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# Mycophenolate mofetil treatment for primary glomerular diseases

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**Mycophenolate mofetil treatment for primary glomerular diseases.**

*Background.* Treatment of primary glomerular diseases may be unsuccessful or have potential toxicities. Therefore, we evaluated the use of mycophenolate mofetil (MMF) for empirical treatment of primary glomerulopathies.

*Methods.* Forty-six patients with biopsy-proven primary glomerulopathies received MMF for ≥3 months as adjunctive or primary treatment. Median (range) 24-hour urine protein to creatinine ratio ($U_{p/c}$) and serum creatinine at the start and end of MMF therapy were compared using the Wilcoxon signed-ranks test.

*Results.* Overall, the median $U_{p/c}$ decreased from 4.7 (range <0.1, 20.3) to 1.1 (<0.1, 14.3; $P < 0.001$) at the end of MMF treatment with no significant change in median serum creatinine 1.3 (0.6 to 6.1) to 1.2 (0.5 to 6.5) mg/dL. Median serum albumin increased from 3.4 (1.4, 4.6) to 4.1 (1.7, 48) g/dL ($P < 0.001$) and the median serum cholesterol decreased from 270 (148, 795) to 220 (140, 309) mg/dL ($P < 0.001$) post-treatment. For those with minimal change disease, a complete steroid withdrawal was accomplished in 5/6 steroid dependent patients. Focal segmental glomerulosclerosis (FSGS) patients had a median $U_{p/c}$ that decreased from 2.7 (0.1, 20.3) to 0.8 (<0.1, 8.2; $P = 0.001$) in 18 patients. In membranous nephropathy (MN) patients, the median $U_{p/c}$ decreased from 7.3 (0.1, 18.5) to 1.5 (<0.1, 14.3) ($P = 0.001$) in 17 patients. No significant change in median serum creatinine was detected in FSGS or MN patient groups during treatment.

*Conclusions.* Empirical MMF therapy in the majority of patients with primary glomerulopathies was well tolerated and achieved the goals of steroid withdrawal, improvement of nephrotic syndrome, and stabilization of renal function.

Our initial report of treatment of seven patients with various glomerular diseases with mycophenolate mofetil (MMF) showed that partial or complete remissions of nephrotic proteinuria could be achieved in patients with relapsing minimal change disease, membranous nephropathy, and lupus nephritis [1]. Since that time, several additional reports have been published about the clinical efficacy of MMF for the treatment of lupus nephritis [2–4]. In addition, an increasing number of publications have reported favorable responses of various experimental models of glomerular diseases to MMF [5–15], and several additional reports have indicated the clinical efficacy in some patients with primary glomerulopathies [16–18] and pauci-immune necrotizing glomerulonephritis (abstracts; Heering et al, *J Am Soc Nephrol* 9: 456A-7A, 1998; Wen-Ling et al, *J Am Soc Nephrol*, 9: 496A, 1998; Radhakrishnan et al, *J Am Soc Nephrol* 10: 114A, 1999) [19].

The purpose of this study was to determine the efficacy of MMF in the empiric treatment of a group of 46 patients with primary glomerular disease, including intermediate-term follow-up for five (non-lupus) of the patients in our earlier report [1].

## METHODS

### Study population

The study population consisted of patients who attended the outpatient nephrology treatment of a large tertiary referral hospital between 1996 and 1999, who had biopsy proven glomerulonephritis complicated by nephrotic syndrome and/or renal insufficiency, and who received at least three months of treatment with MMF. Patients with secondary forms of glomerulonephritis, such as secondary FSGS from hyperfiltration injury (for example, sickle cell disease) were excluded from this analysis. The most frequent indications for the utilization of MMF as adjunctive (or sometimes primary) treatment of these patients included steroid-resistant (19.7%) or steroid-dependent nephrotic syndrome (32.6%). Other indications included cyclosporine (CsA)-resistant or CsA-dependent nephrotic syndrome or serious side effects from or intolerance of steroid or CsA; azathioprine (AZA)

**Key words:** mycophenolate mofetil, nephrotic syndrome, focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, renal insufficiency.

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dependence; deteriorating renal function; a patient's refusal of steroid treatment; and relapses in progressive renal insufficiency with efforts to discontinue cyclophosphamide (CTX).

### Treatment regimen

All patients were counseled regarding the unproven efficacy and unknown long-term side effects of MMF therapy. This was a retrospective analysis of our clinical practice performed without a formal protocol, and therefore Institutional Review Board (IRB) approval was not obtained. In the majority of patients, MMF was initiated at 0.5 to 0.75 g BID and advanced as appropriate or as tolerated to 0.5 g TID or 1.0 g BID, with one patient receiving 1.5 g BID. Given the reported alterations in the pharmacokinetics of MMF and its metabolite, mycophenolic acid (MPA), in patients with marked reductions in glomerular filtration rate, the dose was carefully titrated and limited to 1.5 g or less daily in most patients with advanced renal insufficiency. The MMF dose was decreased by 25 to 33% for persistent or moderately severe gastrointestinal symptoms. MMF was discontinued temporarily if the total white blood cell (WBC) decreased to $<4000/\mu L$ or if the patient developed a febrile illness or unacceptable gastrointestinal symptoms. It was discontinued permanently if hepatic enzymes increased >2 times the upper limits of normal without other cause or if there developed evidence of malignancy.

The majority of patients (67%) received variable doses of steroid concomitant with initiation of MMF therapy, ranging from very low doses (such as, methylprednisolone 8 mg every other day) to high dose daily steroid or a cyclic oral steroid minipulse strategy [1]. Oral methylprednisolone (MP) minipulse therapy consisted of MP administration in four two-week cycles: 3 mg/kg/day $\times$ 3 days (maximum 240 mg/day and 2 mg/kg/day if age >60 year old) followed by a lower dose for the next 11 days (24 mg/day in cycle 1, 16 mg/day in cycle 2, 12 mg/day in cycle 3, and 8 mg/day in cycle 4). In the absence of relapse, this was followed by 8 mg qod $\times$ 2 weeks and then 4 mg qod $\times$ 2 weeks and then discontinued. In patients receiving other steroid regimens, an effort was made to withdraw and, if possible, discontinue the steroid over the initial three to four months of MMF therapy. Four patients were treated with CsA (#11, 26, 28, 32); one patient was treated with AZA and one with CTX (#37) at the start of MMF therapy. Three patients had short courses of overlapping CsA treatment for six weeks (#26) and two weeks (#11, #32). The CTX dependent patient had a progressive reduction in dose as MMF was introduced over four weeks.

Twenty of the 46 patients were receiving either angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor antagonist (AIIRa) therapy prior to initiation of MMF. In most of those patients who were not receiving either therapy, the ACEi or AIIRa had been discontinued because of intolerance. In hypertensive patients, one or more antihypertensive agents were prescribed and the dosage titrated in an attempt to achieve blood pressures $\leq$130/80 mm Hg. All patients were advised regarding appropriate dietary restrictions including a low sodium (2 g/day) diet. No attempt was made to pursue an aggressive protein restricted diet.

### Follow-up

Clinical and laboratory parameters were monitored on a monthly basis for the initial three to six months of MMF treatment, then at variable intervals thereafter. Laboratory parameters included complete blood count (CBC), serum creatinine ($S_{Cr}$), blood urea nitrogen (BUN), albumin, non-fasting cholesterol, and aspartate aminotransferase (AST). Protein and creatinine excretion rates were measured from spontaneously voided, non-supervised, 24-hour urine collections or from 'spot' morning urine samples (7.8% of measurements) when the former could not be obtained. These latter samples were provided by the patient during the clinic visit and were thus obtained at approximately the same time of day throughout the study period. In order to avoid inaccuracies due to the under- or over-collection of the 24-hour urine samples, proteinuria was adjusted for the concomitant creatinine excretion of results expressed as the urine protein-to-creatinine ratio ($U_{p/c}$). In addition, data on the use of ACEi/AIIRa and 3-hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors was abstracted from the medical records, where there was a definite comment regarding the use or non use of the medication type.

### Study end points

This study reports the outcome with the first consecutive treatment course with MMF and provides additional information regarding the subsequent clinical course. The primary study outcomes were the change in the $U_{p/c}$ ratio and serum creatinine, comparing the levels at the start of MMF treatment with those at the end of the MMF treatment period. The end of MMF treatment was defined as the completion of therapy or the latest data available at the time of collation and analysis. For proteinuria, a complete remission was defined as a reduction in $U_{p/c}$ to $<0.3$; a partial remission as a 50% or greater reduction in $U_{p/c}$, with a post-study $U_{p/c}$ of $\geq 0.3$; stable proteinuria as a reduction of less than 50%, with a post-study $U_{p/c}$ of $\geq 0.3$; and a deterioration as any increase in the $U_{p/c}$ over a baseline value that was $\geq 0.3$. In addition, the proportion of patients with initial nephrotic range proteinuria ($U_{p/c} \geq 2.5$) whose proteinuria had decreased to the sub-nephrotic ($U_{p/c} < 2.5$) range by the end of the follow-up is reported.

Responses in excretory renal function, in those pa-

tients with renal insufficiency, were assessed based on changes in serum creatinine before and at the end of treatment. Renal insufficiency was defined as a serum creatinine >1.4 mg/dL for men and >1.2 mg/dL for women. A favorable response included either a >15% decrease in serum creatinine or stabilization of the serum creatinine in a patient with rapidly rising values prior to MMF treatment. Rapidly rising serum creatinine was defined as a sustained increase ≥20% within 40 weeks prior to initiating MMF treatment. These patients had a baseline serum creatinine of ≥ 2.5 mg/dL at the start of MMF therapy. This time period was selected after review of dates when results were available, but before any comparative analysis was performed. Changes of renal function were also estimated using the four-variable simplified MDRD glomerular filtration rate (GFR) equation (abstract; Levey, *J Am Soc Nephrol* 11:155A, 2000). This formula uses age, race, serum creatinine, and sex to estimate GFR per 1.73 $m^2$ and has been highly correlated with GFR estimates using the original validated six variable ($S_{Cr}$, BUN, albumin, sex, age, race) equation used in the MDRD study [20].

