Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

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Abstract

Background. IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. Up to 40% progress to end-stage renal disease (ESRD) over 10–20 years. Currently, treatment is limited. We studied the use of mycophenolate mofetil (MMF) vs placebo in a group of North American IgAN patients at high risk for progressive disease.

Methods. Included were 32 patients aged 18–75 years from multiple centres who had their biopsies read at Columbia and who had at least 1 g of proteinuria per day plus at least two of the following risk factors: (i) male sex; (ii) hypertension >150/90 mmHg or requiring antihypertensive medications; (iii) creatinine clearance, measured by 24 h urine collection, <80 and >20 ml/min at time of enrolment; and (iv) presence of glomerulosclerosis or tubulointerstitial atrophy and fibrosis on renal biopsy. Patients were randomized to either 1 year of MMF, titrated up to a dose of 1000 mg bid, or placebo. Total follow-up was 2 years. All patients received angiotensin inhibition medication. The primary outcome was a 50% increase in baseline serum creatinine (SCr). Secondary outcomes were an increase of 0.5 mg/dl SCr, ESRD and a 50% reduction in proteinuria.

Results. The mean baseline SCr was 2.4 mg/dl. No statistically significant differences were observed for any outcome. Five of 17 who received MMF vs two of 15 patients in the placebo group reached a 50% increase in SCr ($P=0.4$). In both groups, all patients who reached the primary outcome also reached ESRD. Ten who received MMF vs seven who received placebo had a 0.5 mg/dl increase in SCr ($P=0.7$). Only three MMF and two placebo patients had a 50% reduction in 24 h proteinuria. No serious adverse events occurred in either group.

Conclusion. No benefit was seen in patients who received MMF in this high risk group, probably reflecting the relatively advanced stage of disease of our population. We conclude that MMF is probably not effective in patients with IgAN who already have moderate renal insufficiency.

Keywords: clinical trial; glomerulonephritis; IgA nephropathy; mycophenolate mofetil

Introduction

IgA nephropathy (IgAN) is now recognized as the most frequent form of primary glomerulonephritis worldwide [1]. The course of IgAN is variable, with some patients having stable renal function over decades and others developing nephrotic syndrome, hypertension and progressive renal failure. Fifteen to 40% of patients progress to end-stage renal disease (ESRD) over 10–20 years [2].

The appropriate therapy of IgAN remains uncertain. Since the pathogenesis of IgAN may involve abnormal production, glycosylation and removal of IgA with subsequent immune complex deposition and inflammation in glomeruli, many treatments have targeted the immune system [3–13]. Given that many patients do well without treatment, many physicians have been reluctant to use potentially toxic immunosuppressive drugs in the general IgAN population.

Mycophenolate mofetil (MMF) is an immunosuppressive agent with established efficacy in renal, hepatic and cardiac transplant patients. MMF is rapidly absorbed from the gastrointestinal tract after oral administration and is metabolized to form mycophenolic acid (MPA), an active metabolite. MPA acts
by inhibiting proliferation of T and B lymphocytes [14]. Investigators have begun to look at its potential role in treating primary glomerulonephritis, with some encouraging results in small uncontrolled trials [15–17]. To date, two small randomized clinical trials using MMF in IgAN have been conducted [18,19]. Neither assesses a North American population. Moreover, the benefits of MMF in a group of IgAN patients with high risk for progression to ESRD have not been defined.

The primary objective of this study was to evaluate the safety and efficacy of MMF as a therapeutic regimen on renal survival in a US population of patients with IgAN at high risk for progressive renal insufficiency.

Methods

The study was a double-blind, randomized, placebo-controlled trial conducted at Columbia University. The study protocol was approved by the institutional review board at Columbia University, and all patients gave written informed consent.

