Thymoglobulin and Cyclophosphamide as Treatment for Diffuse Cutaneous Systemic Sclerosis

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Systemic sclerosis (SSc) is an autoimmune disease which is associated with the development of organ fibrosis and vasculopathy (1). Patients with severe, early diffuse cutaneous SSc and significant internal organ involvement have a mortality rate of 50% at five years (2). 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 cells (5). A retrospective, open, controlled study of 103 SSc patients with multiple cycles suggested improved survival (6).

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-cell, and increased T regulatory cells. In a pilot study, thymoglobulin was studied as single agent therapy (7). Matteson et al (8) treated 10 patients with ATGAM alone, at total dose of 10 mg/kg on 5 consecutive days; two patients having improvement.

Our center initiated trials in high dose autologous transplantation immunosuppressive therapy (ASCT) as treatment for SSc (9). There have been durable responses 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. In this letter, we describe the outcome of four patients treated with the combination.

Patients were treated with cyclophosphamide 2.5 g/m^2 IV on day 1 with mesna IV (total 2.5 g/m^2, divided in three doses). IV hydration was started 4 hours prior to cyclophosphamide (at 2-3 cc/kg/hour) 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, it was infused 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 methylpredinisone 2 mg/kg IV, Benadryl 25-50 mg IV, and acetaminophen 650 mg po was given. Patients with a history of chronic long-term 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 (ANC) < 500 cells/mm^3 and for VZV. CMV antigenemia monitoring was done. Patients (3 men and 1 woman, age 42-52 years) had already received a median of 4 different regimens of therapy (range 1-5) before study treatment, were 26 months from initial diagnosis (range 22-35), and all had already failed to control disease with standard cyclophosphamide therapy. Organ systems involved included skin (n=4) with modified Rodman skin score (MRSS) of 16, 17, 25, 29, cardiac (n=3), pulmonary (n=4) (with DLCO 40, 38, 31, 26%) and gastrointestinal (n=3).

There were no CMV reactivations. All three patients who completed therapy had evidence of coagulase-negative staphylococcal bacteria treated with vancomycin. Non-hematological 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), cardiac (grade 3, n=2). One patient died of regimen-related toxicity second to anaphylaxis/cardiac pulmonary arrest. ANC $\geq$ 500 cells/mm^3 was reached on D1, 8, 10. No patients received blood product transfusions. No patients had platelet count < 20,000 cells/mm^3; 2 patients never reached < 50,000. Patients were hospitalized 6-10 days.

All three patients who completed therapy had improvement in their MRSS by 35-53%, and improvement in HAQ-Disability Index by 50-92%. Pulmonary function remained stable in one patient and improved in the other two (FVC by 21-33%, FEV1 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 pre-existing SSc-cardiac involvement; both had a history of previous episodes of arrthymias. One patient remains in remission at 69 months, having required no additional therapy.

Although this data is as yet purely anecdotal, this treatment combination appears encouraging and may signal greater response than monotherapy. This combination of cyclophosphamide and thymoglobulin, though, 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 high-risk SSc patients with progressive disease, especially those who are not candidates for ASCT.

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