Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study

Konstantinos Tselios, Dafna D. Gladman, Jiandong Su, and Murray B. Urowitz

ABSTRACT. ***Objective.*** Mycophenolate mofetil (MMF), along with corticosteroids, is considered as the standard of care in lupus nephritis (LN); however, little is known regarding its efficacy in extrarenal manifestations of systemic lupus erythematosus (SLE). We aimed to determine its effectiveness in nonrenal SLE.

Methods. One hundred seventy-seven patients with SLE were enrolled; 105 for whom MMF was introduced for active LN (mean age 35.6 ± 10.7 yrs, mean disease duration 8.9 ± 7.8 yrs) and 72 for extrarenal manifestations (mean age 38.6 ± 11.7 yrs, mean disease duration 11.7 ± 9.2 yrs). The main indication for MMF initiation was based on the respective SLE Disease Activity Index element that was present at that time. Patients were subdivided according to the major nonrenal manifestation. Improvement was defined as the absence of the initial clinical or laboratory manifestation after 6 and 12 months.

Results. Cumulatively, the initial clinical manifestation or hematological abnormality was resolved in 42/72 nonrenal patients (58.3%) after 6 months and in 45/72 (62.5%) after 12 months. Corticosteroid dose was reduced in 44/72 patients (61.1%, $p < 0.001$, mean dose 18.4 ± 12.6 mg/day at baseline to 12.1 ± 9.0 mg/day after 12 mos, $p < 0.05$). In renal patients, 40 (38.1%) had complete resolution of the extrarenal manifestation after 6 months, while 53 (50.5%) achieved complete response after 12 months. Prednisone dose was reduced in 73/105 patients (69.5%) after 12 months (mean dose 29.2 ± 16.6 mg/day at baseline to 15.3 ± 9.7 mg/day, $p < 0.001$).

Conclusion. MMF seems to be an efficacious alternative in refractory to standard of care nonrenal manifestations of SLE in the long term, allowing for disease activity control and significant reduction in corticosteroid dose. (J Rheumatol First Release January 15 2016; doi:10.3899/jrheum.150779)

Key Indexing Terms:
MYCOPHENOLATE MOFETIL SYSTEMIC LUPUS ERYTHEMATOSUS
NONRENAL MANIFESTATIONS

Mycophenolate mofetil (MMF), along with corticosteroids, is considered as the standard of care in lupus nephritis (LN), either as induction or maintenance therapy[1,2,3]. It is currently recommended by the European League Against Rheumatism (EULAR) and the European Renal Association-European Dialysis and Transplant Association as the first choice in LN class III and IV (level of evidence 1, strength of statement A) and an equivalent choice in LN class V (level of evidence 2, strength of statement B)[4]. Further, the American College of Rheumatology (ACR) considers it equivalent to cyclophosphamide in LN class III/IV (level A) and pure membranous LN (class V); its use is also encouraged in LN with cellular crescents[5]. However, little is known regarding its efficacy in extrarenal manifestations of systemic lupus erythematosus (SLE) because most evidence comes from uncontrolled, observational studies and small case series[6,7,8]. In addition, in a posthoc analysis of the Aspreva Lupus Management Study (ALMS), the investigators concluded that MMF is efficacious in treating nonrenal manifestations, particularly mucocutaneous, musculoskeletal (MSK), and hematologic features[9].

The aim of our present study was the assessment of the effectiveness of MMF in nonrenal manifestations of SLE in 2 different patient cohorts with or without renal involvement.

MATERIALS AND METHODS

Using the electronic database of the University of Toronto Lupus Clinic

From the Centre for Prognosis Studies in Rheumatic Diseases, University of Toronto Lupus Clinic, University Health Network, Toronto, Ontario, Canada.

Konstantinos Tselios is financially supported by the Geoff Carr Fellowship from Lupus Ontario.

K. Tselios, MD, PhD, Centre for Prognosis Studies in Rheumatic Diseases, University of Toronto Lupus Clinic, University Health Network;
D.D. Gladman, MD, FCRPC, Centre for Prognosis Studies in Rheumatic Diseases, University of Toronto Lupus Clinic, University Health Network;
J. Su, MB, BSc, Centre for Prognosis Studies in Rheumatic Diseases, University of Toronto Lupus Clinic, University Health Network;
M.B. Urowitz, MD, FRCPC, Centre for Prognosis Studies in Rheumatic Diseases, University of Toronto Lupus Clinic, University Health Network.

