Mycophenolate as Maintenance Therapy for Lupus Nephritis with Impaired Renal Function

F. Rivera\textsuperscript{a} M.L. Illescas\textsuperscript{b} E. López-Rubio\textsuperscript{b} J. Fulladosa\textsuperscript{c} R. Poveda\textsuperscript{c} J. Baltar\textsuperscript{d} G. Fernández-Juárez\textsuperscript{e} J. Ballarín\textsuperscript{f} A. Oliet\textsuperscript{g} A. Vigil\textsuperscript{g} J. Lucas\textsuperscript{h} M. Sierra\textsuperscript{i} M.A. Frutos\textsuperscript{j} P. García-Frias\textsuperscript{j} C. Ramos\textsuperscript{k} E. Mérida\textsuperscript{l} M. Praga\textsuperscript{l} A. Segarra\textsuperscript{m} on behalf of the Glomerular Spanish Glomerular Study Group (GLOSEN)

\textsuperscript{a}Hospital General Universitario de Ciudad Real, Ciudad Real, \textsuperscript{b}Hospital General Universitario de Albacete, Albacete, \textsuperscript{c}Hospital Universitari de Bellvitge, Barcelona, \textsuperscript{d}Hospital Universitario Central de Asturias, Asturias, \textsuperscript{e}Fundación Hospital Alcorcón, Madrid, \textsuperscript{f}Fundació Puigvert, Barcelona, \textsuperscript{g}Hospital Severo Ochoa, Leganés, \textsuperscript{h}Hospital Universitario Infantil La Fé, Valencia, \textsuperscript{i}Hospital San Pedro de Logroño, Logroño, \textsuperscript{j}Hospital Universitario Carlos Haya, Málaga, \textsuperscript{k}Hospital Clinic Universitari de Valencia, Valencia, \textsuperscript{l}Hospital Universitario 12 de Octubre, Madrid, and \textsuperscript{m}Hospital Vall d’Hebron, Barcelona, Spain

Key Words

Lupus nephritis · Systemic lupus erythematosus · Mycophenolate · Renal failure

Abstract

Background: Mycophenolate (MF) is effective as a maintenance therapy after induction therapy in patients with lupus nephritis (LN). However, little is known about its role in patients with impaired renal function. The purpose of this study was to evaluate the efficacy and safety of MF as a maintenance therapy for LN and its association with renal function.

Methods: Data were obtained for 56 Spanish patients who were receiving MF as a maintenance therapy for LN. Patients were classified into two groups according to renal function at the initiation of MF treatment: group 1 (estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m\textsuperscript{2}) and group 2 (eGFR < 60 ml/min/1.73 m\textsuperscript{2}). The primary endpoints of the study were the rates of renal relapse and responses, and their relationship with baseline renal function. Secondary outcomes were the appearance of side effects during treatment.

Results: At initiation of MF treatment, the only differences between the groups were for age, hemoglobin levels, anti-DNA antibody titer, proteinuria, and renal function. In group 1 (n = 38), the eGFR was 98 ± 34 ml/min/1.73 m\textsuperscript{2} and in group 2 (n = 18) the eGFR was 43 ± 14 ml/min/1.73 m\textsuperscript{2}. Only 3 cases had an eGFR <30 ml/min/1.73 m\textsuperscript{2}. No significant differences were observed in the rate of relapse at 6 months (group 1: 20%; group 2: 23%) or at 12 months (group 1: 25%; group 2: 17%). Response rates were also similar in both groups. Side effects were unremarkable.

Conclusions: MF is effective and safe as a maintenance therapy for LN both in patients with normal renal function and in those with renal impairment.

