Efficacy and Adverse Events of Mycophenolate Mofetil Versus Cyclophosphamide for Induction Therapy of Lupus Nephritis

Systematic Review and Meta-Analysis

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Abstract: We performed a systematic review and meta-analysis of randomized controlled trials to compare complete remission and adverse events (that is, infection, leukopenia, and gastrointestinal [GI] symptoms) between mycophenolate mofetil (MMF) and cyclophosphamide (CYC) for the treatment of lupus nephritis (LN). We identified trials from MEDLINE using the PubMed and Ovid search engines, and from The Cochrane Central Register of Randomized Controlled Trials. Eligible studies were randomized controlled trials comparing MMF with CYC with 1 of following outcomes: complete remission, complete/partial remission, infection, leukopenia, GI symptoms, serum creatinine, 24-hour urine protein, and urine albumin. Data were independently extracted by 2 reviewers. Five trials with a total of 638 patients were eligible for review. While the MMF group tended to achieve complete remission more frequently than the CYC group, this was not significant (pooled risk ratio [RR], 1.60; 95% confidence interval [CI], 0.87–2.93). Pooling based on the 4 homogeneous trials yielded similar results—that is, no benefit of MMF compared with CYC groups (RR, 1.15; 95% CI, 0.74–1.77). The complete or partial remission rates were also not different (pooled RR, 1.21; 95% CI, 0.97–1.48) among the groups. The adverse events (infection, renal function, and GI symptoms) were not significantly different, except for leukopenia, which was lower in the MMF group.

In summary, patients treated with MMF and CYC had similar remission rates, but the MMF group had less frequent leukopenia than the CYC group. Further large-scale trials are needed to confirm these results.

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Abbreviations: CI = confidence interval, CYC = cyclophosphamide, df = degree of freedom, GI = gastrointestinal, LN = lupus nephritis, MMF = mycophenolate mofetil, NNH = number needed to harm, NNT = number needed to treat, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RR = risk ratio, SE = standard error, SLE = systemic lupus erythematosus, SMD = standardized mean difference, WHO = World Health Organization.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of autoantibodies and immune complexes and the development of chronic inflammation. The disease has a prevalence of 1 case per 2000 persons; it predominately affects young women and is more common in African-Americans and Asians than in whites.[7] There is significant morbidity and mortality related to the disease itself or its treatment complications, and quality of life is often severely affected. Lupus nephritis (LN) is a common renal manifestation of the disease, with about 30% of patients with SLE developing nephritis by 3 years after diagnosis.[20] The immune system plays a major role in the pathogenesis of LN, with the production of autoantibodies leading to immune complex deposition in the kidneys;[12] this initiates an inflammatory response and results in lymphocyte and macrophage infiltration in the glomeruli.

There are 6 classes of LN.[24] These include minimal mesangial LN (World Health Organization [WHO] class I), mesangial proliferative LN (WHO class II), focal LN (WHO classes III), diffuse segmental (WHO class IV-S) or global LN (WHO class IV-G), membranous LN (WHO class V), and advanced sclerosing LN (WHO class VI). The severity of LN varies from minimal lesions to advanced sclerosis, which may progress to end-stage renal disease. Treatment of LN remains a challenge because of the heterogeneity of the disease and the unpredictable outcomes. The main treatment goal is disease remission, which is associated with longer patient survival[5] and reduced renal flares, chronic renal failure, and end-stage renal disease.

Cyclophosphamide (CYC) is an immunosuppressive drug that has been used for the treatment of class III-V LN. Previous researchers have found that a combination regimen of CYC and corticosteroids is more effective than corticosteroids alone, and this combination remains the current standard treatment.[3,6,15] Adverse effects of CYC, however, such as severe infection or ovarian failure, have been frequently reported,[8] and thus alternative immunosuppressive drugs such as azathioprine and mycophenolate mofetil (MMF) are increasingly used. The efficacy and adverse events of these drugs have been studied and reviewed. However, many trials[1,2,4,13,21] comparing MMF with CYC for induction therapy have a small sample size (for example, 20–140), and hence suffer from insufficient power. The small sample size has also limited subgroup analyses, making it difficult to identify which types of patients (for example by age, sex, baseline serum creatinine, 24-hour urine protein, and serum albumin) would receive more or less benefit from alternative agents. Previous reviews[9,10,16,17,19,22,25] did not consider other clinical outcomes such as serum creatinine, 24-hour urine protein, and serum albumin, and there have been few randomized trials for induction periods published since the last reviews. We therefore performed a systematic review and meta-analysis with