Address correspondence to Dr. M.B. Urowitz, University of Toronto Lupus Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst St., 1E-410B, Toronto, Ontario M5T 2S8, Canada. E-mail: m.urowitz@utoronto.ca

Accepted for publication November 24, 2015.

longterm observational cohort study, we identified 333 patients with SLE who were ever treated with MMF since September 2002. All patients fulfilled the ACR 1997 revised criteria for SLE classification or had 3 criteria plus a histopathological proof of the disease (renal biopsy)[10]. Subsequently, patients were excluded for whom there were insufficient data for the calculation of the SLE Disease Activity Index 2000 (SLEDAI-2K)[11] at 6 and 12 months after drug initiation. Finally, 72 patients were included for whom MMF was introduced for extrarenal SLE manifestations and 105 patients for whom MMF was initiated for active LN.

All patients have provided written informed consent for studies being conducted in the University of Toronto Lupus Clinic and are approved by the University Health Network Research Ethics Board.

For nonrenal patients with SLE, the precise indication for MMF administration was documented by the respective clinical SLEDAI-2K element that was present at the date of drug initiation. In cases of concurrent existence of 2 or more clinical variables, the most severe manifestation, according to SLEDAI-2K weight, was considered as the main indication for MMF initiation. Twenty-three of these patients (31.9%) had renal involvement in the past, based on kidney biopsy, but LN was inactive when MMF was initiated [21/23, 91.3% were receiving maintenance therapy with azathioprine (AZA)]. Definition of inactive LN was based on no or low proteinuria level (< 0.5 g/day), absence of hematuria (< 5 red blood cells per high power field), aseptic pyuria (< 5 white blood cells per high power field) or casts (0–2 casts per low power field), and stable serum creatinine (as compared with previous and subsequent visits). Patients were further subdivided according to the main indication for which MMF was introduced [i.e., central nervous system (CNS) involvement, skin vasculitis, MSK disease, skin disease, serositis, and hematological disorders]. Additionally, immunological features [anti-dsDNA antibodies titers by Farr assay and complement factor 3 (C3)/C4 serum levels by nephelometry] were followed over time. All these manifestations were nonresponsive to standard of care treatment according to the attending physicians.

Patients with LN were also categorized in subgroups according to the same extrarenal manifestations.

For the evaluation of MMF efficacy, all patients were followed by the same physicians (DDG, MBU) for 6 and 12 months based on the SLEDAI-2K. Improvement was defined as the absence of the initial feature on the 6- and 12-month SLEDAI-2K sheet, indicating a complete resolution of the occasional clinical manifestation or laboratory abnormality.

Statistical analysis. Baseline patient characteristics such as age, sex, and SLE duration, along with disease activity (measured by SLEDAI-2K), laboratory tests, and treatment information at 6 and 12 months of followup were presented as mean ± SD or n (%) and were compared between baseline and 2 followup times; the paired Student t test and the McNemar test were the statistical methods for continuous and dichotomized variables, respectively. Baseline information between renal and nonrenal patients was compared using the Student t test and chi-square test. Organ system improvement percentages were calculated by dividing the number of patients improved by the baseline patients with corresponding organ involved. SAS 9.3 (SAS Institute Inc.) was used as the statistical analysis tool and p = 0.05 was set as the cutoff to reject the null hypothesis.

RESULTS

Nonrenal patients. The baseline characteristics of the patients are shown in Table 1. Briefly, the main indications for MMF initiation were CNS involvement (n = 11), skin vasculitis (n = 2), MSK manifestations (n = 19), skin disease (n = 27, 13 with inflammatory rash, 15 with alopecia, and 7 with mucosal ulcers, patients could have more than 1 manifestation), serositis (n = 8), and hematological abnormalities (n = 10). Forty-five patients were found to be serologically active (increased titers of anti-dsDNA antibodies and/or decreased C3/C4 complement levels). With regard to CNS involvement, 5 patients had organic brain syndrome (acute confusional state), 5 had refractory lupus headache, and 1 patient had psychosis. In all these patients, brain images from magnetic resonance imaging and/or single photon emission-computed tomography (SPECT) were suggestive of CNS involvement (mainly consisting of moderate to severe cerebral hypoperfusion on SPECT). MSK manifestations consisted of arthritis (concurrently affecting > 2 joints) in 18 patients and myositis in 1 patient; serositis consisted of pleuritis in 6 patients and pericarditis in 2, whereas hematological abnormalities consisted of moderate leukopenia and thrombocytopenia in 5 patients each (1 patient with severe thrombocytopenia, platelets < 20,000/μl).

In general, the initial clinical manifestation or hematological abnormality was reversed in 42/72 patients (58.3%) after 6 months and in 45/72 (62.5%) after 12 months. Detailed data for improvement in different subgroups are shown in Table 2 and Figure 1. With regard to CNS nonresponders, 2 patients had persistent lupus headache and 1 patient had refractory organic brain syndrome with evidence of persistent cerebral hypoperfusion on SPECT brain

Table 1. Demographic characteristics, previous therapy, and main clinical (renal and extrarenal) manifestations for mycophenolate mofetil initiation of the patients in both groups. P values result from the Student t test or chi-square test comparing 2 groups. Values are n (%) or mean ± SD unless otherwise specified.

