Corticosteroid Use and Growth After Pediatric Solid Organ Transplantation: A Systematic Review and Meta-Analysis

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Background. A number of corticosteroid minimization and avoidance protocols for post-solid organ transplant have been developed. The study objective was to examine the effect of corticosteroid withdrawal/avoidance on growth and safety parameters in pediatric solid organ transplant recipients. **Methods.** A systematic review using Medline and Embase was performed. All randomized controlled trials (RCT) and observational studies comparing corticosteroid withdrawal/avoidance to controls receiving corticosteroids in pediatric transplant recipients which reported growth as change in height or final height were included. Two reviewers independently abstracted study data and assessed quality. **Results.** The search yielded 930 records, 14 separate studies involving 1146 patients. Renal RCTs ($n = 5$) showed that corticosteroid withdrawal/avoidance was associated with a significant increase in growth (mean difference in height standard deviation score [SDS], 0.18; 95% confidence interval [95% CI], 0.07-0.29; $P = 0.001$) compared with those remaining on steroids. In liver RCTs ($n = 2$), mean difference in height SDS was -0.20 (95% CI, -1.08 to 0.68 ; $P = 0.66$). Results for renal observational studies ($n = 5$) was 0.34 (95% CI, 0.03 - 0.65 ; $P = 0.03$). The most pronounced effect was seen in prepubertal children with SDS of 0.28 (95% CI, 0.14 - 0.41 ; $P < 0.0001$). In pubertal participants this was not observed (SDS, 0.06 ; 95% CI, -0.04 to 0.15 ; $P = 0.24$). Corticosteroid withdrawal/avoidance was not associated with acute rejection (odds ratio [OR], 0.87 ; $P = 0.63$), graft failure (OR, 0.45 ; $P = 0.08$), or death (OR, 0.34 ; $P = 0.16$) in renal trials. **Conclusions.** Corticosteroid withdrawal/avoidance in pediatric renal transplantation is associated with a significant improvement in height. Prepubertal patients appeared to have the greatest benefit. Importantly, the improvement in growth was not accompanied by increased rejection or worsening patient/allograft survival in the short term.

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Solid organ transplantation is the only therapy for children with end-stage organ failure. As immunosuppressive therapies have evolved, patient and transplant allograft survival have also improved substantially in the pediatric population.^{1,2} However, much of the evidence and guidelines for posttransplant care stems from adult studies which are not always appropriate for the pediatric population as children often have very different needs and comorbidities compared with adults.^{3,4} For example, the goal of optimizing growth posttransplant is unique to young children and may represent an often overlooked patient-centered outcome. Children with end-stage renal disease who have moderate to severe growth failure have an increased risk of morbidity and mortality⁵ as well as reduced self-esteem.⁶

Multiple factors affect recovery of growth after transplantation including the type of solid organ transplanted and age.⁷ Kidney recipients between 1 and 6 years and liver transplant recipients less than 2 experience significant catch-up growth compared with other ages.^{8,9} Transplant function is important especially in renal transplantation with those displaying reduced function and those requiring a new organ having reduced growth velocity after transplantation. Height deficit at the time of transplantation also impacts potential growth recovery⁷ and pubertal status, with prepubertal children having greater gains in height.¹⁰ Lastly, but perhaps most importantly because it is modifiable is the use

of corticosteroids. Corticosteroids form the backbone of most immunosuppressive regimens however they have many potential adverse effects.¹¹ Children receiving excess glucocorticoids often have a reduced growth rate which appears to be mediated by suppression of growth hormone as well as a direct effect on the growth plate.¹² Corticosteroid withdrawal and complete avoidance have been used posttransplantation in an effort to reduce potential steroid toxicity. The effect of these alternative regimens on growth posttransplantation has not been determined.

The objective of this systematic review was to identify and analyze the data on corticosteroid withdrawal and avoidance after pediatric solid organ transplantation specifically focusing on the outcome of growth. Secondary objectives were the safety of corticosteroid withdrawal/avoidance by examining the outcomes of acute rejection, graft function, graft and patient survival. We hypothesized that corticosteroid withdrawal/avoidance would be associated with greater growth without compromising graft function or survival compared with those who remain on steroid therapy.

METHODS

Search Strategy

We conducted systematic electronic searches using Ovid Medline (1946 to 2014 May 6) and Embase (1947 to 2014 May 6). Bibliographies from recent reviews and published studies were searched as well as abstracts from scientific meetings. There was no restriction based on language.

