Mycophenolate Mofetil for Induction Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis

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Background and Objectives: Although the accepted standard of care for induction of lupus nephritis has been cyclophosphamide, recent trials suggest that mycophenolate mofetil may be as or more effective and less toxic. A systematic review and meta-analysis were performed to determine the risk for failure to induce remission of lupus nephritis in patients who were treated with mycophenolate mofetil compared with cyclophosphamide.

Design, Setting, Participants, & Measurements: Studies were identified by a search of electronic databases, bibliographies, and conference proceedings and by contacting experts. Randomized trials that compared mycophenolate mofetil with cyclophosphamide for induction therapy in adults with biopsy-proven lupus nephritis were eligible. The primary outcome was failure to induce a remission of nephritis as defined by the original studies (based on proteinuria, renal function, and urine sediment).

Results: Four studies that included 268 patients and had homogeneous results across studies were identified. In a fixed-effects model, the pooled relative risk for failure to induce remission for mycophenolate mofetil compared with cyclophosphamide was 0.70. The relative risk for the composite outcome of death or end-stage renal disease for mycophenolate mofetil compared with cyclophosphamide was 0.44. Leukopenia and amenorrhea occurred more frequently in cyclophosphamide-treated patients.

Conclusions: Treatment of lupus nephritis with mycophenolate mofetil compared with cyclophosphamide reduces the risk for failure to induce remission during induction therapy and may reduce the risk for death or end-stage renal disease. Mycophenolate mofetil may be considered as a first-line induction therapy for the treatment of lupus nephritis in patients without severe renal dysfunction.


Lupus nephritis is a common and severe manifestation of systemic lupus erythematosus (SLE) that can lead to ESRD and death (1). In the past 20 yr, treatment of lupus nephritis has advanced significantly, and induction therapies that combine cyclophosphamide and corticosteroids have improved renal outcomes compared with treatment with steroids alone (2,3). These benefits, however, continue to be tempered by significant drug-related toxicity (4–7).

In an attempt to limit therapy-related toxicity, mycophenolate mofetil (MMF), an antirejection drug that is used in solid-organ transplantation, has been studied. Evidence from early observational studies suggested that MMF may be efficacious in inducing remission of lupus nephritis (8–11). More recently, randomized, controlled trials (RCT) comparing MMF and cyclophosphamide as induction agents in lupus nephritis have also been completed (12–15) with similar results. Conclusions based on these trials, however, are limited given their small sample sizes. In addition, none of the studies was powered to detect a difference in the more clinically relevant long-term outcomes of death or ESRD. Given the increasing popularity of MMF in the treatment of SLE, we performed a systematic review and meta-analysis of RCT to assess the relative risk for failure to induce remission and the composite end point of death or ESRD for MMF compared with cyclophosphamide in lupus nephritis.

Materials and Methods

Search Strategy

We searched PubMed (1996 through March 2006), MEDLINE (1966 through March 2006), EMBASE (1980 through March 2006), and CENTRAL (Cochrane Controlled Clinical Trials Register 1996 through March 2006) using the OVID search engine. Two comprehensive search themes were developed and combined using the Boolean operator “and.” The first theme, lupus nephritis, was created by using the Boolean search term “or” to search for the following terms, text words, and database-specific thesaurus terms: “Lupus nephritis” or “glomerulonephritis” or “nephritis” or “systemic lupus erythematosus” or “lupus” or “SLE.” The second theme, MMF, was created using a text word and database-specific thesaurus terms search for “mycophenolate.
We tested for publication bias using funnel plots, Begg’s test for asymmetry across trials was evaluated using a Q statistic for heterogeneity. From both the original and the extended study duration for the purposes of assessing the secondary outcomes. The presence of heterogeneity across trials was evaluated using a Q statistic for heterogeneity. We tested for publication bias using funnel plots, Begg’s test for asymmetry and an Egger’s test. All statistical analyses were performed using Stata version 9.0 (Stata Corp., College Station, TX).

**Role of the Funding Source**

No external funding was obtained. All authors had full access to all study data, and all took full responsibility for the decision to submit for publication.

