Tacrolimus versus cyclosporine microemulsion for heart transplant recipients: a meta-analysis
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CRD summary
The authors found that tacrolimus as a primary immunosuppressant for heart transplant recipients was associated with comparable survival and a significant reduction in acute rejection compared to cyclosporine micro-emulsion. However, rates of new-onset diabetes may have been higher in the tacrolimus group. The review was well conducted and the conclusions appear reliable.

Authors' objectives
To compare the effects of tacrolimus and cyclosporine micro-emulsion as immunosuppressants for heart transplant recipients.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials were searched. Search terms were reported. Search dates varied across sources, but spanned 1966 to June 2008. References of relevant articles and conference proceedings were handsearched. There was no language restriction.

Study selection
Randomised controlled trials comparing tacrolimus and cyclosporine micro-emulsion as initial immunosuppressive therapy in heart transplant patients were eligible for inclusion, provided they reported at least one of the review outcomes. Primary review outcomes were mortality at one year and acute rejection at six months and one year (measured by endomyocardial biopsy or treated rejections). Other review outcomes of interest were withdrawal from therapy, new-onset diabetes requiring insulin, post-transplant hypertension, malignancy, renal failure needing dialysis and other adverse events. Studies in which solid organs as well as the heart were transplanted were excluded.

All studies in the review included adults; two included children. The studies used similar induction therapies and most used the same concomitant immunosuppression in both study arms (steroid, mycophenolate mofetil and/or azathioprine); one included sirolimus. All used trough-level monitoring to guide the dose of tacrolimus (range 0.03 to 0.3 mg/kg daily) and cyclosporine micro-emulsion (range 3 to 10 mg/kg daily). Definitions of acute rejection varied across the studies (see review for details). Duration of follow up ranged from six to 60 months.

Data were abstracted by more than one reviewer working independently using a pre-designed form. Disagreements were resolved by consensus.

Assessment of study quality
The following criteria from the Jadad scale were used to assess study validity: adequacy of randomisation; blinding; and management of withdrawals and dropouts. Each study was awarded up to 10 points for criteria met. Disagreements on study validity were resolved by consensus between the reviewers.

Data extraction
Risk ratios were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals. Data were extracted by two authors independently. Disagreements were resolved by consensus. Authors were contacted for additional data as required.

Methods of synthesis
Studies were combined using a fixed-effect model or the Mantel-Haenszel random-effects model to obtain pooled risk ratios and 95% confidence intervals. Heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Values of $p\leq 0.1$ ($X^2$ test) or 50% ($I^2$ statistic) represented significant heterogeneity. Publication bias was assessed using funnel plots. Sensitivity analyses were performed to investigate the impact of choice of statistical model and of excluding
randomised controlled trials including children, small samples (n≤26), short duration (≤six months) and with differing baseline medication. The impact of differing concomitant medications was investigated by subgroup analyses.

**Results of the review**

Seven randomised controlled trials (n=885, range 21 to 334) were included in the review. Jadad scores ranged from 4 to 8. Only one randomised controlled trial reported adequate randomisation and allocation concealment. None used blinding. All randomised controlled trials had complete follow-up. Six randomised controlled trials had clearly described withdrawals and dropouts. Three randomised controlled trials specifically reported use of intention to treat analysis.

**Tacrolimus versus cyclosporine micro-emulsion**

Primary outcomes: There was no statistically significant difference between the groups in one-year mortality rates (risk ratio 0.70, 95% confidence interval: 0.45, 1.08, p=0.11, five randomised controlled trials). Risk of acute rejection was significantly lower in the tacrolimus group at six months (risk ratio 0.61, 95% confidence interval: 0.49, 0.75, p=0.00001, five randomised controlled trials) and one year (risk ratio 0.69, 95% confidence interval: 0.48, 0.98, p=0.04, five randomised controlled trials).

Other outcomes: Significantly fewer patients withdrew from tacrolimus treatment (risk ratio 0.57, 95% confidence interval: 0.40, 0.83, p=0.003, six randomised controlled trials) or had post-transplantation hypertension (risk ratio 0.88, 95% confidence interval: 0.81, 0.96, p=0.004, five randomised controlled trials). However, the incidence of new-onset diabetes requiring insulin was significantly higher in the tacrolimus group (risk ratio 1.65, 95% confidence interval: 1.18, 2.29, p=0.003, four randomised controlled trials). There was no statistically significant difference between the groups in the incidence of malignancy or renal failure requiring dialysis.

There was statistically significant heterogeneity for the outcome of acute rejection at one year (p=0.007, I²=72%). A random-effects model was used. For other analyses, no significant heterogeneity was detected and a fixed-effect model was used. In sensitivity analysis, use of a random-effects model negated the statistical significance of the findings for new-onset diabetes. Other sensitivity and subgroup analyses did not materially affect the pooled results. Funnel plots showed no evidence of significant publication bias.

The review also reported results for other adverse events, for which there were insufficient data for meta-analysis.

**Authors' conclusions**

Tacrolimus as a primary immunosuppressant for heart transplant recipients was associated with comparable survival and a significant reduction in acute rejection compared to cyclosporine micro-emulsion. However, rates of new-onset diabetes may have been higher in the tacrolimus group.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without language restriction. Steps were taken to minimise the risk of bias and error in the review by having more than one reviewer independently conduct the processes of study selection, validity assessment and data extraction. Relevant validity criteria were considered, although details of the validity of individual studies were not reported. Appropriate statistical techniques were used to combine the data, assess for heterogeneity and investigate clinical and methodological differences between the studies. Although the quality of the primary studies was suboptimal and overall sample numbers were small, the review findings were consistent. The review was well conducted and the authors’ conclusions appear reliable.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that further well-powered randomised controlled trials could investigate whether tacrolimus was associated with a statistically significant difference in survival rates compared to azathioprine microemulsion. They suggested subgrouping results by gender and ethnicity.
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