For convenience, patients were defined as being on an increased dose of ACEi, AIIRa, or HMG CoA reductase inhibitors if they either started the agent or increased their dose of these medications during the course of the study; a stable dose was defined as being on the same dose or a clinically equivalent dose of a similar agent; and a decrease in dose was defined as either stopping or reducing the dose of the agent during the course of the study.

### Statistical analysis

The internal consistency of the data was assessed using time trend analysis (identifying values which differed substantially from the previous recorded values) and using box plots to identify outlying values for a given distribution; the accuracy of the identified values was confirmed by comparison with the original clinical record. Wilcoxon signed-ranks test was used as appropriate to compare data from the start and end of the treatment period, as defined above. In cases where there was incomplete paired data, analysis was conducted on available data with the number of subjects included in the analysis clearly stated. In all analyses a two-tailed type I error rate of 0.05 was used. Analyses were performed using SPSS Base 7.5 (SPSS, Inc., Cary, NC, USA) Values are presented as median (range) unless otherwise stated.

## RESULTS

### Total study group

This patient cohort was comprised of 18 women and 28 men, 78.3% were Caucasian, 17.4% African American, and 4.3% Asian. The mean (standard deviation) age was 45.5 years (16.4), range 16 to 78 years. The primary glomerular diseases represented included minimal change disease (MCD) in 15.2%, focal segmental glomerulosclerosis (FSGS) in 39.1%, membranous nephropathy (MN) in 37%, and miscellaneous etiologies in 8.7% [comprised of 3 patients with IgA nephropathy (IgAN), and 1 with membranoproliferative glomerulonephritis (MPGN)]. At the time of study entry 31 patients (67.4%) had nephrotic range proteinuria and 23 (50%) had renal insufficiency. Baseline $U_{p/c}$ and serum creatinine were 4.7 (<0.1 to 20.3) and 1.3 mg/dL (0.6 to 6.1), respectively. Overall, 67.4% were treated with steroids in addition to MMF and 43% by an ACE inhibitor (51% excluding the patients with MCD) prior to initiating MMF. At the end of the treatment period, 23 of 46 (50%) were on ACEi (59% if MCD excluded). The median (range) dose and duration of MMF therapy was 2 g/day (0.75 to 3.00) and 8 months (3 to 26). The demographic, clinical, and treatment details of individual patients, stratified by histopathologic diagnosis, are provided in Table 1. Follow-up data on patients completing a course of MMF is summarized in Table 2.

The $U_{p/c}$ pre MMF treatment was 4.7 (<0.1 to 20.3) and decreased significantly to 1.1 (<0.1 to 14.3) at the end of the MMF treatment period ($P < 0.001$; Fig. 1A). Over the course of treatment, 7 patients (15.6%)—including 5 who were initially nephrotic—had a complete remission of proteinuria, with a median percent reduction of 98%; 17 patients (37.8%)—including 15 nephrotics—had a partial remission, with a median percent reduction of 74%, and 5 patients (11.1%)—including 2 nephrotics—had an increase in proteinuria. Sixteen of the 31 (51.6%) initially nephrotic patients improved to having non-nephrotic range proteinuria by the end of the study.

The serum albumin ($N = 39$) increased significantly from 3.4 (1.4 to 4.6) g/dL pre-MMF to 4.1 (1.7 to 4.8) g/dL ($P < 0.001$; Fig. 1B). The serum cholesterol ($N = 29$) decreased from 275 (168 to 795) mg/dL to 218 (140 to 309) mg/dL at the end of the MMF treatment period ($P < 0.001$; Fig. 1C). The change in mean arterial pressure (MAP; $N = 39$) was −5.3 (−32 to 19.3) mm Hg ($P = 0.008$). Similar significant changes were present for the individual diastolic and systolic blood pressure (data not shown).

As shown in Table 3, there was no significant change in the measured serum creatinine over the course of the study. However, the overall GFR as estimated by 100 multiplied by the reciprocal of serum creatinine or the modified four-variable MDRD formula significantly increased. Using the four-variable MDRD formula, GFR increased from 59.4 (11.4, 191.0) mL/min/1.73 $m^2$ to 67.3 (10.3, 191.0) mL/min/1.73 $m^2$ ($P = 0.032$; Fig. 1D and Table 4). Renal insufficiency resolved in 4 of the 23 (17.4%) patients with renal insufficiency initially, 3 with

**Table 1.** Clinical course of MMF treatment cohort

| Sex/race age/patient | MMF treatment indication | Duration *months* | Dose *g* | Steroid | ACEi/ AIIRa (+/−) | Scr pre→post (mo) *mg/dL* %Δ | Up/c pre→post (mo) %Δ | Comments/latest follow-up |
|---|---|---|---|---|---|---|---|---|
| MCD | | | | | | | | |
| 1) 46AAF | SD/CsAD | 6 | 0.75 BID | None | − | 1.0 → 1.0 (6) NA | 6.0 → 0.1 (6) CR | 2 relapses retreated with MMF; sustained CR $S_{Cr}$ = 1.2, 5 mo after MMF D/C |
| 2) 35W F | SD | 26 | 0.75 BID | MP64 mgQD | − | 1.1 → 0.9 (26) NA | 6.0 → <0.1 (26) CR | Complete steroid withdrawal; sustained CR 6 mo after MMF D/C |
| 3) 23WM | SD/CsAI | 6 | 0.75 BID | P20 mQD | − | 0.8 → 0.8 (6) NA | 4.6 → 2.8 (6) −39% | Relapse when *P* < 10 mgQD; Hodgkins lymphoma dx post 3 yrs of P and 6 mo of MMF; S/P chemo ℞ sustained CR 17 mo after MMF D/C; complete steroid withdrawal after chemotherapy |
| 4) 41WM | SD/CsAD | 6 | 1.0 BID | MP Mini | − | 1.3 → 1.3 (6) NA | 2.4 → <0.1 (6) CR | Complete steroid withdrawal by 3 mo; sustained CR 2-1/2 yrs after MMF D/C |
| 5) 35AAF | SD | 11 | 1.0 BID | P20 mgQD | − | 1.0 → 0.7 (2) NA | <0.1 → <0.1 (11) | Complete steroid withdrawal; sustained CR 1 yr after MMF D/C |
| 6) 69WM | SD/CsAD | 3 | 1.0 BID | P20 mgQD | − | 1.7 → 1.6 (3) NA | 5.3 → 5.8 (3) +9% | MMF resistant, CR with Tacrolimus and Scr = 1.7 13 mo after MMF D/C; complete steroid withdrawal after Tacrolimus |
| 7) 74W F | SD | 6 | 0.75 BID | P40 mgQD | − | 0.6 → 0.7 (5) NA | 4.4 → 0.38 (5) −91% | Complete steroid withdrawal; stable after 2 month MMF D/C |
| FSGS | | | | | | | | |
| 8) 65WM | SD/↑Scr | 11 | 0.75 BID | MP12 mgQD | − | 2.5 → 2.6 (12) +% | 2.0 → 2.1 (12) +5% | Complete steroid withdrawal; $S_{Cr}$ = 4.3, 3 yrs after D/C, Up/c = 1.8 15 mo after MMF D/C |
| 9) 32WM | ↑Scr | 10 | 0.5 BID | None | − | 6.1 → 6.5 (10) +7% | ND — | Rapidly rising $S_{Cr}$ before MMF with slower rise thereafter; continues on MMF ℞ |
| 10) 28WM | NS | 4 | 0.75 BID | None | + | 2.0 → 2.0 (4) | 2.8 → 0.7 (4) −75% | Reversible leukopenia at 5 mo; CR 3 mo after MMF D/C and $S_{Cr}$ = 2.0 8 mo after MMF D/C |
| 11) 29WM | SD/CsAD | 11 | 0.75 BID | P20 mgQD | + | 1.2 → 1.1 (11) NA | 0.6 → 0.4 (11) −33% | Relapse 3 mo after MMF and steroid withdrawal; Up/c 3.4 → 0.8 after 2 mo retreatment with MMF and steroids; continues MMF ℞ |
| 12) 55W F | CsAD/SI | 4 | 1.0 BID | None | + | 0.8 → 0.6 (6) NA | 8.7 → 1.8 (6) −79% | Continues MMF ℞; complete CsA withdrawal |
| 13) 18WM | NS/↑Scr | 8 | 1.0 BID | MP Mini | + | 1.7 → 0.9 (8) −47% | 3.3 → <0.1 (8) CR | CR and normal $S_{Cr}$ by 3 mo; complete steroid withdrawal; sustained CR and $S_{Cr}$ = 0.8 11 mo after MMF D/C |
| 14)35AAM | NS | 22 | 1.0 BID | MP48 mgQD | + | 2.0 → 3.1 (22) +55% | 7.5 → 3.9 (22) −48% | Progressive steroid withdrawal; MP 8 QD; continues MMF ℞ |
| 15) 41AAF | ↑Scr | 8 | 0.5 BID | None | + | 2.8 → 3.2 (8) +14% | 2.0 → 0.2 (8) CR | $S_{Cr}$ 2.8 9 mo after MMF D/C |
| 16) 34 A F | SD AZAD | 24 | 0.75 BID | P15 mgQD | − | 0.7 → 0.7 (24) NA | <0.1 → <0.1 (24) NA | Progressive steroid withdrawal (MP 7.5, 5 mg altQD) without relapse; azathioprine withdrawal |
| 17) 37AAF | SR/↑Scr | 13 | 0.5 TID | MP8 mgQOD | + | 1.7 → 2.3 (13) +35% | 20.3 → 4.9 (13) −86% | Complete steroid withdrawal; $S_{Cr}$ = 2.4, Up/c = 2.4 8 mo after MMF D/C |
| 18) 56WM | NS/↑Scr | 8 | 0.5 TID | MP24 mgQD | − | 3.8 → 3.2 (8) −16% | 9.7 → 8.2 (7) −15% | Continues on MMF ℞; MP 12 mg QD |
| 19) 27WM | SR | 10 | 1.0 BID | MP12 mgQD | + | 1.2 → 1.2 (10) NA | 2.2 → 0.7 (10) −68% | Complete steorid withdrawal; $S_{Cr}$ = 1.3, Up/c = 1.3 6 mo after MMF D/C |
| 20) 50WM | SDI/CsAD I | 6 | 1.0 BID | None | + | 1.7 → 1.7 (6) NA | 1.2 → 0.8 (6) −33% | Complete CsA withdrawal; MMF D/C 2° to mild ↑ liver enzymes with concomitant ETOH use; Up/c = 3.0, $S_{Cr}$ = 1.6 10 mo after MMF D/C; Up/c = 1.4 and liver enzymes normal after 4 mo MMF retreatment |