Introduction

The optimal therapeutic approach for severe lupus nephritis (LN) involves an induction phase to achieve remission followed by maintenance therapy (sequential therapy) to prevent relapses, maintain remission, reduce smoldering activity leading to chronic renal failure, and prevent long-term side effects of therapy and death [1–3].
The reported incidence of renal flares during the maintenance phase of treatment ranges from 27 to 66%. This large difference is probably due to the different definitions used for the diagnosis of renal flare, differences in the populations studied, and the use of different therapeutic regimens [4]. Indeed, the choice of drug to be administered for long-term maintenance therapy remains open to debate because mycophenolate (MF) or azathioprine (AZA) [5] are preferred to cyclophosphamide (CYC), whose side effects restrict long-term maintenance therapy [6, 7]. According to the results of recent randomized controlled trials, MF is considered to be superior to AZA for consolidating remission and preventing relapses and progression to chronic renal failure [8, 9]. However, most of the patients included in these trials have normal renal function at the beginning of maintenance therapy, and little is known about the outcome in patients with renal insufficiency at the beginning of maintenance therapy.

Using data from our national survey on the use of MF to treat LN, we performed a retrospective uncontrolled study involving 56 patients from 14 centers in Spain to assess the efficacy and safety profile of MF as a maintenance therapy in patients with LN and its association with renal function at the beginning of maintenance therapy. They had all received intravenous CYC as the induction therapy and were switched to MF for maintenance therapy.

**Subjects and Methods**

**Patients**

From 2008 to 2011, 14 nephrology departments belonging to the Spanish Group for the Study of Glomerular Disease (GLOSEN) participated in the study. Data from patients with LN who had received MF were collected using a uniform protocol. The inclusion criteria were as follows: (1) diagnosis of systemic lupus erythematosus according to the criteria of the American College of Rheumatology, (2) biopsy-proven LN, (3) use of MF as a maintenance therapy following induction therapy, irrespective of whether renal remission is achieved, and (4) treatment for a minimum of 3 months. Switching from the induction phase to the maintenance phase was made according to personal expertise or local treatment schedules of treatment of each participating renal unit. The exclusion criteria were those conditions in which MF was contraindicated. No comparisons were made with other immunosuppressive maintenance therapies. The study sample comprised 56 cases that met the criteria.

**Data Collection**

Data were compiled from the medical records of participating centers and included age, gender, ethnicity, histopathological LN class (at the moment of induction treatment) according to the 2003 classification of the International Society of Nephrology/Renal Pathology Society, type and doses of drugs administered as the induction treatment, BMI, and blood pressure (mm Hg). Analytical variables included hemoglobin (g/dl), white cell counts (cells/mm³), serum creatinine (mg/dl), estimated glomerular filtration rate (eGFR, ml/min/1.73 m²) calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation \[ eGFR = 175 \times \text{serum creatinine} – 1.154 \times \text{age} – 0.203 \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)} \] [10], proteinuria (g/24 h), titers of antinuclear and anti-dsDNA antibody, and levels of complement fractions (C3 and C4, mg/dl). Types and doses of MF (mofetil or sodium), corticosteroids used as maintenance therapy, and antihypertensive drugs were recorded. Follow-up was considered to be the period in which patients received MF; the events that appeared after withdrawal were not collected. We also recorded complications occurring during treatment, side effects, occurrence of end-stage renal disease (need for chronic dialysis or renal transplantation), and deaths. Data were recorded when starting MF (baseline) and at 3, 6, and 12 months, and then every 6 months up to 60 months.

Patients were categorized into two groups based on eGFR at initiation of maintenance MF: group 1 (≥ 60 ml/min/1.73 m²) and group 2 (<60 ml/min/1.73 m²).

Relapse was defined as doubling of proteinuria (≥ 1 g/24 h in patients with ≤0.5 g/24 h at initiation of MF maintenance therapy, and ≥2 g/24 h in patients with >0.5 g/24 h at initiation of MF maintenance therapy) or by a ≥50% decrease in eGFR. The rate of relapse was evaluated at each assessment point during follow-up. These criteria were based on the definitions proposed by Dooley et al. [9] and Contreras et al. [11]. Complete response was defined as a return to the normal or previous eGFR and proteinuria ≤0.5 g/24 h. Partial response was defined as a decrease in urine protein to <3.5 g/24 h and a ≥50% decrease in proteinuria in patients with baseline urine protein ≥3.5 g/24 h, or as a 50% decrease in proteinuria in patients with baseline proteinuria <3.5 g/24 h. In both situations, the eGFR had to have stabilized (±25%) or improved. Both complete response and partial response were considered a response, as in our previous study [3].

