

Allogeneic Hematopoietic Cell Transplantation for Refractory Myasthenia Gravis

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Objective: To describe a patient with intractable myasthenia gravis (MG) who was treated with a matched sibling peripheral blood stem cell transplantation.

Design: Case report.

Patient: A 17-year-old boy with MG diagnosed at 11 months of age who was previously treated with pyridostigmine, intravenous immunoglobulin, corticosteroids, thymectomies, azathioprine, mycophenolate mofetil, plasmaphereses, rituximab, and high-dose cyclophosphamide.

Results: The patient underwent a reduced-toxicity conditioning with intravenous busulfan, fludarabine, and alemtuzumab, followed by a peripheral blood stem cell infusion from his HLA-matched sibling. Before transplantation, the patient was receiving frequent plasmaphereses, intravenous immunoglobulin, and pyridostigmine. He had ophthalmoplegia, oropharyngeal

and limb muscle involvement, and limited mobility. At 40 months posttransplantation, his oropharyngeal and skeletal muscle weakness has completely resolved, he is not taking any medications for MG, and he is an avid athlete. However, his ophthalmoplegia persists, and his anti-acetylcholine receptor antibody levels remain elevated.

Conclusions: Following allogeneic hematopoietic stem cell transplantation, the presence of anti-acetylcholine receptor antibodies was not sufficient for inducing symptoms of MG. This confirms that additional immune mechanisms are important in pathogenesis of this disease. Allogeneic transplantation may be a therapeutic option for patients with severe, refractory MG. However, little is known about the long-term efficacy of allogeneic transplantation for this disease, and long-term follow-up is warranted.

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MYASTHENIA GRAVIS (MG) is an autoimmune disease caused by failure of neuromuscular transmission because of decreased sensitivity of the postsynaptic membrane to the neurotransmitter acetylcholine. The anti-acetylcholine receptor (AChR) antibody and complement cascade are implicated in the autoimmune attack against the AChR, which leads to a loss of AChRs.^{1,2} Acetylcholinesterase inhibitors are used to diagnose the disorder and treat the symptoms. This therapy is often coupled with immunomodulation to decrease antibody production, target its removal, and/or decrease the inflammatory environment, which contributes to the triggering and maintenance of the anti-AChR autoimmune response. Myasthenia gravis typically presents in adulthood, but children as young as 1 year of age have been diagnosed with the disorder. It is difficult to make a diagnosis of MG in children

younger than 1 year of age, given the overlap with other inherited muscle weakness disorders and the rare presence of demonstrable antibodies in this age group. Most patients' MG is well controlled with acetylcholinesterase inhibitors, but some require additional immunomodulation with treatments like intravenous immunoglobulin, plasmapheresis, corticosteroids, and thymectomy.

High-dose cyclophosphamide has been used in 16 patients with refractory MG.³⁻⁵ High-dose cyclophosphamide is thought to reset the immune system by eliminating mature lymphocytes while leaving hematopoietic precursors intact. Long-term follow-up indicates good initial responses in most patients undergoing this therapy (90%); however, recurrence of disease and requirement for continual immunosuppression occurs in most patients by 5 years posttreatment (80%).³

Observations that allogeneic transplantations performed for hematopoietic disorders resulted in the cure of certain co-

existing autoimmune disorders opened the door for this modality of treatment for selected patients with severe autoimmune disorders who had not responded well to conventional therapy, high-dose immunosuppressive therapy, or autologous transplantation.⁶ To our knowledge, this article describes the first patient with MG to be treated with allogeneic transplantation.

REPORT OF A CASE

The patient is a 17-year-old African American boy who initially presented at 11 months of age with ptosis and difficulties chewing, which progressed to generalized weakness. Repetitive nerve stimulation and an edrophonium test confirmed MG and the patient began taking pyridostigmine. Intravenous immunoglobulin was added to the patient's drug regimen for 6 months, but the benefits only lasted 2 days. He had a partial thymectomy at the age of 2 years and a second, complete thymectomy at the age of 5 years. By the age of 3 years, he had developed ophthalmoplegia, which over time became unresponsive to pyridostigmine. At the age of 6 years, AChR antibodies were detected. At the age of 7 years, he had bilateral upper frontalis sling suspension for ptosis, which was blocking his superior visual fields. Until the age of 11 years, in addition to pyridostigmine, he was treated with corticosteroid medication and a brief course of azathioprine, which was discontinued because of adverse effects. His neurologic condition deteriorated between the ages of 11 and 14 years; during that period, the following treatments were performed: immunosuppression with mycophenolate mofetil (which had to be discontinued owing to mood swings and suicidal thoughts), multiple infusions of intravenous immunoglobulin, multiple plasmaphereses, and 4 weekly doses of rituximab. He had limited benefit from the intravenous immunoglobulin therapy and plasmaphereses and no benefit from rituximab. At the age of 13 years and 10 months, he received a course of high-dose cyclophosphamide (50 mg/kg/d for 4 days) without stem cell rescue. Prior to treatment with high-dose cyclophosphamide, the patient was able to walk only 1 block before getting tired and was using an electric scooter to get to school. He required a soft-food diet. He had ophthalmoplegia, facial diplegia, and difficulty keeping his jaw closed. Skeletal muscle strength was mildly decreased symmetrically.

