Tolerability of Mycophenolate Mofetil in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To quantify the adverse events (AE) associated with mycophenolate mofetil (MMF) in patients with systemic lupus erythematosus (SLE), to examine the relationship between AE and dosage of MMF, and to assess the overall tolerability of MMF in SLE patients.

Methods. A consecutive cohort of adults with SLE who received MMF between October 1996 and June 1999 was identified. Charts were reviewed for baseline data, AE, MMF dosing characteristics, and clinical response at baseline, 3 months, and at final followup or drug discontinuation.

Results. The 54 SLE patients were followed for a mean of 12.4 ± 7.0 person-months. Baseline characteristics: 92.6% female, 72.2% white, mean age 38.3 years, and a mean of 9.6 years since diagnosis. Twenty-one of 54 patients (38.9%) had a total of 28 gastrointestinal AE. Twenty-four of 54 (44.4%) patients had a total of 37 infections, only one of which required hospitalization. Leukopenia occurred 3 times but never required dose adjustment. AE occurred at a similar rate at all MMF doses. Kaplan-Meier estimates show most drug discontinuation occurred in the first 2.5 months and 73% of patients were still on the drug at 12 months. Sixteen of 54 patients discontinued MMF because of AE (n = 9), lack of efficacy (n = 3), pregnancy (n = 2), and administrative reasons (n = 2). Clinical improvement in patients was noted with significant decreases in disease activity measured by the SLEDAI and prednisone dose at 3 months and at final followup.

Conclusion. The majority of patients tolerated MMF. A range of doses was tolerated and associated with clinical improvement, suggesting that a flexible dosing schedule should be considered when using MMF in patients with SLE. (J Rheumatol 2003;30:1508–12)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS MYCOPHENOLATE MOFETIL
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Pharmacotherapy for systemic lupus erythematosus (SLE) has reduced the morbidity and mortality from this disease substantially. Despite the efficacy of many immunosuppressive medications, however, the short and longterm toxicity of the available agents limits their use[1]. Mycophenolate mofetil (MMF, CellCept®), an inhibitor of *de novo* purine synthesis[2,3], has been successfully used as an immunosuppressive in transplantation medicine[4-6]. Although MMF has gained widespread favor as an alternative immunosuppressive in patients with SLE[7], information regarding its toxicity profile in the SLE population remains primarily anecdotal. While MMF toxicity has been thoroughly evaluated in transplantation[8], MMF side effects may differ in patients with SLE due to differing concomitant medications, comorbid conditions, and levels of renal dysfunction. These factors may also lead to tolerability of different doses than might be expected in transplantation patients. Our objectives were to quantify the adverse events (AE) associated with MMF use in patients with SLE, to examine the relationship between AE and dosage of MMF, and to assess the overall tolerability of MMF in patients with SLE.

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MATERIALS AND METHODS

Patients and data collection. This is a retrospective chart review in a cohort of SLE patients. The study was approved by the University of Michigan Institutional Review Board. Adults followed at The University of Michigan who satisfied American College of Rheumatology (ACR) criteria[9,10] for SLE were included. The cohort included the subset of these SLE patients who had MMF prescribed from October 1996 through June 2000. The initial date is the date of the patient's first use of MMF at this institution. Appropriate patients were identified through review of rheumatology nursing logs of all current and inactive patients on immunosuppressive agents. Three of the investigators reviewed all charts using a standard data collection template. The diagnosis of SLE was confirmed for all patients. For data collection related to MMF use, patient records were reviewed from the start of MMF (baseline) through the time of the chart review or drug discontinuation (final time point). Gender, race, and age at diagnosis were

determined. Baseline characteristics including age, disease duration, SLICC/damage index[11] were determined from the start of medication usage. Indications for treatment were inferred from review of the patient chart and divided into 3 categories: steroid sparing, poor response to current therapy, or AE to current medication. The manifestations of lupus activity at the start of MMF were recorded. AE information was obtained from physician evaluations and nursing phone call records from baseline to the final time point. All cytopenias not present at baseline were recorded as an AE. Episodes of gastrointestinal (GI) AE were based on patient report. The infectious AE, other than reported viral upper respiratory infections, were confirmed by physician evaluation at the time of the event. The total daily dose of MMF at which any AE occurred was recorded. All major dosage adjustments were recorded with the exception of dosage escalation that occurred over less than a 2-week period. Reasons for drug discontinuation were inferred from review of the written chart and were divided into AE, administrative reasons, pregnancy, and lack of efficacy. Clinical response, measured by daily oral prednisone dose and Systemic Lupus Disease Activity Index (SLEDAI) score[12] were determined at baseline, 3 months, and the final time point. Laboratory tests including complement components 3 and 4, anti-double stranded (ds) DNAantibodies, and serum creatinine were recorded. Intermittent pulse intravenous methylprednisolone was not included in the analysis of steroid dosing.

