Efficacy and safety of mycophenolate mofetil for IgA nephropathy: An updated meta-analysis of randomized controlled trials

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Abstract. The efficacy and safety of mycophenolate mofetil (MMF) for immunoglobulin A nephropathy (IgAN) remains debatable. Therefore, the present meta-analysis was conducted with randomized controlled trials (RCTs). PubMed/MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were analyzed to identify eligible trials. The pooled risk ratio (RR) with 95% confidence interval (CI) was estimated for all the dichotomous outcome measures. A total of eight RCTs with nine publications (n=510 patients) were included. No significant difference was noted between therapeutic regimens with and without MMF for renal remission and end stage renal disease (ESRD) of patients with IgAN (seven trials; RR, 1.250; 95% CI, 0.993-1.574; P=0.057; and four trials; RR, 0.728; 95% CI, 0.164-3.236; P=0.676). To further define the effects of MMF for renal remission, subgroup analysis was performed, demonstrating that MMF was significantly more effective compared with the placebo (three trials; RR, 2.152; 95% CI, 1.198-3.867; P=0.010), although the immunosuppressive regimens with MMF had no significantly different effects compared with those without MMF (four trials; RR, 1.140; 95% CI, 0.955-1.361; P=0.146), indicating that MMF was superior to placebo and had a similar efficacy to other immunosuppressants for renal remission. In addition, subgroup analysis for ESRD revealed no significant differences between MMF and placebo and between the immunosuppressive regimens with and without MMF (three trials; RR, 0.957; 95% CI, 0.160-5.726; P=0.962; and one trial; RR, 0.205; 95% CI, 0.010-4.200; P=0.303). Furthermore, there were no significant differences between the therapeutic regimens with and without MMF in terms of the risk of adverse events. The present meta-analysis demonstrated that MMF was more effective compared with the placebo, may have similar efficacy to other immunosuppressants in terms of inducing renal remission of IgAN and may not increase the risk of adverse events. The long-term effects of MMF on the prognosis of patients with IgAN require verification in further studies.

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis globally (1). According to the International Kidney Biopsy Survey, IgAN was diagnosed in 22% of all glomerular diseases in Europe and in up to 39% in Asia (2). The clinical manifestations of IgAN are variable, ranging from isolated hematuria to rapidly progressive renal dysfunction. Correspondingly, the histological lesions are diverse, ranging from mild mesangial proliferative glomerulonephritis to crescentic glomerulonephritis. Approximately 50% of patients with IgAN develop end-stage renal disease (ESRD) within 30 years, which indicates that IgAN is an important cause of ESRD (3).

The pathological lesions of IgAN are characterized by mesangial IgA (primarily IgA1) deposits, viewed by immunofluorescence, frequently concomitant with the deposition of IgG and complement factor 3 (1). Therefore, IgAN is considered to be an immune-mediated kidney disease and is treated through administration of immunosuppressive treatments, including mycophenolate mofetil (MMF) (4). Mycophenolic acid (MPA) is an active compound derived from MMF, which inhibits inosine 5'-monophosphate dehydrogenase reversibly and non-competitively and is essential for *de novo* biosynthesis of guanine nucleotides and lymphocyte proliferation (5,6). MMF has been commonly used in patients undergoing solid organ transplantation (7,8) and in recent years it has been applied in IgAN. However, the efficacy and safety of MMF in IgAN remains controversial. Randomized controlled trials (RCTs) and previous meta-analyses led to inconsistent conclusions (9-21). Various studies have determined that there were no differences between therapeutic regimens that did and did not utilize MMF in patients with IgAN (10,12,15,16). However, other studies have demonstrated that the therapeutic regimens with MMF were superior to those without (11,13,14,17). The previously published meta-analyses also demonstrated different results; some demonstrated the superiority of MMF for IgAN (19,21), but others failed to exhibit any

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difference (18,20). Therefore, the efficacy and safety of MMF for IgAN is yet to be fully elucidated. To examine the efficacy and safety of MMF for IgAN, a meta-analysis of RCTs was performed in the present study on the basis of the most complete evidence.

Materials and methods

Data sources and searches. Two independent assessments of the literature were performed using three computerized databases, PubMed/MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (https://www.embase.com/login) and the Cochrane Central Register of Controlled Trials (CCRCT; http://www.cochranelibrary.com), prior to October 2017. The following medical subject heading terms and text words were used: Mycophenolate mofetil, mycophenolic acid and IgA nephropathy. The searches were restricted to clinical trials in the three databases. No language restriction was applied.

