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ORIGINAL ARTICLE

Steroid sparing protocols following nonrenal transplants; the evidence is not there. A systematic review and meta-analysis

Simon R. Knight and Peter J. Morris

Clinical Effectiveness Unit, Centre for Evidence in Transplantation, Royal College of Surgeons of England and the London School of Hygiene and Tropical Medicine, University of London, London, UK

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Correspondence
Simon Knight, Clinical Effectiveness Unit, Centre for Evidence in Transplantation, The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE, UK.
Tel.: 0207 869 6604; fax: 0207 869 6644;
e-mail: sknight@rcseng.ac.uk

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Simon Knight has received a travel bursary from Roche. Peter Morris chairs a DSMB for Bristol Myers Squibb and has received lecture fees and expenses in the past from Novartis, Roche, Genezyme and Astellas.

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Summary

We have recently reported that steroid avoidance or withdrawal (SAW) following renal transplantation results in an increase in acute rejection (AR) rates but does not affect graft or patient survival. Cardiovascular risk factors were significantly reduced. It cannot be assumed that the same risks and benefits apply to nonrenal transplants and we have therefore extended this work to evaluate SAW protocols in nonrenal organ transplantation. A detailed literature search identified nine relevant studies; seven in liver, one in cardiac and one in pancreatic transplant recipients. In liver recipients no difference in AR, graft or patient survival was identified. A significant reduction in the risk of new-onset diabetes was observed with SAW, with trends towards benefits in other cardiovascular risk factors, but meta-analysis was hampered by the small number of studies and significant heterogeneity. Some benefits in cardiovascular risk factors were also identified in the cardiac and pancreatic transplant recipients, but again this evidence is of limited quality. Whilst the trend in effect of SAW in nonrenal recipients appears to be similar to that in renal recipients, the lack of robust evidence requires further randomized controlled trials before the true risk/benefit ratio of SAW in nonrenal transplant recipients can be ascertained.

Introduction

Corticosteroids were introduced in conjunction with azathioprine in renal transplant recipients in the 1960s in an attempt to prevent the inevitable AR seen at that time with azathiaprine alone [1]. During the subsequent development of transplantation immunosuppression, corticosteroids became a mainstay of maintenance drug therapy – a practice which later extended to regimens used in the transplantation of other solid organs. Corticosteroid use is associated with many side effects [2], but the development of newer, more effective, induction and maintenance agents has led to a great interest in dose reduction, withdrawal, and even complete avoidance of steroids following transplantation.

We have recently reported a comprehensive systematic review and meta-analysis of steroid avoidance or withdrawal (SAW) regimens following renal transplantation [3]. Meta-analysis of 34 studies (including 5637 patients) demonstrated that whilst there is an increased risk of AR following SAW, there was only a very marginal reduction in graft function with no difference in graft or patient survival over the length of follow-up reported. Furthermore, there were significant benefits in terms of cardiovascular risk reduction, with reductions in the incidence of hypertension, new onset diabetes and hypercholesterolemia.

There has also been a gradual trend towards SAW following transplantation of other solid organs [4]. There are specific concerns following transplantation of the heart, liver and pancreas which make avoidance of long-term corticosteroid therapy desirable. One of the most common indications for liver transplantation is Hepatitis C infection, with histological recurrence seen in nearly half of patients at 1 year post-transplant [5]. The use of methylprednisolone for the treatment of AR episodes leads to a 4- to 100-fold increase in HCV RNA levels, which are in turn associated with an increased histological severity of graft injury [6]. Whilst the impact of lower maintenance steroid doses is less clear, these findings have added impetus to the avoidance or early withdrawal of steroids in liver transplant recipients. As the primary indication for the majority of pancreas-alone or simultaneous pancreas-kidney (SPK) transplants is poorly controlled diabetes mellitus with or without subsequent diabetic nephropathy, it seems logical that corticosteroid use is minimized owing to the tendency for their use to produce glucose intolerance. Unsurprisingly, there is an increasing trend towards steroid avoidance or early withdrawal particularly following not only pancreas-alone, but also in SPK transplants [4]. Similarly, the impact of long-term steroid use on the risk of cardiovascular disease is likely to be detrimental following cardiac transplantation.