(Continued)

**Table 1. (Continued)**

| Sex/race age/patient | MMF treatment indication | Duration *months* | Dose *g* | Steroid | ACEi/ AIIRa (+/−) | Scr pre→post (mo) *mg/dL* %Δ | Up/c pre→post (mo) %Δ | Comments/latest follow-up |
|---|---|---|---|---|---|---|---|---|
| FSGS | | | | | | | | |
| 21) 65WF | NS | 4 | 0.75 TID | P50 mgQD | + | 0.9 → 0.9 (4) NA | 2.7* → 0.7 (4) −74% | Rapid steroid withdrawal; $S_{Cr}$ = 1.2 15 mo and Up/c = 0.9 12 mo after MMF D/C |
| 22) 16WM | NS | 4 | 1.0 BID | MP mini | − | 0.6 → 0.6 (4) NA | 8.2 → 6.7 (3) −18% | Complete steroid withdrawal; Up/c = 2.2 after low dose Tacrolimus added to MMF for 2 mo (FK level <6) |
| 23) 46WM | ↑Scr | 4 | 1.0/0.75 QD | MP mini | + | 2.3 → 2.3 (4) NA | 1.0 → 1.1 (4) +10% | Complete steroid withdrawal; MMF D/C 2° to depression, fatigue |
| 24) 52AAF | ↑Scr | 10 | 1.5 BID | None | − | 4.9 → 5.6 (10) +14% | 1.9* → 0.5* (6) −74% | Scr = 6.8 2 mo after MMF D/C |
| 25) 37WM | ↑Scr/NS | 5 | 1.0 BID | MP mini | + | 3.9 → 6.3 (5) +61% | 6.2 → 3.9* (5) −37% | Complete steroid withdrawal; $S_{Cr}$ = 6.6 2 weeks after MMF D/C |
| MN | | | | | | | | |
| 26) 30WM | SR/CsAD | 6 | 1.0 BID | None | − | 1.0 → 1.0 (6) NA | <0.1 → 0.2 (6) NA | Complete CsA withdrawal; Up/c ↑ to 1.0 9 mo after MMF D/C; Up/c 1.0 → 1.7 with 12 mo MMF repeat ℞; $S_{Cr}$ = 1.0 |
| 27) 60WF | NS/↑Scr | 7 | 0.5 TID | None | + | 3.5 → 1.7 (7) −51% | 12.8 → 7.7 (7) −40% | D/C MMF 2° to pneumonia; Up/c = 7.8 → 1.1 (−86%), $S_{Cr}$ = 1.9 with 8 mo MMF retreatment; Up/c = 7.1, $S_{Cr}$ = 1.8 3 mo after MMF D/C |
| 28) 44WM | SR/CsAD | 13 | 1.0 BID | None | + | 1.1 → 1.2 (8) NA | 7.3 → 1.2 (13) −84% | MMF D/C because of arm squamous cell CA, CsA continued; Up/c = 0.8, $S_{Cr}$ = 1.5 5 mo after MMF D/C |
| 29) 57WM | SR/CsAR | 25 | 0.75 BID | MP mini | + | 1.5 → 1.2 (24) −20% | 8.6 → 3.6 (24) −58% | Continues MMF ℞ and MP 4 mg QD |
| 30) 35AAF | SR/CsAD | 8 | 1.0 BID | None | − | 0.8 → 0.6 (6) NA | 4.0 → 1.2 (7) −70% | Complete CsA withdrawal; Up/c = 1.8, $S_{Cr}$ = 0.8 28 mo after MMF D/C |
| 31) 48W F | SR/CsAI | 12 | 0.75 BID | MP8 mgQD | − | 0.8 → 0.5 (12) NA | 4.7 → <0.1 (12) CR | Complete steroid withdrawal; sustained CR 2 yrs after MMF D/C |
| 32) 56AM | SD/CsAD AZAI | 25 | 1.0 BID | MP12 mgQD | − | 1.1 → 1.1 (25) NA | 0.3 → 0.6 (25) +100% | Complete CsA withdrawal; continues MMF ℞ and MP 8 mgQD |
| 33) 75WM | NS/↑Scr CsAR | 24 | 1.0 BID | MP mini | − | 1.9 → 1.4 (24) −26% | 7.1 → 2.3 (24) −68% | Continues MMF ℞ and Medrol 6 mgQD |
| 34) 43W F | SI/CsAI | 6 | 1.0 BID | MP12 mgQD | − | 0.7 → 0.7 (6) NA | 3.6 → 1.1 (5) −69% | Complete steroid withdrawal, but 2 relapses after MMF D/C; retreatment with MMF × 2 with response; chlorambucil resistant; $S_{Cr}$ = 0.8, ↑ Up/c = 7.0 19 mo after MMF D/C 3rd time |
| 35) 70WM | NS | 16 | 0.75 BID | MP mini | − | 1.1 → 1.1 (16) NA | 9.3 → 0.1 (16) CR | Complete steroid withdrawal; Up/c = 0.1 1 mo after MMF D/C |
| 36) 44WF | SR/↑Scr | 4 | 0.75 BID | MP24 mgQD | − | 2.9 → 2.8 (4) NA | 10.5 → 6.0 (4) −38% | Complete steroid withdrawal; MMF D/C 2° to erosive gastritis. $S_{Cr}$ ↑ 3.5 after MMF D/C; $S_{Cr}$ = 2.8 with MMF retreatment; Up/c = 8.0 5 mo and $S_{cr}$ = 2.4 2 yrs after second course MMF D/C |
| 37) 69WM | SD/CTXD | 18 | 0.25/0.5 BID | P10 mgQOD | − | 2.9 → 3.2 (17) +10% | 6.7 → 5.2 (9) −22% | Complete CTX withdrawal; continues MMF ℞ and P 5 mg po QD |
| 38) 54WM | NS, SI | 10 | 1.0 BID | MP mini | + | 1.8 → 1.7 (10) NA | 12.3* → 5.4 (10) −56% | MP D/C after 1 mo MMF; $S_{Cr}$ = 2.2 1 mo after MMF D/C |

(Continued)

**Table 1. (Continued)**

| Sex/race age/patient | MMF treatment indication | Duration *months* | Dose *g* | Steroid | ACEi/ AIIRa (+/−) | Scr pre→post (mo) *mg/dL* %Δ | Up/c pre→post (mo) %Δ | Comments/latest follow-up |
|---|---|---|---|---|---|---|---|---|
| MN | | | | | | | | |
| 39) 60WM | NS | 10 | 0.5 BID | MP32 mgQD | − | 0.8 → 0.8 (8) NA | 7.8 → 0.3 (10) −96% | Continues MMF ℞ and MP 12 QD |
| 40) 31WF | CsA R | 8 | 1.0 BID | None | − | 1.0 → 0.7 (8) NA | 5.5 → 1.5* (8) −66% | Complete CsA withdrawal; CR Up/c = 0.1, $S_{Cr}$ = 0.8 24 mo after MMF D/C |
| 41) 66WM | SR | 7 | 1.0 BID | P50 mgQD | − | 1.3 → 1.1 (4) −15% | 18.5* → 7.2 (4) −61% | Complete steroid withdrawal; partial remission with MMF; CR with low dose CsA added during 4th month of MMF (CsA level <60) |
| 42) 42AAF | CsAI | 7 | 1.0 BID | None | + | 1.2 → 1.1 (7) | 13.3 → 14.3 (6) +8% | Renal vein thrombosis documented 2 mo after MMF D/C; refuses alternative ℞ 2° h/o breast cancer; $S_{Cr}$ = 1.8 12 mo after MMF D/C |
| IgAN | | | | | | | | |
| 43) 25WM | SD/↑Scr | 6 | 1.0 BID | P5 mgQD | + | 3.9 → 2.3 (5) −41% | 6.3 → 1.2 (4) −81% | Complete steroid withdrawal; $S_{Cr}$ = 3.4 3 mo after MMF D/C & tonsillectomy; MMF restarted; Up/c 3.4 → 0.9 (17)-$S_{Cr}$ 3.4 → 3.0 (21)-after MMF retreatment |
| 44) 28WF | SD | 19 | 1.0 BID | P10 mgQD | + | 1.0 → 1.3 (19) +30% | 0.9 → 0.5 (19) −44% | Complete steroid withdrawal; bilateral aseptic necrosis of hips from steroids after MMF ℞; continues MMF ℞ |
| 45) 31WM | ↑Scr | 4 | 0.5 TID | None | + | 1.8 → 1.5 (3) −17% | <0.1 → <0.1 (4) NA | $S_{Cr}$ = 1.7 1 yr after MMF D/C |
| MPGN | | | | | | | | |
| 46) 78WM | NS | 11 | 0.5 BID | None | 0 | 2.2 → 2.2 (11) NA | 4.9 → 3.9 (11) −20% | $S_{Cr}$ ↓ 1.7 on 1.0 g BID MMF to 0.5 g BID 2° to GI symptoms; MMF D/C 2° to pneumonia; $S_{Cr}$ ↑ 2.6 6 mo after MMF D/C |

Patient number, age, sex, race, indication for MMF therapy, duration of MMF therapy, MMF dose, presence or absence of concomitant steroid and ACEi/AIIRa use, serum creatinine at the start and last month of MMF prescription (℞) with % change from baseline, $U_{p/c}$ at the start and last month of MMF ℞ with % change from baseline, and brief follow-up are listed for each patient. Abbreviations are: MCD, minimal change disease; FSGS, focal and segmental glomerulosclerosis; MN, membranous nephropathy; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; W, white; A, Asian; AA, African American; M, male; F, female; ND, not determined; NS, nephrotic syndrome; CsA, cyclosporine; AZA, azathioprine; S, steroid; CTX, cyclophosphamide; P, prednisone; MP, methylprednisolone; I, intolerant; D, dependent; R, resistant; ↑Scr, progressive renal insufficiency; ACEi, ACE inhibitor; AIIRa, angiotensin II receptor antagonist.

