Systematic Review and Meta-Analysis

Medicine®

OPEN

Mycophenolate mofetil in the treatment of Chinese patients with lupus nephritis

A PRISMA-compliant meta-analysis

Haitao Zhang, PhD[a,*], Minlin Zhou, PhD[a], Xiaoyan Han, MD[b], Yang Yang, PhD[b], Xin Yu, MD[b]

Abstract

Backgroud: 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 (58 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

Editor: Worawit Louthrenoo.

This study was funded by Shanghai Roche Pharmaceuticals Ltd. We thank David Murdoch of Edanz Medical Writing for providing medical writing support, which was funded by Shanghai Roche Pharmaceuticals Ltd.

Some of the results from this study were presented at the 2018 meeting of the American Society of Nephrology (ASN) in San Diego, CA, USA, on October 23–28, 2018; and at the 2019 American College of Rheumatology/Association of Rheumatology Professionals Annual Meeting in Atlanta, GA, USA, on November 23–28, 2019.

This study was funded by Shanghai Roche Pharmaceuticals Ltd. We thank David Murdoch of Edanz Medical Writing for providing medical writing support, which was funded by Shanghai Roche Pharmaceuticals Ltd.

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.

[a] National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing Clinical School of Second Military Medical University, Nanjing University School of Medicine, Nanjing, [b] Shanghai Roche Pharmaceuticals Ltd., Shanghai, PR China.

[*] Correspondence: Haitao Zhang, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing Clinical School of Second Military Medical University, Nanjing University School of Medicine, 305 East Zhongshan Road, Nanjing, 210002, PR China (r-mail: htzhang163@163.com).

How to cite this article: Zhang H, Zhou M, Han X, Yang Y, Yu X. Mycophenolate mofetil in the treatment of Chinese patients with lupus nephritis: a PRISMA-compliant meta-analysis. Medicine 2020;99:33(e21121).

Received: 21 January 2020 / Received in final form: 24 April 2020 / Accepted: 11 May 2020

http://dx.doi.org/10.1097/MD.0000000000021121

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),[7] 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.[9] 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 <0.3 g 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.[15–18,20–26]

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 χ^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 2.0 g/d (1 trial, 37 patients),[21] 1.0–1.5 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,[16,17,20,23,24,26,30] 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: $P = .17$; χ^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).

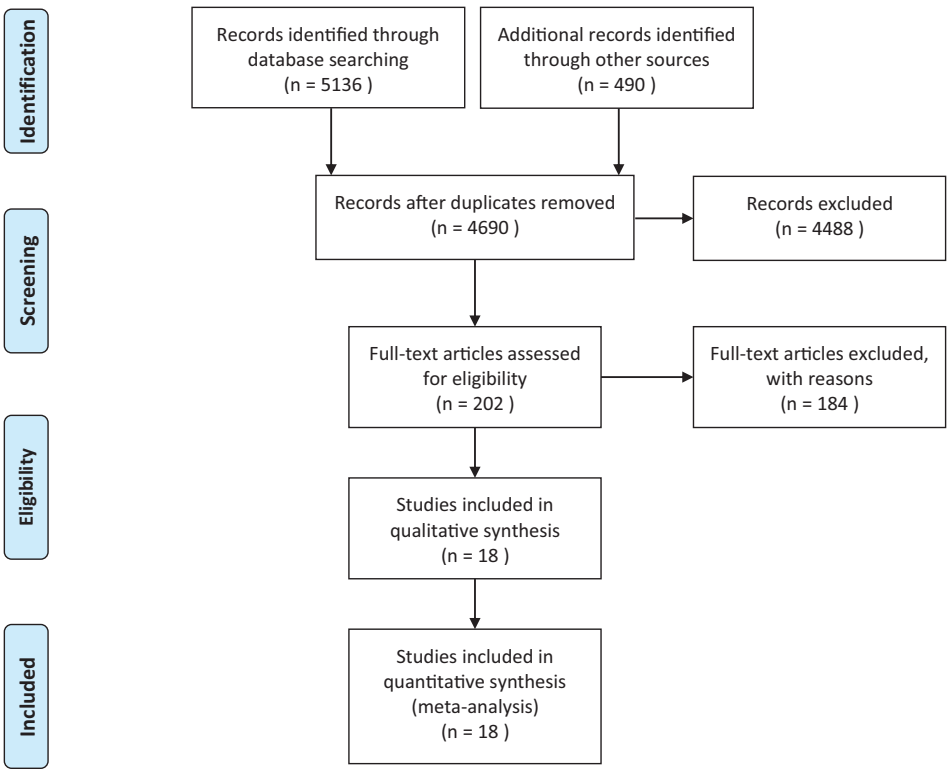

Figure 1. Study selection.

