Mycophenolate mofetil in the treatment of Chinese patients with lupus nephritis
A PRISMA-compliant meta-analysis

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Abstract

Background: Mycophenolate mofetil (MMF) has been recommended for the treatment of lupus nephritis (LN). Although inter-racial differences exist regarding the appropriate dose and efficacy of MMF in patients with LN, no definitive meta-analysis has yet been conducted in Chinese patients. This analysis investigated the efficacy and safety of MMF in Chinese patients with proliferative LN.

Methods: A systematic literature search was conducted to select randomized controlled trials that reported at least one of the following: complete remission (CR), partial remission, total remission (TR; defined as complete remission + partial remission), relapse rate, serum creatinine, creatinine clearance, end-stage renal disease, death, infections, amenorrhea, leukopenia, alopecia, gastrointestinal symptoms, or liver damage.

Results: Eighteen trials (927 patients) were included; 14 (750 patients) reported CR, partial remission, and TR. Two trials (68 patients) reported relapse rates during maintenance treatment: MMF induction significantly improved CR and TR vs cyclophosphamide (relative risk 1.34, 95% confidence interval: 1.13–1.58; \( P < .001 \); relative risk 1.16, 95% confidence interval: 1.02–1.33; \( P = .03 \)), and was associated with significantly lower risks of infection (\( P < .001 \)), amenorrhea (\( P < .001 \)), leukopenia, and alopecia. No significant difference in relapse rate was evident between the MMF and azathioprine groups (\( P = .66 \)).

Conclusion: According to this meta-analysis of 18 trials, MMF is significantly more effective than cyclophosphamide induction, and is associated with reduced incidences of infections, amenorrhea, leukopenia, and alopecia in Chinese patients with proliferative LN.

Abbreviations: ALMS = Aspreva Lupus Management Study, CI = confidence interval, CR = complete remission, CYC = cyclophosphamide, LN = lupus nephritis, MMF = mycophenolate mofetil, PR = partial remission, RCT = randomized controlled trial, RR = relative risk, TR = total remission.

Keywords: azathioprine, cyclophosphamide, lupus nephritis, meta-analysis, mycophenolate mofetil

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XYH, YY, and XY are employees of Shanghai Roche Pharmaceuticals Ltd. The other authors declare that they have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article and its supporting information files.

Supplemental Digital Content is available for this article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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1. Introduction

In China, lupus nephritis (LN) is the most common secondary glomerulonephritis, with peak prevalence between age 20 and 40 years.\(^1\) LN accounts for 2.37% to 25.00% of all renal disease in Han Chinese.\(^2\) Thus, achieving early and sustained remission in LN is important for preventing long-term complications and death.

Globally, mycophenolate mofetil (MMF) and cyclophosphamide (CYC) have been recommended as induction therapy for proliferative LN for many years.\(^3\)–\(^5\) However, some inconsistency has emerged from the treatment results of several studies. For example, MMF plus corticosteroid therapy proved at least as effective and less toxic than CYC plus corticosteroid combination therapy in several clinical trials.\(^6\)–\(^8\) In all patients in the Aspreva Lupus Management Study (ALMS),\(^9\) MMF was not superior to CYC as induction treatment, but was more effective than the CYC in LN patients from mixed or Black races. In addition, MMF demonstrated superiority over azathioprine as maintenance therapy for LN in several studies.\(^10\) Importantly, LN prognosis and attendant treatment efficacy are related to race or ethnicity.\(^10\)–\(^11\) Among patients with severe LN, Black patients were significantly more often associated with more aggressive renal disease with worse outcomes than White patients.\(^10\) Black or Hispanic race or ethnicity was a better predictor of renal response to MMF.\(^11\)–\(^12\)

A previous meta-analysis of 5 randomized controlled trials (RCTs) in Asian and non-Asian patients with LN reported that MMF was more effective and was associated with fewer adverse effects in induction therapy than pulsed intravenous CYC therapy, and no significant differences in prognosis and the risk of herpes zoster infection or amenorrhea were noted between MMF and azathioprine in maintenance therapy.\(^13\) An updated meta-analysis is needed to clearly document the therapeutic profile of MMF, specifically in Chinese patients.

The principal objectives of this original meta-analysis were to investigate the efficacy and safety of MMF compared with CYC as induction therapy in Chinese patients with proliferative LN, to evaluate the maintenance therapy of MMF vs azathioprine, and to provide more accurate data for the treatment of Chinese patients with LN.