**Table 2.** Follow up data of patients completing MMF

| Pt # | Urine protein/creatinine (months on MMF) Pre → Post ..... (months after MMF D/C) ..... Latest Relapse(+) | Serum creatinine Pre → Post ..... Latest | Med Δ |
|---|---|---|---|
| Minimal change | | | |
| 1 | 6.0 (6)→ CR ..... (2) ..... 2.0+ | 1.0 → 1.0 ..... 1.0 | |
| 2 | 6.0 (26)→ CR ..... (2) ..... CR | 1.1 → 0.9 | −S |
| 3 | 4.6 (6)→ 2.8 ..... (17) ..... CR | 0.8 → 0.8 | MMF D/C |
| 4 | 2.4 (6)→ CR ..... (30) ..... CR | 1.3 → 1.3 | −S |
| 5 | <0.1 (11)→ <0.1 ..... (5) ..... <0.1 | 1.0 → 0.7 | −S |
| 6 | 5.3 (3)→ 5.8 ..... (13) ..... CR | 1.7 → 1.6 ..... 1.7 | +T |
| FSGS | | | |
| 8 | 2.0 (11)→ 2.1 ..... (36) ..... 1.8 | 2.5 → 2.6 ..... 4.3 | −S |
| 10 | 2.8 (4)→ 0.7 ..... (8) ..... CR | 2.0 → 2.0 ..... 2.0 | |
| 11 | 0.6 (11)→ 0.4 ..... (21) ..... 3.4 | 1.2 → 1.1 | −S |
| 13 | 3.3 (8)→ CR ..... (11) ..... CR | 1.7 → 0.9 ..... 0.8 | −S |
| 15 | 2.0 (8)→ CR | 2.8 → 3.2 (9)..... 2.8 | |
| 17 | 20.3 (13)→ 4.9 ..... (8) ..... 2.4 | 1.7 → 2.3 ..... 2.4 | −S |
| 19 | 2.2 (10)→ 0.7 ..... (6) ..... 1.3 | 1.2 → 1.3 ..... 1.3 | −S |
| 20 | 1.7 (6)→ 1.7 ..... (4) ..... 3.0+ | 1.7 → 1.7 ..... 1.6 | MMF D/C |
| 21 | 2.7 (4)→ 0.7 ..... (15) ..... 0.9 | 0.9 → 0.9 ..... 1.2 | −S |
| 24 | 1.9 (10)→ 0.5 | 4.9 (10)→ 5.6 (2)..... 6.8 | |
| 25 | 6.2 (5)→ 3.9 | 3.9 (5)→ 6.3 (0.5)..... 6.6 | −S |
| MN | | | |
| 26 | <0.1 (6)→ 0.2 ..... (9) ..... 1.0+ | 1.0 → 1.0 ..... 1.0 | |
| 27 | 12.8 (7)→ 7.7 ..... (3) ..... 7.1+ | 3.5 → 1.7 ..... 1.8 | MMF D/C |
| 28 | 7.3 (13)→ 1.2 ..... (5) ..... 0.8 | 1.1 → 1.2 ..... 1.5 | MMF D/C |
| 30 | 4.0 (18)→ 1.2 ..... (28) ..... 1.8 | 0.8 → 0.6 ..... 0.8 | |
| 31 | 4.7 (12)→ CR ..... (24) ..... CR | 0.8 → 0.5 | |
| 34 | 3.6 (6)→ 1.1 ..... (2) ..... 2.0+ | 0.7 → 0.7 ..... 0.7 | −S |
| 35 | 9.3 (10)→ CR ..... (1) ..... CR | 1.1 → 1.1 | −S |
| 36 | 10.5 (4)→ 6.0 ..... (6) ..... 8.0+ | 2.9 → 2.8 ..... 3.5 | |
| 38 | 12.3 (10)→ 5.4 | 1.8 (10)→ 1.7 (1)..... 2.2 | −S |
| 40 | 4.4 (6)→ 1.5 ..... (24) ..... CR | 1.0 → 0.7 ..... 0.8 | |
| 42 | 13.3 (7)→ 14.3 | 1.2 (7)→ 1.1 (12)..... 1.8 | |
| IgA/MPGN | | | |
| 43 | 6.3 (6)→ 1.2 ..... (3+) ..... 1.0 | 3.9 → 2.3 ..... 3.4 | −S |
| 45 | <0.1 (4)→ 0.1 | 1.8 (4)→ 1.5 (12)..... 1.7 | |
| 46 | 4.9 (11)→ 3.9 | 2.2 (11)→ 2.2 (6)..... 1.6 | MMF D/C |

Follow up data on patients who completed a course of MMF therapy is provided. Urine protein creatinine ratios ($U_{p/c}$) at the start and end of MMF therapy are given between the arrows. Last follow-up is provided. After the ....., relapse is denoted first by the + sign. The number in the parentheses represents months of MMF treatment, the number in the second parentheses represents months after MMF was discontinued. The serum creatinine ($S_{cr}$) is shown in a similar fashion. Numbers in the parentheses for $S_{Cr}$ are only given if different from $U_{p/c}$ data. Medication changes are described as − if a medication is withdrawn, or + if active MMF. D/C denotes adverse effect of MMF requiring withdrawal. Abbreviations are: $U_{p/c}$, urine protein creatinine ratio; $S_{Cr}$, serum creatinine (mg/dL); −, drug withdrawal; +, addition of medication; MMF D/C is noted for MMF withdrawal secondary to adverse reaction; S, steroids; T, Tacrolimus; CR, complete remission.

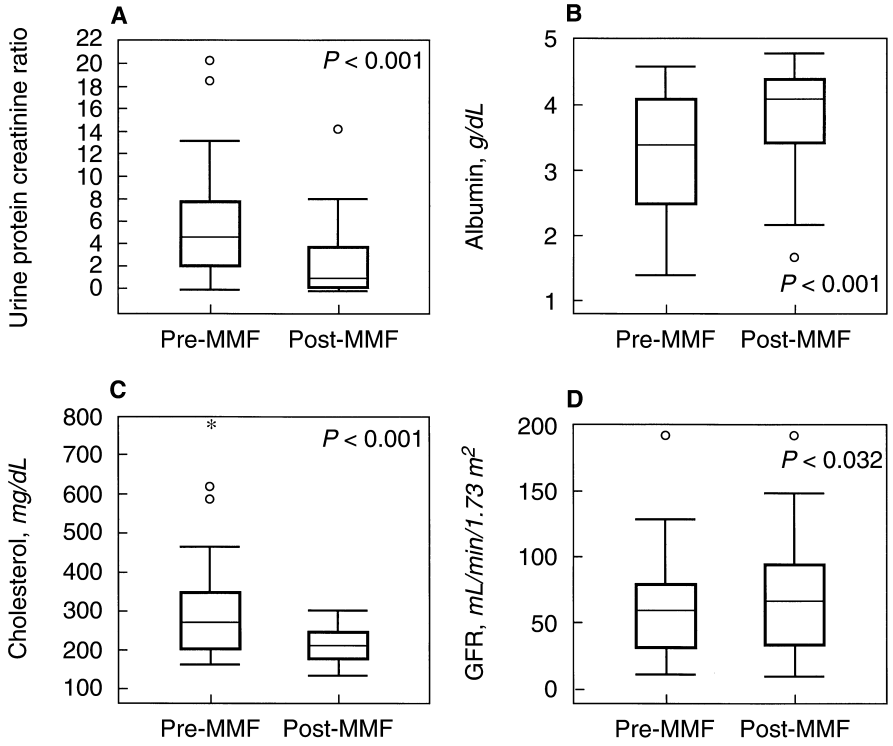


**Fig. 1. Median plus interquartile range of urine protein-to-creatine ratio ($U_{p/c}$), serum albumin, and serum cholesterol and estimated glomerular filtration rate (GFR).** (*A*) Median plus interquartile range, pre- and post-mycophenolate mofetil (MMF) treatment, of the $U_{p/c}$ ratio is shown for the entire study population. (*B*) Median plus interquartile range of serum albumin prior to and after MMF treatment of the overall group is demonstrated. (*C*) Median plus interquartile range pre- and post-MMF treatment serum cholesterol for the overall group is shown. (*D*) Median plus interquartile range pre- and post-treatment GFR as estimated by the modified four-variable MDRD equation.

MN, 1 with FSGS; only 1 patient (who had IgA nephropathy) developed de novo renal insufficiency.

During the study period, 7 of 46 (15.2%) patients decreased their ACEi/AIIRa use, 28 (60.9%) continued on the same dose, and 11 (23.9%) increased their dose. With regards to lipid lowering therapy over follow-up, 4 of 29 patients (13.8%) decreased their dose, 17 (58.6%) remained on a constant dose, and 8 (27.6%) increased their dose. There was no significant difference between changes in $U_{p/c}$, $S_{Cr}$, blood pressure control, serum albumin ($S_{Alb}$), or serum cholesterol ($S_{Chol}$) in patients who increased their dose of ACEi/AIIRa or HMG CoA reductase inhibitor as compared with those who did not.

### Minimal change disease

The 7 patients with MCD had a median (range) age of 41 (23 to 74) years, 3 were male, 5 were Caucasian, and 2 were African-American. Five of 7 patients were nephrotic in the setting of a normal serum creatinine. Baseline $U_{p/c}$ and $S_{Cr}$ was 4.6 (0.1 to 6.0) and 1.0 (0.6 to 1.7) mg/dL. The indication for MMF treatment was steroid ± CsA dependence in each, and 6 of 7 received some form of concomitant steroid treatment. With the exception of patients #2 and #4, the steroid and its dose were those in place prior to MMF.