**Results**

**Identification of Studies**

Progress through stages of the systematic review is summarized in Figure 1. A total of 1158 unique citations were identified by our search strategy, 1117 of which were excluded on initial screening. Of the 41 studies that underwent further review, 4 RCT (13,14,18,19) and two nonrandomized trials (12,20) were identified for systematic review. Five of these studies were published in peer-reviewed journals, and one was published in abstract form (19). There was agreement between reviewers on the selection of 39 of the 41 studies selected for review ($k = 1.0$) and complete agreement for the studies that were selected for meta-analysis and their validity assessment.

**Study Characteristics**

A total of 268 patients were included in the four RCT, 133 of whom were treated with MMF and 135 of whom were treated with cyclophosphamide (Table 1). The mean age of patients ranged from 28 to 42 yr, with most patients of female gender (range 79 to 94%). The most common ethnic group was Asian

**Quantitative Data Synthesis**

We used the fixed-effects model of Mantel-Haenszel (17) to estimate the pooled RR with 95% confidence intervals (CI) for study outcomes, using data from all eligible RCT. Given the small number of RCT, we performed a sensitivity analysis that included all controlled studies irrespective of treatment allocation. For studies with no reported events in one group, statistical methods of approximation were used to calculate RR (17). Two studies reported on the outcomes of death and ESRD at multiple time points (13,15,18). Analyses were undertaken using data from both the original and the extended study duration for the purposes of assessing the secondary outcomes. The presence of heterogeneity across trials was evaluated using a Q statistic for heterogeneity. We tested for publication bias using funnel plots, Begg’s test for asymmetry and an Egger’s test. All statistical analyses were performed using Stata version 9.0 (Stata Corp., College Station, TX).

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followed by black (30%). Baseline mean (SD) serum creatinine measurements ranged from 93.3 (46.0) to 112.7 (65.8) μmol/L in the MMF group and from 94.0 (40.2) to 113.1 (36.9) μmol/L in the cyclophosphamide group; baseline mean (SD) proteinuria ranged from 1.8 (1.2) to 6.2 (4.1) g/24 h in the MMF group and from 3.0 (1.8) to 4.4 (3.6) g/24 h in the cyclophosphamide group. A total of 238 patients had proliferative lupus nephritis (World Health Organization [WHO] class III/IV), and 30 patients showed pure membranous lupus nephritis (WHO class V). All trials used adjunctive therapy with corticosteroids. One RCT used oral cyclophosphamide as a comparator (18), and three RCT compared MMF with intravenous cyclophosphamide (13,14,19). Dosing of MMF varied across studies, ranging from 1 to 3 g/d.

Definitions of failure to induce remission differed only slightly between trials and in all four studies were based on absolute levels and changes in proteinuria, serum creatinine, and activity of urine sediment (Table 2).

Characteristics of the nonrandomized trials included in the sensitivity analysis are shown in Table 3. The mean baseline proteinuria and serum creatinine measurements were of similar values to the RCT. Notably, in the study by Hu et al. (12), patients were treated with MMF only when cyclophosphamide failed.

### Validity Assessment

Trial quality was limited, as demonstrated by the Jadad scores reported in Table 1. No trials were blinded, and only one trial used allocation concealment (13). Only one trial performed an intention-to-treat analysis (13); however, for two other trials no patients were lost to follow-up, and in the remaining trial, only one patient in each arm was lost to follow-up (18). The only potentially important difference between treatment groups that we identified for any trial was the greater baseline proteinuria among MMF recipients in the study by Ong et al. (14). In studies that reported extended follow-up periods, no mention of loss to follow-up was made.

