Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study

Lakshmanan Senthil Nayagam1, Anirban Ganguli1, Manish Rathi1, Harbir S. Kohli1, Krishan L. Gupta1, Kusum Joshi2, Vinay Sakhuja1 and Vivekanand Jha1

1Department of Nephrology and 2Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Background. The current treatment regimes for patients with nephrotic syndrome due to idiopathic membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) are based on steroids and/or cytotoxic agents. Data on the effect of mycophenolate mofetil (MMF) for these conditions are scarce and confounding.

Methods. We compared the efficacy of an MMF-based therapy with standard therapies in inducing remission in adult nephrotics with MN and FSGS in a randomized pilot study. MMF was given at 2 g/day for 6 months along with prednisolone at 0.5 mg/kg/day for 2–3 months. Conventional therapy was prednisolone 1 mg/kg/day for 3–6 months for FSGS and alternating monthly cycles of steroids and cyclophosphamide for 6 months for MN. The primary end point was change in urinary protein/creatinine ratio.

Results. A total of 54 patients (21 MN and 33 FSGS) were recruited; 28 were randomized to receive MMF (group A) and 26 were on conventional treatment (group B). There was no difference in the proportion of patients achieving remission in two groups (64 and 80% in MN and 70 and 69% in FSGS). The frequency of relapses and incidence of infections was also similar. FSGS patients in group A achieved remission faster and received a lower cumulative steroid dose.

Conclusions. A 6-month treatment with MMF is as effective as the conventional treatment for primary treatment of MN and FSGS in the short term. It induces remission faster and reduces steroid exposure in FSGS patients. Studies with more cases and longer follow-up are required to evaluate its impact on preservation of kidney function.

Keywords: controlled trial; focal segmental glomerulosclerosis; membranous nephropathy; mycophenolate mofetil; outcome

Introduction

Progressive immune-mediated glomerulonephritides constitute a significant proportion of CKD burden around the world, and form the largest group of patients with end-stage kidney disease in developing countries [1,2]. Membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) are the commonest primary glomerular diseases encountered in adults. Persistence of nephrotic syndrome portends a poor prognosis, and remission of proteinuria offers the best hope of good long-term renal outcome [3–5]. The current treatment regimes are centred on steroids and alkylating agents, and induce remission in about 50–80% of patients [6–9]. Nephrologists are on the lookout for alternative agents that can induce remission while minimizing the likelihood of relapse and therapeutic toxicity. Preliminary reports (anecdotal and uncontrolled studies) suggest that mycophenolate mofetil (MMF) is effective in several types of glomerulonephritis both as a primary therapy and after failure of primary therapy [10–23]. The data, however, are scarce and confounding. Randomized studies are needed to confirm and consolidate these initial reports and determine its long term effectiveness.

In a pilot study, we compared the efficacy of an MMF-based treatment protocol with that of conventional (steroid/alkylating agent-based) therapy in inducing remission of the nephrotic state in idiopathic MN and FSGS and their side-effect profiles. Short-term follow-up results are reported in this communication.

Patients and methods

This was a randomized open-label study. The study population consisted of adult patients with nephrotic syndrome and biopsy-proven FSGS or MN. Kidney biopsies were evaluated by light microscopy and immunofluorescence. Patients with systemic illness, malignancy, diabetes mellitus, hepatitis virus positivity, renal vein thrombosis, pregnant women and those who had received steroids or immunosuppressive drugs previously were excluded. The study was approved.
by the Institute Ethics Committee, and all patients provided informed consent.

Protein and creatinine excretion rates were measured from spontaneously voided, non-supervised, 24-h urine collections. In order to avoid inaccuracies due to under or over-collection of the urine samples, proteinuria was adjusted for the concomitant creatinine excretion, and expressed as urine protein-to-creatinine ratio (Up/c, mg/mg). Nephrotic syndrome was defined as Up/c > 3.5, or > 2.5 along with serum albumin < 2.2 g/dl, oedema and hyperlipidaemia.

After diagnosis, all patients with estimated glomerular filtration rate (eGFR) of > 60 ml/min were started on escalating doses of angiotensin-converting inhibitors (ACEI) and/or angiotensinogen receptor blockers (ARB). If needed, diuretics and additional antihypertensive agents were used to achieve appropriate blood pressure control. All patients were advised as to appropriate dietary modifications and 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors were used wherever indicated.