**Outcomes**

The primary endpoints of the study were as follows: (1) number and percentage of patients who relapsed or achieved renal response (complete or partial), (2) time to renal flare and maintenance of response, analyzed using survival curves, and (3) relationship between flares and response and baseline renal function at initiation of treatment with MF. The secondary outcomes were the appearance of side effects, number of cases that progressed to end-stage renal disease (need for chronic dialysis or renal transplantation), and deaths overall and in both groups.

**Statistical Analyses**

Continuous variables were reported as means ± SD or medians, according to their Gaussian distribution. Qualitative variables were reported as percentages. Continuous data were compared using an unpaired t test or Mann-Whitney test, as appropriate. \( \chi^2 \) and Fisher’s exact tests were used to compare qualitative variables. Serial data were compared within and between groups using repeated-measures analysis (paired t test or Wilcoxon test). The cumulative probability of relapse-free survival was estimated using Kaplan-Meier plots and analyzed using a log-rank test. We calculated the hazard ratio and 95% CI using the univariate Cox proportional hazards model. Logistic regression (Cox proportional hazards) was applied to explore relevant factors. \( p < 0.05 \) (2-tailed) was considered to indicate statistical significance. Statistical analysis was performed using SPSS 15.0.1.

Rivera et al.
Results

The baseline characteristics of the patients overall and in the two groups are shown in Table 1. Most patients were aged 15–65 years (94.6%), whereas those aged less than 15 years accounted for 5.4%. No patients were aged over 65. All patients had received corticosteroids and pulses of CYC as the induction treatment. The median number of pulses of CYC was 6 (range: 3–15), which was similar in both groups (p = 0.19), and the median dose of CYC was similar in both groups (p = 0.19).
of pulses of CYC was 0.85 g (range: 0.4–2), which was also similar in both groups (p = 0.46). No patient received MF or other schedules for the induction treatment. At initiation of MF as maintenance therapy, 38 patients (67.8%) had normal renal function (group 1) and 18 (32.1%) had decreased renal function (group 2); only 3 cases (5.4%) had an eGFR <30 ml/min. All of the patients received renin-angiotensin blockers. Both groups were similar except for age at initiation of MF, hemoglobin levels, anti-DNA antibody titer, and proteinuria (table 1). The mean follow-up was 24 months. During this period, 2 patients received cyclosporine (1 in each group), 1 received tacrolimus (in group 1), and 1 received rituximab (in group 2).

The main parameters during MF treatment are indicated in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000350756). Follow-up longer than 36 months was considered negligible because of the large number of missing cases after this point. Paired tests showed that mean blood pressure, leukocyte count, serum creatinine, eGFR, and prednisone dose did not differ from baseline values. On the other hand, values for hemoglobin, C3, C4, and MF dose increased significantly, whereas antinuclear and anti-dsDNA antibody titers and proteinuria values decreased. Renal function did not change during follow-up in group 1, whereas in group 2, the eGFR increased from 43.7 ± 14.3 ml/min/1.73 m² to 55.5 ± 21.7 at 6 months (paired t test, p < 0.005) and 65.5 ± 25 at 12 months (paired t test, p < 0.001). Exposure to prednisone and MF was similar in both groups of patients at each point during follow-up (online suppl. table 2).

**Primary Outcome: Renal Relapse and Response**

The number and percentage of cases that relapsed are indicated in table 2 (13.2, 21.6, 22.4, and 20.8% at months 3, 6, 12, and 24, respectively). No statistically significant differences were found in the percentage of patients who relapsed in either group at each follow-up visit (table 2). The cumulative rate of relapse is shown in figure 1. The cumulative rate of relapse over time was similar in both groups (fig. 2). The time to relapse was 10.5 ± 6.8 months (median: 9), which was similar in both groups (p = 0.88). Of the 3 patients with an initial eGFR <30 ml/min, 1 relapsed at 6 months.

