Calcineurin-inhibitor minimization in liver transplant patients with calcineurin-inhibitor-related renal dysfunction: a meta-analysis


CRD summary
The review found that, compared with routine regimens, calcineurin inhibitor minimisation improved renal (kidney) function in liver transplant patients with renal impairment, with similar acute rejection rates and patient survival but higher infection rates. The low quality of included trials and problems with the analysis and reporting of safety outcomes mean that the results are not reliable.

Authors’ objectives
To evaluate the efficacy and safety of calcineurin inhibitor minimisation protocols in liver transplant recipients with calcineurin inhibitor-related renal dysfunction.

Searching
MEDLINE, EMBASE and Cochrane Database of Systematic Reviews were searched from inception; search terms were reported. The search was not restricted by language or date of publication.

Study selection
Randomised controlled trials (RCTs) that reported renal function in liver transplant recipients with calcineurin inhibitor renal impairment were eligible for inclusion. Eligible trials had to compare calcineurin inhibitor minimisation regimen with a routine calcineurin inhibitor regimen. The authors also identified relevant observational studies.

Calcineurin inhibitor minimisation was defined as an initial calcineurin inhibitor dose of at least 25% of the routinely administered dose, or complete calcineurin inhibitor withdrawal. Trials were restricted to those of patients with one of the following criteria before enrolment: glomerular filtration rate below 60mL/min, serum creatinine level over 1.5mg/dL or creatinine clearance rate below 70mL/min. The primary endpoints were glomerular filtration rate, serum creatinine level and creatinine clearance rate. Secondary endpoints were episodes of acute rejection; incidence of infection and patient survival.

The included trials were mainly conducted in North America and Western Europe, with one in China and Brazil. All the trials were small, ranging from eight to 145 patients. In almost all trials, there were more men than women (where reported). The calcineurin inhibitors used were cyclosporin A, tacrolimus, everolimus, and sirolimus. The initial trough levels were 32 to 250ng/mL for cyclosporin A and 2.3 to 12ng/mL for tacrolimus (where stated). Concomitant drugs used were prednisone, azathioprine and/or mycophenolate mofetil.

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

Assessment of study quality
Each RCT was rated for allocation concealment, use of intention-to-treat analysis, blinding, and description of handling of missing data.

Two reviewers performed the quality assessment; disagreements were resolved by consultation with a third reviewer.

Data extraction
Outcomes were extracted from each trial to calculate odds ratios (OR) or mean differences for each RCT; these were estimated with 95% confidence intervals (CIs).

Two reviewers extracted the data.

Methods of synthesis
The trials were pooled using a random-effects model. Heterogeneity was assessed using $I^2$ and $T^2$.
Results of the review
Ten RCTs (625 patients) were included in the review. The risk of bias of the included trials was relatively high. None of the trials was double blinded. Allocation concealment was described in three trials. Three trials conducted an intention-to-treat analysis. Missing data handling was described adequately in one trial. Duration of follow-up ranged from six to 36 months.

Glomerular filtration rate (five RCTs, 340 patients): Glomerular filtration rate was significantly higher in the calcineurin inhibitor minimisation group compared with the routine calcineurin inhibitor regimen group (WMD 9.14mL/min, 95% CI 5.85 to 12.43) with no evidence of statistical heterogeneity. The effect was significant in the mycophenolate mofetil subgroup of four trials (WMD 9.10mL/min, 95% CI 5.64 to 12.55; 257 patients), but not in the one trial that used sirolimus.

Serum creatinine level (seven RCTs, 357 patients): Serum creatinine level was significantly lower in the calcineurin inhibitor minimisation group compared with the routine calcineurin inhibitor regimen group (WMD -0.21mg/dL, 95% CI -0.35 to -0.06) with some evidence of statistical heterogeneity ($I^2=39\%$). The effect was significant in the mycophenolate mofetil subgroup of six trials (WMD -0.27, 95% CI -0.39 to -0.14; 341 patients), but not in the one trial that used sirolimus.

Creatinine clearance rate (five RCTs, 285 patients): Creatinine clearance rate was not significantly different in the calcineurin inhibitor minimisation group compared with the routine calcineurin inhibitor regimen group. Subgroup analyses found no significant effect in any drug class group (mycophenolate mofetil, sirolimus or everolimus), but did approach statistical significance in the two trials that used sirolimus (WMD 10.56mL/min, 95% CI -1.40 to 22.51).

Results from the observational studies were broadly similar to those from the RCTs for glomerular filtration rate and serum creatinine level, but showed a beneficial effect of calcineurin inhibitor minimisation on creatinine clearance rate which was not apparent in the RCT data.

Safety outcomes: There was no difference in acute rejection rate (10 studies) between the minimisation and the routine regimen groups. The results for incidence of infection and patient survival differed between the text and the forest plots, so were not clear.

Authors' conclusions
Calcineurin inhibitor minimisation improved renal function in liver transplant patients with renal impairment compared with routine regimens. Acute rejection rate and patient survival were similar in patients on minimisation protocols, but infection rates were higher.

CRD commentary
The study addressed a clear question. The search strategy was described, but was restricted to published studies, which raised the possibility of publication bias. It was not clear whether steps were taken to minimise error or bias in the study selection phase of the review. Study quality was assessed appropriately; error and bias in this assessment and data extraction were minimised as these were performed by two reviewers.

The methods used to pool the data were appropriate for the effectiveness outcomes. The authors acknowledged that the minimisation protocols might not be comparable, and presented all the results stratified according to the drugs used. Some of the safety outcomes were relatively common, so odds ratios were not appropriate.

The authors acknowledged that the quality of the included trials was low. Few details of the patients included in the review were given, so the generalisability of the results was not clear. The authors noted that the length of follow-up for the included trials was relatively short, which may have hindered the ability of the review to detect an effect on survival. For the incidence of infection and patient survival outcomes, the authors' results and conclusions were not clear; the higher rates of infection mentioned in the text were not borne out in the forest plot (figure 6).

The low quality of the included trials means that authors' conclusions of effectiveness may not be reliable. Given problems with the analysis and reporting of the safety outcomes, these are not reliable.

Implications of the review for practice and research
Practice: The authors stated that mycophenolate mofetil is a good option to reduce calcineurin inhibitor exposure in liver transplant recipients with renal dysfunction, without increasing rejection and infection rates.

Research: The authors stated that future studies are required to determine whether the improved renal function associated calcineurin inhibitor minimisation can prolong long-term patient or graft survival, and which minimisation protocol is the most effective.

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