TABLE 1. Definitions and Outcome Measurements Used in Included Trials

Study First Author (ref.)	Complete Remission	Partial Remission	Infection	Leukopenia	GI Symptoms
Appel[1]	Normal serum creatinine, proteinuria ≤0.5 g/d, and inactive urinary sediment: WBC ≤5/HPF, RBC ≤5/HPF, dipstick <2, no RBC casts	Proteinuria/creatinine ratio to ≤3 if baseline ratio >3, or 50% decrease of ratio if baseline ratio ≤ 3, and stabilization (±25%) or improvement of serum creatinine at 24 wk	Nasopharyngitis, urinary tract infection	Did not describe	Diarrhea, nausea, vomiting, abdominal pain
Wang[23]	Normal serum creatinine and albumin, proteinuria ≤0.4 g/d, and urine RBC ≤10 × 104/mL	≥50% Decreased serum creatinine, ≥50% improvement of proteinuria, and serum albumin ≥3.0 g/dL	Herpes zoster	WBC <4 × 109/L	Did not describe
Ginzler[13]	Return to ±10% of serum creatinine, proteinuria, and urine sediment	50% Improvement in any of renal functions (serum creatinine, proteinuria, or urine sediment) without worsening of the rest (±10%)	Pneumonia, lung abscess, candidiasis, cellulitis, skin abscess, Herpes zoster/simplex, upper respiratory tract infection, urinary tract infection	Lymphocyte <0.8 × 109/L, neutrocyte <1 × 109/L	Nausea, vomiting bloating, epigastric pain, acute/chronic diarrhea, rectal bleeding
Ong[21]	Proteinuria <0.3 g/d and urinary RBC <10/HPF	Stable baseline serum creatinine (±20%) or reduced serum creatinine ≥20%, urinary RBC <10/HPF, and proteinuria <3 g/d if baseline >3 g/d or ≥50% reduced proteinuria or <1 g/d if baseline ≤3 g/d	Pneumonia, septicemia, Herpes zoster	WBC <3.5 × 109/L	Did not describe
Chan[4]	Proteinuria <0.3 g/d, normal serum albumin, and normal urinary sediment	≥ 50% Improvement in proteinuria (0.3–3 g/d) and serum albumin >3.0 g/dL	Herpes zoster	WBC <3.5 × 109/L	Did not describe

Abbreviations: HPF = high power field, RBC = red blood cells, WBC = white blood cells.

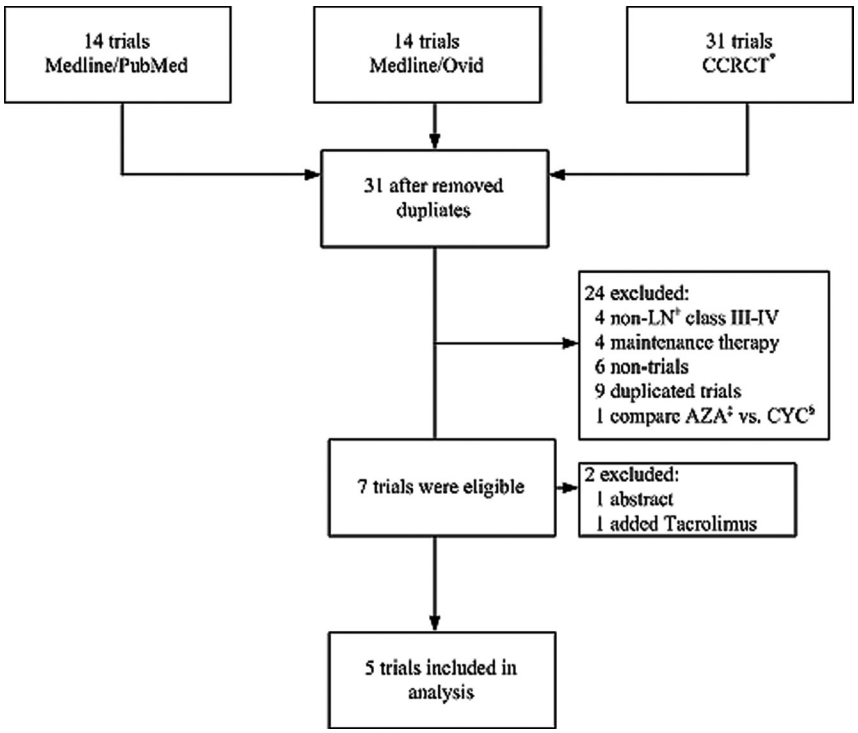

FIGURE 1. Flow diagram of trial selection. Abbreviations: *CCRCT = Cochrane Central Register of Randomized Controlled Trials, †LN = lupus nephritis, ‡AZA = azathioprine, §CYC = cyclophosphamide.

