Mycophenolate Mofetil Therapy in Lupus Nephritis: Clinical Observations

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Abstract. Controlled clinical trials in renal transplantation have demonstrated that mycophenolate mofetil is well tolerated and has lower renal transplant rejection rates than azathioprine regimens. This study reports on the clinical experiences at two institutions with mycophenolate mofetil (MMF) for severe lupus nephritis. Twelve patients with relapsing or resistant nephritis previously treated with cyclophosphamide therapy and one patient who refused cyclophosphamide as initial therapy for diffuse proliferative nephritis but accepted MMF were included. During combined MMF/prednisone therapy, serum creatinine values remained normal or declined from elevated values: mean change in serum creatinine was $-0.26 \pm 0.46 \mu\text{M/L}$, $P = 0.039$. Proteinuria significantly decreased: mean change in urine protein-to-creatinine ratios was $-2.53 \pm 3.76$, $P = 0.039$. Decreased serum complement component C3 and elevated anti-double-stranded DNA antibody levels at baseline improved in some, but not all, patients. The mean initial dose of MMF was 0.92 g/d (range, 0.5 to 2 g/d). The mean duration of therapy was 12.9 mo (range, 3 to 24 mo). Adverse events included herpes simplex stomatitis associated with severe leukopenia ($n = 1$), asymptomatic leukopenia ($n = 2$), nausea/diarrhea ($n = 2$), thinning of scalp hair ($n = 1$), pancreatitis ($n = 1$), and pneumonia without leukopenia ($n = 1$). Recurrence of the pancreatitis led to discontinuation of MMF in this patient; all other adverse events resolved with dose reduction. It is concluded that MMF is well tolerated and has possible efficacy in controlling major renal manifestations of systemic lupus erythematosus. Controlled clinical trials are needed to define the role of MMF in the management of lupus nephritis.

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disorder characterized by abnormalities in T and B cell function and frequent renal involvement. The treatment of patients with SLE who have severe glomerulonephritis remains controversial. Clinical trials of intermittent intravenous cyclophosphamide therapy demonstrate greater long-term renal, but not overall, survival compared with corticosteroid therapy (1–4). Longer duration of cyclophosphamide therapy is associated with fewer relapses of nephritis and better renal outcome (4). However, a significant proportion of patients with proliferative lupus nephritis demonstrates poor renal response to intermittent intravenous cyclophosphamide (CyP) therapy (5,6). The optimal therapy for patients with CyP-resistant or relapsing lupus nephritis remains unclear. Increased exposure to CyP is associated with increased risk of infection, infertility, and long-term risks of malignancy (7).

Mycophenolate mofetil (MMF) is hydrolyzed to mycophenolic acid (MPA), the active immunosuppressant compound (8). MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, a critical, rate-limiting enzyme in the de novo synthesis of purines (9). Because lymphocytes require a fully functioning de novo pathway for purine synthesis and proliferation, MMF functions as a relatively selective antimetabolite. MMF exerts a fivefold more potent inhibition of the inducible isoform of inosine monophosphate dehydrogenase expressed in stimulated lymphocytes compared with the isoform constitutively expressed in resting cells (10). In vitro, MMF blocks proliferation of both B and T cells, inhibits antibody formation and the generation of cytoxic T cells, and decreases the expression of adhesion molecules on lymphocytes impairing their ability to bind to endothelial cells (11–13). In a murine model of lupus nephritis, MMF therapy prolongs overall survival and delays the onset and severity of nephritis (14). Historical data on the effectiveness of MPA as a single agent in the treatment of psoriasis (15) and small pilot studies suggest that MMF therapy is beneficial in patients with other autoimmune disorders, including rheumatoid arthritis, autoimmune hemolytic anemia, antineutrophil cytoplasmic antibody-associated vasculitis, and IgA nephropathy (16–18). A recent study of MMF in glomerular disease included successful short-term treatment of two patients with lupus nephritis (19). Herein, we report a clinical series of 13 patients treated with MMF for severe lupus nephritis at two academic centers, the University of North Carolina at Chapel Hill (UNC) and Ohio State University (OSU).
Materials and Methods

Patient Selection

Patients in these studies had SLE with documentation of at least four criteria from the 1982 revised American College of Rheumatology criteria for classification of SLE (20). Twelve patients were offered MMF therapy for resistant or relapsing lupus nephritis; patient 13 received MMF after he and his parents refused initial CyP therapy for diffuse proliferative lupus nephritis. All but patient 13 had previously received one or more courses of oral or intravenous cyclophosphamide therapy, and many had also received previous courses of azathioprine (AZA) or methotrexate therapy (Table 1). With the exception of patient 13, patients were offered MMF therapy in an attempt to avoid further CyP therapy and with the hope that MMF would be more effective than AZA in treating active lupus nephritis. Patients 1 to 6 had undergone renal biopsy at varying points to define lupus nephritis before initial CyP therapy. Patients 7 to 13 had undergone repeat renal biopsy for recurrent nephritis before considering further immunosuppressant therapy and were required to demonstrate active diffuse proliferative glomerulonephritis (DPGN; World Health Organization [WHO] class IV). Nine patients had a history of SLE-DPGN previously treated with corticosteroids and CyP for at least 6 mo before repeat biopsy. Four patients had received two prior courses of CyP. Four patients had declining renal function while receiving CyP and two had relapsing nephritis after attaining remission with CyP.