Characteristics	Nonrenal, n = 72	Renal, n = 105	p
Female	65 (90.3)	86 (81.9)	0.122
Age at diagnosis, yrs	38.6 ± 11.7	35.6 ± 10.7	0.082
Race			
White	39 (54.2)	45 (42.9)	0.337
Black	19 (26.4)	28 (26.7)	
Asian	5 (6.9)	14 (13.3)	
Others	9 (12.5)	18 (17.1)	
Disease duration, yrs	11.7 ± 9.2	8.7 ± 7.8	0.02
Previous immunosuppressive			
treatment	45 (62.5)	63 (60)	
Azathioprine	21 (29.17)	42 (40)	
Cyclophosphamide	4 (5.56)	12 (11.43)	
Methotrexate	16 (22.2)	6 (5.7)	
Cyclosporine	0	3 (2.86)	
Others	4 (5.56)	0	
CNS involvement	11 (15.3)	7 (6.7)	0.063
Vasculitis	2 (2.8)	6 (5.7)	0.356
MSK features	19 (26.4)	11 (10.5)	0.006
Renal disease	0 (0)	105 (100)	< 0.001
Skin disease	27 (37.5)	30 (28.6)	0.212
Serositis	8 (11.1)	7 (6.7)	0.297
Immunologic abnormalities	45 (62.5)	85 (81)	0.006
Fever	1 (1.4)	5 (4.8)	0.223
Hematologic abnormalities	10 (13.9)	3 (2.9)	0.006

CNS: central nervous system; MSK: musculoskeletal; immunologic abnormalities: increased anti-dsDNA titers and/or decreased C3/C4 serum levels; C3: complement factor 3; C4: complement factor 4; hematologic abnormalities: systemic lupus erythematosus-related leukopenia or thrombocytopenia.

Table 2. Improvement of clinical and laboratory manifestations in 6 and 12 months. Values are n (%) unless otherwise specified.

Variables	Time	Nonrenal, n = 72	Renal, n = 108
CNS	Baseline	11	7
	6 mos	8 (72.7)	3 (42.9)
	12 mos	8 (72.7)	6 (85.7)
Vasculitis	Baseline	2	6
	6 mos	2 (100)	6 (100)
	12 mos	1 (50)	6 (100)
MSK manifestations	Baseline	19	11
	6 mos	11 (57.9)	10 (90.9)
	12 mos	14 (73.7)	11 (100)
Renal	Baseline	0	105
	6 mos	0 (0)	20 (19)
	12 mos	0 (0)	29 (27.6)
Skin disease	Baseline	27	30
	6 mos	7 (25.9)	10 (33.3)
	12 mos	11 (40.7)	16 (53.3)
Serositis	Baseline	8	7
	6 mos	6 (75)	4 (57.1)
	12 mos	5 (62.5)	7 (100)
Immunological abnormalities	Baseline	45	85
	6 mos	11 (24.4)	15 (17.6)
	12 mos	12 (26.7)	15 (17.6)
Hematological abnormalities	Baseline	10	3
	6 mos	8 (80)	2 (66.7)
	12 mos	6 (60)	2 (66.7)

CNS: central nervous system; MSK: musculoskeletal.

imaging. Concerning hematologic abnormalities, white blood cell count was increased from 2533 ± 572/μl at baseline to 4167 ± 1063/μl at 6 months and 4650 ± 1412/μl at 12 months. For thrombocytopenia (data available for 3 patients), platelet count was 49,667 ± 37,005/μl at baseline, 297,000 ± 316,564/μl at 6 months, and 88,000 ± 41,940/μl at 12 months.

SLEDAI-2K was reduced from 5.7 ± 4.4 at baseline to 4.1 ± 4.1 at 6 months ($p = 0.002$) and to 4.5 ± 4.8 after 12 months (Table 3). In addition, corticosteroid dose (prednisone or equivalent) was significantly reduced (18.4 ± 12.6 mg/day at baseline to 15.6 ± 10.5 mg/day at 6 mos, $p < 0.05$, and 12.1 ± 9.0 mg/day after 12 mos, $p < 0.05$) whereas 44/72 patients (61.1%) were able to reduce the prednisone dose after 12 months ($p < 0.001$). It should be mentioned that 19/72 patients (26.4%) were managed with an increase in prednisone dose in parallel with MMF initiation (from 16.5 ± 15.3 mg/day to 17.03 ± 13.04 mg/day). In addition, 5/72 patients (6.9%) were treated with intravenous (IV) methylprednisolone pulses shortly before MMF initiation (4 patients received one 500-mg pulse and 1 patient received 1000 mg once); no other corticosteroid pulses were administered during the followup period.

