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Myasthenia gravis exacerbation after discontinuing mycophenolate

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Myasthenia gravis exacerbation after discontinuing mycophenolate: A single center cohort study

Abstract

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

Methods:

We identified 88 MG patients who took MMF during the five-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 MGFA status).

Results:

There were 14 patients who suffered a 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 MG patients taking MMF, discontinuation or marked reduction of MMF causes MG exacerbation.

Key Words

[179] Myasthenia

[132] Autoimmune diseases

[23] Clinical trials Observational study (Cohort, Case control)

[176] All Neuromuscular Disease

[324] Class IV

Introduction

Moderate to severe myasthenia gravis (MG) caused by auto-antibodies 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 to permit the 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 have demonstrated the efficacy of MMF as a treatment in MG. However, two randomized controlled trials failed to prove that MMF enhances reduction in prednisone dose. The authors of the trials have offered several possible explanations for these findings, naming inadequate duration of MMF treatment as the probable factor. Here we present a retrospective cohort analysis of exacerbations in all MMF-treated MG patients 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.

METHODS

The primary research question for this project was if in MG patients taking MMF, discontinuation or marked reduction of MMF causes MG exacerbation. This study provides Class IV evidence that in MG patients 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 ($p = 0.0002$).

We searched the University of California, Davis (UCD) clinical database for patients treated during the five-year period 01/01/2007–12/31/2011, 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 serological and/or electrophysiological findings. Four patients were not included due to this criterion. (2) Treatment with MMF for at least one month's duration, during at least a 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 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 if 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 MMF. We used the Cox proportional hazards model in the counting process formulation using the R program coxph(). For each patient we determined one or two time intervals whose end points are defined by entry into the time period (01/01/2007) on MMF or starting MMF therapy, stopping MMF therapy, and by an exacerbation or the end of the study period (12/31/2011). Statistical significance used the robust score test with the cluster formulation, which is robust to intra-patient 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 serological (83 AChR Ab+, 2 MuSK Ab +) or clinical and electrodiagnostic evidence (two had decrement on repetitive stimulation and one had increased jitter on single fiber EMG) of MG, with disease onset ranging from age 8 to 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 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 to 72 months (median 36) 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 cases that underwent an exacerbation of MG following MMF discontinuation/reduction, there was a lag time of 6 to 118 weeks (median 16). Four patients in our cohort tapered or stopped MMF without suffering 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 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 very striking fact that 13/14 patients who had an exacerbation had stopped/reduced MMF therapy, this makes statistical estimates of the exact hazard ratio rather imprecise. Nonetheless, the evidence that the increase in risk is at least large is quite 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 a 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; 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's 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 Hobson-Webb's 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 MG patients 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 RCT's and our study may be that MMF is better at maintain 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 noncompliance with their prescribed MMF treatment yet not suffered an exacerbation, thereby making us overestimate the effect of MMF in maintaining minimal manifestation status/remission. Incomplete data sets are often a limitation for retrospective case studies, we feel that 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. Inadequate attention to this lag in biological effects could have played a role in the failure of the randomized clinical trials of MMF (see above). The data presented here suggest 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.

Abbreviations:

Acetylcholine receptors	AChR
Intravenous immunoglobulin	IVIG
Myasthenia Gravis	MG
Myasthenia Gravis Foundation of America	MGFA
Mycophenolate mofetil	MMF
University of California, Davis	UCD

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Table 1. Demographic, disease and treatment characteristics. Age is significantly lower for patients with exacerbation (p = 0.0061). No other differences are statistically significant.

	Stopped MMF and had exacerbation	Stopped MMF without exacerbation	Continued MMF and had exacerbation	Continued MMF without exacerbation
No.	13	4	1	70
Mean/Median Age at Entry (range)	48/47 (23–71)	46/41 (26-76)	35	62/65 (20–91)
Gender female	5	3	1	29
MGFA Class I IIA IIB IIIA IIIB IVA IVB V	 1 1 1 1 0 0 6 3	 0 0 1 1 0 0 2 0	 0 0 1 0 0 0 0 0	 5 6 5 1 14 0 26 13
Highest measured AChR Ab (median nmol/L, range)	42 (2-80)	45 (17-92)	48	49 (2-93)
Mean/Median Dose of MMF (g/day)	1.92/2.00	2.12/2.00	3/3	2.21/2.00
Thymectomy	7	3	1	34
Mean/Median Duration in years of MG at Entry (range)	7/7 (1–12)	6/6/ (1–10)	2	6/4 (0–26)

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**	**1**
Age at MG Onset (yr)/Sex	43/ M	31/F	25/F	21/F	39/ M	38/F	68/M	57/ M	55/ M	50/ M	3
MGFA Class	IVB	V	V	IVB	IIA	V	IVA	IIIB	I	IIIA	V
AChR Ab (nmol/L) Normal <0.4	48	11.4	26	2.6	2.7	0.3	18	43	6.8	34	4
Thymectomy (T=thymoma)	Y; T	Y; T	N	Y	Y	N	N	N	N	N	Y
Initial R/MM induced by:	P/P y	P/PE/C y	P/Py/I G	P/P E	P	P/Py/P E/IG/M	P/Py/ PE/M	Py/ M	UK	UK	T I
Maintenance MMF dose (g/day)	2	2	2	1	2	2	2	2	2	2	2
Maintenance P dose (mg/day)	11	5	25	5	0	0	10	0	0	0	0
Duration R/mm before MMF change (mo)	24	72	24	60	48	60	36	9	81	10	3
Lag between MMF Discontinuation/Reduction and MG exacerbation (mo)	4	7	6	3	7	6	2	1.5	8	2	2

Y=yes; N=no; P=prednisone; Py=pyridostimine; Cy=cyclosporine; PE=plasma exchange; IG=intravenous immunoglobulin; M=mycophenolate mofetil; Fi=financial; PlPr=planned

pregnancy; Pr=pregnancy; Ta=taper immunosuppression, Th=Thymectomy, R/MM= Remission/Minimal Manifestation, *= 6 weeks after the last MMF decrease.

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