Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials

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CRD summary
This review assessed the effects of calcineurin inhibitor (CNI) withdrawal from a sirolimus-based immunosuppressive regimen in kidney transplantation. The authors concluded that the withdrawal of CNI is associated with a short-term increase in rejection, but with a significant improvement in renal function and reduction in hypertension. This was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the effects of calcineurin inhibitor (CNI) withdrawal from sirolimus-based immunosuppressive regimens in patients undergoing kidney transplantation.

Searching
MEDLINE (1966 to July 2004), EMBASE (1980 to July 2004) and the Cochrane CENTRAL Register (Issue 2, 2004) were searched without language restrictions; the search terms were reported. In addition, the authors searched four named relevant renal and transplantation journals (2001 to August 2004), abstracts of the American Transplant Congress (2001 and 2004) and reference lists, and contacted the authors of eligible studies for details of unpublished and ongoing studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies with initial immunosuppressive regimens consisting of sirolimus plus CNI (cyclosporine or tacrolimus) that compared planned withdrawal of CNI with the continuation of sirolimus plus CNI were eligible for inclusion. Studies of complete CNI avoidance were excluded. All but one of the included studies used cyclosporine. All of the included studies also used prednisolone. CNI was withdrawn 2 to 3 months after transplantation.

Participants included in the review
Studies of adult patients receiving a primary or repeat renal transplant from either a living or a deceased donor were eligible for inclusion. Studies of patients receiving dual organ transplants were excluded. Most of the included studies were conducted in low-risk patients, most patients were Caucasians, very few were diabetics, and most were undergoing primary transplantation. Some studies excluded planned antibody induction, delayed graft function and highly sensitised patients. Most studies only included patients with adequate and stable renal function and no significant acute rejection in the month before study entry. Where reported, the mean age of the participants was 40 to 46 years.

Outcomes assessed in the review
The primary outcomes included acute rejection, serum creatinine or creatinine clearance, allograft survival and patient survival. The secondary outcomes included blood-pressure, total cholesterol, triglycerides and post transplant diabetes. For studies reporting outcomes at multiple time periods; data for 1-year outcomes were used in the primary analyses.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies. Any disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals. The maximum possible score was 5 points. The authors did not state how the quality of the studies was assessed, or how many reviewers performed the quality assessment.

**Data extraction**

Two reviewers independently extracted the data using a standardised data extraction form. Any differences were resolved by reaching consensus. The proportion of patients achieving complete withdrawal and data for the outcomes of interest were extracted for each study. Risk ratios (RRs) and risk differences (RDs) were calculated for dichotomous outcomes, while mean differences with 95% confidence intervals (CIs) were calculated for continuous outcomes. Authors of missing information were contacted for further data. Intention-to-treat data were used for the analyses.

**Methods of synthesis**

How were the studies combined?

Pooled RRs and RDs with 95% CIs were calculated for dichotomous data, while weighted mean differences (WMDs) with 95% CIs were calculated for continuous outcomes. Fixed-effect models were used in the absence of significant heterogeneity and a random-effects model (DerSimonian and Laird) where heterogeneity was significant.

How were differences between studies investigated?

Heterogeneity was assessed using the Q-statistic. Meta-analyses were repeated after including data for 3-year outcomes, only studies that used cyclosporine, and only studies published in peer-reviewed journals. Where significant heterogeneity was found, potential reasons for this were discussed.

**Results of the review**

Six RCTs (n=1,047) were included in the primary analysis, with another included in the sensitivity analysis.

The median Jadad score was 2 (range: 1 to 3). None of the RCTs reported double-blinding.

Acute rejection.

There was a statistically significant increase in the risk of acute rejection after CNI withdrawal compared with control (3 RCTs; RR 2.36, 95% CI: 1.34, 4.15, P=0.003). No significant heterogeneity was observed (P=0.96). The absolute RD was 6.0% (95% CI: 2, 10, P=0.002). The results were similar when using data for the 3-year follow-up.

There was a statistically significant increase in the risk of total acute rejection (before or after CNI withdrawal) with CNI withdrawal compared with control (6 RCTs; RR 1.59, 95% CI: 1.2, 2.1, P=0.001). No significant heterogeneity was observed (P=0.64). The absolute RD was 8.0% (95% CI: 3, 12, P=0.0006). The results were similar when using data for the 3-year follow-up, only studies that used cyclosporine, and only studies published in peer-reviewed journals.

Graft and patient survival.

There was no statistically significant difference between CNI withdrawal and control for graft loss (6 studies; RR 0.87, 95% CI: 0.46, 1.64, P=0.66) or patient death (6 studies; RR 0.88, 95% CI: 0.40, 1.96, P=0.76). No significant heterogeneity was observed (P=0.79 and P=0.99, respectively).

Renal function.

CNI withdrawal was associated with a significant increase in creatinine clearance (WMD 7.49 mL/minute, 95% CI: 5.08, 9.89, P<0.0001; 5 RCTs). No significant heterogeneity was observed (P=0.63). The results were similar when using only data for studies that used cyclosporine. CNI withdrawal was associated with a significant decrease in serum creatinine (WMD -0.19 mg/dL, 95% CI: -0.28, -0.10, P<0.0001; 4 RCTs).

Blood-pressure.
CNI withdrawal was associated with a statistically significant decrease in the risk of hypertension (RR 0.56, 95% CI: 0.40, 0.78, P=0.0006; 3 RCTs). No significant heterogeneity was observed (P=0.23). Reductions were statistically significant for both systolic (WMD -7.02 mmHg, 95% CI: -10.25, -3.79, P<0.0001) and diastolic (WMD -3.2 mmHg, 95% CI: -5.29, -1.11, P=0.003) blood-pressure.

Total cholesterol and triglycerides.

There was no statistically significant difference between CNI withdrawal and control for total cholesterol (WMD 0.53 mmol/L, 95% CI: -0.26, 1.31, P=0.19; 4 RCTs) or triglycerides (WMD 0.17 mmol/L, 95% CI: -0.33, 0.68, P=0.5; 4 RCTs). Statistically significant heterogeneity was observed (P<0.001) for both analyses.

Diabetes mellitus.

There was no statistically significant difference between CNI withdrawal and control for post-transplant diabetes mellitus (RR 0.93, 95% CI: 0.49, 1.78, P=0.83; 4 RCTs). No statistically significant heterogeneity was observed (P=0.6).

Authors' conclusions
The withdrawal of CNI is associated with an increased risk of rejection in the short term, but with a significant improvement in renal function and reduction in hypertension. No firm conclusions on long-term outcomes could be drawn.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise language and publication bias. However, the authors did not investigate the potential for publication bias. Two reviewers independently selected studies and extracted the data, thus reducing the potential for bias and errors during these steps of the review. However it was unclear if the same measures were applied during the validity assessment. Validity was assessed using specified established criteria and adequate details of each included study were given. The data were combined in a meta-analysis and statistical heterogeneity was assessed. The influence on the results of drug and type of publication were explored. Potential reasons for significant heterogeneity were discussed. This was a well-conducted review and the authors' conclusions are likely to be robust.

Implications of the review for practice and research
Practice: The authors suggested that patients undergoing CNI withdrawal should be closely monitored for rejection. They also cautioned that the results from this review are based on low-risk patients and may not generalise to higher risk patients.

Research: The authors stated that longer term follow-up is needed to assess the effects of withdrawal on patient and graft survival.

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