Patients were followed up on this regime for 6 months, and those who continued to be nephrotic, as defined earlier, were randomized into two treatment groups; patients with initial eGFR of < 60 ml/min were randomized at the time of first visit. Treatment allocation was on the basis of minimization, using the following parameters: (MN or FSGS), sex and eGFR. Minimization is a valid alternative to randomization, and ensures uniformity between the two groups with respect to the characteristics used in the allocation process.

Group A patients received MMF at 2 g/day in two divided doses for 6 months along with prednisolone at 0.5 mg/kg/day for 8–12 weeks. MMF dose was decreased by 0.3 mg/kg/day for 27 days alternating with oral cyclophosphamide at 2 mg/kg/day for 30 days. FSGS patients received oral prednisolone at 1 mg/kg/day in a single morning dose for 12–24 weeks, followed by tapering over the next 8 weeks.

Patients were monitored every 2 weeks for first 2 months, monthly for the next 4 months and every 3 months thereafter. Up/c, serum creatinine and total leucocyte count (TLC) were monitored at each visit; and serum albumin, fasting cholesterol and alanine aminotransferase were measured after 1, 3, 6 and 12 months. TLC was monitored every 2 weeks during cyclophosphamide therapy. Details of any event, e.g. leucopenia and infectious episodes were recorded. The cumulative steroid dose was calculated for all patients. The primary study outcome was the change in the Up/c. Complete remission (CR) was defined as a reduction in Up/c to < 0.3, partial remission (PR) as reduction in Up/c to 0.3–2 or < 50% of baseline, whichever was lower, along with stable eGFR.

Statistical analysis was performed using SPSS v13. The internal consistency of the data was assessed using time-trend analysis. Fisher’s exact test was used to compare categorical variables, Mann–Whitney and Wilcoxon signed-ranks tests were used to compare data between groups and within groups, respectively. All tests were two-sided and the level of significance was set at < 0.05.

Results

A total of 54 patients were recruited, 28 (11 MN, 17 FSGS) in group A and 26 (10 MN, 16 FSGS) in group B. The baseline patient characteristics (Table 1) were comparable between the two groups. Histological parameters in terms of stages (for MN), proportion of sclerosed glomeruli and degree of tubular atrophy and interstitial fibrosis were also similar.

Table 2 shows the details of response to treatment. A total of 19 (68%) patients in group A and 19 (73%) in group B achieved CR or PR (P = 0.77). One MN patient randomized to group A, who was lost to follow-up after

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>28</td>
<td>26</td>
<td>1.0</td>
</tr>
<tr>
<td>MN</td>
<td>11</td>
<td>10</td>
<td>0.40</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>17</td>
<td>16</td>
<td>0.76</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.2 ± 12.6</td>
<td>33.1 ± 12.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>2:1</td>
<td>1:1</td>
<td>0.07</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>8.5 ± 3.2</td>
<td>9.2 ± 2.8</td>
<td>0.57</td>
</tr>
<tr>
<td>Urine protein:creatinine ratio (mg/mg)</td>
<td>4.68 ± 1.82</td>
<td>4.95 ± 1.65</td>
<td>0.87</td>
</tr>
<tr>
<td>Range</td>
<td>3.2–9.8</td>
<td>3.4–10.1</td>
<td>0.23</td>
</tr>
<tr>
<td>MDRD GFR (ml/min)</td>
<td>86 ± 12.6</td>
<td>82 ± 11.8</td>
<td>0.93</td>
</tr>
<tr>
<td>No. of cases with eGFR &lt; 60 ml/min</td>
<td>6</td>
<td>5</td>
<td>0.51</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.7 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MN</th>
<th>FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Number of cases</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Follow up duration (months)</td>
<td>18.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Range</td>
<td>14.6–20.8</td>
<td>13.1–18.8</td>
</tr>
<tr>
<td>Remissions</td>
<td>CR</td>
<td>5</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Time to remission (weeks)</td>
<td>9.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Relapses</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cumulative prednisolone dose (g)</td>
<td>1.8 ± 0.3</td>
<td>2 ± 0.4</td>
</tr>
</tbody>
</table>

CR, complete remission, PR, partial remission.

* One patient achieved CR after restarting MMF.

* Two achieved CR after restarting steroids.
1.5 months, was included in the non-responder category. The time to remission was similar in the two groups in MN, but was significantly shorter for group A in FSGS. FSGS patients randomized to group A also received a significantly lower cumulative steroid dose ($P < 0.0001$).