Table 1

Basic clinical data for the 18 included studies.

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 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 and to 5–7.5 mg/d at 12–15 mo, then maintained at the same dose thereafter	CYC: oral 2.5 mg/kg/d × 6 mo; mt with AZA	24	CR, PR, TR	IV
Feng et al[22]	30/30	T: 29.9 (1.8) C: 35.4 (2.1)	MMF: 2 g/d × 6 mo Pred: initially 0.5 mg/kg/d, then rd	CYC: IV 0.5 g every 2 wk × 6 mo	6	CR, PR, TR,	III/IV/V
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 Pred: initially 10–30 mg/d, then rd to 10–15 mg/d	CYC: IV 0.75–1.00 g/m^2/mo × 6, then mt at 1\4 dose for 1 yr MP: 0.5–1.0 g/d (total dosage 2.0–3.0 g), then Pred 0.8 mg/kg/d, then rd	6	%UP ↓ by ≥50%	IV
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 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	CYC: IV 0.75–1.0 g/m^2 per mo × 6 mo	6	CR, PR, TR	IV
Li et al[18]	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/m^2 per mo × 6 mo	6	CR, PR, TR	III/IV/V or combined
He et al[16]	30/30	NA	MMF: 1.5–2.0 g/d × 6 mo 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	CYC: IV 0.75 g/m^2 per mo × 6–9 mo	6	CR, PR, TR	III/IV/V
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 Pred: initially 1.0 mg/kg/d for 8 wk then reduced 10% every 1 wk to 0.5 mg/kg/d then reduced	CYC: IV 20 mg/kg per mo × 6 mo, then AZA mt for 6 mo	12	CR, PR, TR	IV

(*continued*)

Table 1

(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
			2.5 mg/d every 2 wk until a maintenance dose 10 mg/d was reached				
Li[17]	20/19	T: 31.0 (7.0) C: 33.0 (6.0)	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/m^2 per mo × 6 mo	6	CR, PR, TR	IV
Liang[33]	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/m^2 per mo × 6–12 mo	12	24-hr UP	III/IV
Liu et al[19]	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 Pred: initially 30 mg/d then rd to 10 mg/d	CYC: IV (total dose: 8–10 g)	12	CR, PR, TR,	IV
Peng et al[21]	37/34	T: 38.1 (11.7) C: 36.9 (10.2)	MMF: 1.0–2.0 g/d × 6 mo Pred: dose not reported	CYC: IV 0.5–1.0 g/m^2 per mo × 6 mo	6	CR, PR, TR	III/IV/V
Zhu et al[30]	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 MP: 0.5–30 mg/d (total dose 2.5–3 g); then Pred: 0.8–1.0 mg/kg/d, then rd at 4–8 wk to 0.3–0.5 mg/kg/d at 6 mo	CYC: IV 0.75–1.0 g/m^2 per mo × 6 mo; every 3 mo thereafter	12	%UP ↓ by ≥50%	IV
Hu[32]	39/39	38.4 (6.2)	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/m^2 per mo × 12 mo	12	CR, PR, TR	IV
Lv[20]	33/33	38.9 (12.3)	MMF: initially 1.5 g/d, then mt with rd to 0.5 g/d MP: 0.5 g × 3 d Pred: 45 mg/d	CYC: IV 1.0 g/m^2 × 2 d per mo × 6 mo	6	CR, PR, TR	IV
Qin[23]	44/44	T: 45.2 (4.5) C: 45.2 (4.3)	MMF: 1.5–2.0 g/d MP: 0.5 g × 3 d Pred: 0.6–0.8 mg/kg/d × 30 d, then 10 mg/d	CYC: IV 0.75–1.0 g/m^2 per mo × 6 mo	6	CR, PR, TR	IV+V
Shi et al[31]	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 MP:10–30 mg/d	CYC: IV 0.4 g/m^2 × 2 d every 2 wk × 3 mo; every mo thereafter	6	Only safety events	IV
Zhang[25]	16/19	NA	MMF: 1.0 g/d (<50 kg) or 1.5 g/d (≥50 kg) × 6 m; then mt at 1\2 dose for 6 m Pred: 0.8–1.0 mg/kg/d for 4–8 wk then reduced by 5 mg every 1 wk to 20–30 mg/d	CYC: IV 0.75–1.0 g/m^2 per mo × 12 mo	12	CR, PR, TR	IV
Zhang et al[26]	25/25	45.2 (13.5)	MMF: 1.5–2.0 g/d × 6 mo MP: 0.5 g/d × 3 d Pred: 0.6–0.8 mg/kg/d × 1 mo, then reduced by 5 mg every 1 wk to 10 mg/d	CYC: IV 0.75–1.0 g/m^2 per mo × 6 mo	6	CR, PR, TR	IV+V

