Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials

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Abstract

Background. The outcomes of previous trials of mycophenolate mofetil (MMF) in treating severe lupus nephritis (LN) are not in exact agreement. This meta-analysis of randomized controlled trials (RCTs) assesses the benefits and harms of MMF in the induction and maintenance therapy of severe LN.

Methods. We searched Medline, EMBASE and the Cochrane Collaboration Database for RCTs that compared MMF with other immunorepressive regimens for treating lupus nephritis and extracted data for remissions, side effects and prognosis in induction therapy and prognosis and side effects in maintenance therapy, and we summarized the combined results of the data of the RCTs as relative risk (RR).

Results. We analysed five RCTs with 307 patients—four RCTS providing the data for comparing MMF with cyclophosphamide (CYC) for induction therapy and two RCTs providing the data for comparing MMF with azathioprine (AZA) for maintenance therapy of severe LN. Overall, compared with CYC, induction therapy with MMF reduced the risk of infection significantly (RR 0.65, \(P<0.001\)). It also significantly increased the complete remission rate compared with intravenous CYC (RR 3.10, \(P=0.006\)). Compared with intravenous CYC, induction therapy with MMF reduced the incidence of leucopenia significantly (RR 0.66, \(P=0.04\)). The prognosis and other side effects were not significantly different between MMF and CYC induction therapies. There was no significant difference between the patients receiving MMF and those receiving AZA for maintenance therapy in prognosis or the risks of amenorrhoea and herpes zoster.

Conclusions. MMF has higher efficacy in inducing remission in severe LN than pulsed intravenous therapy with CYC. Induction therapy with MMF is also associated with fewer side effects than induction therapy with CYC. Compared with AZA, MMF also is an alternative for maintenance therapy of severe LN without significant difference in the prognosis or risks of amenorrhoea and herpes zoster.

Keywords: azathioprine; cyclophosphamide; immunosuppression; lupus nephritis; meta-analysis; mycophenolate mofetil

Introduction

Renal injury is the main cause of mortality and morbidity in patients with systemic lupus erythematosus (SLE) [1,2]. Lupus nephritis (LN) may present as its only clinical manifestation, or as a part of multiorgan involvement. Previous reports have demonstrated that focal, diffuse proliferative and membranous nephritides (World Health Organization classes III, IV, V [3]) have poor prognoses [4,5], especially class IV LN [6–8], and they usually require active interventions to inhibit their progression to renal failure.

Though notable improvements have been made over several recent decades in treating LN, some patients do not respond to available immunosuppressive regimens or have relapses repeatedly, and finally develop end-stage renal disease (ESRD). Pulsed intravenous therapy with high doses of cyclophosphamide (CYC) followed by quarterly doses in combination with steroids has been the standard treatment for severe LN [9–12]. Several recent reports have suggested that initiating treatment with low-dose intravenous CYC and following it by azathioprine (AZA) for maintenance could be as effective as the high-dose CYC regimen, and with fewer side effects [13–15].
However, the above treatments are associated with adverse effects, such as leucopenia, alopecia, infection, herpes zoster, gonadal toxicity, haemorrhagic cystitis, amenorrhoea, and with the potential of predisposing patients to malignancies.

Mycophenolate mofetil (MMF), a relatively new immunorepressor with selective inhibitory effects on proliferative T and B lymphocytes, has been used in various autoimmune diseases, including severe LN, and it has proven to be effective with fewer side effects [16,17]. Still, the conclusions of several recent randomized controlled trials (RCTs) [18–22] of MMF in the treatment of severe LN do not agree exactly. These recent reports also do not indicate a precise dosage and duration for the administration of MMF in induction or maintenance therapy of severe LN. The aim of this systematic literature review and meta-analysis was to evaluate the benefits and harms of MMF in the induction or maintenance therapy of severe LN.

