Mycophenolate Mofetil in Systemic Lupus Erythematosus: Efficacy and Tolerability in 86 Patients

CECILIA N. PISONI, FRANCISCO J. SANCHEZ, YOUSUF KARIM, MARIA J. CUADRADO, DAVID P. D'CRUZ, IAN C. ABBS, MUNTHER A. KHAMASHTA, and GRAHAM R.V. HUGHES

ABSTRACT. ***Objective.*** To assess the indications, efficacy, and tolerability of mycophenolate mofetil (MMF) in patients with systemic lupus erythematosus (SLE) resistant to other immunosuppressive therapy.

Methods. Records of 93 patients with SLE were retrospectively reviewed. Seven patients were excluded. The remaining 86 patients received other immunosuppressive drugs before MMF. Efficacy was measured by changes in daily oral prednisolone dose, European Consensus Lupus Activity Measurement Index (ECLAM), erythrocyte sedimentation rate (ESR), C-reactive protein, and dsDNA antibody titer. In renal patients, changes in serum creatinine, creatinine clearance, chromium-51 EDTA glomerular filtration rate (EDTA-GFR), and 24 hour urine protein excretion were also evaluated.

Results. Indications for MMF were mainly renal involvement (59% of patients), uncontrolled disease activity (14%), and other SLE related manifestations (13%). Overall, we found a significant reduction in the steroid dosage, ECLAM, ESR, and anti-dsDNA antibody titer. Renal patients (n = 35) showed a significant reduction in urinary 24 hour protein excretion. Levels of serum creatinine, creatinine clearance, and EDTA-GFR showed no significant change during treatment. Thirty-seven patients (42.8%) developed adverse events. Gastrointestinal intolerance in 25 (29%) and infections in 20 (23.2%) were the most frequent. The drug was discontinued in 14 (16.3%) patients due to side effects and 6 patients discontinued MMF because they achieved disease remission and were trying to conceive. MMF was stopped due to lack of efficacy in 12 patients.

Conclusion. Our data suggest that MMF is a good therapeutic alternative for patients with SLE and renal involvement or refractory disease activity. (J Rheumatol 2005;32:1047–52)

Key Indexing Terms:
MYCOPHENOLATE MOFETIL SYSTEMIC LUPUS ERYTHEMATOSUS
TREATMENT LUPUS NEPHRITIS LUPUS DISEASE ACTIVITY

Mycophenolate mofetil (MMF), an immunosuppressive agent, was initially used in the treatment of transplant recipients. It has a variety of immunosuppressive effects, including selective suppression of T and B lymphocyte proliferation, and has been used in many autoimmune inflammatory conditions[1].

Systemic lupus erythematosus (SLE) is a multisystem disease that can involve virtually any organ or system. Renal disease has been recognized as a major complication and several therapeutic approaches, all including immunosuppressive drugs such as cyclophosphamide or azathioprine, have been used. The short and longterm toxicity of these drugs limits their use in a substantial number of patients. Over the last 6 years MMF has emerged as an alternative mainly for patients refractory to other therapies. These studies have shown it is highly effective and generally well tolerated[2-4]. Following its early success in the treatment of lupus nephritis, MMF is now being used to control other SLE manifestations. Case reports and small case series with other indications for MMF use have recently appeared[1,3,5,6]. We evaluated the indications, efficacy, and safety of MMF in treatment of patients with SLE resistant to other immunosuppressive therapy.

MATERIALS AND METHODS

Patients and data collection. We retrospectively studied 93 SLE patients treated with MMF followed in the Louise Coote Lupus Unit at St. Thomas' Hospital, London. Two patients were excluded because they did not fulfil the American College of Rheumatology (ACR) criteria for SLE and 5 patients were excluded for missing data. All patients included in the analysis had ≥ 4 of the ACR classification criteria for SLE[7,8]. MMF was prescribed during the period between January 1998 and June 2003. Patients who received MMF were identified from hospital pharmacy recorded prescriptions. A systematic review of patient files, using a standard data collection protocol, was performed. Data were collected from the beginning of MMF treatment to the endpoint, defined as last followup or discontinuation date.