Overall, 3 of 5 initially nephrotic patients (#1, 2, 4) had complete remissions in proteinuria by the end of the study. Change in $U_{p/c}$ with MMF treatment was −91.4 (−98.0 to 9.0)%, $P = 0.05$. In 2 of these (#2 and #4), the remission has been sustained following discontinuation of the initial (and only) course of MMF. Patient #1 initially relapsed twice when MMF was stopped, responding again to MMF monotherapy; she was MMF dependent for 30 months of MMF treatment before a sustained remission was achieved. Complete withdrawal of steroids was achieved in 5 of the 6 patients. Patient #3 had a substantial partial remission ($U_{p/c}$ 4.6 → 0.6) by 3 months of MMF treatment, but relapsed with attempts at steroid withdrawal. In addition, he presented with a neck mass after only 6 months of treatment with MMF and a total 30 months of prednisone. Biopsy disclosed Hodgkin's lymphoma. Both lymphoma and nephrotic proteinuria remitted completely with chemotherapy. One patient (#6) was MMF resistant.

### Focal segmental glomerulosclerosis

The 18 patients with FSGS had a median (range) age of 37 (16 to 65) years, 66.7% were male, 13 (72.2%) were Caucasian, 4 (22.2%) were African American and 1 (5.6%) was Asian. Quantitation of proteinuria was not available in 1 patient. At study entry the $U_{p/c}$ and $S_{Cr}$ values were 2.7 (0.1 to 20.3) and 1.85 (0.6 to 6.1) mg/dL, respectively. Twelve of 18 (66.7%) patients had renal insufficiency and 9 of 17 (52.9%) had nephrotic proteinuria despite $ACE_i$/AIIRa therapy in 7 of 9. Indications for MMF treatment included steroid resistance or steroid ± CsA dependency and/or progressive (sometimes rapidly deteriorating) renal insufficiency.

**Table 3.** Mean and median values $U_{p/c}$, serum albumin, serum cholesterol, mean arterial pressure, serum creatinine, and 100/serum creatinine in the overall group and subgroups of primary glomerulopathies before and at the end of MMF treatment

| | | Pre-MMF | | Post MMF | | |
|---|---|---|---|---|---|---|
| | *N* | Mean ($\bar{x} \pm SD$) | Median (range) | Mean ($\bar{x} \pm SD$) | Median (range) | *P* |
| Overall group | | | | | | |
| $U_{p/c}$ | 45 | 5.6 (4.7) | 4.7 (.1, 20.3) | 2.4 (3.0) | 1.1 (0.1, 14.3) | <0.001 |
| Serum albumin[a] | 41 | 3.3 (0.96) | 3.4 (1.4, 4.6) | 3.9 (0.7) | 4.1 (1.7, 4.8) | <0.001 |
| Serum cholesterol[b] | 30 | 307.6 (139.0) | 270 (148, 795) | 219.9 (42.4) | 220.0 (140, 309) | <0.001 |
| Mean arterial pressure[c] | 41 | 99.7 (13.0) | 100.0 (72.7, 130.0) | 94.2 (10.3) | 94.0 (73.3, 111.3) | 0.008 |
| Serum creatinine | 46 | 1.8 (1.2) | 1.3 (0.6, 6.1) | 1.8 (1.4) | 1.2 (0.5, 6.5) | 0.39 |
| 100/serum creatinine | 46 | 77.5 (39.8) | 76.9 (16.4, 166.7) | 85.0 (46.5) | 83.3 (15.4, 200) | 0.03 |
| MCD | | | | | | |
| $U_{p/c}$ | 7 | 4.1 (2.2) | 4.6 (0.1, 6.0) | 1.3 (2.2) | 0.1 (0.1, 5.8) | 0.05 |
| Serum albumin | 6 | 3.2 (1.3) | 3.5 (1.4, 4.6) | 3.9 (1.1) | 4.2 (1.7, 4.6) | 0.14 |
| Serum cholesterol | 3 | 274.5 (78.0) | 258.5 (204, 426) | 233 (25.4) | 241 (205, 254) | 0.66 |
| Mean arterial pressure | 6 | 93.6 (10.9) | 93.3 (78.0, 110.0) | 93.8 (13.4) | 97.3 (73, 111) | 0.89 |
| Serum creatinine | 7 | 1.07 (0.35) | 1.0 (0.6, 1.7) | 1.0 (0.3) | 0.9 (0.7, 1.6) | 0.20 |
| 100/serum creatinine | 7 | 102.6 (35.0) | 100.0 (58.8, 166.7) | 108.7 (31.2) | 111.1 (62.5, 142.9) | 0.47 |
| FSGS | | | | | | |
| $U_{p/c}$ | 17 | 4.7 (5.1) | 2.7 (0.1, 20.3) | 2.2 (2.5) | 0.8 (0.1, 8.2) | 0.001 |
| Serum albumin | 17 | 3.4 (1.1) | 3.7 (1.4, 4.6) | 4.1 (0.6) | 4.2 (2.7, 4.8) | 0.01 |
| Serum cholesterol | 14 | 301.2 (175.7) | 223 (148, 795) | 203.9 (46.0) | 187.5 (140, 309) | 0.002 |
| Mean arterial pressure | 16 | 101.7 (12.0) | 100.0 (77.3, 130.0) | 91.9 (10.6) | 92.0 (73.3, 109.3) | 0.02 |
| Serum creatinine | 18 | 2.3 (1.5) | 1.9 (0.6, 6.1) | 2.5 (1.9) | 2.2 (0.6, 6.5) | 0.25 |
| 100/serum creatinine | 18 | 66.5 (43.8) | 54.4 (16.4, 166.7) | 69.5 (50.8) | 46.7 (15.4, 166.7) | 0.93 |
| MN | | | | | | |
| $U_{p/c}$ | 17 | 7.7 (4.8) | 7.3 (0.1, 18.5) | 3.4 (3.8) | 1.5 (0.1, 14.3) | 0.001 |
| Serum albumin | 14 | 2.96 (0.66) | 2.95 (2.10, 4.50) | 3.5 (0.6) | 3.6 (2.2, 4.6) | 0.006 |
| Serum cholesterol | 11 | 334.9 (126.9) | 312 (168, 623.0) | 235.1 (40.0) | 222 (179, 301) | 0.05 |
| Mean arterial pressure | 15 | 99.4 (15.6) | 97.3 (72.7, 130.0) | 94.6 (9.5) | 93.3 (80.0, 110.0) | 0.14 |
| Serum creatinine | 17 | 1.5 (0.8) | 1.1 (0.7, 3.5) | 1.3 (0.7) | 1.1 (0.5, 3.2) | 0.03 |
| 100/serum creatinine | 17 | 83.7 (34.7) | 90.9 (28.6, 142.9) | 97.9 (45) | 90.9 (31.3, 200) | 0.01 |

Abbreviations are: *N*, patient number; *P*, *P* values are calculated using the Wilcoxon signed-ranks test.
[a] Units in g/dL
[b] Units in mg/dL
[c] Units in mm Hg

**Table 4.** Change in serum creatinine

| | Pre-treatment median (range) | Post-treatment median (range) | *P* value (Wilcoxon signed-ranks test) |
|---|---|---|---|
| Serum creatinine *mg/dL* | 1.3 (0.6, 6.1) | 1.2 (0.5, 6.5) | 0.492 |
| 100/serum creatinine | 76.9 (16.4, 166.7) | 83.3 (15.4, 200) | 0.027 |
| 4-variable simplified MDRD GFR *mL/min/1.73 m²* | 59.4 (11.4, 191.0) | 67.3 (10.3, 191.0) | 0.032 |

100/serum creatinine and estimated GFR using the four-variable simplified MDRD equation.

Twelve of 18 initially received concomitant steroid treatment; in 8 of those 12, the drug and its dose were the same as those prior to MMF and, in 4, steroids were initiated at the same time as MMF in a previously described protocol [1]. MMF was used as the only immunosuppressive medication in the other 6 patients.

The $U_{p/c}$ decreased by a median of 48%, being 0.8 (<0.1 to 8.2) at the end of the MMF treatment period ($P = 0.001$; Table 2). Two patients (#13, #15)—including one from the nephrotic group—had a complete remission of proteinuria; 6 patients (35.3%)—including 4 from the nephrotic group—had a partial remission; and 2 patients (11.1%)—both non-nephrotic—had an increase in their proteinuria of 5 and 10%. In the 9 patients with nephrotic range proteinuria, $U_{p/c}$ pretreatment was 7.5 (2.7 to 20.3) and decreased to 3.9 (0.1 to 8.2) post-therapy ($P = 0.008$). One nephrotic patient (#13) experienced a complete remission that has been sustained over 11 months following discontinuation of MMF. The magnitude ($U_{p/c}$) for the responses in proteinuria in the nephrotic FSGS patients is illustrated in Figure 2. There was a significant reduction in $S_{Chol}$ and in the MAP, together with a significant improvement in $S_{Alb}$ levels (Table 2).