### Quantitative Data Synthesis

Three of the four studies that were included in the meta-analysis showed no significant difference between MMF and cyclophosphamide for the RR for failure to induce remission (14,18,19), whereas one study showed a significant reduction in the RR for failure to induce remission in patients who received MMF (13). The pooled RR for failure to induce remission for MMF compared with cyclophosphamide, using a fixed-effects model, was 0.70 (95% CI 0.54 to 0.90; \( P = 0.004 \)), suggesting a significant treatment benefit for MMF (Figure 2). The Q statistic did not detect significant heterogeneity between trials (\( P = 0.76 \)). Because of the lack of heterogeneity, a random-effects model was done only as a sensitivity analysis and did not differ significantly from the fixed-effects model. Inclusion of the non-RCT in a sensitivity analysis did not alter the summary statistic (Figure 3) with a pooled RR for failure to induce remission for MMF compared with cyclophosphamide of 0.68 (95% CI 0.53 to 0.85; \( P = 0.001 \)). There was no evidence of heterogeneity (\( P = 0.93 \)).
Analysis of the composite outcome of death or ESRD at the end of the prespecified study duration showed a nonsignificant lower risk for patients who were treated with MMF compared with cyclophosphamide (pooled RR 0.35; 95% CI 0.10 to 1.22; \( P = 0.10 \); Figure 4). Analysis of the composite outcome of death or ESRD using the extended study follow-up showed a significant lower risk for patients who were treated with MMF compared with cyclophosphamide, with a pooled RR of 0.44 (95% CI 0.23 to 0.87; \( P = 0.02 \); Figure 5). No heterogeneity was detected in either analysis, with \( P = 0.41 \) and 0.31, respectively.

Treatment-related adverse events for RCT between 6 and 12 mo duration are summarized in Table 4. In general, too few events were observed in most categories, resulting in several empty cells. For this reason, we chose to subject only the RR for infection to meta-analysis. The RR for infection for patients who

### Table 2. Definitions of failure to induce remission used in studies for primary analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of Failure to Induce Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flores-Suarez and Villa (19)</td>
<td>Proteinuria &gt;2.9 g/d or &gt;15% increase in serum creatinine from basal</td>
</tr>
<tr>
<td>Ong et al. (14)</td>
<td>Reduction in proteinuria &lt;50% or &gt;3 g/d or &gt;20% increase in serum creatinine from basal</td>
</tr>
<tr>
<td>Ginzler et al. (13)</td>
<td>Reduction in proteinuria &lt;50% or &gt;10% increase in serum creatinine from basal</td>
</tr>
<tr>
<td>Chan et al. (18)</td>
<td>Reduction in proteinuria &lt;50% or &gt;3 g/d or any progressive renal impairment</td>
</tr>
</tbody>
</table>

### Table 3. Characteristics of non-RCT included in sensitivity analysis of the RR for failure to induce remission (complete or partial)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Follow-Up (mo)</th>
<th>Method of Treatment Allocation</th>
<th>MMF Dosage (g/d)</th>
<th>Patients (n)</th>
<th>Treatment Failures</th>
<th>CYC Dosage</th>
<th>Patients (n)</th>
<th>Treatment Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. (12)</td>
<td>2002</td>
<td>6</td>
<td>MMF for refractory LN</td>
<td>1</td>
<td>23</td>
<td>7</td>
<td>0.75 to 1 g/m² intravenously</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Lin et al. (20)</td>
<td>2002</td>
<td>12</td>
<td>MMF for those able to afford</td>
<td>1.5</td>
<td>10</td>
<td>4</td>
<td>0.6 g intravenously every 1 to 2 wk</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

*LN, lupus nephritis.

![Forest plot of the relative risk (RR) for treatment failure for lupus nephritis treated with mycophenolate mofetil (MMF) compared with cyclophosphamide (CYC; randomized, controlled trials [RCT]).](image)

**Figure 2.** Forest plot of the relative risk (RR) for treatment failure for lupus nephritis treated with mycophenolate mofetil (MMF) compared with cyclophosphamide (CYC; randomized, controlled trials [RCT]).
were treated with MMF compared with cyclophosphamide was 0.64 (95% CI 0.39 to 1.06; \( P = 0.085 \)). No patients who were treated with MMF developed amenorrhea compared with six of 106 patients who were treated with cyclophosphamide. The proportions of patients who experienced other adverse effects seemed grossly equal between the MMF- and cyclophosphamide-treated groups. There was no evidence of publication bias by Egger’s \(( P = 0.87)\) or Begg’s test \(( P = 1.0)\), although the number of identified trials was small and the utility of such tests to assess the possibility of bias in this situation is extremely limited.