From the Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, London, UK.

C.N. Pisoni, MD, Research Fellow; F.J. Sanchez, MD, Research Fellow; Y. Karim, MRCP, MRCPath, Lecturer in Immunology; M.J. Cuadrado, MD, PhD, Consultant Rheumatologist; D.P. D'Cruz, MD, FRCP, Consultant Rheumatologist; I. Abbs, BSc, FRCP, Consultant Nephrologist; M.A. Khamashta, MD, PhD, FRCP, Consultant Physician; G.R.V. Hughes, MD, FRCP, Consultant Rheumatologist.

Address reprint requests to Dr. C.N. Pisoni, Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, 4th floor, Lambeth Wing, Lambeth Palace Road, London SE1 7EH, UK. E-mail: ceciliapisoni@yahoo.com.ar

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Baseline demographic characteristics, disease duration, clinical features, serology, associated antiphospholipid syndrome, previous immunosuppressive therapy, concomitant medication, and European Consensus Lupus Activity Measurement Index (ECLAM) were recorded at the initial timepoint of starting MMF[9]. Indications for MMF treatment, starting dose, maximum dose, duration of treatment, adverse effects, and reasons for drug discontinuation were obtained from review of the patient chart. Patients who received MMF for less than 3 months, those who received MMF as maintenance treatment after remission with cyclophosphamide, and those starting MMF in other hospitals were excluded from the efficacy analysis. Data for efficacy analysis were available for the majority of patients. Efficacy of MMF treatment was measured by changes in daily oral prednisolone dose, ECLAM, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), C3 fraction of complement, and double-stranded DNA (dsDNA) values between baseline and the final timepoint. The methodology for C3 changed during the period of study, and only results tested with the same technique are included. In renal patients, the following variables were added to efficacy evaluation: changes in serum creatinine, creatinine clearance, albumin, chromium-51 EDTA glomerular filtration rate (EDTA-GFR) measurements, and 24 hour urine protein excretion, between baseline and the final endpoint. Renal biopsies were studied by light, electron, and immunoperoxidase microscopy and classified according to the WHO classification for lupus nephritis[10].

Data analysis. The SPSS 11.01 statistical package was used for data management and analysis. Descriptive statistics including mean, median, and standard deviation were performed for all variables.

Baseline and followup data of patients treated for more than 3 months were compared by Wilcoxon's test for paired data to assess efficacy. Paired T test was used to assess efficacy when the variable distribution was normal. Chi-square was used to test associations between categorical variables. P values < 0.05 were considered statistically significant.

RESULTS

Baseline clinical measures. Patients' demographic and clinical details and concomitant medication are summarized in Table 1.

All patients received one or more immunosuppressive agents before starting MMF and 93.8% were treated with steroids. Azathioprine was always discontinued due to inefficacy or intolerance. Cyclophosphamide was discontinued in 26 (30.2%) patients after partial or no remission was achieved and in 4 (4.7%) patients after complete remission was obtained. In the remaining patients cyclophosphamide was stopped due to adverse events.

Indications for MMF therapy. The indications for treatment with MMF were: 59 patients (68.6%) lupus nephritis and 29 patients (31.6%) uncontrolled disease activity or other system involvement (Table 2). The mean time taking MMF treatment was 16 ± 12.71 months and the maximum dose was 1.39 ± 0.4 g (range 0.5–2.5 g).

Efficacy. Efficacy data were analyzed only in patients starting MMF treatment at St. Thomas' Hospital where full baseline data were available and who were followed for at least 3 months. The numbers of patients analyzed for measures relating to disease activity and renal outcome are given in Tables 3 and 4, respectively.

Disease activity. We found a significant reduction in the steroid dosage, ECLAM score, ESR, and anti-dsDNA antibody titer, and an increase in complement C3 levels. CRP did not show a significant reduction (Table 3).

