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[Intervention Review]

# Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients

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## ABSTRACT

### Background

Liver transplantation is an established treatment option for end-stage liver failure. Now that newer, more potent immunosuppressants have been developed, glucocorticosteroids may no longer be needed and their removal may prevent adverse effects.

### Objectives

To assess the benefits and harms of glucocorticosteroid avoidance (excluding intra-operative use or treatment of acute rejection) or withdrawal versus glucocorticosteroid-containing immunosuppression following liver transplantation.

### Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded and Conference Proceedings Citation Index - Science, Literatura Americana e do Caribe em Ciências da Saúde (LILACS), World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, and The Transplant Library until May 2017.

### Selection criteria

Randomised clinical trials assessing glucocorticosteroid avoidance or withdrawal versus glucocorticosteroid-containing immunosuppression for liver transplanted people. Our inclusion criteria stated that participants should have received the same co-interventions. We included trials that assessed complete glucocorticosteroid avoidance (excluding intra-operative use or treatment of acute rejection) versus short-term glucocorticosteroids, as well as trials that assessed short-term glucocorticosteroids versus long-term glucocorticosteroids.

### Data collection and analysis

We used RevMan to conduct meta-analyses, calculating risk ratio (RR) for dichotomous variables and mean difference (MD) for continuous variables, both with 95% confidence intervals (CIs). We used a random-effects model and a fixed-effect model and reported both results where a discrepancy existed; otherwise we reported only the results from the fixed-effect model. We assessed the risk of systematic errors

using 'Risk of bias' domains. We controlled for random errors by performing Trial Sequential Analysis. We presented our results in a 'Summary of findings' table.

### Main results

We included 17 completed randomised clinical trials, but only 16 studies with 1347 participants provided data for the meta-analyses. Ten of the 16 trials assessed complete postoperative glucocorticosteroid avoidance (excluding intra-operative use or treatment of acute rejection) versus short-term glucocorticosteroids (782 participants) and six trials assessed short-term glucocorticosteroids versus long-term glucocorticosteroids (565 participants). One additional study assessed complete post-operative glucocorticosteroid avoidance but could only be incorporated into qualitative analysis of the results due to limited data published in an abstract. All trials were at high risk of bias. Only eight trials reported on the type of donor used. Overall, we found no statistically significant difference for mortality (RR 1.15, 95% CI 0.93 to 1.44; low-quality evidence), graft loss including death (RR 1.15, 95% CI 0.90 to 1.46; low-quality evidence), or infection (RR 0.88, 95% CI 0.73 to 1.05; very low-quality evidence) when glucocorticosteroid avoidance or withdrawal was compared with glucocorticosteroid-containing immunosuppression. Acute rejection and glucocorticosteroid-resistant rejection were statistically significantly more frequent when glucocorticosteroid avoidance or withdrawal was compared with glucocorticosteroid-containing immunosuppression (RR 1.33, 95% CI 1.08 to 1.64; low-quality evidence; and RR 2.14, 95% CI 1.13 to 4.02; very low-quality evidence). Diabetes mellitus and hypertension were statistically significantly less frequent when glucocorticosteroid avoidance or withdrawal was compared with glucocorticosteroid-containing immunosuppression (RR 0.81, 95% CI 0.66 to 0.99; low-quality evidence; and RR 0.76, 95% CI 0.65 to 0.90; low-quality evidence). We performed Trial Sequential Analysis for all outcomes. None of the outcomes crossed the monitoring boundaries or reached the required information size. Hence, we cannot exclude random errors from the results of the conventional meta-analyses.

### Authors' conclusions

Many of the benefits and harms of glucocorticosteroid avoidance or withdrawal remain uncertain because of the limited number of published randomised clinical trials, limited numbers of participants and outcomes, and high risk of bias in the trials. Glucocorticosteroid avoidance or withdrawal appears to reduce diabetes mellitus and hypertension whilst increasing acute rejection, glucocorticosteroid-resistant rejection, and renal impairment. We could identify no other benefits or harms of glucocorticosteroid avoidance or withdrawal. Glucocorticosteroid avoidance or withdrawal may be of benefit in selected patients, especially those at low risk of rejection and high risk of hypertension or diabetes mellitus. The optimal duration of glucocorticosteroid administration remains unclear. More randomised clinical trials assessing glucocorticosteroid avoidance or withdrawal are needed. These should be large, high-quality trials that minimise the risk of random and systematic error.

## PLAIN LANGUAGE SUMMARY

### Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients

#### Review question

We assessed whether avoiding or withdrawing glucocorticosteroids was better or worse than continuing to use glucocorticosteroids for immunosuppression after liver transplantation.

#### Background

Glucocorticosteroids are used to prevent rejection of the liver after transplantation by suppressing the immune system. Some centres use glucocorticosteroids indefinitely after liver transplantation whilst others slowly reduce them, and others do not use glucocorticosteroids at all. Glucocorticosteroids have a number of important adverse effects, which may lead to illness and sometimes death in liver transplantation. These adverse effects include diabetes mellitus, high blood pressure, and infection.

With recent developments in immunosuppression, glucocorticosteroids no longer feature as the main immunosuppressant used following transplantation. The use of new immunosuppressant medication may mean that glucocorticosteroids may no longer be necessary after transplantation. Rather than helping to prevent rejection of the liver graft they might cause adverse effects. The benefits of avoiding glucocorticosteroids or withdrawing them after a short while remain unclear.

#### Study characteristics

We searched for trials comparing glucocorticosteroid avoidance or withdrawal to continuing glucocorticosteroids. Seventeen randomised clinical trials were included, of which 16 trials involving 1347 participants provided numeric data for the meta-analyses. All of the studies assessed adults who had received a liver transplant. Of the 16 randomised clinical trials included in the meta-analyses, 10 trials assessed avoidance of glucocorticosteroids compared with slowly reducing glucocorticosteroids (782 participants) and six trials assessed withdrawal of glucocorticosteroids following a slow reduction compared with a longer reduction or long-term use of glucocorticosteroids (565 participants). Only eight trials reported on the type of donor used. The evidence is current to May 2017.

#### Key results

Rejection, severe rejection, and kidney failure may be increased by avoiding or withdrawing glucocorticosteroids compared with continuing glucocorticosteroids. Diabetes mellitus and high blood pressure may be reduced by avoiding or withdrawing

glucocorticosteroids compared with continuing glucocorticosteroids. We did not find any difference in survival of the patients, survival of the liver, other adverse effects, or health-related quality of life.

**Quality of the evidence**

We assessed all of the trials we included as being at high risk of bias, which means that they may overestimate the benefits and underestimate the harms of avoiding or withdrawing glucocorticosteroids. The evidence was either low quality or very low quality.

**Conclusion**

There is still some uncertainty about the benefits and harms of avoiding or withdrawing glucocorticosteroids after transplantation. Avoiding or withdrawing glucocorticosteroids appears to increase rejection, severe rejection, and kidney failure but seems to reduce diabetes mellitus and high blood pressure. We found no other obvious benefits or harms of avoiding or withdrawing glucocorticosteroids. More randomised clinical trials are needed to assess avoidance and withdrawal of glucocorticosteroids for liver transplanted patients.