Mean MMF dose was 1350 ± 712.5 mg/day at baseline, 1512.5 ± 725 mg/day at 6 months, and 1662.5 ± 800 mg/day at 12 months (Table 3). Forty-five patients (45/72, 62.5%) were taking immunosuppressives (other than MMF) on the date of MMF initiation (details are given in Table 1); after 12

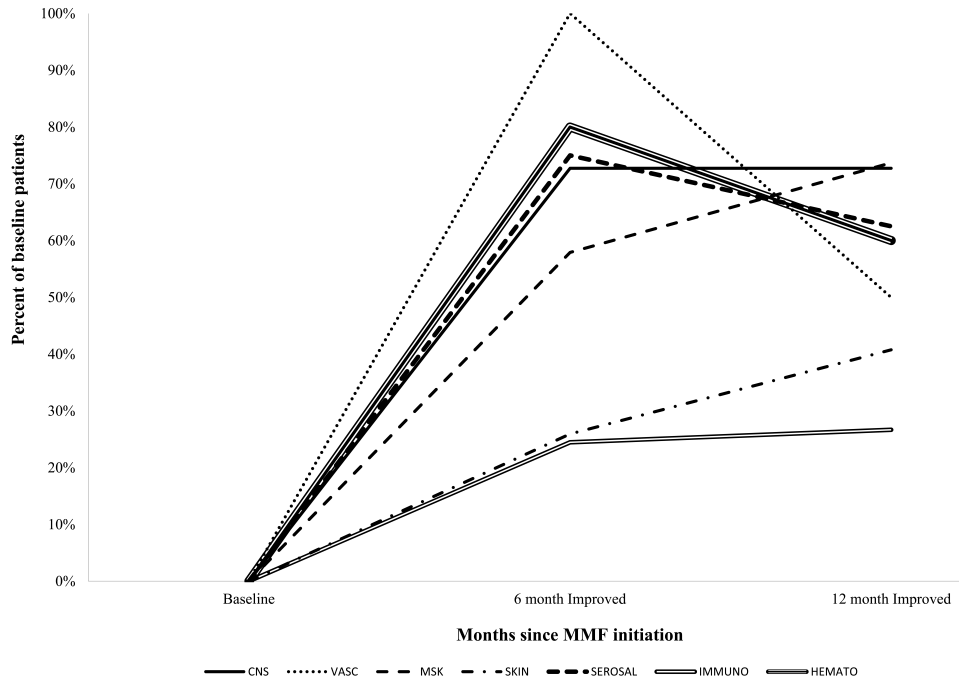

Figure 1. Percentage improvement of the various clinical and laboratory SLEDAI-2K manifestations in 6 and 12 months after MMF initiation in patients with nonrenal disease. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; MMF: mycophenolate mofetil; CNS: central nervous system involvement; VASC: vasculitis; MSK: musculoskeletal disease; SKIN: skin disease; SEROSAL: serositis; IMMUNO: immunologic abnormalities; HEMATO: hematologic abnormalities.

Table 3. Alterations in SLEDAI and prednisone dose, mean MMF dose, and evolution of immunologic abnormalities in our patients. P values result from the paired Student t test or McNemar test comparing 6/12 months with baseline. Values are n (%) or mean ± SD unless otherwise specified.

Variables	Time	Nonrenal, n = 72	p	Renal, n = 105	p
SLEDAI-2K	Baseline	5.7 ± 4.4		13.8 ± 6.5	
	6 mos	4.1 ± 4.1	< 0.005	9.6 ± 5.8	< 0.0001
	12 mos	4.5 ± 4.8		9.0 ± 6.2	< 0.0001
No. patients with a SLEDAI-2K decrease by 4	Baseline	0		0	
	6 mos	15 (20.8)	< 0.05	37 (35.2)	< 0.001
	12 mos	13 (18.1)	< 0.05	42 (40)	< 0.001
No. of patients with a SLEDAI-2K increase by 4	Baseline	0		0	
	6 mos	5 (6.9)		6 (5.7)	
	12 mos	7 (9.7)	0.32	6 (5.7)	1
Clinical SLEDAI-2K, excluding immunological and hematological abnormalities	Baseline	4.8 ± 4.1		12.5 ± 6.2	
	6 mos	3.4 ± 3.8	0.0072	8.6 ± 5.5	< 0.001
	12 mos	3.8 ± 4.7	0.1332	7.9 ± 5.9	< 0.001
No. patients who reduced prednisone dose	Baseline	0		0	
	6 mos	33 (45.8)	< 0.001	66 (62.9)	< 0.0001
	12 mos	44 (61.1)	< 0.001	73 (69.5)	< 0.0001
No. patients who increased prednisone dose	Baseline	19 (26.4)		33 (31.4)	
	6 mos	16 (22.2)	< 0.001	18 (17.1)	< 0.001
	12 mos	11 (15.3)	< 0.001	15 (14.3)	< 0.001
Average prednisone dose, mg/day	Baseline	18.4 ± 12.6		29.2 ± 16.6	
	6 mos	15.6 ± 10.5	< 0.05	21.2 ± 12.4	< 0.005
	12 mos	12.1 ± 9.0	< 0.05	15.3 ± 9.7	< 0.005
MMF dose, mg/day	Baseline	1350 ± 712.5		1687.5 ± 1000	
	6 mos	1512.5 ± 725		1625 ± 950	
	12 mos	1662.5 ± 800		1687.5 ± 1000	
Anti-dsDNA, Farr assay, +	Baseline	34 (47.2)		72 (69.9)	
	6 mos	27 (38)		61 (58.1)	< 0.05
	12 mos	26 (36.1)		59 (57.3)	< 0.05
Low C3	Baseline	25 (34.7)		64 (60.9)	
	6 mos	18 (25.0)	< 0.05	44 (41.9)	< 0.05
	12 mos	19 (26.4)	< 0.05	44 (42.3)	< 0.05
Low C4	Baseline	12 (16.7)		29 (27.6)	
	6 mos	8 (11.1)	< 0.05	15 (14.3)	< 0.05
	12 mos	7 (9.7)	< 0.05	19 (18.3)	< 0.05