(*continued*)

Table 1
(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
Maintenance phase - clinical data							
Chan et al[15]	33/31	T: 38.1 (10.2) C: 41.8 (8.9)	MMF: a dose of 500 mg twice daily for at least another year before further tapering in stable patients Pred: 5–7.5 mg/d maintained at the same dose	AZA: 1–1.5 mg/kg/d and continued for at least another 1 yr before tapering in stable patients	12	Relapse	IV
Jiang et al[28]	25/21	T: 37.0 (10.0) C: 39.0 (11.0)	MMF: 1 g/d Pred: 10 mg/d	AZA 1.5 mg/kg/d	6	relapse	IV

*Mean (standard deviation), unless otherwise stipulated.
AZA = azathioprine, C = control group, CR = complete remission, CYC = cyclophosphamide, d = day(s), IV = intravenous, LN = lupus nephritis, mo = month(s), MMF = mycophenolate mofetil, MP = methylprednisolone pulse, mt = maintenance therapy, PR = partial remission, Pred = prednisone, rd = reduced dose, T = treatment group, TR = total remission, UP = urinary protein, w = week(s), yr = year.

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: $P < .001$; χ^2 78; I^2 83%, 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.[15] A fixed effects model was used for meta-analysis as there was no significant heterogeneity among studies ($P = .93$; χ^2 0.01; I^2 0%). 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

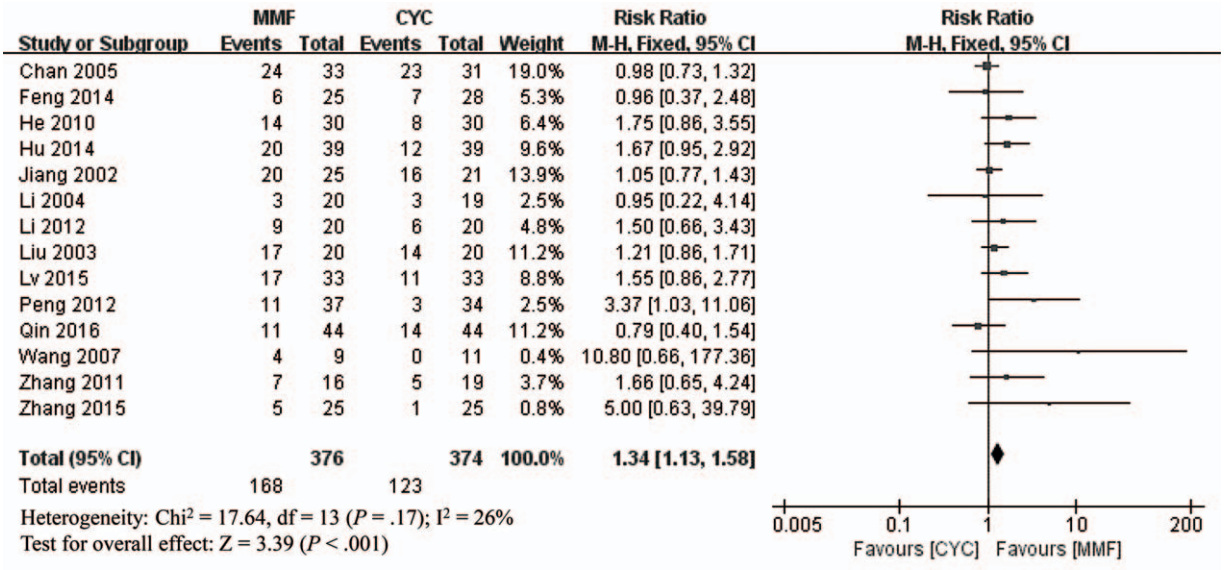

Figure 2. Complete remission after mycophenolate mofetil vs cyclophosphamide induction therapy. CI = confidence interval, CYC = cyclophosphamide, df = degrees of freedom, M-H = Mantel-Haenszel, MMF = mycophenolate mofetil.