**Methods**

**Inclusion criteria**

To be selected for analysis, a study had to meet all of the following criteria: (i) The study was an RCT. (ii) The study compared MMF plus steroid with other immunorepressive regimen(s) in either induction or maintenance therapy of LN. (iii) The study was of patients with biopsy-proven LN class III, IV or V.

**Search strategy**

We performed searches in three electronic databases—Medline/Pubmed (January 1990 to June 2006), EMBASE (January 1990 to June 2006) and Cochrane Central Register of Controlled Trials—without restriction of language and using the following subject heading terms or keywords: lupus nephritis, lupus glomerulonephritis, proliferative glomerulonephritis, membranous glomerulonephritis, systemic lupus erythematosus and mycophenolate mofetil. The titles and abstracts of the articles these searches yielded were analysed by two of the authors (Z.B. and L.Y) independently to ascertain conformity with the inclusion criteria. The reference lists of the selected publications also were screened for trials that might meet our inclusion criteria. The full text of an article was reviewed carefully if the screening of its title and abstract was unclear as to its admissibility.

**Study validity assessment**

The unmasked evaluation of a study’s validity was done independently and in duplicate. We assessed the quality of the studies according to standard criteria [23] (allocation concealment, blinding of participants, intention to treat analysis, and completeness of follow-up). When necessary data were missing or incomplete, we contacted the investigators of the selected trials for clarification. We reported a validated quality assessment score, according to the criteria of Jadad [24].

**Data extraction**

Two independent reviewers (Z.B. and L.Y) analysed each included trial. Discrepancies were resolved in conference. Data were extracted for the following parameters of interest: In induction therapy—(i) number of complete remission patients; (ii) number of partial remissions; (iii) overall number of remissions; (iv) number of patients who had side effects, including amenorrhoea, gastrointestinal symptoms, herpes zoster, infection, or leucopenia; (v) number of patients who developed ESRD during follow-up; and (vi) number of patients who died during follow-up. And in maintenance therapy—(i) number of patients with ESRD; (ii) number of patients whose serum creatinine doubled; (iii) number of patients who died; (iv) number of patients who had relapses; (v) number of patients who had side effects, including amenorrhoea or herpes zoster. Between the trials included in our meta-analysis, there are a few differences in the definitions of complete remission, partial remission and relapse (shown in supplementary Table 1); but the differences are slight—and the internal criteria of each trial have the same effects on the extraction of data from either the MMF group or the control group. Thus, after discussion among all of the authors of this paper, we decided to pool these data for evaluation and proceeded with the belief that combining these data would not introduce significant bias. We obtained the number of patients with amenorrhoea and the number of patients with herpes zoster (which rarely recurs, because immunity acquired against the varicella-zoster virus after the first infection is lasting) by calculating the data using the formula provided by Contreras [20]. The numbers of patients with other side effects, including gastrointestinal symptoms, infection or leucopenia, (to be expressed as the ratio of the number of events to the number of patient-years of follow-up) could not be obtained from the paper by Contreras [20].

**Statistical analyses**

The distribution, in an individual RCT, of patients with various types of LN in the MMF group versus the control group was analysed by the chi-square test. The pooled relative risk (RR) and 95% confidence intervals (CI) were computed with random effects models following the DerSimonian and Laird method for analysing dichotomous outcomes. Heterogeneity of treatment effects among studies was tested using I² statistics. Funnel plots, Egger’s regression asymmetry test and Begg’s test were used to probe for publication bias. Forest plots were used for graphic representation of data. The vertical lines in these plots—positioned at 1, for RR—represent equivalence in efficacy between the experimental and control treatments. Trials shown to the left of that line showed a reduction in risk with the experimental intervention, those on the right showed an increase in risk with the experimental intervention. A solid square and horizontal line represent the RR with 95% CIs respectively. The surface area of the black square represents the relative quantitative contribution of the trial to the analysis (weight). The horizontal line indicates the 95% CI. The diamond-shaped symbol is the summary estimate of effect expressed as an RR with 95% CIs, which is a weighted average of the pooled treatment effects across all trials. A P
value of <0.05 was considered statistically significant. All data were analysed with STATA 8.0.

