Mycophenolate mofetil for myasthenia gravis: An open-label pilot study

Article abstract—In an open-label study, 12 patients with refractory MG or who were taking only corticosteroids and required additional immunosuppression received mycophenolate mofetil 1 g twice daily for 6 months. A reduction of three points in a quantified MG score and two points in a manual muscle test or a reduction of 50% in corticosteroid dose defined efficacy. Eight patients improved, beginning after 2 weeks to 2 months. No major side effects were observed.

NEUROLOGY 2001;56:97–99

E. Ciafaloni, MD; J.M. Massey, MD; B. Tucker–Lipscomb, RN, BSN, APN; and D.B. Sanders, MD

Mycophenolate mofetil (MM) (CellCept, Roche Laboratories, Nutley, NJ) is a novel and potent immunosuppressive agent. It blocks purine synthesis in activated T and B lymphocytes and selectively inhibits their proliferation while leaving other cell lines intact.[1] It has been proven effective in preventing organ rejection in renal transplant patients when used with corticosteroids and cyclosporine.[2,3] It has a strong safety profile and no major organ toxicity or mutagenic effect.[2-5] Immunosuppressive therapy is effective in MG, and the use of corticosteroids, azathioprine, and cyclosporine have changed the prognosis of this autoimmune disease. Unfortunately, these agents all carry serious side effects, and some patients do not tolerate them or respond adequately to them. The possibility of a new effective and safe immunosuppressive agent to add to our MG treatment armamentarium is very attractive. The use of MM in MG has not been studied, but successful treatment of one patient with severe, refractory MG suggested its potential role in this disease.[6]

Patients and methods. This open-label pilot trial investigated the short-term efficacy and safety of MM in patients with MG. Patients between the ages of 18 and 80 years, with acquired MG diagnosed according to accepted clinical, electrophysiologic, and pharmacologic criteria[7] who had or had not undergone thymectomy and who had or did not have elevated acetylcholine receptor antibodies (AChR Ab) were eligible for the study. Two groups of patients were studied: 1) patients with refractory MG defined by a quantified MG (QMG)[8] score of at least 10 and a manual muscle test (MMT) score (figure) of at least 5, despite treatment with corticosteroids and azathioprine for at least 2 years or cyclosporine for at least 1 year; and 2) patients taking corticosteroids as sole therapy for at least 8 months and requiring additional immunosuppression to heighten the clinical improvement or to reduce the corticosteroid side effects. No plasmapheresis, IV immunoglobulin treatment, or change in medication dose was permitted for 3 months before enrollment. Anticholinesterase medications were continued, and examinations were performed 4 hours after the most recent dose. MM was administered in an oral dose of 1 g every 12 hours for 6 months, and clinic visits were performed every 2 months. The primary measure of efficacy was a reduction of at least 3 points in the QMG and at least 2 points in the MMT, or a reduction of at least 50% in corticosteroid dose for at least 3 months without worsening of the QMG and MMT scores. An activities of daily living (ADL)[9] questionnaire was also administered by phone every week for the first month and at clinic visits every 2 months thereafter, and was considered a secondary test of efficacy. The QMG and ADL scores have previously been validated in assessing MG.[8,9] MMT is a physician-applied scoring system of strength in muscles that are typically affected in MG (see the figure). All QMG tests were performed by the same nurse (B.T.L.) and MMT by one of the two senior investigators (J.M.M., D.B.S.). AChR Ab were measured at baseline and at the end of 6 months at the Mayo Medical Laboratory, Rochester, MN. Single-fiber electromyography (EMG) of the extensor digitorum communis or frontalis muscle was performed in the Duke University Medical Center EMG laboratory by the same examiner (J.M.M. or D.B.S.) at baseline and at the end of 6 months. Safety was assessed by physical and laboratory examinations, evaluation of vital signs, and monitoring of adverse reactions.