Renal outcome. Protein excretion in 24 hours, steroid doses, and ECLAM showed significant reductions. Serum creatinine levels, creatinine clearance, and EDTA-GFR values showed no significant change during treatment (Table 4).

Other indications. The clinical response of patients with skin disease will be described in a separate publication. The 3 patients treated for hematological disorders, 2 with autoimmune hemolytic anemia, had a good response, and one patient with low platelet count remained stable undergoing MMF treatment. The single patient with transverse

Table 1. Clinical and demographic characteristics.

Clinical Characteristics	N = 86 (%)
Age, yrs, mean ± SD	36.83 ± 8.8
Female sex	76 (88.4)
Race	
Caucasian	44 (51.2)
Black	24 (27.9)
Asian	16 (18.6)
Other	2 (2.3)
Duration of SLE, yrs	10.2 ± 6.6
Renal histopathology, WHO classification	
I	1 (3)
II	0 (0)
III	11 (33)
IV	12 (36)
V	9 (27)
Previous immunosuppressive treatment	
Cyclophosphamide	43 (50)
Azathioprine	75 (87.2)
Methotrexate	10 (11.6)
Concomitant treatment	
Aspirin	18 (20.9)
Warfarin	22 (25.6)
Hydroxychloroquine	24 (27.9)
ACE inhibitors	23 (26.7)
AIIRA inhibitors	5 (5.8)
Diuretics	15 (17.4)

SLE: systemic lupus erythematosus, WHO: World Health Organization, ACE: angiotensin converting enzyme, AIIRA: angiotensin II receptor antagonist.

Table 2. Indication for treatment with MMF.

	N (%)
Lupus nephritis	59 (68.6)
Other indications	27 (31.6)
Disease activity	14 (16.3)
Skin involvement	6 (7.0)
Hematological disorder	3 (3.5)
Cerebral lupus	1 (1.2)
Lung involvement	1 (1.2)
Vasculitis	1 (1.2)
Transverse myelitis	1 (1.2)

Table 3. Efficacy evaluation of MMF treatment (n = 53 patients).

Variable	N	Initial	Followup	p
Steroid dose, mg/day	53	17.95 ± 10.98	10.86 ± 8.43	< 0.0001
ESR, mm/h	40	38.2 ± 30.24	29.19 ± 21.2	0.003
CRP, mg/l	39	9.29 ± 10.51	6.91 ± 4.74	NS
C3, g/l	34	0.66 ± 0.28	0.84 ± 0.31	< 0.0001
Anti-dsDNA, IU/ml	46	47.41 ± 43.72	30.3 ± 41.11	0.004
ECLAM score	51	3.83 ± 1.84	2.49 ± 1.59	< 0.0001

ECLAM: European Consensus Lupus Activity Measurement, NS: not significant.

Table 4. Efficacy evaluation of MMF treatment in renal patients (n = 35).

Variable	N	Initial	Followup	p
Steroid dose, mg/day	35	17.71 ± 10.57	9.38 ± 6.37	< 0.0001
ESR, mm/h	26	36.27 ± 27.54	28.9 ± 22.66	0.01
CRP, mg/l	24	7.95 ± 5.06	6.22 ± 2.72	NS
C3, g/l	23	0.66 ± 0.26	0.77 ± 0.26	< 0.003
Anti-dsDNA, IU/ml	33	40.63 ± 40.78	31.36 ± 42.19	NS
ECLAM score	35	3.66 ± 1.83	2.44 ± 1.61	0.002
Albumin, g/l	34	30.26 ± 5.92	31.69 ± 9.5	0.4
Serum creatinine, µmol/l	34	88.37 ± 30.5	84.44 ± 24.35	NS
Creatinine clearance, ml/min	13	91.74 ± 39.81	88.6 ± 23.63	NS
EDTA-GFR, ml/min	29	75.61 ± 26.37	71.43 ± 26.37	NS
24 hour proteinuria, g/24h	31	3.01 ± 2.5	1.85 ± 3.6	0.001

ECLAM: European Consensus Lupus Activity Measurement, EDTA-GFR: chromium-51 EDTA glomerular filtration rate, NS: not significant.

myelitis failed to respond. One patient with interstitial lung disease had improved transfer factors by DLCO with MMF treatment. The patient with vasculitis was lost to followup.

