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Original Investigation

Induction and Maintenance Treatment of Proliferative Lupus Nephritis: A Meta-analysis of Randomized Controlled Trials

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Background: Lupus nephritis accounts for ~1% of patients starting dialysis therapy. Treatment regimens combining cyclophosphamide with steroids preserve kidney function but have significant side effects. Newer immunosuppressive agents may have improved toxicity profiles.

Study Design: Systematic review and random-effects meta-analysis, searching MEDLINE (1966 to April 2012), EMBASE (1988-2011), and the Cochrane Renal Group Specialised Register.

Setting & Population: Patients with biopsy-proven proliferative lupus nephritis (classes III, IV, V+III, and V+IV).

Selection Criteria: Randomized controlled trials.

Intervention: Immunosuppressive treatment regimens used for induction and maintenance therapy of lupus nephritis.

Outcomes: Mortality, renal remission and relapse, doubling of creatinine level, proteinuria, incidence of end-stage kidney disease, ovarian failure, alopecia, leukopenia, infections, diarrhea, vomiting, malignancy, and bladder toxicity.

Results: 45 trials (2,559 participants) of induction therapy and 6 (514 participants) of maintenance therapy were included. In induction regimens comparing mycophenolate mofetil (MMF) with intravenous cyclophosphamide, there was no significant difference in mortality (7 studies, 710 patients; risk ratio [RR], 1.02; 95% CI, 0.52-1.98), incidence of end-stage kidney disease (3 studies, 231 patients; RR, 0.71; 95% CI, 0.27-1.84), complete renal remission (6 studies, 686 patients; RR, 1.39; 95% CI, 0.99-1.95), and renal relapse (1 study, 140 patients; RR, 0.97; 95% CI, 0.39-2.44). MMF-treated patients had significantly lower risks of ovarian failure (2 studies, 498 patients; RR, 0.15; 95% CI, 0.03-0.80) and alopecia (2 studies, 522 patients; RR, 0.22; 95% CI, 0.06-0.86). In maintenance therapy comparing azathioprine with MMF, the risk of renal relapse was significantly higher (3 studies, 371 patients; RR, 1.83; 95% CI, 1.24-2.71).

Limitations: Heterogeneity in interventions and definitions of remission and lack of long-term outcome reporting.

Conclusions: MMF is as effective as cyclophosphamide in achieving remission in lupus nephritis, but is safer, with a lower risk of ovarian failure. MMF is more effective than azathioprine in maintenance therapy for preventing relapse, with no difference in clinically important side effects.

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INDEX WORDS: Lupus nephritis; systemic lupus erythematosus (SLE); proliferative glomerulonephritis; systematic review; meta-analysis; cyclophosphamide (CYC); mycophenolate mofetil (MMF).

Lupus nephritis occurs in about half the people with systemic lupus erythematosus, leading to end-stage kidney disease in 5%-10% at 10 years.[1] The most common secondary glomerulonephritis leading to end-stage kidney disease,[2] lupus nephritis accounts for 1% of incident renal replacement therapy patients.[3] Young women and African Americans predominantly are affected and also may have a more aggressive and less responsive form of the disease.

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Diagnosis of lupus nephritis requires kidney biopsy to allow histologic classification according to the joint World Health Organization (WHO), International Society of Nephrology, and Renal Pathology Society (ISN/RPS) criteria. Patients with ISN/RPS 2003 class I and II lesions have a good prognosis and typically, no specific treatment is indicated. Proliferative disease (WHO classes III, IV, and mixed pictures of III+V and IV+V) is more fulminant and therapy must be more aggressive to achieve remission and avoid substantial kidney injury and premature death. WHO class IV lupus nephritis is the most aggressive and has the worst prognosis, with reported 5-year survival of 17% without intensive immunosuppressive treatment.[4] Treatment of lupus nephritis typically involves an intensive induction of remission phase (induction therapy) followed by a less intensive maintenance phase.

Cyclophosphamide-containing regimens, usually with concomitant corticosteroids, were established as first-line therapy for inducing disease remission and have improved survival to >90%.[1,4,5] However, response to treatment often is slow, and although remission is induced in a significant proportion of patients, risk of relapse remains considerable, variably reported at 18%-46%.[6] Treatment also is associated with risks and side effects, including alopecia, gastrointestinal symptoms, bladder toxicity, infections, ovarian failure, and malignancy. The incidence of ovarian failure is reported at 17%-100%, depending on recipient age and total cumulative cyclophosphamide dose.[7]

In 2004, we conducted a systematic review of immunosuppressive treatment of proliferative lupus nephritis.[8,9] Subsequently, numerous trials have been published evaluating newer agents: mycophenolate mofetil (MMF), tacrolimus, and rituximab, all proposed as alternative, potentially less toxic, and more effective therapies.[10-22] The aim of our study was to evaluate the relative effects of newer versus established immunosuppressive therapies for the induction and maintenance treatment of lupus nephritis.

METHODS

Protocol

Methodology is reported according to PRISMA guidelines. The protocol for this systematic review (registration number CD002922) can be found at the Cochrane Renal Group Website.

Inclusion Criteria

We included randomized controlled trials (RCTs) and quasi-RCTs, whether published or unpublished, that evaluated any of the following treatment options, alone or in combination: corticosteroids, cyclophosphamide, MMF, tacrolimus, rituximab, azathioprine, cyclosporine, plasma exchange, and intravenous (IV) gamma globulins. Only trials enrolling patients with biopsy-proven lupus nephritis classes III, IV, V+III, and V+IV were included.

Search Strategy

MEDLINE (1966 to April 2012), EMBASE (1988-2011), and The Cochrane Renal Group Specialised Register were searched for identification of relevant RCTs. The following medical subject heading terms and text words were used: lupus nephritis, proliferative glomerulonephritis, membranous glomerulonephritis (to identify studies including patients with active proliferative and membranous lupus nephritis), and systemic lupus erythematosus. Relevant text words relating to eligible interventions also were searched.

Data Extraction and Risk of Bias

Two reviewers working independently assessed each trial, with disagreements resolved in consultation with a third investigator. Data were extracted for the following outcomes: all-cause mortality; renal indexes (end-stage kidney disease, relapse, doubling of serum creatinine level, deterioration in kidney function [>20% worsening of serum creatinine], stability in kidney function [<20% worsening of serum creatinine], complete and partial renal remission [defined respectively as return to normal serum creatinine level, urinary protein excretion <0.5 g/24 h, inactive urinary sediment, and a decrease to <3.0 g/24 h protein excretion if baseline ≥3.0 g/24 h or ≥50% reduction if <3.0 g/24 h at baseline, and stabilization of serum creatinine ±25%][10]); remission in proteinuria (both complete and partial remission); serum creatinine level; creatinine clearance (milliliters per minute); daily proteinuria (grams per 24 hours); and treatment-related side effects (ovarian failure [sustained amenorrhea], major infection, herpes zoster infection, bone toxicity [avascular necrosis or fracture], bladder toxicity [hemorrhagic cystitis], development of any malignancy, alopecia, leukopenia [leukocytes $<4 \times 10^9$/L], and adverse gastrointestinal effects, including diarrhea, nausea, and vomiting).

