with cyclophosphamide and prednisolone. Four patients showed a favorable response to treatment, with partial or complete remission of disease activity, during a follow-up period of 5 to 12 mo. One patient had progressive retro-orbital granuloma, which resulted in enucleation of the eye. Side effects of treatment were mild, with no serious infectious complications (55). A further report suggested that ATG may also be useful in patients with Wegener granulomatosis who are dialysis-dependent at diagnosis (56). Monoclonal anti–T cell antibodies have also shown sustained remission in small open studies (57). The use of these agents requires further study, but they do underline the importance of T cells in the pathogenesis of ANCA-associated vasculitis.

Deoxyspergualin (DSG) is a new immunosuppressive agent that has been successfully used in acute renal allograft rejection and various animal models of autoimmune disease. The mode of action is not fully understood. It has been shown to interfere with the intracellular chaperoning by heat shock protein 70 and the activation of nuclear factor–κB (NF-κB). It leads to maturation arrest of early B cell, T cell, and neutrophil precursors.

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<th>Patient</th>
<th>Presentation</th>
<th>Presentation Age</th>
<th>Follow-Up</th>
<th>Weeks/BVAS (Normal = 0)</th>
<th>Days/CRP (Normal Range, &lt;10 mg/L)</th>
<th>Adverse Events</th>
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<td>66</td>
<td>16 mo</td>
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* BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein.
resulting in transient, reversible noncumulative bone marrow suppression. DSG may be not only immunosuppressive; it may also induce long-term tolerance. DSG prevented dendritic cell, the archetypal antigen-presenting cell, maturation with failure to express CD83, CD86, and MHC II (58). CD83 and CD86 are required for co-stimulation of T cells to produce an immune response. In an animal model of renal transplantation, long-term tolerance of the graft was achieved using DSG (59). Interestingly, DSG also has a bactericidal effect on Staphylococcus aureus, which has been implicated in the pathogenesis of Wegener granulomatosis.

In an open-label multicenter pilot study, DSG was used to induce remission in 19 patients with active refractory Wegener granulomatosis, all of whom were unresponsive or had contraindications for standard therapy (eight were receiving cyclophosphamide immediately before starting DSG). Patients received 0.5 mg/kg DSG daily until white blood cells fell to 3 × 10⁹/L; they were then given a 14-d rest before repeating six cycles over 6 to 8 mo. Complete remission was achieved in seven patients and partial remission in seven patients. Of the eight patients who had active disease while receiving cyclophosphamide, one patient achieved full remission, five achieved partial remission, and two relapsed within the six treatment cycles. Treatment was well tolerated, with no deaths or episodes of septicemia (60). DSG may be a useful alternative for cyclophosphamide, but further studies are required.

Future Therapies

Immunoblation using high-dose cytotoxic medication followed by stem cell rescue has led to prolonged remission in a few refractory cases of vasculitis (61). However, in one report of two patients receiving stem cell transplants, both relapsed within 3 yr (62), suggesting that immunoblation may just act as enhanced immunosuppression. Further studies are required and are very dependent on the safety of this procedure.

To maintain remission, azathioprine and methotrexate are frequently used, but both are myelotoxic and often not tolerated by patients. Furthermore, methotrexate is contraindicated in renal failure. Leflunomide is a new immunosuppressant that acts as a selective inhibitor of de novo pyrimidine synthesis. In rheumatoid arthritis, leflunomide was shown to have similar potency to methotrexate and sulfasalazine. It does not accumulate in renal failure and does not cause leucopenia. Recently, leflunomide was successfully used to maintain remission in generalized Wegener granulomatosis (63).

Future directions for therapy may also include blockade of other proinflammatory cytokines, including interleukin-1 (IL-1) using IL-1 receptor antagonists. These agents have been used with some success in rheumatoid arthritis. T cell co-stimulation is necessary for activation. This pathway may be blocked by the use of the CTLA4-Ig chimeric protein. A strong association between certain CTLA4 alleles and Wegener granulomatosis has been shown, suggesting that this novel therapeutic agent may have an important role in future therapies. Other promising biologic agents for therapy of vasculitis include anti-CD20 monoclonal antibody (rituximab), which causes lysis of B cells; its successful use to induce remission in a patient with chronic relapsing Wegener has been reported (64).

Conclusion

Since the advent of the use of cyclophosphamide and corticosteroids in patients with ANCA-associated vasculitis, the outlook for patients has dramatically improved. The current challenge lies in the tailoring of immunosuppression to reduce treatment-associated morbidity and mortality without compromising organ damage. Novel therapeutic agents, including newer immunosuppressants and biologic agents, are being subjected to large randomized controlled trials using the gold standard of cyclophosphamide and corticosteroids as controls, thereby improving the evidence base for treatment of this challenging disease and improving the outlook for patients.

References


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/