Results

In all, the combined searches identified 422 published articles. We excluded 392 studies after screening titles and abstracts for conformity with the inclusion criteria (Figure 1). After reviewing the full text of the remaining studies, we excluded another 20 publications: 12 of them were not RCTs, seven were reviews and one was a case report. We finally had five RCTs, comprising 307 patients, to include in our review.

Trial characteristics

Table 1 shows the characteristics of the RCTs we included in this meta-analysis—level of renal function, type of pathology, and medical intervention. A total of 307 patients had been assessed in the five studies, which ranged from 42 to 140 patients in size. Of the five trials, four provided the data for comparing the efficacy of MMF plus a steroid (MMF regimen) with that of CYC plus a steroid (CYC regimen) in induction therapy [18,19,21,22], and two trials provided the data on the efficacy of the MMF regimen against AZA plus steroid (AZA regimen) in maintenance therapy [19,20]. Only one trial compared the efficacy of the MMF regimen with that of the CYC regimen in maintenance therapy [20]—which, therefore, cannot be subjected to meta-analysis. The Chan trial of 2005 [19] is an extension of the Chan trial of 2000 [18], with additional patients and a longer follow-up. The distributions of different types of LN in the MMF and the control groups were similar in individual RCTs (data not shown).

Trial qualities

Table 2 demonstrates that the quality of individual trials was variable. Allocation concealment was adequate in three trials, and intention-to-treat unclear in two trials. No trial was double-blinded. All trials reported an intention to treat analysis. Of the five trials, three reported no losses to follow-up, 1.4% and 3.1%, respectively.

Trial outcomes

Publication bias analysis. The Funnel plots, Egger regression asymmetry test and Begg’s test applied to individual trials did not disclose any publication bias (data not shown).

Comparison of MMF regimen with CYC regimen in induction therapy. Of the five trials, four compared the efficacy and side effects of the MMF regimen with those of the CYC regimen in the induction therapy of severe LN. The Chan trial of 2005 [19] included all of the 42 patients enrolled in the trial of 2000 [18]; so for this meta-analysis, we adopted the data mainly

![Flow diagram of studies considered for inclusion.](image)
of the later trial [19]. The earlier paper [18] was reviewed for potentially useful information on those 42 patients.

MMF did not increase the following rates compared with CYC (Figure 2): complete remission (three trials, RR 1.81, 95% CI, 0.70 to 4.68, \( P = 0.22 \), heterogeneity \( P = 0.03, \chi^2 = 7.27, I^2 = 72.5\% \); partial remission (three trials, RR 1.06, 95% CI, 0.71–1.59, \( P = 0.78 \), heterogeneity \( P = 0.71, \chi^2 = 0.70, I^2 = 0\% \); or overall remission (three trials, RR 1.20, 95% CI, 0.85–1.69, \( P = 0.31 \), heterogeneity \( P = 0.05, \chi^2 = 6.06, I^2 = 67.0\% \)). Significant heterogeneity existed in complete remission and overall remission across the trials, which comes from the effect of the Ginzler trial [21] as determined by a Galbraith Plot for heterogeneity (data not shown). However, after excluding the Ginzler trial, the differences between MMF and CYC remained insignificant in both the complete remission (RR 1.13, 95% CI, 0.62–2.07, \( P = 0.69 \), heterogeneity \( P = 0.24, \chi^2 = 1.40, I^2 = 28.5\% \)) and the overall remission (RR 1.01, 95% CI, 0.92–1.10, \( P = 0.91 \), heterogeneity \( P = 0.71, \chi^2 = 0.14, I^2 = 0\% \)).

