Mycophenolate mofetil in the treatment of IgA nephropathy: a systematic review
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CRD summary
The authors concluded that limited evidence showed no benefit of mycophenolate mofetil in moderately advanced IgA nephropathy and a reduction in proteinuria in less advanced disease. There were limitations in reporting of review methods and conclusions were based on limited evidence, so any conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness and safety of mycophenolate mofetil (MMF, an immunosuppressive agent) in IgA nephropathy (IgAN).

Searching
PubMed (from 1996), EMBASE (from 1988) and The Cochrane Library were searched using reported search terms. No language restrictions were applied. Two ongoing studies were excluded.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs that compared mycophenolate mofetil with other immunosuppressive agents in adult patients with biopsy proven IgA nephropathy were eligible for inclusion. Two ongoing studies were excluded. The review assessed: renal function (serum creatinine level, doubling of serum creatinine and end-stage renal failure); proteinuria (remission of proteinuria and total proteinuria); and adverse events (leukopenia, gastrointestinal complaints and infection).

The included studies evaluated mycophenolate mofetil in a titrated dose of 1 to 2 g/day and compared mycophenolate mofetil with placebo and/or angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) or prednisolone. Most patients had renal impairment at baseline (baseline creatinine 1.46 to 2.5 mg/dL). Studies used three different histological grading classification systems; three studies were in high-risk patients and one study was in low-risk patients. Co-interventions included ACEI/ARB, salt-restricted diet and fish oil. The duration of follow-up ranged from 1.5 to 3.0 years.

Three reviewers screened titles and abstracts, but it was unclear whether the screening was performed independently and how many reviewers subsequently selected studies.

Assessment of study quality
Validity was assessed in terms of allocation concealment, blinding, use of intention-to-treat analysis and completeness of follow-up.

It was not entirely clear whether three reviewers independently assessed validity.

Data extraction
Dichotomous measures were expressed as relative risks and continuous measures as mean differences, with 95% confidence intervals (CI).

Three reviewers independently extracted data and resolved discrepancies through consensus. Attempts were made to contact authors for missing data.

Methods of synthesis
Where studies were comparable, pooled relative risks and weighted mean differences with 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Other studies were combined in a narrative synthesis.
Results of the review
Four RCTs were included (n=168). Two studies used adequate methods of allocation concealment, one reported blinding and two reported intention-to-treat analysis; three reported no losses to follow-up and one reported a 6% loss.

Renal function: In two studies (n=66) of high-risk patients, mycophenolate mofetil was associated with a statistically significant increase in serum creatinine compared to placebo (weighted mean difference 0.17 μmol/L, 95% CI: 0.09 to 0.25, p<0.0001). No significant heterogeneity was found. In one study (n=40) in lower-risk patients, there was no statistically significant difference between mycophenolate mofetil and placebo in the overall rate of change in serum creatinine.

Proteinuria: In high-risk patients there was no statistically significant difference between mycophenolate mofetil and placebo in urinary excretion of protein (two studies), doubling of creatinine (two studies), partial remission (three studies) or end-stage renal failure (one study). In low-risk patients (one study, n=40), mycophenolate mofetil was associated with a statistically significant reduction in the time-average percentage change in proteinuria (p=0.003) and a significantly higher partial remission rate compared to ACEI/ARB (80% versus 30%, p=0.0019). In high risk patients (one study, n=62), mycophenolate mofetil was associated with a significant reduction in proteinuria (0.6 versus 1.4 g/day, p<0.05) and a significant increase in complete remission rates compared to prednisolone (44% versus 19%, p<0.05).

Adverse events: All studies reported that mycophenolate mofetil was well tolerated. Gastrointestinal disturbances were reported in 9% to 12% of mycophenolate mofetil patients, leukopenia in 0 to 5% and the total infection episode rate was 0 to 15%. No serious infections were reported in mycophenolate mofetil groups.

Authors' conclusions
Limited evidence showed no benefit of mycophenolate mofetil in moderately advanced IgA nephropathy and a reduction in proteinuria in less advanced disease. Further research was required.

CRD commentary
The review question was clearly stated. Inclusion criteria were clearly stated, but not adhered to. Eligible studies were those that compared mycophenolate mofetil with other immunosuppressive agents, but only one study that used prednisolone as the control met these criteria. Other studies used ACEI/ARB or placebo as controls and these agents are not immunosuppressive. Several relevant sources were searched and no language restrictions were applied, but no attempts were made to minimise publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was unclear whether similar steps were taken in study selection and validity assessment. Validity was assessed and results were reported. Pooling only comparable studies was appropriate. There were limitations in reporting of review methods and conclusions were based on limited evidence, so any conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger studies were required to compare combination therapy that included mycophenolate mofetil with monotherapy in patients in both early and advances stages of IgA nephropathy.

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