Mycophenolate mofetil in the treatment of IgA nephropathy: a systematic review

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ABSTRACT

Introduction: The aim of this study was to determine the effectiveness of mycophenolate mofetil (MMF) in IgA nephropathy (IgAN).

Methods: A search through Cochrane Library, EMBASE and PubMed was carried out. Randomised controlled trials (RCTs), which compared MMF with conventional treatments, were identified. Patients' baseline, treatment strategies and study end-points were compared.

Results: Four RCTs (168 patients) were selected. All patients had histologically-confirmed IgAN and proteinuria greater than 1 g/day. The follow-up duration ranged from 1.5 to 3.0 years. MMF was used at a titrated dose of 1–2 g/day. In the two trials with subjects having moderate to high risk for progressive disease, MMF did not demonstrate any significant difference in retarding the decline in renal function and proteinuria reduction. One trial concluded that there was a trend towards worse outcomes when MMF was used in moderately-advanced disease. Only one trial involving subjects with less advanced disease (reflected by a favourable histological grade) showed a significant decrease in proteinuria in the MMF-treated group. No serious adverse events occurred in all the four trials using MMF.

Conclusion: No benefit was seen in moderately-advanced IgAN treated with MMF. In a selected group of patients with less advanced disease, MMF was effective in proteinuria reduction. Larger randomised studies are needed to confirm or reject these results.

Keywords: glomerulonephritis, IgA nephropathy, mycophenolate mofetil, nephropathy, proteinuria

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INTRODUCTION

IgA nephropathy (IgAN) is now recognised as the most common primary glomerulonephritis worldwide.[1] The course of IgAN is variable, and 15%–40% of patients progress to end-stage renal disease over 10–20 years.[2] The pathogenesis of IgAN is complex and not completely understood. Humoral immunity is believed to play an important role, characterised by the predominate mesangial IgA_1 deposition and associated secondary inflammatory response.[3,4] Therapeutic efforts have been directed at either reducing or preventing antigen entry, and altering the abnormal immune response and its consequences. However, to date, the appropriate therapy for IgAN remains uncertain and curative therapy is still not available. Proposed therapies include fish oil,[5-13] angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARB).[14] A meta-analysis concluded that the optimal management of IgAN remains uncertain and all outcomes favour the use of immunosuppressive interventions, with steroids appearing to be the most promising.[15]

Mycophenolate mofetil (MMF) is a highly effective immunosuppressive agent with an acceptable safety profile that was shown in large-scale clinical trials.[16-18] MMF acts by inhibiting T- and B-lymphocyte proliferation, and induces apoptosis of activated T-lymphocytes, reduces synthesis of antibodies, and may decrease the migration of inflammatory cells into glomeruli after antibody deposition.[19] Trials have been done to look at its potential role in treating various primary glomerulonephritis.[20,21] To date, four randomised controlled trials (RCTs) using MMF in IgAN have been conducted with conflicting conclusions.[22-25] Given the burden of the disease and the known risks of progression, the lack of an accepted effective therapy, as well as the conflicting evidence of MMF in the treatment of IgAN, this systematic review was conducted to summarise the benefits and side effects of using MMF in the treatment of IgAN. The following outcomes were compared:

(1) Renal function: serum creatinine level, doubling of serum creatinine and end-stage renal failure (ESRF).
(2) Proteinuria: remission of proteinuria, total urinary protein, urine protein to creatinine ratio.
(3) Adverse events.

METHODS

We included RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, or other predictable methods),

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comparing MMF vs. other immunosuppressive therapies (corticosteroids, cytotoxic agents, others) for the treatment of IgAN. Only studies enrolling adult patients with biopsy-proven IgAN were included. Electronic searches were performed in PubMed (1996–2006), EMBASE (1988 –2006) and Cochrane Library, using a combination of Medical Subject Heading (MeSH) terms and text words related to IgAN, MMF and glomerulonephritits. Additionally, relevant text words relating to all investigated interventions were used. Based on standard systematic review methods, results of these searches were screened initially in their title and abstract form by three of the authors (Tan CHR, Loh PT, Yang WS) according to the above-mentioned inclusion criteria. Studies that clearly did not meet the inclusion criteria (i.e. animal studies, non-RCTs, RCTs of interventions that were not stated in the inclusion criteria, and non-IgAN cases) were excluded. When there was doubt, the full text was analysed. There was no restriction on language.