Study selection and outcome measures. Two independent assessments evaluated all retrieved titles and abstracts for eligibility and a detailed evaluation by full-text review of the publications that were likely to meet the inclusion criteria was performed. The present meta-analysis included RCTs, which investigated efficacy and/or safety of MMF for patients with IgAN and reported at least one outcome measure, including primary endpoint of renal remission (i.e., complete and partial remission) and secondary endpoints of ESRD and adverse events. The original definitions of complete and partial remission were very similar among the included trials and were therefore applied in the present meta-analysis. Any disagreement or uncertainty was discussed for consensus.

Study quality assessment. The methodological quality of the included RCTs was assessed twice, according to Cochrane recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (22,23). The following six items were considered for the assessment of methodological quality: Adequate generation of randomization, blinding, allocation concealment, incomplete outcome data, selective outcome reporting and possible sources of other bias. The procedure of assessment was performed according to the following criteria: 'Yes' (low risk) or adequate, if the item was described clearly and adequately; 'no' (high risk) or inadequate, if the item was not described adequately; or 'unclear' if the information was insufficient to judge the risk of bias as 'low' or 'high.' The quality of assessment was evaluated using the κ statistic. κ statistic was calculated with the following formula: $\kappa = (p_0 - p_e)/(1 - p_e)$, $p_0 = (a + d)/(a + b + c + d)$, $p_e = p_{yes} + p_{no}$, $p_{yes} = (a + b)/(a + b + c + d) \cdot (a + c)/(a + b + c + d)$, $p_{no} = (c + d)/(a + b + c + d) \cdot (b + d)/(a + b + c + d)$. Where a, b, c, and d represent the data in the 4-fold table.

Data extraction and synthesis. Two independent data extractions of the characteristics of the included RCTs (country, sample size, study period, regimens of the treatment and control groups, definitions of complete and partial remission and duration of follow-up), study population (age, sex, population setting, clinical and laboratory parameters) and outcome measures (renal remission, ESRD and adverse events) were performed.

The pooled risk ratio (RR) with 95% confidence interval (CI) was estimated for all dichotomous outcome measures. Heterogeneity was assessed with Cochran's Q test (heterogeneity χ^2) and I^2 and H statistics. Since the estimated intervention effects in the included trials were not consistent, data synthesis was performed using the random effects model (Knapp-Hartung method). Random effects meta-regression was performed to examine the sources of heterogeneity by evaluating the correlations between logRRs of the primary endpoint and co-variables [characteristics of the population and the included trials that may be associated with outcomes (sex, age, population settings, country, laboratory parameters at baseline and the periods of follow-up)]. Subgroup analysis was applied when the source of heterogeneity was identified. Publication bias was investigated using Egger's regression analysis and visual examination of funnel plots.

Stata 11.0 (StataCorp LLC, College Station, TX, USA) was used for all analytical procedures. Two-sided P-values <0.05 were considered to indicate a statistically significant difference and P<0.10 was applied for heterogeneity tests.

Results

Description of included trials. A total of 42 publications were identified in the trial selection process following exclusion of duplications from the three electronic databases (PubMed/MEDLINE, EMBASE and CCRCT). The screening process is summarized in Fig. 1. A total of 20 articles were excluded in the first round, including 16 irrelevant articles and four reviews, and 22 full-text articles were further evaluated for eligibility. A further 13 publications were excluded for the following reasons: One as non-RCT, six as study protocols of clinical trials and six as multiple publications. Consequently, eight RCTs with nine publications (9-17) (510 participants) were included in the present meta-analysis to evaluate the efficacy and safety of MMF for patients with IgAN. Tang *et al* (13,14) reported short-term and long-term outcomes of the same trial in two publications.

The baseline characteristics of trials and study populations are listed in Table I. The population refers to patients with overt proteinuria; patients with severe renal dysfunction were excluded. Renal pathological lesions were considered as inclusion criteria in six of the included trials. Four of the eight included trials compared MMF with a placebo and the other four trials compared immunosuppressive regimens with and without MMF. Mean ages and percentage of male patients ranged from 28.5 to 42.7 years and from 35.0 to 84.4%, respectively. The periods of follow-up ranged between 6 and 72 months. Furthermore, the definitions of renal remission (i.e., complete remission and partial remission) in the included trials are described in Table II, illustrating similarities.