Study Selection

An initial screen of identified titles and abstracts was performed by 1 investigator (A.T.) with clearly irrelevant records removed at this stage. A second screen to identify potentially relevant studies was independently performed by 2 reviewers (A.M. and A.T.). If no abstract was available, the full text was obtained. Full-text versions of potentially eligible studies were obtained and independently screened by 2 reviewers (N.F. and A.T.) to determine their eligibility based on the selection criteria. Any disagreements during the screening process were resolved through discussion among the authors in accordance with the selection criteria. We included studies that met the following criteria: (1) randomized controlled trial (RCT), prospective nonrandomized interventional study, prospective or retrospective cohort or case control study involving solid organ transplant recipients; (2) participants were all 21 years or younger or study included adults but presented pediatric and adult data separately; (3) compared early (within 7 days posttransplant), intermediate (7 days to 1 year), or late (after 1 year post transplant) steroid withdrawal or complete steroid avoidance as defined by Grenda et al,¹³ to participants who were still on steroids (either daily or alternate day); (4) the study reported growth as either change in height (using a standard deviation score or absolute change) or final study height in both groups.

We excluded (1) any study that used historical controls because the immunosuppressive medications may be significantly different between periods, (2) cross-sectional studies and any other study that lacked a control arm, (3) animal studies, (4) abstracts without a full-text publication, and (5) studies before the year 1990 due to changes in immunosuppressive protocols.

Data Abstraction

Data were abstracted independently by 2 investigators (A.T. and N.F.) using a standardized data abstraction form. Any disagreement was resolved by a third investigator (G.K.). Our primary outcome was growth as assessed by either change in height standard deviation score (SDS) or change in cm/inches also known as growth velocity if height SDS was not provided. Height SDS can be used to compare a child's height to a normal population standard typical for age, race, and sex. In children with chronic diseases, a negative height SDS can measure how much a child deviates from the average population. If the change was not calculated or provided, then final height reported (SDS) was used and compared between corticosteroid withdrawal/avoidance and the control group. Secondary outcomes included acute rejection, transplant failure, and death. For renal transplant recipients, estimated glomerular filtration rate (eGFR) or creatinine clearance was abstracted. We also collected information on the following characteristics: primary author, publication year, country, solid organ type, and language. For data related to the study participants, we abstracted: age, sex, race, pubertal status, bone age, deceased versus living organ, history of dialysis, baseline body mass index and whether or not participants received growth hormone therapy. Immunosuppressive medications used during the induction and maintenance phases were abstracted. When data was only available in figures, the GNU image manipulation program (GIMP 2.8; <http://www.gimp.org/>) was used to extract data. If individual studies had more than 1 published report we extracted all relevant data and combined it as 1 study but referenced all published reports.

Risk of Bias Assessment

Study quality was independently assessed by 2 reviewers (A.T. and N.F.). Randomized controlled trials were assessed using the Cochrane Collaboration Risk of Bias assessment tool¹⁴ which evaluates randomization, allocation concealment, blinding, and follow-up. The overall assessment was based on what was determined from the individual section. If 1 or more of the domains was rated as high risk of bias, the study was classified as being at high risk of bias. If all domains were classified as low risk, then the trial was considered low risk and if there was a mix of unclear and low risk it was classified as unclear. Observational studies were assessed using the Ottawa Newcastle scale¹⁵ which assesses selection, comparability and outcome of a study and uses a star point system. The maximum number of stars that can be assigned is 9. We categorized the studies based on the following cutoffs which have been previously used in a meta-analysis by Wallis et al¹⁶; more than 7 low risk of bias, scores of 5 to 7 indicated moderate risk of bias, and scores less than 5 indicated high risk of bias.

Statistical Analysis

Data were analyzed using Review Manager, version 5.2 (RevMan; The Cochrane Collaboration, Oxford, UK). Continuous data were expressed as mean difference with 95% confidence intervals (95% CIs) and dichotomous data were presented as an odds ratio with 95% CIs. For RCTs, mean differences were pooled using a random effects model.¹⁷ Heterogeneity was evaluated using the I^2 index.¹⁸ Sensitivity analyses were performed to identify sources of heterogeneity

based on the following subgroups (if data was available): organ type (eg, kidney transplant, liver transplant), prepubertal participants, late corticosteroid withdrawal separate from early withdrawal/avoidance, length of follow up, pubertal status, and methodological quality (low risk vs high risk of bias). Analyses for each organ type were kept separate. This study was conducted and prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (www.prisma-statement.org). In the case where SEM was provided, we calculated the SD based on the following equation: $SD = SE * \sqrt{N}$. For most of the observational studies, the baseline and final height were provided however not the mean change. The mean change was therefore obtained by subtracting the final mean height SDS from the baseline. The SD of the change was obtained for each group by calculating a correlation coefficient as per the Cochrane handbook (<http://handbook.cochrane.org>).