Figure 1 shows the course of proteinuria over the follow-up period. The proteinuria declined significantly from the pre-treatment values in both groups A and B in MN and FSGS, but there was no difference between the two treatment groups at any time point.

Table 3 shows the evolution of selected laboratory parameters before treatment and at last follow-up. The eGFR value did not differ significantly ($P > 0.05$) either within or between groups. Serum albumin levels increased or cholesterol decreased significantly over time in both groups. Again, no difference was noted between the two treatment arms.

**Complications**

Two patients in group A developed infections requiring hospitalization and permanent discontinuation of therapy. The first developed disseminated tuberculosis 14 weeks into therapy, whereas the other developed bacterial pneumonia with type 1 respiratory failure. Both recovered with appropriate antimicrobial therapy. Cytopenias or liver function abnormalities were not noted. One patient developed mild gastrointestinal discomfort that responded to one-step dose reduction of MMF. Three patients developed infective complications in group B, none required hospitalization. One patient of FSGS developed sputum-positive pulmonary tuberculosis after 22 weeks of steroid therapy. Institution of anti-tubercular therapy along with steroid tapering led to full recovery. Two patients on cyclophosphamide and steroids for MN required temporary cessation of therapy; the first had a urinary tract infection and mild leucopenia in the second month of therapy and required antibiotics and interruption of therapy for 3 weeks. Treatment was interrupted for 2 weeks in the second patient who developed herpes zoster. Acyclovir was given for 7 days, and treatment reinstituted once the lesions had healed.

**Discussion**

MMF has been tried in an uncontrolled fashion in a variety of primary glomerular diseases including minimal change disease, MN and FSGS [10–23]. The use has been largely limited to cases that have failed initial therapy, with published reports showing significant improvements in proteinuria in the short to intermediate term. Treatment protocols, however, have been heterogeneous in terms of MMF dose and duration, and the concomitant therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MN Baseline</th>
<th>Follow-up</th>
<th>$P$-value</th>
<th>FSGS Baseline</th>
<th>Follow-up</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD GFR (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>85 ± 10.8</td>
<td>81 ± 12.5</td>
<td>0.43</td>
<td>87 ± 14.2</td>
<td>83 ± 13.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Group B</td>
<td>80 ± 13.4</td>
<td>76 ± 11.9</td>
<td>0.48</td>
<td>84 ± 10.1</td>
<td>79 ± 12.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>2.7 ± 0.7</td>
<td>3.3 ± 0.5</td>
<td>0.031</td>
<td>2.8 ± 0.6</td>
<td>3.4 ± 0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Group B</td>
<td>2.7 ± 0.4</td>
<td>3.4 ± 0.5</td>
<td>0.019</td>
<td>2.6 ± 0.5</td>
<td>3.1 ± 0.8</td>
<td>0.025</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>320 ± 118</td>
<td>205 ± 77</td>
<td>0.019</td>
<td>287 ± 112</td>
<td>196 ± 56</td>
<td>0.008</td>
</tr>
<tr>
<td>Group B</td>
<td>340 ± 208</td>
<td>193 ± 53</td>
<td>0.04</td>
<td>294 ± 101</td>
<td>189 ± 65</td>
<td>0.001</td>
</tr>
</tbody>
</table>
This is the first trial to evaluate the efficacy of MMF as a primary therapy for two common primary glomerular diseases, MN and FSGS. Rather than compare it with a placebo arm, we compared this regime to the currently used (conventional) therapies at our centre.

For both conditions, the MMF-based protocol was similar in efficacy to the conventional protocol, with the advantage of reducing the steroid exposure and achieving remission sooner in the case of FSGS. We noted no difference in the side-effect profile of the two regimes, and the relapse rates were also similar.

The frequency of FSGS has increased rapidly in recent years, and it has become a leading cause of nephrotic syndrome amongst adults in many parts of the world. About 60–70% of nephrotic adults with FSGS achieve remission of proteinuria and maintain stable long-term renal function after prolonged therapy with corticosteroids as used in the conventional treatment arm in this study [24,25]. In a meta-analysis, only 15% of patients who received corticosteroids for 16 weeks or less entered CR of proteinuria, whereas 61% of those receiving treatment for longer periods obtained CR. Moreover, most responders obtained remission after 6 months [25]. Therefore, the current standard of care is to treat these patients with steroids for 4–6 months before switching over to second-line therapies [24].