Methodological quality assessment was accomplished with a high estimated level of consistence (κ statistic=1.0), which is described in detail in Table III. The sequence generation was adequate in three trials and unclear in five trials due to insufficient information. Allocation concealment was adequate in two trials and unclear in the other six. Blinding was performed adequately in two trials, inadequately in two and was unclear
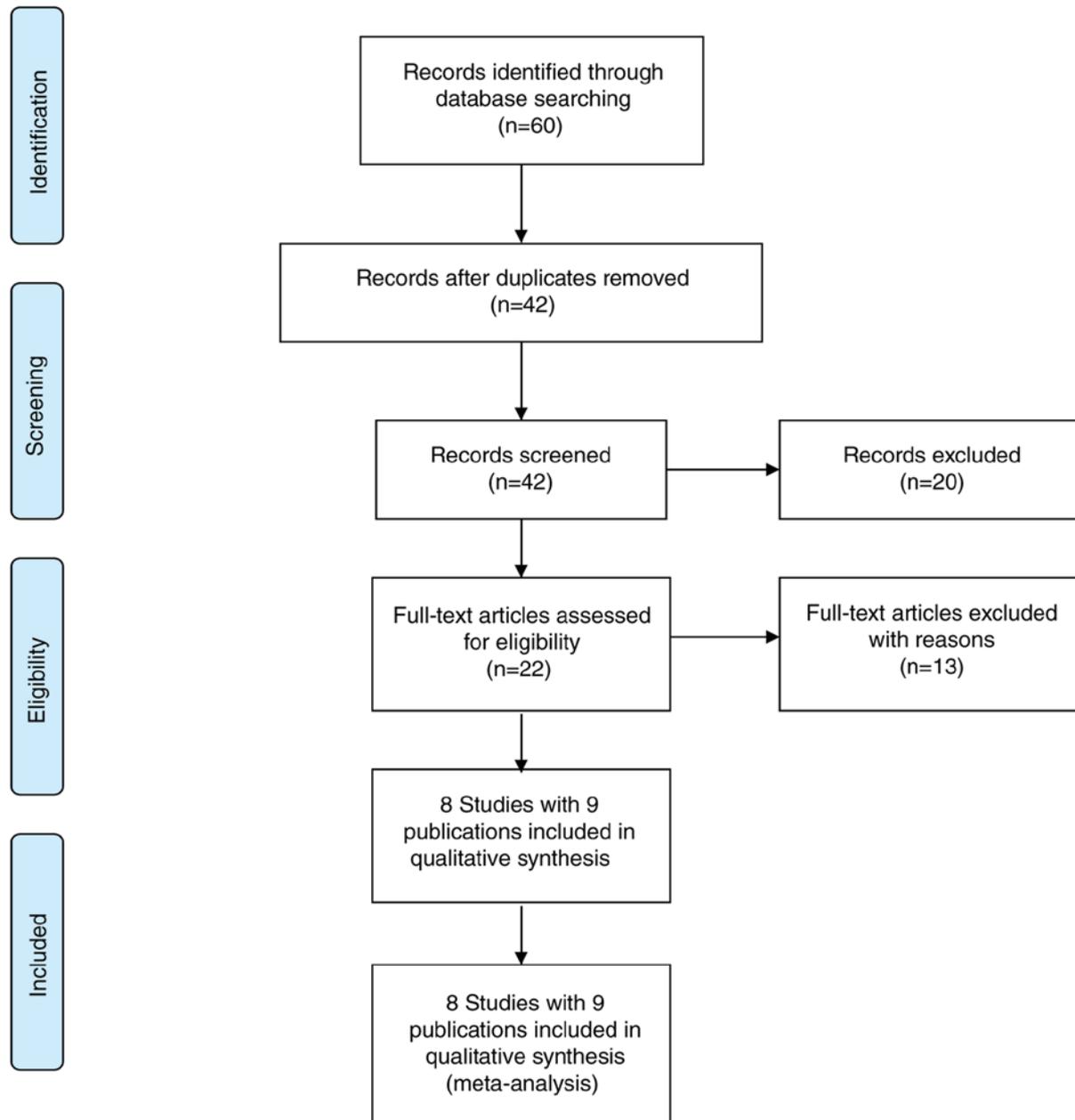
Figure 1. Flow chart of study selection process.

in four. Incomplete outcome data were addressed adequately in six trials and inadequately in two. Selective reporting was adequate in six trials and inadequate in two. A total of six trials were free of other bias, one trial was unclear and one trial had a high risk of bias due to early termination.

Effect of MMF on renal remission. A total of seven trials with 478 participants reported data on renal remission. The funnel plots exhibited asymmetry (Fig. 2A). Egger's regression analysis demonstrated no significant publication bias (P=0.297; Fig. 2B). The pooled effects (RRs) were homogeneous (I^2=36.0%; Q=9.38, degrees of freedom, df=6; P=0.153; H=1.3; 95% CI, 1.0-1.9) according to the random effects model and there was no significant difference between therapeutic regimens with and without MMF for renal remission in patients with IgAN (Fig. 3A; RR, 1.250; 95% CI, 0.993-1.574; P=0.057).

