Mycophenolate mofetil: A safe and promising immunosuppressant in neuromuscular diseases

Article abstract—The authors report the use mycophenolate mofetil (MM) in the treatment of neuromuscular diseases. Thirty-eight patients (32 with MG, three with inflammatory myopathy, and three with chronic acquired demyelinating neuropathy) were treated with MM for an average duration of 12 months. All patients tolerated MM without major side effects. Twenty-four patients improved either in their functional status or in their ability to reduce corticosteroid dose. Mean time to improvement was 5 months.

NEUROLOGY 2001;56:94–96

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Immune-mediated neuromuscular diseases are currently treated with several immunosuppressive agents including corticosteroids, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, and interferon.[1-3] In spite of this variety of choices, the risk/benefit ratios of these medications are variable in individual patients, and more favorable alternatives are needed. Mycophenolate mofetil (MM) inhibits proliferation of T and B lymphocytes selectively by blocking purine synthesis only in lymphocytes.[4] It has been successfully used for treatment of allogeneic transplants[5] and other immune-mediated diseases.[6-8] Side effects are modest and include diarrhea, abdominal pain, nausea, peripheral edema, drug-induced fever, and leukopenia. We assessed MM in the treatment of neuromuscular diseases.

Patients and methods. Thirty-eight patients being treated with MM were retrospectively analyzed. The demographics of the patients and details of their treatments are outlined in table 1. The indications for starting treatment with MM in these patients were to serve either as an adjunct in the treatment of the autoimmune disease (35) or as a steroid-sparing agent (26). Thirty-five patients were receiving other immunomodulating agents, including corticosteroids (32), azathioprine (8), cyclosporine-A (4), methotrexate (3), and plasma exchange or IV immunoglobulin (10). Fifteen myasthenic patients had undergone thymectomy. Four patients received only MM. Patients received MM 1 g twice daily by mouth for an average of 12 months (range, 3 to 36 months). Improvement was defined as either $\geq$1 grade improvement in functional status[9] as defined in table 2, or a reduction in the required dose of steroids by $\geq$10 mg every other day. Improvement by $\geq$1 grade in any of the individual parameters of the scale listed in the columns in table 2 was considered to be improvement in the functional status. If patients were taking an alternative formulation of steroids (prednisolone or deflazacort) or daily dose treatments, their equivalent every other day prednisone dose was calculated.

For nonmyasthenic patients, the functional status was determined using the functional impairment (activities of daily living [ADL]) or muscle strength (Medical Research Council [MRC] grades 0 to 5) columns (see table 2). The MRC score of the weakest muscle was used as an index for assessing the response to MM. Monthly monitoring of complete blood count was performed on all patients. Patients were regularly followed up at intervals varying from 1 to 3 months.

Results. Overall, 24 (63%) patients benefited from the treatment (22 with MG, one with CIDP, and one with IM), measured either as improved functional status (20) or as a corticosteroid-sparing effect (17) (see table 1). The mean time to improvement was 5 months (range 2 to 12 months). Patients with MG comprised the largest group (32), and 69% of these patients improved while taking MM. This included three patients who were taking MM as their only immunosuppressive medication. The addition of MM allowed a reduction in the steroid dose requirement in 50% and improvement in the functional grade in 59% of the patients with MG (figure, A and B). Ten patients (31%) who have been taking MM for an average of 8 months (3 to 17 months range) have failed to show any benefit. These patients continue taking MM and are being followed up to evaluate a possible delayed response. Myasthenic patients who benefited from the treatment had been taking MM for a longer period of time (mean 13 versus 8 months) than those who did not benefit; and the patients with a more favorable response had a diagnosis of MG established for a shorter time (mean 7.5 versus 14 years) than the patients who failed to show benefit with MM.

Among the three patients with inflammatory myopathy (IM), one patient, who had polymyositis, improved. The other two patients with IM had inclusion body myositis, and were unresponsive to other immunosuppressive agents and did not improve. One of three patients with

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Received May 30, 2000. Accepted in final form August 15, 2000.