Risk of bias of the included RCTs was assessed using the standard domains defined by the Cochrane risk-of-bias tool.[23] When data were missing or incomplete, investigators of the trials were contacted for clarification.

Statistical Analysis

Results of meta-analysis were expressed as risk ratios (RRs) for dichotomous outcomes and mean differences for continuous outcomes, both with 95% confidence intervals (CIs). Heterogeneity was analyzed using a Cochran Q test (n−1 *df*), with $P < 0.05$ denoting statistical significance and I^2 measuring the proportion of variation in estimates of effect due to heterogeneity beyond chance.[24] A random-effects model was used to provide more conservative estimates of effect in the presence of known or unknown heterogeneity.[25] Planned evaluation of potential sources of heterogeneity by subgroup analysis and metaregression was not possible due to the small numbers of trials within each intervention comparison.

RESULTS

Literature Search

We identified 124 reports (1,929 participants) with which to update the 2004 review (Fig 1). Thirty-two were new reports of studies already included in the original review (22 new patients previously unreported) and 92 were reports of 25 new studies (1,909 participants). There were 45 trials of induction therapy (2,559 participants) and 6 trials of maintenance therapy (514 participants, 227 of whom participated in a 2-phase induction and maintenance trial). This brought

DATABASE SEARCH		
REVIEW 2004	UPDATE 2012	
	MEDLINE	8
	EMBASE	7
	COCHRANE RENAL SPECIALIZED REGISTER	219
920	TOTAL	234

Excluded 884

36 **INCLUDED FOLLOWING FULL TEXT REVIEW** 124

Excluded 99

Ongoing trials 11

REVIEW 2004 36 Reports of 25 trials		
INTERVENTION	**TRIALS**	**PARTICIPANTS**
INDUCTION:	***23***	***861***
MMF vs CYC	1	42
High vs low dose CYC	1	90
Long vs short course CYC	1	65
CYC +/- steroid vs steroid	6	200
CYC or Aza + steroid vs steroid	1	111
Aza +/- steroid vs steroid	3	94
CsAvs steroid	1	10
PEX + IS vs IS	5	173
IV vs oral steroid	1	22
PEX vs IS	2	40
Misoprostol + steroid vs steroid	1	14
MAINTENANCE:	***2***	***54***
CYC vsIVIg	1	14
CYC vsCsA	1	40
TOTAL	**25**	**915**

UPDATE 2012 124 Reports 92 reports of 25 new trials 32 new reports of previously included trials‡		
INTERVENTION	**TRIALS**	**PARTICIPANTS**
INDUCTION	***22***	***1676***
MMF vs CYC	6	680
Azavs CYC	1	59
Tacrovs CYC	2	106
Tacrovs MMF	1	109
CYC vsCsAvsAza	1	22
CYC vs MMF vsTacro	2	100
Rituximabvs steroid	1	144
Rituximabvs CYC	1	19
IV vs PO CYC	1	32
CYC vsCsA	2	74
High vs low dose steroid	1	81
High vs low dose CYC	2	163
IV CYC + PO steroid vs IV steroid + Aza	1	87
MAINTENANCE:	***4****	***460****
MMF vsAza or CYC**	3**	391**
AzavsCsA	1	69
TOTAL	**25**	**1909**

TOTAL 160 reports of 50 trials, 2846 participants		
INTERVENTION	**TRIALS**	**PARTICIPANTS**
INDUCTION:	***45***	***2559***
MMF vs CYC*†	7	744
MMF vsTac	1	109
High vs low dose CYC	3	253
IV vs PO CYC	1	32
Long vs short CYC	1	65
IV vs PO steroid	1	22
IV CYC + PO steroid vs IV steroid + Aza	1	87
Aza, Tac or CsAvs CYC	5	239
CYC or Aza or CsA +/- steroid vs steroid	11	415
Rituximabvs steroid	1	144
Rituximabvs CYC	1	19
PEX + IS vs IS	5	173
PEX vs IS	2	40
Misoprostol + steroid vs steroid	1	14
High vs low dose steroid	1	81
CYC vsCsAvsAza	1	22
CYC vs MMF vsTacro	2	100
MAINTENANCE:	***6****	***514****
MMF vsAza or CYC**	3**	391**
AzavsCsA	1	69
CYC vsIVIg	1	14
CYC vsCsA	1	40

Figure 1. Inclusion and exclusion of search results. Abbreviations: ALMS, Aspreva Lupus Management Study; Aza, azathioprine; CsA, cyclosporine; CYC, cyclophosphamide; IV, intravenous; IVIg, intravenous immunoglobulin; LN, lupus nephritis; MMF, mycophenolate mofetil; PEX, plasma exchange; PO, oral; Tac, tacrolimus. **Includes continuation of 227 induction patients to maintenance phase of ALMS 2009. ‡Further data published for 22 new patients to Chan 2000 study[26] since 2004 review.