Study patients

Patients referred from multiple centres were evaluated at the New York Presbyterian Hospital (NYP) and entered into the study between August 2000 and June 2003. All patients had biopsy-proven IgAN with renal biopsy samples examined independently by two pathologists. Patients aged 18–75 years were included if they had ≥1 g proteinuria daily while on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) plus at least two of the following risk factors: (i) male sex; (ii) hypertension ≥150/90 mmHg or requiring antihypertensive medications; (iii) decreased creatinine clearance (CrCl) ≤80 ml/min at time of enrolment; or (iv) presence of glomerulosclerosis, tubulointerstitial fibrosis and/or crescent formation in ≥25% of the biopsy sample. Excluded were patients with any of the following: (i) age <18 or >76 years; (ii) pregnant females and females unwilling to use contraception; (iii) presence of malignancy, infection, liver disease or systemic lupus erythematosus, Henoch–Schoenlein purpura or other serious systemic disease; (iv) CrCl ≤20 ml/min; (v) presence of other diagnosis on renal biopsy; (vi) patients who received corticosteroids or other immunosuppressive agents <6 months prior to randomization; and (vii) >50% active crescents on biopsy, as we were uncomfortable giving such patients placebo.

Treatment regimen and evaluations

Patients were randomized using permuted blocks of four, known only to the research pharmacy, to either MMF or placebo titrated up to a dose of 1000 mg bid. Patients were treated for up to 52 weeks and followed for up to 1 year after treatment. Patients and physicians were blinded to the therapy by use of identical capsules for both MMF and placebo. Compliance was ascertained by both pill counts at follow-up visits and random pill counts over the phone. There were no crossovers in therapy. All patients were seen initially by the investigators at NYP and then followed along with the primary nephrologists if they were an outside referral. Patients were assessed by a nephrologist at 2 month intervals for the initial year of therapy and subsequently every third month. At interval visits, investigators recorded symptoms, physical findings including blood pressure recordings, and laboratory data including routine chemistry, serum creatinine (Scr), complete blood count and 24 h urinary protein excretion. Patients who developed gastrointestinal side effects had their dose reduced to a minimal dose of 500 mg daily. If symptoms persisted, the drug or placebo was discontinued but the patient was still followed for 1 year.

All patients received an ACEI or an ARB, or both at study entry, and other antihypertensives were included as needed to maintain blood pressure at optimal levels (target ≤130/80 mmHg). Due to their uncertain efficacy but lack of toxicity, patients were allowed to take fish oils at their own or at their physician’s discretion.

Primary and secondary outcomes

The primary outcome was a sustained 50% increase in Scr from baseline observed for at least two consecutive months of follow-up. This has been shown to be a specific marker of disease progression in many glomerular diseases and has been used in several trials of IgAN [9,11]. Secondary outcomes were a 0.5 mg/dl increase in Scr from baseline, ESRD and a 50% reduction in 24 h protein excretion.

Covariates

Demographics such as age, sex, race and body mass index (BMI) were recorded. The dose of MMF or placebo taken was standardized by the number of weeks needed for the equivalent of 1 g twice a day to be achieved. For ACEI or ARB use, the doses were standardized using the amount used relative to the starting antihypertensive dose for each brand (arbitrarily = 1) and adjusted for renal function if the brand required the latter. The total standardized angiotensin II inhibition was thus recorded as the sum of the standardized ACEI + ARB doses. The total number of antihypertensive drugs was recorded. The use of fish oils prior to and concurrent with the study was recorded, as well as the exposure to steroids 6 months or more prior to the study start date. The use of HMG CoA reductase inhibitors was also recorded.

Baseline and follow-up renal function was measured by the Scr, the 24 h CrCl normalized to 1.73 m body surface area (BSA) and the glomerular filtration rate (GFR); 1.73 m² BSA calculated using the modified MDRD equation [20,21]. Baseline and follow-up proteinuria were measured using a 24 h collection for most cases, and spot protein:creatinine ratios in some cases. The baseline blood pressure, serum albumin and white blood cell count were the average of the two most recent values recorded prior to randomization, and follow-up values were the means of all values recorded at follow-up visits.

The following histopathological criteria were recorded: percentage glomerulosclerosis (percentige of glomeruli which were globally sclerotic); percentage of the renal cortex with vascular disease in the form of arteriosclerosis or arteriolar sclerosis. Vascular disease was graded on a scale of 0 = absent,
Mycophenolate mofetil in IgA nephropathy

1 = mild, 2 = moderate and 3 = severe. Patterns of glomerular disease were assessed using the IgAN grading system of Haas [22]. Disease activity was also assessed by the presence of cellular crescents as well as the amount (1+ to 3+) of mesangial deposits on electron microscopy. Because we enrolled patients who had renal biopsies up to 5 years prior to the study start date, the time between the biopsy and the study start date was recorded as 'lead time'.