2. Materials and methods

2.1. Review criteria

The meta-analysis protocol was listed with the international prospective register of systematic reviews (PROSPERO; CRD42018086209), and the review was compiled in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.\(^14\)

Studies selected for inclusion in the analysis were RCTs, regardless of allocation concealment and/or blinding, in Chinese patients with biopsy-proven LN (type III, IV, V, III/V, or IV/V). The interventions evaluated were induction therapy with MMF plus corticosteroids vs intravenous CYC plus corticosteroids with a treatment duration ≥6 months, and maintenance therapy with MMF vs azathioprine. Studies had to report at least one of the following clinical outcomes: complete remission (CR), partial remission (PR), total remission (TR; defined as CR + PR), relapse rate, serum creatinine, creatinine clearance, end-stage renal disease, death, infections, amenorrhea, leukopenia, alopecia, gastrointestinal symptoms, or liver damage.

Studies with the following criteria were excluded: MMF in the control group; immunosuppressive therapies (eg, tacrolimus and CD20 monoclonal antibodies) other than MMF, CYC, or hormones were administered; or only the abstract was published. For duplicate publications, only the article with the most complete information was included.

2.2. Search strategy

The following databases were searched: PubMed and EMBASE (from January 1979–January 2018), Cochrane Collaboration (first issue in January 2018), plus Medline, National Guideline Clearinghouse, Best evidence, China Science and Technology Journal Database, China National Knowledge Infrastructure database, Wanfang database, and SinoMed (all searched in January 2018). Grey literature was also searched for World Health Organization International Clinical Trials Registry Platform data. English language literature was searched using the following strategy: (MMF AND (cyclophosphamide OR azathioprine)) AND (lupus nephritis OR lupus glomerulonephritis OR proliferative glomerulonephritis OR membranous glomerulonephritis OR systemic lupus erythematosus). Chinese-language literature was searched as follows: (OR OR) AND (OR AND). Furthermore, reference lists from each of the selected articles were manually searched to locate additional relevant articles for inclusion.

2.3. Data extraction and quality assessment

Two reviewers independently selected and assessed each identified clinical trial. Disagreements about study selection were resolved by consensus or judged by a third expert reviewer. Basic data were extracted from eligible articles. Primary outcome indicators included CR, TR, and relapse rates. The secondary outcome was safety, including the incidence of infection, leukopenia, gastrointestinal symptoms, alopecia liver damage, and menstrual abnormalities (menstrual disorders and amenorrhea).

TR was defined as the sum of CR + PR, according to the definitions in the original articles that reported on these 3 outcomes. In 7 of these studies, CR was defined as urinary protein <0.3g per 24 hours, serum albumin concentration, and renal function normal or improved (reduced to at least 10%–20% of baseline levels) or stable.\(^15\)–\(^21\) In 11 of the 12 studies, PR was defined as a decrease in urinary protein of >50% at 24 hours, renal function and albumin improved, and serum creatinine stable (decreased relative to baseline) or decreased to 20% of baseline.\(^1\)–\(^3\),\(^6\),\(^9\)–\(^12\),\(^26\)

Safety indicators were infection, amenorrhea, leukopenia, alopecia, gastrointestinal symptoms, and liver damage.

During the literature quality assessment, the risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1).\(^27\) The following characteristics were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and possible sources of other bias. Each item was judged as “low risk of bias,” “high risk of bias,” or “unclear.” Disagreements were resolved through discussion or by a third reviewer. For missing information in a specific article, the corresponding author was contacted to obtain the required data.
2.4. Statistical analyses

Heterogeneity was assessed with Cochran $Q$ (heterogeneity $\chi^2$) and $I^2$. Sensitivity analyses were performed on factors that might contribute to heterogeneity. The fixed effects model was applied for pooling in the situation of no significant heterogeneity; otherwise, the random effects model was applied. For categorical variables, relative risk (RR) and 95% confidence intervals (CIs) were used to indicate effect size. Funnel plots and Forest plots were used for graphical representation of data. Meta-analysis was performed using Review Manager version 5.3 software (The Nordic Centre, The Cochrane Collaboration, 2014; Copenhagen, Denmark). A threshold of two-sided $P < .05$ was considered statistically significant.