Whilst there are many theoretical benefits of SAW protocols in these settings, it is not known what the effect of avoiding steroids is on the immunological risk to such grafts. If the rejection risk is higher, bearing in mind that failure of liver and heart transplants generally results in death, safe withdrawal may not be possible despite the benefits in terms of side-effect profiles. This review is designed to identify the evidence for the safety and efficacy of steroid withdrawal or avoidance following transplantation of other solid organ types, to guide clinical practice in these areas.

Materials and methods

Methodology of this review is similar to that of our recent study in renal transplant recipients, described in detail elsewhere [3]. Briefly, a systematic literature search was performed using OVID Medline and Embase, the Cochrane Central Registry of Controlled Trials, the Transplant Library from the Centre for Evidence in Transplantation (which includes hand-searched journals and conference proceedings) and trial registries (clinicaltrials.gov, the national research register and current controlled trials). To avoid missing potentially relevant references, searches were performed using only Mesh keywords and free-text aliases for transplantation and corticosteroids in each database, without limiting searches further using terms for sparing and avoidance. No date or language limits were applied. References of included studies and previous relevant reviews were scanned for potentially relevant studies that had been missed in literature searching. The final date for literature searches was 20 June 2011.

Inclusion criteria specified any prospective randomized study in nonrenal solid organ transplant recipients, in which outcomes in patients receiving maintenance steroids from the time of transplantation were compared with a cohort either in which steroids were withdrawn at any time post-transplant or were avoided completely. Studies of steroid avoidance/withdrawal in renal transplant recipients are considered elsewhere [3]. Studies in which steroids were used for other conditions and in which steroid doses were minimized, but not withdrawn completely, were excluded. Studies were only included if patients in the steroid arm were maintained on steroids until the report of follow-up data.

The primary outcome in this analysis was the incidence of AR. Secondary outcomes were patient and graft survival, graft function, hypertension, diabetes, serum cholesterol and triglycerides, infection and malignancy. In the case of liver transplantation, recurrence of hepatitis C infection was also considered.

Studies are referred to throughout this article by the first author and year of the first peer-reviewed publication from that study. In the absence of any peer-reviewed publications, the first author and year of the first published abstract is used. Demographic, quality and outcome data were extracted from the included studies into a custom-designed online database by the lead author (SRK). The quality of the extracted data was confirmed by double-checking by the second author (PJM). Disagreements were resolved by discussion. There was also continuous cross-checking of previous entries during the data analysis.

Quality was assessed both by means of the Jadad score (a score of 3 or greater is considered good quality) and a description of allocation concealment and analysis based on intention-to-treat [7]. When assessing study quality, all reports from a trial are assessed, and the information pooled.

Where adequate data were available, statistical meta-analysis was performed using the *metafor* package for the R statistical language. For binary outcomes the relative risk (RR) was used as a summary statistic, with the weighted mean difference (WMD) used for continuous outcomes. All summary effects are presented with a 95% confidence interval (CI). If an outcome is reported at more than one time-point for a single study, the most recent follow-up data is used.

Heterogeneity was quantified using both the Cochran Q test and I^2 test. A P-value of <0.1 was regarded as

significant for the Cochran Q test. The I^2 test describes the percentage of total variation across the studies that is ascribable to heterogeneity rather than chance (over 40% is generally regarded as indicating significant heterogeneity) [8]. In the absence of heterogeneity, studies were combined using a fixed effects meta-analysis. If visual inspection of the forest plot or a high I^2 value suggested heterogeneity, potential causes were explored by looking for methodological differences between the studies. In the presence of heterogeneity, a residual maximum likelihood model (REML) random effects meta-analysis was performed.

Results

Nine relevant studies were identified in the literature search (31 publications): seven in liver transplantation, one in cardiac transplantation and one in pancreatic transplantation (Fig. 1). No relevant studies were identified in small bowel or lung transplant recipients.

Liver transplantation

Demographics and study quality

Twenty-five publications from seven studies were identified that compared maintenance steroids with steroid withdrawal or avoidance in liver transplant recipients [9–33]. The seven studies included a total of 725 patients. Of the 25 publications, 14 were papers in peer-reviewed journals and 11 were abstracts. Details of the included studies, including concomitant immunosuppression and time of steroid withdrawal are shown in Table 1. In the studies from Moench, Tisone, Reggiani and Llado the control group patients were withdrawn from steroids at variable times post-transplant; therefore only the outcomes reported prior to the time of steroid withdrawal in the control group are considered here.