Table 1. Summary of Included Studies

Trial	WHO/ISN Classification	N	Randomized Intervention[a]	Intervention Duration (mo)	F/U (mo)
			Induction Trial: MMF vs Other IS Agent		
Chan[26] (2000)[b]	IV-S, IV-G	64	MMF (2 g/d) vs oral CYC (2.5 mg/kg/d)	24	23
Ginzler[19] (2005)[b]	III, IV, V	140	MMF (3 g/d) vs IV CYC (0.5-1 g/m^2/mo)	6	6
Ong[27] (2005)[b]	III, IV	54	MMF (2 g/d for 6 mo) vs IV CYC (0.75-1 g/m^2/mo)	6	6
Mullic-Bacic[28] (2008)[b]	III, IV, V	45	MMF (2 g/d for 6 mo then 1 g/d for 18 or 12 mo) vs IV CYC (0.5-1 g/m^2/mo)	24	6
Sundel[12] (2008)[b]	III, IV, V	24	MMF (3 g/d) vs IV CYC (0.5-1 g/m^2/mo)	24	6
Li X[15] (2009)[b]	III, IV, V, or combination	60	MMF (1.5-2 g/d) vs Tac (0.08-0.1 mg/kg/d) vs IV CYC (0.5-0.75 g/m^2/mo)	24	6
Appel[16] (2009)[b]	III, IV, V, III+V, IV+V	370	MMF (3 g/d) vs IV CYC (0.5-1 g/m^2/mo)	6	6
Mok[13] (2009)[b]	III, IV-G+S, V, V+IV/III	109	MMF (2-3 g/d) then Aza (2 mg/kg/d) vs Tac (0.06-0.1 mg/kg/d) then Aza (2 mg/kg/d)	6	30
El-Shafey[29] (2010)[b]	III, IV	47	MMF (2 g/d) vs IV CYC (0.5-1 g/m^2/mo)	6	6
			Induction Trial: MMF + Tac vs Other IS Agent		
Bao[17] (2008)[b]	IV+V	40	MMF (2 g/d) + Tac (4 mg, 2×/d) vs IV CYC (0.75 g/m^2, then 0.5-1.0 g/m^2)	6-9	6-9
			Induction Trial: CYC vs Other IS Agent		
Steinberg[30] (1971)	—	15	Oral CYC + oral steroids vs oral steroids	2.5	3
Fries[31] (1973)	—	10	CYC vs oral steroids	—	39
Ginzler[32] (1976)	DPLN	12	CYC + Aza vs Aza + oral steroid	—	6
Donadio[33] (1978)	DPLN	50	Oral CYC (2 mg/kg/d) vs oral steroid	—	4
Austin[34] (1986)	DPLN	101	Oral CYC (up to 4 mg/kg/d) vs oral CYC + Aza (1 mg/kg/d) vs IV CYC (0.5-1 g/m^2 every 3 mo) vs oral steroid (1 mg/kg/d) vs Aza (up to 4 mg/kg/d) + oral steroid	—	75
Sesso[35] (1994)	—	29	IV CYC (0.5-1 g/m^2/d) vs IV methylprednisolone	14	15
Gourley[36] (1996)	III, IV	82	IV CYC (monthly for 6 or 12 mo, every 3 mo for 24 or 12 mo) vs IV methylprednisolone + IV CYC vs IV methylprednisolone (×3, then monthly for 12 mo)	>12	>60
Lui[37] (1997)[b]	IV	34	Oral CYC (1 mg/kg/d) + Aza (1 mg/kg/d) vs CsA (5 mg/kg/d) + Aza (1 mg/kg/d)	24	12
Adam[38] (2004)[b]	III, IV, Vc, Va, b, V	22	IV CYC (0.75 g/m^2/mo) vs CsA (1-2 mg/kg/d) vs Aza (1-2 mg/kg/d)	6	6
Grootscholten[10] (2006)[b]	IV, Vd	87	IV CYC (0.75 g/m^2 bimonthly) vs methylprednisolone (1 g, ×3) + Aza (2 mg/kg/d)	24	69
Dyadyk[39] (2007)	IV	59	Oral CYC (1.5-3.5 mg/kg/d) vs Aza (1.5-2 mg/kg/d)	22	120
Hong[40] (2007)[b]	IV	25	IV CYC (0.5-0.75 g/m^2/mo) vs Tac (0.1 mg/kg/d)	6	6
Chen[41] (2011)[b]	III, IV-S, IV-G(a) or (A/C), V, V+III, V+IV	81	IV CYC (0.75 g/m^2/mo) vs Tac (0.05 mg/kg/d, trough 5-10 ng/mL)	6	6
			Induction Trial: CYC Dose Comparison		
Houssiau[42] (2002)[b]	III, IV, Vc, d	90	IV CYC (0.5-1.5 g 6 monthly pulses then 2 quarterly pulses) then Aza (2 mg/kg/d) vs IV CYC (0.5 g 6 fortnightly pulses) then Aza (2 mg/kg/d)	30	42
Sabry[43] (2009)[b]	IV	46	IV CYC (0.5 g/mo for 6 mo, then 2× quarterly) vs IV CYC (1g, ×6, then 2× quarterly)	—	1
Mitwali[44] (2011)[b]	IV	117	IV CYC (10 mg/kg/mo for 6 mo, bimonthly for 12 mo) then Aza (1 mg/kg/d for 246 fortnightly pulses mo) vs IV CYC (5 mg/kg/mo for 6 mo, bimonthly for 36 mo) then Aza (1 mg/kg/d for 24 mo)	42 or 66	80 (mean)
			Induction Trial: CYC Route of Administration		
Yee[45] (2004)[b]	III, IV	32	IV CYC (10 mg/d) vs oral CYC (2 mg/kg/d for 3 or 12 mo) then Aza (1.5 mg/kg/d)	24	48
			Induction Trial: CYC Duration of Treatment		
Boumpas[46] (1992)	IV	65	IV CYC (single monthly dose for 6 mo) vs IV CYC (single monthly dose for 6 mo then quarterly for 24 mo) vs IV methylprednisolone (single monthly dose for 6 mo)	6 or 24	10

(Continued)

Table 1 (Cont'd). Summary of Included Studies

Trial	WHO/ISN Classification	N	Randomized Intervention[a]	Intervention Duration (mo)	F/U (mo)
			Induction Trial: RTX vs Other IS Agent		
LUNAR[21] (2009)[b]	III, IV	144	RTX (1 g on d 1, 15, 168, 182) + MMF (3 g/d) vs MMF (3 g/d)	6	12
Li[20] (2009)[b]	III, IV	19	RTX (1 g on d 0, 15) vs RTX (1 g) + IV CYC (0.75 g/m^2 on d 0, 15)	48	12
			Induction Trial: Steroid vs Other IS Agent		
Hahn[47] (1975)	9/24 DPLN	24	Oral steroid vs Aza	—	12
Balletta[48] (1992)	—	10	Methylprednisolone (2-3 mg/kg/d) then oral steroid (1 mg/kg/d) vs CsA (15 mg/kg bd) + oral steroid	—	>12
Belmont[49] (1995)	7/14 PLN	14	Misoprostol + oral steroid (1 mg/kg, 4×/d) vs oral steroid (1 mg/kg, 4×/d)	2	18
Cade[50] (1973)	DPLN	54	Oral steroid vs Aza vs oral steroid + Aza vs Aza + heparin	—	36
			Induction Trial: Steroid Dose Comparison		
MyLupus[11,22] (2010)	III, IV	81	EC mycophenolate sodium + oral steroid (1 mg/kg/d) vs EC mycophenolate sodium + oral steroid (0.5 mg/kg/d)	6	6
			Induction Trial: Steroid Route of Administration		
Barron[51] (1982)	LN	22	Oral steroid (2 mg/kg/d) vs methylprednisolone (×6) then oral steroid (2 mg/kg/d)	3-6	60
			Induction Trial: PEX ± IS vs Other IS Agent		
Clark[52] (1981)[b]	DPLN	12	PEX + Aza vs Aza	12	12
Clark[53] (1984)	DPLN	39	PEX + conventional IS vs conventional IS	—	18
Doria[54] (1994)	LN	18	PEX + conventional IS vs IS + methylprednisolone vs Aza + oral steroid	—	12
Lewis[55] (1992)[b]	—	86	PEX + oral CYC vs oral CYC	—	30
Wallace[56] (1998)[b]	—	19	PEX + IV CYC (0.75 g/m^2) vs IV CYC (0.75 g/m^2)	8	24
Derksen[57] (1988)	III or IV	20	PEX vs oral steroid + IS	—	6
Nakamura[58] (2002)	IV	20	PEX vs IV CYC	—	6
			Maintenance Trial: MMF vs Other IS Agent		
Contreras[18] (2004)[b]	III, IV Vb	59	MMF (up to 3 g) vs IV CYC (0.5-1 g/m^2) + Aza (1-3 mg/kg/d)	25-30	72
ALMS[59] (2009)[b]	III, IV, III/V, IV/V, V	227	MMF (2 g) vs Aza (2 mg/kg/d)	36	36
MAINTAIN[14] (2009)[b]	III, IV, Vc, Vd	105	MMF (2 g) vs Aza (2 mg/kg/d)	53	53
			Maintenance Trial: CYC vs Other IS Agent		
Fu[60] (1998)	III, IV, V	40	Oral CYC (2 mg/kg/d) vs CsA (2.5 mg/kg, 2×/d)	12	12
Boletis[61,62] (1999)	III/IV	14	IV CYC vs IVIg	18	18
Cyclofa-lune[63] (2010)[b]	III, IV	40	IV CYC (10 mg/kg/d, ×8, over 9 or 12 mo, then 4-5 doses orally at 10 mg/kg every 6-8 wk for 52 wk) vs CsA (4-5 mg/kg/d for 9 or 12 mo then taper over 9 or 12 mo)	18	18
			Maintenance Trial: CYC vs Aza		
Moroni[64,65] (2004)[b]	IV, Vb or c	69	CsA (4 mg/kg/d) vs Aza (2 mg/kg/d)	24	12 to 48