Statistical analysis
A sample size of 50 patients per group was calculated based on an expected rate of the primary outcome of 45% in the placebo group vs 20% in the MMF group to achieve an error of 0.05 and 80% power. This was based on rates of the same outcome in other studies of IgAN with an inflation factor taking into account our inclusion of patients with worse renal function (CrCl 20–80 ml/min) [9,11].

For covariates, baseline and follow-up comparisons between the MMF and placebo groups were performed with the Fisher’s exact test for binary variables, and the non-parametric Wilcoxon rank sum test for continuous variables. Because of differential rates of follow-up, Kaplan–Meier survival functions with the log-rank test were used to calculate the cumulative rates of the primary and secondary outcomes in the two groups. Patients were censored either at the time of outcome or at the last follow-up date. Cox proportional hazards were used to adjust for baseline differences between the two groups that arose despite randomization. Two-tailed P-values of <0.05 were considered significant for all tests. All analyses were done as intention to treat. Interim analyses at 1.5 and 3 years were censored for safety. All statistics were done using SPSS 11.5 (SPSS Inc., Cary, NC).

Results

Study patients
Between August 2000 and May 2003, 32 patients who met the inclusion criteria and who provided written informed consent were enrolled in the study. Seventeen patients were randomized to MMF and 15 to placebo.

Baseline characteristics (Table 1)
Demographic variables were similar in both groups except there were more females in the placebo group. Baseline CrCl as calculated from the SCr and 24 h CrCl/1.73 m² BSA was worse (although not statistically significant) in the MMF group than the placebo group (2.6 vs 2.2 mg/dl, P = 0.48 and 57 vs 75 ml/min, P = 0.18). By using the four variable MDRD equation, however, the calculated GFR/1.73 m² BSA was similar in both groups (38 vs 41 ml/min, P = 0.72). The 24 h proteinuria, serum albumin, cholesterol and use of HMG CoA-reductase inhibitors were similar. Systolic blood pressure was slightly, but not statistically significantly higher in the MMF group (136 vs 131 mmHg, P = 0.70). Fish oil use was similar, although more patients in the placebo group had previously received steroids (four vs one, P = 0.16).

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>MMF (n = 17)</th>
<th>Placebo (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (range)</td>
<td>39 (19–72)</td>
<td>37 (22–59)</td>
<td>0.59</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>4</td>
<td>0.16</td>
</tr>
<tr>
<td>Race: Caucasian/Asian/Hispanic</td>
<td>10/4/3</td>
<td>13/1/1</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI: mean (SD)</td>
<td>31 (12.4)</td>
<td>28 (6.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>24 h CrCl/1.73 m²</td>
<td>57 (28.6)</td>
<td>75 (42.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>BSA ml/min: mean (SD)</td>
<td>38 (22.2)</td>
<td>41 (26.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>MDRD GFR ml/min: mean (SD)</td>
<td>2.6 (1.2)</td>
<td>2.2 (0.72)</td>
<td>0.48</td>
</tr>
<tr>
<td>Serum albumin: mean (SD)</td>
<td>3.9 (0.34)</td>
<td>3.8 (0.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum cholesterol: mean (SD)</td>
<td>194 (35.7)</td>
<td>192 (36.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>Systolic BP: mean (SD)</td>
<td>136 (19.2)</td>
<td>131 (10.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diastolic BP: mean (SD)</td>
<td>84 (10.6)</td>
<td>86 (7.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Past fish oil use: n (%)</td>
<td>5 (29)</td>
<td>6 (40)</td>
<td>0.55</td>
</tr>
<tr>
<td>Past steroid use: n (%)</td>
<td>1 (6)</td>
<td>4 (27)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 2. Histological characteristics