Three independent reviewers (Tan CHR, Loh PT, Yang WS) assessed each article that met the selection criteria and abstracted the data of interest; discrepancies were resolved by consensus. Data extracted from the selected RCTs were sample size, demographics, ESRF, doubling of serum creatinine level, remission of proteinuria, total urinary protein, urine protein to creatinine ratio, drop-out rate, inability to tolerate treatment, hospitalisation and treatment-related side effects (in particular, leucopenia, gastrointestinal complaints or infection). Methods quality of the selected RCTs was assessed by using standard criteria, looking for allocation concealment, blinding of participants, investigators and outcome assessors, use of intention-to-treat analysis and completeness of follow-up. When data was missing or incomplete, attempts were made to contact the various authors and investigators of the trials via written correspondence for further clarification. For dichotomous outcomes (ESRF, doubling of serum creatinine, remission of proteinuria, adverse events), results were expressed as relative risk (RR) with 95% confidence intervals (CI) for individual studies. Data was pooled using the random effects model. For continuous variables (total urinary protein, urine protein to creatinine ratio), the weighted mean difference (WMD) was used. Heterogeneity was analysed using a χ^2 test on n-1 degree of freedom, with a p-value of 0.05 used for statistical significance.

RESULTS

Our search identified 638 published articles, 81 of which were retrieved for detailed evaluation on the basis of the publication abstract (Fig. 1). Major reasons for exclusion

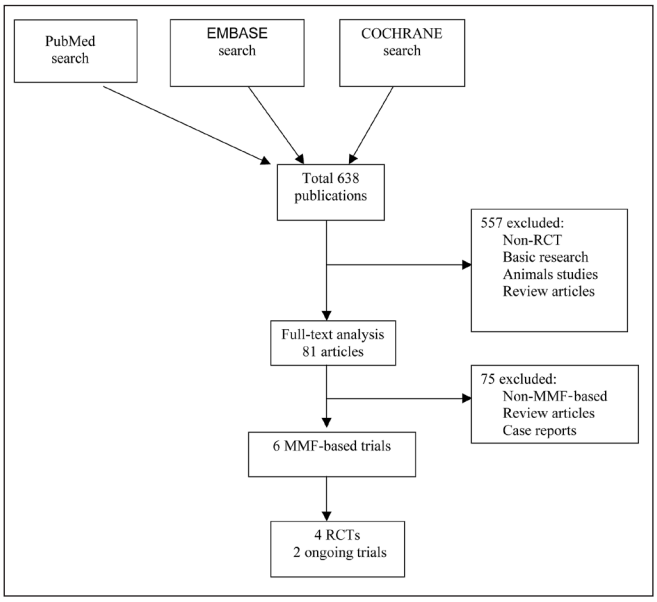

Fig. 1 Flow chart indicating the number of citations retrieved by individual searches and the final number of RCTs included in the systematic review. Reasons for exclusions are provided.

were non-RCTs, basic research and animal studies, review articles, non-IgAN conditions and non-MMF-based treatment. Six RCTs were identified using MMF in adult IgAN, but two were excluded from the final analysis as they were ongoing trials.[26,27] The characteristics of interventions administered, sample size and duration of follow-up in this review are listed in Table I. Three RCTs compared MMF with a placebo,[23-25] while one RCT compared MMF against prednisolone.[22] The duration of follow-up was 1.5–3.0 years. ACEI/ARB were used in three RCTs,[23-25] and the doses were titrated accordingly to achieve target blood pressure. There was no mention of usage of ACEI/ARB in one trial.[22] In two of the trials, all the patients were instructed by dieticians to have a salt-restricted diet.[23,24] Only one trial mentioned the use of fish oil during the follow-up period.[25]

The baseline renal function of various trials is listed in Table II. Most of the patients had renal impairment at baseline (baseline creatinine 1.46–2.6 mg/dL). Various classifications were used for the histological grading; three of the four trials had unfavourable or moderately-advanced histological grading at the baseline.[22,23,25] Only one RCT had a favourable histological grading with minimum glomerulosclerosis at baseline.[24] Not all the outcomes were analysed or reported by each individual trial. Two trials were still in progress and will be evaluated upon publication.[26,27] The trial quality was variable and unclear in general (Table III). Of the four trials, two trials were single centre based,[22,23] one trial involved two centres[24] and one was a multicentre trial.[25] Results of our systematic