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; MMF: mycophenolate mofetil; C3: complement factor 3; C4: complement factor 4.

months, 14 of them continued the treatment [methotrexate (MTX) in 10/72, 13.9% and others in 4/72, 5.6% at 6 and 12 mos, respectively]. Patients with inactive LN were receiving maintenance treatment with AZA. Additional medications used were antimalarials (hydroxychloroquine or chloroquine) in stable doses in 58 patients (80.6%). MMF was discontinued after 6 months in 6 patients, 4 because of side effects (2 with recurrent bacterial infections and 2 with gastrointestinal side effects), and 2 because of lack of efficacy; after 12 months, the drug was discontinued in another 5 patients (2 because of recurrent infections and 3 because of lack of efficacy).

After successful resolution of the initial manifestation after 6 months, relapses were observed in 1 patient with vasculitis, 1 patient with serositis, and 2 patients with hematological abnormalities (Table 2).

Renal patients. In patients with LN (n = 105, baseline characteristics in Table 1), 7 had concomitant CNS involvement, 6 vasculitis, 11 MSK features, 30 skin disease (10 with inflammatory rash, 21 with alopecia, and 8 with mucosal ulcers, patients could have more than 1 manifestation), 7 serositis, 5 fever, and 3 hematological abnormalities. Eighty-five patients had active serology (positive anti-dsDNA antibodies and/or low C3/C4 complement levels). CNS manifestations (more than 1 distinct manifestation could occur in 1 patient) consisted of seizures in 1 patient, acute psychosis in 4, organic brain syndrome (acute confusional state) in 6, visual disturbances in 4, cranial neuropathy in 1, lupus headache in 1, and cerebrovascular event in 1. In all these cases, other possible diagnoses were carefully excluded. MSK manifestations consisted of arthritis (concurrently affecting > 2 joints) in 11 patients; serositis consisted of 5 cases with pleuritis, 1 with pericarditis, and 1 with concomitant pleuritis and pericarditis, whereas hematological abnormalities included 2 patients with leukopenia and 1 with thrombocytopenia.

After 6 months, 40 patients had complete resolution of the extrarenal manifestation (38.1%), while 53 (50.5%) achieved complete response after 12 months. Concerning CNS involvement, only 1 patient, experiencing organic brain syndrome, did not respond after 12 months (based on

persistent cerebral hypoperfusion on SPECT imaging). Interestingly, 20 patients (19%) showed complete response concerning LN in 6 months and 29 (27.6%) in 12 months. With regard to immunologic features, 15 patients (14.3%) were negative for anti-dsDNA antibodies and had normal C3/C4 complement levels at 6 and 12 months. Detailed data for improvement in different subgroups are shown in Table 2 and Figure 2.

SLEDAI-2K was reduced from 13.8 ± 6.5 at baseline to 9.6 ± 5.8 at 6 months and 9.0 ± 6.2 after 12 months ($p < 0.0001$). Prednisone dose was reduced in 66/105 patients (62.9%) at 6 months and in 73 (69.5%) after 12 months; mean prednisone dose was reduced from 29.2 ± 16.6 mg/day to 15.3 ± 9.7 mg/day after 12 months ($p < 0.001$; Table 3). Thirty-three patients (31.4%) increased the prednisone dose at the date of MMF initiation from 19.34 ± 14.56 mg/day to 25.06 ± 15.46 mg/day. In addition, 7/105 patients (6.7%) were treated with IV methylprednisolone shortly before MMF introduction (1 patient with 1000 mg, 2 patients with 500 mg, 3 with 250 mg, and 1 with 40 mg; each received 1 pulse). Mean MMF dose was 1687.5 ± 1000 mg/day at baseline and remained stable at 12 months. Other medications used were antimalarials (hydroxychloroquine or chloroquine) in stable doses in 82 patients (78.1%). At the time of MMF initiation, 63/105 patients (60%) were taking immunosuppressives (other than MMF; details given in Table 1); after 12 months, these drugs were continued in 9 patients (MTX in 6/105, 5.7% and cyclosporine in 3/105, 2.9%). Of note, MMF was continued uninterrupted for 12 months in all these patients; in addition, no extrarenal relapse was observed during the followup period.

