

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.

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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

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mofetil" or "mmf" or "mycophenolic acid" or "cellcept." Citations identified from electronic databases were supplemented by reviewing the reference lists of all identified research and review articles, by reviewing the conference proceedings of the American Society of Nephrology from 2001 to 2005, and by contacting experts in the field.

Study Selection and Data Abstraction

Two individuals (M.J. and M.W.) independently evaluated articles for eligibility in a two-stage procedure. In the first stage, all identified abstracts were reviewed. Those that met the inclusion criteria or those for which there was uncertainty as to eligibility were selected for full-text review in the second stage. Articles that were selected by either individual were reviewed by both M.J. and M.W. in the second stage and evaluated on both inclusion and exclusion criteria. Inclusion criteria consisted of (1) study design (controlled trial of three or more patients), (2) study population (patients with biopsy-proven lupus nephritis), (3) intervention (MMF), and (4) and outcome (trials with explicit definition and reporting of renal remission or change in proteinuria or serum creatinine or GFR). Studies were eligible for inclusion whether published or unpublished and irrespective of language. Exclusion criteria were use of MMF for maintenance therapy but not induction therapy or studies that included children.

The same reviewers independently extracted data from all primary studies that fulfilled the inclusion criteria, with disagreement resolved by consensus. Data extracted included study design; details of treatment protocol; and baseline demographic, clinical, laboratory, and renal biopsy information. Data on the following outcomes were extracted when reported: Proteinuria; serum creatinine, GFR, complete renal remission, partial renal remission, treatment failure, mortality, progression to ESRD, and treatment-related toxicities. When outcomes were not reported, we attempted to contact authors for additional information.

The methodologic quality of the included studies was independently scored by M.J. and M.W., with disagreements resolved by consensus. Criteria that were used to assess quality included method of randomization; allocation concealment, blinding, use of placebo, reporting of losses to follow-up, intention-to-treat analysis, and important baseline differences between groups. An overall quality score was determined for each study as described by Jadad *et al.* (16).

Study Outcomes

The primary outcome was the relative risk (RR) for failure to induce remission (total or partial), as defined in the original articles on the basis of the degree of proteinuria, renal function compared with baseline, and urinalysis. The secondary outcome was the RR for the composite outcome of death or ESRD. We also tabulated the frequency of adverse events by treatment group.

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 asym-

metry 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 ($\kappa = 1.0$) 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

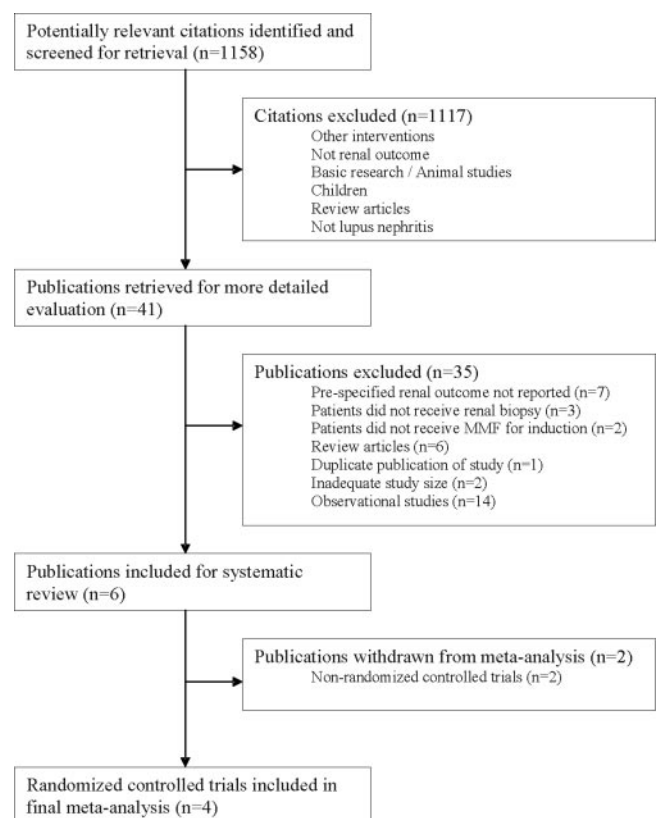


Figure 1. Flow diagram of study selection process.