RESULTS

Literature Search

The initial search identified 930 unique records (Figure 1) and 48 citations were initially eligible for full-text review. Upon review of the full publications, 33 were excluded. Thus, 15 full-text publications reporting on 14 separate studies (n = 1146 pediatric patients) met eligibility and were included.

Description of Included Studies

There were 7 RCTs (n = 635 patients) and 7 observational studies (n = 511 patients) included in the review. Five studies originated from the United States, 5 from Europe, 3 from

South America, and 1 from both the US and Mexico. Twelve studies assessed growth in kidney transplant recipients and 2 in liver transplantation patients. There were no studies assessing growth in heart, lung, pancreas, or small bowel transplant recipients. All reports included pediatric patients only with the exception of a liver trial that was primarily adult based but included a subset of children (n = 33).¹⁹ Growth was evaluated as the primary outcome for 5 RCTs and as a secondary outcome in 1 study. Three studies excluded patients receiving growth hormone, whereas the rest of the studies made no mention of growth hormone. The timing of follow up growth assessment ranged from 6 months posttransplant to 5 years (Table 1).

Risk of Bias Assessment

All RCTs had some degree of bias (Table 2) mainly due to a lack of blinding of participants and personnel (n = 4 trials), unclear blinding of the outcome assessment (n = 5 trials) or selective outcome reporting (n = 4 trials). Because all trials were classified overall as high risk of bias, sensitivity analyses could not be performed. All observational studies had bias, most of which was moderate. This was mainly in the comparability of the 2 groups. The baseline height was not always comparable between the groups, and the studies did not always adjust for these differences. In some studies, the steroid protocol was chosen by the physician, likely introducing selection bias (Table 3).

Growth in Corticosteroid Withdrawal/Avoidance Trials

When we compared growth among the 5 renal RCTs, the mean difference was 0.18 (95% CI, 0.07-0.29; $P = 0.001$; $I^2 = 37\%$, $\chi^2 = 6.35$, $P = 0.1$). When we compared growth

FIGURE 1. Flow diagram demonstrating electronic search results.

TABLE 1.
Characteristics of included studies

Study	Organ	Sample size		Mean age (SD), y		Steroid intervention CW/A group	Other immunosuppression		Baseline height (SDs)		Adjustment	Follow-up, mo
		CW/A	CS	CW/A	CS		Steroid dose in controls		CW/A	CS		
Meriq et al ²⁰ 2013	Kidney	14	16	6 (3.3)	6.4 (3.9)	Early	Both groups: BS, Tac, MMF on days 0-2 2 mg/kg per day MP, days 3-4; 2 mg/kg per day of prednisone, days 5-30 1.5 mg/kg per day. At 1 mo, 1.0 mg/kg per day, then, 0.25 for a month, then 0.12		-2.5 (3.5) ^a	-2.0 (4.2) ^a	Mixed linear model treatment group, pubertal status and baseline height	12
Sarwal et al ²¹ 2012	Kidney	60	70	11.8 (5.4)	11.9 (6.1)	Avoidance	Both groups: DC, Tac, MMF prednisone 10 mg/kg perioperative then 2 mg/kg per day if <40 kg or 1.5 mg/kg per day if >40. taper at 1, 2, 4, 6, 12, 16 wk by doses 0.5, 0.4, 0.3, 0.2, 0.15, and 0.1 mg/kg per day. 0.1 was achieved by 6 mo at latest		-1.2 (1.4)	-1.3 (1.3)	Mixed model of repeated measures. Does not specify if adjusted	36
Benfield et al ²² 2010	Kidney	73	59	11.4 (4.9)	11.9 (5.7)	Intermediate	Both groups: BS, SRL, CsA MP 10 mg/kg perioperative and postoperative day 1. Prednisone on day 2 at 2 mg/kg per day, tapered to 0.15 mg/kg per day by day 74. Maintained at that dose		-1.4 (2.3)	-1.6 (2.1)	Analysis of covariance adjusting for baseline	36
Grenda et al ²³ 2010	Kidney	98	98	10.8 (4.2)	11.3 (4.1)	Early	CW/A: DC, Tac, MMF CS: Tac, MMF Steroids: bolus of CS 300-600 mg/m ² IV on day 0. Then, 60 mg/m ² on day 1, 40 mg/m ² on days 2-7 then reduced in decrements of 10 mg/m ² per week to get to <10 mg/m ² on days 43-183		NR	NR	Analysis of covariance adjusting for baseline height, treatment group and pubertal status	6
Hocker et al ^{24,25} 2009/2010	Kidney	23	19	9.8 (1)	11.0 (0.9)	Late	Both groups: CsA, MMF, prednisone 5 mg/m ² per day		-1.3 (1.3)	-1.2 (1.2)	Does not specify	12
Spada et al ²⁶ 2006	Liver	36	36	2.9 (1.5-4.3)	2.8 (1.5-4.2)	Avoidance	CW/A: BS, Tac CS: Tac IV MP 2 mg/kg per day on days 1-6 then oral prednisolone on day 7 at 1 mg/kg per day (max dose of 40/day) tapered to achieve steroid free at 3-6 mo		-2.3 (2.1)	-2.6 (2.0)	Does not specify	12
McDiarmid et al ¹⁹ 1995	Liver	13	20	7.8 (4.1)	5.9 (3.7)	Late	Both groups: CsA or AZA IV MP 10 mg/kg per day if <20 postoperative day 1, tapered to 0.3 mg/d PO of prednisone by day 6. Tapered between months 3 to 6 such that by 1 y they are on 0.15 to 0.2 mg/kg		-1.4 (0.81)	-2.3 (1.0)	Not adjusted	12