Abbreviations: ALMS, Aspreva Lupus Management Study; Aza, azathioprine; CsA, cyclosporine; CYC, cyclophosphamide; DPLN, diffuse proliferative lupus nephritis; EC, enteric-coated; F/U, follow-up; IS, immunosuppression; ISN, International Society of Nephrology; IV, intravenous; IVIg, intravenous immunoglobulin; LN, lupus nephritis; LUNAR, Lupus Nephritis Assessment with Rituximab Study; MMF, mycophenolate mofetil; PEX, plasma exchange; PLN, proliferative lupus nephritis; PO, oral; RTX, rituximab; Tac, tacrolimus; WHO, World Health Organization.

[a]Dose shown is the initial dose.

[b]Steroids included in both arms of study.

the review total to 160 reports of 50 trials involving 2,846 randomly assigned participants (Fig 1).

Authors of 10 trials were contacted for clarification of trial methods or results, and 9 authors responded to our requests with supplementary data (Belmont, Doria, Donadio, Fries, Gourley, Houssiau, Solomons, Wofsy, and Florez-Suarez).

Trial Characteristics

Table 1 lists characteristics of interventions administered and histologic classification for the 50 included trials. Comparators for induction therapy included cyclophosphamide, MMF, enteric-coated mycophenolate sodium, tacrolimus, azathioprine, cyclosporine, rituximab, and plasma exchange. Comparators for maintenance

Table 2. Risk-of-Bias Summary

	Selection Bias		Performance and Detection Biases		Attrition Bias		
	Random Sequence Generation	Allocation Concealment	Blinding, Subjective Outcomes	Blinding, Objective Outcomes	Incomplete Outcome Data	Selective Reporting	Other Bias
Induction Trials							
Adam[38] (2004)	?	?	●	●	●	●	●
Appel[16] (2009)	●	●	●	●	●	●	?
Austin[34] (1986)	●	?	?	?	?	?	?
Balletta[48] (1992)	?	?	●	●	●	?	●
Bao[17] (2008)	●	●	●	●	●	●	?
Barron[51] (1982)	○	○	●	●	○	○	●
Belmont[49] (1995)	?	?	●	●	●	●	●
Boumpas[46] (1992)	?	●	●	●	●	●	?
Cade[50] (1973)	○	?	●	●	?	?	?
Chan[26] (2000)	●	?	●	●	●	●	?
Chen[41] (2011)	●	●	●	●	●	●	?
Clark[52] (1981)	?	?	●	●	●	●	●
Clark[53] (1984)	?	?	●	●	?	?	?
Derkson[57] (1988)	●	?	?	?	?	?	?
Donadio[66] (1974)	●	?	●	●	?	○	●
Donadio[33] (1978)	●	?	●	●	?	?	?
Doria[54] (1994)	?	?	?	?	?	?	?
Dyadyk[39] (2007)	?	?	?	?	?	?	?
El-Shafey[29] (2010)	●	?	●	●	●	●	●
Fries[31] (1973)	?	?	?	?	?	?	●
Ginzler[19] (2005)	●	●	●	●	●	●	?
Ginzler[32] (1976)	?	●	●	●	●	●	●
Gourley[36] (1996)	●	●	●	●	●	●	●
Grootsholten[10] (2006)	●	●	●	●	●	●	?
Hahn[47] (1975)	●	●	●	●	●	●	●
Hong[40] (2007)	?	?	?	?	?	?	?
Houssiau[42] (2002)	●	?	●	●	●	●	●
Lewis[55] (1992)	●	?	●	●	●	●	●
Li, X[15] (2009)	?	?	●	●	●	●	●
Li[20] (2009)	●	●	●	●	●	●	?
Lui[37] (1997)	?	?	?	?	?	?	?
LUNAR[21] (2009)	●	?	●	●	●	●	?
MAINTAIN[14] (2009)	●	?	●	●	●	●	●
Mitwalli[44] (2011)	?	?	?	?	?	?	?
Mok[13] (2009)	?	?	?	?	?	?	?
Moroni[64,65] (2004)	●	●	●	●	●	●	?
Mulic-Bacic[28] (2008)	?	?	?	?	?	?	?
MyLupus[11,22] (2010)	?	?	?	?	?	?	?
Nakamura[58] (2002)	?	?	?	?	?	?	?
Ong[27] (2005)	●	●	●	●	●	●	?
Sabry[43] (2009)	○	○	●	●	●	●	●
Sesso[35] (1994)	?	?	●	○	●	?	●
Steinberg[30] (1971)	●	●	●	●	●	●	?
Sundel[12] (2008)	?	?	?	?	?	?	?
Wallace[56] (1998)	?	?	?	?	?	?	?
Yee[45] (2004)	●	?	●	●	●	○	●

(Continued)

Table 2 (Cont'd). Risk-of-Bias Summary

	Selection Bias		Performance and Detection Biases		Attrition Bias		
	Random Sequence Generation	Allocation Concealment	Blinding, Subjective Outcomes	Blinding, Objective Outcomes	Incomplete Outcome Data	Selective Reporting	Other Bias
Maintenance Trials							
ALMS[59] (2009)	●	●	●	●	●	●	?
Boletis[61,62] (1999)	?	●	●	●	●	●	●
Contreras[18] (2005)	●	●	●	●	●	●	?
Cyclofa-lune[63] (2010)	●	●	●	●	●	●	●
Fu[60] (1998)	●	●	●	●	●	○	●
MAINTAIN[14] (2009)	●	?	●	●	●	●	●
Moroni[64,65] (2004)	●	●	●	●	●	●	?