Table 1. Characteristics of RCT included for meta-analysis of the RR for failure to induce remission (complete or partial)^a

Study	Jadad Score	Year	Follow-Up (mo)	MMF				CYC					
				Dosage (g/d)	Patients (n)	Pure Class V	Treatment Failures	Deaths/ESRD	Dosage	Patients (n)	Pure Class V	Treatment Failures	Deaths/ESRD
Flores-Suarez and Villa (19)	2	2004	12	NR	10	3	4	0/0	NR	10	0	8	3/0
Ong <i>et al.</i> (14)	3	2005	6	2	19	0	8	0/1	0.75 to 1 g/m ² intravenously	25	0	12	0/0
Ginzler <i>et al.</i> (13)	3	2005	6	3	71	14	34	0/0	0.75 to 1 g/m ² intravenously	69	13	48	0/2
Chan <i>et al.</i> (18)	2	2005	12	2	33	0	1	4/4 ^b	2.5 mg/kg orally	31	0	2	8/7 ^b
			63 ^b					0/0					0/2
								0/0 ^b					2/2 ^b

^aCYC, cyclophosphamide; MMF, mycophenolate mofetil; NR, not reported; RCT, randomized, controlled trial; RR, relative risk.

^bExtended follow-up.

(42%), followed by black (30%). Baseline mean (SD) serum creatinine measurements ranged from 93.3 (46.0) to 112.7 (65.8) $\mu\text{mol/L}$ in the MMF group and from 94.0 (40.2) to 113.1 (36.9) $\mu\text{mol/L}$ 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 ($P = 0.93$).

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

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

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

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

^aLN, lupus nephritis.

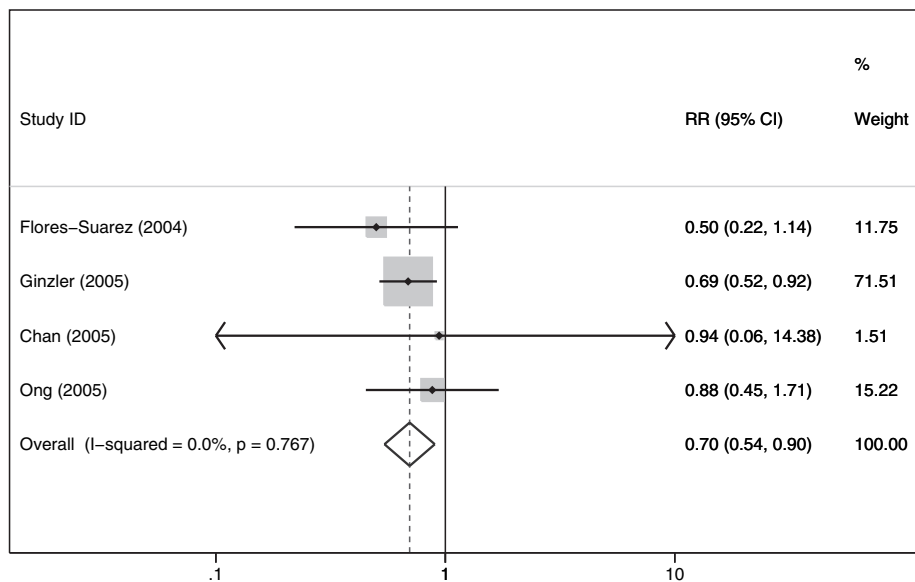


Figure 2. Forest plot of the relative risk (RR) for treatment failure for lupus nephritis treated with mycophenolate mofetil (MMF) compared with cyclophosphamide (CYC; randomized, controlled trials [RCT]).