Random effects meta-regression was performed, which indicated no significant interactions between treatment effect, trial and population characteristics. Further subgroup analysis was performed according to the therapeutic regimens in the control groups of a placebo or other immunosuppressants, which demonstrated that MMF was significantly superior compared with a placebo (Fig. 3B; three trials; RR, 2.152; 95% CI, 1.198-3.867; P=0.010). The immunosuppressive regimens with MMF had no significantly different effects compared with immunosuppressive regimens without MMF (Fig. 3B; four trials; RR, 1.140; 95% CI, 0.955-1.361; P=0.146).

Effect of MMF on ESRD. A total of four trials with 282 participants reported data on ESRD. The included effects (RRs) were heterogeneous (I^2=54.0%; Q=6.53, df=3; P=0.089; H=1.35; 95% CI, 1.0-2.6) according to the

Table I. Characteristics of the included trials.

Author, year	Country	Population setting	No. of patients	Male, %	Mean age, years	eGFR, ml/min/1.73 m²	SCr, μmol/l	UPE, g/day	Regimens in MMF groups (treatment time)	Regimens in control groups (treatment time)	Follow-up, months	(Refs.)
Hou et al, 2017	China	IgAN with active proliferative lesions; UPE ≥1.0 g/day; eGFR ≥30 ml/min/1.73 m²	174	44.3	31.5	MMF: 90.2 (64.4-109.6); Control: 94.3 (72.2-111.4)	MMF: 85.4 (68.1-109.6); Control: 80.4 (64.1-105.7)	MMF: 2.37±1.23; Control: 2.47±2.01	MMF 1.5 g/day + prednisolone (6m)	Prednisone (6m)	12	(9)
Hogg et al, 2015	USA	IgAN with UPCR ≥0.6 g/day (males) or ≥0.8 g/day (females); and eGFR ≥50 ml/min/1.73 m² or ≥40 ml/min/1.73 m² in those already receiving RASI	44	62.0	32.0	MMF: 95.3±36.5; Control: 105.6±49.0	NS	MMF: 1.59±0.90; Control: 1.40±0.56	MMF 25-36 mg/kg/day (12m)	Placebo	12	(10)
Liu et al, 2014	China	IgAN ≥Lee III, UPE ≥1.0 g/day, and SCr <267 μmol/l	84	60.7	38.6	MMF: 56.5±17.4; Control: 52.9±18.8	MMF: 134.7±35.2; Control: 127.3±31.4	MMF: 2.83±0.65; Control: 2.77±0.81	MMF 1.5 g/day + prednisone (12m);	CTX + prednisone (12m)	18	(11)
Liu et al, 2010	China	IgAN with nephrotic syndrome	40	52.5	32.0	NS	MMF: 92.8±26.1; Control: 96.4±24.6	MMF: 4.9±2.4; Control: 4.8±2.6	MMF 1.5 g/day + prednisone (6m)	LEF + prednisone (6m)	6	(12)
Tang et al, 2010; Tang et al, 2005	China	IgAN with UPE >1 g/day, SCr ≤300 μmol/l, and Haas subclass II-IV	40	35.0	42.7	MMF: 75±7.3; Control: 69±7.1	MMF: 135.25±15.03; Control: 145.86±20.33	MMF: 1.8±0.21; Control: 1.87±0.28	MMF 1.5-2.0 g/day (6m)	Placebo (6m)	72	(13,14)
Frisch et al, 2005	USA	IgAN with UPE >1 g/day plus ≥2 of the following risk factors: male sex, hypertension, CrCl <80 ml/min and severe lesions on biopsy	32	84.4	38.1	MMF: 38±22.2; Control: 41±26.3	MMF: 229.84±106.08; Control: 194.48±63.65	MMF: 2.7±1.6; Control: 2.7±1.4	MMF 2.0 g/day (12m)	Placebo (12m)	24	(15)
Maes et al, 2004	Belgium	IgAN with CCr 20-70 ml/min/1.73 m² and/or >1 g/day/1.73 m² and/or hypertension and/or histologic unfavorable criteria	34	70.6	40.5	MMF: 60±7; Control: 69±7	MMF: 129.06±7.07; Control: 122.88±8.84	MMF: 1.9±0.3; Control: 1.3±0.4	MMF 2 g/day (36m)	Placebo (36m)	36	(16)
Chen et al, 2002	China	IgAN with Lee IV-V, interstitial area with inflammatory cell infiltration, UPE ≥2.0 g/day and SCr <355 μmol/l	62	75.8	28.5	NS	NS	MMF: 3.2±1.7; Control: 2.9±1.5	MMF 1.0-1.5 g/day (>6m)	Prednisone 0.8 mg/kg/day (>6m)	18	(17)

UPE, urinary protein excretion; eGFR, estimated glomerular filter rate; UPCR, urine protein–creatinine ratio; SCr, serum creatinine; CrCl/CCr, creatinine clearance; IgAN, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RASI, renin-angiotensin inhibitors; CTX, cyclophosphamide; LEF, leflunomide; NS, not stated.

