Immunoglobulin A Nephropathy: Mycophenolate Mofetil Therapy

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Abstract:
Immunoglobulin A Nephropathy (IgA) is the most common primary glomerulonephritis all over the world. The cause of IgA nephropathy is variable, with some patients having stable renal function over decades and others developing nephrotic syndrome, hypertension and progressive renal failure. Most clinicians employ therapy with angiotensin converting enzyme inhibitors or more recently, angiotensin 2 receptor blockers for hypertension and proteinuria. Mycophenolate mofetil (MMF) is increasingly used to treat primary glomerulopathies but there are limited data concerning the efficacy of Mycophenolate mofetil in the primary treatment of progressive IgA nephropathy. Its effectiveness and safety in IgA nephropathy has been evaluated in four major trials, prospective placebo-controlled randomized trials, which have produced conflicting results. The conflicting results range from a reduction in proteinuria towards a worse outcome in mycophenolate mofetil group.

Introduction:
The term glomerulonephritis means inflammation of the glomerulus and related structures. Glomerular diseases are most simply defined as either primary in which the disease process is confined to the kidney or as a secondary in which a systemic disease impacts the kidney. Glomerulonephritis is recognized as the second most common cause of end-stage renal failure world-wide.[1]

Immunoglobulin A (IgA) is the most common cause of primary glomerulonephritis.[2] It slowly progresses to end-stage renal disease (ESRD) in up to 50% of patients.[3,4] The remaining patients enter a sustained clinical remission or have persistent low grade hematuria or proteinuria. A minority of patients may experience a rapidly progressive glomerulonephritis with crescent formation on biopsy. Occasionally, reversible acute renal failure occur during episodes of gross hematuria.[5]

There are two separate approaches to the therapy of IgA nephropathy. General intervention to slow progression that are not specific to IgA nephropathy including control of blood pressure, angiotension converting enzyme inhibitor (ACEI) and/or angiotension 2 receptor blocker (ARB) in patients with protenuria and statin, along therapy of corticosteroids with or without other immunosuppressive agents.[6,7]

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase involved in de novo purine synthesis. It is a suppressor of both T and B cell lymphocyte proliferation and has been successfully used for the prevention of acute and chronic rejection of renal allografts.[8-11]
Currently MMF is recommended for use with cyclosporine and steroids in patients receiving allogenic renal and other organ transplants.[12]

MMF may have therapeutic application beyond immune-suppression in transplant patients. This is particularly true for immune-mediated glomerular disease. Preliminary results suggest that MMF is effective in several types of glomerulonephritis.[13]
This study was carried out for clinical appraisal of MMF in management of IgA nephropathy.

Material and Methods:
Pubmed database and Cocbrane library was searched from January 1998 to July 2007 by the use of the terms "Mycophenolate mofetil (MMF) and glomerulonephritis". Articles were included:

1- If the studies were randomized control, double blind and cohort designs investigating the MMF in treatment of IgA nephropathy.

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2- The study population consisted of patients who received at least three months of treatment with MMF.
3- Diagnosis of the disease made by renal biopsy.
4- Patients aged 18-75 years.
5- The primary study outcomes were the change in the urinary protein excretion, serum creatinine, plasma albumin, renal function comparing the levels at the start of MMF treatment with those at the end of therapy.

The following questions were addressed for the critical appraisal of four out of thirteen studies on MMF use in primary glomerular disease:[14-18]

1. What was the research question?
2. Did the researcher use an appropriate study design to answer the question?
3. Was an appropriate group of subjects studied?
4. Was the sample size justified?
5. Were all subjects classified into exposure groups using the same procedure?
6. Was the assignment of patients to treatments randomized?
7. What was the outcome measured?
8. Was systematic bias avoided or minimized?
9. Were all patients entered into the study properly accounted for?
10. Were there any missing data?
11. Was the control group appropriate?
12. Were side-effects and adverse outcomes documented?
13. How large was the treatment effect?
14. Did the results of the study fit with other available evidence?

Results:

The role of mycophenolate mefetil (MMF) in IgA nephropathy has been evaluated in four major trials Tables 1,2,3 and 4.

Chen (2002)[4] investigated the effective and safety of MMF in 62 Chinese patients with IgA nephropathy. The initial dose of MMF was 1 g/day. Another 31 patients were given prednisolone orally, in a dose of 0.8 mg/kg/day as a control. The duration of treatment was 18 months. After 3 months, there was a decrease of proteinuria (1.9±1.6 g/day vs 3.2±1.7 g/day; p=0.01) and improvement of plasma albumin (41±6 g/L vs 37±6 g/L; p=0.01). At the 12th and 18th months, the proteinuria in MMF group significantly improved than the control (0.8±0.8 g/day vs 1.4±1.6 g/day; and 0.6±0.7 g/day vs 1.4±1.3 g/day; p=0.05 respectively). The remission rate and total effective rate of MMF group were higher than those of the control (44.4% vs 19.1% and 88.9% vs 61.9%; p=0.05 respectively) Table 1.

Table 1: A randomized control trial of MMF treatment in severe IgA nephropathy.