Continued next page

TABLE 1. (Continued)

Study	Organ	Sample size		Mean age (SD), y		Steroid intervention CW/A group	Other immunosuppression		Baseline height (SDs)		Adjustment	Follow-up, mo
		CW/A	CS	CW/A	CS		Steroid dose in controls	CW/A	CS			
Observational Delucchi et al ²⁷ Prospective 2011	Kidney	55	41	8 (4.0)	8.6 (4.4)	Early	Both groups: BS, Tac, MMF on days 0-2; 2 mg/kg per day of MP, days 3-4; 2 mg/kg per day of prednisone, days 5-30 1.5 mg/kg per day at 1 month 1.0 mg/kg per day, then 0.25 for a month, then 0.12 mg/kg per day CW/A: DC, Tac, MMF CS: CsA, MMF steroids; MP 4 mg/kg per day for 3 d postoperative MP tapered down from 0.5 mg/kg per day to 0.2 mg/kg per day by postoperative month 4. Then maintained at 0.2 mg/kg per day		-2.4 (1.2)	-2.4 (1.3)	Mixed linear model adjusted for baseline height, pubertal status and treatment	60
		9	8	9.0 (0.13)	8.4 (0.8)	Late			-2.2 (1.6)	-2.7 (0.9)	Time and chronological age	32
Ferraris et al ²⁸ Retrospective 2010	Kidney	129	57	11 (6.7)	12.5 (6.1)	Complete avoidance	Both groups: DC, Tac, MMF, prednisone 10 mg/kg perioperative then 2 mg/kg per day if <40 kg or 1.5 mg/kg per day if >40. Taper at 1, 2, 4, 6, 12, and 16 wk to doses of 0.5, 0.4, 0.3, 0.2, 0.15, and 0.1 mg/kg per day.		-1.2 (1.5)	-1.1 (1.5)	Does not specify	60
		21	39	14 (3)	14 (3)	Early			-0.9 (1.6)	-1.9 (1.6) ^b	Does not specify	24
Chavers et al ³⁰ Prospective 2009	Kidney	19	30	12.9 (5.0)	12.4 (5.1)	Avoidance	Both groups: DC, Tac, MMF CS: ATG, CsA, Azathioprine was started at 2 mg/kg per day orally, then tapered to 0.45 mg/kg per day at 1 mo posttransplant, and then to 0.25-0.3 mg/kg per day at 1 yr Both groups: DC, Tac, MMF Corticosteroid 10 mg/kg intraoperative then 3 mo post-wean to 0.1 and then 1 mg/kg per day. Final dose, 0.5 mg/kg per day.		-0.9 (1.1)	-1.6 (1.1)	Does not appear to be adjusted	12
		20	20	10.1 (4.9)	10.2 (4.5)	Late			-1.6 (1.3)	-1.3 (1.3)	Does not specify	46
Bhakta et al ³¹ Retrospective 2008	Kidney	52	11	NR	NR	Intermediate	Both groups: Tac, MMF intraoperative IV MP 14-25 mg/kg bolus then postoperative prednisone tapered from 3-10 mg/kg per day down to 0 at 4-6 or 6-12 mo. Does not specify what does controls are maintained on.		NR	NR	Does not appear to be adjusted	12
		52	11	NR	NR	Intermediate			NR	NR	Does not appear to be adjusted	12