TABLE 2. Characteristics of Patients in Included Trials

Study Year	Intervention	N	% Withdrawal	Kidney Biopsy	Mean Age (yr)	% Female	Renal Function*			Follow-Up (mo)
							Serum creatinine (mg/dL)	24-h Urine Protein (g/d)	Serum albumin (g/L)	
Appel[1] 2009	MMF 1–3 g/d +steroids	185	17.3	Class III–V	31.90	84.60	1.14 ± 0.12	–	–	12
	IV CYC 0.75–1 g/m^2 + steroids	185								
Wang[23] 2007	MMF 1.5–2 g/d + steroids	9	0.0	Class IV with NNV	31.43	–	1.50 ± 0.53	4.10 ± 2.38	26.12 ± 5.03	6
	IV CYC 0.75–1 g/m^2 + steroids	11								
Ginzler[13] 2005	MMF 1–3 g/d + steroids	71	17.1	Class III–V	31.76	90.00	1.07 ± 0.51	4.25 ± 3.30	27.51 ± 7.58	6
	IV CYC 0.75–1 g/m^2 + steroids	69								
Ong[21] 2005	MMF 2 g/d + steroids	19	24.1	Class III–V	30.84	84.10	1.07 ± 0.44	2.48 ± 1.54	28.99 ± 6.82	6
	IV CYC 0.75–1 g/m^2 + steroids	25								
Chan[4] 2005	MMF 2 g/d + steroids	33	4.7	Class IV	39.89	81.25	1.27 ± 0.64	5.35 ± 3.87	27.55 ± 5.30	12
	Oral CYC 2.5 mg/kg per day + steroids	31								

Abbreviations: IV = intravenous, NNV = noninflammatory necrotizing vasculopathy.
*Mean ± SD.

the aims of comparing complete and partial remission, as well as adverse events (infection, leukopenia, and gastrointestinal [GI] symptoms) between MMF and CYC regimens. In addition, we compared other clinical outcomes (serum creatinine, 24-hour urine protein, and serum albumin). Patients and clinical factors were incorporated in analyses if data were available.

METHODS

Study Search and Selection

One reviewer (NK) electronically searched the MEDLINE database using PubMed (National Library of Medicine, Bethesda, MD) (1951 to December 2009) and Ovid (WoltersKluwer, New York, NY) (1966 to December 2009), and The Cochrane Central Register of Randomized Controlled Trials (CENTRAL—The Cochrane Library issue 4, 2009) (United States Cochrane Center, Baltimore, MD). Search terms used without language restriction were as follows: (mycophenolate mofetil or mycophenolate) and cyclophosphamide and (lupus nephritis or glomerulonephritis), limited to randomized controlled trial. (See Appendix for more details about the search strategies for each database).

Two reviewers (NK and AT) independently screened titles and abstracts. Trials with the following criteria were included: trial included adult patients (aged ≥18 yr) with WHO Class III–V LN; trial compared MMF plus corticosteroids with CYC plus corticosteroids for induction therapy; and trial reported outcomes as complete/partial remission, change in serum creatinine, proteinuria, or serum albumin. For trials with multiple publications, we selected the publication with the most complete information. Disagreements in selection were resolved by discussion and consensus.

Data Extraction and Risk Assessment

Two reviewers (NK and AT) independently performed data extraction. We extracted trial characteristics (for example, study design, sample size, treatment dosage and duration, WHO classification, renal biopsy information) and definitions (complete remission and complete/partial remission). We also extracted numbers of complete remission, complete/partial remissions, and numbers of adverse events between treatment groups. In addition, we extracted mean serum creatinine, 24-hour urine protein, and serum albumin after treatments whenever available.

Outcomes of interest for the current study were complete remission alone, complete or partial remission, and adverse events (for example, infection, leukopenia, and GI symptoms). In addition, continuous outcomes such as the change of serum creatinine, 24-hour urine protein, and serum albumin were considered. Definitions of these outcomes used in the original papers were extracted as described in Table 1.

Two independent reviewers (AI and AT) assessed risk of bias or methodologic quality of the included trials using Cochrane criteria and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[14,18] which considered adequate generation of randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and possible sources of other bias. Each item was judged as follows: "Yes" or adequate (low risk of bias) if that item was clearly described in detail for the method, "No" (high risk of bias) or inadequate if not described in adequate detail, or "Unclear" if a judgment could not make. Any disagreement was resolved by discussion and consensus.

