Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials

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CRD summary
This review assessed the effects of steroid withdrawal from triple therapy with cyclosporine or tacrolimus and mycophenolate mofetil. The authors concluded that steroid withdrawal increases acute rejection but not early graft failure. Given the limitations of the review, and the poor reporting of some review methodology, it is not possible to guarantee the reliability of the conclusions.

Authors' objectives
To evaluate the effect of steroid withdrawal on rejection and graft failures in renal transplant patients who have received triple therapy with steroids, cyclosporine A or tacrolimus, and mycophenolate mofetil (MMF) or sirolimus for at least a week.

Searching
MEDLINE, EMBASE, the Cochrane Library, DARE, and CINAHL were searched up to March 2003; the search terms were reported. No language restrictions were applied. References of recent publications that the authors considered important were screened, as were abstracts from international transplantation society scientific meetings (2001 to 2003) that had been published in Transplantation Proceedings, Transplantation or American Journal of Transplantation.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The duration of follow-up ranged from 3 to 24 months.

Specific interventions included in the review
Studies of treatment with triple therapy consisting of cyclosporine A or tacrolimus combined with MMF or sirolimus, where one arm experienced steroid withdrawal after more than a week of treatment and the other continued steroid treatment, were eligible for inclusion. Studies of steroid avoidance, or trials where participants received steroids for less than 7 post-transplant days, were excluded. No studies that used sirolimus were identified; all included studies evaluated either cyclosporine or tacrolimus combined with 1 or 2 g MMF per day and steroids. Steroid withdrawal commenced 3 or 6 months post-transplantation, and generally took place over 2 to 10 weeks (one trial seemed to have withdrawn the steroids abruptly).

Participants included in the review
Studies of patients undergoing renal transplant were eligible for inclusion. Some studies only included patients who had not experienced acute rejections, while others excluded patients with repeated, severe or vascular acute rejection; one study included any post-transplant patients. No further details relating to the participants were provided.

Outcomes assessed in the review
Studies evaluating acute rejection or renal allograft failure on an intention-to-treat basis were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how studies were selected for the review, or how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the criteria developed by Kasiske (see Other Publications of Related Interest). This assessment involved 13 criteria relating to the following: peer-review; institutional review board approval; source of funding; use of a sample size calculation; description of inclusion or exclusion criteria; similarity at baseline; use of a placebo; adequacy of randomisation; description of statistical methods; description of drop-outs and withdrawals; use of an intention-to-treat analysis; and clearly defined end points. The maximum score was 14. The authors also recorded whether the study was double-blind.

The authors did not state how the studies were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**
Two reviewers independently reviewed all of the included studies. The time steroid withdrawal commenced and was completed and the incidence of rejection or renal allograft failure were extracted from each study. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for each study. Where reported, information on serum creatinine, creatinine clearance, serum lipids, blood-pressure, serum glucose, bone density and infections were also extracted.

**Methods of synthesis**
How were the studies combined?
The pooled RR and risk difference (RD), along with 95% CIs, were calculated using a fixed-effect model (Mantel-Haenszel).

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared statistic. Meta-analyses were repeated after excluding one trial that only reported data for complete withdrawal of steroids. A subgroup analysis was used to examine the influence of drug (cyclosporine or tacrolimus) and quality (high- and low-quality trials).

**Results of the review**
Six RCTs (n=1,519) were included in the review.

One study scored 2 for quality, one scored 2.5, one scored 3.5, one scored 11 and two scored 11.5. Two of the trials were double-blind and four were open. The three low-quality trials were published as abstracts and the three high-quality trials as full papers in peer-reviewed journals.

Acute rejection (5 RCTs).
The proportion of patients with acute rejection ranged from 0 to 23% with steroid withdrawal and from 0 to 14% with steroid maintenance; the difference was significant (RD 0.08, 95% CI: 0.05, 0.11, P<0.001). However, there was statistical heterogeneity between the studies (P<0.005). The proportion of people with acute rejection was, therefore, significantly higher after steroid withdrawal (RR 2.28, 95% CI: 1.65, 3.16, P<0.00001). There was no statistical heterogeneity between the studies for this analysis (P=0.23). There were no differences in the results when one trial using data only for complete withdrawal of steroids was analysed, when trials using cyclosporine or tacrolimus were analysed separately, or between high- and low-quality trials.

Graft failure (4 RCTs).
The proportion of graft failures ranged from 0 to 6% with steroid withdrawal and from 0 to 7% with steroid maintenance; the difference was not significant (RD -0.01, 95% CI: -0.03, 0.01, P=0.28). The proportion of people with acute rejection was not significantly higher after steroid withdrawal. There was no statistical heterogeneity between the studies for either analysis (P=0.85 and P=0.94, respectively). There were no differences in the results when trials using cyclosporine or tacrolimus were analysed separately, or between high- and low-quality trials.

The results for graft function and metabolic effects were also reported.
Authors’ conclusions
Steroid withdrawal resulted in a low but significant risk of acute rejection, but did not increase the risk of early graft failure.

CRD commentary
The review question was clear with well-defined inclusion criteria. The authors undertook a comprehensive search for published trials without language restrictions, thus reducing the risk of language bias. However, there was a potential for publication bias that the authors did not assess. It seems that data extraction was undertaken in duplicate, thereby reducing the potential for error and bias, but it was unclear whether similar steps were taken at the study selection and quality assessment stages of the review. Although the quality of the studies was assessed, several criteria related to the funding and publication of the data, and allocation concealment was not assessed. In addition, blinding in the RCTs was noted but did not form part of the quality score. Appropriate statistical methods were used. Given the limitations of the review and the lack of reporting of some review methodology, it is not possible to guarantee the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that steroid withdrawal trials with the new immunosuppressants are required, with extended controlled follow-up to confirm graft stabilisation.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenal Cortex Hormones /supply & distribution /therapeutic use; Calcineurin Inhibitors; Cyclosporine /therapeutic use; Drug Administration Schedule; Drug Therapy, Combination; Humans; Kidney Transplantation /immunology; Mycophenolic Acid /analogs & derivatives /therapeutic use; Randomized Controlled Trials as Topic; Tacrolimus /therapeutic use

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Record Status
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.