2.5. Ethical approval

No ethical approval was needed for this study because the data were from existing published studies with informed consent obtained by primary investigators; no new patient data were collected.

3. Results

3.1. Characteristics of eligible studies

A total of 18 eligible RCTs (5 English language articles and 13 Chinese language articles; total of 927 patients) were included in the final analysis (Fig. 1). Basic information from each article is outlined in Table 1. He et al$^{[16]}$ and Zhang et al$^{[25]}$ did not report age; otherwise, baseline data for all items were well-matched between constituent studies. Among the 18 trials, a range of induction therapy dosages of MMF were used: 2.0 g/d (3 trials, 88 patients)$^{[15,22,28]}$, 1.5 to 2.0 g/d (6 trials, 185 patients)$^{[16,18,19,23,24,26]}$, 1.0 to 1.5 g/d (4 trials, 83 patients)$^{[17,29–31]}$, 0.75 to 2.0 g/d (1 trial, 23 patients)$^{[32]}$, 1.5 g/d (1 trial, 33 patients)$^{[20]}$, and 1.0 g/d (<50 kg) or 1.5 g/d (≥50 kg) (2 trials, 55 patients)$^{[25,33]}$. Dosages of intravenous cyclophosphamide were 0.75 to 1.00 g/m$^2$ body surface area monthly in 12 trials including 314 patients$^{[16,18,20,22–26,29–31,33]}$; other trials with 146 patients evaluated different dosages of cyclophosphamide (Table 1). Corticosteroid dosages varied widely between studies. Of the 18 trials, 7 trials were initiated with intravenous methylprednisolone$^{[16,17,20,22–26,29–31,33]}$, and the others were initiated with different oral dosage of prednisolone (Table 1). An assessment of the risk of publication bias for each of the 18 eligible studies is shown in Supplemental Digital Content Fig. S1, http://links.lww.com/MD/E714.

3.2. Efficacy of induction therapy

3.2.1. Complete remission between MMF and CYC therapy.

The effect of MMF on CR is shown in Fig. 2. Fourteen RCTs reported CR, and the fixed effects model was used for meta-analysis (heterogeneity test: $P = .17$; $\chi^2$ 17.64; $I^2$ 26%). The CR rate was significantly higher in the MMF group (n = 376, 44.7%) than in the CYC group (n = 374, 32.9%) with the RR of 1.34 (95% CI: 1.13–1.58; $P < .001$). Asymmetry in the CR plot was detected by Egger test for publication bias and a sensitivity analysis was applied (Supplemental Digital Content Fig. S2a and S2b, http://links.lww.com/MD/E714). A total of 17 studies were included in the sensitivity analysis after imputing four studies estimated by linear regression method. The results after adjustment showed no obvious asymmetry, suggesting that publication bias was nullified and the adjusted RR was 1.20 (95% CI: 0.95–1.51).

