SHORT REPORT

ABSTRACT: We report a patient with myasthenia gravis (MG) who had marked clinical benefit in response to treatment with mycophenolate mofetil as documented by serial quantitative measures of strength and muscle fatigue. Our patient had experienced either adverse side effects or a suboptimal response to the usual immunosuppressive agents used in MG. Mycophenolate mofetil was used in combination with cyclosporine and prednisone and allowed for significant reductions in dosage of these immunosuppressants. We conclude that mycophenolate mofetil deserves further study as a therapeutic agent in MG. In particular, its role as a steroid-sparing agent and as a drug to be used in combination immunotherapy in more severe or refractory cases of MG should be investigated.

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TREATMENT OF MYASTHENIA GRAVIS WITH MYCOPHENOLATE MOFETIL: A CASE REPORT

MATTHEW N. MERIGGIOLI, MD, and JULIE ROWIN, MD

Rush–Presbyterian–St. Luke's Medical Center, Section of Neuromuscular Disorders, Department of Neurological Sciences, 1725 West Harrison Street, Suite 1106, Chicago, Illinois 60612, USA

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Mycophenolate mofetil (MM) is a potent immunosuppressive agent currently approved for use in the prophylaxis of organ rejection in patients receiving allogeneic organ transplantations. There are several reports of its effectiveness in other autoimmune diseases including lupus nephritis, a disorder commonly resistant to therapy.[6] There is one previous report of successful treatment of a patient with refractory myasthenia gravis (MG) using MM.[4] We report an additional case of a patient with poorly controlled MG in whom treatment with MM resulted in excellent control of myasthenic signs and symptoms as documented by serial quantitative strength testing. In our patient, MM was used in combination with cyclosporine and prednisone and allowed for tapering of these immunosuppressive agents.

CASE REPORT

A 26-year-old woman developed fluctuating ptosis and diplopia in November 1996. She subsequently developed fatigable weakness of both legs as well as difficulty in chewing and swallowing. Clinical examination revealed bilateral ptosis and bilateral weakness of the medial rectus muscles, especially on the left. Voluntary eye closure was complete but easily overcome. Neck flexion and proximal upper and lower extremity strength was graded at 4/5 (MRC scale). Finger extensors were 4–/5. She was diagnosed with MG in January 1997 on the basis of abnormal single-fiber electromyography. Acetylcholine-receptor–binding antibodies were initially normal, but were mildly elevated (1.0 nmol/L [normal = 0.0–0.8]) when assessment was repeated. She underwent transthoracic thymectomy in February 1997, at which time hyperplastic thymic tissue was found. After thymectomy, she was treated with high-dose daily prednisone (1 mg/kg per day) and pyridostigmine (120 mg three times daily).

While on prednisone (60 mg/20 mg on alternate days) during tapering of her steroid dose in July 1997, she experienced an exacerbation of her MG with neck weakness ("trouble holding my neck up"), dysphagia, and leg weakness. Clinical examination showed increased weakness of neck flexion and hip flexion, which were both little better than antigravity. Finger extensors were 4–/5. The remainder of her examination was unchanged. Azathioprine was added (2 mg/kg per day) and her pyridostigmine dose was increased but her weakness persisted and she required hospital admission and five plasma-exchange treatments. Her azathioprine dose was in-

Abbreviations: MG, myathenia gravis; MM, mycophenolate mofetil; MRC, Medical Research Council; QMGS, quantitative myasthenia gravis score

Key words: myasthenia gravis; mycophenolate mofetil

Correspondence to: M. N. Meriggioli; e-mail: mmeriggi@rush.edu

creased to 3 mg/kg per day and she was again started on high-dose daily prednisone (60 mg/day). With the increase in azathioprine dose, her prednisone was gradually tapered to 50 mg on alternate days, but in September 1998 she developed liver toxicity necessitating discontinuance of the azathioprine. She was started on cyclosporine (5 mg/kg per day), but she remained clinically symptomatic 3 months later despite adequate cyclosporine serum levels and moderate-dose (50 mg) alternate-day prednisone.