Results. Twelve patients entered the study (table 1) (seven men, five women; mean age, 56 years). All patients completed the study. Eleven patients had had thymectomy 7 months to 42 years earlier (mean, 16 years). The duration of MG varied from 7 months to 47 years (mean, 19 years). Seven patients met the criteria for group 1 (Patients 1 through 7; see table 1) and five for group 2 (Patients 8 through 12; see table 1). Eight patients (67%) improved, six by QMG and MMT scores (Patients 2, 3, 5, 6, 8, and 11; table 2), and two by reduction of corticosteroid dose (Patients 9 and 10; see table 2). These two patients also had some improvement of QMG and MMT scores. One patient worsened (Patient 12; see table 2), two improved only by QMG score (6 and 5 points), and one only by MMT score (10 points), and therefore were considered un-

From the Division of Neurology, Duke University Medical Center, Durham, NC.

Supported by a grant from Roche Pharmaceuticals, Inc., Nutley, NJ.

Received May 25, 2000. Accepted in final form August 24, 2000.

Address correspondence and reprint requests to Dr. Emma Ciafaloni, Duke University Medical Center, Division of Neurology, DUMC 3403, Durham, NC 27710; e-mail: ciafa001@mc.duke.edu

See also page 94

		Right	Left	SUM
1.				
	Lid ptosis	_____	_____	_____
	Diplopia	_____	_____	_____
Cranial	Eye closure	-	-	_____
Nerves	Cheek puff	-	-	_____
	Tongue protrusion	-	-	_____
	Jaw closure	-	-	_____
	Cranial Muscle Score		_____	
2.				
	Neck flexion	-	-	_____
	Neck extension	-	-	_____
	Shoulder abduction	_____	_____	_____
	Elbow flexion	_____	_____	_____
Limb	Elbow extension	_____	_____	_____
Muscles	Wrist extension	_____	_____	_____
	Grip	_____	_____	_____
	Hip flexion	_____	_____	_____
	Knee extension	_____	_____	_____
	Knee flexion	_____	_____	_____
	Ankle dorsiflexion	_____	_____	_____
	Ankle plantar flexion	_____	_____	_____
	Limb muscle score		_____	
			TOTAL	_____

Figure. Manual muscle testing. Score each function as: 0 = normal; 1 = 25% weak/mild impairment; 2 = 50% weak/moderate impairment; 3 = 75% weak/severe impairment; 4 = paralyzed/unable to do.

changed. Wilcoxon signed-rank sum analysis of all study patients showed improvement in MMT, QMG, and ADL scores at 6 months compared with baseline ($p < 0.023$, 0.001, and 0.004). Improvement in the ADL scores was seen as early as 2 weeks after MM treatment was begun, and improvement was seen in all responders at the first follow-up visit (2 months). In eight of 10 patients, the corticosteroid dose was reduced. Mestinon was discontinued in two and decreased in four of eight patients. Cyclosporine was decreased by 50% in two of three patients. Wilcoxon signed-rank sum analysis of AchR-binding Ab levels showed a reduction at 6 months compared with

Table 1 *Clinical characteristics of study patients*

Patient no./sex	Age at study, y	Age at MG onset, y	Thymus histology	Medications	AChR Ab
Group 1					
1/M	69	29	Thymoma	Aza/pred/pyr	+
2/M	64	57	Hyperplasia	Cya/pred/pyr	+
3/F	52	36	Hyperplasia	Cya/pred/pyr	+
4/M	44	25	Hyperplasia	Cya/pyr	+
5/M	65	56	Atrophic	Aza/pred	+
6/F	65	57	Thymoma	Aza/pred/pyr	+
7/F	38	36	Hyperplasia	Aza	−
Group 2					
8/M	48	25	Hyperplasia	Pred/pyr	−
9/F	52	10	Atrophic	Pred	−
10/M	74	63	Not done	Pred	+
11/M	57	10	Atrophic	Pred/pyr	+
12/F	43	42	Hyperplasia	Pred/pyr	−

AChR-Ab = acetylcholine receptor antibodies; Aza = azathioprine; pred = prednisone; pyr = pyridostigmine.