Each patient was informed that the use of MMF (CellCept®, Roche Laboratories, Nutley, NJ) represented a new application of MMF in treating human diseases. The patients were offered MMF therapy as an alternative to further cyclophosphamide therapy for nephritis as an FDA-approved drug for a nonapproved indication.

Therapy

MMF doses were chosen arbitrarily. The starting dose for MMF was 0.5 to 2 g/d. The MMF dose was increased to maximum doses of 1.0 to 2.5 g/d with the goal to suppress renal sediment activity and improve serum creatinine, unless gastrointestinal or hematologic toxicity developed.

Prednison therapy varied with SLE activity. Four patients received pulse intravenous methylprednisolone at 7 mg/kg per d for 3 d: three for rapidly increasing serum creatinine and/or proteinuria and active urinary sediment and one with severe arthralgias, rash, and polyserositis without rapidly declining renal function. In the remaining patients, prednisone doses remained lower (5 to 40 mg per day) when MMF therapy was begun.

Agents to control BP included diuretics, angiotensin-converting enzyme inhibitors (ACE), calcium channel blockers, angiotensin receptor blockers (ARB), and beta blockers as prescribed by the treating physician. Those patients receiving ACE, calcium channel blockers, or ARB did not have their doses changed during MMF therapy.

Statistical Analyses

All mean values are shown ± 1 SD and P values < 0.05 are considered statistically significant. Changes in laboratory values from baseline to last follow-up were compared using a nonparametric test for paired data.

Results

Baseline Clinical Parameters

Table 1 displays the baseline clinical characteristics of the study patients. The patients included four men and nine women.

<table>
<thead>
<tr>
<th>Patient-Center</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Race</th>
<th>SLE〈 (yr)</th>
<th>Renal Biopsy</th>
<th>Previous Therapy</th>
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<tbody>
<tr>
<td></td>
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<td></td>
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<td>Class〈</td>
<td>Year</td>
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<td>W</td>
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<td>13-UNC</td>
<td>16</td>
<td>M</td>
<td>W</td>
<td>3</td>
<td>IV</td>
<td>1996</td>
</tr>
</tbody>
</table>

a W, white; B, black; H, Hispanic; SLE, systemic lupus erythematosus; CyP, cyclophosphamide; AZA, azathioprine; MTX, methotrexate; MMF, mycophenolate mofetil.
b Patients were followed through either Ohio State University (OSU) or The University of North Carolina (UNC).
c Years since diagnosis of SLE.
d World Health Organization (WHO) classification. Patients 1 to 6 had dominant renal manifestations with renal biopsy in the past; patients 7 to 13 underwent renal biopsy before MMF therapy.
e Organ involvement at the start of MMF therapy: K, kidney; J, joint; S, skin; H, hematologic.
g Given in months/total dose (g).
h Intravenous CyP.
with average age 34.8 (range, 16 to 48 yr old). The racial
distribution included one Hispanic, four black, and eight white
patients. The mean duration of SLE was 9.5 yr (range, 2.5 to 20
yr). Nine patients had active renal disease as the sole manifes-
tation of lupus activity at entry. Renal pathology had demon-
strated WHO class IV in all but patient 1, who manifested
WHO class V nephritis.

**Therapy**

Table 2 shows the MMF and prednisone therapy used during
this study. The mean duration of therapy was 12.9 mo (range,
3 to 24 mo). During follow-up, the MMF dose tended to
decrease either in response to MMF side effects or to determine
whether SLE remission could be maintained at a lower dose of
MMF. The prednisone dose tapering schedule during MMF
therapy varied by practitioner, but generally occurred at the
rate of 10 mg each 2 to 4 wk after the first month until a
maintenance dose of 5 to 10 mg of prednisone was reached.
Two patients discontinued prednisone therapy during treatment
with MMF.