She was referred for a second opinion regarding other options for treatment of her MG. Examination revealed bilateral ptosis at rest which worsened with sustained upgaze. Extraocular muscle testing showed bilateral medial rectus weakness. Facial muscles, neck flexors, and proximal extremity muscles were graded at 4/5 (MRC scale). She was unable to hold her tongue in her cheek. Quantitative myasthenia gravis score[1] (QMGS) was 18. Forced vital capacity was 71% of predicted. Her fatigable weakness was functionally limiting to the point that she obtained a leave of absence from her job. She complained of severe fatigue after only 5 min of household chores.

After 6 months on cyclosporine, her renal function deteriorated and the cyclosporine dose was adjusted to 3.4 mg/kg per day on 8 January 1999. Her clinical examination was unchanged as reflected by a stable QMGS of 18. Mycophenolate mofetil (MM) was added at a dose of 1 g twice daily on 3 February 1999, at a time when the clinical examination and QMGS were unchanged. Three weeks later, the patient noted a marked improvement in her symptoms of fatigable weakness. Clinical evaluation 1 month after starting MM revealed objective improvement. She had mild right ptosis and bilateral medial rectus weakness. Facial strength, tongue protrusion, and palatal elevation were all normal. Strength was full in the upper extremities with the exception of the left finger extensors (4/5). Lower extremity strength was normal. Serial QMG scores have shown steady improvement in clinical status, as illustrated in Table 1.

On her most recent examination (January 2000), she had only subjective diplopia and a minimal right ptosis with prolonged upgaze. Bulbar and extremity strength were normal. In addition, the patient's cyclosporine and prednisone doses had been reduced to 150 mg/day and 15 mg on alternate days, respectively, without exacerbation of symptoms. Her pyridostigmine requirement had decreased to 90 mg/day. Her forced vital capacity had improved to 86% of predicted. Renal function had returned to normal. She had returned to full-time work and was able to perform vigorous aerobic exercise four times per week. We have monitored her serum chemistries, complete blood counts, electrocardiograms, and urinalyses on a monthly basis. She has had two urinary tract infections, which were treated with antibiotics, but has experienced no other significant side effects.

DISCUSSION

Mycophenolate mofetil is a novel immunosuppressive agent that inhibits the de novo pathway of guanosine nucleotide synthesis required for B- and T-lymphocyte proliferation.[2,10] This mechanism of action makes it a particularly promising agent in MG. Although the production of acetylcholine-receptor–binding antibodies in MG is a B-cell function, there is extensive evidence that T cells play a significant role in the autoantibody response.[5,7,11] Thus, by inhibiting the proliferation of B and T cells, MM may inhibit both acetylcholine-receptor–specific T-cell proliferation and the production of acetylcholine-receptor autoantibodies.

Table 1. Summary of clinical improvement in a patient with MG treated with mycophenolate mofetil.

	Date									
	7 Dec 98	8 Jan 99	3 Feb 99*	25 Feb 99	8 Mar 99	25 Mar 99	29 Apr 99	17 Jun 99	21 Oct 99	6 Jan 00
QMGS	18	18	18	18	15	9	11	8	ND	10
MMT	20	20	20	20	9	7	6	6	6	6
Pyridostigmine dose	360	360	360	360	270	180	180	180	180	90
Prednisone dose†	40	40	40	40	40	30	25	20	20	15
Cyclosporine dose	300	200	175	150	150	150	150	150	150	150

MMT, manual muscle testing[3]; QMGS = quantified myasthenia gravis score; ND, not done. Medication doses (mg) represent total daily dose. The MMT score is a composite score derived from the testing of the following muscle groups: eyelid elevators; extraocular muscles; facial muscles; tongue muscles; masticatory muscles; neck flexors/extensors; shoulder abductors; forearm flexors/extensors; wrist extensors; finger flexors; hip flexors; knee extensors and flexors; ankle dorsiflexors; and plantar flexors. Each muscle group is scored as: 0 = normal; 1 = 25% weak/mild impairment; 2 = 50% weak; 3 = 75% weak/severe impairment; 4 = paralyzed.

