Steroid-free versus steroid-containing immunosuppression for liver transplant recipients

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Clinical Question:
Is avoiding or withdrawing steroids better or worse than continuing to use steroids for immunosuppression after liver transplantation?

Bottom Line:
There is uncertainty based on low to very low-quality evidence that avoiding or withdrawing steroids after liver transplantation affects mortality, graft loss, or infection rates. There is low-quality evidence that avoiding or withdrawing steroids among liver transplant recipients reduces hypertension, diabetes mellitus and total serum cholesterol values. However, avoiding or withdrawingsteroids also increases acute rejection, steroid-resistant rejection and creatinine values.

Evidence Profile

No. of trials: 17[a]
No. of randomized clinical trials: 17[a]
Study years: 1998 to 2013
No. of participants: 1347[a]
Men: 73%[b] **Women:** 27%[b]
Race/ethnicity: Not reported
Age, mean (range): 50 (42-58) years[c]
Settings: Outpatient or inpatient transplant centers

Countries: United States (n=2), China (n=3), Germany (n=1), Italy (n=5), Belgium (n=1), Spain (n=2), France (n=1), Czech Republic (n=1)
Intervention: Avoidance or withdrawal of steroids for immunosuppression
Comparison: Steroid-containing immunosuppression regimen
Primary outcomes: • All-cause mortality • Graft loss including death • Acute rejection • Infection
Secondary outcomes: • Chronic and steroid-resistant rejection • Cardiometabolic complications: diabetes mellitus, hypertension, hyperlipidemia • Hepatitis C virus (HCV) recurrence • Malignancy and post-transplantation lymphoproliferative disorder (PTLD) • Renal function[d] • De novo autoimmune hepatitis • Health-related quality of life
Prespecified subgroup analyses: • Different immunosuppressive agents • Co-interventions • Duration of treatment with steroids • Trials before the year 2000 compared to trials in and after year 2000
Follow-up: 13 to 108 months

[a] 1 trial of the 17 was published only in abstract form and thus only 16 trials had data available on a total of 1347 participants for meta-analysis.
[b] Sex ratio only reported in 12 of 17 trials
[c] Age only reported in 14 of 17 trials
[d] Renal failure requiring dialysis, renal insufficiency, estimated glomerular filtration rate, serum creatinine

Introduction

Liver transplant recipients must take life-long immunosuppressive medication to prevent organ allograft rejection. Currently available oral immunosuppressive agents include calcineurin inhibitors (e.g., cyclosporine, tacrolimus), antiproliferative agents (e.g., azathioprine, mycophenolate mofetil), mammalian target of rapamycin inhibitors (e.g., sirolimus, everolimus), induction agents (e.g., rabbit antithymocyte globulin, basiliximab, etc.) and glucocorticosteroids (e.g., prednisone). Historically, steroids have formed the backbone of immunosuppressive regimens after liver transplantation. However, advancements in immunosuppression over the past 20 years have led many transplant centers to adopt steroid-sparing immunosuppression protocols. Long-term immunosuppression, and in particular steroid use, carries with it substantial adverse effects including increasing risk of infection, bone loss and cardiometabolic diseases (e.g., obesity, hypertension, diabetes, and hyperlipidemia) .[1] In

fact, cardiovascular diseases are the leading cause of morbidity and mortality after liver transplantation.[2,3] Thus, clinicians must aim to maximize the benefit of immunosuppressive agents to prevent rejection while minimizing their adverse effects. This article summarizes a recent 2018 Cochrane review[4] assessing the effects of steroid-minimization or avoidance among liver transplant recipients compared to steroid-containing immunosuppression protocols on mortality, graft loss, rejection and infection in addition to a variety of secondary cardiometabolic outcomes.

Summary of Findings

The authors identified 17 randomized clinical trials, but only 16 had available data for meta-analysis for a total of 1347 participants performed between 1998 and 2013. Most (10 of 16) trials assessed complete postoperative steroid avoidance (excluding intra-operative use or treatment of acute rejection) versus short-term steroids (n=782). The remaining 6 trials assessed short-term steroids versus long-term steroids (n=565). One study assessed complete postoperative steroid withdrawal but could not be incorporated into quantitative analysis since it was only published in abstract form and did not report the number of participants allocated to each arm. There was substantial heterogeneity between duration of steroid use in the steroid-containing arm of each included trial. Steroid administration was reported as 64 days (n=1), three months (n=7), three to six months (n=1), six months (n=2), nine months (n=1), 25 months (n=1), indefinitely (n=2) and not reported at all (n=1). Five trials began prior to 2000, and the remaining 11 trials were published from 2000 onwards. All trials used a concomitant calcineurin inhibitor (tacrolimus (n=5), cyclosporine (n=11)). Seven trials used an antiproliferative agent and nine trials used induction therapy (rabbit antithymocyte globulin (n=2), basiliximab (n=5) and daclizumab (n=1)). Most (12 of 16) trials were single center studies, and all included an adult-only, predominantly male (73%) population. Follow-up for all endpoints ranged from 13 to 108 months.