<table>
<thead>
<tr>
<th></th>
<th>MMF (n = 17)</th>
<th>Placebo (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead time months: mean (range)</td>
<td>17 (0.5–52)</td>
<td>11 (0.4–38)</td>
<td>0.85</td>
</tr>
<tr>
<td>% GS: mean (range)</td>
<td>38 (11–79)</td>
<td>44 (0–71)</td>
<td>0.25</td>
</tr>
<tr>
<td>% TA/IF: mean (range)</td>
<td>36 (5–75)</td>
<td>47 (5–75)</td>
<td>0.11</td>
</tr>
<tr>
<td>Vascular index</td>
<td>1.3</td>
<td>1.4</td>
<td>0.35</td>
</tr>
<tr>
<td>HAAS class: mean (SD)</td>
<td>4.5 (0.9)</td>
<td>4.9 (0.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>HAAS class 5 (n)</td>
<td>11</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>HAAS class 4 (n)</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>HAAS class 3 (n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>HAAS class 2 (n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>1–25% cellular crescents (n)</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>25–50% cellular crescents(n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Messangial deposits (EM)</td>
<td>4/14</td>
<td>4/10</td>
<td>NS</td>
</tr>
<tr>
<td>1+</td>
<td>6/14</td>
<td>4/10</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>4/14</td>
<td>2/10</td>
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</tr>
</tbody>
</table>

Histological characteristics (Table 2)
The two groups were well matched with respect to histological findings. Both groups exhibited a similar
degree of glomerulosclerosis, tubular atrophy and interstitial fibrosis, and vascular disease. Of note, the overall degree of glomerulosclerosis was 41% and the extent of tubular atrophy and interstitial fibrosis was 42%, consistent with the cohort’s high risk for progressive disease. The lead time from biopsy to study start was slightly longer (17 vs 11 months, \( P = 0.85 \)) in the MMF group.

**Outcomes (Table 3)**

No statistically significant differences in outcomes were noted between the two groups. Overall there was a trend towards worse outcomes in the MMF group. The rate of the primary outcome of a 50% increase in SCr from baseline was five out of 17 (16.3/100 person-years) vs two out of 15 (6.0/100 person-years) in the MMF vs placebo groups. The secondary outcome of a 0.5 mg/dl increase in SCr occurred at a rate of 10 out of 17 (55.6/100 person-years) vs seven out of 15 (28.9/100 person-years), and the ESRD rate was five out of 17 vs two out of 15 (15.9 vs 5.9/100 person-years) in the MMF vs placebo groups. All patients who had a 50% increase in SCr developed ESRD. The cumulative probabilities of event-free survival for the main outcomes were calculated using the Kaplan–Meier method (Figure 1). No statistically significant differences in survival were noted for any outcome. Only three patients in the MMF group and two patients in the placebo group had a 50% reduction in proteinuria.

Due to differences in baseline characteristics between the two groups, multivariable regression using the Cox proportional hazards method was performed (Table 4). The crude hazard ratio (HR) of MMF for the primary outcome was 2.28 [95% confidence interval (CI) 0.44–11.8]. In controlling for the baseline renal function, arguably the most important predictor of progression of renal insufficiency, models using the MDRD GFR and the 24 h CrCl standardized to a body surface area of 1.73 m\(^2\) were used. Other variables that were controlled for in the models included BMI, baseline systolic blood pressure, previous steroid use and lead time from renal biopsy to study entry. The full model adjusted HR of MMF for the primary outcome was 1.62.
(95% CI 0.07–35). No HRs were statistically significant, with very wide CIs reflecting the small sample size. However, there was a consistent trend towards worse outcomes in the MMF group even when adjusting for the worse baseline renal function in the latter group.

**Compliance, adverse events, blinding**

The mean total length of follow-up (the time from entry into the trial to the time of the last recorded serum creatinine) was 59 and 75 weeks in the MMF and placebo groups, respectively ($P = 0.23$) (Table 3). The actual mean durations of treatment (standardized as the length of time a dose of 1 g bid study medication was taken, ascertained by pill counts) were 30 and 32 weeks in the MMF and placebo groups, respectively, indicating an equal exposure to study medication. Six patients in the MMF group and five patients in the placebo group received the full 52 weeks of treatment. Ten vs 11 patients received at least 6 months of therapy. Two patients in the placebo and one in the MMF group did not complete treatment due to a lack of compliance as ascertained by pill counts. Three patients in the MMF group did not complete treatment due to ESRD. Finally, five patients in the placebo and four in the MMF group did not complete the full year of therapy as they were censored at the time the study was terminated. All patients were analysed as intention to treat whether or not they completed the full 1 year of therapy.