**Mycophenolate mofetil started.*

†Alternate-day treatment.

We used the quantitative myasthenia gravis score as modified by Barohn et al.[1] to follow our patient's response to therapy. In this scoring system, 13 parameters are measured and scored on a 0–3-point scale (total score range 0–39). Our patient's QMGS improved from 18 to 10. Barohn et al.[1] determined a change of greater than 2.6 units to be of clinical significance. Improvement in the manual muscle testing score and a lessening in the patient's steroid and pyridostigmine requirements are further indicators of clinical benefit.

Treatment with MM resulted in excellent control of myasthenic signs and symptoms and sustained objective improvement on quantitative strength and endurance testing in this patient. The onset of improvement was rapid, occurring approximately 3 weeks after treatment initiation. The addition of MM allowed tapering of the corticosteroid and cyclosporine doses without exacerbation of myasthenic symptoms. The most frequent adverse reactions associated with the use of MM include diarrhea, leukopenia, sepsis, and vomiting.[10] As with other immunosuppressants, there is a higher frequency of certain types of infections.[8] The side-effect profile of MM compares favorably to that of azathioprine and cyclosporine. No severe adverse effects have been seen in our patient to date.

Therapeutic options for immunosuppressive treatment of MG are currently limited.[9] MM may offer an alternative agent for use as a steroid-sparing agent. In addition, MM could also be used in combination with other immunosuppressant agents (i.e., cyclosporine), thus lowering the dose needed for optimal clinical effect and improving the tolerability of these agents. Our case report highlights the need for a controlled clinical trial to examine the role of MM in the treatment of MG.

REFERENCES

1. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. Ann NY Acad Sci 1998;841:769–772.
2. Behrend M. A review of clinical experience with the novel immunosuppressive drug mycophenolate mofetil in renal transplantation. Clin Nephrol 1996;45:336–341.
3. Dyck PJ. Quantitating severity of neuropathy. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Philadelphia: WB Saunders; 1993. p 686–697.
4. Hauser RA, Malek, AR, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. Neurology 1998;51:912–913.
5. Hohlfeld R, Toyka KV, Michels M, Heininger K, Conti-Tronconi B, Tzartos SJ. Acetylcholine receptor-specific human T-lymphocyte lines. Ann NY Acad Sci 1987;505:27–38.
6. Jayne D. Non-transplant uses of mycophenolate mofetil. Curr Opin Nephrol Hypertens 1999;8:563–567.
7. Lennon VA, Lindstrom JM, Seybold ME. Experimental autoimmune myasthenia gravis: cellular and humoral immune responses. Ann NY Acad Sci 1976;274:283–299.
8. Moreso F, Seron D, Morales JM, Cruzado JM, Gil-Vernet S, Perez JL, Fulladosa X, Andres A, Grinyo JM. Incidence of leukopenia and cytomegalovirus disease in kidney transplants treated with mycophenolate mofetil combined with low cyclosporine and steroid doses. Clin Transplant 1998;12:198–205.
9. Osterman PO. Current treatment of myasthenia gravis. Progr Brain Res 1990;84:151–161.
10. Simmons WD, Rayhill SC, Sollinger HW. Preliminary risk-benefit assessment of mycophenolate mofetil in transplant rejection. Drug Safety 1997;17:75–92.
11. Yi Q, Pirskanen R, Lefvert AK. Human muscle acetylcholine receptor reactive T and B lymphocytes in the peripheral blood in patients with myasthenia gravis. J Neuroimmunol 1993;42:215–222.