^a Prepubertal only.
^b Significant difference.
Early, withdrawal within 7 days; intermediate, withdrawal >7 days and <1 year; late, withdrawal >1 year; avoidance, no steroids given.
CW/A, corticosteroid withdrawal/avoidance; CS, corticosteroid; BS, basiliximab; DC, dactizimab; Tac, tacrolimus; MMF, mycophenolate mofetil; Aza, azathioprine; CsA, cyclosporine; ATG, antithymocyte globulin; SRL, sirolimus; MP, methylprednisone, NR, not reported; PO, oral; IV, intravenous.

TABLE 2.**Risk of bias and methodological quality assessment of included RCTs**

Abstract	Sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants Personnel (Performance Bias)	Blinding of assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective outcome reporting (Reporting bias)	Overall risk
Merick et al ²⁰	Low	Low	High	Unclear	Low	Low	High
Sarwal et al ²¹	Low	Unclear	High	Unclear	Low	High	High
Benfield et al ²²	Low	Low	Low	Unclear	Unclear	High	High
Grenda et al ²³	Low	Low	High	Unclear	Low	Low	High
Hocker et al ^{24,25}	Low	Low	High	Unclear	Low	Low	High
Spada et al ²⁶	Unclear	Unclear	Unclear	Unclear	Low	High	High
McDiarmid et al ¹⁹	Low	Unclear	Unclear	Unclear	High	High	High

Rating was based on the Cochrane risk of bias tool.¹⁴

Low risk of bias implies potential bias is unlikely to alter the study results.

Unclear risk of bias raises some doubt regarding the results.

High risk of bias greatly weakens the validity of the results.

among the 2 liver trials, the mean difference was -0.20 (95% CI, -1.08 to 0.68 ; $P = 0.66$; $I^2 = 76\%$; $\chi^2 = 4.12$, $P = 0.04$; Figure 2). When analyzed by corticosteroid regimen, renal RCTs using an early withdrawal/avoidance strategy^{20,21,23} ($n = 3$) had a pooled mean difference in height SDS of 0.16 (95% CI, -0.04 to 0.36 ; $P = 0.13$; $I^2 = 50\%$; $\chi^2 = 4.03$; $P = 0.13$) compared with those remaining on steroids and among the renal studies with intermediate/late protocols^{22,24} ($n = 2$), the mean difference in height SDS was 0.22 (95% CI, 0.09 - 0.36 ; $P = 0.0008$; $I^2 = 0$; $\chi^2 = 0.40$; $P = 0.52$). Test for subgroup difference was not significant ($\chi^2 = 0.15$; $P = 0.70$; $I^2 = 0\%$). Length of follow-up differed among the 5 renal trials; 2 renal trials had follow up for 12 months and had a pooled mean difference in height SDS of 0.37 (95% CI, 0.12 - 0.63 ; $P = 0.004$; $I^2 = 7\%$; $\chi^2 = 1.07$; $P = 0.3$). Two renal trials had 36 months of follow-up with a pooled mean difference in height SDS of 0.15 (95% CI, -0.01 to 0.31 ; $P = 0.07$; $I^2 = 22\%$; $\chi^2 = 1.29$; $P = 0.26$). Test for subgroup difference was not significant ($\chi^2 = 2.31$; $P = 0.13$; $I^2 = 56.8\%$).

In 1 observational study Li et al,²⁹ the growth data were presented by age categories without group sample sizes and thus the data could not be pooled. Elli³² provided the mean change in height SDS without a measure of variance which precluded pooling. When the 5 remaining observational studies were pooled ($n = 262$ patients), corticosteroid withdrawal/avoidance was associated with a significant improvement in the end of study height SDS at 1 year 0.72 (95% CI, 0.37 - 1.07 ; $P < 0.0001$; $I^2 = 16\%$; $\chi^2 = 4.73$; $P = 0.32$;

Figure 3A). Similarly, when change in height SDS was analyzed, corticosteroid withdrawal/avoidance was associated with a significant improvement 0.34 (95% CI, 0.03 - 0.65 ; $P = 0.03$; $I^2 = 75\%$; $\chi^2 = 16.15$; $P = 0.003$; Figure 3B).