![Study selection diagram](http://links.lww.com/MD/E714)
**Table 1**

| Reference       | Sample size (T/C) | Age (yr) | Treatment regimen in MMF group                  | Treatment regimen in CYC group | Treatment duration (mo) | Major outcome measures | Pathologic type of LN |
|-----------------|-------------------|----------|-------------------------------------------------|--------------------------------|------------------------|------------------------|-----------------------|
| Induction phase – clinical data |                    |          |                                                 |                                |                        |                        |                       |
| Chan et al[15]  | 33/31             | T: 38.1 (10.2) C: 41.8 (8.9) | MMF: 2 g/d × 6 mo; mt with rd                   | CYC: oral 2.5 mg/kg/d × 6 mo; mt with AZA | 24                     | CR, PR, TR             | N                     |
|                 |                    |          | Pred: initially 0.8 mg/kg/d and tapered to reach 10 mg/d at approximately 6 mo. The dose of Pred was reduced further to 7.5 mg/d at 9–12 mo from baseline to 5–7.5 mg/d at 12–15 mo, then maintained at the same dose thereafter. |                                |                        |                        |                       |
| Feng et al[22]  | 30/30             | T: 29.9 (1.8) C: 35.4 (2.1) | MMF: 2 g/d × 6 mo                               | CYC: IV 0.5 g every 2 wk × 6 mo | 6                      | CR, PR, TR, IIIWWV     |                       |
|                 |                    |          | Pred: initially 0.5 mg/kg/d, then rd             |                                |                        |                        |                       |
| Hu et al[29]    | 23/23             | T: 28.0 (8.8) C: 29.5 (10.2) | MMF: initially 1.0–1.5 g/d, then 0.5–1.0 g/d 3–6 mo later | CYC: IV 0.75–1.00 g/m²/mo × 6, then mt at 1:4 dose for 1 yr | 6                      | %UP ↓ by ≥50%          | N                     |
|                 |                    |          | Pred: initially 10–30 mg/d, then rd to 10–15 mg/d |                                |                        |                        |                       |
| Wang et al[24]  | 9/11              | T: 32.2 (12.0) C: 30.8 (12.7) | MMF: 1.5–2.0 g/d × 6 mo                         | CYC: IV 0.75–1.0 g/m² per mo × 6 mo | 6                      | CR, PR, TR             | N                     |
|                 |                    |          | MP: 0.5 g/d × 3 d; Pred: initially 0.6–0.8 mg/kg/d every 4 wk, then the daily dose of Pred was tapered by 5 mg every 1 wk until the dose was 20 mg/d, after which it was reduced by 5 mg every 2 wk, until a maintenance dose of 10 mg/d was reached. |                                |                        |                        |                       |
| Lü et al[16]    | 20/20             | T: 26.5 (range 16–62) C: 33.0 (range 17–64) | MMF: 1.5–2.0 g/d × 6 mo Daily doses of Pred were started at 0.8–1.0 mg/kg/d orally at a maximum dose of 60 mg/d, reduced by 10 mg every 2 wk until the dose was 40 mg/d, after which it was reduced by 5 mg every 2 wk, until a maintenance dose of 10 mg/d was reached. | CYC: IV 0.5–0.75 g/m² per mo × 6 mo | 6                      | CR, PR, TR, IIIWWV or combined |                       |
|                 |                    |          | Pred: initially 0.6–0.8 mg/kg/d every 4 wk, then the maximum dose was 40 mg/d. After 4 wk, reduced by 5 mg/d to 20 mg/d every 2 wk, and then by 2.5 mg/d every 2 wk until a maintenance dose of 10 mg/d was reached. |                                |                        |                        |                       |
| He et al[26]    | 30/30             | NA       | MMF: 1.5–2.0 g/d × 6 mo                          | CYC: IV 0.75 g/m² per mo × 6–9 mo | 6                      | CR, PR, TR             | IIIWWV                |                       |
|                 |                    |          | MP: 0.5 g/d × 3 d; Pred: initially 0.6–0.8 mg/kg/d, the maximum dose was 40 mg/d. After 4 wk, reduced by 5 mg/d to 20 mg/d every 2 wk, and then by 2.5 mg/d every 2 wk until a maintenance dose of 10 mg/d was reached. |                                |                        |                        |                       |
| Jiang et al[28] | 25/21             | T: 37.0 (10.0) C: 39.0 (11.0) | MMF: initially 2.0 g/d × 6 mo, then mt at 1:2 dose for 6 mo | CYC: IV 20 mg/kg per mo × 6 mo, then AZA mt for 6 mo | 12                     | CR, PR, TR             | N                     |
|                 |                    |          | Pred: initially 1.0 mg/kg/d for 8 wk then reduced 10% every 1 wk to 0.5 mg/kg/d then reduced |                                |                        |                        |                       |