Data analysis. SAS 6.12 (Cary, NC) was used for data management and analysis. Descriptive statistics (mean, median, standard deviation, and proportions) were performed for all variables. Chi-square was used to test associations between categorical variables. The AE rate was calculated by dividing the number of AE at each dose by the total person-years of exposure at each dose. Linear regression was used to determine the association between MMF dose and the number of AE per person year (AE rate). Logistic regression was used to examine the association between baseline serum creatinine level and development of an AE. Kaplan-Meier estimates were used to characterize time to drug discontinuation. One-way ANOVA for repeated measures was used to compare continuous variables (prednisone dose, SLEDAI, serum creatinine, complements C3 and C4, and anti-dsDNA antibodies) across the 3 study time points. Anti-dsDNA antibody levels were log transformed because this variable was not normally distributed.

RESULTS

Sixty-three patients with SLE who were prescribed MMF were identified through review of the immunosuppressive clinic charts. Eight were excluded because they did not fulfill 4 ACR criteria for the classification of SLE, and one was excluded because she never began treatment with MMF. A total of 54 patients were analyzed. Mean followup time was 12.4 ± 7.0 person-months with a total followup time of 56 person-years.

Baseline characteristics. Baseline characteristics are detailed in Table 1. Concomitant medications at the start of MMF therapy were corticosteroids in 54 (100%) patients, hydroxychloroquine and/or quinacrine in 38 (70.4%), a nonsteroidal antiinflammatory drug (NSAID) in 31 (58.5%), and cyclophosphamide in 8 (15.4%). Thirty-five (64.8%) and 37 (68.5%) patients received azathioprine or cyclophosphamide, respectively, at some point in the course of their SLE. A wide range of disease manifestations was present at the start of MMF therapy (Table 2). Twenty-six (48.2%) patients started MMF due to a perceived need for steroid or cyclophosphamide sparing on the part of the primary rheumatologist, 18 (33.3%) patients due to a poor response to current therapy, and 10 (18.5%) patients due to an AE on their current regimen.

Table 1. Baseline characteristics (n = 54).

	Mean (SD)	%
Age, yrs	36.8 (12.2)	
Gender, female	—	92.6
Race		
White	—	72.2
Black	—	25.9
Asian	—	1.9
Disease duration, yrs	9.6 (7.0)	—
Age at diagnosis, yrs	27.3 (10.7)	—
SLICC/damage index	1.8 (2.3)	—
SLEDAI	5.0 (4.3)	—
Serum creatinine, mg/dl	1.3 (1.0)	—
Prednisone dose, mg	20.1 (15.4)	—

Table 2. Active disease manifestations at start of MMF therapy. * Patients (n = 54) could have more than one disease manifestation at the start of MMF therapy; percentages total more than 100.

Disease Manifestation	n (%)
Renal	26 (48.2)
Arthritis	16 (29.6)
Mucocutaneous	12 (22.2)
Neurologic	10 (18.5)
Pleuritis	8 (14.8)
Leukocytopenia	5 (9.3)
Pericarditis	4 (7.4)
Thrombocytopenia	4 (7.4)
Pulmonary	3 (5.6)
Hemolytic anemia	1 (1.9)

AE. Thirty-six out of 54 (66.7%) SLE patients had an AE (0.64 AE/person-year) possibly or probably related to MMF. There were 2 serious AE: one patient developed prostate cancer and one was hospitalized for pneumonia (0.035 serious AE/person-year). Twenty-one of 54 patients (38.9%) had a total of 28 GI AE (0.5 GI AE/person-year). Table 3 shows the distribution of these events. There was no significant difference in GI AE for those patients also taking NSAID or an anti-malarial agent. Twenty-four of 54 patients (44.4%) had a total of 37 infectious AE (0.66 AE/person-

Table 3. Gastrointestinal adverse events.

Adverse Event	Episodes* n (%)
Nausea	15 (27.8)
Diarrhea	8 (14.8)
Vomiting	4 (7.4)
Abdominal pain	1 (1.9)

* Number of episodes is equivalent to the number of subjects because no subject experienced more than one episode of the same type of gastrointestinal adverse event.

year). Table 4 shows the number of infectious AE identified during the 56 person-year followup time. There were 3 cases of leukopenia, none of which required MMF dose adjustment. Table 5 displays the AE rate at each dose of MMF. The AE rate was not increased with higher daily doses of MMF ($p = 0.32$). Baseline serum creatinine as a continuous variable was not associated with an increased rate of AE of any type (odds ratio 1.4, 95% confidence interval 0.57,3.43).