Table II. Definitions of renal remission in the included trials.

Author, year	Complete remission	Partial remission	(Refs.)
Hou *et al*, 2017	Undetectable proteinuria and a stable SCr level (≤25% above the baseline)	0.4<UPE <1.0 g/day, serum albumin level ≥35 g/l, and stable SCr (≤25% above the baseline)	(9)
Hogg *et al*, 2015	UPCR <0.2 g/g	UPCR <50% of level at time of randomization	(10)
Liu *et al*, 2014	UPE <0.4 g/day, serum albumin >35 g/l and stable renal function	UPE declined from ≥50% of the basal value, with stable renal function	(11)
Liu *et al*, 2010	UPE <0.3 g/day, normal levels of serum albumin and SCr and <5/HP RBCs in urinary sediment	UPE 0.3-3.0 g/day or reduced to ≥50% of that before therapy, serum albumin level ≥30 g/l, stable or improved renal function and the decreased RBC count in the urinary sediment	(12)
Tang *et al*, 2005	UPE <0.3 g/day	Decline of UPE ≥50% over baseline value, but UPE >0.3 g/day	(14)
Frisch *et al*, 2005	NS	≥50% decrease in proteinuria	(15)
Chen *et al*, 2002	UPE <0.2 g/day and normal renal function	≥50% decrease in proteinuria and SCr decreased to normal level or declined ≥50% of basal level	(17)

SCr, serum creatinine; UPCR, urine protein-creatinine ratio; UPE, urinary protein excretion; HP, high power field; NS, not stated; RBC, red blood cell.

Table III. Risk analysis of potential bias.

Author, year	Adequate sequence generation	Adequate allocation concealment	Blinding	Address incomplete outcome data	Selective outcome report	Free of other bias	(Refs.)
Hou *et al*, 2017	Yes	Yes	Yes	Yes	Yes	Yes	(9)
Hogg *et al*, 2015	Yes	Unclear	Unclear	No	No	Yes	(10)
Liu *et al*, 2014	Unclear	Unclear	Unclear	Yes	Yes	Yes	(11)
Liu *et al*, 2010	Unclear	Unclear	Unclear	Yes	Yes	Yes	(12)
Tang *et al*, 2005	Unclear	Unclear	No	Yes	Yes	Yes	(14)
Frisch *et al*, 2005	Yes	Yes	Yes	Yes	Yes	No[a]	(15)
Maes *et al*, 2004	Unclear	Unclear	Unclear	No	No	Unclear	(16)
Chen *et al*, 2002	Unclear	Unclear	No	Yes	Yes	Yes	(17)

Yes, low risk of bias; no, high risk of bias; unclear, a judgement could not be made. [a]The study was terminated early as interim analysis revealed no MMF benefit.
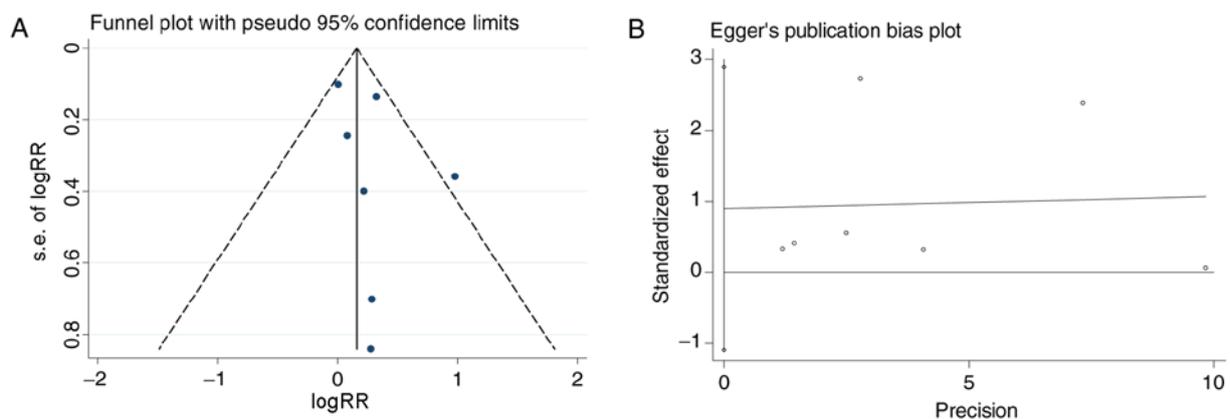