The number and percentage of cases that achieved a response (partial or complete) are detailed in table 3 (57.9, 68.6, 71.4, and 75% at months 3, 6, 12, and 24, respectively). No statistically significant differences were found in the percentage of patients who achieved a response in either group at each follow-up visit (table 3). At the beginning of the maintenance phase, 34% of the cases did not achieve any response after the induction treatment (all from group 2), whereas 46% were in partial remission and the remaining 20% were in complete remission. The rates of complete responses were more frequent in group 1 than in group 2 during each period of follow-up (online suppl. table 3). The cumulative rate of response is shown in figure 3. The cumulative rate of response over time was similar in both groups (fig. 4). The median time to achieve a response was 10.5 months, which was similar in both groups (p = 0.34).

Univariate and multivariate analyses showed that gender, baseline eGFR, proteinuria and LN class (including class III and IV or class II and V) were not associated with the rate of relapse or with the rate of response during follow-up.

**Secondary Outcomes**

With regard to adverse effects, 13 patients (23.2%) developed gastrointestinal symptoms (nonspecific discomfort and diarrhea) and 13 (23.2%) presented infections (2 of unknown origin, 4 herpes zoster, 4 uncomplicated urinary tract infections, 2 upper respiratory tract infections, and 1 pneumonia). Treatment with MF had to be withdrawn in 8 cases (13.3%), mainly at the physician’s request.

### Table 2. Relapses (total and by group) based on renal function at initiation of MF as maintenance treatment and during follow-up

<table>
<thead>
<tr>
<th></th>
<th>3rd month (n = 38)</th>
<th>6th month (n = 51)</th>
<th>12th month (n = 49)</th>
<th>24th month (n = 24)</th>
<th>36th month (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5 (13.2)</td>
<td>11 (21.6)</td>
<td>11 (22.4)</td>
<td>5 (20.8)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Group 1/total group 1</td>
<td>4/30 (13.3)</td>
<td>7/34 (20.6)</td>
<td>8/32 (25)</td>
<td>4/20 (20)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>Group 2/total group 2</td>
<td>1/8 (12.5)</td>
<td>4/17 (23.5)</td>
<td>3/17 (17.6)</td>
<td>1/4 (25)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>p1</td>
<td>0.95</td>
<td>0.81</td>
<td>0.72</td>
<td>0.82</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Values represent n (%). 1 Fisher’s exact test at each assessment point during follow-up between group 1 and group 2.
In 2 cases treatment was withdrawn at the patient’s request. The treatments withdrawn were similar in both groups (p = 0.20, data not shown). One patient developed end-stage renal disease and none died (table 4).

### Discussion

We investigated the safety profile of MF as a maintenance therapy in patients with LN after administration of the induction treatment and the relationship between renal function and renal relapse in patients taking MF. Our results complete our previous finding that MF is useful as an induction treatment, even in cases with decreased renal function [3]. However, in the present study no patient received MF as the induction therapy and the results could only be applied to those who were treated with CYC at induction. Although our studies were neither controlled trials nor prospective analyses, they do provide valuable and rigorous data on the role of MF in LN in a representative Spanish population. We included patients with class II and V disease because the
diagnoses were made at the beginning of the induction phase with CYC; all of these patients had severe proteinuria and/or decreased eGFR when starting maintenance therapy (data not shown). We estimated renal function in our LN patients by using the MDRD eGFR equation, as recommended by Patel et al. [10]. Considering that the role of MF in long-term treatment of severe LN remains unsolved [5], we think our results are useful for clinicians.