He tolerated high-dose cyclophosphamide well and his white blood cell count recovered within 2 weeks. He had a good clinical response and became symptom free except for limitations in his eye movements. He stopped taking pyridostigmine for 3 months for the first time in 12 years. However, 4 months following treatment with high-dose cyclophosphamide, his muscle weakness returned, and pyridostigmine treatment and plasmapheresis were reinstated with only minimal benefit. At this point, he was being home-schooled owing to his limited mobility. Sixteen months following cyclophosphamide treatment, after the patient and his family signed a consent form, an allogeneic peripheral blood stem cell transplantation from an HLA-matched sibling was performed on an experimental protocol approved by our

institutional committee on human research. The conditioning regimen consisted of 46 mg of alemtuzumab (total dose) delivered for 3 consecutive days followed by targeted intravenous busulfan (continuous concentration of 600 ng/mL) given in 16 doses for 4 days and 160-mg/m² fludarabine for 4 days. He received 5×10^6 granulocyte colony-stimulating factor–mobilized CD34⁺ peripheral blood cells/kg from his HLA-matched sister. Graft-vs-host disease prophylaxis consisted of 4 doses of methotrexate (days 1, 3, 6, and 11 posttransplantation) and cyclosporine (stopped at 1 year posttransplantation). His absolute neutrophil count was more than 500/ μ L on day 13, and he was transfusion independent by day 9. He was discharged on day 30 after a course complicated by mucositis, which required total parenteral nutrition for 11 days and patient-controlled analgesia with morphine sulfate for 11 days, 1 episode of *Staphylococcus epidermidis* bacteremia, which was treated with intravenous vancomycin, and cytomegalovirus reactivation, which was treated with a 2-week course of ganciclovir. Engraftment studies have repeatedly shown greater than 90% donor chimerism in whole blood, 99% or greater donor cells in CD14/15 and CD19 subsets, and greater than 60% donor cells in the CD3⁺ fraction. The patient achieved T- and B-cell immune reconstitution at 7 months posttransplant. During the next year, he was weaned off of pyridostigmine, developed normal muscle strength, and lost 60 pounds. Results of his most recent examination were remarkable for slow pupillary reaction, right eye amblyopia, and lack of extraocular movements bilaterally with a negative forced duction test. We believe that his ophthalmoplegia is related to permanent destruction of AChR, resulting in functional denervation. His oropharyngeal muscles are normal and his speech is normal. Acetylcholine receptor antibody levels, which in the past have shown poor correlation with his clinical symptoms, remain elevated following transplantation (10.77 nmol/L at the last measurement). At 40 months posttransplantation, he remains free of all treatments for MG, plays basketball, and is completely independent.

COMMENT

Allogeneic hematopoietic stem cell transplantation is the ultimate approach to establishing a new immune system and has been effective in treating autoimmune disorders in humans and animal models. Given that conventional approaches to treatment and high-dose cyclophosphamide failed in our patient and that he had decreased mobility, was taking high doses of pyridostigmine, and was dependent on plasmapheresis, we considered trying a matched/related allogeneic hematopoietic cell transplantation. Allogeneic transplantation has historically been considered a last-resort treatment owing to transplantation-related mortality and the possibility of developing acute and chronic graft-vs-host disease. Chronic graft-vs-host disease can mimic an autoimmune disorder and may require prolonged immunosuppression in some patients. Even MG can develop as a neurologic manifestation of chronic graft-vs-

host disease.⁷ However, with the introduction of reduced toxicity-conditioning regimens, such as the one used in this patient, transplantation-related mortality has significantly decreased. In our recently published experience,⁸ which used matched/related donors for nonmalignant disorders with busulfan/fludarabine- or busulfan/cyclophosphamide-based conditioning regimens, there were no transplantation-related deaths in 14 patients who underwent a matched/related transplantation; only 1 patient with adrenoleukodystrophy died of progressive disease.⁸ Similar results have been obtained by other pediatric transplantation centers, with survival rates in excess of 90% in children with nonmalignant disorders treated with reduced-intensity conditioning regimens and fully matched (related or unrelated) donor transplantations.⁹ Thus, a transplantation with a matched sibling should no longer be considered a last-resort therapy if it may improve symptoms of a disease that would otherwise require life-long treatments. However, many questions related to allogeneic transplantation in autoimmune disorders remain unanswered, including the risk of disease recurrence. There have been several cases reported in which autoimmune disease recurred between 10 months and 5 years after allogeneic transplantation.¹⁰ More experience is required to identify predisposing risk factors and the mechanisms of recurrence. Presently, it is unknown if the degree of donor chimerism plays a role in the risk of disease recurrence. Our patient remains a stable mixed chimera with more than 60% donor T cells and more than 99% donor B cells. If he were to become symptomatic, we would consider giving him donor lymphocyte infusions with the goal of converting his chimerism to full donor. However, while he is asymptomatic, we cannot justify taking the risk of graft-vs-host disease related to donor lymphocyte infusions. In light of the patient's "new" immune system, the presence of anti-AChR antibodies was not sufficient for the manifestation of MG symptoms, confirming that additional immune mechanisms are important in pathogenesis of this disease.^{1,2}

We believe that allogeneic transplantation is a therapeutic option for patients with severe refractory MG who have tried other therapies and whose quality of life is significantly affected by this disease (for example, ventilator-dependent patients or those in a wheelchair) if a suitable donor can be identified. However, little is known

about the long-term efficacy of allogeneic transplantation, warranting that such treatment be done as part of an investigational study that includes long-term follow-up of patients.

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