Figure 2. Publication bias. (A) Funnel plots and (B) Egger's regression analysis. RR, risk ratio; s.e., standardized effect.
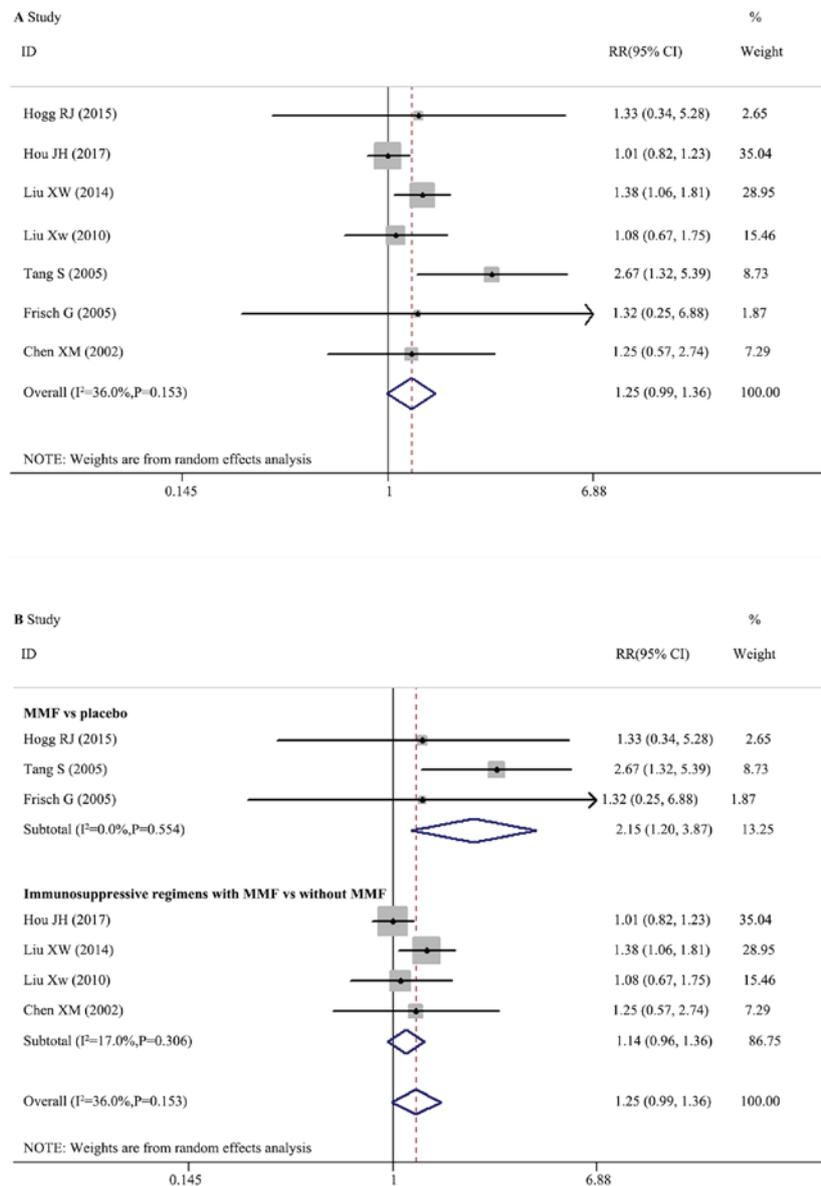
Figure 3. (A) Meta-analysis of the effect of MMF on renal remission in patients with IgAN; (B) subgroup analysis of renal remission rates according to different therapeutic regimens. MMF, mycophenolate mofetil; IgAN, immunoglobulin A nephropathy; RR, risk ratio; CI, confidence interval.

random effects model. The pooled RR was 0.728 (95% CI, 0.164-3.236), which demonstrated that the therapeutic regimens with MMF had no significantly different effects on the ESRD of patients with IgAN compared with regimens without MMF (Fig. 4A; P=0.676). Subgroup analysis based on therapeutic regimens illustrated that there were no significantly different effects on the risk of ESRD between MMF and a placebo (three trials; RR, 0.957; 95% CI, 0.160-5.726; P=0.962) and between the immunosuppressive regimens with MMF and without MMF (Fig. 4B; one trial; RR, 0.205; 95% CI, 0.010-4.200; P=0.303).