Data Synthesis

For dichotomous outcomes, risk ratio [RR] with 95% confidence interval [CI] for each trial was estimated. Presence of heterogeneity between studies was assessed using the Cochran Q

TABLE 3. Risk of Bias of Included Trials*

Study	Adequate Sequence Generation	Adequate Allocation Concealment	Blinding	Address Incomplete Outcome Data	Selective Outcome Report	Free of Other Bias	Description of Other Bias
Appel[1]	Yes	Yes	Yes	Yes	Yes	Yes	
Wang[23]	No	Yes	Yes	Yes	Yes	Yes	
Ginzler[13]	Yes	Yes	Yes	Yes	Yes	Yes	
Ong[21]	Yes	Yes	Yes	Yes	Yes	No	Unbalance baseline proteinuria and ACEI/ARB used
Chan[4]	No	Yes	Yes	Yes	Yes	Yes	

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocking agents.
*Yes = low risk of bias; No = high risk of bias.

(heterogeneity chi-square), and I^2statistics. The random effects model (DerSimonian and Laird method) was applied for all pooling. To explore sources of heterogeneity, meta-regression was used to assess the association between lnRR of (complete/partial remissions) and covariables (for example, age, sex), baseline serum creatinine, 24-hour urine protein, and serum albumin. When the source of heterogeneity was detected, subgroup or sensitivity analysis was performed accordingly. Publication bias was explored using funnel plots and the Egger regression asymmetry test.

Finally, number needed to treat (NNT) or number needed to harm (NNH) was estimated for dichotomous outcomes. The number of patients who would experience disease recovery or be harmed by complications (for example, infection, leukopenia, and GI symptoms) was estimated if 100 patients were treated.

For continuous outcomes, mean differences of serum creatinine, 24-hour urine protein, and serum albumin between baseline and 6 months after induction period according to 2 treatment groups were summarized using standardized mean difference (SMD). The p value of < 0.05 was considered statistically significant except where the heterogeneity test $p < 0.10$ was used. All data were analyzed with STATA version 10.0 (StataCorp LP, College Station, TX).

RESULTS

We identified 59 publications from 3 databases, as summarized in Figure 1. Twenty-eight publications were removed due to duplication, which left 31 titles or abstracts screened. Twenty-four papers were excluded for reasons described in Figure 1, leaving 7 trials eligible for review.[1,2,4,11,13,21,23] Two of 7 trials were excluded: 1 was available only as an abstract[11] and contacting the author for additional data was unsuccessful; another trial[2] added tacrolimus in the MMF group, which also has an immunosuppressive effect. Five trials[1,4,13,21,23] were finally included in the analysis.

Trial characteristics are described in Table 2. All 5 trials compared remission at 6 and/or 12 months between MMF plus corticosteroids versus CYC plus corticosteroids. CYC was administered intravenously in 4 trials[1,13,21,23] and orally in 1 trial.[4]

The MMF and CYC dosages were adjusted according to various criteria, ranging from 1 to 3 g/d for MMF and 0.75–1 g/m^2 of body surface area for CYC. Mean age of patients in these trials ranged from 30.8 to 39.9 years, and most patients were female patients with biopsy-proven nephritis WHO class III–V. Serum creatinine at baseline was quite different across trials, ranging from 1.07 to 1.50 mg/dL. The 24-hour urine protein was quite similar (range, 4.10–5.35 g) except for 1 study[21] where this was lower than the other trials (mean, 2.48 g). This was also seen with serum albumin, which was similar across all trials (range, 26.12–28.99 g/L).

Risk assessment was performed following PRISMA guidelines[14,18] by 2 reviewers and is described in Table 3. The estimated level of agreement was moderately high (Kappa statistic = 0.62). Among the 5 trials, 2 trials[4,23] did not adequately describe the method of sequence generation, and 1 trial[21] might have bias from other sources—that is, imbalance in baseline proteinuria and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker.

Complete Remission

Five trials[1,4,13,21,23] (n = 638 patients) reported complete remission between MMF (n = 317) and CYC (n = 323) groups and thus were included in pooling treatment effects (Table 4). The included treatment effects (RRs) were heterogeneous (I^2 = 59.2%, chi-square = 9.80 [degree of freedom {df} = 4], p = 0.044), and thus the DerSimonian and Laird method was applied for pooling. The pooled RR for complete remission was 1.60 (95% CI, 0.87–2.93), which slightly favored MMF although this did not reach statistical significance (Figure 2). We explored the possible source of heterogeneity using meta-regression by fitting mean age, percentage of female patients, baseline serum creatinine, 24-hour urine protein, and serum albumin into the meta-regression model one by one. This suggested that only the percentage of female patients could explain heterogeneity by reducing I^2 to be 0, though its coefficient was not significant (coefficient = 0.47, standard error [SE] = 0.33, p = 0.232). The trial by Ginzler et al[13] had 90% female patients, which is higher than the other 4 trials (81%–85%). We thus performed a sensitivity analysis with the 4 trials with lower percentages of female patients. The pooled effect was less heterogeneous (chi-square = 4.11 [df = 3], p = 0.250, I^2= 26.9%) with a pooled RR of 1.15 (95% CI, 0.74–1.77). This could be interpreted to mean that MMF had approximately 15% higher benefit, but the chance could be from 26% lower to 77% higher benefit compared with CYC group. Using the Egger test on the 5 trials, we found borderline evidence of bias (coefficient = 2.03, SE = 0.64, p = 0.049) from the small study effects. We then performed a funnel plot study, which suggested that the trial by Ginzler et al[13] lay outside the pseudo 95% CI and might be the cause of heterogeneity or bias (Figure 3). Eliminating that trial yielded nonsignificant coefficient of bias (coefficient = 1.56, SE = 0.38, p = 0.054).