Growth During Puberty

Eight studies ($n = 5$ RCTs^{20,21,23,24,26}; $n = 3$ observational^{25,27,28}); $n = 339$ patients) reported growth data in prepubertal children, defined either by Tanner stage or aged younger than 5 years. Five studies reported change in height SDS over 12 months ($n = 4$) or 6 months ($n = 1$), whereas 3 studies reported the 12-month final height SDS. Pooled data for the 4 renal RCTs demonstrated a mean difference in the change in height (SDS, 0.33 ; 95% CI, 0.13 - 0.53 ; $P = 0.001$; $I^2 = 21\%$; $\chi^2 = 3.81$; $P = 0.28$) for prepubertal patients in the corticosteroid withdrawal/avoidance group. Only 2 of these RCTs^{21,22} provided data for pubertal participants. Pooled data from these studies demonstrated that the change in height SDS was not significantly different between corticosteroid withdrawal/avoidance compared with controls (SDS, 0.05 ; 95% CI, -0.04 to 0.15 ; $P = 0.24$; $I^2 = 0$; $\chi^2 = 0.17$; $P = 0.68$). Test for subgroup difference demonstrated was significantly different ($\chi^2 = 5.94$; $P = 0.01$; $I^2 = 83.2\%$). Pooled data for the 2 observational studies^{25,28} that provided 12-month final height showed that corticosteroid withdrawal/avoidance was associated with a significant improvement in height (SDS, 1.07 ; 95% CI, 0.11 - 2.04 ; $P = 0.03$; $I^2 = 0$; $\chi^2 = 0.01$; $P = 0.92$). Final height for pubertal patients was only provided in the study by Hocker et al precluding any meta-analysis.

TABLE 3.**Risk of bias in observational studies**

	Selection (4 items)	Comparability (1 item)	Outcome (3 items)	Total	Classification
Delucchi et al ²⁷	3 ***	1 *	1*	5****	Moderate
Ferraris et al ²⁸	4****	0	2**	6*****	Moderate
Chavers et al ³⁰	3***	0	2**	5*****	Moderate
Bhakta et al ³¹	2**	0	3***	5*****	Moderate
Hocker et al ²⁵	1*	1*	1*	3***	High
Li et al ²⁹	4****	1*	2**	7*****	Moderate
Ellis ³²	3***	0	0	3***	High

Each domain has a series of numbered items within which a study can be awarded a maximum of 1 star.

For example, the domain "selection" includes four different items such as "representativeness of cohort," whereas comparability includes only 1 item.

The following cutoffs were used to assess categorize bias: >7 low risk of bias, 5 - 7 moderate risk of bias, <5 high risk of bias.

FIGURE 2. Standardized height results for pooled renal and liver randomized controlled trials.

Li et al²⁹ demonstrated that for both younger age categories (<6 years, 6 to 12 years) the growth velocity was significantly better in the steroid free groups. This finding was not consistent in those >12 years. Hocker et al²⁷ reported height velocity in prepubertal patients was 9.1 ± 0.9 versus 5.7 ± 0.8 cm/year, respectively, in those who had stopped taking steroids compared with controls, whereas the height velocity in pubertal patients was 4.4 ± 0.9 versus 3.7 ± 0.9 cm/year

for those who remained on steroids. In the observational study by Ferraris et al,²⁸ height velocity in prepubertal children over 12 months after late steroid withdrawal was 5.85 (±3.06) cm compared with 3.23 (±1.17) cm in the cortico-steroid maintenance group but the significance between groups was not reported. The study included only prepubertal patients and thus growth in pubertal patients was not evaluated.

FIGURE 3. Standardized height results for pooled renal observational studies.

Acute Rejection

All reported episodes of acute rejection were confirmed by biopsy with the exception of 1 episode in the RCT by Hocker et al in the steroid withdrawal group. Five renal RCTs reported acute rejection and 1 liver RCT.^{20–24,26} There were 30 independent episodes of acute rejection out of 305 participants in the corticosteroid withdrawal/avoidance group compared to 41 of 301 (1 patient had 2 rejection episodes) in the control group. Pooling of the renal data showed no significant effect of corticosteroid regimen on rejection (odds ratio [OR], 0.87; 95% CI, 0.50–1.52; $P = 0.63$; $I^2 = 0\%$; $\chi^2 = 3.97$; $P = 0.41$). When we repeated the analyses excluding the study by Hocker et al, the results remained unchanged (OR, 0.87; 95% CI, 0.5–1.54). In the 3 observational studies that adequately reported acute rejection,^{25,28,31} pooling of the data showed no significant effect of corticosteroid regimen on rejection (OR, 0.91; 95% CI, 0.27–3.07; $P = 0.88$; $I^2 = 57\%$; $\chi^2 = 4.66$; $P = 0.1$).