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

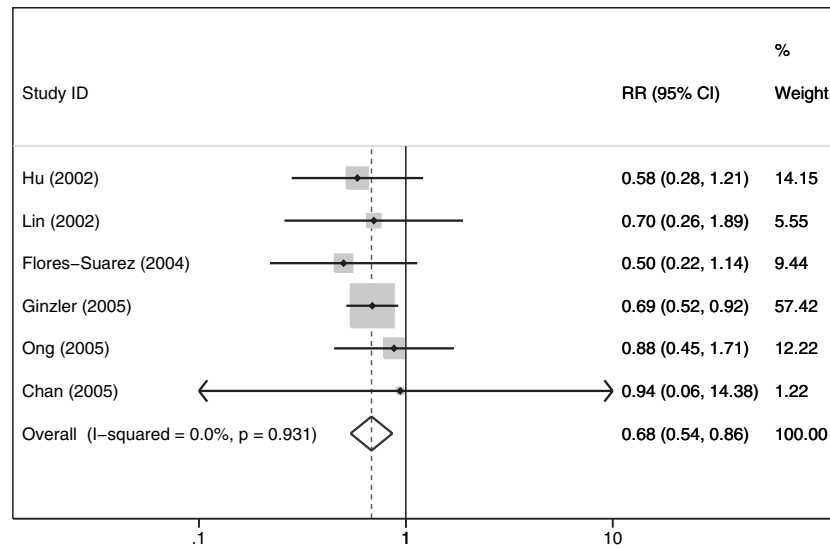


Figure 3. Forest plot of a sensitivity analysis for the RR for treatment failure for lupus nephritis treated with MMF compared with CYC when non-RCT are included.

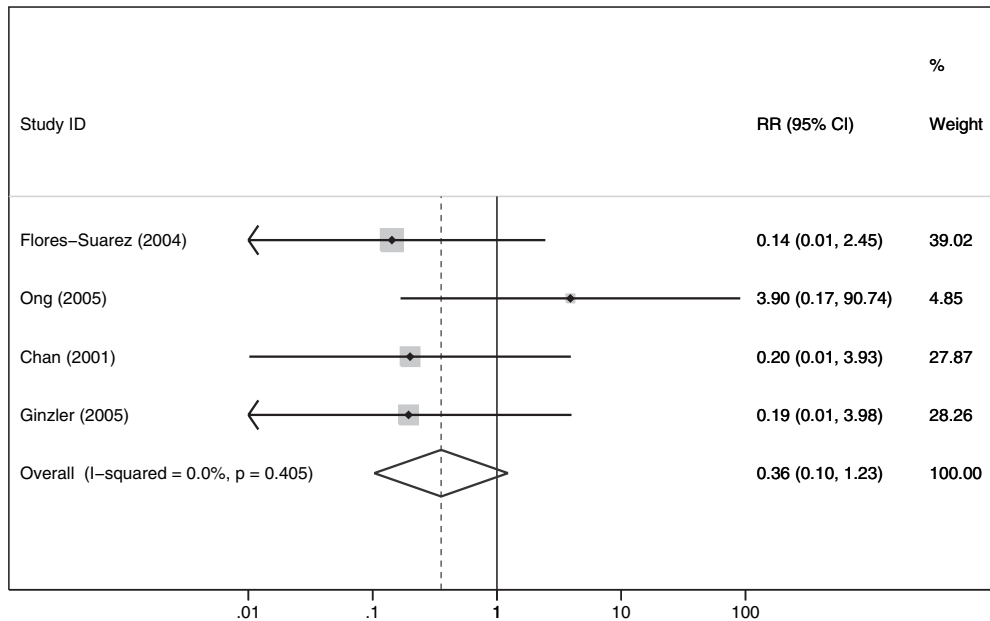


Figure 4. Forest plot of the RR for death or ESRD for lupus nephritis treated with MMF compared with CYC at end of original study duration (RCT).