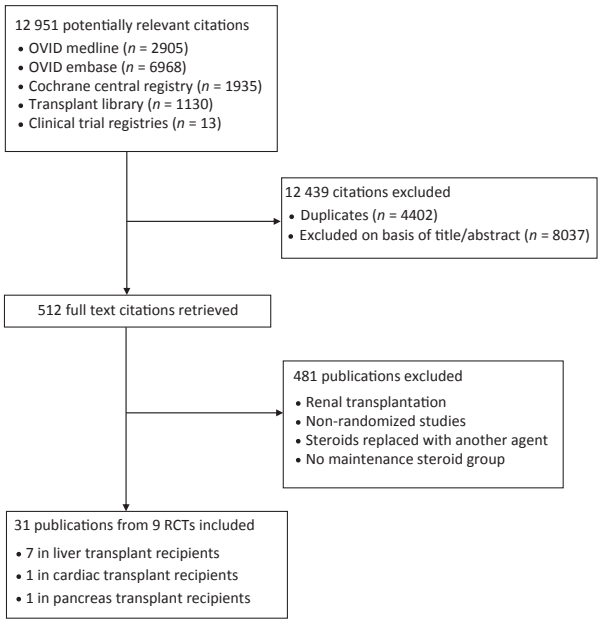

Figure 1 Flow chart to show the inclusion and exclusion of studies during the review process. RCT, randomized controlled trial.

Quality assessment of the studies is also shown in Table 1. Five of the seven studies (71%) have a Jadad score of ≥3, whilst only two studies (29%) reported an intention-to-treat analysis, and 4 (57%) described an adequate method of allocation concealment. Thus, overall the quality of the trials included ranged from high (4 trials) to low (2 trials) with one moderate quality trial.

The study from McDiarmid *et al.* includes both adult and paediatric transplant recipients. As results are not reported separately in the original article, they will be considered together with the other four adult studies in this analysis.

Acute rejection

Incidence of AR was reported in 5 of 7 studies (412 patients) [9,13,25,29,33]. Two studies reported a statistically significant increase in the risk of AR [13,25]. The high rate of AR in the study group in the trial from Reggiani led to recruitment being halted [13]. However, overall meta-analysis demonstrates a nonsignificant increase in risk of AR (RR 1.44, 95% CI: 0.89–2.33, $P = 0.14$, random effects analysis, $I^2 = 44.78\%$, Cochran Q $P = 0.13$; Fig. 2).

Three studies reported data on the severity of rejection episodes [9,13,25]. The study from Reggiani *et al.* demonstrated a significantly higher rejection activity index (RAI) in the steroid withdrawal arm. Pageaux also reported trend towards a higher incidence of grade II/III AR (28.6% vs. 18.9%; $P = 0.12$). Tisone reported no difference in the severity of AR between groups.

Patient and graft survival

Only two studies reported survival data (278 patients) [25,29]. Belli reported no difference in the incidence of death between groups (18% in the steroid group vs. 20% in the withdrawal group). Pageaux demonstrated no difference in patient survival, graft survival including death or graft survival excluding death with a functioning graft.

Graft function

Three studies reported information on serum liver function parameters (213 patients) [9,29,33]. No differences were observed between serum bilirubin, alkaline phosphatase (ALP) or aspartate transaminase (AST) in any study. Tisone *et al.* demonstrated a significantly higher glutamyl-gamma-transferase (GGT) in the steroid-treated group

Table 1. Demographics and quality assessment of studies investigating steroid avoidance/withdrawal in liver transplant recipients.

Name	Year	Time of withdrawal	Patients (control/study)	Immunosuppression	Jadad	ITT	AC	Follow-up	References
Tisone	1998	Avoidance	45 (22/23)	CsA ME/AZA	3	No	No	3 months*	[9–12]
Reggiani	2005	Avoidance	30 (18/12)†	Tac/MMF	2	No	No	3 months*	[13,14]
Llado	2006	Avoidance	198 (102/96)	CsA ME/BsL	3	Yes	Yes	3 months*	[15–17]
Moench	2007	Day 14	110 (54/56)	Tac	5	Yes	Yes	6 months*	[18–23]
Pageaux	2004	Day 14	174 (90/84)	CsA ME/BsL	4	No	Yes	1 year	[24–26]
Belli	1994	Month 3	104 (50/54)	CsA SIM/AZA/ALG	2	No	No	5 years	[27–32]
McDiarmid‡	1995	Month 12§	64 (31/33)	CsA SIM/AZA	3	No	Yes	1 year	[33]

Studies are labelled by first author and year of first full peer-reviewed publication. Time of steroid withdrawal is point at which steroids are completely withdrawn (end of taper).