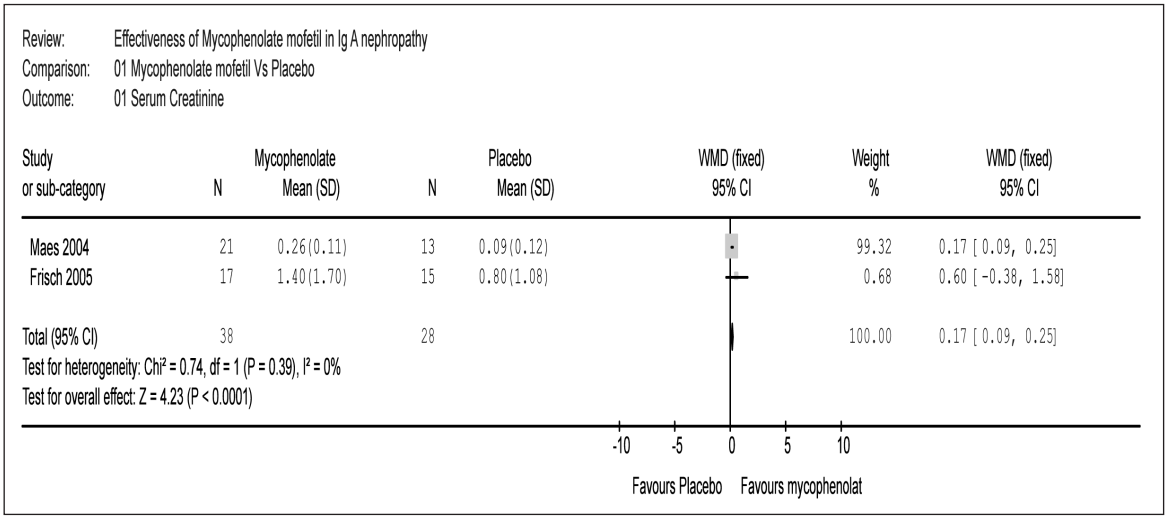

Fig. 2 Forest plot shows the effect of MMF vs. placebo on serum creatinine. There is a significant higher level of serum creatinine in the MMF-treated group at the end of treatment.

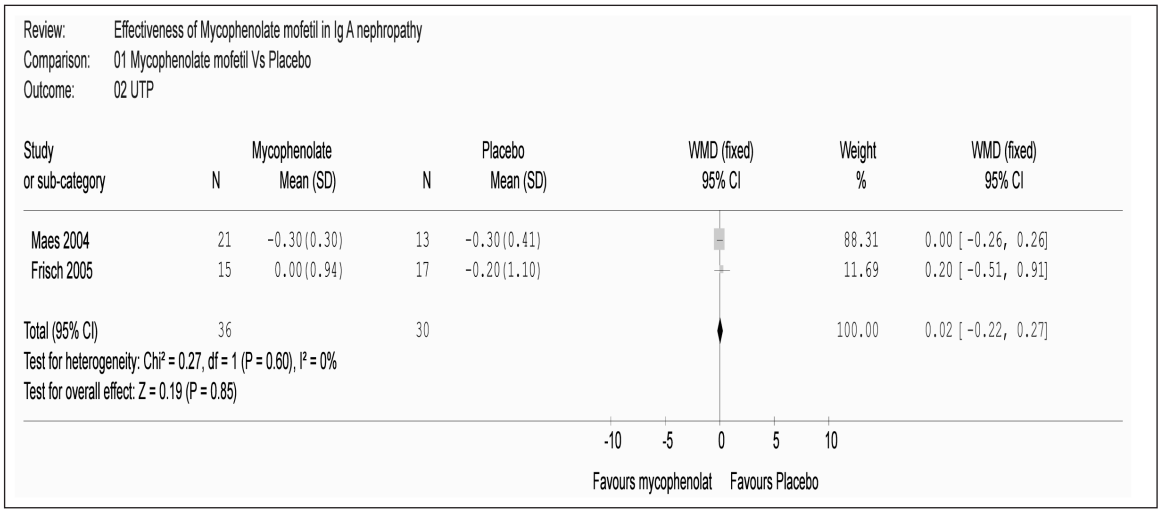

Fig. 3 Forest plot shows the effect of MMF on proteinuria. There is no significant reduction in proteinuria between the MMF- and placebo-treated groups.

review are shown in Figs. 2 and 3. These are forest plots, with a vertical line at 1.0 representing equivalence in risk for an outcome with experimental and control treatments (null hypothesis). The RR for each outcome and its 95% CI are indicated by a solid square and a line. The size of the solid square represents the contribution (weight) of the trial to the analysis. Diamond-shaped symbols represent the summary estimator of overall effect pooling the weighted effect of individual RCTs.