No deaths or serious infections occurred in any patients during the study period. Two patients in each group stopped therapy early due to gastrointestinal side effects. No episodes of leukopenia [white blood cell (WBC) count $< 3000 \times 10^9$ cells/l] occurred. The mean WBC count during treatment was 6.2 for the MMF group and 6.8 for the placebo group. One patient receiving placebo developed a deep vein thrombosis which was felt to be a consequence of nephrosis since he had had one prior to entering the study.

Treating physicians and patients were blinded to drug assignment at all times. Since gastrointestinal side effects and WBC count were similar in both groups, they were unlikely to have helped the physicians or patients predict drug assignment.

**Follow-up characteristics** (Table 5)

No statistically significant differences in follow-up values for covariates were noted. The mean follow-up SCr and 24 h urinary protein excretion in the MMF group were worse than placebo (4 mg/dl and 3.1 g/day vs 3 mg/dl and 2.7 g/day). Both systolic and diastolic blood pressure were similar and reasonably well controlled in both groups, as were the total number of blood pressure medications required and AT2 blockade given.

**Discussion**

There are only a small number of trials using MMF in IgAN. Chen et al. compared the use of MMF 0.5–0.75 g twice daily with prednisone 30–40 mg daily in 62 Chinese patients with IgAN (30 with >72 weeks...
follow-up) and showed a benefit with respect to SCr and proteinuria [18]. With a similar sample size and inclusion criteria to our study, Maes et al. randomized 34 IgAN patients in Belgium to either MMF 2 g daily or placebo. After 3 years of follow-up, no significant differences in SCr or proteinuria were found, although the study probably lacks sufficient power [19].

This study is the first North American randomized double-blind clinical trial to investigate the efficacy of MMF in the treatment of patients with IgAN who have moderately advanced disease. The study was terminated before the a priori calculated sample size of 50 per group was reached because the second scheduled interim analysis done by the independent study monitor revealed a trend towards a worse outcome in the MMF group that would have made it very unlikely to show a benefit for MMF given our rate of recruitment and our target sample size. The intention to treat analysis of the 32 patients enrolled in the study reveals a seemingly slightly higher rate of the primary outcome of a sustained 50% increase in serum creatinine from baseline in the MMF group (HR 1.6 vs 2.1) even when adjusting for baseline renal function. Higher rates of the secondary outcomes of a sustained 0.5 mg/dl increase in SCr and ESRD were also observed in the MMF group. Only three patients in the MMF and two in the placebo group had a 50% reduction of 24 h proteinuria. The CIs for the HRs of these outcomes are very wide and are thus unstable estimates of actual risk, reflected in non-significant P-values in all cases. Because of the trend towards a worse outcome in the MMF group, the investigators and the study monitor agreed that stopping the study early would be in the best interest of the participants.

The lack of benefit for MMF is probably due to the presence of relatively advanced disease in both groups at the start of the study. The original study design was to select a group at high risk for progressive disease in order to ensure sufficient numbers of end-points in a disease entity where the majority experiences a relatively benign course. We succeeded perhaps too well in this regard, recruiting a population in which 29% of the MMF group and 13% of the placebo group achieved ESRD after a mean of 105 weeks of follow-up. In retrospect, the patients may have been too far advanced with respect to irreversible renal fibrosis to demonstrate a benefit from controlling inflammation and other immunological responsive factors. The low rate of a 50% reduction in proteinuria in both groups may also reflect the advanced state of the patients and that all patients were already on blockers of the renin–angiotensin system prior to and during the study.

Importantly, the follow-up blood pressures, use of ACEIs and ARBs, and total amount of blood pressure medication use were nearly equal during the study period. We therefore believe that the important potential for bias due to blood pressure control and use of ACEIs and ARBs was minimized in this study. The use of fish oils during the trial was minimal and similar in both groups, with only two patients in the MMF and one in the placebo group on them (Table 5). In addition, there were no serious complications of therapy during the brief period of study. It is important to note that the small sample size and the relatively brief period of follow-up do not allow us to conclude that MMF is safe in patients with advanced disease, especially with respect to late complications such as malignancy.