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-

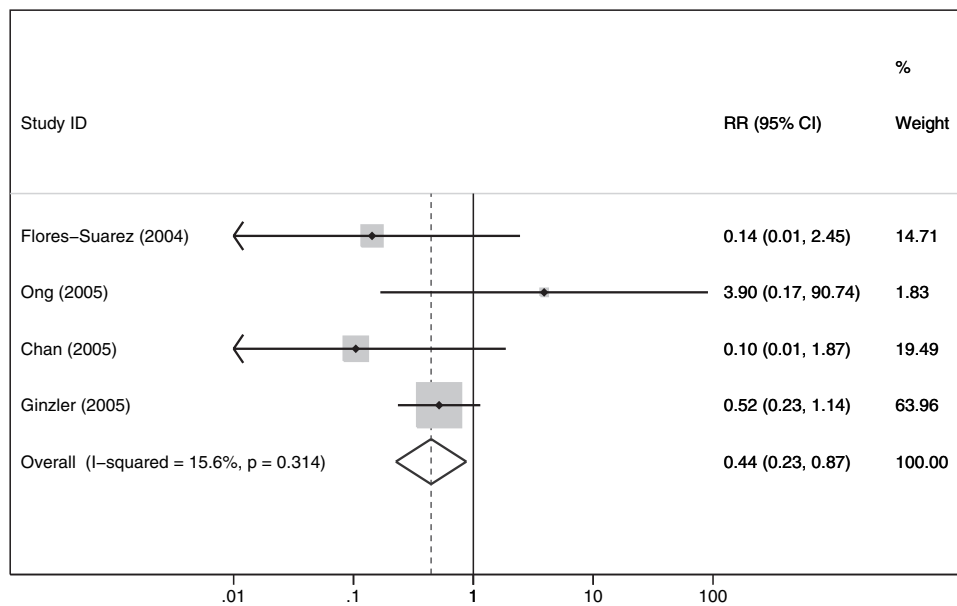


Figure 5. Forest plot of the RR for death or ESRD for lupus nephritis treated with MMF compared with CYC using extended follow-up data (RCT).

Table 4. Comparison of adverse events by treatment group in RCT with 6 to 12 mo of follow-up^a

Study	Patients		Infections		Amenorrhea		Gastrointestinal		Leukopenia	
	MMF	CYC	MMF	CYC	MMF	CYC	MMF	CYC	MMF	CYC
Chan <i>et al.</i> (15)	21	21	4	10	0	3	1	0	0	2
Flores-Suarez and Villa (19)	10	10	4	3	0	1	2	0	1	5
Ong <i>et al.</i> (14)	19	25	6	6	NR	NR	0.08 ^b	0.07 ^b	7	13
Ginzler <i>et al.</i> (13)	71	69	4	11	0	2	38	27	NR	NR
Total	121	125	18	30	0	6	41	27	8	20

^aNR, not reported.

^bReported as events per patient-year.

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 con-

sidered, 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-

tween studies (range 3 to 48% for MMF groups and 6 to 80% for cyclophosphamide groups). The role of chance, however, may account for a significant amount of this variability given the small size and short duration of each individual trial. This highlights the need for adequately powered RCT and meta-analyses. The trials also differed in racial mix, with two studies including only Asian patients (14,18), one including only Hispanic patients (19), and one including a mixed but predominantly black population (13). The lack of heterogeneity in the RR for treatment failure among these studies, despite their differences in racial mix, is reassuring in that our study results are generalizable across races. However, there are inadequate data to examine directly treatment allocation–race interactions to make any final conclusions on this topic.

Although our conclusions are based on a small number of randomized trials, they are strengthened by the homogeneity of study results and lack of any obvious publication bias. The reduction in death and ESRD may be driven by use of MMF as a maintenance agent as well as an induction agent, thereby representing a difference between MMF and other maintenance immunosuppressive agents. However, that the results favor MMF for both outcomes studied (failure to induce remission and the composite of death or ESRD) strengthens the evidence for the efficacy of MMF as an induction agent.

The results of this meta-analysis should be interpreted in light of the study limitations as well as the limitation of each of the primary studies. First, the generalizability of these study results is limited. Patients who had lupus nephritis and were included in these trials had relatively preserved renal function, and no randomized trials have shown MMF to be equivalent or superior to cyclophosphamide in patients with severe renal impairment. Although additional clinical trials directed at patients with severe renal impairment are warranted, it should be recognized that the majority of patients who present with proliferative lupus nephritis have relatively preserved kidney function. There were also very few patients with WHO class V (membranous) lupus nephritis in these studies; therefore, the results cannot be extrapolated to this population with any confidence. Second, although we did not detect evidence of publication bias, the use of statistical tests to detect such bias with so few available studies in the first place is unhelpful. Finally, the overall low quality of the available studies is a limitation. It is encouraging, however, to find that the results of lower quality studies are comparable with those of the most recent and methodologically sound study. In addition, although these results are statistically significant, all results, particularly the composite of death or ESRD, are based on a relatively small number of events and may therefore be susceptible to random error. Small meta-analyses (*i.e.*, analyses of fewer than several hundred events) should be regarded with caution even in the presence of statistically significant results (22). Given these limitations, another large, high-quality RCT with long-term follow-up is warranted (23).

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.

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