During the last decade, the results of at least 9 trials have been reported [8, 9, 11–17], and several retrospective studies [18–20] have focused on the best drug schedule in the maintenance phase of treatment of LN. The results allow us to conclude that short-term induction with intravenous CYC followed by maintenance therapy with MF or AZA was more efficacious than other treatment schedules [11–13, 15]. However, until recently, no large-scale trials have compared MF with AZA. In the MAINTAIN trial [8], which included 105 European patients, renal flares were less frequent in MF-treated patients (18.9%) than in AZA-treated patients (25%) at 5 years, although the differences were not statistically significant. The ALMS trial [9], which is an extended study analyzing MF as an induction treatment for LN in 227 patients of different ethnic and geographic origins, found that MMF was superior to AZA with respect to treatment failure and renal relapse (12.9 vs. 23.9%, respectively) [21]. Therefore, it can be concluded that MF should be the first choice in long-term therapy in LN, with slight superiority over AZA [5, 22–26]. Although we did not make comparisons with other drugs in the present study, our results indicate a relatively low rate of renal flares using MF (21% at 6 months and 22% at 12 months) and a sustained renal response (68% at 6 months and 71% at 12 months), findings that are closer to those of MAINTAIN [8] than those of ALMS [9],

Table 4. Adverse effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Overall (n = 56)</th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n = 12)</th>
<th>p1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>13 (23.2)</td>
<td>10 (76.9)</td>
<td>3 (23.1)</td>
<td>0.42</td>
</tr>
<tr>
<td>Infections</td>
<td>13 (23.2)</td>
<td>11 (84.6)</td>
<td>2 (15.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>1 (1.7)</td>
<td>0</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

Values represent n (%). 1 Group 1 vs. group 2.
probably because of the ethnicity of the patients included. Finally, it is worth noting that renal relapses were recorded during therapy with MF in about 20% of the patients in most studies, as well as in ours. Therefore, other therapeutic schedules (based mainly on calcineurin inhibitors) have been tried, with promising results [14, 17, 27]. In fact, 4 patients in our study took other immunosuppressive drugs (3 calcineurin inhibitors and 1 rituximab) while taking MF; however, their low numbers prevented us from drawing solid conclusions about efficacy.

According to the results of the ALMS trial [9], the rates of treatment failure for MF during the maintenance phase were lower after induction with CYC than after induction with MF (11 vs. 21%), suggesting that CYC could be a good option for initial therapy in severe LN. In the present study, all patients received CYC as the induction treatment; therefore, we cannot draw conclusions by comparing with MF. However, if we compare renal response (complete or partial) in the present study with that of our previous publication in which we reviewed the results of MF as the induction therapy, we see that the rates of renal response were quite similar (between 70 and 80% at 12 months) [3]. Therefore, in our experience, induction therapy with CYC or MF does not affect renal response during follow-up in patients receiving MF as the maintenance therapy. However, this observation warrants more detailed investigation. The apparent discrepancies between the main trials on MF in long-term therapy could also be explained by the patient’s initial renal status. In the ALMS trial [9], only those patients who had complete or partial remission after the initial induction therapy were analyzed; other studies included nonresponders [8, 11, 13]. In our study, MF was started irrespective of renal response, as only 20% of the cases were in complete remission and 34% were nonresponders after CYC induction therapy. In our opinion, including all patients irrespective of the response to induction treatment in order to evaluate the role of MF or other treatments is more representative of clinical practice since many patients do not reach a response. The results of the ALMS trial would have been worse if nonresponders had been included. Although the schedule of CYC as the induction treatment used in our retrospective investigation is not homogeneous, it is closer to the treatments based on short courses and relatively low doses than the classic treatments based on high doses for more than 6 months.

Little is known about the role of MF in patients with normal renal function. Most studies analyze patients with normal renal function [8, 13, 18–20], and only two included cases with elevated serum creatinine and/or decreased eGFR at the initiation of maintenance therapy with MF [9, 11]. However, no studies include subanalyses of the effect of baseline renal function on renal relapse and response. Although the median eGFR was normal in all of our patients, 32% of the cases had renal insufficiency. Bearing this observation in mind, we found that MF was effective in terms of relapse rate and renal response even when renal function was decreased. However, since most of our patients did not have severe renal failure (the mean eGFR in group 2 was 43 ml/min/1.73 m²) and only 3 patients had an eGFR <30 ml/min/1.73 m², we could not draw definite conclusions in this subgroup, even though 2 of the 3 did not relapse during 6 months of follow-up.