Note: Review of authors' judgments about each risk of bias item for each included study.
Abbreviations: ●, good quality (low risk of bias); ?, unclear quality (unclear risk of bias); ○, less good quality (high risk of bias); ALMS, Aspreva Lupus Management Study; LUNAR, Lupus Nephritis Assessment with Rituximab Study.

therapy included cyclophosphamide, MMF, azathioprine, and cyclosporine. All trials conducted since 2004 included steroids in each intervention arm. All patients had biopsy-proven proliferative lupus nephritis, with most recent trials including patients with class IV lupus nephritis.

Induction therapy compared MMF versus another immunosuppressive agent (10 trials, 953 participants; comparator was cyclophosphamide or tacrolimus), cyclophosphamide versus another immunosuppressive agent (14 trials, 672 participants; comparator was azathioprine, tacrolimus, cyclosporine, or steroid), steroid versus another immunosuppressive agent (5 trials, 118 participants; comparator was azathioprine, cyclosporine, or misoprostol), plasma exchange with or without conventional immunosuppression versus conventional immunosuppression alone (7 trials, 213 trials), and rituximab versus another immunosuppressive agent (2 trials, 163 participants; comparator was cyclophosphamide or other immunosuppression). High- versus low-dose comparisons were made in 3 induction trials with cyclophosphamide (253 participants) and 1 trial with steroid (1 trial, 81 participants). IV versus oral route of administration was compared in 1 induction trial each of cyclophosphamide and steroid. Duration of therapy was compared in 1 trial (65 patients) of long- versus short-course cyclophosphamide.

Considering maintenance therapy, 4 studies (460 participants) compared azathioprine plus corticosteroid to another immunosuppressive agent (MMF, cyclophosphamide, or cyclosporine)[14,18,59,61,64]; 1 study (14 participants), IV cyclophosphamide to IV immunoglobulin[61]; and 1 study, IV cyclophosphamide to cyclosporine (40 participants).[60]

The maintenance phase of 1 trial[26] underwent a significant postrandomization protocol adjustment for participants originally randomly assigned to induction with MMF. The MMF induction trial arm originally switched to maintenance azathioprine at 1 year, but the protocol changed mid-trial to continuing MMF for 2 years. This was prompted by an unexpectedly high rate of renal relapse in the azathioprine maintenance group. Data for participants on the original protocol were not reported separately to the adjusted protocol, so accordingly, only the induction phase data of this trial could be included in synthesis.

Risk of Bias

Trial quality was variable (Table 2). Reporting of details of study methodology was incomplete for most studies. Allocation concealment was adequate in only 17 trials,[10,16-20,27,30,32,36,41,42,46,47,63,64] and 25 studies reported adequate sequence generation.[10,14,16-21,26,27,29,30,33,34,36,41,42,45,47,55,57,60,63,64,66] Five studies adequately reported blinding of objective and subjective outcomes,[21,26,30,32,49] and 4 studies adequately reported blinding of subjective outcomes.[21,30,32,49] Incomplete outcome data were addressed adequately in 31 studies,[10,14-21,26,27,29,30,32,36,41,42,45-47,55,60,63] and 27 studies were free of selective reporting.[10,14-21,26,27,29,30,32,36,38,41-43,46,47,49,52,62,63,65,67] Six studies reported their source of funding to be an independent or academic funding body and thus were considered to be free of potential other bias. Thirty-four of 50 included trials were analyzed based on intention-to-treat analysis.

Outcomes

Induction Therapy

Five main immunosuppression class comparisons and 24 different outcomes were evaluated (Table 1).

