Calcineurin inhibitor sparing with mycophenolate in kidney transplantation: a systematic review and meta-analysis


CRD summary
The review found that calcineurin inhibitor limitation (with mycophenolate immunosuppression) following kidney transplant had a short-term benefit on kidney function, and appeared to have no adverse effects, other than in one subgroup (patients who chose calcineurin inhibitor elimination). Despite relatively low quality of the included studies, the authors’ conclusions reflect the data presented and are likely to be reliable.

Authors' objectives
To assess the safety and efficacy of calcineurin inhibitor sparing (minimisation or elimination) with mycophenolate immunosuppression following kidney transplant.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from inception to March 2008; search terms were reported. Three trial databases, bibliographies of identified studies and previously published reviews were also searched. The authors of identified studies were contacted. Hand searches were made of the table of contents of relevant journals (listed in the review). Unpublished studies were identified by contacting the manufacturers of relevant drugs and searching abstracts of relevant conferences. The search was not restricted by language, but was limited to clinical trials and randomised controlled trials (RCTs).

Study selection
RCTs that compared calcineurin inhibitor sparing with continuation of or conversion to mycophenolate versus standard or higher dose calcineurin inhibitor treatments in patients receiving kidney transplants were eligible for inclusion.

Outcome criteria were kidney transplant function, graft survival, mortality and acute rejection rate. Secondary outcomes were listed in the review.

Most of the included trials involved patients of low to moderate immunological risk. Individual trial inclusion/exclusion criteria varied. Recruitment was restricted to deceased donor transplant recipients in one trial and to first-time recipients in five trials. In included trials, the calcineurin inhibitor used was mainly cyclosporine, but tacrolimus was also used. Most trials used mycophenolate mofetil, a few used mycophenolate sodium. Mycophenolate was not used in the control arm of seven trials. Calcineurin inhibitor sparing began between 0 and 30 months post-transplant.

It was not clear how many reviewers performed the initial search and study selection. Two investigators independently examined each study to record eligibility; disagreements were resolved by discussion.

Assessment of study quality
Trial quality was assessed by two authors independently, using the five criteria on the Jadad scale. Allocation concealment and intention-to-treat analysis were assessed. Discrepancies were resolved by discussion.

Data extraction
Outcomes were taken for the primary endpoint for each trial, and additionally for six, 12, and 24 months post-intervention (where available). Where one trial was published more than once, the index publication was used, with additional outcome data from subsequent publications used where necessary. In the case of missing outcome data, authors were contacted for further details.

Transplant function was assessed using measured or calculated glomerular filtration rate or serum creatinine. Where creatinine clearance was reported, this was substituted for glomerular filtration rate in the meta-analysis.

Trials were divided into five subgroups: de novo calcineurin inhibitor minimisation but not complete avoidance;
elective calcineurin inhibitor minimisation but not complete elimination; elective calcineurin inhibitor elimination; calcineurin inhibitor minimisation but not complete elimination in patients with transplant dysfunction; and calcineurin inhibitor elimination in patients with transplant dysfunction.

Data extraction was performed by two authors independently. Discrepancies were resolved by discussion.

Methods of synthesis
Fixed-effect meta-analysis was used to synthesise the results, using Mantel-Haenzsel odds ratios (OR) for dichotomous outcomes and weighted mean differences (WMD) for continuous variables. Heterogeneity was assessed using Cochrane's Q statistic. Reasons for heterogeneity were explored when the test for heterogeneity was p<0.1.

Funnel plots were used to assess publication bias.

Results of the review
Twenty comparisons from 19 trials were included in the review (3,485 participants, based on figures in Table 1). There was no evidence of publication bias. Trial quality was low, with no trial assigned a Jadad score of over 3 out of 5 points. Exclusion of the two trials with a Jadad score of 1 did not alter the results for primary outcomes. Allocation concealment was reported as adequate, but intention-to-treat analysis was not presented in seven trials. Median follow-up was 12 months.

Kidney transplant function: Calcineurin inhibitor sparing improved glomerular filtration rate (WMD 4.4 mL/minute, 95% CI 2.9 to 5.9; 17 trials) and glomerular filtration rate change from baseline (WMD 4.6 mL/min, 95% CI 2.5 to 6.7; nine trials). The effect was lower, but remained significant in studies which reported intention-to-treat analyses compared to per-protocol analyses. A similar pattern to the glomerular filtration rate results was seen for the outcome of serum creatinine.

Graft survival (14 trials): There was no clear evidence of an effect of calcineurin inhibitor sparing on graft survival, either when excluding graft loss because of death or including death with a functioning graft.

Mortality (12 trials): There were no significant differences in mortality between the two groups.

Acute rejection rate (14 trials): There was significant heterogeneity between the five subgroups for the acute rejection outcome. No rejections occurred in patients with deteriorating function after calcineurin inhibitor sparing. In the elective calcineurin inhibitor elimination group, elimination was associated with an increase in biopsy-proven acute rejection (OR 2.23, 95% CI 1.57 to 3.17; six trials).

There were no consistent effects of calcineurin inhibitor sparing on other outcomes.

Authors’ conclusions
Calcineurin inhibitor sparing strategies with adjunctive mycophenolate may be beneficial for kidney transplant recipients.

CRD commentary
Clear intervention, design and outcome criteria were used. The search strategy was comprehensive; attempts were made to identify unpublished as well as published studies. It seemed unlikely that any important studies were missed. Independent study selection, data extraction and quality assessment means that the risk of errors in the review process was minimised. The lack of participant descriptions meant that it was not clear whether the results may only pertain to a certain subgroup of patients. The meta-analysis used was appropriate.

The authors’ conclusions reflect the data presented and are likely to be reliable.

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

Research: The authors stated that longer term studies, particularly of tacrolimus, were required to investigate whether the short term beneficial effect of calcineurin inhibitor sparing could be maintained. They also stated that further research to determine the ideal range of tacrolimus and cyclosporine was required, as was a comparison of calcineurin inhibitor minimisation with elimination in patients with deteriorating graft function, as well as studies of patients with higher immunological risk.

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