Low to very low-quality evidence suggests that there is uncertainty of effect between steroid avoidance or withdrawal compared to steroid-containing immunosuppression for mortality (19% steroid-free versus 17% steroid-containing; RR 1.15, 95% CI 0.93-1.44), graft loss including death (19% steroid-free versus 15% steroid-containing; RR 1.15, 95% CI 0.90-1.46), or infection (31% steroid-free versus 36% steroid-containing; RR 0.88, 95% CI 0.73-1.05; Table 1) among liver transplant recipients. Acute rejection (22% steroid-free versus 17% steroid-containing; RR 1.33, 95% CI 1.08-1.64; low-quality evidence) and steroid-resistant rejection (5% steroid-free versus 3% steroid-containing; 2.14, 95% CI 1.13-4.02; very low-quality evidence) were more frequent among recipients in whom steroid-avoidance or withdrawal was used compared to steroid-containing immunosuppressive regimens. Among 4 trials with 309 participants reporting renal function outcomes, creatinine levels were higher when steroid-avoidance or withdrawal was compared to steroid-containing immunosuppression (mean difference (MD) 0.11 mg/dL, 95% 0.07-0.16, very low-quality evidence). On the other hand, diabetes (21% steroid-free versus 26% steroid-containing; RR 0.88, 95% CI, 0.66-0.99; low-

quality evidence) and hypertension (29% steroid-free versus 38% steroid-containing; RR 0.76, 95% CI 0.65-0.90, low-quality evidence) were less frequent in the steroid-avoidance or withdrawal groups compared to steroid-containing groups. Serum total cholesterol was also lower in steroid-avoidance or withdrawal compared with steroid-containing regimens (MD -18.49 mg/dL, 95% CI -22.02 to -14.96, very low-quality evidence). There is uncertainty surrounding benefits or harms across the remaining secondary outcomes assessed in this review based on low to very low-quality evidence (Table 1).

Discussion

Among 16 randomized clinical trials in 1,347 liver transplant recipients, there is uncertainty of benefit or harm for steroid avoidance or withdrawal versus steroid continuation on the primary outcomes of mortality, graft loss including death or infection rates after liver transplantation. Steroid avoidance or withdrawal was associated with lower hypertension, diabetes and serum cholesterol. These benefits are offset by higher acute rejection, steroid-resistance rejection and raised serum creatinine compared to steroid-containing immunosuppression regimens. There is uncertainty of benefit or harm for other outcomes of interest including chronic rejection, cytomegalovirus infection, hepatitis C recurrence, malignancy, post-transplant lymphoproliferative disorder, renal insufficiency, hyperlipidemia, cholesterol or hypercholesterolemia. The overall quality of evidence was low in this review thus tempering the clinical implications of these findings.

Limitations

Most trials were small with a high risk of bias across at least one domain, which lowers the quality of evidence. One trial was terminated early due to a higher rate of rejection within the steroid-free arm which may exaggerate the effect as truncated trials are known to demonstrate more extreme intervention effects.[6] There is uncertainty of the benefits and harms of steroid avoidance or withdrawal versus steroid-containing immunosuppressive regimens among liver transplant recipients.

Heterogeneity in the duration and dosing regimen for steroids between each study also adds to uncertainty. There may be an optimum, short duration of steroid administration with which acute rejection in the early post-transplant phase can be prevented without significant impact on cardiometabolic adverse events. There may also be an opportunity for stratified immunosuppression with those considered to be low-risk of rejection or high-risk of cardiometabolic disease being offered steroid-free immunosuppression.

The studies in this meta-analysis excluded retransplantation, multi-organ transplantation and pediatric participants.