Author	Chen 2002[15]
Methods	Randomization
Participants	N=62 patients, China Mean urine protein > 2 g/day.
Intervention	MMF vs prednisone (n=31 patients)
Outcome	- Decrease urinary protein and improvement of plasma albumin in MMF group. - Serum Cholesterol and triglyceride were lower in MMF group (remission of proteinuria). - The effective rate was 50% in MMF group and 28.6% in the control. - Histopathology at 12 months in MMF group showed that interstitial lesions were alleviated.
Note	Total course of treatment was 18 months. Serum creatinine was high in prednisone group at 72 weeks.

Tang and Co-workers (2005)[16] investigated 40 patients with IgA nephropathy who had persistent proteinuria (> 1 g/day) despite conventional treatment with angiotensin converting enzyme inhibitors (ACEI), Table 2.

Table 2: Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy.

Author	Tang 2005[16]
Methods	Randomization controlled trial
Participants	N=40 patients, Hong Kong persistent proteinuria (> 1 g/day) Use of ACEI during follow up
Intervention	Compared MMF with conventional therapy.
Outcome	- 16 patients (80%) in MMF group vs 6 patients (30%) in the control reached the primary end point (reduction of proteinuria by ≥ 50% over the entry point) - Significant decline in proteinuria in MMF group. - Increase in serum albumin and decrease in serum IgA levels in MMF group. - No change in plasma lipids.
Notes	Treatment was for 72 weeks. No difference in serum creatinine and creatinine clearance rate.

Patients were randomized to receive MMF 1.5-2.0 g/day according to body weight for 24 weeks or continue conventional therapy and followed for 72 weeks. The primary end point was reduction of proteinuria by 50% or more over entry point. The remission of proteinuria (complete or partial) was the primary end point with respect to efficacy in this study.
Over the 18–month study, a total of 22 patients (16 patients in MMF vs 6 patients in the control) had remission of proteinuria (P = 0.001).

In MMF group, the remission of proteinuria was complete in 4 patients and partial in 12 patients. In the control group, only one patient achieved complete remission of proteinuria and five patients had partial remission, whereas 14 patients (70%) had persistent proteinuria throughout the study.

The improvement of proteinuria in MMF group was associated with an increase in serum albumin level from 3.83 ± 0.06 g/dL at the baseline to 3.94 ± 0.07 g/dL at the end of treatment (p= 0.003). There was no significant change in serum albumin in the control group.
The mean serum IgA in MMF group dropped from 360 ± 30 mg /dL at the baseline to 320 ± 30 mg /dL at the end of treatment (P=0.001) but was unchanged in the control. There was no difference in the overall rates of change in serum creatinine, creatinine clearance and plasma lipids between the two groups over the study period.

In contrast, Maes (2007)[17] randomized 34 patients with IgA nephropathy (Table 3) who were treated with salt restriction, angiotensin converting enzyme inhibitor (ACEI) and MMF 2 g/day (N=21) or placebo (N=13) for 36 months.

The primary end point of the study was the loss of renal function, defined as a decrease of 25% or more in the inulin clearance during the 3 year treatment period.

Secondary end point were the cumulative percentage of patients that were free of death, development of end-stage renal disease (ENRD), defined as chronic repetitive dialysis on renal transplantation or discontinuation of therapy due to adverse events or non-compliance, and the cumulative percentage of patients whom serum creatinine increased by 50% or more over 3 years.

By the end of the study there was no significant difference in the cumulative percentage of patients whom serum creatinine increased by 50% or more (P=0.156).

Survival free of ESRD was in both groups (P=0.187). Adverse events leading to discontinuation of treatment or refusal to continue therapy were also similar in both groups (P=0.742).
There were no significant differences in serum creatinine (P=0.65), 24 hours proteinuria (P=0.17) and inulin clearance (P=0.57) at 3 years follow up.

Table 3: Mycophenolate mofetil in IgA nephropathy: results of a 3 – year prospective placebo-controlled randomized study.

Author	Maes 2004[17]
Methods	Prospective placebo-controlled randomized study
Participants	N=34 patients, University of Leuven. No difference in gender. Age 18 years and older. Proteinuria unfavourable features (impaired renal function; proteinuria; hypertension; severe lesions on biopsy. Use of ACEI during follow up
Intervention	MMF 2 g/day (N=21) vs placebo (N=13).
Outcome	There was no difference in the percentage of patients with a decrease of 25% or more in the inulin clearance or with a serum creatinine increase of 50% or more over 3 years. No significant difference was noted between the groups for inulin clearance, serum creatinine, proteinuria, blood pressure or other parameters of renal function.
Note	The treatment follow-up 36 months.

Similarly Frisch et al (2005)[18] were unable to demonstrate benefit of MMF in patients with moderately advanced IgA nephropathy in a placebo controlled randomized study, Table 4. The study patients had a mean serum creatinine of 2.4 mg/dL and mean urine protein excretion of 2.7 g/day and thus were at high risk of progressive renal disease. All patients had optimum blood pressure control with ACEI. They included patients who had at least 1 g/day urinary proteinuria plus at least two of the following risk factors: male sex, hypertension, creatinine clearance ≤ 80 ml/minute at time of enrollment, presence of glomerulosclerosis in Tubuls-interstitial atrophy and fibrosis and/or crescent formation in > 25% of the renal biopsy.