Although the remission rates in FSGS were equivalent in the two regimes, patients on MMF-based therapy enjoyed the advantage of receiving a significantly lower cumulative steroid dosage and achieved remission faster. Choi et al. [10], in their uncontrolled study also noted the steroid sparing properties of MMF in FSGS.

Optimal management of patients with MN remains controversial. Some favour a conservative approach, whereas others support treating all nephrotics with alkylating agents and steroids. In the study of Ponticelli et al. [26], the 10-year renal survival was 92 and 60% in the treated patients and controls, respectively. We also noted similar response rates in our MN population [27] and currently treat all patients with a combination of steroids and cyclophosphamide. This regime has been suggested as the gold standard to which other therapies for MN should be compared [28].

In this study, the MMF-based protocol was comparable in terms of efficacy with the conventional protocol in nephrotics with MN. About 64% patients achieved CR, which is higher than 53% as reported earlier [10]. None of the patients exhibited MMF dependency. It must be pointed out that MMF-treated patients also received steroids. Whether MMF alone would have been equally effective in inducing remission remains a matter of speculation.

The optimal dose and duration of MMF therapy remains uncertain. Based on our experience in kidney transplant recipients, we used MMF at 2.0 g/day. Most studies have used dosages between 1.5–2 g/day, with some going up to 3 g/day [29]. In children, a dose of 250–500 mg/m² has been suggested [30]. Some workers suggest a concentration-controlled dosing for optimal response [14]. Also, whether a longer duration of exposure to MMF than the 6-month regime would have improved the response rate is unclear. The relapse rate was fairly low in the MMF-treated patients, suggesting that remission induced by a 6-month course of MMF and steroids can last in the intermediate term. In one study, most responders had significant reductions in proteinuria within 2 months. The authors concluded that failure to respond by 6 months constituted treatment failure [11]. Extending the treatment period to 1 year in patients in whom the response appears after 6 months has been suggested [10].

It must be pointed out that remission of nephrotic syndrome and changes in proteinuria, serum albumin and serum cholesterol are only surrogate markers of disease progression. Long-term follow-up would be needed to evaluate the long-term effectiveness of MMF in preservation of renal function. Ample data, however, exist supporting the view that a CR is associated with a marked protection from future ESRD in patients with MN and FSGS, whether the remission is spontaneous or treatment related. Whereas ~25–30% of MN patients do achieve spontaneous remission [31], remissions without treatment are rare in FSGS. Recognizing the possibility that some patients may attain spontaneous remission, we included only those who continued to remain nephrotic after a 6-month follow-up during which they received ACEIs and/or ARBs. In our experience, it is unlikely for patients to enter into spontaneous remission after 6 months.

This was only a pilot study aimed to compare the efficacy and safety of the MMF-based regime with the conventional therapy, and was not powered to demonstrate superiority of one over the other. While the number of patients was small, we could show that it induced remission in an equivalent proportion of cases.

It can be argued on the basis of the Up/c that patients in this study were at low risk of progression. However, this degree of persistent proteinuria was despite a 6-month observation period during which patients received ACEI and/or ARBs. These patients also continued to have significant hypoalbuminaemia which could also limit the amount of excreted protein.

MMF-based therapy does not offer any advantage over conventional management in terms of the likelihood of attaining a remission, but can be considered in a selected group where toxicities related to steroids and/or cytotoxic agents are a concern; such as children, diabetics, those wanting to avoid the dysmorphism associated with long-term steroid use and those wanting to avoid the bone marrow and gonadal toxicities associated with alkylating agents. Treatment cost remains an important consideration, especially in economically poor countries. The cost of MMF-based therapy was several-fold higher than that of the conventional modality, and the choice of therapy must take this factor into account. On the basis of this pilot study, we can conclude that in the short term, MMF is as effective as a first line agent as conventional forms of therapy in the management of adults with nephrotic syndrome due to FSGS and MN and is well tolerated. MMF-based therapy seems to induce remission faster and reduces exposure to steroids in FSGS. Studies with a larger number of cases and long-term follow-up are needed to determine the duration of MMF therapy and effect on preservation of renal function.

Acknowledgements. This study was supported by a grant from M/s Panacea Biotec Ltd, New Delhi, India.
Conflict of interest statement. None declared.


(See related article by X. Li et al. Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome. Nephrol Dial Transplant 2008; 23: 1919–1925.)

References


Received for publication: 10.5.07
Accepted in revised form: 16.7.07

L. S. Nayagam et al.