TABLE 4. Frequencies Between Treatments and Outcomes and Estimated Treatment Effects

			Outcome			
Remission	**Study**	**Treatment**	**Yes**	**No**	**RR**	**95% CI**
Complete remission	Appel[1]	MMF	16	169	1.07	0.54–2.09
		CYC	15	170		
	Wang[23]	MMF	4	5	10.80	0.66–177.34
		CYC	0	11		
	Ginzler[13]	MMF	16	55	3.89	1.37–11.05
		CYC	4	65		
	Ong[21]	MMF	5	14	2.19	0.60–8.06
		CYC	3	22		
	Chan[4]	MMF	24	9	0.98	0.73–1.32
		CYC	23	8		
Pooled RR					1.60	0.87–2.93
Complete/partial remission	Appel[1]	MMF	104	81	1.06	0.88–1.28
		CYC	98	87		
	Wang[23]	MMF	6	3	2.44	0.84–7.13
		CYC	3	8		
	Ginzler[13]	MMF	37	34	1.71	1.12–2.61
		CYC	21	48		
	Ong[21]	MMF	13	6	1.56	0.91–2.66
		CYC	11	14		
	Chan[4]	MMF	32	1	1.00	0.92–1.09
		CYC	30	1		
Pooled RR					1.20	0.97–1.48
			Outcome			
Adverse Events	**Study**	**Treatment**	**Yes**	**No**	**RR**	**95% CI**
Infection	Appel[1]	MMF	126	59	1.14	0.97–1.32
		CYC	111	74		
	Wang[23]	MMF	1	8	3.60	0.16–79.01
		CYC	0	11		
	Ginzler[13]	MMF	4	67	0.35	0.12–1.06
		CYC	11	58		
	Ong[21]	MMF	6	13	1.32	0.50–3.44
		CYC	6	19		
	Chan[4]	MMF	4	29	0.31	0.11–0.87
		CYC	12	19		
Pooled RR					0.77	0.39–1.49
Leukopenia	Wang[23]	MMF	0	9	0.28	0.02–5.22
		CYC	2	11		
	Ginzler[13]	MMF	19	52	0.64	0.40–1.02
		CYC	29	40		
	Ong[21]	MMF	7	12	0.71	0.35–1.43
		CYC	13	12		
Pooled RR					0.65	0.44–0.96
GI symptoms	Appel[1]	MMF	113	72	0.94	0.81–1.10
		CYC	2	18		
	Wang[23]	MMF	0	9	0.13	0.01–2.19
		CYC	4	7		
	Ginzler[13]	MMF	38	33	1.37	0.95–1.97
		CYC	27	42		
	Chan[4]	MMF	3	30	2.82	0.31–25.68
		CYC	1	30		
Pooled RR					1.09	0.74–1.60