ITT, intention-to-treat; AC, allocation concealment; CsA, Cyclosporine; ME, microemulsion; SIM, Sandimmune; Tac, tacrolimus; AZA, azathioprine; MMF, mycophenolate mofetil; BsL, basiliximab; ALG, anti-lymphocyte globulin.

*Patients in the control group were withdrawn from steroids prior to study completion. Outcomes are considered only to the point of withdrawal in the control group; †Recruitment stopped at interim analysis; ‡Study includes mixture of paediatric and adult patients; §Steroids withdrawn in stable patients, mean time in withdrawal group 42 months, control group 43 months.

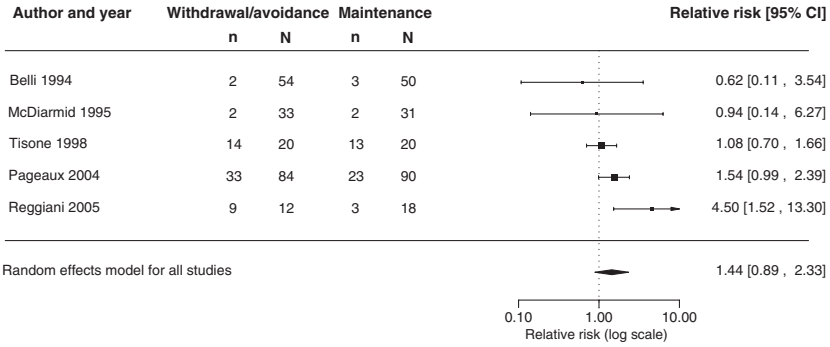

Figure 2 Forest plot to show the relative risk of acute rejection in liver transplant recipients with steroid avoidance/withdrawal. Square boxes show treatment effects for individual studies. Diamond shows summary treatment effect for overall analysis derived from a random effects model. Horizontal lines show 95% confidence intervals. RR >1 favours maintenance steroids. Tests for heterogeneity: I^2 = 44.78%, Cochran Q P = 0.13. *n*, number of patients with acute rejection; *N*, total number of patients in arm; CI, confidence interval.

at 90 days post-transplant (128 U/ml vs. 79 U/ml, $P < 0.001$), and higher ALP levels at 30 days post-transplant (179 U/ml vs. 103 mU/ml, $P < 0.02$).

Hypertension

Four studies (582 patients) reported incidence of hypertension [16,20,25,29]. There was a nonsignificant reduction in hypertension with steroid withdrawal (random effects, RR 0.66, 95% CI: 0.40–1.08, $P = 0.1$; Fig. 3). Significant heterogeneity was identified in this analysis (Cochran Q $P = 0.0015$, $I^2 = 83.9\%$), mainly resulting from a larger reduction in risk in the study from Belli. Excluding this study reduced the effect size seen, although there is significant residual heterogeneity (RR 0.82, 95% CI: 0.60–1.14, $P = 0.24$, $I^2 = 60.6\%$, Cochran Q $P = 0.08$).

New onset diabetes

Five studies reported incidence of diabetes following transplantation (646 patients) [16,20,25,29,33]. McDiarmid reported no new-onset diabetes in either arm of the study. Meta-analysis demonstrates a significant reduction in the risk of new-onset diabetes with steroid avoidance/withdrawal (fixed effects, RR 0.57, 95% CI: 0.42–0.77, $P = 0.0002$; Fig. 4) with minimal heterogeneity ($I^2 = 0\%$, Cochran Q $P = 0.64$).

Serum lipids

Incidence of hypercholesterolaemia was significantly higher in the steroid maintenance group at 6 months in the study from Moench *et al.* (41.3% vs. 10.8%, $P = 0.002$) although this difference disappeared following withdrawal of maintenance steroids by month 12 [20]. This was the only study to report this outcome. Serum cholesterol levels were reported in four studies (472 patients) [16,20,29,33]. Meta-analysis demonstrates a nonsignificant reduction in serum cholesterol with steroid withdrawal (random effects, −26.2 mg/dl, 95% CI: −58.4 to 6.03, $P = 0.11$; Fig. 5a) but significant heterogeneity is seen (Cochran Q $P = 0.002$,

