Myasthenia gravis exacerbation after discontinuing mycophenolate

A single-center cohort study

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ABSTRACT

Objective: To determine whether discontinuation or marked reduction of mycophenolate mofetil (MMF) in patients with myasthenia gravis (MG) causes MG exacerbations.

Methods: We identified 88 patients with MG who took MMF during the 5-year period 2007–2011 at our MG clinic. We then performed detailed chart reviews and recorded all MG exacerbations and their relationship to MMF and other treatment changes. We also recorded demographic data and disease characteristics (including antibody status and Myasthenia Gravis Foundation of America status).

Results: There were 14 patients who had an MG exacerbation during the study period. Of these, 13 had discontinued MMF therapy, with a median time until exacerbation of 16 weeks after discontinuation (9 patients) or marked dose reduction (4 patients) of MMF therapy (exacerbation in the absence of change in any other component of the immunosuppressive regimen). Using the cluster option in a Cox regression analysis, the MMF coefficient was -5.32 , with a standard error of 1.05 and a p value of 0.0002, corresponding to an estimated hazard ratio of 204.

Conclusions: This retrospective cohort study suggests that discontinuation/marked reduction of MMF therapy may increase the risk of MG exacerbation many fold, supporting the hypothesis that MMF plays a role in the maintenance of MG remission/minimal manifestation status.

Classification of evidence: This study provides Class IV evidence that in patients with MG taking MMF, discontinuation or marked reduction of MMF causes MG exacerbation. *Neurology*® 2016;86:1159–1163

GLOSSARY

AChR = acetylcholine receptors; **MG** = myasthenia gravis; **MGFA** = Myasthenia Gravis Foundation of America; **MM** = minimal manifestations; **MMF** = mycophenolate mofetil; **MuSK** = muscle-specific kinase; **PR** = pharmacologic remission; **RCT** = randomized controlled trial; **UCD** = University of California Davis.

Moderate to severe myasthenia gravis (MG) caused by autoantibodies against the neuromuscular junction proteins, acetylcholine receptors (AChR), or muscle-specific kinase (MuSK) is most commonly treated with high-dose corticosteroids followed by dose tapering. To reduce the risk of disease exacerbation during tapering and to limit side effects of long-term steroid treatment, many regimens include immunosuppressant medications as steroid-sparing agents.¹ One such agent, azathioprine, has been demonstrated in a randomized controlled trial (RCT) to permit reduction in prednisone use over time.² Mycophenolate mofetil (MMF) has frequently replaced azathioprine in organ transplantation and in treatment of some autoimmune diseases because of efficacy and favorable safety profile. Several open-label studies and case series^{3,4} have demonstrated the efficacy of MMF as a treatment in MG. However, 2 RCTs failed to prove that MMF enhances reduction in prednisone dose.^{5,6} The authors of the trials offered several possible explanations for these findings, naming inadequate duration of MMF treatment as the probable factor.^{4,7,8} Here we present a retrospective cohort analysis of exacerbations in all MMF-treated patients with MG from a single clinic in relation to discontinuation or marked dose reduction of MMF. Our objective is to show the effect MMF withdrawal/dose reduction has on the risk of MG exacerbations.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

This study provides Class IV evidence that in patients with MG taking MMF, discontinuation or reduction of MMF increases the hazard ratio of MG exacerbation by an estimated 204-fold (the coefficient of MMF in the Cox regression was -5.32 with a standard error of 1.05 and a z score of -5.08) ($p = 0.0002$).

METHODS The primary research question for this project was if in patients with MG taking MMF discontinuation or marked reduction of MMF causes MG exacerbation.

We searched the University of California Davis (UCD) clinical database for patients treated during the 5-year period January 1, 2007, to December 31, 2011, using the terms MG—diagnosis code and mycophenolate—pharmacy code. We also searched the MG clinic patient list. We identified 133 potential patients. After chart review, 88 met our inclusion and exclusion criteria: (1) MG diagnosis defined as clinical symptoms of MG along with supporting serologic or electrophysiologic findings. Four patients were not included due to this criterion. (2) Treatment with MMF for at least 1 month's duration, during at least part of the 5-year study period. Thirty-one patients were not included as they did not take MMF. (3) Stable, well-controlled MG, defined as Myasthenia Gravis Foundation of America (MGFA) pharmacologic remission (PR) or minimal manifestations (MM) status. Two patients did not meet this criterion. This is required to allow patients to meet MGFA criteria for MG exacerbation. Because the goal was to study the effect of discontinuing or reducing MMF, we excluded patients who also discontinued other MG medications. Six patients were excluded for this reason. Two patients did not have sufficient data

recorded in the electronic medical records to permit us to determine whether they were taking MMF. Discontinuation/reduction of MMF was defined as a reduction of MMF by 50% or greater, for at least 1 month. Exacerbations were defined according to MGFA criteria.