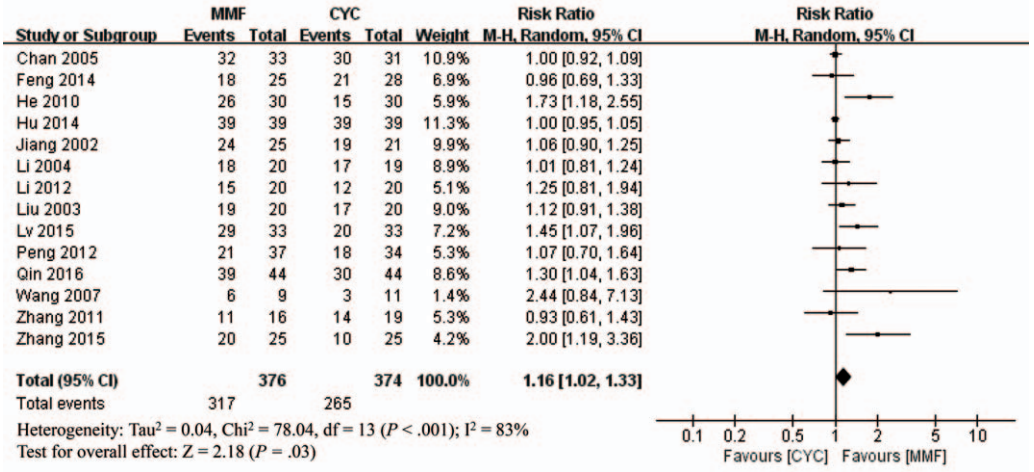

Figure 3. Total remission after mycophenolate mofetil vs cyclophosphamide induction. CI = confidence interval, CYC = cyclophosphamide, df = degrees of freedom, M-H = Mantel-Haenszel, MMF = mycophenolate mofetil.

studies documented that renal remission was more likely to be attained with MMF than with low- or high-dose CYC.[34] However, a meta-analysis found no statistically significant difference in CR rates between MMF and CYC; there was a trend towards significance.[36] 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.[15,28] 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),[34] 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 (RR range 0.65–0.79), amenorrhea (0.15–0.22), leukopenia (0.25–0.66), and alopecia (0.22) than 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