Renal Function

Four renal RCTs provided eGFR using Schwartz formula.^{21–24} There was no significant difference between the corticosteroid withdrawal/avoidance group and the control group (mean difference, -0.16 mL/min per 1.73 m²; 95% CI, -6.09 to 5.77 ; $P = 0.96$; $I^2 = 85\%$; $\chi^2 = 20.49$; $P = 0.0001$). Five observational studies reported an eGFR using Schwartz formula at the final visit or after 12 months of follow-up.^{25,27,28,30,31} There was no significant difference between the corticosteroid withdrawal/avoidance group and the control group (mean difference, -0.43 mL/min per 1.73 m²; 95% CI, -12.52 to 11.66 ; $P = 0.94$; $I^2 = 72\%$; $\chi^2 = 14.29$; $P = 0.006$).

Patient and Allograft Survival

Six RCTs reported allograft survival.^{20–24,26} Thirteen transplants failed of 304 participants in the corticosteroid withdrawal/avoidance group compared with 19 of 298 in the control group. This difference was not statistically significant among the 5 renal RCTs (OR, 0.45; 95% CI, 0.18–1.10; $P = 0.08$; $I^2 = 36\%$; $\chi^2 = 3.10$; $P = 0.21$). Four observational studies reported allograft failure.^{28,30–32} There were 5 of 117 allograft failures in the corticosteroid withdrawal/avoidance group and 13 of 85 in the control arm. The difference was significant with the corticosteroid withdrawal/avoidance group associated with less graft loss (OR, 0.29; 95% CI, 0.09–0.94; $P = 0.04$; $I^2 = 76\%$; $\chi^2 = 4.09$; $P = 0.04$). Six RCTs reported patient survival.^{20–24,26} Overall, there were 6 deaths among 304 participants in the corticosteroid withdrawal/avoidance group and 8 among 298 in the control group. The difference was not statistically significant among the 5 renal RCTs (OR, 0.34; 95% CI, 0.07–1.54; $P = 0.16$; $I^2 = 64\%$; $\chi^2 = 2.80$; $P = 0.09$). Six observational studies reported patient survival.^{27–32} There were 6 deaths among 285 corticosteroid withdrawal/avoidance participants and 5 of 186 among the control arm. The difference was not statistically significant (OR, 0.81; 95% CI, 0.22–2.93; $P = 0.75$; $I^2 = 39\%$; $\chi^2 = 4.94$; $P = 0.18$).

DISCUSSION

This systematic review and meta-analysis included data from 7 randomized trials and 7 observational studies involving 1146 pediatric transplant recipients. We observed

a significant improvement in growth posttransplant when corticosteroid withdrawal or avoidance protocols were used among renal studies. This finding was consistent in both the renal randomized and observational studies. The improvement in growth was most pronounced in the studies whose participants were younger. Importantly, this improvement in growth did not occur at the expense of more rejection, allograft loss, or patient death.

In addition to being statistically significant, the findings from our analysis are clinically important to both patients and clinicians. Overall, we found a mean change in height (SDS, 0.18; 95% CI, 0.07–0.29) for those renal transplant recipients on a corticosteroid withdrawal/avoidance regimen. For an average female renal pediatric transplant recipient with a height SDS of -1.5 , receiving a transplant with a corticosteroid withdrawal/avoidance protocol, this would result in a gain in height that was 1.0 cm more over a year than the gain in height if they were on a steroid-containing regimen. This gain in height could be as low as 0.3 cm but as high as 2.0 cm. Similarly, for an average male renal pediatric transplant recipient with a height SDS of -1.5 , receiving a transplant with a corticosteroid withdrawal/avoidance protocol would result in a gain in height that was 1.3 cm more over a year than the gain in height if they were on a steroid-containing regimen. This gain in height could be as low as 0.2 cm but as high as 2.5 cm. Gains in height such as these are slightly lower compared to values obtained in growth hormone trials for short stature³³; however, the baseline height of those receiving growth hormone therapy was much lower than in the steroid withdrawal trials. The lack of a growth benefit with steroid withdrawal/avoidance from the 2 pooled liver trials may be explained by the small sample size included as well as the shorter follow-up time. The study by McDiarmid et al¹⁹ also noted that the control sample was maintained on a very low of prednisone and thus may be similar to the withdrawal group.

With respect to safety, there was no difference in eGFR, acute rejection, graft or patient survival between the corticosteroid withdrawal/avoidance group and the control arm. Most RCTs required that a biopsy be performed if rejection was suspected, whereas others also mandated routine protocol biopsies. Only 1 study labeled a rejection episode without biopsy evidence.²⁴ It is important to note that selection criteria varied among the trials we evaluated with 2 studies^{23,24} including higher risk patients, whereas 1 study²¹ excluded those with PRA levels less than 20%. This may explain the nonsignificant difference in acute rejection rates.