Dosing. Of the 16 patients who discontinued MMF either on their own or on the advice of their physician, 9 (56.3%) did so for a recorded AE possibly or probably related to MMF, 2 (12.5%) did so for administrative reasons (e.g., lack of insurance), and 2 (12.5%) did so for planned or concurrent pregnancy. Three (18.8%) SLE patients discontinued MMF due to lack of efficacy. Figure 1 shows the distribution of doses at last followup. Kaplan-Meier estimates (Figure 2) show that 73% of patients continued MMF for at least 12 months.

Clinical course. The prednisone dose and SLEDAI score showed significant improvement over the 3 study time points. The changes in serum creatinine, complement C3 and C4, and anti-dsDNA antibodies over time were not significant (Table 6).

Table 4. Infectious adverse events.

Adverse Event	n
Cystitis	7
URI	6
Bronchitis	6
Cellulitis	4
Pneumonia	3
HSVstomatitis	3
Pharyngitis	2
Varicella zoster	2
Otitis media	1
Condyloma	1
Paronychia	1
Pyelonephritis	1

* Each patient could have more than one episode of the same type of infection.

Table 5. Adverse event (AE) rate at each MMF dose.

MMF dose, mg	AE, n	Person-Years, n	AE per person-year
125	0	0.32	0
250	2	1.83	1.09
500	4	2.73	1.47
750	0	0.45	0
1000	19	11.26	1.69
1250	0	0.42	0
1500	14	13.18	1.06
2000	27	22.58	1.20
2500	2	1.75	1.15
3000	1	0.75	1.34

DISCUSSION

To evaluate the tolerability of MMF in SLE patients, we analyzed the first adults with SLE treated at this institution. Most previously published AE data originate from the transplant literature in which patients are on a triple regimen including prednisone and usually cyclosporine in addition to MMF. These AE include GI side effects, such as nausea, vomiting and diarrhea, leukopenia, infection, and malignancy[8]. The frequency of GI AE in this series is comparable to that noted in studies of MMF in renal transplantation. Infectious AE were generally minor. The followup time was too short to expect any malignancies related to MMF treatment. The slowly progressive nature of prostate cancer makes it unlikely that this AE was related to treatment with MMF. Although one may expect an increase in AE with renal dysfunction and decreased clearance of the drug and its metabolites, there was no relationship between creatinine level and AE identified. Most importantly, AE associated with MMF treatment were not dose-related in this population. Most practitioners suggest a dose decrease in response to an adverse event.

MMF termination occurred for a variety reasons. Although AE occurred in 37 of the patients during the entire study period, they were mild and only 9 of all patients discontinued MMF due to AE. Most drug terminations occurred in the first few months of therapy and did not appear dose-dependent.

At the time these patients started therapy, the MMF dosing was based on experience in renal transplantation. There were no explicit criteria used to determine the initial MMF dose and subsequent dose escalation. Although patients were not treated according to a specific protocol, 2000 mg/day was widely accepted as the target dose among physicians at this institution. At the present time, although MMF dose is usually standardized at 2000 mg/day, the dose is sometimes adjusted for body size and renal function[8]. Our results show that less than half of the patients were able to maintain treatment with MMF at 2000 mg/day, and a wide range of doses was tolerated at last followup. Treatment within the dose range of 1000-2000 mg/day was associated with clinical improvement comparable to that observed in other open, uncontrolled series. Since serum concentrations of MMF can vary at the same daily dose[13-15], the poor predictive value of daily dose for AE and clinical response is not unexpected. Presently, the balance of clinical response and toxicity may be the best method for dose adjustment.

Our study was limited by its retrospective design. This can be a significant impediment to capturing all AE during the course of MMF treatment. The clinical response data is difficult to interpret particularly since this is an uncontrolled study. One should be cautious in interpreting the favorable clinical response at 3 months; however, it is notable that this effect is sustained at the final followup time which is, on average, 1 year later. Furthermore, the SLEDAI is validated

