

Thymoglobulin and Cyclophosphamide as Treatment for Diffuse Cutaneous Systemic Sclerosis

To the Editor:

Systemic sclerosis (SSc) is an autoimmune disease associated with the development of organ fibrosis and vasculopathy¹. Patients with severe, early diffuse cutaneous SSc and significant internal organ involvement have a mortality rate of 50% at 5 years². There are many aspects of SSc that support the hypothesis that it is an autoimmune disease and might respond to immunosuppressive therapy^{3,4}.

Immunosuppressive agents like cyclophosphamide have been investigated as treatment for SSc. Cyclophosphamide can affect immune function by decreasing circulating B and T cells⁵. A retrospective, open, controlled study of 103 SSc patients with multiple cycles suggested improved survival⁶.

To date, the immunomodulatory effect of thymoglobulin is not fully understood but includes increased T cell clearance from blood, modulation of T cell activation, elimination of cytotoxic T cells, and increased T regulatory cells. In a pilot study, thymoglobulin was studied as single-agent therapy⁷. Matteson, *et al*⁸ treated 10 patients with Atgam[®] (antithymocyte globulin) alone, at total dose of 10 mg/kg on 5 consecutive days; 2 patients had improvement.

Our center initiated trials in high-dose autologous stem-cell transplant (ASCT) immunosuppressive therapy as treatment for SSc⁹. Durable responses have been seen. However, some patients had too many comorbidities or the disease had progressed to the point that they were no longer reasonable candidates for ASCT. We wished to try a less intensive immunosuppressive approach in these patients. At the time of initiation of this study, only very limited data existed on treating patients with intermediate doses of cyclophosphamide plus thymoglobulin. We describe the outcome of 4 patients treated with the combination.

Patients were treated with cyclophosphamide 2.5 g/m² intravenously (IV) on Day 1 with mesna IV (total 2.5 g/m², divided in 3 doses). IV hydration was started 4 hours prior to cyclophosphamide (at 2–3 cc/kg/h) and continued throughout the cyclophosphamide infusion and for 24 hours thereafter. Thymoglobulin at 0.5 mg/kg IV (based on adjusted ideal body weight) was given on Day 2, 2 mg/kg on Day 3, and 2.5 mg/kg/day on Days 4–6. On the first day, thymoglobulin was infused over 8 hours and on the following days over 6 hours, if tolerated. Thymoglobulin was provided at no charge to the patient by Sangstat (now Genzyme). Prior to each dose of thymoglobulin, premedication with methylprednisone 2 mg/kg IV, Benadryl (diphenhydramine) 25–50 mg IV, and acetaminophen 650 mg po was given. Patients with a history of chronic longterm prednisone use had steroids tapered slowly to prevent clinical manifestations of adrenal insufficiency. If systolic or diastolic blood pressure increased by 10% over baseline, enalapril was started at a dose of 2.5 mg daily and increased as needed. Prophylactic antibiotics were given at absolute neutrophil count < 500 cells/mm³ and for varicella zoster virus. Cytomegalovirus (CMV) antigenemia monitoring was done. Patients (3 men and 1 woman, ages 42–52 yrs) had already received a median of 4 different regimens of therapy (range 1–5) before study treatment and were 26 months from initial diagnosis (range 22–35 mo), and all had already failed disease control with standard cyclophosphamide therapy. Organ systems involved included skin (n = 4) with modified Rodnan skin score (MRSS) of 16, 17, 25, 29; cardiac (n = 3); pulmonary (n = 4; with DLCO 40%, 38%, 31%, and 26%); and gastrointestinal (n = 3).

There were no CMV reactivations. All 3 patients who completed therapy had evidence of coagulase-negative staphylococcal bacteria treated with vancomycin. Nonhematological toxicity included grade 2 coagulopathy (n = 1), hepatic (grade 2, n = 1; grade 3, n = 1), metabolic (grade 2, n = 2), pain (grade 2, n = 1), and cardiac (grade 3, n = 2). One patient died of regimen-related toxicity secondary to anaphylaxis/cardiac pulmonary arrest. Absolute neutrophil count ≥ 500 cells/mm³ was reached on Days 1, 8, and 10. No patient received blood product transfusions. No patient had platelet count < 20,000 cells/mm³; 2 patients never reached < 50,000. Patients were hospitalized 6–10 days.

All 3 patients who completed therapy had improvement in their MRSS by 35%–53%, and improvement in Health Assessment Questionnaire-Disability Index by 50%–92%. Pulmonary function remained stable in one patient and improved in the other 2 (forced vital capacity by 21%–33%, forced expiratory volume-1s by 14%–32%, and DLCO by 29%–31%).

Two patients had initial responses for nearly one to 3 years, but eventually died of cardiac events associated with life-threatening underlying preexisting SSc-cardiac involvement; both had a history of previous episodes of arrhythmias. One patient remains in remission at 69 months, having required no additional therapy.

Although these data are anecdotal, this treatment combination appears encouraging and may signal greater response than monotherapy. This combination of cyclophosphamide and thymoglobulin, however, cannot be considered curative, but it did give some durable responses after one course. Caution should be used in giving this therapy to very ill individuals, as there was one death associated with thymoglobulin. Given the marginal clinical reserve of these patients, there is little ability to compensate in life-threatening situations. This combination may offer an alternative regimen for patients with high-risk SSc with progressive disease, especially those who are not candidates for ASCT.

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