There was no significant change in serum creatinine in the FSGS patients as a group over the study period;

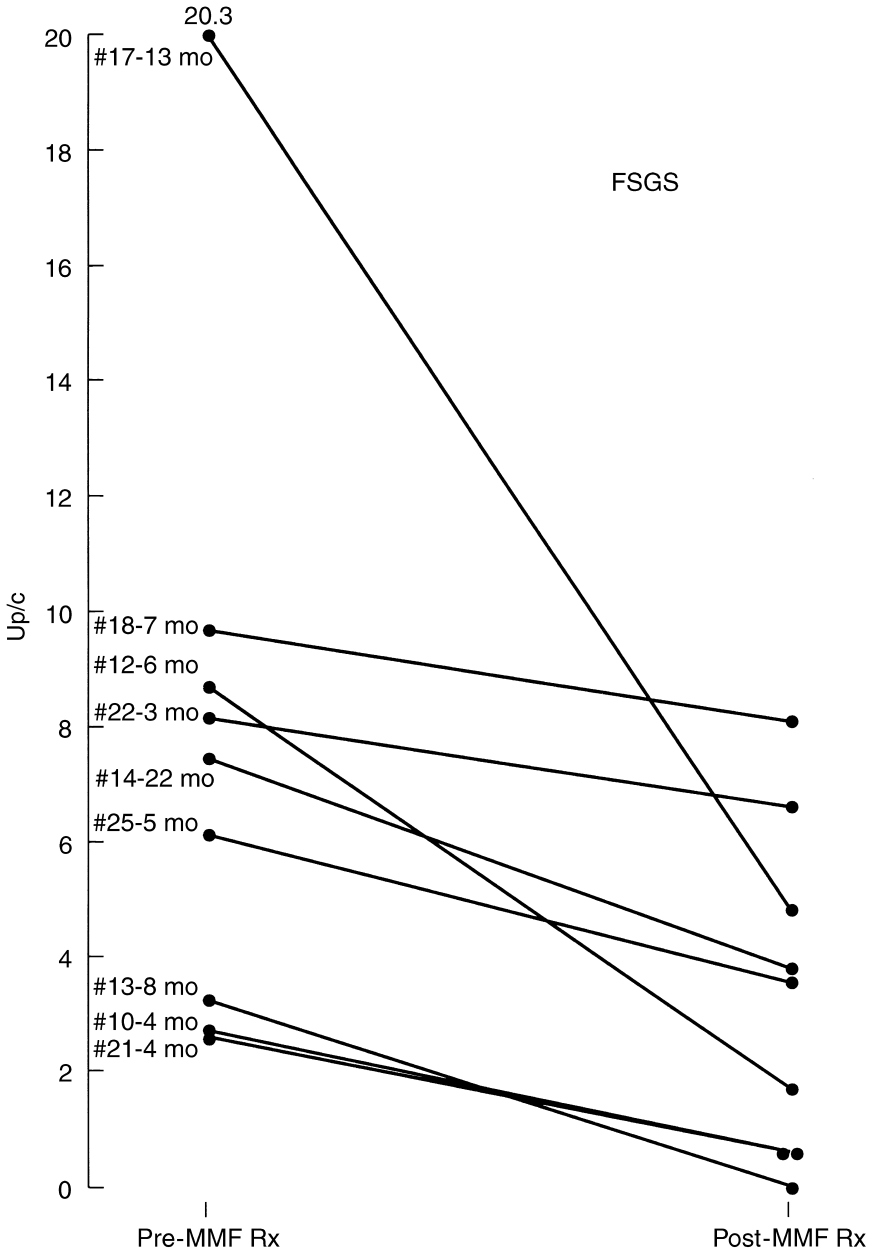


**Fig. 2. $U_{p/c}$ at initiation and at the end of the MMF treatment period in individual nephrotic FSGS patients.** # is the patient identification number in Table 1. mo = months of MMF therapy.

renal insufficiency resolved in 1 of 12 cases, with no cases developing de-novo renal insufficiency during MMF therapy. Two (#13, 18) of 12 patients with renal insufficiency ($S_{Cr}$ 1.7 and 3.8 mg/dL, respectively) manifested improved excretory renal function. One of those two (#18) with rapidly deteriorating renal function manifested a marked slowing of the rate of progression over the ensuing 40 weeks. In 3 patients (#14, 17, 25), renal function continued to deteriorate over 5 to 22 months. One of these patients (#25) had collapsing FSGS on biopsy in a solitary kidney. In the other 7 patients (#8, 9, 10, 15, 20, 23, 24), renal function stabilized over 4 to 12 months.

Of the 17 patients receiving either ACEi or AIIRa, 4 patients increased their dose, 7 patients remained on a constant dose, and 6 decreased their dose of ACEi/AIIRa over the course of the study. There was no significant association between change in ACEi/AIIRa status and change in proteinuria, $S_{Cr}$ or MAP. Of the 14 patients receiving an HMG CoA reductase inhibitor, 4 increased their dose, 7 stayed on a constant dose, and 3 decreased their dose, with no significant independent association between the change in medication use and the improvement in serum cholesterol level.

Of 12 patients initially receiving concomitant steroid therapy, it was withdrawn completely without relapse in 8. One patient relapsed and steroid was resumed, and 3 patients continued on low dose (MP $\leq$12 mg/day) treat-

ment. Two of the 3 CsA dependent patients and 1 AZA dependent patient did not require restarting of these medications. MMF was discontinued in one patient (#20) because of reversible mild increases in serum transaminase levels with concomitant alcohol use. (The patient has subsequently been retreated, with normal liver enzymes, after abstinence from alcohol.)

### Membranous nephropathy

The 17 patients with MN had a median (range) age of 54 (30 to 75) years, 58.8% were male, 14 (82.4%) were Caucasian, 2 (11.8%) were African-American and 1 (5.9%) was Asian. Fifteen patients (88.2%) had nephrotic range proteinuria and six (35.3%) had renal insufficiency. At baseline, $U_{p/c}$ and $S_{Cr}$ were 7.3 (0.1 to 18.5) and 1.1 (0.7 to 3.5) mg/dL, respectively. Indications for MMF treatment included steroid (11/17) ± CsA (4/17) or CTX (1/17) dependency, steroid or CsA resistance, steroid or CsA intolerance, suboptimal response to CsA, and progressive renal insufficiency. Three patients received MMF monotherapy.

In all patients with membranous nephropathy, the median percent reduction in $U_{p/c}$ was 61.1%, being 1.5 (<0.1 to 14.3) at the end of MMF treatment period ($P = 0.001$). The magnitude for the responses in proteinuria to MMF in the nephrotic MN patients is illustrated in Figure 3. In the 15 patients with nephrotic range proteinuria, $U_{p/c}$ was 7.8 (3.6 to 18.5) pretreatment and was 2.3 (<0.1 to 14.3) post-treatment ($P = 0.001$). Two patients (13.3%), both of whom who were nephrotic, achieved a complete remission; 8 patients (60%), all of whom were nephrotic, achieved a partial remission; and 2 patients (13.3%), including 1 nephrotic, had increased proteinuria. Eight of the 15 (53.3%) nephrotic patients improved to subnephrotic proteinuria with treatment. Two patients relapsed after MMF was stopped, and they both responded to retreatment.

With MMF treatment there was no change in median serum creatinine or mean arterial pressure. There were significant improvements in serum albumin and cholesterol (Table 2). Three of 6 patients (#27, 29, 33) with renal insufficiency experienced substantial improvement in excretory renal function. One patient (#37) had an increase in serum creatinine of 10% after 17 months of treatment.

Of the 14 patients receiving ACEi or AIIRa, 5 patients increased, 8 patients remained on a constant dose, and 1 decreased their dose over the course of the study. There was no significant association between change in ACEi/AIIRa status and change in the above clinical parameters. Of the 15 patients receiving HMG CoA reductase inhibitors, 5 increased, 8 stayed on a constant dose, and 2 decreased their dose of lipid lowering medication, with no significant independent association between the change in medication use and improvement in $S_{Chol}$ level.

Progressive steroid withdrawal and CsA withdrawal was successfully achieved in the majority (14 of 15, 93.3%) of patients with steroid or CsA dependency. In one patient (#37) who was both steroid and CTX dependent, MMF treatment permitted a reduction in steroid dose and CTX was stopped shortly after starting MMF. MMF dependency was observed in 4 patients (#26, 27, 34, and 36). One patient (#28) developed mild reversible leukopenia. Three patients had MMF discontinued. One patient (#36) developed severe erosive gastritis, one patient (#27) developed pneumonia, and one patient (#28) developed squamous cell cancer of the arm with prior and continued steroid and CsA treatment.

### IgAN

Two of the 3 patients had renal insufficiency and one had, in addition, nephrotic proteinuria. The other patient (#44) was steroid dependent and had suffered serious complications from steroid therapy. Patient #43 experienced substantial improvement in excretory renal function and a partial remission in proteinuria. He relapsed after 3 months, however, when MMF was discontinued while he underwent tonsillectomy, but he responded again following resumption of MMF. Two patients (#43 and 45) showed improvement in renal function while receiving MMF. All three patients had been on fish oil prior to and during MMF therapy.

### MPGN

Patient #46 had both renal insufficiency and nephrotic proteinuria. Excretory renal function transiently improved until gastrointestinal symptoms required a dosage reduction. He did, however, experience a substantial partial remission in proteinuria.

### Steroid- and/or CsA-resistant nephrotic patients

There were 10 patients (#17, 19, 28, 29, 30, 31, 33, 36, 40, 41) with nephrotic proteinuria who had previously failed to respond to steroids ($N = 7$) or CsA ($N = 2$); one (#29) had failed to respond to both. Of these resistant patients, 2 had FSGS (#17, 19) and the remainder had MN. One MN patient (#31) had a complete and sustained (more than 2 years after MMF stopped) remission. In these 10 patients, $U_{p/c}$ decreased significantly from 7.2 (2.2, 20.3) pre MMF to 1.9 (0.1, 7.2) with MMF treatment ($P = 0.005$). Three of the patients had remained on a constant dose of ACEi/AIIRa, 4 on an increased dose, and 3 on a decreased dose; 5 had remained on a constant dose of HMG CoA reductase inhibitor with 3 reducing their dose and 2 increasing their dose over the course of follow-up.