(continued)
| Reference | Sample size (T/C) | Age (yr) | Treatment regimen in MMF group | Treatment regimen in CYC group | Treatment duration (mo) | Major outcome measures | Pathologic type of LN |
|-----------|------------------|----------|--------------------------------|--------------------------------|------------------------|------------------------|------------------------|
| Li         | 20/19            | T: 31.0 (7.0) C: 33.0 (6.0) | 2.5 mg/d every 2 wk until a maintenance dose 10 mg/d was reached MMF: 1.0–1.5 g/d × 6 mo MP: 0.5 g/d × 3 d Glucocorticoid: intermediate – small dose | CYC: IV 0.5–0.75 g/m² per mo × 6 mo | 6 | CR, PR, TR | V |
| Liang      | 23/20            | T: 35.8 (9.0) C: 33.8 (10.0) | MMF: 0.75–2.0 g/d × 3–12 mo Pred: 10–30 mg/d | CYC: IV 0.5–1.0 g/m² per mo × 6–12 mo | 12 | 24-hr UP | III/IV |
| Liu et al  | 20/20            | T: 37.0 (10.0) C: 35.0 (8.0) | MMF: 1.5–2.0 g/d × 6 mo, then mt at 1/2 dose for 6 mo | CYC: IV (total dose: 8–10 g) | 12 | CR, PR, TR, | |
| Peng et al | 37/34            | T: 38.1 (11.7) C: 36.9 (10.2) | Pred: dose not reported | CYC: IV 0.5–1.0 g/m² per mo × 6 mo | 6 | CR, PR, TR | III/V |
| Zhu et al  | 14/14            | T: 27.2 (3.9) C: 28.7 (5.4) | MMF: initially 1.0–1.5 g/d × 6 mo, then rd 0.5–1.0 g/d × 6 mo | CYC: IV 0.75–1.0 g/m² per mo × 6 mo; every 3 mo thereafter | 12 | %UP ↓ by ≥50% | V |
| Hu         | 39/39            | T: 38.4 (6.2) C: 38.0 (6.0) | MMF: 1.0–g/d (<50 kg) or 1.5 g/d (≥50 kg) × 6 mo; then mt at 1/2 dose for 6 mo Pred: 1.0 mg/kg/d | CYC: IV 0.75–1.0 g/m² per mo × 12 mo | 12 | CR, PR, TR | V |
| Lu         | 33/33            | T: 38.9 (12.3) C: 38.5 (12.0) | MMF: initially 1.5 g/d, then mt with rd to 0.5 g/d MP: 0.5 g/d × 3 d Pred: 45 mg/d | CYC: IV 1.0 g/m² × 2 d per mo × 6 mo | 6 | CR, PR, TR | V |
| Qin        | 44/44            | T: 45.2 (4.5) C: 45.2 (4.3) | MMF: 1.5–2.0 g/d | CYC: IV 0.75–1.0 g/m² per mo × 12 mo | 6 | CR, PR, TR | N+V |
| Shi et al  | 26/27            | T: 30 (8) C: 35 (10) | MMF: 1.0–1.5 g/d × 3 mo, then rd 0.75–1.0 g/d × 3 mo | CYC: IV 0.4 g/m² × 2 d every 2 wk × 3 mo; every mo thereafter | 6 | Only safety events | V |
| Zhang      | 16/19            | T: 30 (8) C: 35 (10) | MMF: 1.0 g/d (<50 kg) or 1.5 g/d (≥50 kg) × 6 mo; then mt at 1/2 dose for 6 mo | CYC: IV 0.75–1.0 g/m² per mo × 12 mo | 12 | CR, PR, TR | V |
| Zhang et al| 25/25            | T: 45.2 (13.5) C: 45.2 (13.5) | MMF: 1.5–2.0 g/d × 6 mo | CYC: IV 0.75–1.0 g/m² per mo × 12 mo | 6 | CR, PR, TR | N+V |
Table 1 (continued).

| Treatment regimen in MMF group | Treatment regimen in CYC group |
|--------------------------------|--------------------------------|
| **Reference**                  | **Reference**                  |
| Jiang et al[28]                 | Jiang et al[28]                 |
| 25/21                           | 25/21                           |
| T: 37.0 (10.0)                  | T: 37.0 (10.0)                  |
| Pred: 5–7.5 mg/d                | Pred: 5–7.5 mg/d                |
| C: 39.0 (11.0)                  | C: 39.0 (11.0)                  |

Subgroup analysis indicated that study quality (medium vs low) and duration (≤6 vs >6 months) significantly affected CR rates (Supplemental Digital Content Table S1, http://links.lww.com/MD/E714). MMF was associated with a higher rate of CR compared to CYC in medium quality studies (RR 1.37; 95% CI: 1.12–1.67; P = .002) and at both ≤6 months (RR 1.28; 95% CI: 1.08–1.53; P = .006) and >6 month follow-up (RR 1.67; 95% CI: 1.03–2.70; P = .04).

3.2.2. TR of MMF vs CYC. TR was reported by 14 RCTs and evaluated using the random effects model (heterogeneity test: P < .001; I² 78%; Fig. 3). There was a significantly higher TR rate in the MMF (84.3%, n = 376) group compared with the CYC (70.90%, n = 374) group (RR 1.16; 95% CI: 1.02–1.33; P = .03).