**Renal Outcomes**

Table 3 shows the renal and serologic parameters at baseline
and at most recent testing. Mean duration of follow-up was
13.2 mo (range, 3 to 24). Proteinuria significantly decreased
from a mean protein-to-creatinine ratio (P/C) at entry of 5.45 ±
3.37 to 2.92 ± 2.52; the mean change in P/C ratios was
−2.53 ± 3.76; \( P = 0.039 \). As can be seen in Figure 1,
proteinuria declined during MMF therapy in 10 patients. Seven
of the 10 patients with nephrotic-range proteinuria at baseline
showed decreased urine protein-to-creatinine ratios of less than
3.5 at last follow-up. As shown in Figure 2, serum creatinine
either remained stable or improved in all patients with the
exception of patient 9, who discontinued therapy due to pan-
creatitis. Mean serum creatinine significantly declined from
149.0 ± 88.5 at entry to 123.2 ± 62.4 \( \mu \text{M/L} \) at last follow-up;
mean change in serum creatinine was −0.26 ± 0.46; \( P =
0.039 \). Excluding patient 9 from analysis, urine protein-to-
creatinine ratios showed a mean change of −3.31 ± 2.62 \( P =
0.012 \) and serum creatinine showed a mean change of −0.34 ±
0.37, \( P = 0.012 \).

Serum C3 level increased in four patients with hypocomple-
mentemia at entry, but decreased from normal values in patient
9 after discontinuation of MMF therapy. Serum anti-double-
stranded DNA levels fell in four of the six patients who
initially had high anti-double-stranded DNA levels. Not shown
is that abnormal urine sediments (hematuria and/or urinary
acellular casts) were present at baseline in all 13 patients. At last
testing, the abnormal urine sediments have reverted to normal
in six of 13 patients.

**Toxicity**

White blood cell counts were measured at 1, 2, and 4 wk
after the start of MMF therapy and then at least 4 to 8 wk
thereafter. Patients 4 and 6 became leukopenic. The white
count returned to normal with reduction in the MMF dose.
However, the leukopenia in patient 6 was severe and was
associated with severe herpes simplex stomatitis. She had
received MMF 1.5 g/d for 2 mo by the time the severe leuko-
penia occurred. She is now receiving 1 g/d MMF and main-
taining a normal white count. Patient 13, with long-standing
immune-mediated leukopenia, had an increase in white blood
cell counts while receiving MMF. Patient 4 experienced no-
ticeable scalp hair loss. The MMF dose was decreased in
response to these complaints. Three patients developed mild
gastrointestinal symptoms of nausea and/or diarrhea. The
symptoms disappeared with a reduction in the MMF dose.
Patient 8 developed severe nausea, vomiting, and diarrhea

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Dose MMF (g/d)</th>
<th>Current Dose MMF (g/d)</th>
<th>Duration of MMF (mo)</th>
<th>Total Dose MMF (g)</th>
<th>Initial Dose Prednisone (mg/qd)</th>
<th>Current Dose Prednisone (mg/qd)</th>
<th>Duration of Prednisonea (mo)</th>
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<td>Pulse</td>
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</table>

a Duration of prednisone = duration of prednisone since institution of MMF.

b Pulse = 7 mg/kg per d times 3 d of intravenous methylprednisolone.
associated with volume depletion requiring withholding therapy and reinstitution at lower dose. At MMF doses of 0.5 g/d, patient 9 developed pancreatitis (abdominal discomfort, weight loss, and elevated serum amylase and lipase) that recurred on rechallenge with MMF. Abdominal ultrasound remained normal, and no long-term sequelae have been noted at 6 mo since MMF was discontinued.

**Discussion**

The treatment of patients with severe lupus nephritis remains controversial. Corticosteroids and intermittent intravenous CyP therapy remain the mainstay of therapy with improved renal survival at the cost of long-term adverse events, including increased risk of infection, infertility, avascular necrosis, osteoporosis, and long-term risks of malignancy (7). MMF was recently approved for clinical use on the basis of three large prospective controlled double-blind trials in renal transplantation (21–23). In those trials, MMF (2 or 3 g daily) was shown to be superior to azathioprine (1 to 2 mg/kg daily) or placebo in preventing renal allograft rejection. With most immunosuppressive agents, increasing the degree of immunosuppression increases the likelihood of side effects of immunosuppression.