Toxicity and adverse effects. Eighty-six patients were included in this analysis (Table 5). Thirty-seven patients (42.8%) developed adverse events. Gastrointestinal (GI) intolerance (nausea and diarrhea) was the most frequent adverse event observed in 25 patients (29%), followed by infections in 20 (23.2%) patients. The development of infections was independent of corticosteroid dose, white blood cell count, and uremia. The mean dose of MMF was significantly higher (1.8 g/day) in patients who developed infections compared with those who did not develop infections (1.5 g/day; p = 0.03).

Table 5. Adverse events of MMF treatment.

	N (%)
Gastrointestinal	25 (29)
Infections*	20 (23.2)
Chest	8 (40)
Upper respiratory tract	4 (20)
Cellulitis	3 (15)
Herpes zoster	3 (15)
Fungal	2 (10)
Sepsis	2 (10)
Warts	2 (10)
Other	9 (45)
Depression	2 (2.3)
Hematological	1 (1.1)

* Some patients had more than one infection.

The drug was discontinued in 14 (16.3%) patients, (GI complaints: 7, infections: 4, depression: 2, hematological: 1). A reduction in MMF dose was enough to control side effects in 11 (12.8%) patients.

Six patients discontinued MMF because they achieved disease remission and were trying to conceive. In 12 patients MMF was stopped due to lack of efficacy; the mean MMF dose in these patients was 1.8 g/day.

Kaplan-Meier survival estimation showed that 16% of patients abandoned treatment within the first 3 months, and the probability of continued treatment at 1 year was 67.5% and at 30 months was less than 50% (Figure 1).

DISCUSSION

MMF is an immunosuppressive therapy that is routinely used in clinical transplants. Early reports indicated that it offered lower acute rejection rates than azathioprine-containing regimens in renal transplantation[11]. It is now being used in a variety of disease manifestations in SLE patients with good benefit. In active SLE, activated lymphocytes and autoantibodies are characteristic. MMF inhibits inosine monophosphate dehydrogenase (IMPDH), which catalyzes

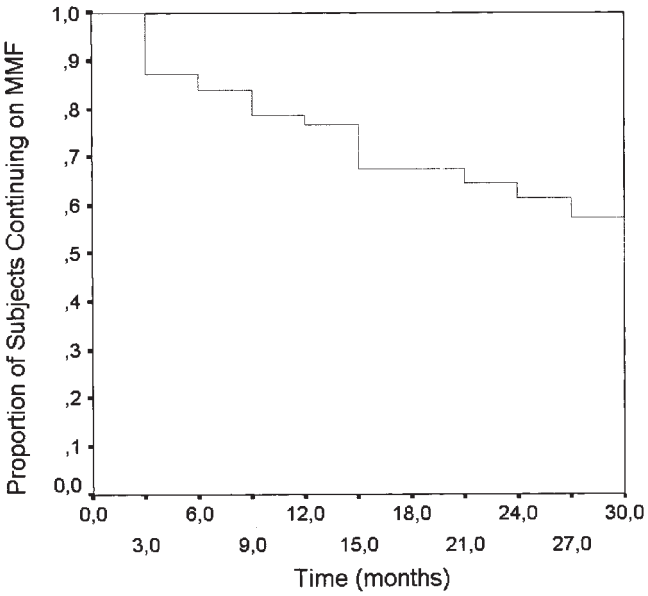

Figure 1. Kaplan-Meier survival estimation of patients continuing MMF over time.

a rate-limiting step in the de novo synthesis of purine nucleotides. Because lymphocytes are dependent on de novo synthesis, there is specific inhibition of T and B lymphocytes[3,12]. IMPDH has an inducible isoform upregulated only in proliferating lymphocytes. Mycophenolic acid, the active metabolite of MMF, inhibits this isoform 5 times more than the type I isoform present in resting lymphocytes[13].