Adverse events. Data on adverse events were analyzed (Fig. 5), indicating no significant difference between the therapeutic regimens with and without MMF in terms of the risk of gastrointestinal symptoms (seven trials; n=471; RR, 0.913; 95% CI, 0.458-1.821; P=0.796), diarrhea (three trials; n=142; RR, 4.092; 95% CI, 0.698-24.000; P=0.118), infections (seven trials;

n=654; RR, 1.350; 95% CI, 0.963-1.892; P=0.081), leukopenia (one trial; n=84; RR, 0.333; 95% CI, 0.014-7.956; P=0.497), hepatic dysfunction (three trials; n=299; RR, 0.797; 95% CI, 0.369-1.719; P=0.562), alopecia (two trials; n=259; RR, 0.446; 95% CI, 0.170-1.173; P=0.102) and menstrual disorders (one trial; n=84; RR, 0.143; 95% CI, 0.008-2.683; P=0.193).

Discussion

The present meta-analysis of RCTs demonstrated that therapeutic regimens with or without MMF did not have significantly different effects on the rates of renal remission, ESRD or adverse events for patients with IgAN. Subgroup analyses indicated that MMF was superior to the placebo for renal remission, although not different for ESRD. In addition, immunosuppressive regimens with MMF had no significantly different effects for renal remission or ESRD compared with immunosuppressive regimens without MMF.
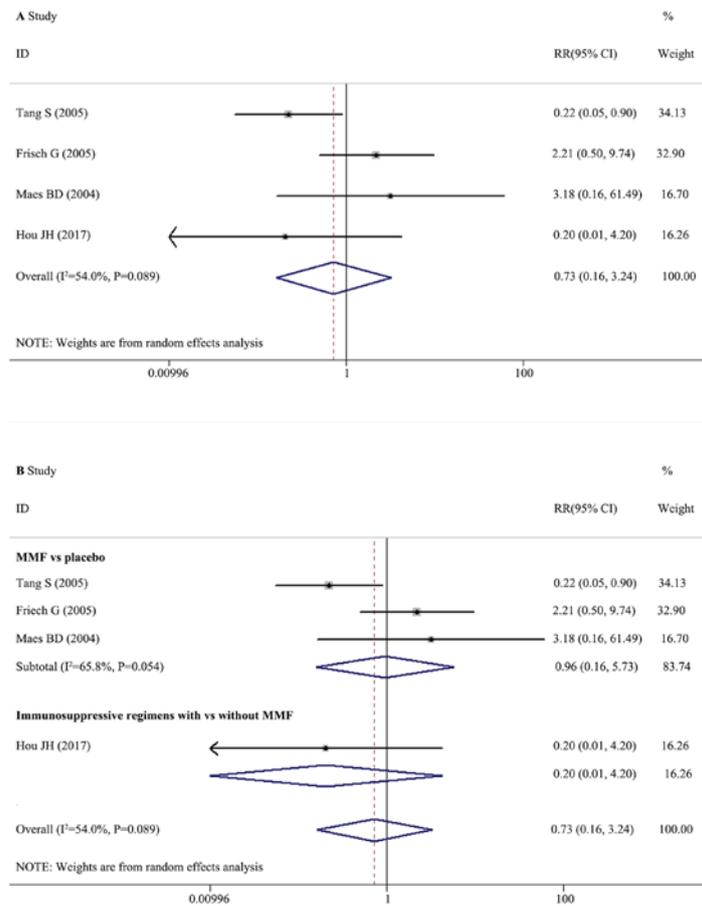
Figure 4. (A) Meta-analysis of the effect of MMF on ESRD in patients with IgAN; (B) subgroup analysis of ESRD rates according to different therapeutic regimens. MMF, mycophenolate mofetil; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; RR, risk ratio; CI, confidence interval.
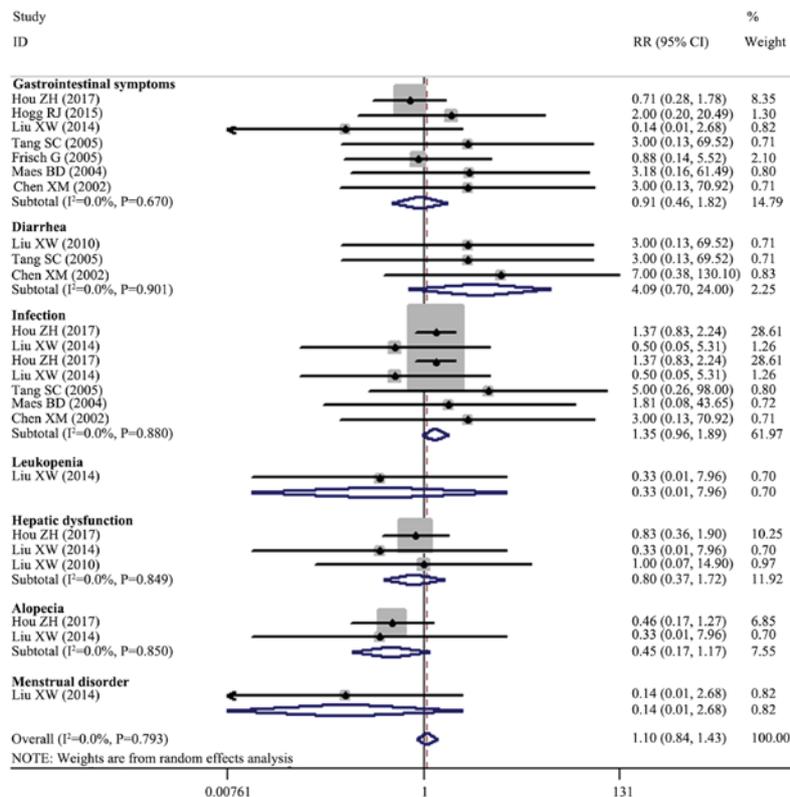

