A systematic review of the adverse effects of tacrolimus in organ transplant patients

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CRD summary
The authors stated that no firm conclusion on the efficacy of tacrolimus to prevent graft rejection in organ transplantation could be made due to variation across studies. Despite weaknesses in the review process, given the variation between the studies the authors’ cautious conclusions reflect the evidence presented and appear appropriate.

Authors' objectives
To assess the efficacy and safety of tacrolimus in organ transplantation patients.

Searching
PubMed and Science Direct databases and Blackwell and Ovid were searched for studies published in English from 1980 to 2007; search terms were reported. Reference lists of relevant articles were screened for additional articles.

Study selection
Randomised controlled trials (RCTs) of tacrolimus compared to other immunosuppressants (steroid and cyclosporine) to prevent graft rejection after organ transplant in adult patients were eligible for inclusion. Outcomes of interest were biopsy proven acute rejection at three months, graft survival at one year, post-transplant diabetes mellitus, hypertension and neurotoxicity.

In the included studies tacrolimus dosage ranged from 0.05 to 0.20mg/kg twice daily. Doses were adjusted to achieve trough level in the whole blood from 0.2ng/mL to 15 or 20ng/mL in the first three months and 5 to 15ng/mL thereafter. Comparators included cyclosporine, microemulsified cyclosporine or steroids. Participants were diagnosed with end-stage liver cirrhosis or end-stage renal disease. Mean age ranged from 42.4 to 57 years.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Quality was assessed with criteria of randomisation, study bias, sample size, length of study and intention-to-treat analysis.

The authors did not state how many reviewers assessed quality.

Data extraction
Data for relevant outcomes were extracted and used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.

Methods of synthesis
Where there was no heterogeneity, data were pooled using a fixed-effect model. Where there was evidence of significant heterogeneity a random-effects model was used. Heterogeneity was assessed using Cochran's Q test and the I² statistic (I²>50%, Cochran Q<0.05 indicated significant heterogeneity).

Results of the review
Seven RCTs (2,415 participants) were included in the review. Only one study met all the quality criteria. Only two studies described randomisation clearly. Study duration ranged from six months to 12 years.

There were no significant differences between tacrolimus and control groups for acute rejection at three months (OR 0.77, 95% CI 0.52 to 1.13; six RCTs, I²=68.4%) and graft survival at 12 months (OR 1.11, 95% CI 0.72 to 1.71; six RCTs, I²=68.1%).

Patients treated with tacrolimus were significantly more likely to develop post-transplant diabetes (OR 1.90, 95% CI...
1.09 to 3.30; seven RCTs, $I^2=74.4\%$) and neurotoxicity (OR 1.61, 95% CI 1.15 to 2.25, 4 RCTs, $I^2=49.5\%$) but less likely to develop hypertension (OR 0.80, 95% CI 0.65 to 0.98; six RCTs, $I^2=14.2\%$).

**Authors’ conclusions**
No firm conclusion on the efficacy of tacrolimus to prevent graft rejection in organ transplantation could be made due to variation across studies.

**CRD commentary**
The review question was clear and inclusion criteria were defined. Some relevant sources were searched. The limitation to studies published in English risked language bias. The last search date was 2007 and so the results may not be applicable to contemporary practice. Study quality was assessed and some results were reported. The authors did not report their methods for study selection, quality assessment and data extraction so it was unclear whether steps were taken to reduce reviewer error and bias. The authors highlighted variation between studies in terms of study population, length of study and differences in measuring effects of treatment. There were some discrepancies between the abstract and the text and forest plots in reporting the results of the review.

The authors’ cautious conclusions reflect the evidence presented and given the variation in the studies and weaknesses in the review process appear appropriate.

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

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

**Research:** The authors suggested further studies should investigate the long-term efficacy of tacrolimus intervention following organ transplantation and assess correlations between genetic profiles and blood levels of the drug and graft outcomes.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.