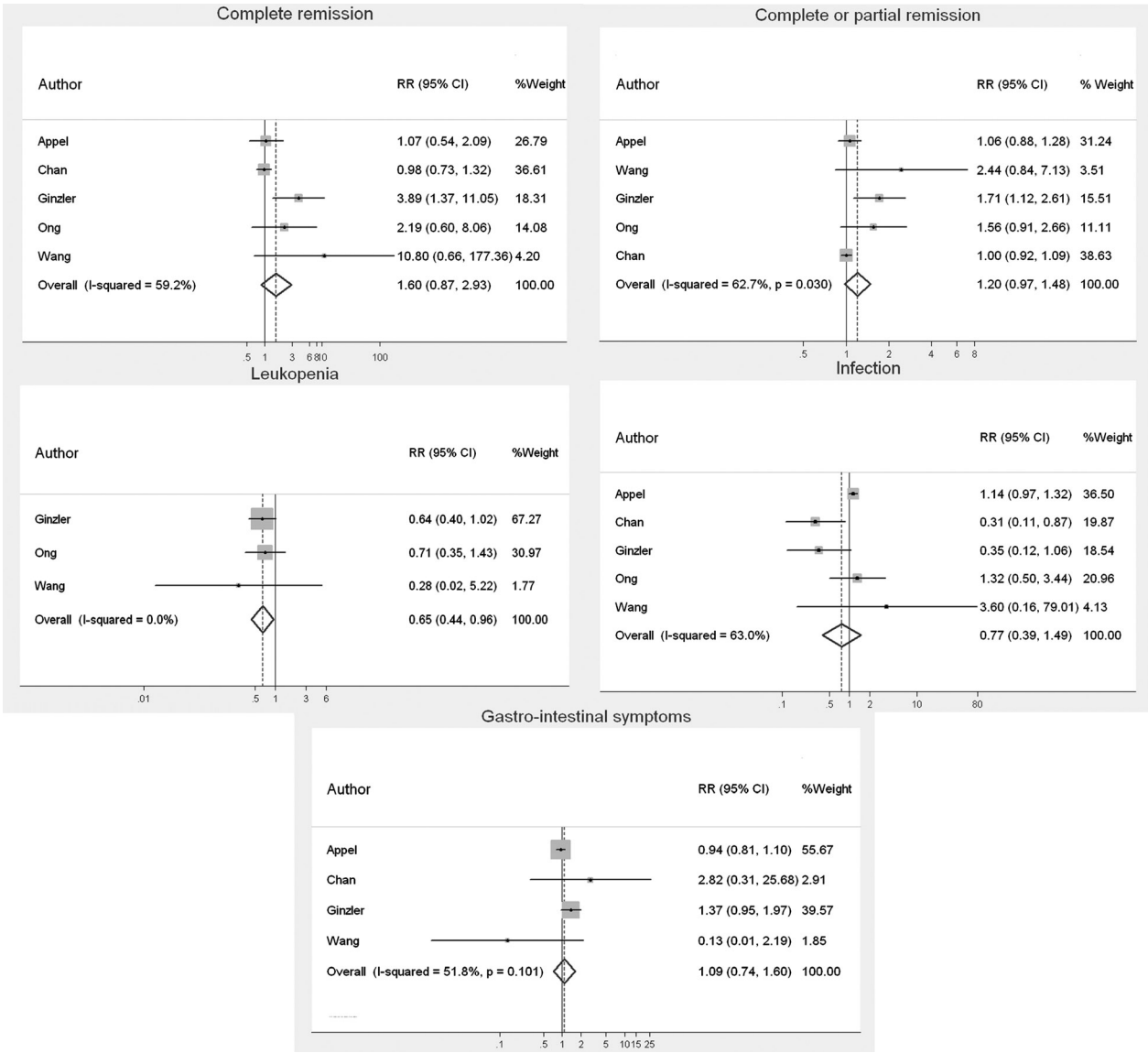

FIGURE 2. Forest plots of remission and adverse outcomes. Abbreviations: *RR = relative risk, †CI = confidence interval.

Complete or Partial Remission

All 5 trials[1,4,13,21,23] (n = 638) included complete or partial remission outcomes (Table 4). There was evidence of heterogeneity among these trials (I^2 = 62.7%, chi-squared = 10.72 [df = 4], p = 0.030). The pooled RR was 1.20 (95% CI, 0.97–1.48), which indicated that complete or partial remission was not significantly different between 2 groups (Figure 2).

Adverse Outcomes

Adverse outcomes (infection, leukopenia, and GI symptoms) are described in Table 4. All 5 trials[1,4,13,21,23] (n = 638) reported data for infection. Treatment effects on infection were heterogeneous (chi-square = 10.8 [df = 4], p = 0.029, I^2 = 63.0%), and the pooled RR was 0. 77 (95% CI, 0.39–1.49). The MMF group tended to have lower infection than the CYC group, but this effect was not significant. Three trials[4,13,23] (n = 206 patients) were included in pooling for leukopenia. These trials

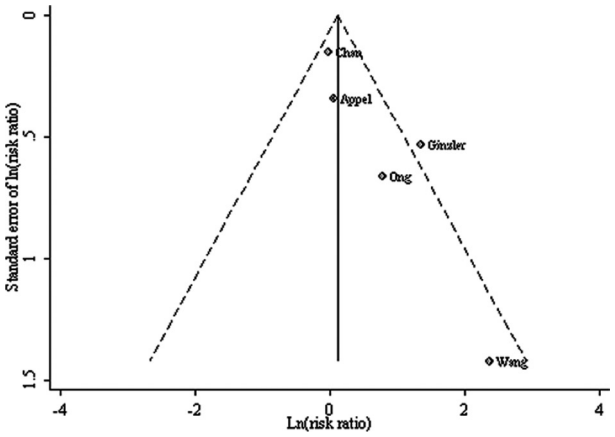

FIGURE 3. Funnel plot of complete remission.