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Table 1 *Demographics and details of 38 patients treated with mycophenolate mofetil*

Characteristics	MG (n = 32)	Inflammatory myopathy (n = 3)	CIDP (n = 3)
Mean age, y (range)	52 (21–83)	63 (44–74)	62 (60–64)
Sex, M:F	13:19	2:1	1:2
Patients with other treatments, n	28	3	3
Indication for treatment, n			
Primary	29	3	3
Steroid-sparing	25	—	1
Duration of treatment, mo, mean (range)	11 (3–36)	19 (16–22)	13 (6–22)
Time to improvement, mo, mean (range)	4.8 (2–12)	—	4
Strength improvement, n (%)	19 (59)	1 (33)	1 (33)
Steroid-sparing, n (%)	16 (50)	0 (0)	1 (33)

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy.

chronic inflammatory demyelinating polyradiculoneuropathy has also shown improvement in strength as well as a reduced requirement of methylprednisolone dosage.

No patient had major side effects. Three patients had mild gastrointestinal discomfort, one with diarrhea. In one patient, the dose of MM had to be reduced to 1 gram per day (500 mg twice daily) because of gastrointestinal side effects. One patient had depressed mood, which she attributed to MM. Four patients misunderstood the dose of MM and mistakenly took only 500 mg twice daily for 2 months before the dose was corrected to 1 gram twice daily. All patients had monthly monitoring of complete blood count; none developed leukopenia. No patient discontinued the medication because of side effects. Although not a side effect, there was considerable concern by several patients regarding the cost of the medication.

Discussion. MM is the 2-morpholinoethyl ester of mycophenolic acid, an agent that inhibits the proliferation of B and T lymphocytes through noncompetitive, reversible inhibition of inosine monophosphate dehydrogenase, a key enzyme in the de novo synthetic pathway of guanine nucleotides.[4] There are two pathways for purine biosynthesis—the de novo pathway and the salvage pathway. Lymphocytes only use the de novo pathway, whereas other cells use both pathways. The de novo pathway is competitively regulated. It is down regulated by adenosine nucleotides, and up regulated by guanosine nucleotides. Mycophenolic acid blocks inosine monophosphate dehydrogenase, an enzyme that is responsible for conversion of inosine monophosphate to guanosine monophosphate; hence, synthesis of guanosine is blocked and synthesis of adenosine is enhanced, both resulting in inhibition of purine synthesis only in the lymphocytes.[4]

The safety and efficacy of MM in combination with corticosteroids and cyclosporine-A for the prevention of renal rejection has been shown in randomized, double-blind, multicenter trials.[5] It has also been reported to be of benefit in other immune-mediated diseases such as rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosus.[6-8] The principal adverse reactions associated with MM include diarrhea, leukopenia, sepsis, vomiting, and a higher frequency of certain types of infections. It is thought to entail a lower risk for late malignancies than

Table 2 *Classification for functional status of MG*

Functional grade	Functional impairment (ADL)	Ocular (ptosis/ diplopia)	Facial muscle weakness	Bulbar muscle weakness	Arm abduction time	Muscle strength (0–5)	FVC, %
0	None	Normal	Normal	Normal	>3 min	5	>80
1	Minimal; independent ADL	Intermittent	Mild	Normal	>3 min	5−	>80
2	Mild; independent ADL	Constant	Significant	Mild, intermittent	>3 min	4+	>80
3	Moderate; independent ADL	Constant	Significant	Significant, continuous	<3 min & >90 s	4+	<80 & >50
4	Moderately severe; assisted ADL	Constant	Significant	Severe, not debilitating	<90 s & >30 s	4−	<80 & >50
5	Severe; dependent ADL, crisis	Constant	Significant	Severe, debilitating	≤30 s	≤3	≤50

ADL = activities of daily living; FVC = forced vital capacity.