Although this study was randomized, there were some differences in baseline characteristics. Most importantly, there was a small difference in baseline renal function between the two groups. The mean SCr was 2.6 vs 2.2 in the MMF vs placebo groups at the time of enrolment. To estimate renal function more accurately, the 24h CrCl indexed to 1.73 m² BSA as well as the MDRD GFR were calculated. The measured CrCl was 57 vs 75 ml/min/1.73 m² and the MDRD GFR was 38 vs 41 ml/min/1.73 m² in the MMF vs placebo groups. Furthermore, there was a higher baseline SBP in the MMF (136 mmHg) vs placebo (131 mmHg) groups, although both groups subsequently achieved comparable blood pressure control. There was also a slightly lower rate of previous steroid use in the MMF (n = 1) vs placebo (n = 4) groups. Due to the small study size, the fact that none of these differences was statistically significant does not mean that they are not important. Taken together, these discrepancies could have potentially introduced bias contributing to the qualitative trend towards worse outcomes in the MMF group. Even when these variables, including the baseline renal function, were adjusted for in the Cox regression, we failed to demonstrate a benefit in the MMF study arm.

With respect to the baseline renal function in this study, it should be noted that the pathology showed a similar mean 38 vs 44% glomerulosclerosis and 36 vs 47% tubulointerstitial fibrosis in the MMF vs placebo groups, indicating a histologically relatively advanced group, perhaps with somewhat less chronicity in the former. The Haas classes were similar, although the number of patients with cellular crescents and the amount of mesangial deposits were slightly higher in the MMF group. Overall, there were no major differences in histology at the time of biopsy and, if anything, there was slightly less chronicity and more activity in the MMF group. However, the mean 17 vs 11 months lead time between the biopsy and study start makes the histology less predictive, and it is likely that the degree of chronicity was worse at the time of enrolment, as reflected by the moderately elevated mean SCr in both groups. Although the histology may have been slightly better in the MMF group at the time of biopsy, the longer lead time could partially account for the worse renal function at the start of the study, and thus perhaps the worse outcome. When comparing the results of this study with other treatment trials in IgAN, the advanced disease as reflected by the histology and worse baseline renal function (SCr 2.4 mg/dl and CrCl/1.73 m² 65 ml/min) is an important factor. For example, in Pozzi’s trial of steroids [5], the mean baseline SCr and CrCl/1.73 m² were 1.0 mg/dl
and 90 ml/min, and in Donadio’s trial of fish oils [7] they were ~1.5 mg/dl and 82 ml/min. In Maes’ trial of MMF [19], the baseline SCrs and inulin clearances were 1.43 mg/dl and 71.5 ml/min/1.73 m². Finally, the relatively short length of treatment and follow-up may have been a factor in failing to show a benefit in favour of MMF.

Is it possible that (i) MMF actually hastened the demise in the treated group and (ii) should it be contraindicated in the population studied? We believe the answer to the first question is no. Once again, due to the small sample size, the small difference in outcomes could have been due to chance alone. Furthermore, the longer lead time from biopsy and the worse renal function at baseline in the MMF group may have contributed to the worse outcomes. Finally, we cannot explain mechanistically why MMF would worsen renal outcomes. With respect to the second question, we believe the use of MMF in patients with relatively advanced disease is probably not a good idea, as it is probably not effective and thus exposes the patient to unnecessary potential complications such as infections and malignancy.

In conclusion, our double-blind randomized clinical trial to examine the efficacy of MMF in the treatment of IgAN failed to demonstrate a benefit in patients at high risk for progression of renal disease who already have baseline moderate renal insufficiency. The use of MMF proved safe and without major complications over the short period studied. Our findings are similar to the recent study by Maes et al. [19]. The major limitations of this study were the small sample size (resulting in insufficient statistical power), the relatively advanced nature of IgAN in the population studied and the relatively short length of treatment and follow-up. Although the study may be interpreted in various ways, it emphasizes the need for much larger multi-centre trials examining the role of MMF and other immunosuppressive medications in the treatment of IgAN in North America, especially in patients with earlier disease and better preserved renal function at the time of therapy initiation.

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