TABLE 5. Estimation of Number Needed to Treat and Number Needed to Harm According to Outcome

	NNT/NNH	
Outcome	**Point Estimate**	**95% CI**
Complete remission		
Complete remission	NNT = 10	NNH = −47, NNT = 3
(excluding Ginzler et al trials)	NNT = 28	NNH = −16, NNT = 5
Complete or partial remission	NNT = 10	NNH = −76, NNT = 4
Infection	NNH = −15	NNH = −6, NNT = 7
Leukopenia	NNH = −9	NNH = −6, NNH = −74
GI symptoms	NNT = 32	NNH = −11, NNT = 5

were homogeneous (chi-square = 0.38 [df = 1], p = 0.825, I^2 = 0%) and the pooled RR was 0.65 (95% CI, 0.44–0.96) (Figure 2). This suggests that leukopenia occurred significantly less frequently in patients treated with MMF compared with CYC. Four trials[1,4,13,23] (n = 594) were included in pooling for GI symptoms; GI symptoms were not significantly different between the 2 groups (pooled RR, 1.09; 95% CI, 0.74–1.60). Only 2 trials[4,13] (n = 179 patients) reported ovarian failures, and data were not sufficient to pool.

Number Needed to Treat/Number Needed to Harm

The NNT/NNH for each outcome was estimated as described in Table 5. For complete remission, the NNT for all 5 trials was 10 (95% CI: NNH = −47, NNT = 3), indicating that if 100 patients were treated with MMF instead of CYC, 10 extra patients would experience complete remission. Excluding the trial by Ginzler et al[13] that caused heterogeneity and/or publication bias resulted in an NNT of 28 (95% CI: NNH 16, NNT 5), that is, only 4 extra patients would experience complete remission for every 100 patients treated with MMF. The NNT for complete or partial remission was similar to that for complete remission alone. The NNH for infection and leukopenia were −15 (95% CI: NNH −6, NNT 7) and −9 (95% CI: NNH −6, NNH −74), respectively. This indicates that 7 and 11 fewer patients suffer from infection and leukopenia respectively for every 100 patients treated with MMF.

Renal Function

Renal function after the induction period is summarized in Table 6. Three trials[13,21,23] (n = 174) reported serum creatinine after induction therapy. There was no heterogeneity among these trials (I^2 = 0%, chi-square = 0.14, p = 0.933). Applying the SMD method for pooling suggested a statistically not significant pooled SMD of 0.21 (95% CI, −0.09 to 0.51). Three trials[13,21,23] (n = 204) were included in pooling for mean 24-hour urine protein and mean serum albumin. There was evidence of heterogeneity in 24-hour urine protein and serum albumin; I^2 was 76.9% and 38.9%, chi-square was 8.65 (p = 0.013) and 3.27 (p = 0.195), respectively. The pooled SMDs of 24-hour urine protein and serum albumin were −0.31 (95% CI, −1.32 to 0.69) and 0.78 (95% CI, −0.92 to 2.45), respectively, which were not statistically significant (Table 6).

DISCUSSION

In the current updated systematic review, we have summarized current evidence of clinical outcomes and side effects of MMF and CYC for induction therapy of LN. Our results suggest a potential small advantage of MMF over CYC in complete remission or partial remission, although the results are not significant. Only 1 adverse effect, leukopenia, was significantly less frequent (35% lower) in patients treated with MMF instead of CYC; infection and GI symptoms were similar. Renal function (that is, serum creatinine, 24-hour urine protein, and serum albumin) after induction therapy was also similar between the MMF and CYC groups. Results were consistent after excluding 1 trial[13] that caused heterogeneity or publication bias.

The current review provides more complete evidence than previous reviews[9,10,16,19,22,25] for a number of reasons. First, we considered more relevant outcomes (that is, complete remission, partial remission, leukopenia, infection, GI symptoms, serum creatinine, 24-hour urine protein, and serum albumin) than previous reviews. Also, some data in the review by Mak et al[17] were extracted from abstracts, and thus risk of biases in these studies could not be fully assessed. NNT and NNH for these dichotomous outcomes were also estimated and reported. The current review included a greater number of trials with a larger sample size than previous reviews. Finally, in this review we explored possible causes of heterogeneity and publication bias, and excluded a suspected trial which yielded consistent results of treatment effects on complete remission.