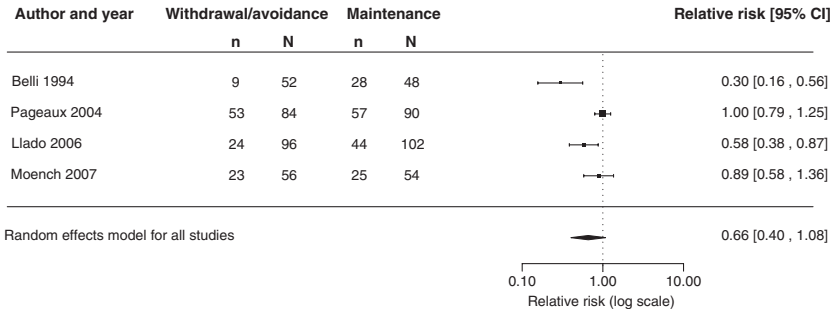

Figure 3 Forest plot to show the relative risk of hypertension in liver transplant recipients with steroid avoidance/withdrawal. Square boxes show treatment effects for individual studies. Diamond shows summary treatment effect for overall analysis derived from a random effects model. Horizontal lines show 95% confidence intervals. RR >1 favours maintenance steroids. Tests for heterogeneity: I^2 = 83.9%, Cochran *Q* *P* = 0.0015. *n*, number of patients with hypertension; *N*, total number of patients in arm; CI, confidence interval.

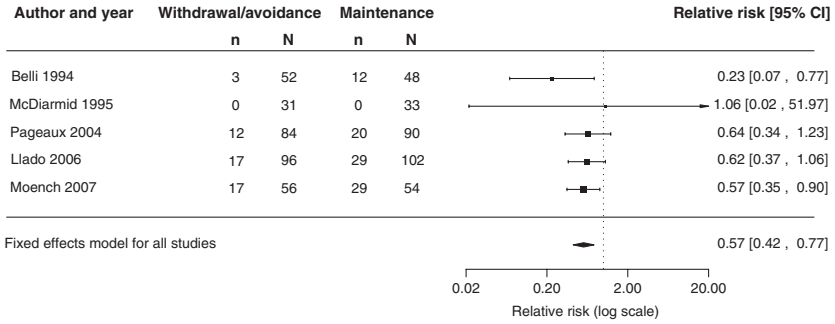

Figure 4 Forest plot to show the relative risk of new onset diabetes in liver transplant recipients with steroid avoidance/withdrawal. Square boxes show treatment effects for individual studies. Diamond shows summary treatment effect for overall analysis derived from a random effects model. Horizontal lines show 95% confidence intervals. RR >1 favours maintenance steroids. Tests for heterogeneity: I^2 = 0%, Cochran *Q* *P* = 0.64. *n*, number of patients with diabetes; *N*, total number of patients in arm; CI, confidence interval.

I^2 = 84.7%). Again, a large proportion of the heterogeneity arises from the study from Belli, in which a larger reduction in cholesterol level is seen with steroid withdrawal. Removing this study reduces the effect size seen, although significant heterogeneity remains (−14.2 mg/dl, 95% CI: −38.2 to 9.8, *P* = 0.25, I^2 = 67.2%, Cochran *Q* *P* = 0.06).

Moench *et al.* also reported the incidence of hypertriglyceridaemia, demonstrating a significant reduction in patients in whom steroids were withdrawn (32.4% vs. 54.3%, *P* = 0.046). Three studies (408 patients) reported mean serum triglyceride levels [16,20,29]. Meta-analysis demonstrates a significant reduction in triglyceride levels with steroid withdrawal (random effects −37.0 mg/dl, 95% CI: −70.5 to −3.5, *P* = 0.03; Fig. 5b). Again, the presence of significant heterogeneity is seen (Cochran *Q* *P* = 0.04, I^2 = 72.9%), which can be attributed to a larger effect size in the study from Belli. Removing this study still demonstrates a significant reduction in triglyceride levels with SAW (−21.95 mg/dl, 95% CI: −40.5 to −3.4, *P* = 0.02) with no residual heterogeneity (I^2 = 0.0%, Cochran *Q* *P* = 0.57).

Recurrent hepatitis C

Pageaux and Belli both report recurrence rates for hepatitis C infection, demonstrating no difference between groups [25,29]. Tisone demonstrated a higher HCV RNA level at 1–3 months in patients treated with steroids, but it is not known whether or not this difference is statistically significant [9].