Although MMF appears to have substantial potential, its exact role in therapy of lupus has not been fully clarified. Most studies have examined MMF use in lupus nephritis[12,14-16], particularly proliferative disease (WHO Class IV). However, MMF use in a small number of lupus patients has been reported for various other indications, such as refractory thrombocytopenia[17], refractory skin disease, uncontrolled disease activity[3,18], and pulmonary hemorrhage[19].

The treatment for proliferative lupus nephritis varies, particularly between Europe and North America, but generally involves intravenous cyclophosphamide [either National Institutes of Health (NIH) or low dose regimen] and corticosteroids[20,21]. The Euro-Lupus Study used intravenous cyclophosphamide followed by maintenance therapy with azathioprine[22]. Cyclophosphamide use has resulted in a reduction in mortality and endstage renal failure over the years, but is associated with a high rate of adverse events including amenorrhea, particularly relevant for young women with SLE, malignancy, and infections. Further, 15% are refractory to cyclophosphamide and 30% to 50% of the patients may still develop endstage renal disease[23].

There have been several studies since 1998 of the successful use of MMF to treat lupus nephritis, mainly class IV[2,24,25]. Chan, *et al* in 2000 treated 21 patients with class IV lupus nephritis with MMF and prednisolone, and compared them with 21 patients treated with oral cyclophosphamide and prednisolone followed by azathioprine[12]. They observed complete remission in 81% of the patients treated with MMF compared with 76% in the cyclophosphamide group, with a significant reduction of 24 hour proteinuria in both groups[12]. A more recent study[14] investigated the efficacy of MMF in 75 patients with biopsy proven proliferative lupus nephritis, 26 of whom were refractory to conventional therapy. Proteinuria over 24 hours, anti-dsDNA levels, SLE Disease Activity Index (SLEDAI) score, and hypocomplementemia were significantly improved after MMF treatment. Hu, *et al* followed 46 patients with proliferative lupus nephritis, 23 treated with MMF and the other 23 treated with cyclophosphamide pulse therapy, both groups receiving similar supplemental steroid treatment[15]. They showed reductions in 24 hour proteinuria. Repeat renal biopsies after 6 months of treatment in 15 MMF patients and 12 cyclophosphamide patients showed more marked reduction in glomerular immune deposits, with less glomerular necrosis, crescents, and vascular changes in the MMF group. A recent study from Kapitsinou, *et al* showed remission in 10/18 patients, with improvement in proteinuria and steroid-sparing effect[16]. The 4 patients with partial response had class V disease.

Contreras, *et al* treated 59 patients with class III, IV, and V lupus nephritis with intravenous cyclophosphamide (induction), and for the maintenance therapy the patients were randomized to azathioprine, MMF, or intravenous cyclophosphamide for 1 to 3 years. They observed that patients treated with MMF or azathioprine had a higher event-free survival rate for the endpoint of death and chronic renal failure compared with cyclophosphamide. The relapse-free survival endpoint was also higher in the MMF group compared with the cyclophosphamide group. The incidence of adverse events and hospitalizations was lower in the azathioprine and MMF group[26].

Ginzler, *et al* compared MMF with intravenous cyclophosphamide for induction therapy of active lupus nephritis (class III, IV, V). Seventy-one patients were randomized to MMF and 69 to the NIH intravenous cyclophosphamide protocol for a period of 24 weeks. The primary and secondary endpoints were complete and partial remission, respectively. There were 14 complete remissions with MMF compared to 4 in intravenous cyclophosphamide and 21 partial remissions taking MMF compared to 14 on intravenous cyclophosphamide. The investigators concluded that MMF was as effective as their standard regimen for induction therapy in proliferative lupus nephritis[27].