Compared with CYC, MMF decreased the risk of infection significantly (three trials, RR 0.65, 95% CI, 0.51–0.82, \( P < 0.001 \), heterogeneity \( P = 0.40, \chi^2 = 1.81, I^2 = 0\% \)). The incidences of amenorrhoea (three trials, RR 0.22, 95% CI, 0.04–1.22, \( P = 0.08 \), heterogeneity \( P = 0.80, \chi^2 = 0.45, I^2 = 0\% \) and leucopenia (three trials, RR 0.61, 95% CI, 0.37–1.03, \( P = 0.07 \), heterogeneity \( P = 0.26, \chi^2 = 2.68, I^2 = 25.3\% \)) were reduced by MMF, but the differences did not reach statistical significance. MMF increased the incidence of gastrointestinal symptoms (three trials, RR 1.33, 95% CI, 0.97–1.84, \( P = 0.08 \), heterogeneity \( P = 0.84, \chi^2 = 0.35, I^2 = 0\% \)), but here too the differences were not statistically significant (Figure 3).

We also compared the prognoses of patients receiving MMF induction therapy with those of patients receiving CYC induction therapy by pooling the cases of ESRD and deaths in two

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### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Number enrolled</th>
<th>Age</th>
<th>Renal pathology</th>
<th>Renal function</th>
<th>Intervention</th>
<th>Follow-up duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginzler et al. [21]</td>
<td>E 71</td>
<td>32.5±10</td>
<td>Class III, IV, V</td>
<td>Ccr &gt; 30 ml/min or Scr &lt; 265 μmol/l</td>
<td>MMF + Pred</td>
<td>36.2±16.9</td>
</tr>
<tr>
<td></td>
<td>C 69</td>
<td>31.0±9</td>
<td>Class III, IV, Vb</td>
<td>Scr &lt; 200 μmol/l</td>
<td>IV CYC + Pred</td>
<td>37.2±16.9</td>
</tr>
<tr>
<td>Ong et al. [22]</td>
<td>E 19</td>
<td>21.8±3.2</td>
<td>Class III, IV, Vb</td>
<td>Scr &lt; 200 μmol/l</td>
<td>MMF + Pred</td>
<td>37.8±7</td>
</tr>
<tr>
<td>Chan et al. [18]</td>
<td>E 21</td>
<td>36±11</td>
<td>Class IV</td>
<td>Scr &lt; 300 μmol/l</td>
<td>MMF + Pred for 12 mo then AZA</td>
<td>Mean 12</td>
</tr>
<tr>
<td></td>
<td>C 21</td>
<td>39±9</td>
<td>Class IV</td>
<td>Scr &lt; 400 μmol/l</td>
<td>Oral CYC + Pred for 6 mo then AZA</td>
<td>52.2±19.7</td>
</tr>
<tr>
<td>Chan et al. [19]</td>
<td>E 33</td>
<td>38.1±10.2</td>
<td>Class IV</td>
<td>Scr &lt; 400 μmol/l</td>
<td>MMF + Pred for 12 mo then decreased dose of MMF for maintenance</td>
<td>63.9±17.6</td>
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<tr>
<td></td>
<td>C 31</td>
<td>41.8±8.9</td>
<td>Class IV</td>
<td>Scr &lt; 400 μmol/l</td>
<td>Oral CYC + Pred for 6 mo then AZA for maintenance</td>
<td>52.2±19.7</td>
</tr>
<tr>
<td>Contreras et al. [20]</td>
<td>E 20</td>
<td>32±11</td>
<td>Class III, IV, Vb</td>
<td>Ccr &gt; 20 ml/min</td>
<td>IV CYC + Pred for less than 7 mo then MMF for maintenance</td>
<td>Median 29</td>
</tr>
<tr>
<td></td>
<td>C 20</td>
<td>33±12</td>
<td>Class III, IV, Vb</td>
<td>Ccr &gt; 20 ml/min</td>
<td>IV CYC + Pred for less than 7 mo then IV CYC for maintenance</td>
<td>Median 25</td>
</tr>
<tr>
<td></td>
<td>C 19</td>
<td>33±10</td>
<td>Class IV</td>
<td>Ccr &gt; 20 ml/min</td>
<td>IV CYC + Pred for less than 7 mo then AZA for maintenance</td>
<td>Median 30</td>
</tr>
</tbody>
</table>

E, experimental group; C, control group; F/M, female to male ratio; Scr, serum creatinine; Ccr, creatinine clearance; Pred, prednisone; MMF, mycophenolate mofetil; CYC, cyclophosphamide; AZA, azathioprine.

