Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk: a meta-analysis

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CRD summary
This review compared the effects of steroid avoidance or withdrawal with steroid maintenance in renal transplant recipients and concluded that avoiding or withdrawing steroids increased risk of acute rejection, did not substantially affect graft function or survival and provided cardiovascular benefits. As many of the primary trials were of poor quality the reliability of the conclusion is unclear.

Authors' objectives
To compare the effects of steroid avoidance or withdrawal with steroid maintenance in renal transplant recipients.

Searching
MEDLINE, EMBASE, The Cochrane Library, Transplant Library (updated to August 2009), and a range of clinical trial registries including ClinicalTrials.gov were searched without language or date restrictions until 18 January 2008. Search strategy details were reported, but search terms were not. Reference lists of included papers were searched for further relevant studies.

Study selection
Prospective randomised and pseudo-randomised trials were eligible for inclusion if: patients were adult renal transplant recipients; the intervention was steroid withdrawal or avoidance (steroids were not provided in the first place); and the comparison was steroid maintenance therapy. Studies were excluded if steroids were used to treat other conditions or steroid doses were minimised, but not withdrawn or excluded.

Publication dates ranged from 1983 to 2008. Time of withdrawal in non-avoidance groups ranged from one day to over two years. Immunosuppressive regimens included anti-lymphocyte globulin, azathioprine, basiliximab, cyclosporine microemulsion, mycophenolate mofetil and mycophenolate sodium. The primary outcome was incidence of any acute rejection (as proven by biopsy where reported), otherwise the study authors' definition was used. Secondary outcomes extracted included patient and graft survival, hypertension, diabetes, hypercholesterolaemia, infection, malignancy, cataracts and bone complication.

It was unclear how many reviewers were involved in study section.

Assessment of study quality
The Jadad checklist was used to assess study quality. Scores of 3 or more out of 5 were considered good.

It was unclear how many reviewers were involved in validity assessment.

Data extraction
Data were extracted to calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences with 95% CIs for continuous outcomes. For patient and graft survival data, the hazard ratio (HR) was extracted where possible; if not possible the method of Parmar, Torri and Stewart was used to estimate the HR. If an outcome was reported for more than one time point within a single study, the most recent follow-up data was extracted. Where means for continuous outcomes were not reported, and unless the range appeared skewed, the median was used as an estimate of the mean. If the standard deviation (SD) was not reported, but sample size and range were reported, the standard deviation was estimated using the method of Walter and Yao.

One reviewer extracted and another reviewer checked data. Disagreements were resolved by discussion.

Methods of synthesis
Risk ratios with 95% CIs or hazard ratios with 95% CIs were pooled for binary outcomes and weighted mean
differences (WMDs) with 95% CIs pooled for continuous outcomes.

The $I^2$ test was performed to assess statistical heterogeneity (no definitions of low, medium and high heterogeneity were provided). If no or low heterogeneity was identified, a Mantel-Haenszel fixed-effect model was used to combine binary outcomes; otherwise subgroup analyses, mixed-effects models and funnel plots were used to try to identify the source of heterogeneity. If the source of heterogeneity could not be identified, a DerSimonian and Laird random-effects model was used.

Sensitivity analysis was performed to assess impact of using estimated means/standard deviations on overall results.

**Results of the review**

One hundred and nineteen publications that reported 34 studies met the inclusion criteria (n=5,637 patients). Most studies (19 studies or 56%) did not achieve a Jadad score of 3 or more, which indicated poor study quality. Less than half (15 studies or 44%) reported intention-to-treat analysis or adequate allocation concealment (13 studies or 38%).

**Acute response:** Overall, steroid avoidance and withdrawal regimens had an increased risk of acute response compared to controls (RR 1.56, 95% CI 1.31 to 1.87, random-effects model; 31 studies).

**Patient and graft survival and graft function:** No statistically significant differences were identified between groups for patient survival (fixed-effect model; 27 studies), graft survival (fixed-effect model; 24 studies) and death-censored graft loss (fixed-effect model; 20 studies). However, statistically significant differences were identified between groups for serum creatinine (higher in withdrawal/avoidance group WMD 4.24 mmol/L, 95% CI 2.08 to 6.40, fixed-effect model; 25 studies) and creatinine clearance (lower in withdrawal/avoidance group WMD -3.06 mL/min, 95% CI -4.66 to -1.45, fixed-effect model; 15 studies).

**Cardiovascular risk factors:** Steroid avoidance and withdrawal groups had a statistically significantly decreased risk of hypertension (RR 0.90, 95% CI 0.85 to 0.94, fixed-effect model; 15 studies), hypercholesterolaemia (RR 0.76, 95% CI 0.67 to 0.87, random-effects model; 13 studies), new-onset diabetes (RR 0.64, 95% CI 0.50 to 0.83, fixed-effect model; 16 studies) and a reduced level of mean serum cholesterol (WMD -0.39 mmol/L, 95% CI -0.59 to -0.19, random-effects model; 14 studies), but not triglyceride levels (random-effects model; 12 studies).

**Other outcomes:** Steroid avoidance and withdrawal was associated with a statistically significantly increased risk of leukopenia (RR 1.66, 95% CI 1.42 to 1.93, fixed-effect model; nine studies), but not total infection (random-effects model; 13 studies), cytomegalovirus infection (fixed-effect model; 11 studies), malignancy (fixed-effect model; 11 studies), or cataracts (random-effects model; six studies).

**Heterogeneity, subgroup analyses and sensitivity analysis:** The presence of significant heterogeneity was indicated by the choice of statistical model (fixed-effect or random-effects) in the above results. Full heterogeneity, subgroup analysis and sensitivity analysis details were provided in the report.

**Authors’ conclusions**

There was an increase in risk of acute rejection in steroid withdrawal and avoidance groups, but only a small effect on graft function, no measurable effect on graft or patient survival and significant benefits in cardiovascular risk profiles.

**CRD commentary**

This review addressed a clear question using relevant inclusion and exclusion criteria. The search was thorough, not restricted by date or language and clearly described. A standard checklist was used to assess study validity. How the reviewers performed study validity and selection was not clearly reported, which introduced the possibility of reviewer error and bias. Data extraction was clearly described and appeared appropriate. Sufficient primary study characteristics were provided. The methods of synthesis (which included assessment and attempted correction for heterogeneity and sensitivity analyses) appeared comprehensive and appropriate (although heterogeneous studies may produce spurious pooled results even when pooled using a random-effects model). The review and synthesis were generally well conducted, but due to the poor quality of the majority of the included trials the reliability of the conclusions is unclear.

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

**Practice:** The authors stated that steroid avoidance and withdrawal protocols seem justified with current
immunosuppressive protocols in low-risk recipients.

Research: None stated.

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