To date, no systematic review has pooled data on growth measurements in pediatric transplant recipients using corticosteroid withdrawal/avoidance immunosuppression. The Cochrane group³⁴ conducted a systematic review on corticosteroid withdrawal/avoidance in adult and pediatric kidney transplant recipients. The review included only 1 pediatric RCT published as an abstract in 2005³⁵ and the remaining studies included were observational. The primary focus of the Cochrane review was safety including rates of acute rejection and graft failure. The growth parameters were only reported in a descriptive fashion. As there was only 1 pediatric RCT, there was no pooling of data. A meta-analysis published by Wu et al³³ in 2013, assessed the efficiency and safety of growth hormone therapy post-renal transplant. It included 5 pediatric RCTs and found that those receiving

growth hormone therapy demonstrated significantly higher growth velocity rates than those not receiving growth hormone (mean difference SDS, 0.52; 95% CI, 0.37–0.68). They did not assess whether pubertal status impacted potential growth and none of the RCTs included used corticosteroid withdrawal/avoidance protocols posttransplant.

Recently, Franke et al.³⁶ published the results of a large prospective study which followed growth (median follow up of 3.4 years) among 389 pediatric renal transplant recipients. Mean height during the observation period was -1.74 SDS and was significantly lower compared with healthy children ($P < 0.001$). The authors found that prolonged steroid exposure significantly impaired catch-up growth, that is, mean annual steroid dosage (in mg/kg) was negatively associated with linear growth (β , -1.89 ; 95% CI, -2.68 to -1.10 ; $P < 0.01$). A recent retrospective single center study by Klare et al.,¹⁰ followed up 74 kidney transplant patients (there was no comparison group) who had been weaned off steroids within 6 months after transplant. Mean follow-up was 8.5 years. They found complete catch up growth occurred in all prepubertal patients (standardized height velocity was 2.9 SDS for the first year compared with healthy children) but was incomplete in 20% of those who were pubertal. Significant predictors of catch up growth in this study were age and height deficit at time of transplant. The study was able to conclude that prepubertal patients weaned off steroids were able to have sustained catch-up growth and reached adult height that was within normal limits. Similarly, in our meta-analysis, the studies which assessed growth separately by pubertal status demonstrated a greater growth benefit from steroid withdrawal in the prepubertal patients.

There have been other observational studies that have assessed long-term growth after steroid withdrawal. Many of these studies were retrospective in nature and lacked a comparator group and were therefore not included in this systematic review. Most of the studies included in our meta-analysis reported a negative baseline height SDS suggesting a growth restricted state; however, most were greater than -2.0 suggesting the baseline height was not below the 2nd percentile. This is in keeping with recent data from the North American Pediatric Renal Transplant Cooperative Study that have shown the height SDS at time of transplant have improved from -2.5 in 1987 to between -1 and -1.5 in 2009.³⁷

The main strength of our review was our ability to meta-analyze data and make conclusions with regard to an important clinical question. The main limitation of our study was the moderate heterogeneity found with respect to the growth data. This is likely related to the variability in the population studied, interventions used, outcomes assessed as well as the methodological quality of the included studies. For example, most of the studies included in our review made no mention of whether participants received growth hormone therapy. The length of follow-up was variable with 1 study reporting height at 6 months postwithdrawal and another reporting it at 3 years. However, almost all studies reported the change after 1 year of intervention, and these data were consistent and included. As with all systematic reviews, we were limited by the quality of the individual studies. In this particular review, most of the studies were not blinded. At the participant level, this could have led to differential adherence given the known side effects of corticosteroids. This, however, would have biased our findings toward the null. Finally,

follow-up of individual RCTs was relatively short, and none provided achieved adult height, which is the most clinically relevant outcome.⁷

In conclusion, corticosteroid withdrawal or avoidance in pediatric renal transplantation is associated with a clinically significant improvement in height. The findings were consistent across renal study designs. As with other studies examining pediatric growth, prepubertal patients had the greatest benefit from corticosteroid withdrawal/avoidance, whereas pubertal patients do not appear to have the same benefit. Importantly, the improvement in growth was not accompanied by increased rejection or worsening patient/allograft survival in the short term. Although these findings are currently relevant to patients and clinicians, future studies need to focus on longer-term outcomes, such as achieved adult height and late-onset acute rejection.

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