Despite the improvements made in the current review, there may be some limitations. Although all the randomized controlled trials included here are fairly similar in baseline characteristics of patients, definitions of complete and partial remission, and duration of follow-up, there were a few differences that might introduce bias in our analysis. For example, drug dosages and adjustment (dosages of MMF = 1–3 g/d, dosages of intravenous

TABLE 6. Mean Difference and Estimated Standardized Mean Difference for Continuous Outcomes

		Serum Creatinine (mg/dL)					24-h Urine Protein (g)				Serum Albumin (g/L)			
Study	**Treatment**	**N**	**Mean**	**SD**	**SMD**	**95% CI**	**Mean**	**SD**	**SMD**	**95% CI**	**Mean**	**SD**	**SMD**	**95% CI**
Wang[23]	MMF	8	0.94	0.23	0.33	−0.63 to 1.29	1.35	1.60	–0.59	−1.56 to 0.39	40.00	2.40	0.54	−0.44 to 1.51
	CYC	9	0.85	0.30			2.20	1.30			38.00	4.60		
Ginzler[13]	MMF	62	0.91	0.25	0.23	−0.14 to 0.59	2.03	2.79	0.26	−0.11 to 0.62	34.20	4.20	−0.06	−0.42 to 0.31
	CYC	54	0.85	0.28			1.46	1.27			34.40	2.50		
Ong[21]	MMF	17	1.24	1.90	0.13	−0.49 to 0.75	1.10	0.60	−0.66	−1.30 to -0.02	36.70	4.30	0.40	−0.23 to 1.02
	CYC	24	1.07	0.70			1.90	1.50			34.50	6.30		
Pooled SMD					0.21	−0.09 to 0.51	Pooled SMD		−0.31	−1.31 to 0.69	Pooled SMD		0.78	−0.92 to 2.48

Abbreviations: SD = standard deviation.

CYC = 0.75–1 g/m^2 of body surface area) and routes of administration (oral vs. intravenous CYC) differed among some trials and might contribute to heterogeneity of treatment effects. Performing a meta-analysis of summary data, we were not able to explore what dosages or routes of administration were most beneficial, nor to adjust for these differences. To do this, individual patient data are required.

In summary, results of the current review suggest that there are insufficient data to distinguish a statistical difference in efficacy between MMF and CYC on complete remission, complete/partial remission, infection, and GI symptoms, but there is a definite decreased risk of leukopenia with MMF. Further large scale trials are needed to confirm these results.

APPENDIX: SEARCH STRATEGIES

A. Search strategies: MEDLINE (PubMed)

("mycophenolate mofetil"[All Fields] OR mycophenolate [All Fields]) AND ("cyclophosphamide" [MeSH Terms] OR "cyclophosphamide" [All Fields] OR "Azathioprine" [All Fields]) AND (("lupus nephritis [MeSH Terms] OR ("lupus" [All Fields] AND "nephritis" [All Fields]) OR "lupus nephritis" [All Fields]) OR ("glomerulonephritis" [MeSH Terms] OR "glomerulonephritis" [All Fields])) AND "randomized controlled trial" [Publication Type].

B. Search Strategies: MEDLINE (Ovid)

1. Mycophenolate mofetil.af.
2. Mycophenolate.af.
3. Cyclophosphamide.af.
4. Azathioprine.af.
5. Lupus Nephritis.af.
6. Glomerulonephritis.af.
7. 1 and 5
8. 6 and 1
9. 2 and 5
10. 6 and 2
11. 3 and 5
12. 6 and 3
13. 4 and 5
14. 6 and 4
15. 3 and 7
16. 8 and 3
17. 3 and 9
18. 3 and 10
19. 1 and 13
20. 1 and 14
21. 13 and 2
22. 2 and 14
23. 22 or 21 or 18 or 19 or 16 or 17 or 20 or 15
24. limit 23 to randomized controlled trial

C. Search Strategies: CENTRAL (Issue 4, 2009) Cochrane Central Register of Controlled Trials

#1 (Mycophenolate mofetil):ti,ab,kw
#2 (Mycophenolate):ti,ab,kw
#3 (Cyclophosphamide):ti,ab,kw
#4 (Azathioprine):ti,ab,kw
#5 (Lupus Nephritis):ti,ab,kw
#6 (Glomerulonephritis):ti,ab,kw
#7 (#1 AND #5)
#8 (#1 AND #6)
#9 (#2 AND #5)
#10 (#2 AND #6)
#11 (#3 AND #5)
#12 (#3 AND #6)
#13 (#4 AND #5)
#14 (#4 AND #6)
#15 (#3 AND #7)
#16 (#3 AND #8)
#17 (#3 AND #9)
#18 (#3 AND #10)
#19 (#4 AND #7)
#20 (#4 AND #8)
#21 (#4 AND #9)
#22 (#4 AND #10)
#23 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

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