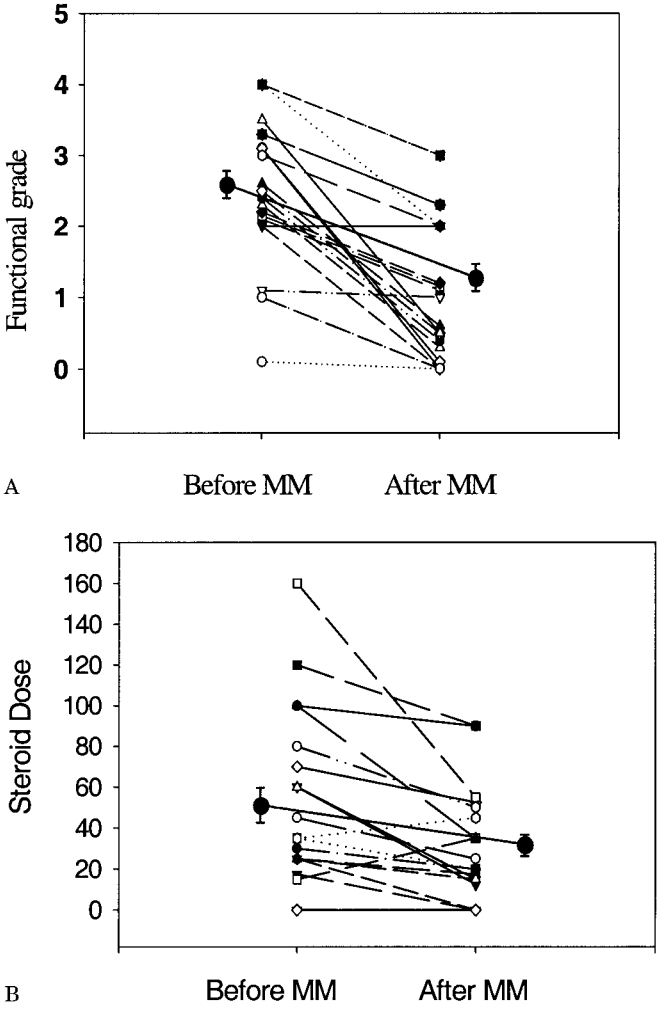

Figure. (A) Functional grade before and after mycophenolate mofetil (MM) treatment in the 32 patients with MG. The solid line in the middle (connecting two solid circles) is the mean functional grade before (2.2) and after MM (1.2). The change was significant ($p < 0.001$*). (B) The requirement of corticosteroids before and after MM treatment in the 32 patients with MG. The mean dose of steroids (shown by the solid line connected two solid circles) before was 50 mg and after treatment was 27 mg every other day. These changes were also significant (*$p = 0.001$*) .*

other drugs such as azathioprine and cyclophosphamide, which can be mutagenic or can decrease T-cell surveillance over lymphomas related to Epstein–Barr virus.[4]

Our study of MM use in patients with different neuromuscular diseases showed that the drug is safe and well tolerated. Over two-thirds of the patients with MG showed improvement in functional status or were able to lower the dosage of corticosteroids. This included some patients who were taking MM as the only treatment, and others who had remained refractory to conventional agents. Patients who did not respond in our study were treated on average for a shorter time period and had longer duration of disease than the responders. Although the drug was well tolerated in other neuromuscular diseases as well, we are not able to comment on its effectiveness in these conditions in view of the small numbers and the otherwise refractory patients included in this study.

There has been only one previous report of the use of MM in MG, in a 26-year-old woman who had MG for 12 years and improved rapidly while taking MM.[10] In comparison to this case report, the onset of action in our patients is rather delayed. In an established autoimmune disease such as MG, treatment with a drug that is not cytocidal would not be expected to produce rapid benefit.[6-8] Because preexisting autosensitized lymphocytes are not eliminated by MM, improvement depends upon these lymphocytes dying, which occurs gradually.[4]

Immunomodulatory treatment for MG entails evaluating several factors, including onset of action of the available agents, their efficacy, and their side effects.[1] Although MM appears to have a long delay in its onset of action, it is efficacious and has the advantage over corticosteroids, azathioprine, and cyclosporine-A in that the undesirable side effects of weight gain, cushingoid features, hyperglycemia, bone loss, increased irritability, insomnia, cataracts, liver toxicity, idiosyncratic reactions, nephrotoxicity, and hypertension are absent.

Our study is limited by the fact that most patients were on concomitant medications and the study was retrospective. However, given the relative paucity of adverse effects, and this preliminary open-label data, other confirmatory studies and randomized controlled trials are warranted.

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