For the effect of MMF vs. placebo on serum creatinine, only two trials reported this outcome and the results were analysed.[23,25] MMF-treated patients had a significantly higher serum creatinine level at the end of treatment compared to the placebo group (66 patients: WMD 0.17 umol/L, 95% CI 0.09–0.25)(Fig. 2). There was no significant heterogeneity between these trials (heterogeneity χ^2 = 0.74, p = 0.39). Tang et al, who reported renal function as rate of change in creatinine clearance, did not show any difference in the overall rate of change in serum creatinine between the MMF-treated groups vs. placebo over the study period [24] The median change in serum creatinine was –0.013 mg/dL/year in the MMF group and +0.108 mg/dL/year in the control group (p = NS). No absolute serum creatinine level was available, hence we were unable to pool the result of this trial with the above-mentioned two trials.

For the effect of MMF on urinary protein excretion, only two trials reported such outcomes and the analysis showed no significant difference in urinary protein excretion between the MMF-treated group and the placebo group (66 patients: WMD 0.02 g/day, 95% CI –0.22 to 0.27)(Fig. 3). Tang et al, however, reported a significant decline in the time-average percentage change in proteinuria in the MMF group, while control subjects displayed a modest rise (p = 0.003).[24] No absolute proteinuria level was available to allow pooling of data with the above two trials for final analysis. When MMF was compared to prednisolone, Chen et al reported a

Table I. Randomised interventions in the trials of MMF in the treatment of IgAN in this systemic review.

Reference	No. of patients	Randomised (intervention vs. control)	Follow-up duration (years)
Maes et al[23]	34	MMF vs. placebo	3
Frisch et al[25]	32	MMF vs. placebo	2
Tang et al[24]	40	MMF vs. ACE-I/ARB	1.5
Chen et al[22]	62	MMF vs. prednisolone	1.5
	Total 168		

Table II. Baseline renal function and histological grading.

Reference	Level of proteinuria (g/day)	Serum creatinine (mg/dL)	GFR / clearance	Histology
Maes et al[23]	1.6–1.9	1.46–1.72	Inulin clearance 69–73 ml/min/1.73m	Unfavourable: high risk (Churg and Sobin Grade II–IV)
Frisch et al[25]	2.7	2.2–2.6	GFR 38–41 ml/min	Unfavourable: high risk (Majority HAAS class ≥ 4. Overall glomerulosclerosis 41%)
Tang et al[24]	1.8	1.53–1.65	Creatinine clearance 69–75 ml/min/1.73m	Lower risk HAAS grade II–III Minimum glomerulosclerosis
Chen et al[22]	2.9–3.2	No data	No data	Unfavourable Lee's grade IV and V

Table III. Quality assessment of RCTs included in this systematic review.

Reference	Allocation concealment	Blinding	Intention-to-treat analysis	Lost to follow-up
Maes et al[23]	Adequate	Not stated	Not reported	6%
Frisch et al[25]	Adequate	Yes	Yes	Nil
Tang et al[24]	Unclear	Not stated	Yes	Nil
Chen et al[22]	Unclear	Not stated	Not reported	Nil

significant reduction of proteinuria in the MMF group (0.6 ± 0.7 g/day vs. 1.4 ± 1.3 g/day, $p < 0.05$).[22]

For the effect of MMF on partial remission (defined as 50% reduction) of proteinuria, Frisch et al reported no significant difference between the MMF group vs. placebo group.[25] Maes et al also noted similar findings.[23] In contrast, Tang et al showed that 80% of the MMF-treated patients experienced partial remission as compared to 30% in the control group ($p = 0.0019$).[24] For complete remission, Chen et al reported a higher complete remission rate (44.4% vs. 19.1%, $p < 0.05$) in the MMF group compared to the control group.[22]