DISCUSSION

MMF is a selective inhibitor of inosine monophosphate dehydrogenase that catalyzes purine nucleotide synthesis; through this mechanism, it inhibits T and B cell proliferation and autoantibody production. Further, it was demonstrated that it induces activated T cell apoptosis, downregulation of the expression of adhesion molecules, and inhibits dendritic cell maturation[12]. Several clinical trials have demonstrated its efficacy and safety in LN, and thus it is considered as the standard of care in such patients[4,5]. Surprisingly, there are no solid data with regard to its efficacy in other SLE manifestations; most evidence comes from uncontrolled and observational studies. In our present observational cohort study, we showed that MMF has considerable efficacy in neuropsychiatric, MSK, cutaneous, serological, and hematological lupus manifestations, as well as a significant corticosteroid-sparing effect.

With regard to CNS involvement, MMF along with corti-

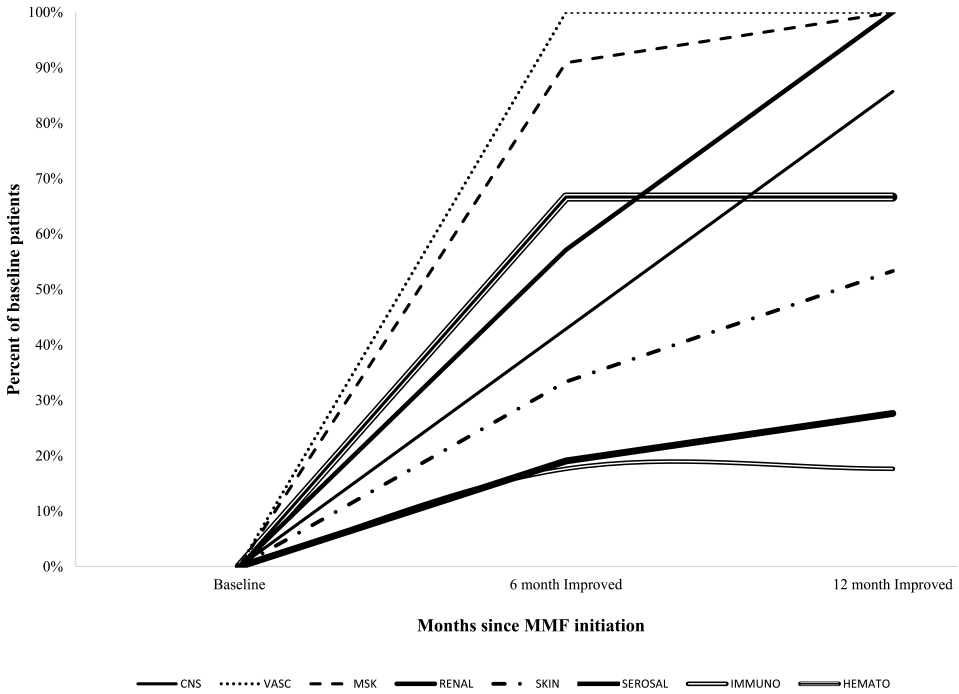

Figure 2. Percentage improvement of the various extrarenal clinical and laboratory SLEDAI-2K manifestations in 6 and 12 months after MMF initiation in patients with renal disease. Renal improvement refers only to complete resolution of lupus nephritis according to the SLEDAI-2K description (no casts, no hematuria, no proteinuria > 0.5 g/day). SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; MMF: mycophenolate mofetil; CNS: central nervous system involvement; VASC: vasculitis; MSK: musculoskeletal disease; SKIN: skin disease; SEROSAL: serositis; IMMUNO: immunologic abnormalities; HEMATO: hematologic abnormalities.

costeroids led to complete resolution of the initial clinical manifestation (mainly lupus headache and organic brain syndrome) in 14/18 patients (77.8%) after 12 months. Previous information on this issue is sparse and comes from case series on myelopathy and acute confusional state[13,14,15,16]. In the posthoc analysis of the ALMS study, 3 patients in the MMF arm had neurologic manifestations at baseline and 1 of them did not respond after 24 weeks[9]. Further, in a recent retrospective study, neuropsychiatric involvement was the main indication for MMF initiation in 6 patients with SLE; however, the authors did not provide detailed information on their clinical phenotype and course[17]. Because of the lack of evidence, MMF is not mentioned as an additional immunosuppressive to corticosteroids in the EULAR recommendations for the management of neuropsychiatric SLE[18]; however, it is believed that it may be involved in refractory manifestations that are characterized by autoimmune-mediated inflammatory mechanisms[19].