Egger test results showed that no publication bias was observed within TR data (Supplemental Digital Content Fig. S2c, http://links.lww.com/MD/E714). Subgroup analysis indicated higher TR with MMF at ≤6-month follow-up (RR 1.20; 95% CI: 1.04–1.38; P = .01, Supplemental Digital Content Table S1, http://links.lww.com/MD/E714). A higher trend of TR approaching statistical significance with MMF compared with CYC was found in medium quality studies (RR 1.17; 95% CI: 0.99–1.39; P = .07).

3.3. Safety of MMF vs CYC during induction therapy

No significant heterogeneity was identified in reports of various adverse effects of MMF vs CYC induction therapy. Thus, meta-analyses using the fixed effects model revealed that MMF vs CYC induction therapy in Chinese patients with LN was associated with significantly lower risks of infection (RR 0.52; 95% CI: 0.38–0.71; P < .001; Fig. 4A), amenorrhea (RR 0.21; 95% CI: 0.11–0.39; P < .001; Fig. 4B), gastrointestinal symptoms (RR 0.48; 95% CI: 0.32–0.71; P < .001), leukopenia (RR 0.44; 95% CI: 0.23–0.83; P = .01), and alopecia (RR 0.12; 95% CI: 0.04–0.37; P < .001) (Table 2).

3.4. Relapse rate of MMF vs azathioprine during maintenance therapy

Two RCTs (58 patients) reported relapse rates during 1.0 g/d MMF maintenance therapy over 6 to 12 months. Azathioprine dosages were 1.5 mg/kg/d over 6 months[28] and 1 to 1.5 mg/kg/d over 12 months.[18] A fixed effects model was used for meta-analysis as there was no significant heterogeneity among studies (P = .93; I² 0%; P = .52). No significant difference in relapse rate was evident between the MMF and azathioprine groups (RR 1.16; 95% CI: 0.59–2.28; P = .66).

4. Discussion

This large meta-analysis of Chinese patients with proliferative LN found that: induction therapy with MMF was markedly more effective than CYC regarding CR and TR; MMF vs CYC was associated with significantly lower risks of infection, amenorrhea, leukopenia, and alopecia; and MMF was no different from azathioprine regarding relapse rate as maintenance therapy.

Similarly, several studies have found MMF more likely than CYC to attain CR during induction treatment.[13,34–37] A previous meta-analysis in Asian and non-Asian LN patients reported that MMF was 3.1 times more likely to produce CR than CYC (P = .006).[13] Another meta-analysis including 65
studies documented that renal remission was more likely to be attained with MMF than with low- or high-dose CYC. However, a meta-analysis found no statistically significant difference in CR rates between MMF and CYC; there was a trend towards significance. In addition, MMF was similar to azathioprine (RR 1.15; \(P = .68\)) in reducing relapse rate during maintenance treatment in this study.

Our meta-analysis included only 2 studies of MMF use as maintenance therapy. Both reported that MMF was as or more effective than CYC-azathioprine and had fewer side effects. Additionally, when we added the relapse rate from another potential maintenance study (relapse rate and CR/PR analysis at 12 months),\(^{19}\) we found no statistically significant difference from the previous 2 studies\(^{15,28}\) (RR = 1.06; 95% CI: 0.56, 2.01). These findings generally concur with those from the network meta-analysis, in which maintenance MMF therapy was associated with a lower rate of the composite of renal relapse or renal failure than azathioprine (RR 0.59; 95% CI: 0.38, 0.90),\(^{14}\) and azathioprine was associated with a significant increased risk of renal relapse vs MMF (RR 1.83; 95% CI: 1.24–2.71).\(^{38}\)

Induction therapy with MMF has consistently been associated with significantly lower risks of infection, amenorrhea, leukopenia, and alopecia than with CYC.\(^{13,34,38}\) In other large meta-analyses in Asian and non-Asian patients with LN, MMF was linked with considerably lower risks of infection, amenorrhea, leukopenia, and alopecia than with CYC.\(^{13,34,38}\) Lower MMF dosing in Asian vs non-Asian patients may be similarly efficacious and further improve tolerability.\(^{4}\) A Taiwanese study reported that low-dose MMF was associated

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**Figure 2.** Complete remission after mycophenolate mofetil vs cyclophosphamide induction therapy. CI = confidence interval, CYC = cyclophosphamide, df = degrees of freedom, M-H = Mantel-Haenszel, MMF = mycophenolate mofetil.