Pharmacotherapy in SLE has reduced morbidity and mortality, although the short and longterm toxicity of the immunosuppressants used to treat major organ involvement limit their use. In general, the most frequent adverse events

with MMF are GI, infectious, and hematological. GI side effects can improve with dose reduction, and on the whole these are not severe.

Patients with SLE appear to carry an increased risk of infection, although this risk is usually associated with the use of corticosteroids and immunosuppressants. A retrospective study of MMF tolerability in SLE showed 44% of patients experienced infections. The most common were cystitis, upper respiratory tract infection, bronchitis, and cellulitis[4]. In our group of patients, 23.2% had infections and we found a similar pattern, with mainly respiratory tract infection, cellulitis, and herpes zoster, although not cystitis.

Ginzler, *et al* found similar numbers of bacterial, fungal, and viral infections in both the MMF and intravenous cyclophosphamide groups, but deep infections (pneumonia, lung abscess, gram-negative sepsis, necrotizing fasciitis) occurred only in the cyclophosphamide group[27]. Chan, *et al* found no significant difference in infections between MMF and cyclophosphamide (oral) groups[12]. Kang and Park have suggested the incidence of infections in patients treated with MMF seems to be lower than in patients treated with cyclophosphamide[28].

Experience of clinical trials of MMF in renal transplantation showed an increased risk of tissue-invasive cytomegalovirus infections and of lymphoproliferative malignancies[11]. However, the risks may differ between SLE and transplant patients, as the latter often receive a 3-drug regimen. To date, there are no data available on malignancy in SLE patients treated with MMF. In a longterm followup study of 85 patients with psoriasis treated with mycophenolic acid for up to 13 years, the authors reported 7 neoplasias in 6 patients, similar to the normal population matched for age[29].

Bijl, *et al*[30] treated patients with SLE and elevated anti-dsDNA antibodies without clinical signs of disease activity with MMF for 6 months to prevent clinical relapse, and observed a significant reduction in these antibodies, but failed to demonstrate a reduction in SLEDAI. Gaubitz, *et al*[18] reported 10 patients treated with MMF, with significant reduction in disease activity as estimated by the Systemic Lupus Activity Measure (SLAM) and steroid doses. Riskalla, *et al* found significant reduction in SLEDAI and steroid dose at final timepoint of the study in both nonrenal and renal groups[4].

In our series, although lupus nephritis was the most common indication, MMF was used for refractory disease activity, skin involvement, hematological disease, and various other manifestations.

All patients in our group had been treated with azathioprine and/or cyclophosphamide before MMF treatment. In all patients previously treated with azathioprine and some treated with cyclophosphamide, these drugs had to be discontinued due to lack of efficacy or adverse events. None of our patients received MMF as a first-line drug. The promising results we and others have observed may alter this in the future. We found MMF was effective in reducing disease activity in patients with renal and nonrenal disease activity. We found a reduction in ECLAM score, steroid dosage, ESR, and anti-dsDNA and elevation of C3 complement fraction levels in the overall group and in renal patients. In our group of renal patients, we showed a significant reduction in 24 hour urinary protein excretion.

MMF appeared to be well tolerated, and the drug was discontinued due to adverse events in 16.3% of the patients. Patients tended to continue taking MMF unless toxicity developed or they wished to become pregnant. The Kaplan-Meier curve indicated that 67.5% of patients continued MMF at 1 year.

The optimal duration of maintenance therapy with MMF remains to be established. In general, our patients were not switched to other immunosuppressive agents from MMF for maintenance therapy, as we were concerned about the risk of relapse because they had previously failed other immunosuppressive therapy. The general exception was if the patient wished to become pregnant. Patients were advised not to contemplate pregnancy until they had been maintained in remission for an adequate period of time, at least 6 months. Birth malformations are reported in animal studies and hence the use of MMF in pregnancy is not advised[31]. In general, in our practice, patients were switched to azathioprine.

MMF appears to be a safe and successful treatment to maintain remission in patients with lupus nephritis and to control overall disease activity.

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