Concerning MSK manifestations, mainly arthritis, we observed a complete clinical response in 25/30 patients (83.3%) cumulatively after 12 months. Similar findings were reported by Ginzler, *et al*[9]; in the MMF arm, 23/27 patients (85.2%) showed a significant improvement in the MSK domain of the British Isles Lupus Assessment Group (BILAG) index after 24 weeks. Previous reports do not describe articular involvement in detail; in the study by Conti, *et al*, MMF was initiated for MSK manifestations in 36 patients, but no separate analysis for their response was conducted[17]. In the only randomized study published thus far, 1 out of 2 patients with arthritis responded completely after 16 weeks of MMF treatment[8]. The natural course of lupus arthritis is usually benign (nonerosive) and responds satisfactorily to antimalarials and/or low-dose corticosteroids[20]. However, based on our data, MMF could be a reliable alternative in refractory cases.

In our present study, active mucocutaneous involvement (consisting of inflammatory rash and/or alopecia and/or mucosal ulcers) was observed in 57 patients; in 27 (47.4%) of them, it was resolved after 12 months. Ginzler, *et al* reported a significantly higher proportion of patients achieving remission in the mucocutaneous domain of the BILAG index (45/56, 80.4% after 24 weeks), albeit with higher doses of concomitant corticosteroids[9]. In a systematic review, Mok concluded that MMF is effective in cutaneous SLE manifestations because a favorable response was observed in 11/16 patients (68.8%); of note, 12 patients had chronic SLE skin lesions refractory to other immunosuppressives[6]. Gammon, *et al* reported that the addition of MMF to existing therapy led to a complete resolution of antimalarial-resistant discoid lupus erythematosus features in 15/24 patients; in that study, MMF was used in considerably higher doses (2750 mg/day on average)[21]. On the contrary, Yahya, *et al* reported that none of the 3 patients with skin disease who were treated with MMF achieved remission after 16 weeks[8]. The diversity of cutaneous manifestations in SLE, and consequently, differences in the underlying pathogenetic mechanisms, differences in MMF doses, and duration of treatment and concomitant medications may account for these discrepancies.

Serositis (pleuritis and/or pericarditis) was improved in 12/15 of our patients (80%) after 12 months. These manifestations are rarely resistant to adequate doses of corticosteroids; thus, the need for MMF is justified in selected cases and mainly as a steroid-sparing agent. In the only randomized trial of MMF, there was only 1 patient with serositis who did not respond after 16 weeks[8].

With regard to hematological abnormalities (leukopenia and thrombocytopenia), we observed a significant improvement in 8/13 patients (61.5%) cumulatively after 12 months. Because of the study design, we did not include patients with autoimmune hemolytic anemia because this feature is not a part of the SLEDAI. Our findings are in agreement with previous reports; in the ALMS posthoc analysis, 33/62 patients (53.2%) with hematologic abnormalities achieved remission after 24 weeks[9]. Although MMF confers a risk for bone marrow suppression, it was shown to be comparatively safer than AZA and MTX and may increase all peripheral blood cell lineages[22]. Because of this, its use is recommended for refractory severe cytopenias[23,24].

Serologic activity (increased anti-dsDNA titers and/or decreased C3/C4 levels) was reversed after 6 months in 26/130 patients (20%); the precise calculation of mean values was not feasible because of the differences in reference ranges. Moder, *et al* reported a significant decrease in anti-dsDNA titers in 23 nonrenal patients after 6 months of MMF treatment whereas increase in C3 levels did not reach statistical significance[7]. On the contrary, in the ALMS posthoc analysis, almost half of the patients treated with MMF achieved normalization of the C3/C4 levels after 24 weeks; 39% of them had high titers of anti-dsDNA antibodies that eventually fell to low titers at the end of the study[9].

Further, MMF is considered to prevent short-term (6 mos) disease flares when added to treatment of patients with increasing anti-dsDNA titers[23]. However, the question of flare prevention needs further investigation. Posalski, *et al* reported that the flare rate is increased in the second and third year of MMF treatment with patients developing new clinical manifestations[25]. That cross-sectional study was performed in 75 patients (53 with renal involvement) with 63 patients taking MMF after 12 months and less than one-third of them remaining on the drug treatment in the 5-year followup; moreover, there were 22 drug withdrawals because of gastrointestinal toxicity. In this context, definite conclusions on MMF efficacy seem unwarranted. In our present study, such questions could not be addressed because of the short followup (12 mos). However, we did observe disease flares (based on SLEDAI-2K increase ≥ 4) in 7.3% of our patients at 12 months.