Areas in Need of Future Study

High-quality, adequately powered trials using contemporary immunosuppression protocols, varied duration of steroid administration based on current practice patterns and longer periods of follow-up are needed to evaluate the safety and efficacy of steroid avoidance or withdrawal in liver transplant recipients. It may be of benefit to construct a high-quality three-arm trial comparing complete postoperative steroid avoidance, short-term steroids, and long-term steroids. As of May 26, 2020, there is no registered clinical trial that meets these criteria. Such a trial will require multi-center, and possibly, international collaboration in order to obtain adequate sample size across each randomization strata. Limited funding is a major potential barrier. Thus, there is an urgent need for joint collaboration among industry, academia, regulatory, government and transplantation organizations to patner together to conduct these types of high-quality randomized controlled trials in rare cohorts, such as liver transplant recipients.

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Table 1. Summary of Findings for the Effect of Steroid-Withdrawal or Steroid-Avoidance Versus Continuation of Steroids in Liver Transplant Recipients

Outcome[a]	Anticipated Absolute Effects (No. of Cases per 1000 population)[b]		Relative Effect, RR or Mean Difference, MD (95% CI)	No. of Participants	No. of RCTs	Quality of Evidence (GRADE)[c]
	Steroid-containing	Steroid-avoidance				
All-cause mortality	166	191 (154-239)	1.15 (0.93-1.44)	1323	15	Low[d,e]
Graft loss including death	175	203 (159-259)	1.15 (0.90-1.46)	1002	11	Low[d,e]
Acute rejection	173	230 (187-283)	**1.33 (1.08-1.64)**	1347	16	Low[d,e]
Infection	359	316 (262-377)	0.88 (0.73-1.05)	778	8	Very Low[d,e,f]
Chronic rejection	30	33 (17-64)	1.08 (0.56-2.10)	974	9	Very low[d,e,f]

Steroid-resistant rejection	25	54 (29-101)	**2.14 (1.13-4.02)**	1020	10	Very low[d,e,f]
Diabetes Mellitus	261	212 (172-259)	**0.81 (0.66-0.99)***	1185	12	Low[d,f]
CMV infection	95	70 (46-110)	0.74 (0.48-1.16)	786	7	Low[d,e]
HCV recurrence	661	681 (608-760)	1.03 (0.92-1.15)	447	10	Very low[d,e,f]
Malignancy	26	13 (4-45)	0.52 (0.16-1.74)	528	3	Very low[d,e,f]
PTLD	6	14 (2-95)	2.39 (0.36-15.95)	330	2	Very low[d,e,f]
Renal insufficiency	333	310 (243-397)	0.93 (0.73-1.19)	447	4	Very low[d,e,f]
Creatinine (mg/dL)	The mean creatinine ranged from 0.8-1.9	The mean creatinine ranged from 0.75-1.8	**0.11 (0.07-0.16)***	309	4	Very low[d,e,f]
Hypertension	378	288 (246-341)	**0.76 (0.65-0.90)**	1098	10	Low[d,f]
Hyperlipidemia	89	67 (34-131)	0.75 (0.38-1.48)	400	4	Very low[d,e,f]
Hypercholesterolemia	212	119 (68-212)	0.56 (0.31-1.00)	266	2	Very low[d,e,f]
Cholesterol (mg/dL)	The mean cholesterol ranged from 117-207	The mean cholesterol ranged from 128-297	**-18.49 (-22.02, -14.96)**	556	5	Very low[d,e,f]

Abbreviations: CMV, cytomegalovirus; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HCV, hepatitis C virus; MD, mean difference; No., number; PTLD, post-transplant lymphoproliferative disorder; RCTs, randomized clinical trials; RR, risk ratio.

*Fixed effects model, random-effects model for diabetes RR (95% CI)=0.82 (0.64-1.07) and for creatinine MD (95% CI)=0.01 (-0.21-0.23) mg/dL

[a] All outcomes were assessed at latest follow up (range 13 months to 108 months)

[b] The risk in the intervention group is based on the assumed risk in the comparison group, which is calculated from the control arm of the meta-analysis and the relative effect of the intervention.

[c] The GRADE Working Group grades of evidence[5] were as follows: high quality (the true effect lies close to that of the estimate of the effect), moderate quality (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), low quality (the true effect may be substantially different from the estimate of the effect), and very low quality (the true effect is likely to be substantially different from the estimate of effect).

[d] Downgraded because of risk of bias

[e] Downgraded because of imprecision.

[f] Downgraded because of heterogeneity between subgroups; avoidance versus withdrawal.