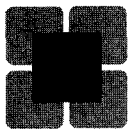

Treating Wegener's granulomatosis: How far have we come?

PRIOR to the advent of treatment with cyclophosphamide and glucocorticoids, the mean survival for a patient with Wegener's granulomatosis was 5 months. Although the daily cyclophosphamide and steroid regimen has improved survival to 80% over 8 years, treatment-related morbidity is common. In addition, relapses have been documented as long as 15 years after remission, and each relapse enhances the risk of disease-related and treatment-related morbidity. We clearly need alternative, less toxic forms of therapy. This brief article discusses the rationale behind the current treatment regimen, as well as the search for new treatments and alternative methods of administering current therapy.

CURRENT REGIMEN

The current treatment regimen consists initially of daily oral therapy with cyclophosphamide 2 mg/kg and prednisone 1 mg/kg for 1 month. In extraordinarily desperate situations, treatment may begin with up to 1 g of methylprednisolone daily for 3 days and up to 4 mg/kg of cyclophosphamide for about 3 days. These doses would then be reduced to the more conventional range. If the patient experiences marked improvement (suppression of disease with stabilization of renal function and at least partial resolution of pulmonary infiltrates), prednisone is tapered to alternate days over the next 2 months. If remission continues, prednisone is then discontinued over several months. Cyclophosphamide is continued for at least 1 year after the patient achieves complete remission and is then tapered by 25-mg decrements every 2 to 3 months until discontinued or until disease recurrence requires an increase in the dose. The patient returns to the standard protocol if a relapse is experienced.

This regimen produces remission in 75% of patients. Remission may occur within 1 to 3 months. However, it may take as long as 5 years for some patients to achieve remission, which unfortunately provides ample time for additive morbidity from the disease and its treatment. Although the standard protocol is designed to minimize daily glucocorticoid therapy and the side effects associated with it, permanent morbidity occurs in essentially all patients: in 86% as a result of the disease itself, and in 42% as a result of treatment with glucocorticoids or cyclophosphamide. Morbidity from treatment includes cyclophosphamide-induced cystitis (43%), pulmonary insufficiency (17%), bladder cancer (2.8% to 4.2%), and infections that require hospitalization and intravenous antibiotics (46%). Half of these infections occur while patients are on daily prednisone and 21% occur while on the alternate-day regimen, compared with 12% while on no immunosuppressive therapy.

THE SEARCH FOR ALTERNATIVES

Is there a reliable disease marker that allows one to anticipate clinical deterioration and to initiate presumptive treatment? Such a marker would permit a shorter duration of treatment using lower drug dosages and thus would diminish subsequent morbidity. One group of investigators suggests that antineutrophil cytoplasmic antibody (ANCA) is that marker. However, presumptive treatment based on ANCA titers does not appear to be viable because ANCA titers and disease activity are discordant in 38% of patients. Only about 25% of patients have a rise in titers before a clinical exacerbation. Therefore, an increase in ANCA titers during remission or smoldering disease has proven to be an insensitive prognostic marker for relapse.

Modification of current approach

Studies of pulse high-dose intravenous cyclophosphamide were motivated by its efficacy in treating lupus nephritis and by the lure of reduced toxicity. Marked improvement in Wegener's granulomatosis is achieved within 1 month in most patients on pulse therapy, but relapse or withdrawal because of toxicity occurs in nearly all patients by 1 to 2 years.

Methotrexate

In ex vivo studies, leukocytes from patients who received single doses of methotrexate revealed diminished lymphocyte proliferation, reduced neutrophil chemotaxis and leukotriene B4 production, and diminished neutrophil adherence to endothelial cells. This last effect carries special importance because neutrophil adherence to endothelial cells may be the initial step toward vessel-wall invasion.

An ongoing open-label pilot trial of methotrexate in patients with biopsy-proven Wegener's granulomatosis provides encouraging results. Patients in the trial have had disease activity for a mean of 6 years before entering the study. Many had failed conventional therapy or discontinued cyclophosphamide because of toxicity. Within 12 months, two thirds of patients have achieved and maintained remission with once-weekly methotrexate, 0.15 to 0.30 mg/kg, and concurrent glucocorticoid administration. Some 65% of those in remission were able to discontinue glucocorticoids. If the outcome is sustained, methotrexate would provide a reasonable alternative to cyclophosphamide, especially in light of the reduced potential for toxicity.

Biologic agents

Biologic agents such as soluble TNF-receptor, IL-1 receptor or IL-1-receptor antagonists promise to provide greater palliation of symptoms and less toxicity than current therapy. These agents are currently under study in other autoimmune diseases. However, such sophisticated forms of immunosuppression do not address the predisposing abnormalities that allow autoimmune disease to be triggered by unknown factors in individuals predisposed to developing Wegener's granulomatosis.

PATHOPHYSIOLOGIC BACKGROUND

Ever since the description of Wegener's granulomatosis in 1931, the search for an infectious agent or precipitant has proven futile.

Evidence is mounting that proteinase 3 antibodies may play a role in Wegener's granulomatosis. Bronchoalveolar lavage studies have identified increased quantities of neutrophils in the airways of patients with active disease. In vitro studies have revealed that ANCA may enhance neutrophil activation, degranulation, and oxidative burst, which may damage endothelial cells. This damage is augmented when the neutrophils are primed by cytokines, which cause proteinase 3 and myeloperoxidase to be expressed on the neutrophil membrane, where reaction to antibody could be facilitated.

Triggering of neutrophilic alveolitis in the upper or lower airway by a variety of airborne stimuli may lead to Wegener's granulomatosis in a predisposed person, ie, one who produces antibodies to proteinase 3. On the other hand, neutrophilic alveolitis in a non-predisposed person, eg, an ANCA-negative person, may be self-limiting or be expressed as a lung disease other than Wegener's granulomatosis.

Until the pathophysiology of Wegener's granulomatosis is more clearly defined, nonspecific immunosuppressive therapies will not likely induce long-term remission without risk of relapse. However, at present they are our best means of producing remission and minimizing morbidity and mortality.

GARY S. HOFFMAN, MD
Department of Rheumatology
The Cleveland Clinic Foundation

SUGGESTED READING

Hoffman GS. Wegener's granulomatosis. Curr Opin Rheumatol 1993; **5:**11–17.

Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: analysis of 158 patients. Ann Intern Med 1992; **116:**488–498.

Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. Treatment of Wegener's granulomatosis with methotrexate. Arthritis Rheum 1992; **35:**1322–1329.

Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. Arthritis Rheum 1993; **36:**365–371.