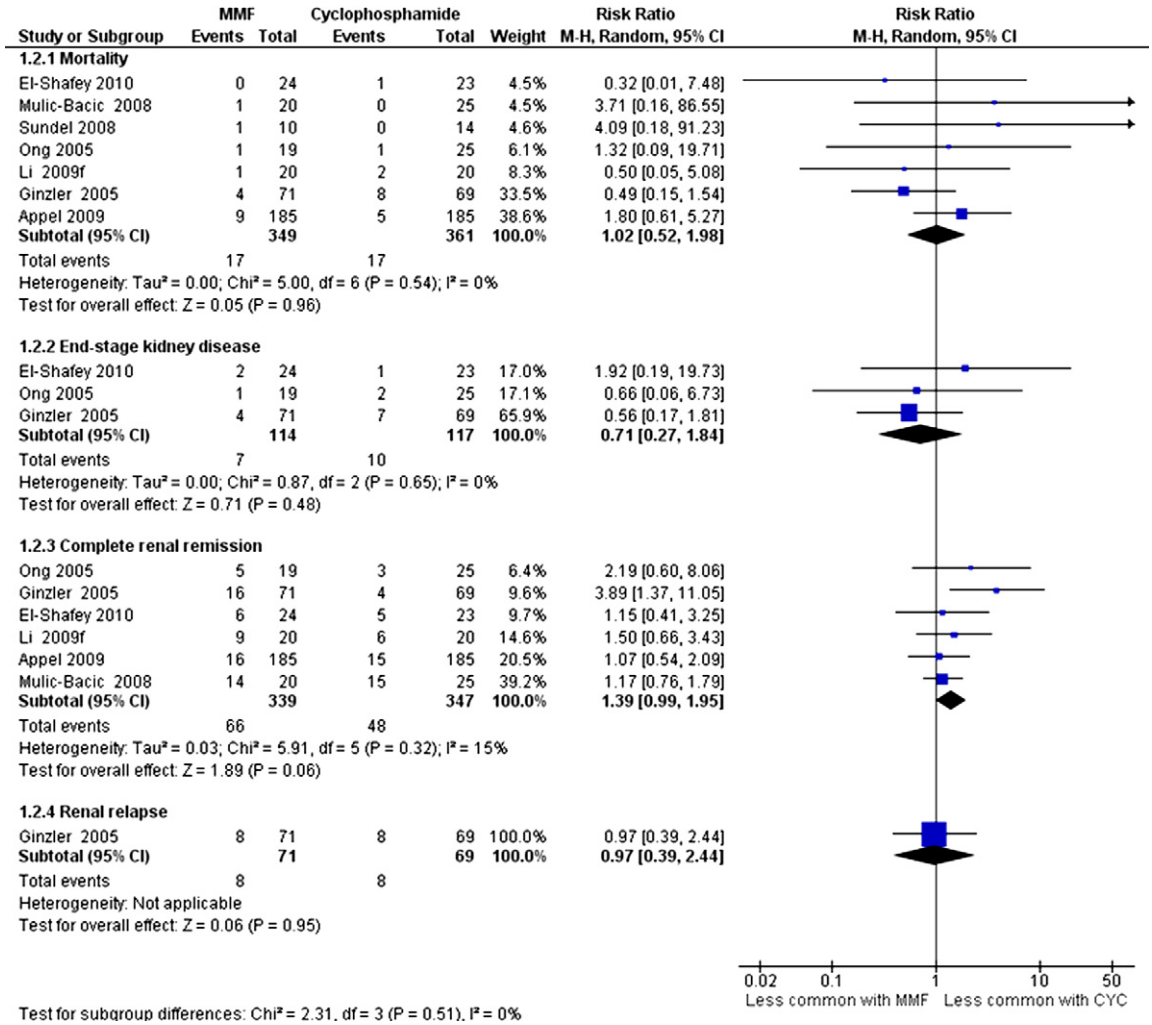

Figure 2. Mycophenolate mofetil (MMF) versus intravenous (IV) cyclophosphamide: main outcomes. Abbreviation: CI, confidence interval.

MMF Versus Other Immunosuppression

MMF versus cyclophosphamide. Overall, there was no difference for mortality or any renal outcome between MMF and cyclophosphamide (Fig 2), but decreased adverse events (Fig 3). Compared with IV cyclophosphamide, there were no differences in complete renal remission (6 studies, 686 participants; RR, 1.39; 95% CI, 0.99-1.95), partial renal remission (6 studies, 686 participants; RR, 1.04; 95% CI, 0.86-1.25; Fig 2; Table 3), or stabilization in kidney function (5 studies, 523 participants; RR, 1.05; 95% CI, 0.94-1.18) with MMF therapy. There was no significant difference in incidence of end-stage kidney disease or risk of renal relapse (Fig 2). MMF-treated participants had an 85%-90% reduced risk of ovarian failure compared with either IV (2 studies, 498 participants; RR, 0.15; 95% CI, 0.03-0.80) or oral cyclophosphamide (1 study, 53 participants; RR, 0.10; 95% CI, 0.01-0.73; Fig 3; Table 3). The incidence of alopecia was 95% less likely with MMF compared with oral cyclophosphamide (1 study, 62 participants; RR, 0.05; 95% CI, 0.00-0.81) and 78% less likely compared with IV cyclophosphamide (2 studies, 522 participants; RR, 0.22; 95% CI, 0.06-0.86; Fig 3). Leukopenia was significantly decreased in MMF-treated patients compared with either oral (1 study, 62 participants; RR, 0.06; 95% CI, 0.00-0.92) or IV cyclophosphamide (5 studies, 653 participants; RR, 0.49; 95% CI, 0.28-0.88; Fig 3). Fewer major infective episodes were seen comparing MMF with oral (1 study, 62 participants; RR, 0.21; 95% CI, 0.05-0.89), but not IV, cyclophosphamide (6 studies, 683 participants; RR, 1.11; 95% CI, 0.74-1.68; Table 3). Herpes zoster infection was no less likely with MMF compared with IV cyclophosphamide (4 studies, 613 participants; RR, 1.35; 95% CI, 0.71-2.58; Table 3). Diarrhea was significantly more common (3 studies, 569 participants; RR, 2.53; 95% CI, 1.54-4.16; Fig 3), but there was no difference in vomiting (2 studies, 522 participants; RR, 0.54; 95% CI, 0.24-1.24) with MMF.

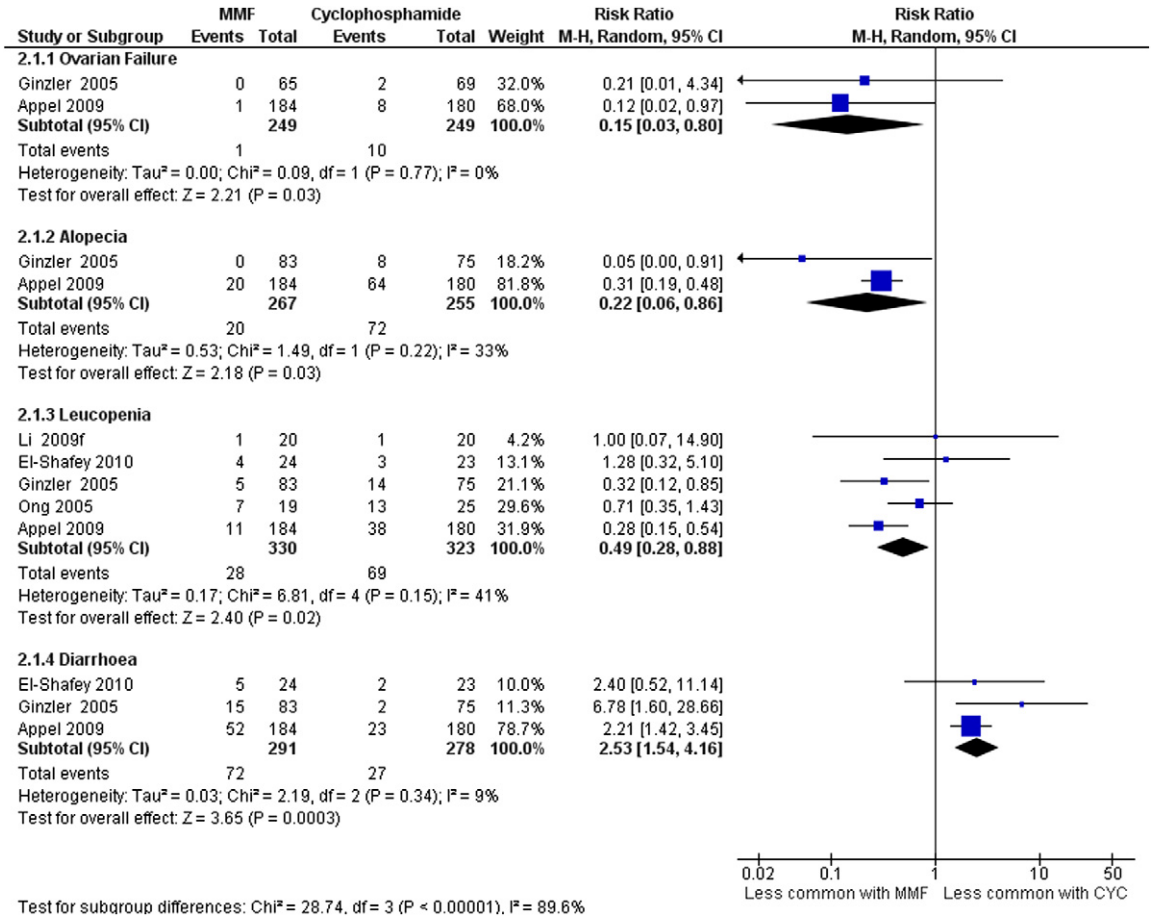

Figure 3. Mycophenolate mofetil (MMF) versus intravenous cyclophosphamide (CYC): main adverse side effects. Abbreviation: CI, confidence interval.