We compared the risk of disease exacerbation while on stable immunosuppression with MMF to the risk of disease exacerbation after discontinuation/reduction of MMF. We used the Cox proportional hazards model in the counting process formulation using the R program `coxph()`. For each patient, we determined 1 or 2 time intervals whose endpoints are defined by entry into the time period (January 1, 2007) on MMF or starting MMF therapy, stopping MMF therapy, and by an exacerbation or the end of the study period (December 31, 2011). Statistical significance used the robust score test with the cluster formulation, which is robust to inpatient correlation. Four of the 88 patients studied were lost to follow-up before the end of the 5-year observation period and only the time during which they were followed was used in the analysis.

Standard protocol approvals, registrations, and patient consents. The study was approved by the UCD institutional review board.

RESULTS All 88 patients studied had clinical and serologic (83 AChR Ab+, 2 MuSK Ab+) or clinical and electrodiagnostic evidence (2 had decrement on repetitive stimulation and 1 had increased jitter on single fiber EMG) of MG, with disease onset ranging from age 8–85 years; 39 were female. We recorded each patient's worst ever MG state. Generally the worst MG state occurred before PR or MM was

Table 1 Demographic, disease, and treatment characteristics

No.	Stopped MMF and had exacerbation	Stopped MMF without exacerbation	Continued MMF and had exacerbation	Continued MMF without exacerbation
	13	4	1	70
Age at entry, y, mean/median (range)	48/47 (23–71)	46/41 (26–76)	35	62/65 (20–91)
Female	5	3	1	29
MGFA Class				
I	1	0	0	5
IIA	1	0	0	6
IIB	1	1	1	5
IIIA	1	1	0	1
IIIB	0	0	0	14
IVA	0	0	0	0
IVB	6	2	0	26
V	3	0	0	13
Highest measured AChR antibodies, nmol/L, median (range)	42 (2–80)	45 (17–92)	48	49 (2–93)
MMF dose, g/d, mean/median	1.92/2.00	2.12/2.00	3/3	2.21/2.00
Thymectomy	7	3	1	34
MG duration at entry, y, mean/median (range)	7/7 (1–12)	6/6 (1–10)	2	6/4 (0–26)

Abbreviations: AChR = acetylcholine receptors; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MMF = mycophenolate mofetil.

Age is significantly lower for patients with exacerbation ($p = 0.0061$). No other differences are statistically significant.

Table 2 Patients with exacerbation after stopping MMF: Additional demographic, disease, and treatment characteristics

	Subject no.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at MG onset, y/sex	43/M	31/F	25/F	21/F	39/M	38/F	68/M	57/M	55/M	50/M	38/M	55/M	17/F
MGFA Class	IVB	V	V	IVB	IIA	V	IVA	IIIB	I	IIIA	V	IVB	IIIB
ACHR antibodies, nmol/L (normal <0.4)	48	11.4	26	2.6	2.7	0.3	18	43	6.8	34	47	10.6	7.0
Thymectomy	Y; T	Y; T	N	Y	Y	N	N	N	N	N	Y; T	Y	Y
Initial R/MM induced by	P/Py	P/PE/Cy	P/Py/IVig	P/PE	P	P/Py/PE/IVig/MMF	P/Py/PE/MMF	Py/MMF	UK	UK	Th/P/IVig	P, IVig	IVig/MMF
Maintenance MMF dose, g/d	2	2	2	1	2	2	2	2	2	2	2	2	2
Maintenance P dose, mg/d	11	5	25	5	0	0	10	0	0	0	0	14	0
Duration R/mm before MMF change, mo	24	72	24	60	48	60	36	9	81	10	32	12	39
Lag between MMF discontinuation/reduction and MG exacerbation, mo	4	7	6	3	7	6	2	1.5	8	2	27 ^a	2	6

Abbreviations: ACHR = acetylcholine receptors; Cy = cyclosporine; IVig = IV immunoglobulin; UK = unknown; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MM = minimal manifestations; MMF = mycophenolate mofetil; P = prednisone; PE = plasma exchange; Py = pyridostigmine; R = remission; T = thymoma; Th = thymectomy.
^a Six weeks after the last MMF decrease.

achieved prior to the study. Basic demographic data and disease characteristics of the 88 patients can be found in table 1.

