Antithymocyte globulin (ATG) has recently been popularized as an effective treatment in myelodysplastic syndrome (MDS). We treated 8 anemic MDS patients (refractory anemia [RA] and refractory anemia with excess blasts [RAEB-1]) with ATG (40 mg/kg/d for 4 days) and prednisone in a phase 2 trial. The study was stopped early according to a preset termination rule because of lack of efficacy. There were no salutary responses. Toxicities included serum sickness (in all patients), transient neutropenia and thrombocytopenia, diarrhea, vomiting, and syncope with a generalized seizure. At least 3 patients had the HLA-DR15 (DR2) allele. We conclude that the risk-benefit ratio of ATG in an unselected population of MDS patients may be unfavorable, and more work is needed to define the subset of patients who will respond to ATG before its widespread use can be recommended.

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**Brief report**

**Antithymocyte globulin has limited efficacy and substantial toxicity in unselected anemic patients with myelodysplastic syndrome**

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**Introduction**

The myelodysplastic syndrome (MDS) includes a heterogeneous group of marrow disorders characterized by ineffective hematopoiesis and a variable risk of leukemic transformation. Because most patients with MDS are diagnosed after the age of 60 years, therapy is often limited to supportive care with transfusions and hematopoietic growth factors. A subset of younger patients may benefit from hematopoietic stem cell transplantation, but new, nontoxic treatments are sorely needed.

Suppression of hematopoiesis by cytotoxic T cells may contribute to anemia in some patients with MDS. MDS can be associated with vasculitides, T-cell large granular lymphocytic disease, and autoimmune conditions, suggesting the presence of immune dysregulation in at least a subset of MDS sufferers and implying that immunomodulation might provide palliative benefit.

Antithymocyte globulin (ATG), derived from immunization of horses or other animals with human thoracic duct lymphocytes, has complex activity within the human hematopoietic milieu. ATG suppresses cytotoxic and potentially inhibitory T lymphocytes, which may indirectly stimulate hematopoiesis via augmentation of hematopoietic growth factor release by T cells and stromal cells, and promotes cellular differentiation.

ATG has long enjoyed a well-established clinical role in the transplantation setting and in the treatment of aplastic anemia. More recently, 34% of patients with MDS have been reported to achieve red cell transfusion independence after 4 days of ATG treatment; platelet responses were observed in 48% of patients with severe thrombocytopenia, and neutrophil responses were observed in 55% of patients. Based on an earlier encouraging report from that cohort, we conducted a nonrandomized, single-institution, single-arm phase 2 trial of ATG in MDS.

**Study design**

Eight anemic (hemoglobin less than 9 g/dL [90 g/L]) MDS patients (5 women; ages 62 to 74 years) with refractory anemia (RA) (2 patients) and refractory anemia with excess blasts (RAEB-1) (6 patients) were recruited from the Mayo Clinic hematology practice between 1998 and 2002. Patient characteristics are given in Table 1. Patients with refractory anemia with ringed sideroblasts (RARS) were excluded because of lack of response to ATG in the study that prompted this trial. Patients with secondary (therapy-related) MDS, poor liver or renal function (bilirubin more than 2 mg/dL [34.2 μM] or creatinine more than 2 mg/dL [176.8 μM]), HIV infection, active nonmalignant malignancy, or poor performance status (Eastern Cooperative Oncology Group [ECOG] 3 or 4) were also excluded. All patients gave informed consent prior to enrollment, and the Mayo Clinic Institutional Review Board approved the study.

ATG (ATGAM; Pharmacia, Peapack, NJ) was administered intravenously at a dose of 40 mg/kg/d for 4 days. Oral prednisone was given at a dose of 1 mg/kg/d and then rapidly tapered unless persistent rash and/or serum sickness prohibited this.