### Table 2. Quality assessment of RCTs included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Intention-to-treat analysis</th>
<th>Lost to follow-up</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginzler et al.</td>
<td>2005</td>
<td>Adequate</td>
<td>None</td>
<td>Yes</td>
<td>2/140 (1.4%)</td>
<td>6</td>
</tr>
<tr>
<td>Ong et al.</td>
<td>2005</td>
<td>Adequate</td>
<td>None</td>
<td>Yes</td>
<td>0/44</td>
<td>6</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>2000</td>
<td>Unclear</td>
<td>None</td>
<td>Yes</td>
<td>0/42</td>
<td>4</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>2005</td>
<td>Adequate</td>
<td>None</td>
<td>Yes</td>
<td>2/64 (3.1%)</td>
<td>6</td>
</tr>
<tr>
<td>Contreras et al.</td>
<td>2004</td>
<td>Unclear</td>
<td>None</td>
<td>Yes</td>
<td>0/59</td>
<td>4</td>
</tr>
</tbody>
</table>
trials [21,22] that did not specify maintenance regimens. The results indicate no significant difference between the two groups in the risks of developing ESRD (two trials, RR 0.58, 95% CI, 0.20–1.65, \( P = 0.30 \), heterogeneity \( P = 0.90 \), \( \chi^2 = 0.02 \), \( I^2 = 0\% \)) or death (two trials, RR 0.46, 95% CI, 0.17–1.30, \( P = 0.14 \), heterogeneity \( P = 0.41 \), \( \chi^2 = 0.67 \), \( I^2 = 0\% \)) (Figure 4).
Comparison of MMF regimen with AZA regimen in maintenance therapy. Two trials assessed the efficacy and side effects of the MMF regimen against the AZA regimen in maintenance therapy of severe LN. Compared with AZA, MMF did not decrease any of the following: incidence of death (two trials, RR 0.70, 95% CI, 0.05–10.1, \( P = 0.80 \), heterogeneity \( \chi^2 = 1.51, I^2 = 33.7\% \)); ESRD (two trials, RR 0.70, 95% CI, 0.05–10.1, \( P = 0.80 \), heterogeneity \( \chi^2 = 1.51, I^2 = 33.7\% \)); relapse (two trials, RR 0.89, 95% CI, 0.41–1.94, \( P = 0.77 \), heterogeneity \( \chi^2 = 0.23, I^2 = 32.1\% \)); doubling of serum creatinine (two trials, RR 0.71, 95% CI, 0.17–3.02, \( P = 0.64 \), heterogeneity \( \chi^2 = 0.80, I^2 = 0\% \)) (Figure 5).

There were no significant differences in the risks of amenorrhea (two trials, RR 0.49, 95% CI, 0.16–1.52, \( P = 0.21 \), heterogeneity \( \chi^2 = 1.01, I^2 = 5\% \)) or herpes zoster (two trials, RR 0.66, 95% CI, 0.11–3.78, \( P = 0.64 \), heterogeneity \( \chi^2 = 1.69, I^2 = 41\% \)) between the MMF and AZA groups (Figure 6). The data on the other side effects—infecion, leucopenia and gastrointestinal symptoms—are shown in supplementary Table 2, and they indicate that gastrointestinal symptoms occurred more frequently in the MMF group than in the AZA group, but MMF tended to decrease the risk of leucopenia.

