Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation

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Authors' objectives
To assess the effectiveness of tacrolimus (Prograf) and mycophenolate mofetil (Cellcept) as maintenance immunosuppressants following renal transplantation.

Searching
The authors searched the electronic databases of MEDLINE (1985 to 1998), EMBASE, and the Cochrane Controlled Trials Register. The tacrolimus search included ‘>Prograf=’, ‘>FK506’, and the CAS registry number. The mycophenolate mofetil search included ‘>Cellcept=’, and the CAS registry number. A subsequently published meta-analysis of tacrolimus was also identified and reviewed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) where tacrolimus or mycophenolate mofetil were compared against a placebo or each other. Duration of tacrolimus trials was 12 months, and 6 months- 3 years for mycophenolate mofetil. Small preclinical and phase II studies were excluded. To be included, the studies had to have a minimum follow-up period of 3 months post-transplantation.

Specific interventions included in the review
Maintenance immunosuppression combinations of:
1. Tacrolimus (Prograf), azathioprine, and prednisolone.
2. Cyclosporin, mycophenolate mofetil (Cellcept), and prednisolone.
3. Cyclosporin, azathioprine, and prednisolone. In the tacrolimus trials, cyclosporin had initial doses of 6.9 mg/kg reducing to an average of 3.5 mg/kg over months 10-12 (European trial) compared to mean dose in the US trial of 5.5 mg/kg, and tacrolimus had initial doses of 0.26 mg/kg reducing to an average of 0.12 mg/kg (European trial) compared to mean dose in the US trial of 0.18 mg/kg.

In the mycophenolate mofetil trials.

Participants included in the review
Male or female patients undergoing renal transplantation.

In the tacrolimus trials, one trial included patients over 18 years of age and the other trial included patients over 6 years of age who were receiving their first or second transplant. Patients were excluded for the following reasons: serological evidence of Human Immunodeficiency Virus; ABO-incompatible grafts; and those undergoing multiple organ transplants. Women who were pregnant, lactating or who were using inadequate contraception were excluded as were patients with significant hepatic disease.

In the mycophenolate mofetil trials, patients were over 18 years of age. Patients were excluded for the following reasons: serological evidence of Human Immunodeficiency Virus; ABO- incompatible grafts; a history of malignant disorders; severe diarrhoea; and gastrointestinal disorders. Women who were pregnant, lactating or who were using inadequate contraception were excluded as were patients with a white blood count or platelet count below a certain level, or a haemoglobin concentration of <6 g/dl at the time of randomisation.

Outcomes assessed in the review
Outcome measures of graft loss or quality and duration of life during the transplant period were measured by a proxy or surrogate outcome measure: the occurrence of acute rejection. A secondary outcome assessed in the trials was the severity of episodes of acute rejection.

How were decisions on the relevance of primary studies made?
The searches were assessed by title and abstract, where available, by one clinical and one analytical support member of the review team.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted for the categories of: trial identification; study design, patient numbers; inclusion criteria; exclusion criteria; study period; mean daily dose; efficacy; withdrawal due to adverse events (tacrolimus); and withdrawal due to adverse events and treatment failure (mycophenolate mofetil).

Methods of synthesis
How were the studies combined?
A narrative synthesis was used.

How were differences between studies investigated?
No statistical tests for homogeneity were carried out. However, the authors visually assessed and discussed the heterogeneity between the studies.

No tests for homogeneity were performed on the trials of mycophenolate mofetil.

Results of the review
Two randomised, open-label, placebo-controlled trials of tacrolimus and three multicentre randomised, double-blind trials of mycophenolate mofetil (one of which was placebo-controlled) were identified for the review. The tacrolimus studies had 860 participants (n = 508 tacrolimus, and n = 352 cyclosporin) and the mycophenolate mofetil studies had 1493 participants (n = 490 3g mycophenolate mofetil, n = 503 2g mycophenolate mofetil, n = 166 placebo and n = 328 azathioprine).

Tacrolimus (2 studies):
Trials of tacrolimus, which replaces cyclosporin, showed a biopsy proven acute rejection rate for cyclosporin of between 43.4% and 46.4%, and between 24.1% and 30.7% for tacrolimus. The absolute decrease in first biopsy proven acute rejection rate was approximately 15-20%. This implies that the number needed to treat (NNT) to avoid acute rejection in one patient is between five and seven. The severity of episodes of corticosteroid resistant acute rejection was lower with tacrolimus at 10.2% compared to 20.7% for cyclosporin in the European trial and 10.7% for tacrolimus compared to 25.1% for cyclosporin in the other trial.

