# Experience with Mycophenolate Mofetil among Jordanian Patients with Myasthenia Gravis

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## ABSTRACT

**Objectives:** To investigate the short- term efficacy and safety of Mycophenolate Mofetil treatment among Jordanian patients with refractory myasthenia gravis.

**Methods:** This study was conducted in King Hussein Medical Centre, Prince Rashed Hospital and Prince Hashem Hospital between January 2007 and January 2009. The study included 18 patients with poorly controlled generalized moderate to severe myasthenia gravis despite treatment with Prednisolone alone or with Azathioprine. All patients received Mycophenolate Mofetil 1.5-2g daily for 9 months. The primary efficacy measure was a reduction of three points in the manual muscle test score and/or a reduction of 50% in corticosteroid dose.

**Results:** All patients completed the study. Twelve patients improved, beginning after 3-5 months. The maximum benefit was after 7 months of treatment. No serious adverse effects were observed.

**Conclusions:** Mycophenolate mofetil is a promising alternative to other currently available immunosuppressive drugs for the treatment of refractory myasthenia gravis.

**Key words:** Myasthenia gravis, Mycophenolate mofetil, Refractory

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## Introduction

Myasthenia gravis (MG) is an uncommon autoimmune condition, in which antibodies against the postsynaptic acetylcholine receptors (AChR) or related structures result in failure of neuromuscular transmission. Current estimates of prevalence in the United States are about 20 per 100.000.[1]

Therapy for myasthenia gravis includes symptomatic treatment with cholinesterase inhibitors, thymectomy for selected patients, immunomodulation with intravenous immunoglobulin (IVIg) and plasma exchange, and immunosuppressive therapies.

Oral immunosuppressants including corticosteroids, azathioprine and cyclosporine have been commonly used in MG. However, variable efficacy, patient tolerance and adverse side effects limit their effectiveness. Thus, more favorable alternatives are needed. Mycophenolate mofetil (MMF) has been successfully used for treating patients with allogenic transplants and immune mediated diseases.[2] The first report suggesting efficacy of MMF in myasthenia gravis appeared in 1998.[3] This was followed by uncontrolled case series,[4-6] a small double-blind controlled trial[7] and a Cochrane review.[8] These studies reported benefit in the majority of MG patients treated with MMF, including those with refractory disease and popularized use of the drug. However, two recently concluded randomized, controlled trials- the Muscle Study Group (MSG) and the Aspreva trials - did not demonstrate additional benefit of MMF over prednisolone as initial immunosuppression in generalized MG or a steroid-sparing effect over a period of 9 months.[9,10] On the other hand, a

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**Table I.** MGFA clinical classification

| | |
|---|---|
| MGFA Class I: | ocular MG |
| MGFA Class IIa: | mild generalized MG, predominant limb or axial muscles involvement |
| MGFAClass IIb: | mild generalized MG, predominant bulbar or respiratory muscles involvement |
| MGFA Class IIIa: | moderate generalized MG, predominant limb or axial muscles involvement |
| MGFA Class IIIb: | moderate generalized MG, predominant bulbar or respiratory muscles involvement |
| MGFA Class IVa: | severe generalized MG, predominant limb or axial muscles involvement |
| MGFA Class IVb: | severe generalized MG, predominant bulbar or respiratory muscles involvement |
| MGFA Class V: | MG cases requiring intubation |

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

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

**Fig. 1.** Manual muscle testing Score (5)

**a. Eating**
0=normal
1=independent but with difficulty
2=with help
3=unable to perform

**b. Dressing**
0=normal
1=independent but with difficulty
2=with help
3=unable to perform

**c. Transferring (in and out of bed or chair)**
0=normal
1=independent but with difficulty
2=with help
3=unable to perform

**d. Toilet use**
0= normal
1= independent but with difficulty
2=with help
3=unable to perform

**e. Bathing**
0= normal
1= independent but with difficulty
2=with help
3=unable to perform

**Fig. 2.** Score for activities of daily living (5)

recently published retrospective analysis has provided class IV evidence that MMF begins to improve AChR-positive MG after 6 months, both with prednisolone and as monotherapy.[11]

In this study, we report local experience using MMF in 18 Jordanian patients with refractory MG, despite treatment with prednisolone with or without azathioprine.

## Methods

This study investigated the short term efficacy and safety of mycophenolate mofetil (MMF) among

Jordanian patients with uncontrolled MG over nine months. The patients were enrolled for this study from Neurology clinics at King Hussein Medical Centre (KHMC), Prince Rashed Hospital, and Prince Hashem Hospital, between January 2007 and January 2009. All patients previously diagnosed with MG and having Class III-IV (moderate-severe) disease according to the Myasthenia Gravis Foundation of America (MGFA) classification (Table I) despite high-dose immunosuppressive treatment were enrolled into the study. The patients may or may not have had previous thymectomy. Patients were considered refractory if they had a baseline manual muscle test (MMT) score of at least 5, despite treatment with prednisolone 20mg/day or more for at least 3 months with or without azathioprine (100-200 mg/day) for at least 12 months. Patients who had undergone treatment with plasmapheresis or intravenous immunoglobulin, or had a change in their immunosuppressive medication during the previous 3 months were excluded. Azathioprine was stopped if used previously, and all patients were started on MMF 500 mg twice daily for 4 weeks, and then the dose was increased as tolerated up to 1 g twice daily.