**Figure 3.** Total remission after mycophenolate mofetil vs cyclophosphamide induction. CI = confidence interval, CYC = cyclophosphamide, df = degrees of freedom, M-H = Mantel-Haenszel, MMF = mycophenolate mofetil.
with good efficacy in patients with LN. In our analysis, MMF efficacy was confirmed at relatively low induction doses (0.75–2.0 g/day) in Chinese patients (Table 1), and MMF was significantly better tolerated than CYC.

This was the first analysis to focus on MMF vs CYC dose and efficacy specifically in the treatment of Chinese patients with LN. Previously, American College of Rheumatology guidelines highlighted that MMF has similar efficacy in various races (ie, Caucasians, Asians, African Americans, and Latin/Hispanic Americans).[4] The ALMS also demonstrated similar results.[7] Interestingly, in a recent cohort analysis in a Hispanic population with LN, MMF induction therapy was at least twice as likely as intravenous CYC (P = .005) or azathioprine (P = .007) to produce CR.[40] The ALMS also suggested that MMF was significantly more effective than intravenous CYC in Hispanic and African American LN patients, but was as effective as intravenous CYC in Asian patients (response rate 53.2% vs 63.9%; not statistically significant). Such efficacy differences may be attributable to inter-racial differences of the activity of drug-metabolizing enzymes, which suggests additional investigation is needed.[11] This underscores the important need for our detailed meta-analysis in the absence of large-scale, high-quality RCTs with CR as a primary endpoint in Chinese patients with LN.

A particular strength of our meta-analysis is that the efficacy and safety of appropriate-dose MMF (≤ 2.0 g/d) have now been confirmed specifically in Chinese patients (n = 927) with (type III, IV, V, III/V, or IV/V LN, information which was not previously available. However, our study had several limitations. First, this meta-analysis included all studies in Chinese patients with type III, IV, V, III/V, or IV/V LN, which could have contributed to

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Table 2

| Adverse event              | No. of studies | MMF (n/N) | CYC (n/N) | RR (95% CI)    | P value |
|----------------------------|----------------|-----------|-----------|----------------|---------|
| Infection                  | 11             | 47/296    | 87/287    | 0.52 (0.38, 0.71) | <.001   |
| Amenorrhea                 | 9              | 8/225     | 45/214    | 0.21 (0.11, 0.39) | <.001   |
| Leukopenia                 | 11             | 10/262    | 20/256    | 0.44 (0.23, 0.83) | .01     |
| Alopecia                   | 6              | 1/159     | 25/157    | 0.12 (0.04, 0.37) | <.001   |
| Gastrointestinal symptoms  | 11             | 27/282    | 59/279    | 0.48 (0.32, 0.71) | .01     |
| Liver damage               | 6              | 4/100     | 12/114    | 0.44 (0.18, 1.12) | .08     |

CI = confidence interval, CYC = cyclophosphamide, MMF = mycophenolate mofetil, RR = relative risk.
heterogeneous clinical outcomes. Eleven of the studies included only type IV patients, while the remaining 7 included patients with III, IV, V, and combined types. Second, not all studies reported every outcome of interest; some degree of publication bias may have occurred despite the use of validated techniques to detect and correct for this. Third, the inclusion of Chinese language studies may make it difficult for non-Chinese speaking researchers to examine the full dataset and replicate our analysis. Fourth, the steroid regimen used in these studies was likely to be highly heterogeneous, which may confound conclusions based on the comparison of short-term clinical outcomes associated with MMF and CYC alone. Additional limitations included variable trial durations, relatively short follow-up periods, and the inclusion of maintenance therapy in just 2 of the RCTs evaluated.

In conclusion, a large database of MMF efficacy and safety data in Chinese patients with proliferative LN now exists. The results confirm that induction therapy with MMF (0.5–2.0g/d) is more effective than CYC at achieving CR and TR. MMF is also more effective than CYC in treating diffuse proliferative lupus nephritis. Shinxi Med J 2004;204:160.

Author contributions
HTZ, MLZ, XYH, YY, and XY conceived and designed the present study. XYH and YY (statistician) contributed to statistical analyses. HTZ, MLZ, and XYH drafted and reviewed the manuscript. All authors read and approved the final manuscript.

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