Only two trials reported the effect of MMF on doubling of serum creatinine.[23,25] Both trials reported no significant difference in the doubling of serum creatinine from the baseline in the MMF group vs. placebo group. Only one trial reported the effect of MMF on ESRF. Frisch et al reported no significant difference in the ESRF rate (29% in MMF group vs. 13% in placebo group, $p = 0.40$).[25] MMF is well-tolerated in all four trials. The incidence of gastrointestinal disturbances in the MMF group was 9%–12% in the MMF-treated group, and all the cases resolved with a reduction of the MMF dose. Leucopenia incidence was 0%–5%. There was no serious infection noted in the MMF group and the total infective episode rate was 0%–15%.

DISCUSSION

This is the first systematic review conducted to examine the current RCT evidence for the use of MMF in the treatment of IgAN. From this review, MMF has been shown to have no beneficial effect on the serum creatinine level, reduction and remission of proteinuria, doubling of serum creatinine and ESRF rate. In fact, the serum creatinine level was significantly higher in the MMF group vs. placebo at the end of treatment. One trial[25] was terminated prematurely, as the interim analysis revealed a trend towards a worse outcome in the MMF group and that would have made it very unlikely to show a benefit for MMF eventually, given their rate of recruitment and target sample size. However, both RCTs used in this final analysis involved patients with a more advanced stage

of disease, as evidenced by unfavourable histological criteria (irreversible renal fibrosis, glomerulosclerosis and tubulointerstitial fibrosis), higher serum creatinine level and proteinuria level at baseline.[23,25] Current clinical and experimental evidence support the view that for any immunosuppressive treatment to be beneficial, the treatment should be administered during the early stages of the disease, well before the histological damage becomes irreversible.[28-30] Hence, the lack of benefit for MMF is probably due to the disease being of relatively advanced at the start of both studies.

On the other hand, Chen et al reported in the Chinese literature that MMF was superior to prednisolone in the reduction of proteinuria in IgAN patients with a higher baseline proteinuria level and unfavourable histological grading. 13 (six in the MMF group and seven in the control group) of the 62 patients in that trial had renal impairment, but their baseline serum creatinine level and the degree of renal impairment were not mentioned.[22] MMF was only effective in three of the patients with baseline renal impairment. It was also not stated whether those subjects had been treated with ACEI/ARB or fish oil prior to and during the study, as such interventions have been shown to affect outcomes of IgAN.[5-14] There was also no mention of blood pressure control in both groups, which is of paramount importance to the progression of renal failure.

As for the less advanced disease, as shown in the trial of Tang et al, MMF was effective in lowering proteinuria.[24] Proteinuria has been widely accepted as a surrogate marker for kidney failure, hence a reduction in proteinuria in the MMF-treated group may indicate the effectiveness of MMF in the treatment of early IgAN. This probably highlighted the importance of early immunosuppressive therapy before irreversible histological damage sets in. In this similar paper, although there was no demonstrable difference in the rate of change in serum creatinine level over the study period (72 weeks) between the MMF and placebo groups, this is not unexpected as renal failure in IgAN usually takes 15–30 years to develop from the time of disease onset.[31]

One major deficiency in these trials was that MMF was used as a monotherapy in the treatment of IgAN. However, most of the immunosuppressive regimes used in the treatment of primary glomerulonephritis have used combination therapies, which include steroids as one of the agents, and some of these trials have shown that combination therapy was more effective in achieving target end points.[32-35] This review showed that MMF as a monotherapy is not effective in the treatment of IgAN, especially in the advanced stage; however, combination therapy of MMF with steroids may yield a more positive outcome. Hence, future trials may be conducted to explore the effectiveness of combination therapy vs. monotherapy. Lastly, the four RCTs in general were small in sample size, resulting in insufficient statistical power. The methodological quality of the four RCTs is generally suboptimal.

In conclusion, MMF did not improve the outcome of IgAN patients with more advanced disease, while MMF may be effective in proteinuria reduction in early IgAN cases. The trials available for the use of MMF in IgAN are small and very limited. The patients involved are of different histological stages, hence making comparison difficult. More trials involving bigger number of patients in both early and advanced stages of IgAN using combination therapy vs. monotherapy are required.

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