The primary efficacy measure was a reduction of at least 3 points in the MMT and/or a reduction of at least 50% in corticosteroid dose for minimum of 3 months without worsening of the MMT scores. The MMT (Fig. 1) is a recently described, physician applied, scoring system of strength in muscles that are typically affected in MG. It has been shown to have acceptable inter rater reliability and to correlate strongly with the more established quantitative myasthenia gravis (QMG) score.[12,13] We also used the Activities of Daily Living (ADL) profile as a secondary efficacy measure. (Fig. 2)

MMT and ADL scores for each patient were always estimated by the same author to ensure optimal reliability.

The patients were followed-up in clinic every month for the first three months, then every two months for the remaining six months. During these clinic assessments, the MMT and ADL scores were measured, possible adverse effects of MMF were noted, and blood tests for complete blood count and biochemical profile were performed.

## Results

All 18 patients completed the study. There were 10 female and eight male patients, aged from 22 to 64 years (mean 41.5 y). Eleven patients had undergone thymectomy 3-10 years earlier. The duration of MG varied from 1 to 12 years (mean 5.1 years). The clinical and treatment details of all patients are provided in Table II.

Table III shows the treatment results. At the end of the study, the primary efficacy measure was achieved in twelve (66.7%) patients, nine of whom had an improvement in the MMT score of 3 or more and were able to reduce their corticosteroid dose by at least 50%. The other three patients did not have an improvement in their MMT score of 3 or more, but were able to reduce their corticosteroid dose by at least 50%. Improvement in all responders started after 3-5 months and was maximal after 7 months. Improvement in the ADL score was seen in 11 patients.

No major side effects were observed. No diarrhea was reported. Two patients developed heartburn and three patients developed mild nausea that improved either spontaneously or with symptomatic treatment. Three patients reported hand tremors that resolved after 2-3 weeks. One patient had muscle cramps. The hemoglobin value decreased in one patient (by 1.9 g/dl), but she was found to have iron deficiency as the cause of her anemia. No significant leukopenia or thrombocytopenias were recorded. No infections occurred.

## Discussion

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an ihibitor of inosine monophosphate dehydrogenase, a key enzyme in the de novo (but not the salvage) pathway of purine synthesis. Since lymphocytes exclusively use the de novo pathway (whereas other cells use both pathways), MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and ihibits their proliferation, thereby suppressing cell mediated immune responses and anibody formation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation. It is through that MMF exert its anti inflammatory activity via all these mechanisms.[14,15] MMF has a strong safety profile and no major organ toxicity or mutagenic effect, and has been used safely and effectively in managing patients with renal transplants.[14] Reports in western countries showed that MM appeared to be effective as adjunctive therapy in the treatment of severe, refractory and steroid-dependant myasthenia gravis.[3-6]

**Table II.** Clinical characteristics of study patients

| Patient no./sex | Age at study, Y | Age at MG onset, Y | Thymus histology | Medications | AChR Ab |
|---|---|---|---|---|---|
| 1/F | 64 | 62 | Thymoma | Pyr/Pred/Aza | + |
| 2/M | 52 | 40 | Atrophic | Pyr/Pred/Aza | + |
| 3/M | 31 | 25 | Atrophic | Pyr/Pred/Aza | - |
| 4/F | 30 | 24 | Hyperplasia | Pyr/Pred/Aza | - |
| 5/F | 24 | 21 | Hyperplasia | Pyr/Pred/Aza | + |
| 6/F | 40 | 32 | Atrophic | Pyr/Pred/Aza | - |
| 7/M | 32 | 25 | Thymoma | Pyr/Pred | + |
| 8/F | 38 | 32 | Atrophic | Pyr/Pred | - |
| 9/F | 26 | 20 | Hyperplasia | Pyr/Pred | + |
| 10/F | 24 | 19 | Atrophic | Pyr/Pred | + |
| 11/M | 22 | 20 | Hyperplasia | Pyr/Pred/Aza | + |
| 12/M | 47 | 44 | No thymectomy | Pyr/Pred/Aza | - |
| 13/F | 52 | 48 | No thymectomy | Pyr/Pred | - |
| 14/M | 53 | 50 | No thymectomy | Pyr/Pred/Aza | - |
| 15/M | 60 | 53 | No thymectomy | Pyr/Pred | + |
| 16/F | 42 | 39 | No thymectomy | Pyr/Pred/Aza | + |
| 17/M | 55 | 54 | No thymectomy | Pyr/Pred/Aza | - |
| 18/F | 55 | 49 | No thymectomy | Pyr/Pred | + |

AChR-Ab = acetylcholine receptor antibodies; Aza = azathioprine; Pred = prednisone; Pyr = pyridostigmine; M=male; F=female