Frequency of MG exacerbation. Of the 14 patients who experienced exacerbations, 13 had recently stopped/reduced MMF (table 2). One of the 88 patients had an exacerbation while on stable MMF dose. The discontinuation/reduction of MMF increased the hazard ratio of MG exacerbation by an estimated 204-fold (the coefficient of MMF in the Cox regression was -5.32 with a standard error of 1.05 and a z score of -5.08) ($p = 0.0002$). Ten of the 13 patients who stopped/reduced MMF and had an exacerbation had been documented to have moderate or severe MG disease (MGFA Class III–V). These patients had been in remission/minimal manifestation for 9–72 months (median 36 months) prior to the discontinuation/reduction of MMF. For 8 patients, the motivation for the sudden discontinuation of the MMF was either the inability of the patient to afford the financial cost of MMF or pregnancy (actual [1 patient] or planned [3 patients]). For the 4 patients who were unable to afford the costs of MMF, this was due to a loss of health care insurance coverage. One patient discontinued MMF due to tinnitus, which did not resolve with discontinuation of MMF. For the remaining 4 cases, the MMF dose reductions were planned to minimize the risk of long-term immunosuppression. For the 13 patients who underwent an exacerbation of MG following MMF discontinuation/reduction, there was a lag time of 6–118 weeks (median 16 weeks). Four patients in our cohort tapered or stopped MMF without having an exacerbation. One of these patients restarted MMF after 2 months, within the average post discontinuation lag. Another developed mild leg weakness, but this never recovered, and we were unable to attribute this symptom to an MG exacerbation. For the group of 71 patients in which no or little change in MMF was made during the period of observation, 1 underwent an exacerbation. She did so after sternal repair surgery.

Patients older than 60 years were less likely to stop MMF therapy and also less likely to have an exacerbation, a classic possible confounder. When this binary age variable was introduced into the Cox regression, it was not significant, nor did it reduce the apparent large increase in risk due to stopping MMF therapy. It should be noted that the striking fact that 13/14 patients who had an exacerbation had stopped/reduced MMF therapy makes statistical estimates of the exact hazard ratio imprecise. Nonetheless, the evidence that the increase in risk is at least large is good.

DISCUSSION This cohort study provides a different type of evidence assessing the efficacy of MMF for

reducing exacerbations of MG. We show that withdrawal of MMF results in an increased hazard ratio for MG exacerbations, which generally occurred with a lag of several months after discontinuation of MMF. Our data support the hypothesis that MMF plays a role in the maintenance of MG remission/minimal manifestation status, because MMF discontinuation/reduction was associated with an MG exacerbation in the absence of a change in any other component of the immunosuppressive regimen. In a recently published series by Hobson-Webb et al.,⁹ maintenance of stable remission was achieved with slow gradual reductions in MMF dosage in a higher proportion (67%) than we observed in our case series (23%). The reasons for this could be many, including the following: (1) The current series captures mostly cases in which the dose had been suddenly discontinued or markedly reduced, as opposed to the controlled slow tapers described in the Hobson-Webb et al. series, and the risk of exacerbation may be greater with a rapid taper or discontinuation. (2) A shorter duration of therapy was a predictor of exacerbation in the Hobson-Webb et al. series and the duration of MMF treatment was generally shorter in our series as compared to theirs (our mean 4.1 years vs their 5.9 years for successful tapers and 4.4 years for unsuccessful). (3) A majority of our tapers occurred due to socioeconomic or patient preference rather than recommendations based on expert clinical acumen and it seems plausible that expert clinicians can predict the likelihood of an exacerbation with a greater accuracy than chance. The exacerbations experienced by the 13 patients with MG discontinuing/reducing MMF were all treated early and were mild, none requiring hospitalization. One of the possible reasons for the seeming discrepancy of a lack of efficacy in the prior RCTs and our study may be that MMF is better at maintaining MG remission than inducing it, but this study does not directly address this question.