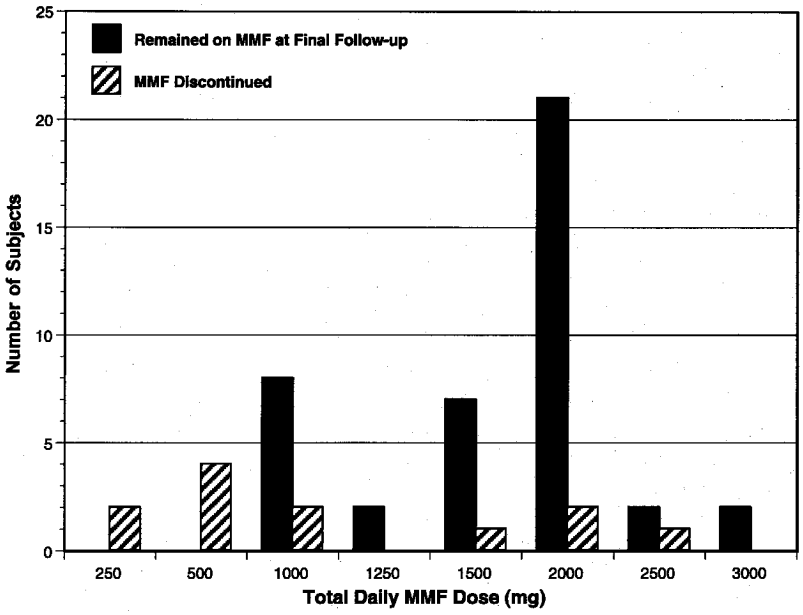

Figure 1. Number of patients receiving each MMF dose at final followup, stratified by those who continued MMF and those who discontinued MMF. The 4 patients who discontinued for non-medication related reasons (pregnancy and administrative) were classified as having continued MMF.

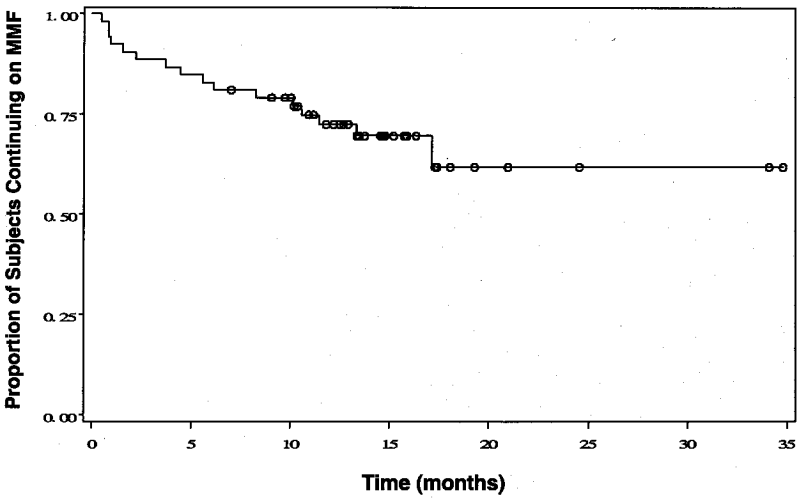

Figure 2. Kaplan-Meier estimate of proportion of patients continuing MMF as a function of time. (●: censored observation, indicates final point of followup for patients continuing MMF).

for prospective studies and may be limited when applied retrospectively.

Our results show that a wide range of MMF doses was well tolerated and associated with a good clinical response. Hence, drug dosing should be individualized and clinical trial design should account for variability of drug tolerance. Cost-effective techniques to measure levels of mycophenolic acid or its phenol glucuronide metabolite in blood by a single determination[16,17] may prove advantageous in clinical care or future research trials.

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Table 6. Clinical course variables among patients with renal disease at baseline, no renal disease at baseline, and all patients across the 3 study time points [data expressed as mean (SD)].

Variable	All Patients	Baseline Renal Disease (n = 26)	No Baseline Renal Disease (n = 28)
SLEDAI score			
Baseline	5.0 (4.3)	4.6 (3.7)	5.3 (4.8)
3 mos	3.5 (3.7)	2.9 (3.4)*	4.4 (4.0)**
Final	2.7 (3.8)*	2.5 (4.5)**	2.9 (3.0)*
Prednisone, mg			
Baseline	20.1 (15.4)	20.4 (15.3)	19.9 (15.7)
3 mos	12.6 (8.8)*	14.0 (10.4)**	11.1 (6.5)*
Final	12.2 (11.5)*	12.1 (11.8)**	12.2 (11.5)**
Serum creatinine, mg/dl			
Baseline	1.3 (1.0)	1.5 (1.3)	1.0 (0.2)
3 mos	1.2 (0.8)	1.4 (1.0)	1.0 (0.2)
Final	1.5 (1.6)	1.8 (2.1)	1.0 (0.3)
C3, mg/dl			
Baseline	98.3 (24.2)	96.8 (25.1)	99.8 (23.8)
3 mos	100.2 (28.2)	97.4 (33.4)	104.3 (18.5)
Final	104.3 (26.2)	101.7 (23.7)	107.5 (29.3)**
C4, mg/dl			
Baseline	21.2 (8.9)	23.5 (10.4)	19.0 (6.6)
3 mos	25.4 (22.4)	28.9 (28.3)	20.1 (5.3)
Final	20.2 (8.5)	21.0 (9.1)	19.2 (7.8)
Anti-dsDNA, log titer			
Baseline	2.9 (1.5)	3.0 (1.5)	2.8 (1.6)
3 mos	2.9 (1.6)	3.1 (1.6)	2.7 (1.6)
Final	2.8 (1.7)	3.1 (1.8)	2.4 (1.4)

All 3-month and final values compared to baseline using one-way ANOVA for repeated measures. * $p \leq 0.01$, ** $p \leq 0.05$, all other comparisons p = NS.

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