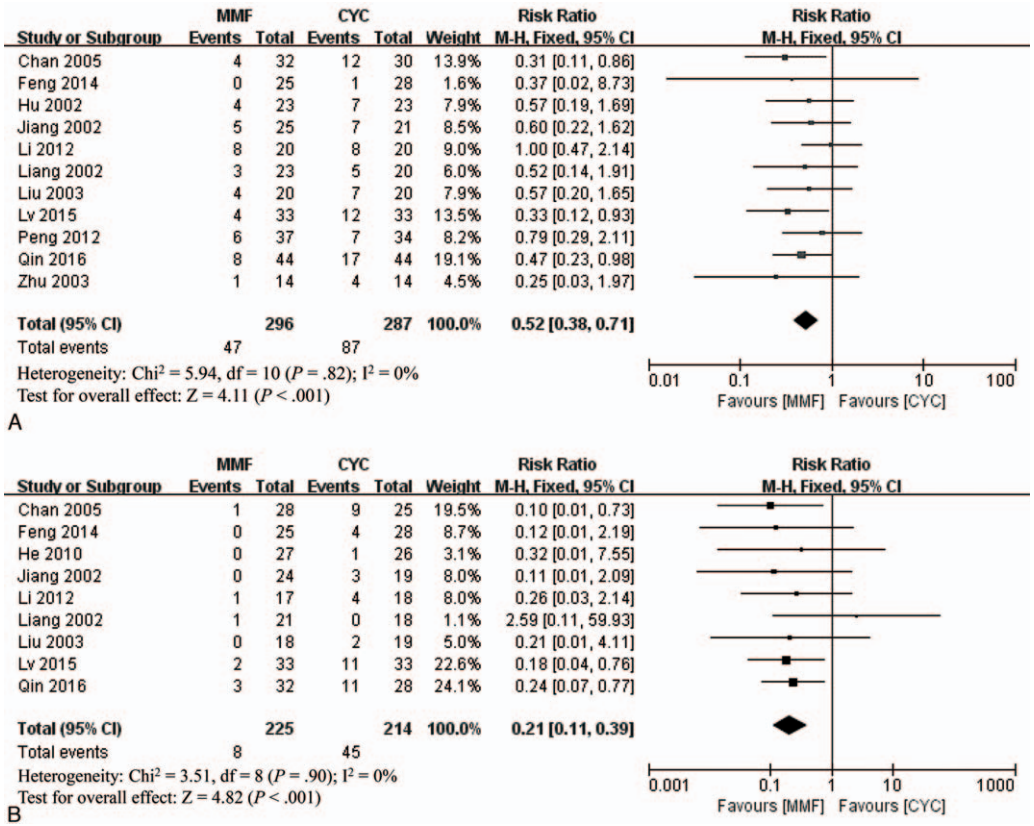

Figure 4. Risks of infection (A) and amenorrhea (B) after mycophenolate mofetil and cyclophosphamide induction. CI = confidence interval, CYC = cyclophosphamide, df = degrees of freedom, M-H = Mantel-Haenszel, MMF = mycophenolate mofetil.

Table 2

Relative risk of adverse events with mycophenolate mofetil vs cyclophosphamide induction therapy.

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	26/256	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)	<.001
Liver damage	6	4/109	12/114	0.44 (0.18, 1.12)	.08

CI = confidence interval, CYC = cyclophosphamide, MMF = mycophenolate mofetil, RR = relative risk.

with good efficacy in patients with LN.[39] 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 interracial 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

heterogeneous clinical outcomes. Eleven of the studies included only type IV patients,[15,18–20,24,25,28–31,33] while the remaining 7 included patients with III, IV, V, and combined types.[16,18,21–23,26,32] 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 (0.5–2.0 g/d) is more effective than CYC at achieving CR and TR. MMF is also associated with relatively low incidences of infections, amenorrhea, leukopenia, and alopecia.

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.

References

[1] Hou JH, Zhu HX, Zhou ML, et al. Changes in the spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China. Kidney Dis (Basel) 2018;4:10–9.

[2] Pan Q, Li Y, Ye L, et al. Geographical distribution, a risk factor for the incidence of lupus nephritis in China. BMC Nephrol 2014;15:67.

[3] Cattran DC, Feehally J, Cook HT, et al. Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int 2012;(Suppl 2):139–274.

[4] Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808.

[5] Bertsias GK, Tektonidou M, Amoura Z, et al. European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012; 71:1771–82.

[6] Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156–62.

[7] Appel GB, Contreras G, Dooley MA, et al. Aspreva Lupus Management Study GroupMycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009; 20:1103–12.

[8] Tang Z, Yang G, Yu C, et al. Effects of mycophenolate mofetil for patients with crescentic lupus nephritis. Nephrology (Carlton) 2008;13:702–7.

[9] Dooley MA, Jayne D, Ginzler EM, et al. ALMS GroupMycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886–95.

[10] Korbet SM, Schwartz MM, Evans J, et al. Collaborative Study GroupSevere lupus nephritis: racial differences in presentation and outcome. J Am Soc Nephrol 2007;18:244–54.

[11] Isenberg D, Appel GB, Contreras G, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology (Oxford) 2010;49:128–40.

[12] Mendoza-Pinto C, Pirone C, van der Windt DA, et al. Can we identify who gets benefit or harm from mycophenolate mofetil in systemic lupus erythematosus? A systematic review. Semin Arthritis Rheum 2017; 47:65–78.

[13] Zhu B, Chen N, Lin Y, et al. Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant 2007;22:1933–42.

[14] Moher D, Liberati A, Tetzlaff J, et al. PRISMA GroupPreferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[15] Chan TM, Tse KC, Tang CS, et al. Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16:1076–84.

[16] He QS, Zhang LY, Ma HJ, et al. Comparison study of mycophenolate mofetil and cyclophosphamide on refractory nephropathy syndrome. China Healthcare Innovation 2010;5:3–4.

[17] Li H. Efficacy of mycophenolate mofetil in treating diffuse proliferative lupus nephritis. Shanxi Med J 2004;204:160.