Nevertheless, concomitant MMF use allowed for a significant reduction in corticosteroid dose (about 33% in nonrenal and 50% in renal patients after 12 mos). These findings are in agreement with previous reports[7,9,17,23]. In addition, patients with active LN had a better response in most clinical extrarenal manifestations at 12 months. This finding may be attributed to the higher cumulative corticosteroid dose received by these patients as compared with the nonrenal patients, because they were administered higher doses of prednisone at all timepoints (baseline, 6 mos, and 12 mos). However, MMF dose was higher for renal patients at the same timepoints and may have contributed to disease activity control.

The limitations of our present study lie in its retrospective nature; in this context, the precise MMF treatment effect cannot be reliably differentiated from the concomitantly used therapies, particularly corticosteroids. Additionally, the relatively short followup period (12 mos) does not allow for generalization of our findings beyond 1 year of continuous administration. However, our study provided data on a larger group of patients than previously reported and the information provided had been prospectively collected.

MMF, even in moderate doses, is an efficacious alternative in refractory nonrenal manifestations of patients with SLE, allowing for disease activity control and a significant reduction in corticosteroid requirement. Further randomized clinical trials could offer additional information on this issue.

REFERENCES

1. Mak A, Cheak AA, Tan JY, Su HC, Ho RC, Lau CS. Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. Rheumatology 2009;48:944-52.
2. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al; ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886-95.
3. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, et al. Treatment for lupus nephritis. Cochrane Database Syst Rev 2012;12:CD002922.
4. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al; European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-82.
5. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012;64:797-808.
6. Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. Scand J Rheumatol 2007;36:329-37.
7. Moder KG, Amin S, Mazlumzadeh M, Crowson C, Ytterberg S. The effect of mycophenolate mofetil on patients with active non-renal SLE. Clin Exp Rheumatol 2007;25:932.
8. Yahya F, Jasmin R, Ng CT, Cheah TE, Sockalingam S. Open label randomized controlled trial assessing the efficacy of mycophenolate sodium against other conventional immunosuppressive agents in active systemic lupus erythematosus patients without renal involvement. Int J Rheum Dis 2013;16:724-30.
9. Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley MA; ALMS Group. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel group clinical trial. Arthritis Rheum 2010;62:211-21.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
11. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
12. Villaroel MC, Hidalgo M, Jimeno A. Mycophenolate mofetil: an update. Drugs Today 2009;45:521-32.
13. Pisoni CN, Sanchez FJ, Karim Y, Cuadrado MJ, D'Cruz DP, Abbs IC, et al. Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. J Rheumatol 2005; 32:1047-52.
14. Lhotta K, Wurzner R, Rosenkranz AR, Beer R, Rudisch A, Neumair F, et al. Cerebral vasculitis in a patient with hereditary complete C4 deficiency and systemic lupus erythematosus. Lupus 2004; 13:139-41.
15. Jose J, Paulose BK, Vasuki Z, Danda D. Mycophenolate mofetil in neuropsychiatric systemic lupus erythematosus. Indian J Med Sci 2005;59:353-6.
16. Mok CC, Mak A, To CH. Mycophenolate mofetil for lupus related myelopathy. Ann Rheum Dis 2006;65:971-3.
17. Conti F, Ceccarelli F, Perricone C, Massaro L, Cipriano E, Pacucci VA, et al. Mycophenolate mofetil in systemic lupus erythematosus: results from a retrospective study in a large monocentric cohort and review of the literature. Immunol Res 2014;60:270-6.
18. Bertsias GK, Ioannidis JP, Aringer M, Bollen E, Bombardieri S, Bruce IN, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074-82.
19. Hanly JG. Diagnosis and management of neuropsychiatric SLE. Nat Rev Rheumatol 2014;10:338-47.
20. Artifoni M, Puéchal X. How to treat refractory arthritis in lupus? Joint Bone Spine 2012;79:347-50.
21. Gammon B, Hansen C, Costner MI. Efficacy of mycophenolate mofetil in antimalarial-resistant cutaneous lupus erythematosus. J Am Acad Dermatol 2011;65:717-21.
22. Bolad W, Magder L, Petri M. Immunosuppressive drugs in SLE differ in their hematologic side-effects. Arthritis Rheum 2009;60 Suppl 10:282.
23. Pego-Reigosa JM, Cobo-Ibáñez T, Calvo-Alén J, Loza-Santamaría E, Rahman A, Muñoz-Fernández S, et al. Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. Arthritis Care Res 2013;65:1775-85.
24. Levine AB, Erkan D. Clinical assessment and management of cytopenias in lupus patients. Curr Rheumatol Rep 2011;13:291-9.
25. Posalski JD, Ishimori ML, Wallace DJ, Weisman MH. Does mycophenolate mofetil prevent extra-renal flares in systemic lupus erythematosus? Results from an observational study of patients in a single practice treated for up to 5 years. Lupus 2009;18:516-21.