By the end of the study there were no statistically significant differences in outcomes between MMF and the control groups. The rate of the primary outcome of a 50% increase in serum creatinine from the baseline was five out of 17 patients treated with MMF versus two out of 15 patients in the placebo (P=0.4).

Table 4: Mycophenolate mofetil vs placebo in patients with moderately advanced IgA nephropathy: A double blind randomized controlled trial

Author	Frisch, 2005[18]
Methods	A double–blind randomized study
Participants	N=32 patients at high risk for progressive disease. Age = 18 – 75 years. At least 1 g/day proteinuria. Male sex. Hypertension > 150/90 mmHg. Creatinine clearance < 80 ml/min. Glomerulosclerosis, tubulo-interstitial atrophy and fibrosis, or crescent in > 25% of the renal biopsy. North American (Columbia University) Multiple Centres.
Intervention	MMF (N = 17) vs placebo (N = 15).
Outcome	Primary outcome was a 50% increase in baseline serum creatinine ESRD 50% reduction in proteinuria No statistically significant differences were observed for any outcome. All patients who reached the primary outcome also reached ESRD.
Note	Treatment for 2-year follow-up. The 24 hours proteinuria, serum albumin and cholesterol were similar in both groups. No serious adverse events occurred in either group.

The secondary outcome of a 0.5 mg/dL increase in serum creatinine occurred at a rate of 10 out of 17 MMF patients versus seven out of 15 placebo patients (P=0.7).
All patients who had a 50% increase in serum creatinine developed ESRD. The mean follow-up serum creatinine (4 mg/dl vs 3.1 mg/dl) and 24 hour urinary protein excretion (3.1 g/day vs 2.7 g/day) in the MMF group were worse than the placebo.

Discussion:
IgA nephropathy is the most common primary glomerulonephiritis over the world.[19] The course of IgA nephropathy is variable with some patients having stable renal function over decades while others developing nephritic syndrome, hypertension and progressive renal failure.
The appropriate therapy for IgA nephropathy remains uncertain. Most clinicians employ therapy with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin 2 receptor blockers (ARB) for control of hypertension and proteinuria.
Despite this, many patients remain significantly proteinuric after treatment with ACEI.
Mycophenolate mofetil (MMF) is a highly effective immunosuppressive drug with an acceptable safety. It has become one of the standard immunosuppressive agents in many transplant centres and has been successfully used in short-term pilot studies to treat immune-mediated glomerulo-pathies and systemic immune disorders. There are limited data concerning the efficacy of MMF in the treatment of progressive IgA nephropathy. The effectiveness and safety of MMF in IgA nephropathy had been evaluated in four major trials which produced conflicting results.
Following a randomized control trial of MMF, Chen showed a benefit with respect to proteinuria and hyperlipidaemia in MMF treatment arm. Serum creatinine was higher in the prednisolone group.
Treatment with MMF was associated with good tolerance. However, it was not stated whether these patients were treated with ACEI, ARB prior to and during the study.[15]
Tang et al reported a greater and sustained reduction of proteinuria in patients treated with MMF, but there was no difference in serum creatinine levels.[16]
Results of a 3-year-prospective placebo-controlled randomized study failed to show an additive effect of MMF versus placebo on the progression of renal disease in patients with unfavourable prognostic features. However, the lack of the beneficial effects of MMF might be explained by the following factors. First, the number of study patients was small because of the single centre design. Second, outcomes of interest in the design should be simple and clinically relevant, in this the development of ESRF would be the ideal outcome. However, the natural history of IgA nephropathy implies that 15-20% of patients reach ESRF in 10 years from the apparent onset of the disease. Nevertheless, it would be unfeasible to treat a cohort of patients with immunosuppressive agent for too many years. Third: patient selection might have influenced the outcome of the study. Only patients with IgA nephropathy without severe renal insufficiency, whom have unfavourable prognostic features, were studied. Thus, it remains unclear whether MMF would be useful in the subset of patients with less severe disease in who immunosuppressive agents could have had a therapeutic impact.[16]
The results of double-blind randomized trial of MMF versus placebo in patients with moderately advanced IgA nephropathy revealed a trend towards a worse outcome in the MMF group. However, the lack of benefit for MMF was probably due to the presence of relatively advanced disease in both groups at the start of the study. The study design was to select a group at high risk for progressive disease in order to ensure sufficient numbers of end-points in a disease entity. Moreover, the relatively short length of treatment and follow-up and the small study size might have been a factor in failing to show a benefit in favour of MMF.[18,19]
In conclusion, there are limited data concerning the efficacy of MMF in the primary treatment of IgA nephropathy. Four major trials of prospective placebo-controlled studies of MMF in IgA nephropathy have produced conflicting results. The conflicting results ranged from a reduction in proteinuria to a trend towards a worse outcome in the MMF group.

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