[18] Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant 2012; 27:1467–72.

[19] Liu GP, Huang JX, Lin L. Clinical study of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Chin J Integr Trad West Nephrol 2003;4:386–8.

[20] Lv X. Evaluation of the intervention effect of mycophenolate mofetil versus CTX regimen in the treatment of patients with lupus nephritis type IV. [In Chinese]. Med Inf 2015;28:194.

[21] Peng SH, Chen T, Chen Y. Mycophenolate mofetil versus cyclophosphamide in the treatment of lupus nephritis: A randomized controlled trial. Chin Gen Pract 2012;15:1722–4.

[22] Feng X, Gu F, Chen W, et al. Mizoribine versus mycophenolate mofetil or intravenous cyclophosphamide for induction treatment of active lupus nephritis. Chin Med J (Engl) 2014;127:3718–23.

[23] Qin Q. Comparison on clinical effect of mycophenolate mofetil and cyclophosphamide treatment of IV combined V type lupus nephritis. [In Chinese]. China Med Pharm 2016;6:92–4.

[24] Wang J, Hu W, Xie H, et al. Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide. Lupus 2007;16: 707–12.

[25] Zhang Y. The comparison of the efficacy from mycophenolate mofetil and cyclophosphamide in treatment of lupus nephritis IV. [In Chinese]. Mod Prev Med Changsha 2011;38:3842–4.

[26] Zhang H, Lin L, Fan L, et al. To compare the efficacy of mycophenolate mofetil and cyclophosphamide in the treatment of patients with type IV combined V lupus nephritis. [In Chinese]. Guide China Med 2015;13:78.

[27] The Cochrane Collaboration. C*ochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. In: Higgins JPT, Green S, eds. The Cochrane Collaboration; 2011.

[28] Jiang WG, Xiao X, Fang JA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative nephritis. Chin J Integr Trad West Nephrol 2002;3:218–21.

[29] Hu W, Liu Z, Chen H, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chin Med J (Engl) 2002;115:705–9.

[30] Zhu B, Zhou ZA, Liu ZD. Comparison of mycophenolate mofetil therapy versus cyclophosphamide treatment in diffuse proliferative lupus nephritis. J Shandong Univ (Health Sci) 2003;41:692–4.

[31] Shi J, Chen B, He X. Clinical efficacy of mycophenolate mofetil in the treatment of 26 patients with refractory type IV lupus nephritis. [In Chinese]. Negative 2006;27:1920.

[32] Liang DP, Huang YJ, Yang HB. Clinical study of mycophenolate mofetil plus prednisone in patients with lupus nephritis. Chin J Prim Med Pharm 2002;9:1060–2.

[33] Hu Y. Clinical efficacy of mycophenolate mofetil in the treatment of 39 cases of type IV lupus nephritis. [In Chinese]. Mod Diagn Treat 2014;25:340–1.

[34] Singh JA, Hossain A, Kotb A, et al. Comparative effectiveness of immunosuppressive drugs and corticosteroids for lupus nephritis: a systematic review and network meta-analysis. Syst Rev 2016;5:155.

[35] Palmer SC, Tunnicliffe DJ, Singh-Grewal D, et al. Induction and maintenance immunosuppression treatment of proliferative lupus nephritis: a network meta-analysis of randomized trials. Am J Kidney Dis 2017;70:324–36.
[36] Chen Y, Sun J, Zou K, et al. Treatment for lupus nephritis: an overview of systematic reviews and meta-analyses. Rheumatol Int 2017;37:1089–99.
[37] Tang KT, Tseng CH, Hsieh TY, et al. Induction therapy for membranous lupus nephritis: a systematic review and network meta-analysis. Int J Rheum Dis 2018;21:1163–72.
[38] Henderson LK, Masson P, Craig JC. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2013;61:74–87.
[39] Weng MY, Weng CT, Liu MF. The efficacy of low-dose mycophenolate mofetil for treatment of lupus nephritis in Taiwanese patients with systemic lupus erythematosus. Clin Rheumatol 2010;29:771–5.
[40] Mejia-Vilet JM, Arreola-Guerra JM, Cordova-Sanchez BM, et al. Comparison of lupus nephritis induction treatments in a Hispanic population: a single-center cohort analysis. J Rheumatol 2015;42: 2082–91.