Cardiac transplantation

Only one study was identified comparing steroid maintenance with withdrawal in cardiac transplant recipients (four publications) [34–37]. This study from Australia randomized 112 patients to either triple (CsA, AZA and steroids) or double (CsA and AZA) therapy. Both groups received induction with steroids and anti-thymocyte globulin (ATG). No method of randomization is given and the study is open label, giving it a Jadad score of 1. Intention-to-treat analysis is used in the report of 5-year results [36].

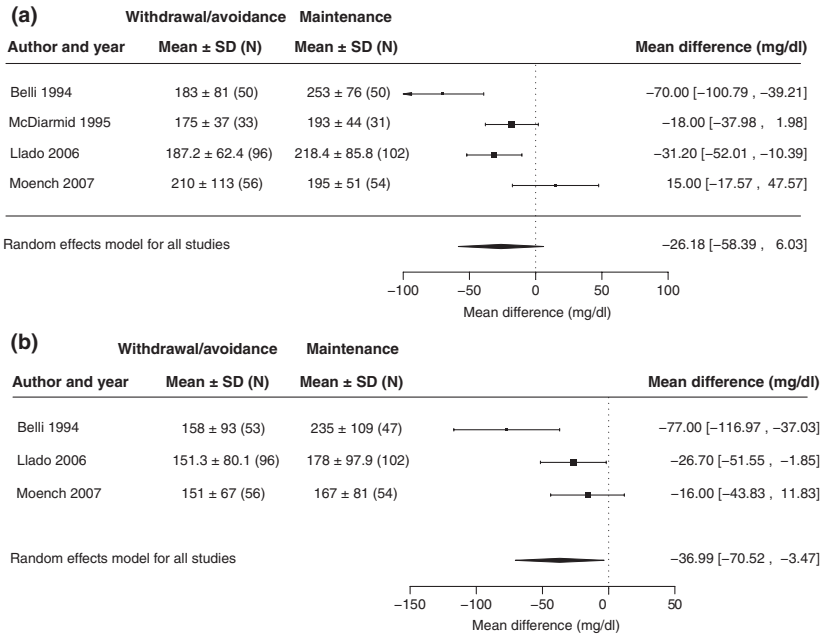

Figure 5 Forest plot to show the mean differences in serum lipid levels in liver transplant recipients with steroid avoidance/withdrawal. (a): Serum cholesterol (mg/dl). (b): Serum triglycerides. Square boxes show treatment effects for individual studies. Diamond shows summary treatment effect for overall analysis derived from a random effects model. Horizontal lines show 95% confidence intervals. SD, standard deviation; *N*, number of patients in arm; CI, confidence interval.

Rejection rate during the first 3 months was significantly higher in the steroid-withdrawal group when compared with maintenance steroids (2.3 ± 0.23 vs. 1.5 ± 0.18 episodes/100 patient days, $P < 0.01$), but did not differ beyond 3 months. The number of patients experiencing steroid resistant rejection requiring ATG or OKT3 was also higher in the steroid-withdrawal group (26.4% vs. 10.2%, $P = 0.033$). Graft and patient survival did not differ at 5 years. Cardiac function was similar between the groups.

Cardiovascular risk factors were improved with steroid withdrawal. Whilst mean blood pressure did not differ at 3 years post-transplant, the number of antihypertensive agents required per patient was significantly higher in the maintenance steroid group (1.3 ± 0.7 vs. 0.8 ± 0.6 agents; $P = 0.016$). The maintenance steroid group also had significantly higher cholesterol levels at 3 years (6.2 ± 0.9 mmol/l vs. 5.4 ± 1.2 mmol/l, $P = 0.022$). Of note, 47% of patients in the steroid withdrawal group required the addition of maintenance steroids during follow-up, largely owing to the increased incidence of rejection.

A follow-up article has reported the effect on quality of life in a subset of 47 patients in this trial [35]. Patients withdrawn from steroids had significantly lower anxiety and greater physical well-being. There were also trends towards lower financial strain and greater sexual satisfaction in the withdrawal group. These results should be interpreted with caution, however, as the subset of patients answering the questionnaire was self selected and not randomized.

Pancreatic transplantation

Only one study was identified reporting a comparison between steroid maintenance and withdrawal greater than 6 months following SPK or pancreas-after-kidney (PAK) transplantation [38,39]. All patients received MMF and tacrolimus. Whilst the study was reported to be randomized, it is open label and no method of randomization is reported. Withdrawals are described, so the Jadad score is 2. Intention-to-treat analysis is not described. The overall numbers of patients included was small (29 SPK, 26 PAK).