MMF plus tacrolimus versus cyclophosphamide. MMF in combination with tacrolimus resulted in a significant increase in number of patients with complete renal remission (RR, 4.33; 95% CI, 1.45-12.91) and complete remission in proteinuria (RR, 4.33; 95% CI, 1.45-12.91; Table 3) compared with IV cyclophosphamide, although with wide CIs and data from only 1 small study (40 patients) recruiting predominantly Asian patients. Proteinuria also was significantly decreased in MMF- and tacrolimus-treated patients versus IV cyclophosphamide (mean difference, −5.89; 95% CI, −7.01 to −4.77).

Rituximab Versus Other Immunosuppression

Two studies compared the addition of rituximab to either MMF or cyclophosphamide versus MMF or rituximab alone. Neither study showed a difference in remission or any adverse events (Table 3).

Maintenance Therapy

Three main immunosuppressive comparisons and 14 different outcomes were evaluated (Table 1). Overall, there was no difference in mortality, but renal outcomes varied among maintenance therapies (Table 3).

MMF versus other immunosuppression. Risk of renal relapse was significantly greater with azathioprine versus MMF (3 studies, 371 participants; RR, 1.83; 95% CI, 1.24-2.71). No differences in incidence of end-stage kidney disease, doubling of creatinine level, or any adverse event except leukopenia (RR, 6.21; 95% CI, 1.69-22.85) were seen (Table 3).

Cyclophosphamide versus other immunosuppression. Comparing cyclophosphamide versus azathioprine, there was no difference in any renal measures or adverse events (Table 3). Comparing cyclosporine versus IV cyclophosphamide, there was significantly less proteinuria (1 trial, 38 participants; mean difference, −0.27; 95% CI, −0.43 to −0.11), but lower creatinine clearances (mean difference, −15.70; 95% CI, −23.71 to −7.69).

Azathioprine versus cyclosporine. No differences in any renal measures were seen. Significantly more major infective episodes (RR, 2.18; 95% CI, 1.01-4.73), but fewer symptoms of gastrointestinal upset

Table 3. Summary of Outcomes: Induction and Maintenance Therapy

Outcome	Comparison	Trials	Participants	RR (95% CI)	I^2
	Induction Therapy				
Partial renal remission	MMF vs IV CYC	6	686	1.04 (0.86-1.25)	0%
	MMF + Tac vs IV CYC	1	40	1.00 (0.47-2.14)	NA
	High- vs low-dose Pred	1	81	1.43 (0.83-2.47)	NA
	RTX + IV CYC vs RTX	1	19	0.75 (0.35-1.62)	NA
	RTX + MMF vs MMF	1	144	2.00 (1.05-3.82)	NA
Complete renal remission	MMF + Tac vs IV CYC	1	40	4.33 (1.45-12.91)	NA
	MMF vs Tac	2	109	1.59 (0.58-4.41)	70%
	High vs low-dose Pred	1	81	1.06 (0.42-2.65)	NA
Complete remission in proteinuria	MMF vs oral CYC	1	62	0.98 (0.74-1.30)	NA
	MMF vs IV CYC	6	686	1.39 (0.99-1.95)	39%
	MMF + Tac vs IV CYC	1	40	4.33 (1.45-12.91)	NA
	MMF vs Tac	1	40	1.00 (0.50-1.98)	NA
Partial remission in proteinuria	MMF vs oral CYC	1	62	1.07 (0.44-2.59)	NA
	MMF vs IV CYC	4	602	1.06 (0.89-1.25)	0%
	MMF + Tac vs IV CYC	1	40	0.75 (0.32-1.77)	NA
Doubling of SCr	MMF vs oral CYC	1	62	0.63 (0.11-3.48)	NA
	MMF + Tac vs IV CYC	1	40	0.33 (0.01-7.72)	NA
Major infection	MMF vs oral CYC	1	62	0.21 (0.05-0.89)	NA
	MMF vs IV CYC	6	683	1.11 (0.74-1.68)	0%
	MMF + Tac vs IV CYC	1	40	0.50 (0.14-1.73)	0%
	MMF vs Tac	2	130	2.11 (0.92-4.80)	0%
	RTX + IV CYC vs RTX	1	19	0.90 (0.07-12.38)	NA
	RTX + MMF vs MMF	1	144	1.00 (0.48-2.08)	NA
HZV infection	MMF vs oral CYC	1	62	0.38 (0.08-1.79)	NA
	MMF vs IV CYC	4	613	1.35 (0.71-2.58)	0%
	MMF + Tac vs IV CYC	1	40	1.00 (0.07-14.90)	NA
Bone toxicity	MMF vs oral CYC	1	62	NE	NE
	CYC vs Aza	1	87	NE	NE
	High- vs low-dose IV CYC	1	89	2.93 (0.12-70.16)	NA
	Long vs short IV CYC	1	40	1.33 (0.34-5.21)	NA
	Maintenance Therapy				
Mortality	Aza vs MMF	3	371	0.58 (0.1-3.49)	0%
	Aza vs CsA	1	69	NE	NE
	Aza vs CYC	1	39	0.12 (0.01-2.03)	NA
ESKD	Aza vs MMF	3	371	1.86 (0.37-9.31)	0%
	Aza vs CsA	1	69	NE	NE
	Aza vs CYC	1	39	0.35 (0.04-3.09)	NA
Renal relapse	Aza vs MMF	3	371	1.83 (1.24-2.71)	0%
	Aza vs CsA	1	69	1.25 (0.51-3.06)	NA
	Aza vs CYC	1	39	0.79 (0.34-1.85)	NA
Doubling of SCr	Aza vs MMF	3	371	2.09 (0.89-4.94)	0%
	Aza vs CYC	1	39	0.79 (0.34-1.85)	NA
Infection	Aza vs MMF	1	105	0.87 (0.31-2.43)	NA
	Aza vs CsA	1	69	2.18 (1.01-4.73)	NA
HZV infection	Aza vs MMF	1	105	1.27 (0.36-4.48)	NA
Leukopenia	Aza vs MMF	2	331	6.21 (1.69-22.85)	0%
	Aza vs CsA	1	69	2.73 (0.95-7.86)	NA
Bone toxicity	Aza vs MMF	1	105	3.06 (0.13-73.36)	NA
Bladder toxicity	Aza vs MMF	1	39	NE	NE
	Aza vs CYC	1	39	NE	NE
GI upset	Aza vs MMF	1	105	1.02 (0.41-2.51)	NA
	Aza vs CsA	1	69	0.30 (0.09-0.97)	NA

Abbreviations: Aza, azathioprine; CI, confidence interval; CsA, cyclosporine; CYC, cyclophosphamide; ESKD, end-stage kidney disease; GI, gastrointestinal; HZV, herpes zoster virus; IS, immunosuppression; IV, intravenous; MMF, mycophenolate mofetil; NA, not applicable; NE, not estimable; Pred, prednisolone; RR, risk ratio; RTX, rituximab; SCr, serum creatinine; Tac, tacrolimus.

