Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review

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CRD summary
This review concluded that mycophenolate mofetil used with a calcineurin inhibitor conferred a clinical benefit over azathioprine by reducing the risk of acute rejections and possibly reducing graft loss in patients receiving kidney transplants. This was a well-conducted review, but these conclusions should be treated cautiously given the poor quality of most of the evidence.

Authors’ objectives
To assess the effectiveness of mycophenolate mofetil for improving outcomes in renal transplant recipients compared with azathioprine.

Searching
The Transplant Library from the Centre for Evidence of Transplantation was searched from January 1995 to June 2007. This library included RCTs identified from PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and transplantation conference proceedings handsearching. Additional searches of MEDLINE, EMBASE and CENTRAL were also made to identify earlier trials (from 1985 to 1995). There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared mycophenolate mofetil with azathioprine as immunosuppressive agents in renal transplant recipients were eligible for inclusion. Trials that evaluated other types of transplant, or that changed more than one immunosuppressant agent between groups, or where randomisation occurred after the time of transplantation, were excluded.

Outcomes of interest were acute rejection incidence, patient survival, graft survival, graft function and side effects (malignancy, infection, gastrointestinal and haematological problems).

The included trials compared varying doses of azathioprine (between 1mg/kg/day to 150mg/day) with varying doses of mycophenolate mofetil (between 1g/day and 3g/day). All patients were also taking a calcineurin inhibitor that included cyclosporine A micro-emulsion, sandimmune or tacrolimus.

Studies were selected by two reviewers independently, with disagreements resolved by consensus.

Assessment of study quality
Trial quality was assessed using the Jadad scale that included randomisation, blinding and reporting of withdrawals. A score of 3 or more out of 5 points was considered good quality. Extra questions covering allocation concealment and description of blinding were added.

Study quality was assessed by two reviewers independently, with disagreements resolved by discussion.

Data extraction
Dichotomous outcomes were extracted as relative risks (RR), continuous outcomes as mean differences (MD), and time to event outcomes as hazard ratios (HR), with their corresponding 95% confidence intervals (CI).

Data were extracted by two reviewers and checked at random by a third.

Methods of synthesis
Trials were pooled in either fixed-effect or random-effects meta-analyses. Heterogeneity was measured using the $I^2$.
statistic. If hazard ratios were not reported, they were estimated using standardised recalculation methods. Subgroup analyses were used to compare drugs for patients on different calcineurin inhibitors and for mycophenolate mofetil dose (below 2g/day, 2g/day or over) using a statistical test of interaction. Sensitivity analyses repeated the models using only moderate to high quality trials (scoring 2 or more points) and investigated the impact of imputing missing data. Publication bias was assessed using funnel plots.

**Results of the review**

Nineteen RCTs (n=3,143 patients) were included in the review. Trial quality was poor, with only two trials scoring 3 or more on the Jadad scale. Only two trials reported adequate allocation concealment and seven used an intention-to-treat analysis. Duration of follow-up ranged from six to 60 months.

**Acute rejection**: Mycophenolate mofetil significantly reduced the risk of acute rejection compared with azathioprine (RR 0.62, 95% CI 0.55 to 0.70; 17 RCTs; I²=6.8%). Subgroup analyses showed that the risk reduction of acute rejection was greater in patients receiving sandimmune (RR 0.53) than microemulsions (RR 0.70); this was also the case in patients receiving higher doses (3g/day) of mycophenolate mofetil (RR 0.48) compared with lower doses (2g/day or less) (RR 0.66). Sensitivity analyses of higher quality trials did not alter the results. There was some evidence of publication bias.

**Patient and graft survival**: Mycophenolate mofetil reduced the hazard of graft loss (HR 0.76, 95% CI 0.59 to 0.98; 11 RCTs; I²=0%) There were no significant differences for patient survival or graft loss, or between subgroups. There was no evidence of publication bias. When the analysis was repeated for higher quality trials, the results were no longer statistically significant, but only three trials were included. There was no evidence of a difference between mycophenolate mofetil and azathioprine for patient survival or graft loss, excluding patient death with a functioning graft.

**Graft function**: Graft function measured by serum creatinine showed no overall difference between groups, but the observed heterogeneity was moderate (I²=40.3%). There was no evidence of a difference in the glomerular filtration rate.

**Side effects**: Mycophenolate mofetil increased the risk of diarrhoea (RR 1.57, 95% CI 1.33 to 1.86; six RCTs; I²=1.5%), but there were no differences between mycophenolate mofetil and azathioprine for vomiting or nausea or for more severe side effects (infections, anaemia, leukopenia or malignancy).

**Authors’ conclusions**

Mycophenolate mofetil used with a calcineurin inhibitor conferred a clinical benefit over azathioprine by reducing the risk of acute rejections and possibly reducing graft loss. This effect was independent of whether mycophenolate mofetil was used with sandimmune, neoral or tacrolimus.

**CRD commentary**

This review had clearly stated study inclusion criteria covering the interventions, participants, study designs and outcomes. The search strategy appeared to be thorough and was not restricted by language. Study selection, data extraction and quality assessment were performed by two reviewers independently to reduce errors or bias.

Trials were quality assessed. The methods of meta-analysis were appropriate and included sensitivity analyses excluding the poor quality trials. The reporting of results in the figures and tables were clear, although there were a few discrepancies in the text.

On the whole, the conduct of this review was good, but these conclusions should be treated cautiously given the poor quality of most of the evidence.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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