The present study is limited by its retrospective nature, but the series has provided an opportunity to test, at least indirectly, the efficacy of MMF in remission/minimal manifestation status maintenance. Conclusions from a retrospective study where the MMF treatment discontinuations were not allocated by formal randomization may have introduced a bias. This could include that the patients who discontinued their MMF against medical advice were more likely to have exacerbations compared to those who remained compliant throughout the study period. Patients may not have reported non-compliance with their prescribed MMF treatment yet not had an exacerbation, thereby making us overestimate the effect of MMF in maintaining minimal manifestation status/remission. Incomplete datasets are often a limitation for retrospective case studies; this is relatively

unlikely to present a major bias in this study as we were able to capture complete data for the analyzed time period for the vast majority of patients (131 of 133).

The relatively long lag between dosage discontinuation/reduction and exacerbation is not surprising. Discontinuation of azathioprine in MG results in a similar lag between discontinuation and relapse.¹⁰ A lag between initiation of MMF treatment and the treatment effects also is characteristic of MG.^{4,7} Inadequate attention to this lag in biological effects could have played a role in the failure of the RCTs of MMF (see above). The data presented here suggest that MMF contributes to the maintenance of remission/minimal manifestation status in MG, as would be desired in a steroid-sparing agent. More definitive conclusions concerning MMF efficacy await a clinical trial designed with consideration of the lag in effect of MMF on MG control in both the initiation of the agent and in its discontinuation.

AUTHOR CONTRIBUTIONS

Björn Oskarsson contributed to design, interpretation of data, drafting and revision of the manuscript. David Rocke contributed to design, statistical analysis, interpretation of data, drafting and revision of the manuscript. Karsten Dengel contributed to design, interpretation of data, drafting and revision of the manuscript. David P. Richman contributed to design, interpretation of data, drafting and revision of the manuscript.

STUDY FUNDING

Supported by the National Center for Advancing Translational Sciences, National Institutes of Health, grant UL1 TR 000002.

DISCLOSURE

B. Oskarsson is supported by Novartis, NIH UL1 TR 000002 and linked award KL2 TR 000134, NINDS U10 NS077422-01, NINDS 1 U01 NS049640-02, and NIEHS R01 ES016848-01A2; and is a speaker for Grifols. D. Rocke serves on the following DSMBs: Conceptus, Inc., 2008–2012, and Hansen Medical, 2001–2012; has received compensation for travel and honoraria from the American College of Phlebology, 2011, and American Statistical Association, 2011 and 2012; is an Associate Editor for *Journal of the American Statistical Association*, *Theory and Methods*, 2005–2011, and *Bioinformatics*, 2005–2011; is a member of the editorial board for *Bioinformatics*, 2012–, *BMC Bioinformatics*, 2005–, *Journal of Bioinformatics: Theory and Applications*, 2005–, *Molecular and Cellular Proteomics*, 2005–2015; is an employee of University of California, Davis; serves as a consultant for ICU Medical 2010–2012, Immuno Concepts 2012, and SciClone Pharmaceuticals 2011; has research support from Celadon, Inc., and the Department of Energy, 2009–2013, National Institutes of Health/National Center for Research Resources, 2006–2016, UC Davis Clinical and Translational Science Center, National Cancer Institute, 2009–2012, National Institutes of Health, National Institute of Allergy and Infectious Diseases R21/R33-AI080604, 2008–2014, Department of Energy DE-FG02-07ER64341, 2006–2011, National Institutes of Health, National Human Genome Research Institute R01-HG003352, 2006–2011. K. Dengel reports no disclosures relevant to the manuscript. D. Richman receives research funding from the Muscular Dystrophy Association of America (255526), The Myasthenia Gravis Foundation of California, and the Myasthenia Gravis Foundation of Illinois; and received travel expenses and an honorarium from Aspreva Pharmaceuticals for an advisory board meeting in 2005 concerning planning for an international clinical trial of mycophenolate mofetil and travel expenses for a 2007 investigators meeting for that trial. Go to Neurology.org for full disclosures.

Received April 26, 2015. Accepted in final form December 7, 2015.

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