(RR, 0.3; 95% CI, 0.09-0.97), were observed with azathioprine versus cyclosporine (Table 3).

DISCUSSION

The availability of new interventions for the management of lupus nephritis requires re-evaluation of established treatment strategies within the context of emerging trial data.

Nine trials involving more than 800 patients with proliferative lupus nephritis comparing cyclophosphamide with MMF show that MMF is as effective as IV cyclophosphamide at inducing complete remission in proteinuria and achieving stable kidney function at 6 months, with no difference in mortality, end-stage kidney disease, or doubling of serum creatinine level. MMF also decreases the risk of ovarian failure, alopecia, and leukopoenia, but with an increase in diarrhea. There was no evidence that the addition of rituximab to MMF and corticosteroids improves remission rates.

For maintenance therapy, MMF appears more effective than azathioprine at preventing renal relapse and with less leukopenia. Mortality, doubling of serum creatinine level, and other adverse effects including major infection were no different between the 2 therapies. Many other interventions, including rituximab, an agent increasingly used in clinical practice, have been trialled in only small studies with inconsistent outcome reporting, thereby precluding their inclusion in data synthesis. The clinical role for these therapies therefore is unclear and warrants caution.

The 2012 American College of Rheumatology clinical guidelines recommend the use of either MMF (2-3 g/d) or IV cyclophosphamide combined with corticosteroids for induction therapy and either azathioprine or MMF for maintenance treatment of class III/IV lupus nephritis. This review supports these recommendations, but suggests that MMF may be the preferred first-line agent in both treatment phases due to an overall better adverse-effect profile, with lower risk of relapse in maintenance therapy.

The strengths of this review are that in contrast to previous meta-analyses,[68,69] we reorganized interventions according to whether they were induction or maintenance therapies, better reflecting clinical practice. Broad inclusion criteria also helped explore the totality of evidence available, rather than limiting meta-analysis by specific immunosuppression regimens, as have previously published systematic reviews.[68-75] Inclusion of unpublished data from conference abstracts minimized publication bias.[76] In the update, 52 new reports came from hand-searching conference proceedings in addition to those already searched by the Cochrane Renal Group. To our knowledge, this is the most comprehensive evidence summary on this topic.

Nevertheless, there are some potential limitations of our study. Considerable clinical heterogeneity in interventions, definitions of remission, and outcome reporting among trials hampered interpretation and presentation of important outcomes in this review. For example, comparing MMF with cyclophosphamide, there was variability among trials in therapeutic dosing, route of administration, and cointerventions. Although some trials had moderate periods of follow-up over 1-2 years, others were substantially shorter and not sufficiently powered to detect events in the clinically important outcomes. Average time to remission with cyclophosphamide is about 10 months.[77] However, follow-up in 10 induction studies was 6 months. Furthermore, the risk of adverse events such as ovarian failure increases after 6 months; thus, the power of existing studies, even when combined, to detect significant differences between interventions is limited. Lack of long-term follow-up data in some studies is particularly relevant to the outcome of end-stage kidney disease, for which a difference between groups may not become noticeable until after several years. Incomplete reporting of outcomes also increases uncertainty. For example, although 9 studies with 844 participants compared MMF with cyclophosphamide, only 4 reported on ovarian failure and 2 reported on doubling of serum creatinine level.

The disease spectrum and proportion of patients with each class of lupus nephritis differed among trials. Furthermore, patient demographics differed among studies for which environmental, socioeconomic, clinical, and genetic factors have been thought to have an important role in explaining ethnic differences in the outcome of lupus nephritis. Comparing MMF with cyclophosphamide, 3 studies included primarily Asian patients,[17,26,27] and 2 of the largest trials comparing MMF with cyclophosphamide included a larger proportion of African American and Hispanic patients.[16,19] Nonwhite populations have a higher risk of relapse, death, and chronic kidney failure compared with white populations[18,78] and often fail to respond to cyclophosphamide therapy.[79-83] One trial[19] included 56% of patients of African American origin and was the only study to show a clear benefit in favor of MMF over IV cyclophosphamide for induction of remission and reduction in daily proteinuria.[19] The Aspreva Lupus Management Study (ALMS),[16] which included 12% African American and 35% Hispanic patients, suggested interactions between group interventions and race that were not explained by differences in disease characteristics.[16] ALMS was the only trial to provide stratified results according to ethnicity and class of lupus, and no trial provided stratified results according to severity of decrease in kidney function, thereby reducing the

power to examine potential differences. Despite the lack of result stratification, variation among trials could be considered a strength. Seven of 10 studies comparing MMF with cyclophosphamide included either Asian and/or African American patients, and all studies included patients with the more severe histologic classification of class IV lupus nephritis. Similarly, considering maintenance therapy, racial distribution varied markedly among trials. Clinical and statistical homogeneity of results suggested that results were valid across race and class of lupus nephritis.

Finally, overall trial quality was variable. The internal validity of the design, conduct, and analysis of the included RCTs was difficult to assess in some studies because of the omission of important methodological details. Only 3 studies[36,47,63] adequately reported all domains of the risk-of-bias assessment (Table 2); therefore, elements of internal bias may be present in the meta-analysis.[82,83]

There are 2 main implications for future research: first, to make better use of existing data, and second, to strategically plan any new trials. Given the inconsistency of outcome definitions and timing of outcome measurements, reanalysis of existing trial data sets may permit a more informative synthesis. Although there have been several multicenter trials since our original review in 2004,[8,9] continued diversity in interventions and comparators has prevented informative synthesis and cross-trial comparison. Lupus nephritis is uncommon, requiring multicenter collaboration for a trial to have an adequate sample size. The importance of follow-up prolonged beyond 6 months is vital to clarify risks and eventual harms of specific treatment regimens. There also is a paucity of data for patient subgroups that may have a greater disease burden, such as African Americans and Asians.

Equivalent remission rates combined with a more favorable side-effect profile support MMF as being superior to cyclophosphamide as induction therapy for lupus nephritis. In maintenance therapy, MMF is superior to azathioprine in preventing renal relapse. Larger collaborative trials reporting longer term clinically relevant outcomes are required to establish optimal dosing and administration schedules, as well as to determine the role for newer biologic agents.

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