**Discussion**

In this meta-analysis of four studies with 268 patients who were treated for lupus nephritis, we found a significant reduction in the risk for treatment failure for MMF compared with cyclophosphamide. In addition, our findings suggest that the risk for death or ESRD may be lower with MMF compared with cyclophosphamide, an important clinical finding not previously demonstrated. There was no evidence of an increased risk for adverse events associated with MMF.

Given concern about infertility and other toxicities with cyclophosphamide treatment, MMF has been considered an im-
portant alternative agent for the treatment of lupus nephritis. However, there has been speculation that MMF may not be as effective for inducing remission in lupus nephritis or, in the long term, may lead to an increased likelihood of relapse compared with cyclophosphamide (21). The study by Ginzler et al. (13) in 2005 was the only individual study to demonstrate a significant benefit of MMF compared with cyclophosphamide in inducing remission of lupus nephritis. Our meta-analysis extends the results of individual randomized trials and suggests a 30% reduction in the risk for treatment failure for MMF. Therefore, the benefit of MMF may translate not only to improved remission rates but also to a reduction in cyclophosphamide-associated toxicity for patients with lupus nephritis.

The composite outcome of death or ESRD is more clinically relevant than treatment failure for lupus nephritis (21); however, individual clinical trials to date have not been powered to detect a difference in these clinical outcomes. Results from our meta-analysis suggest an almost 60% reduction in the composite end point of death or ESRD for MMF compared with cyclophosphamide when the results of extended follow-up are considered, although these findings were NS when outcomes were assessed at the end of the prespecified study duration. This finding is particularly impressive given that a recent meta-analysis of 226 patients who were treated with either cyclophosphamide and glucocorticoids or glucocorticoids alone was unable to find a mortality or ESRD benefit for cyclophosphamide-treated patients (2). This finding, however, is based predominantly on only two studies, one of which did not report loss to follow-up during the extended observation and was based on relatively few events, so caution must be taken in accepting the result despite its statistical significance.

Any systematic review must assess the suitability of identified trials for pooling in a meta-analysis. In this study, all trials that were included in the primary analysis were comparable in several respects: Duration of follow-up; definitions of treatment failure; and patient age, gender, and renal function. Despite these similarities, there are also several differences, including the dosages of MMF used and the route of cyclophosphamide administration. These differences may play a role in the significant variability in the absolute rates of treatment failure be-

![Figure 5. Forest plot of the RR for death or ESRD for lupus nephritis treated with MMF compared with CYC using extended follow-up data (RCT).](image)

![Table 4. Comparison of adverse events by treatment group in RCT with 6 to 12 mo of follow-up](table)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Infections</th>
<th>Amenorrhea</th>
<th>Gastrointestinal</th>
<th>Leukopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMF</td>
<td>CYC</td>
<td>MMF</td>
<td>CYC</td>
<td>MMF</td>
</tr>
<tr>
<td>Chan et al. (15)</td>
<td>21</td>
<td>21</td>
<td>4</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Flores-Suarez and Villa (19)</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ong et al. (14)</td>
<td>19</td>
<td>25</td>
<td>6</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td>Ginzler et al. (13)</td>
<td>71</td>
<td>69</td>
<td>4</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>125</td>
<td>18</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

aNR, not reported.
bReported as events per patient-year.
mide, MMF reduces the risk for failure to induce remission of lupus nephritis and may reduce the risk for death or ESRD. Although these data support the use of MMF as the first-line induction agent for lupus nephritis, there is still a need for further high-quality studies with long-term follow-up to confirm these findings. Although these results are applicable to patients with reasonably preserved renal function, those with severe renal impairment deserve further study.

Conclusions
We have demonstrated that compared with cyclophosphamide, MMF reduces the risk for failure to induce remission of lupus nephritis and may reduce the risk for death or ESRD. Although these data support the use of MMF as the first-line induction agent for lupus nephritis, there is still a need for further high-quality studies with long-term follow-up to confirm these findings. Although these results are applicable to patients with reasonably preserved renal function, those with severe renal impairment deserve further study.

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See the related editorial, “Role of Mycophenolate Mofetil in the Treatment of Lupus Nephritis,” on pages 879–882.

Access to UptoDate on-line is available for additional clinical information 
at http://www.cjasn.org/