No difference was seen in the incidence of AR or in patient or graft survival in either group. In the SPK patients, significantly lower cholesterol and triglycerides were seen in the steroid withdrawal group at 6 months. Benefits were not significant in the PAK group, which the authors ascribe to longstanding steroid use prior to pancreas transplant. Interestingly data regarding glucose intolerance were not reported in this study, despite the importance of avoiding this complication in previously diabetic pancreas transplant recipients.

Discussion

One of the most striking findings of the present review is the relative scarcity of data about steroid withdrawal or avoidance in nonrenal organ transplant recipients when compared to renal transplantation patients. Our review of steroid avoidance and withdrawal in renal transplant recipients identified 34 studies meeting inclusion criteria [3]. With the same inclusion criteria, we have identified only nine relevant studies in all other organ types, most of them in liver transplantation. This lack of evidence in the field of nonrenal transplantation is not unique to the topic of steroid avoidance. In the Transplant Library of randomized controlled trials maintained by the Centre For Evidence in Transplantation, 6750 RCTs are listed, but only 1210 (17.9%) are studies in liver transplant recipients, in contrast to 4477 (66%) in renal transplant recipients. Clearly this relative lack of evidence in nonrenal organ transplantation is of some concern as one cannot extrapolate data from renal transplantation to practice in transplantation of other organs. This deficiency must be addressed with greater efforts to encourage future clinical trials in nonrenal organ transplantation, although accepting that the numbers available make this more difficult.

There are a number of potential reasons why there may be a scarcity of RCTs in this area in nonrenal transplant recipients. The first is one of practicality – smaller numbers of liver, heart and pancreas transplants are performed in smaller numbers of centres than renal transplantation, making recruiting the necessary number of recipients for an adequately powered clinical trial more difficult. Another major difference is in focus of treatment referable to the stakes involved. In renal transplantation, graft failure means a return to dialysis; in liver or cardiac transplantation it means retransplantation or death. There is likely therefore to be more resistance to minimization protocols in these settings. The final consideration is the choice of agent to minimize. In nonrenal transplantation, there may be a preference to withdraw or reduce calcineurin inhibitor (CNI) doses rather than steroids to prevent CNI-mediated nephrotoxicity in the native kidneys.

The majority of the identified studies in the present review involved liver transplant recipients. Although firm conclusions are difficult to draw owing to the relatively small number of patients studied, the broad trends appear to be similar to those seen in renal transplant recipients. Unlike renal transplantation, a significantly increased risk of AR with SAW is not found, although there is a trend towards this and one study was terminated early attributable to excess risk of AR. As in renal transplantation, there appears to be some cardiovascular and metabolic benefit with SAW, with a reduced risk of new-onset diabetes and hypertension, along with a reduction in serum triglyceride levels. One study demonstrated an elevation in the serum ALP and GGT levels in the steroid-treated group in the early post-transplant period, which may result from steroid-mediated cholestasis. Interestingly, however, no study demonstrated a significant difference in serum bilirubin levels.

Interpretation of these findings is made difficult by excessive heterogeneity in some analyses. Visual inspection of the funnel plots suggests that this may in part result from larger effect sizes reported in the study from Belli *et al.* [29]. This may reflect the very high early steroid doses used compared with those used in other studies (20 mg/day continued for 3 months post-transplant) – perhaps also explaining the lower AR rates reported in this study. A recent mixed-effects analysis of our data in renal transplant recipients has shown a similar effect with the steroid dose used in the maintenance arm – the metabolic and cardiovascular benefits seen with SAW are reduced with lower-dose maintenance regimens [40]. It is worth noting that in some analyses (hypertension, serum cholesterol) significant residual heterogeneity was seen even when the study from Belli was excluded. Owing to the small number of studies included, this is difficult to examine further.

Of particular interest is that there is no evidence for a decrease in the risk of recurrent hepatitis C infection following steroid withdrawal. The use of steroids has been associated with increased hepatitis C RNA levels and progression, leading to the suggestion that SAW may help prevent recurrent or progressive disease following transplantation [6]. However, this association is seen predominantly with the use of high doses of methylprednisolone in the treatment of AR, and it is possible that the lower steroid exposure seen with maintenance immunosuppression may have less of an effect. This is supported by a study from Miami which randomized patients undergoing liver transplant for hepatitis C to either maintenance steroids or daclizumab induction [41]. No difference in mean fibrosis stage was seen between groups, although infections and post-transplant diabetes were less frequent in the daclizumab arm. The only feature associated with a higher rate of fibrosis was the incidence of AR.