There was, in addition, significant improvement in $S_{Alb}$ and $S_{Chol}$. Serum albumin increased from 2.6 (1.4, 4.5) g/dL to 3.8 (2.9, 4.6) g/dL ($P = 0.01$) at the end of treatment. Serum cholesterol post-MMF was 212 (160, 225)

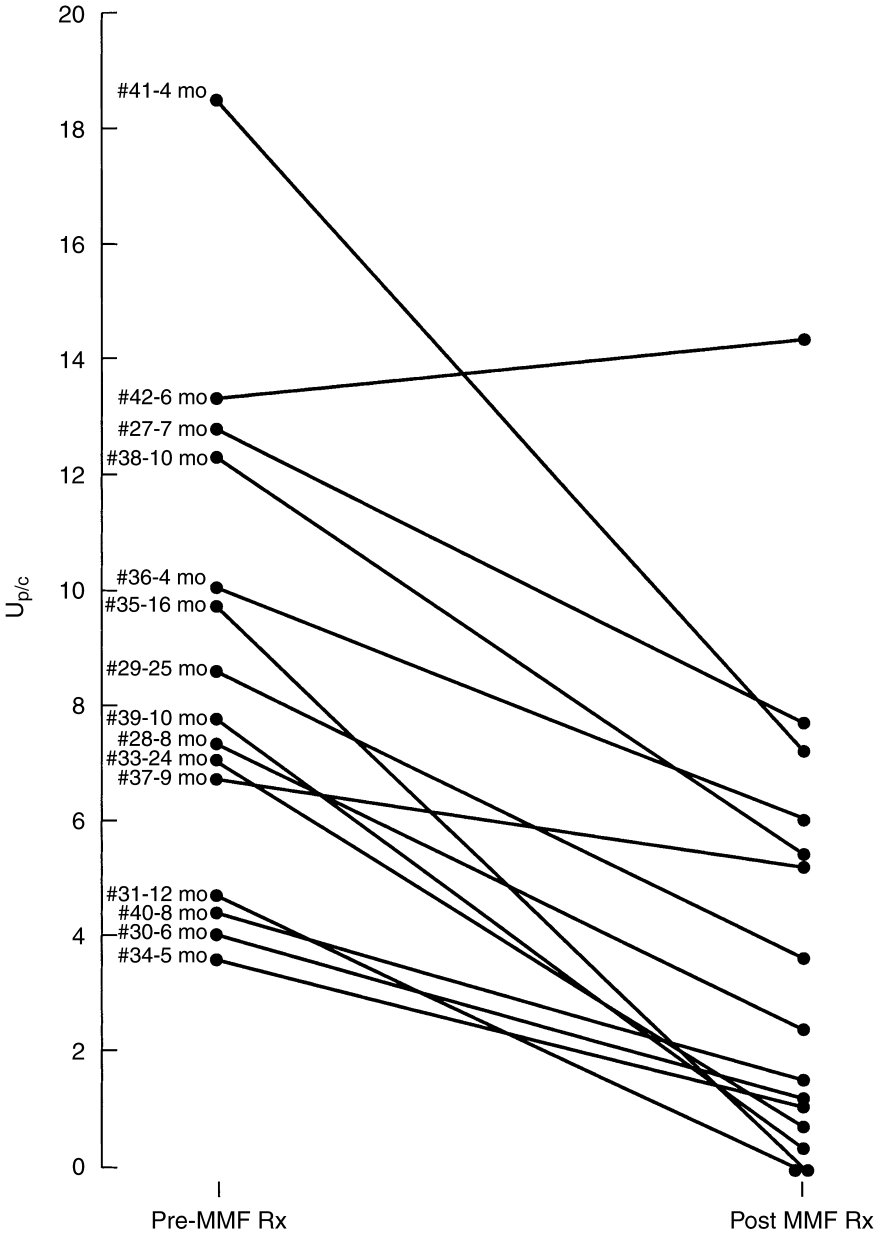


**Fig. 3. $U_{p/c}$ at initiation and at the end of MMF treatment in individual nephrotic membranous nephropathy patients.** # is the patient identification number in Table 1. mo = months of MMF therapy.

mg/dL as compared to the pre-MMF value of 348 (202, 795) mg/dL ($P = 0.01$).

## MMF MONOTHERAPY

Twelve patients (#1, 9, 10, 12, 15, 20, 24, 27, 30, 40, 45, 46) were treated with MMF alone. One patient had minimal change disease, 6 had focal segmental glomerulosclerosis, and 3 had membranous nephropathy. One had IgA nephropathy and 1 had membranoproliferative glomerulonephritis (hepatitis C negative PCR). There were no $U_{p/c}$ data available for patient #9. $U_{p/c}$ decreased from 4.0 to 0.8 ($P = 0.005$) and $S_{Cr}$ values were 1.9 mg/dL at the start of MMF therapy to 1.7 mg/dL ($P = 1.0$) at the end of MMF therapy. Serum albumin increased from 3.95 to 4.15 g/dL ($P = 0.09$), serum cholesterol decreased from 243 to 205 mg/dL ($P = 0.011$), and MAP decreased from 106.6 to 98.7 mm Hg. Three patients (#9, 20, 27) required MMF retreatment because of relapse.

## RAPIDLY INCREASING $S_{Cr}$

Among the patients reported here, there were 8 who not only had renal insufficiency, but who were manifesting a relatively rapid progressive deterioration in renal function prior to the initiation of MMF treatment ($S_{Cr}$ rising $\geq$20% within 40 weeks of initiating MMF treatment). The changes in $S_{Cr}$ in these 8 patients 40 weeks prior to, at the start of, MMF, then 40 weeks following initiation of MMF treatment, are shown in Figure 4. Six

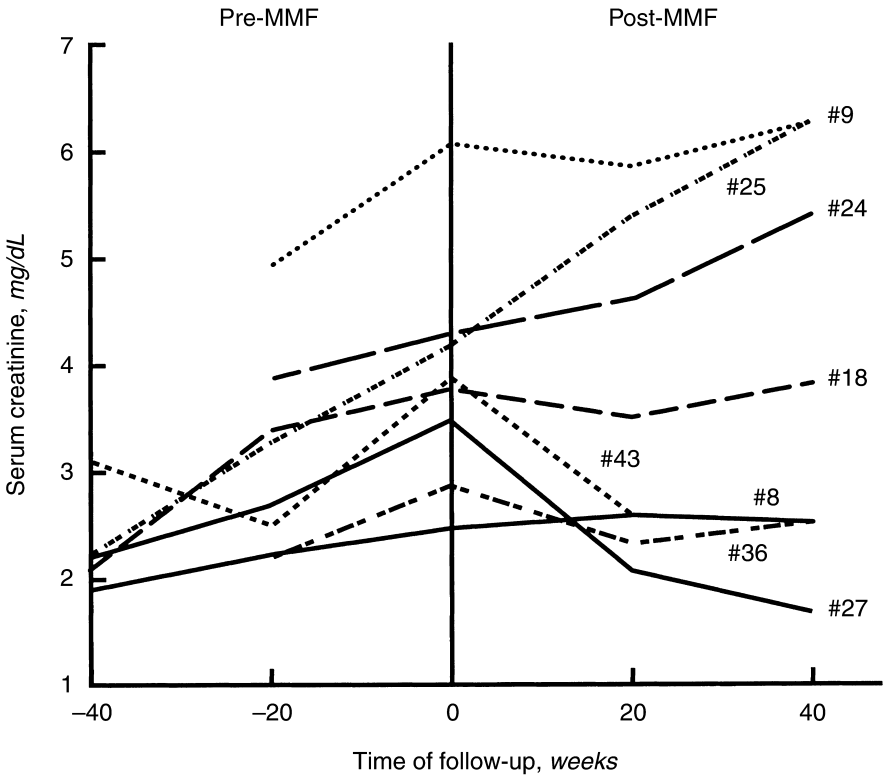


**Fig. 4. Patients with rapidly rising serum creatinine.** Eight patients demonstrated a ≥20% increase in the serum creatinine 40 weeks prior to MMF therapy. The serum creatinines of these 8 patients are shown prior to and after MMF therapy started.

of 8 (#8, 9, 18, 27, 36, 43) manifested either stabilization or improvement in excretory renal function with treatment. The subsequent decrease in some patients was impressive, and in none of these 8 patients was there any evidence of confounding conditions such as volume depletion, heart failure, obstructive uropathy, or exposure to contrast agents, nephrotoxic agents or drugs which might cause impaired glomerular function or acute interstitial nephritis, the correction of which could explain the changes observed.

## ESTIMATE OF GLOMERULAR FILTRATION RATE, TOTAL STUDY GROUP

Estimated GFR significantly improved over the study period whether estimated by 100 multiplied by the reciprocal of serum creatinine, or the four-variable simplified MDRD formula (Table 4).

## DISCUSSION

The results presented here largely confirm and substantially extend our initial observations regarding the efficacy of MMF for the treatment of glomerular diseases. We have not included our additional experiences in patients with lupus nephritis or vasculitis, but have elected in this report to focus on our experience with patients with primary glomerulopathies, predominantly relapsing MCD, FSGS, and MN. The results indicate that the majority of, but not all, treated patients experienced short to intermediate term benefit from MMF therapy, whether in terms of markedly decreased cumulative steroid exposure, complete or partial remission of nephrotic proteinuria or in favorable modifications of the rate of deterioration in renal function. Unfortunately, it is not possible to anticipate the individual response to MMF in advance of therapy. Patients' response to therapy does not appear to be related to the degree of proteinuria. Interestingly, twelve patients were treated with MMF alone and showed a similar decrease in urine protein excretion, increase in serum albumin, decrease in cholesterol and MAP. Not surprisingly, it is now apparent that some patients will fail to respond to MMF and that, similar to the situation with CsA, a proportion of responsive patients will be found to be MMF dependent and relapse when treatment is discontinued.

It is assumed that MMF is effective in the treatment of responsive patients as a result of a combination of its immunosuppressive properties and its other mechanisms of action. Mycophenolic acid (MPA), the pharmacologically active metabolite of MMF, inhibits both T and B lymphocyte proliferation, B lymphocyte antibody production, as well as the glycosylation and expression of adhesion molecules [21–26]. In addition, MPA has been shown to inhibit vascular smooth muscle cell [22] and mesangial cell proliferation [11], to be a selective inhibitor of inducible nitric oxide synthase [27], and to induce

apoptosis in activated T cells [28]. One or another, or a combination of these actions could account for the observed amelioration of various experimental models of glomerular disease, including active [10] and passive Heymann nephritis, hyperfiltration injury in remnant kidney [5–9], mesangial proliferative nephritis [11, 12], and murine lupus nephritis [13–15] (abstracts; Heering et al, *J Am Soc Nephrol* 9:456A-7A, 1998; Wen-Ling et al, *J Am Soc Nephrol* 9:496A, 1998). These same mechanisms are likely to be operative in the amelioration of the inflammation and/or structural remodeling characteristic of human glomerular diseases.