A new preparation of cyclosporin (Neoral) in comparison to the older formulation (Sandimmum) found reductions in acute rejection ranging from 8% to 16% (3 RCTs, 698 participants).

Adverse events for tacrolimus were: increased incidence of tremor; increased diabetes mellitus; increased incidence of alopecia and decreased incidence of hirsutism; and decreased incidence of gingival hyperplasia. Withdrawal rate was statistically significantly higher for tacrolimus (16.5% compared to 2.8% for cyclosporin) due to renal disorders, neurological and cardiovascular complications and opportunistic infections.

Mycophenolate mofetil (3 studies):
The pooled analysis of trials of mycophenolate mofetil, which is used in addition to cyclosporin, indicated that patient survival and graft survival were not statistically different from placebo or azathioprine for either of the mycophenolate mofetil treatment arms. The biopsy proven acute rejection rates at 12 months were 40.8% for conventional treatment and 19.8% and 16.5% for the 2 mg and 3 mg mycophenolate mofetil treatment arms respectively. The absolute decrease in first biopsy proven acute rejection rate was approximately 20-25%. This implies that the number needed to treat (NNT) to avoid acute rejection in one patient is between four and five. The severity of episodes of corticosteroid resistant acute rejection was 19.7% for conventional treatment and 8.8% and 4.9% for the 2 mg and 3 mg mycophenolate mofetil treatment arms respectively. The absolute decrease in steroid resistant rejection was approximately 10-15%. This implies that the number needed to treat (NNT) to avoid acute rejection in one patient is between seven and ten.

Adverse events associated with mycophenolate mofetil were: increased gastrointestinal events, specifically vomiting, abdominal pain and diarrhoea; increased leucopenia and anaemia; and increased incidence of opportunistic infections.

Cost information
The authors state that both tacrolimus and mycophenolate mofetil are more expensive than conventional therapy, but their additional costs need to be balanced against the reduced costs of treating episodes of acute rejection and the potential averted costs of transplant failure, dialysis and retransplantation. There are also advantages to the patient which have not been quantified. Against Neoral cyclosporin, tacrolimus is estimated to cost an extra £1,000 per patient per year. Mycophenolate mofetil is estimated to cost approximately £2,000 more per patient per year than cyclosporin (Sandimmum) and against Neoral cyclosporin the estimate is £3,000 per patient per year.

Authors’ conclusions
There is insufficient direct evidence as yet to make firm conclusions about the value of these drugs as maintenance therapy in the longer-term, although initial evidence indicates that a modest increase in patient and graft survival may be achieved. The comparative cost with conventional therapy depends on the actual steady state dosages achieved.

The evidence for tacrolimus dose response indicates that the effectiveness is likely to be reduced if lower initial doses are used, however there is insufficient evidence to quantify this reduction this result does not necessarily imply that lowering long-term maintenance doses will lead to significant increases in acute rejection.

CRD commentary
The literature search is reasonable and the authors have stated their inclusion and exclusion criteria. It is possible that additional relevant studies may have been found by including non-English publications or unpublished studies. It is possible that there could be publication bias. Extracted data is reported in several tables and discussed in a narrative review due to the limited number of studies available. The authors have reported on how the articles were selected but they do not report who performed the data extraction. The quality of the included studies was not formally assessed however only RCTs were included in the review so these were of a reasonable standard.

The authors did not test for homogeneity because of the small number of trials included in the review but the differences between studies and their drawbacks are acknowledged and discussed in the results synthesis. The review should be viewed with caution because of the methodological limitations of the review.

Implications of the review for practice and research
Practice: The authors state that given the lack of information on risks of infectious complications and malignancy associated with the long-term use of the two new agents, it may be appropriate initially to implement the new agents as primary maintenance in immunologically high-risk patients, while using conventional primary maintenance therapy for immunologically low-risk patients. High-risk factors would include loss of previous transplant to acute rejection, the presence of more than 50% cytotoxic antibodies, and third or subsequent transplant.

Bibliographic details
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