Table 2 *Manual muscle testing (MMT), quantitative MG (QMG), and activities of daily living (ADL) scores at baseline and at 6 months*

	MMT score		QMG score		ADL score	
Patient no.	Baseline	6 mo	Baseline	6 mo	Baseline	6 mo
Group 1						
1	18	8	10	8	6	5
2	13	4	10	5	6	4
3	13	1	10	5	3	0
4	16	22	16	10	6	5
5	7	3	10	4	6	3
6	14	9	10	5	7	2
7	17	17	17	12	12	9
Group 2						
8	8	4	13	9	13	9
9	8	7	12	6	8	1
10	12	4	8	6	0	2
11	36	19	21	17	10	7
12	6	8	5	6	3	2

baseline ($p < 0.016$). The mean group jitter value was unchanged (82.2 μs at baseline and 82.0 μs at 6 months), and the mean group percentage of potential pairs with blocking was insignificantly decreased (28% at baseline and 25% at 6 months). No major side effects were observed. No diarrhea was reported. Two patients reported mild hand tremors that resolved after the first week. The hemoglobin value was decreased in two patients (2.6 and 1.9 g/dL). One of these patients was found to have iron deficiency as the cause of her anemia. Seven of the improved patients elected to continue taking MM at the end of the study, and one did not because of financial reasons.

Discussion. In this open-label pilot study, MM appeared to be effective as adjunctive therapy in the treatment of refractory and steroid-dependent MG. All seven patients with refractory MG had reached a plateau of clinical improvement after receiving steroids and azathioprine or cyclosporine for an adequate period, but still had significant weakness and subjective MG symptoms before MM treatment was begun. They were also still experiencing exacerbations and had previously been unable to reduce their medications without worsening. Five of them experienced significant improvement and were able to decrease their steroid dose while taking MM; two decreased their cyclosporine dose by 50%.

Our data also suggest a steroid-sparing effect of MM, because eight of 11 patients taking prednisone at the time MM treatment was begun were able to decrease the prednisone dose without worsening.

In all eight patients who improved, symptomatic improvement started early, between 2 weeks and 2 months, and persisted throughout the 6 months. There were no major side effects observed, and all patients were able to tolerate the drug. The safe side effect profile and the rapid onset of therapeutic effect, if confirmed in the future, would make MM a very attractive alternative to other currently available immunosuppressants for MG. All our patients were receiving other forms of immunosuppression at the time MM treatment was begun; therefore, the potential role of MM as sole therapy remains to be investigated. Larger, prospective, randomized, controlled trials are needed to confirm our results and to assess long-term efficacy and safety of MM in MG.

References

1. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). Clin Transplant 1996;10:77–84.
2. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. Lancet 1995;345:1321–1325.
3. Sollinger HW for the U.S. Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995;60:225–232.
4. Behrend M. A review of clinical experience with the novel immunosuppressive drug mycophenolate mofetil in renal transplantation. Clin Nephrol 1996;45:336–341.
5. Allison AC, Eugui EM. Preferential suppression of lymphocyte proliferation by mycophenolic acid and predicted long-term effects of mycophenolate mofetil in transplantation. Transplant Proc 1994;26:3205–3210.
6. Hauser RA, Malek AR, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. Neurology 1998;51:912–913.
7. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Inc. Myasthenia gravis: recommendations for clinical research standards. Neurology 2000;55:16–23.
8. Barohn RJ, McIntire D, Herbelin L, et al. Reliability testing of the quantitative myasthenia gravis score. Ann NY Acad Sci 1998;841:769–772.
9. Wolfe GI, Herbelin LR, Nations SP, et al. Myasthenia gravis activities of daily living profile. Neurology 1999;52:1487–1489.