Only the Contreras trial [20] compared MMF with CYC for efficacy in maintenance therapy, concluding that MMF was superior to CYC in maintenance therapy with respect to both prognosis and side effects (but it cannot be subjected to meta-analysis since it is a solitary report).

Sensitivity analysis

We performed a sensitivity analysis to evaluate the robustness of this meta-analysis. Only patients in the Chan trial [19] received daily oral CYC, those in the other trials [21,22] received pulsed intravenous CYC in induction therapy. Previous reports have shown that in treating severe LN daily oral CYC has some effects different from pulsed intravenous CYC [25–27]. After removing the Chan trial [19] the complete remission rate was significantly higher in patients receiving MMF compared with those receiving intravenous pulse CYC (RR 3.10, 95% CI, 1.38–7.01, \( P = 0.006 \), heterogeneity \( \chi^2 = 0.50, I^2 = 0\% \)) (supplementary Figure 1); and the risk of leucopenia was significantly lower in patients receiving MMF compared with those receiving pulsed intravenous CYC (RR 0.66, 95% CI, 0.44–0.97, \( P = 0.04 \), heterogeneity \( \chi^2 = 0.80, I^2 = 0\% \)) (supplementary Figure 2). The other results were not altered significantly after removing the Chan trial [19].

Discussion

In this meta-analysis, we identified five RCTs that compared the MMF regimen with other immunorepressive regimens in induction therapy (four trials) and maintenance therapy (two trials) of severe LN. Overall, the risk of infection was significantly lower in the patients in induction therapy with MMF compared with those receiving CYC. Induction therapy with MMF provided a higher complete remission rate than
intravenous pulse CYC. MMF also was associated with a significantly lower incidence of leucopenia than pulsed intravenous CYC. MMF did not decrease the risks of amenorrhoea or herpes zoster significantly. Gastrointestinal events—such as diarrhoea or nausea and vomiting—happened more frequently in patients receiving MMF than in those receiving CYC or AZA [18–21]. Induction therapy with MMF did not improve prognosis significantly, including the risks of ESRD and death. There was no significant difference in the prognosis (ESRD, doubling of serum creatinine, death, relapse) or in the incidence of amenorrhoea or herpes zoster between maintenance therapy with MMF or AZA.

Intermittent intravenous CYC plus steroid has been adopted as the standard therapy for proliferative LN [11]. Oral AZA has been used for maintenance therapy of LN [15,28]. About 5–15% of patients with
SLE associated with diffuse proliferative glomerular nephritis were refractory to CYC [12,25,29–31]. The treatments mentioned above also are associated with many side effects. Oral administration of MMF is well-absorbed with high bioavailability, and is hydrolysed to MPA [32], which is 5-fold more potent in depressing the type II isozyme of inosine monophosphate dehydrogenase (expressed mainly in activated T and B lymphocytes) than in depressing the type I isozyme (expressed in most other cell types) [33]. MMF has also been reported to have the ability to suppress the recruitment of lymphocytes and monocytes into sites of inflammation [32,34]. Several non-control clinical studies confirmed the efficacy of MMF in CYC-resistant LN patients [17,35–37]. Our analysis shows the complete remission rate to be significantly higher in patients receiving MMF than in those receiving intravenous CYC—after the exclusion of the Chan report (with the patients in the CYC group receiving daily oral doses—which was consistent with prior reports that patients receiving daily oral CYC with a higher cumulative dose of CYC had higher complete remission rates than those receiving pulsed intravenous CYC [25,27]). The risks of side effects such as infection, herpes zoster, gastrointestinal symptoms and leucopenia are not significantly different between the patients receiving daily oral CYC and those receiving pulsed intravenous CYC [25–27]. Therefore, for the purpose of evaluation in this meta-analysis, combining the data on such side effects from trials with different routes of CYC administration will not cause significant bias. Our sensitivity analysis demonstrated that pooling the data on infection, herpes zoster, gastrointestinal symptoms and amenorrhoea did not alter the results of our analysis significantly—after excluding the Chan trial [19]; but the difference between MMF and CYC induction therapy in the risk of leucopenia became statistically significant after the elimination of the Chan trial (the P value decreased from 0.07 to 0.04). Thus MMF could be a potent immunorepressor that is more effective in inducing complete remission in severe LN than CYC—with fewer side effects and, particularly, reduced risks of infection and leucopenia. Though it tends to cause more gastrointestinal symptoms, MMF is also an alternative to AZA for maintenance therapy of severe LN, without significant difference from the latter in prognosis or risks of amenorrhoea or herpes zoster.