The small number of studies precludes any subgroup analyses to determine the effect of different immunosuppressive regimens or withdrawal times in liver transplant recipients. It should also be noted that formal assessment for publication bias is not possible with such a small number of studies.

Two previous systematic reviews have addressed the issue of steroid use in liver transplant recipients [42,43]. Unlike the present review, which concentrates on a comparison between maintenance steroids and SAW, both

these studies compared complete steroid avoidance with steroid withdrawal beyond 3 months following transplantation. Both of these reviews included quite a heterogeneous group of studies including withdrawal at various times from the steroid arm, and studies substituting steroids with other induction agents or maintenance immunosuppression. Both reviews demonstrated an increased risk of AR in studies in which steroids were not replaced by another agent, but a reduction in risk of AR when steroids were replaced by the use of an induction agent. As in the present analysis, steroid avoidance was associated with beneficial metabolic and cardiovascular profiles, including reduced hypertension, new-onset diabetes and serum lipids. Cytomegalovirus infection was also reduced in the steroid avoidance cohorts. Both studies also reported a significant reduction in risk of HCV recurrence with steroid avoidance.

In two of the studies included in the present review, in which steroids were withdrawn from the control group, the initial detrimental effects in metabolic parameters (glucose intolerance, hypertension, lipids) in the control group fell back to baseline following withdrawal. This suggests that the detrimental metabolic effects of steroids may be at least in part reversible and therefore steroid use in the early post-transplant period may be justifiable to reduce the increased risk of AR seen with complete avoidance.

Only one study assessing the impact of steroid minimization was identified in each of cardiac and pancreatic transplantation. The study in cardiac transplant recipients is of poor quality, and dates back nearly 20 years with patients on an outdated regimen of cyclosporine and azathioprine [34–37]. Nonetheless, it supports many of the trends seen in renal and hepatic recipients, with increased early incidence of AR and steroid resistant rejection episodes, along with a reduction in some cardiovascular risk factors. The only other evidence available is a prospective study from the CTS registry, in which cardiac transplant recipients were withdrawn from steroids beyond 6-months post-transplant, and compared to matched controls from the registry [44]. An improvement in graft survival was seen in recipients who were withdrawn from steroids (76.2% vs. 66.9%, $P = 0.0008$). Rates of AR and graft dysfunction did not differ between groups. Not enough data were collected to allow analysis of cardiovascular risk factors in cardiac recipients.

One might suggest that avoidance of recurrent glucose intolerance following pancreas transplantation would be paramount, and yet only one study in steroid avoidance following PAK or SPK transplantation was identified [38,39]. This study did not demonstrate any difference in pancreas graft survival (and thus recurrent diabetes) between the groups. This may reflect the fact that many centres have avoided or minimized steroid use as the inception of their pancreas transplant programmes and therefore such studies have not been performed.

Owing to the small number of included studies it has not been possible to examine the interaction between concomitant immunosuppression and the ability to withdraw steroids. Withdrawal of steroids may alter the metabolism of other immunosuppressant drugs, most notably mycophenolate mofetil [45,46]. The clinical significance of these interactions is uncertain, although our previous study in steroid withdrawal in renal recipients identified no interactions between baseline immunosuppression and outcomes [3].

In summary, the evidence for SAW protocols following nonrenal solid organ transplantation is sparse and it is impossible to draw firm conclusions. However, the trends seen in the available studies in liver transplantation, and to a lesser degree in cardiac transplantation, seem to support the findings in renal recipients of a trend towards an increased risk of AR albeit with no measurable effect on graft or patient survival. The tradeoff from this is that there does appear to be some evidence for a decrease in cardiovascular risk factors in those patients undergoing withdrawal in those studies in which such outcomes are reported. Further, larger scale randomized trials are required in all nonrenal organ transplants to fully ascertain the risks and benefits of steroid avoidance with more modern immunosuppressive regimens.

Authorship

SRK: devised the study and was involved in the search process, quality assessment, data extraction, meta-analysis and manuscript preparation. PJM: involved in the quality assessment, data extraction and manuscript preparation.

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