In the main studies, the target dose varied between 0.5 and 2 g/24 h [8, 9, 11, 13]. In the present study, the mean dose was 1 g/24 h, which is lower than that used in our previous study of induction phase therapy [3], combined with a low and tapering dose of corticosteroids. Exposure to prednisone and MF was comparable between the two groups of patients, dose does not seem to affect response. Therefore, it seems appropriate to monitor blood levels of mycophenolic acid when renal function is decreased [28]. Although we did not perform a second biopsy in our patients, we can speculate that treatment with MF can improve renal function since in patients with renal failure at initiation of treatment, eGFR increased to 51% at 12 months. Indeed, a subsequent subanalysis of the MAINTAIN trial based on per protocol repeated renal biopsies [29] showed that the activity index dropped during follow-up in patients treated with MF or AZA.

With regard to adverse effects, the most relevant studies conclude that MF is well tolerated [8, 9, 11, 13, 18–20]. The main adverse effects are gastrointestinal symptoms and infections, which affect between 13 and 60% of patients [8, 11, 13]. In the largest study [9], serious adverse effects appeared in 23% of cases, and the consequent rate of withdrawal was lower with MF than with AZA. Overall, the mortality rate was low (<4%). In our study, the percentages of digestive symptoms and infections were lower than in other studies (23%), and 13% of patients had to discontinue treatment. Since we did not record any deaths or severe complications, we conclude that MF combined with prednisone is safe. In fact, the new guidelines recommend that MF be used as a first-choice agent in the maintenance phase of treatment of LN [30–33].

MF as Maintenance Therapy for LN
Our study is limited by its retrospective and multicenter nature, as was our previous study about induction after MF treatment [3]. We conclude that MF is efficacious and safe as a maintenance therapy for LN both in patients with normal renal function and in those with renal impairment whose previous induction therapy was based on CYC and steroids.

References


2. Ponticelli C, Glassock RJ, Moroni G: Induc-

3. Rivera F, Fulladosa X, Poveda R, Frutos MA,

4. Flanc RS, Roberts MA, Strippoli GF, Chadban J, Bomback AS, Appel GB: Updates on the treat-


6. Sprangers B, Monahan M, Appel GB: Diagno-


8. Illei GG, Takada K, Parkin D, Austin HA, Crane M, Yarboro CH, Vaughn EM, Kuroiwa T, Danning CL, Pando J, Steinberg AD, Gourley MF, Klippel JH, Balow JE, Boumpas DT: Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive ther-


12. Patel SB, Korbet SM, Lewis EJ: The prognosis of severe lupus nephritis based on the modifi-

13. Chan TM, Tse KC, Tang CS, Mok MY, Li FK: Long-term study of mycophenolate mofetil as continuous induction and maintenance treat-


18. Sahin GM, Sahin S, Kizilas S, Masatlioglu S, Ogu F, Ergin H: Mycophenolate mofetil ver-


20. Rabinić V, Poskurnik M, Kovacik Z, Nes-

21. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, Li L-S, Myler E, San-


24. Mak A, Cheek AA, Tan JY, Su HC, Ho RC, Lau CS: Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. Rheu-

25. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG: Induction and maintenance therapy for lupus nephritis: a systematic review and meta-

26. Henderson LK, Masson P, Craig JC, Roberts MA, Flanc RS, Strippoli GF, Webster AC: Induc-

Acknowledgement

We thank Thomas O’Boyle for proofreading the manuscript.

Disclosure Statement

This study was supported by grants from FIS (Fondo de Investigaciones Sanitarias) 10/02668. The authors of this manuscript declare that there are not any conflicts of interests.