Three previous systematic reviews have evaluated treatments for LN [38–40]. But only the systematic review by Flanc assessed the role of MMF in LN [40] indicating that no difference existed between MMF and CYC in induction of remission (based on the Chan trial [18]); whereas the patients in maintenance therapy with MMF had a greater rate of relapse at 3 years than those on AZA—based on Chan’s prolonged observation (abstract) [41]. Having obtained more data from more trials, including the two in Flanc’s systematic review, we conclude that the MMF regimen is superior to the CYC regimen for inducing complete remission, and that the risk of relapse in maintenance therapy might not be significantly different between the patients receiving MMF and those receiving AZA.

This meta-analysis has several limitations. First, only three of the five trials describe allocation concealment and no trial was double-blinded. Second, though the Contreras trial [20], with Jadad score of 4, was well designed, the number of patients in it was somewhat small—especially at the end of the 3-year follow-up. The numbers of patients in that trial who had some side effects also could not be obtained for this meta-analysis. However, meta-analysis still can combine data from trials with small sample sizes to obtain some useful information. Nevertheless, the data in Contreras’s RCT were promising. Thus, we included it in our meta-analysis. Third, an induction treatment should be given only to patients with severe LN, including class IV or Vb LN. Though the five trials we analysed had enrolled mainly patients with severe LN, a few patients with type III or type V LN (Table 1), who always have better prognoses, had also been included in them. This may introduce some biases in our meta-analysis. However, the small numbers of patients with mild LN and the similar distribution of the patients with different types of LN between the MMF and the control groups in individual trials may mitigate these biases. Fourth, maintenance therapy should be given only to patients who have attained remission by induction therapy. A few patients who were not in remission were also included in the maintenance therapy arms of the two trials [19,20] that were selected for the analysis of MMF for maintenance therapy. However, the relative majority of patients in whom induction therapy led to remission and the similar rates of remissions in the MMF and control groups in either of the two trials could reduce the potential of biases. Fifth, the distribution of race and ethnicity varies from one of these five trials to another. Previous reports have implied that African-Americans have a 3-fold higher incidence of SLE compared with Caucasians, and often develop nephritis [42,43]. Hispanics and Asians also have a greater frequency and severity of nephritis compared with Caucasians [42]. Among the articles selected by us, the Contreras trial [20] and the Ginzler trial [21] included a majority of African and Hispanic patients while the Ong [22] and the Chan trials [18,19] studied mainly Asian patients. Although disease progression may be different between the relatively sensitive cohorts of African, Hispanic or Asian patients, the small number of Caucasians enrolled in the trials we analysed will limit any bias attributable to ethnic differences between cohorts. Only one trial compared the effects of the MMF regimen and the CYC regimen, to conclude that MMF was superior to CYC for maintenance therapy. Therefore, further large scale RCTs are needed to compare the MMF regimen with other immunosuppressive regimens for either induction therapy or maintenance therapy; and they must explicitly report intention-to-treat analyses,
allocation concealment and the use of open-label design.

In conclusion, MMF with its potency to induce complete remission appears to be superior to pulsed intravenous CYC for induction therapy of severe LN. Induction therapy with MMF is also associated with fewer side effects than induction therapy with CYC. Finally, MMF is an alternative choice for the maintenance therapy of severe LN, with no significant difference in prognosis or the risks of amenorrhea or herpes zoster from AZA.

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