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**Table 3.** Laboratory values at the start of MMF therapy (baseline) and at last follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Months Follow-Up</th>
<th>Change in P/C Ratio</th>
<th>Baseline Serum Creatinine (μmol/L)</th>
<th>Baseline C3 (g/L)</th>
<th>Last Serum Creatinine (μmol/L)</th>
<th>Last C3 (g/L)</th>
<th>Baseline anti-DNA</th>
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a P/C, protein-to-creatinine; ND, not done; Neg, negative.
b Serum creatinine in mg/dl = μmol/L ÷ 88.4.
c Serum complement, C3 in mg/dl = g/L ÷ 0.01.
d Farr assay with normal <50. All other tests at OSU performed using a crithidia assay with normal as negative. At UNC, an enzyme-linked immunoabsorbant assay was used with negative as normal.
including infection and bone marrow suppression. However, experience from controlled clinical trials in renal transplantation shows that MMF may be an exception to this generalization because the MMF-treated patients were able to achieve a greater degree of immunosuppression (less renal transplant rejection) yet suffered little increase in the incidence of infection or bone marrow suppression (24). Tissue-invasive cytomegalovirus infection was increased among patients receiving 3 g daily (21–23). In these multidrug immunosuppressive regimens, lymphoproliferative disease including lymphoma developed in three patients receiving MMF compared with zero in the azathioprine group (21) and in four receiving MMF compared with one in the azathioprine group (23). Use of MMF as a single agent may have less risk of malignancy and infection. Long-term therapy of 85 patients with psoriasis for up to 13 yr with mycophenolic acid, the parent compound of MMF, demonstrated no increased cancer rate (15). Therapy of rheumatoid arthritis using MMF as a single agent in more than 600 patients demonstrated primarily gastrointestinal side effects similar to those observed in our patients (nausea, vomiting, diarrhea). No clinically significant hematologic, hepatic, or nephrotoxic toxicity has been noted (16). Data presented in abstract form reporting efficacy and toxicity in more than 350 patients with RA show similar adverse events (25).

Recently, MMF therapy in a murine model of lupus has been shown to improve survival and decrease renal disease with marked reduction in autoantibody formation (14). Similar results are reported in abstract form in other murine strains with lupus-like disease, although improved renal histology and proteinuria were not uniformly associated with changes in serologic markers of lupus activity (26,27). The single previous report of MMF therapy in human lupus nephritis notes improvement in two patients with proliferative nephritis at 2 and 3 mo of therapy (19). The present study examines the outcomes of 13 patients receiving combined MMF/prednisone therapy for severe lupus nephritis. We observed significant improvement in serum creatinine levels and proteinuria over a mean duration of therapy of 12.9 mo (range, 3 to 24 mo). With one exception, our patients tolerated MMF without adverse events requiring discontinuation of the drug. Serologic measures of disease activity improved in some, but not all, patients. To date, two patients were able to discontinue prednisone therapy and remain on MMF as a single agent for nephritis. Long-term follow-up of all patients continues.

Many of our study patients manifested predictors of adverse renal outcome of lupus nephritis at the start of MMF therapy, including elevated serum creatinine, heavy proteinuria, WHO class IV renal pathology, history of recurrent flares of nephritis (28), and black race (5,6). The improvement in proteinuria observed in our patients during MMF therapy could not be attributed to changes in antihypertensive therapy, which was unchanged during this period.

Our results suggest that the doses of MMF usually used in management of renal transplant patients (2 to 3 g/d) may not be needed in lupus patients. MMF dosages in the range of 0.5 to 1.5 g/d may be sufficient to treat lupus nephritis. At these lower doses, MMF was generally well tolerated. The predominant manifestations were gastrointestinal toxicity observed even in those receiving low-dose MMF. MMF is tightly protein bound, and patients with nephrotic syndrome and decreased serum albumin may have increased unbound fraction (29). Substantial thinning of scalp hair was seen in one patient, which reversed with a reduction in MMF dose. The only serious toxicity noted in this study was one patient who developed severe neutropenia complicated by herpes simplex stomatitis, which was reversible. One patient was hospitalized for pneumonia during MMF therapy without leukopenia.

There are important limitations to studies such as this in which patients serve as their own controls, particularly if patients chosen for study are manifesting a relapse (e.g., increase in proteinuria). Under those circumstances, a decrease in proteinuria during an experimental treatment may not represent...
improvement in the underlying disease process. Rather, it may represent proteinuria spontaneously “regressing” to its average value (regression to the mean). However, it is unlikely that regression to the mean can explain the improvement observed during MMF therapy in our patients. Regression to the mean is most relevant to conditions that have a relatively high rate of spontaneous remission, e.g., idiopathic membranous nephropathy. However, it is very unusual for patients with severe lupus nephritis to show spontaneous improvement in proteinuria and renal function, particularly large improvement over a short period of time as we observed in most of our patients. Thus, the improvement observed during MMF and prednisone therapy was likely the result of that treatment. Nevertheless, the above interpretation is a hypothesis that must be tested in controlled, prospective, randomized trials. We suggest that the results of the present study provide strong justification for considering MMF therapy for testing in such trials. We suggest further that the results of the present study provide strong justification for considering MMF therapy for testing in such trials. We suggest that the results of the present study should prove useful in trial design by providing objective data regarding sample size calculation, doses of MMF, and the side effects likely to be encountered in patients with lupus nephritis.

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