**Table III.** Manual Muscle Test (MMT) scores, Activities of Daily Living (ADL) scores and doses of prednisolone (mg) at baseline and 9 months

| Patient no. | MMT score | | ADL score | | Prednisolone dose (mg) | |
|---|---|---|---|---|---|---|
| | Baseline | 9mo | Baseline | 9mo | Baseline | 9mo |
| ***1*** | 20 | 14 | 16 | 12 | 25 | 10 |
| ***2*** | 18 | 14 | 13 | 9 | 30 | 15 |
| ***3*** | 26 | 19 | 18 | 14 | 40 | 15 |
| 4 | 16 | 15 | 12 | 10 | 20 | 20 |
| ***5*** | 32 | 24 | 25 | 15 | 40 | 15 |
| ****6*** | 20 | 18 | 14 | 10 | 35 | 25 |
| 7 | 17 | 17 | 14 | 12 | 35 | 20 |
| *8 | 15 | 9 | 11 | 6 | 25 | 10 |
| 9 | 11 | 12 | 9 | 7 | 20 | 25 |
| 10 | 30 | 28 | 10 | 11 | 35 | 40 |
| **11 | 15 | 16 | 14 | 12 | 25 | 10 |
| **12 | 30 | 33 | 20 | 21 | 30 | 30 |
| ***13*** | 20 | 12 | 19 | 11 | 30 | 10 |
| ***14*** | 22 | 23 | 19 | 16 | 25 | 30 |
| ***15*** | 17 | 10 | 12 | 8 | 40 | 20 |
| ***16*** | 28 | 21 | 24 | 17 | 35 | 15 |
| *17 | 21 | 19 | 21 | 14 | 30 | 15 |
| **18 | 22 | 22 | 16 | 17 | 40 | 35 |

* improved in the MMT score of 3 or more and were able to reduce their corticosteroid dose by at least by 50%.
** improved in the MMT score of less than 3, but were able to reduce corticosteroid dose by at least 50%.
***Bold and Italic patient numbers: improvement in ADL score***

All 18 patients in this study had reached a plateau of clinical improvement after receiving high doses of pyridostigmine, steroids with or without azathioprine. Eleven of these patients had successful thymectomy performed in the early stages of disease. They were still experiencing severe symptom exacerbation and required high dosages of medication. Serious medication-related adverse effects were observed, including steroid-induced hypertension, hyperglycemia, osteoporosis, Cushing`s syndrome, candidal mucocutaneous infection, weight gain and other cosmetic side-effects. Patients required high doses of pyredostigmine, leading to troublesome cholinergic

side effects, such as abdominal pain, diarrhea, excessive respiratory secretions and dyspnea. In addition, pyridostigmine is an expensive drug and is not always readily available. Also, patients on azathioprine required regular monitoring for blood dyscrasias and liver toxicity and surveillance for certain tumors.

After starting MMF, two thirds of our patients had significant clinical improvement. None of them had subsequent myasthenic crises requiring ICU admission after addition of MM. Unlike an earlier case report,[3] we observed symptomatic improvement beginning 3–5 months after starting MMF. Hence, pyridostigmine and other immunosuppressive medications could be significantly reduced without causing worsening of symptoms.

Similar to previous reports,[4-7] our data also suggest a steroid-sparing effect of MMF. All twelve responders were already on high-dose prednisolone when MMF treatment was started and were able to decrease the prednisolone dosage without significant clinical worsening. The reduction was crucial in these patients, as some of them had already developed serious long-term steroid-induced adverse effects.

This observation may provide the motivation for early commencement of MMF in future cases of refractory MG.

All our patients tolerated MMF well. The serum biochemistry and full blood counts that were carried out on all our patients showed no significant abnormalities. While the short-term safety profile appeared good with MMF, the long-term adverse effects in our patients remain unknown. We acknowledge that there have been reports of serious side-effects in myasthenia patients treated with MMF, including recent reports of an association between MMF and Progressive Multifocal Leukoencephalopathy or Posterior Reversible Encephalopathy Syndrome.[16,17] However, long-term safety profiles of MMF in transplant patients have been encouraging.[18] The dosage of MMF used in our patients was 1500-2000 mg per day; other reports have used between 1000 and 2000 mg per day. The optimal dosage remains uncertain in Jordanian patients. In transplant patients, MMF day has been used up to 3500 mg per with few side effects.[19]

As to why the results of the MSG and Aspreva trials were negative and largely different from most other reports, including ours, is uncertain. Several potential reasons, other than lack of drug efficacy in these two studies, have been suggested including: (i) the duration of the trials was too short (neither trial was >36 weeks); (ii) the endpoints were insensitive or too stringent; (iii) the greater-than-predicted response to prednisolone masked any benefit of MMF, perhaps because of differences between subjects; and (iv) patients may not have been representative of the general population of patients of myasthenia.[20,21] Additional, larger, multicentre studies could be useful in answering these questions.

## Conclusion

Our experience suggests that MMF is a promising alternative to other currently available immunosuppressive drugs for the treatment of refractory MG in Jordanian patients.

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