All patients had 10% or fewer marrow blasts at trial enrollment. According to the International Prognostic Scoring System (IPSS), 5 patients fit into the intermediate-1 (INT-1) risk group and 3 were INT-2. The bone marrow was hypocellular in 2 patients (both had normal flow cytometric testing for a paroxysmal nocturnal hemoglobinopathy clone [CD59, CD14, and fluorescently labeled inactive variant of aerolysin (FLAER)], normocellular in 1 patient, and hypercellular in 5 patients. Bone marrow karyotypes are listed in Table 1. Peripheral blood T-cell gene rearrangement studies were done in 7 of 8 patients and failed to demonstrate a clonal T-cell population.

After this study was initiated, reports appeared of an increased frequency of HLA-DR15 (DR2) in MDS patients and positive predictive value of this allele with regard to response to immunosuppressive therapies such as ATG. To study the class II HLA profile of patients in this trial, DNA was extracted from methanol-glacial acetic acid–fixed cells that had been preserved at the time of harvesting.

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Results and discussion

Unfortunately, there were no hematologic responses to ATG and prednisone in the dose and schedule used in this study, and transfusion needs were unaffected. Enrollment of 20 patients was planned, but the study was terminated early due to a predetermined stopping rule.

Systemic toxicity potentially attributable to the drug included classic serum sickness and/or rash in all 8 patients (7 fever, 4 rash, 4 myalgias/arthralgias), diarrhea (2 patients), nausea/vomiting (1 patient), syncope with a generalized tonic-clonic seizure in a patient with no seizure history (1 patient, during the first day of therapy), and reactivation of oral herpes simplex virus (HSV) (1 patient). All toxicities eventually resolved. Transient hematopoietic toxicity was observed but did not lead to any complications. These toxicities included worsening of neutropenia in 1 of 4 already neutropenic patients, new neutropenia in an additional patient, worsening of pre-existing thrombocytopenia in 6 patients, and new, mild thrombocytopenia in the 2 patients who had a normal platelet count at trial enrollment (platelet count of 253 × 10^9/L fell to 60 × 10^9/L, and 412 × 10^9/L fell to 145 × 10^9/L). The nadir platelet count occurred on day 5 of therapy in 6 of 8 patients, and recovery to pretreatment values was rapid.

A sufficient quantity of DNA for HLA typing (range, 47.2 to 70.3 μg) was obtained from 7 of 8 patient samples. In 5 patients, this DNA was of high enough quality to allow successful amplification and HLA class II typing; the other 2 patients are deceased, so additional genetic material is unavailable. In 3 of 5 patients (60%), HLA-DR15 (DR2) was detected; the expected frequency of HLA-DR15 (DR2) in North Americans is 15% to 21%. With 0 hematopoietic responses in 8 patients, the 95% confidence interval for the true response rate to ATG and prednisone in a similar population of MDS patients is 0% to 37%. Although this does not statistically exclude the 34% red cell response rate seen in the study by Molldrem et al, the response rate in this cohort was disappointing.

It is possible that the lack of response occurred by chance alone, but the group enrolled in this study might actually have been expected to have a higher probability of including ATG-responding patients than a more typical consecutive series of MDS patients seen in clinical practice. There were 2 patients in this cohort with a hypocellular marrow (hypocellular MDS may have pathophysiology overlap with aplastic anemia, which often responds to ATG,¹² and 38% of patients in the series reported by Molldrem et al were hypocellular—a more than in most general MDS series), no patients had more than 10% blasts, patients with secondary MDS (which is typically more refractory to treatment than is de novo disease) were excluded, only 2 enrolled patients had an IPSS high-risk karyotype, at least 3 were HLA-DR15 (DR2)-positive, and 6 of 8 patients were thrombocytopenic at trial enrollment (a low platelet count predicted ATG response in the study by Molldrem et al⁸).

Although there may be a subset of MDS patients who will respond to therapy with ATG, we believe this population is not yet clearly defined. HLA-DR15 (DR2) typing alone is not of sufficient predictive value.

In conclusion, in the dose and schedule used in the trial, ATG had no efficacy in a population of patients with intermediate-risk RA and RAEB-1. Given the toxicity observed and the substantial cost of therapy (the direct drug acquisition cost of the 4-day ATG regimen for a typical 70-kg patient is approximately $13,600), future research is needed before this drug might be widely recommended in MDS.

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References