Figure 5. Meta-analysis of the adverse events of therapeutic regimens with and without MMF. MMF, mycophenolate mofetil; RR, risk ratio; CI, confidence interval.

MMF is an immunosuppressive agent, which was first introduced into clinical practice to prevent allograft rejection (24). Subsequently, the clinical application of MMF broadened substantially and it has become part of the first line of treatment in certain types of glomerulonephritis, including lupus nephritis (25,26). MMF is hydrolyzed by esterases in the intestine and blood to release MPA. MPA is able to deplete the pool of deoxyguanosine triphosphate and decrease T and B lymphocyte proliferation by inhibiting inosine 5'-monophosphate dehydrogenase, the rate-limiting enzyme of *de novo* purine synthesis (27,28). It is additionally able to induce apoptosis in immune cells and inhibit the synthesis of fucose- and mannose-containing membrane glycoproteins, altering the surface expression and binding ability of adhesion molecules (6). MPA additionally exerts a direct effect on nonimmune cells, including inhibiting the activation of mesangial cells (28-30). IgAN is an immune-mediated kidney disease and the activation of mesangial cells is a vital part of the pathogenesis of IgAN (31,32). A recent study reported that MMF was able to improve endocapillary hypercellularity and cellular/fibrocellular crescents (33). However, RCTs and previous meta-analyses failed to reach consistent results on the efficacy and safety of MMF in IgAN. At present, this question remains a hot topic in clinical research.

The present meta-analysis of all RCTs, which analyzed the efficacy and safety of MMF in IgAN, including recently published trials (9-11), may supply comprehensive evidence on the use of MMF in IgAN. MMF was superior to placebo for renal remission, but not for ESRD. The majority of included RCTs in the present meta-analysis had short periods of follow-up (6-72 months), which may influence the evaluation of the effects on ESRD. Furthermore, immunosuppressive regimens with MMF exhibited no significant difference on renal remission or ESRD compared with the immunosuppressive regimens without MMF, suggesting that MMF may have a similar therapeutic effect to other immunosuppressants. Additionally, therapeutic regimens with MMF exhibited no significantly different risk of adverse events compared with those without MMF, indicating that MMF did not add to the risk of adverse events.

There are limitations to the present meta-analysis. Risks of biases within the included RCTs may limit the credibility of the present results. Furthermore, the immunosuppressive regimens in the trials varied, including leflunomide plus steroids, cyclophosphamide plus steroids and steroids alone. Further research is required to compare MMF with other immunosuppressant regimens. Additionally, the present study investigated publication bias using funnel plots and Egger's regression analysis, which may have low power to distinguish bias when the included number of trials is small.

In conclusion, the present meta-analysis of the most recent evidence demonstrated that MMF was superior to placebo and may have similar efficacy compared with other immunosuppressants for inducing renal remission in patients with IgAN. MMF may not add to the risks of adverse events. The effect of MMF on the long-term prognosis of patients with IgAN requires verification in further research.

Acknowledgements

Availability of data and materials

The analyzed data generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

LL designed, supervised and mentored the present study; JZ and TB acquired the data; and LL, JZ and LZ performed statistical analysis. The final version of the manuscript was read and approved by all the authors.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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