Steroid dependent MCD is problematic because of the need for repeated moderate-to-high–dose steroid exposure and/or long-term cumulative steroid exposure. In contrast to children, adults with MCD are more likely to be steroid resistant or steroid dependent. Historically, the treatment of relapsing or resistant patients has been with either CsA or a cytotoxic drug. Unfortunately, steroid resistance also often predicts resistance to these second line drugs. In addition, CsA dependency has often been the trade-off for steroid dependency, and cytotoxic drugs carry their well-known potential toxicities. The potential role for MMF in steroid ± CsA dependent MCD is that of an effective steroid sparing agent without the potential adverse renal, hemodynamic, and metabolic effects of CsA. If discontinuation of MMF after 6 to 12 months of treatment is followed by a relapse, our results indicate that retreatment of relapse will likely be effective, and the treating physician always has the option of proceeding to cytotoxic therapy. Alternatively, the results in patient #1 suggest that a more prolonged course of treatment with MMF may ultimately lead to a sustained complete remission after stopping MMF.

Focal segmental glomerulosclerosis is especially significant because it has become the leading cause of nephrotic syndrome in adults and, more importantly, because of its propensity to progress to end-stage renal disease (ESRD). Nephrotic proteinuria and decreased excretory renal function are independent risk factors for progression to ESRD. Induction of complete, and even partial, remission of nephrotic proteinuria has been shown to favorably modify the renal prognosis in FSGS [29]. High-dose and prolonged steroid treatment has been found to be effective for induction of remissions in nephrotic proteinuria in substantial proportions of affected patients [30]. Although generally satisfactorily tolerated, the downside of such treatment includes both the total cumulative steroid exposure and steroid intolerance in a few patients.

Not only was MMF treatment effective in inducing substantial remissions of proteinuria in the majority of nephrotic FSGS patients reported here (including 1 previously steroid-resistant), it was also found to have major steroid-sparing effects. The potential beneficial steroid-sparing efficacy of MMF is also illustrated in a case report by Chandra, Susin and Abitbol, in which a 21-year-old man with an 18 year history of severe relapsing nephrotic syndrome from FSGS, despite multimodal treatment, and complicated by severe steroid toxicity, was subsequently maintained in remission with MMF monotherapy, allowing resolution of all steroid side effects [17]. Since the majority of our nephrotic FSGS patients had concomitant renal insufficiency, it is not surprising that only one experienced a complete remission. It is tentatively encouraging that the one complete remission and two partial remissions have been sustained without steroids after MMF was discontinued. Stabilization, and especially improvement (albeit modest), of excretory renal function in several patients was particularly noteworthy.

The generally favorable responses of nephrotic proteinuria in our cohort of FSGS patients is not felt to represent a realistic expectation for the treatment of a broader spectrum of patients, however, especially those previously resistant to other treatment strategies. Indeed, Radhakrishnan et al reported results for 11 previously steroid and either CsA or CTX resistant patients, who remained nephrotic after MMF treatment, despite a significant decrease in proteinuria (abstract; Radhakrishnan et al, *J Am Soc Nephrol* 10:114A, 1999).

Membranous nephropathy is often complicated by nephrotic syndrome with moderate to severe edema/anasarca, requiring intensive diuretic therapy. Treatment considerations are quite controversial, thereby generating an expanding literature. In our experience, such patients generally respond suboptimally, if at all, to steroids, and those who do often manifest steroid dependency. CsA has been effective, but usually associated with CsA dependency.

We have found MMF to be very effective in ameliorating nephrotic proteinuria and its complications in MN, with responses in our experience equivalent to those achieved with CsA. Although all patients experienced marked clinical improvement, complete remissions were few (2 of 15, 13.3%), and it became apparent that some patients would manifest MMF dependency or relapse with steroid withdrawal despite continued MMF therapy. Nevertheless, MMF had major steroid-sparing effects in the majority of patients. The substantial improvement in excretory renal function in several MN patients in our cohort was again noteworthy. The results in our nephrotic MN patients previously resistant to steroids (and CsA in one) are similar to the results in some of the patients recently reported by Miller et al [18]. In their 16 MN patients previously resistant to steroids, CsA, or cytotoxic drugs, they saw partial remissions in 2 patients, and a 50% reduction in the magnitude of proteinuria in 6 other patients over a six-month period of MMF treatment.

The results of MMF treatment in the patients with IgAN and MPGN were similar to those in the patients

with FSGS and MN. Therefore, MMF may also provide therapeutic benefit for selected patients with diseases other than those associated with the so-called primary nephrotic syndrome. This notion is compatible with the reports of the efficacy of MMF in patients with lupus nephritis [1–4] and other systemic vasculitides [16, 19].

Median serum creatinine did not change pre- and post-MMF treatment in the overall group, however, more precise estimates of glomerular filtration rate revealed a statistically and clinically significant improvement in excretory function in the overall group during MMF treatment. Mean arterial pressure decreased significantly for the group as a whole. Although these changes may have been due to increases in antihypertensive medications in a minority of patients, we feel the major effect on MAP was secondary to improvement in the glomerular disease with MMF therapy.

As with any form of empiric treatment undertaken in the absence of established guidelines, the dose and duration of MMF treatment in this cohort were variable among patients. Therefore, this report can only provide suggestions for consideration regarding these parameters. Our preliminary observations [1] and subsequent experience reported here continue to suggest that for individuals of average stature/build and normal or mildly impaired renal function, there is a threshold dose of 1.5 g/day for efficacy and that an appropriate response can be anticipated with total daily doses of 1.5 to 2.0 g. Individuals of small stature or those with moderately to severely impaired renal function may respond to 1.0 to 1.5 g/day. We suggest caution and careful monitoring in patients with advanced renal insufficiency, given the known alterations in MPA pharmacokinetics under such circumstances [31]. On the other hand, dosing may be suboptimal at 2.0 g/day in large patients or in African American patients. We suspect that optimal dosing in all patients will not be achieved until measurements of serum MPA levels or activity are clinically available. The issue of optimal duration of therapy also remains unresolved. There were 17 patients treated for $\geq$3 to 6 months (#1, 3, 4, 6, 7, 10, 12, 20, 21, 22, 23, 25, 26, 34, 36, 43, 45); 18 patients treated for $\geq$6 to 12 months (#5, 8, 9, 11, 13, 15, 18, 19, 24, 27, 30, 31, 38, 39, 40, 41, 42, 46); 8 patients treated for >12 to 24 months (#14, 16, 17, 28, 33, 35, 37, 44); and 3 patients treated >24 months (#2, 29, 32). In patients who respond dramatically within three months, consideration might be given to an attempt to discontinue treatment after six months. In those who relapse and in those whose maximal response takes three to six months to achieve, we extend the treatment period to at least one year. It is apparent that for some MMF dependent patients, treatment may have to be prolonged well beyond one year to maintain the desired response. If the clinical situation warrants such an approach, at least the patient will be spared the potential problems associated with protracted exposure to steroids and/or calcineurin inhibitors. Details of patients completing a course of MMF therapy are given in Table 2.

In general, MMF was very well tolerated in the doses used in these patients. Adverse effects from MMF were limited and similar to those identified in organ transplant recipients. Most common were gastrointestinal complaints of dyspepsia and/or loose stools. With one exception, these were mild to moderate in severity and resolved either spontaneously or with $H_2$ blocker therapy, proton pump inhibitors, or MMF dosage adjustments. Mild leukopenia occurred in two patients, one with normal and the other with impaired renal function; both resolved rapidly with dosage adjustment and MMF therapy was continued. No other hematologic abnormalities were attributable to MMF. One patient developed a reversible increase in serum transaminase levels with concomitant alcohol use, which prompted discontinuation. The patient has been retreated with MMF for more than four months after abstinence from alcohol, without elevation of liver function tests.

The most serious potential complication of MMF was the manifestation of Hodgkin's lymphoma in one patient with MCD after five months of treatment. Lymphoma has been reported in organ transplant recipients receiving MMF along with steroids and calcineurin inhibitors [32]. Although the development of lymphoproliferative disease is a well-recognized complication of intensive, high dose and/or prolonged multidrug immunosuppression, its development seems quite unusual after only six months of MMF treatment in our case. In addition, it is well recognized that MCD can be the initial paraneoplastic manifestation of underlying Hodgkin's lymphoma, and, compatible with the latter situation, our patient experienced a complete remission of both lymphoma and nephrotic proteinuria with chemotherapy. Nevertheless, it is not possible to exclude a cause and effect relationship between the MMF treatment and the lymphoma at this time.

The authors acknowledge the limitations inherent in this report. First, and foremost, the results are not those of a controlled clinical trial with randomization to receive or not receive concomitant steroid therapy according to prescribed stratified dosing regimens. Thus, issues such as how often, and under what circumstances, MMF monotherapy might be effective, and what dosage regimen of concomitant steroid therapy would achieve optimal results, remain unclear. Second, although the responses in our African American patients were equivalent to those in Caucasian patients, the former represented only 17.4% of our cohort. Thus, our results may not be applicable to a larger, more representative group of African American glomerular disease patients, particularly those with FSGS. Third, the proportion of steroid-resistant patients was relatively small; therefore, the generally

favorable responses seen here may not be applicable to a larger group of such affected patients.

In summary, albeit non-randomized and anecdotal in nature, the results reported here in a substantial number of patients, firmly establish the short-term efficacy of MMF in the treatment of primary glomerular diseases, in particular relapsing MCD, FSGS, and MN. As with all novel treatment strategies, however, the proper role for MMF in the management of glomerular diseases can only be determined from prospective, well-designed clinical trials in appropriately stratified, large patient cohorts. Although the clinical improvement in the majority of patients occurred with the combination of MMF with variable doses of steroid, our results demonstrate that MMF has major steroid-sparing effects and can even be effective as monotherapy. Given the lack of nephrotoxicity and adverse hemodynamic and metabolic effects, MMF represents a suitable alternative to the calcineurin-inhibitors as adjuvant treatment for many patients, especially those with progressive renal insufficiency. In the doses used in this report, MMF is generally well tolerated with few serious side effects, but the risk of lymphoproliferative disease or other long-term adverse sequelae remains indeterminate at this time.

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