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15. Gonwa T, Mendez R, Yang HC *et al.* Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. *Transplantation* 2003; 75: 1213–1220
16. Meier-Kriesche HU, Schold JD, Srinivas TR *et al.* Sirolimus in combination with tacrolimus is associated with worse renal allograft survival compared to mycophenolate mofetil combined with tacrolimus. *Am J Transplant* 2005; 5: 2273–2280
17. Gralla J, Wiseman AC. Tacrolimus/sirolimus versus tacrolimus/mycophenolate in kidney transplantation: improved 3-year graft and patient survival in recent era. *Transplantation* 2009; 87: 1712–1719
18. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247–254
19. Racusen LC, Solez K, Colvin RB *et al.* The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999; 55: 713–723
20. Vitko S, Wlodarczyk Z, Kyllonen L *et al.* Tacrolimus combined with two different dosages of sirolimus in kidney transplantation: results of a multicenter study. *Am J Transplant* 2006; 6: 531–538
21. Sampaio EL, Pinheiro-Machado PG, Garcia R *et al.* Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen. *Clin Transplant* 2008; 22: 141–149
22. Anil Kumar MS, Irfan Saeed M, Ranganna K *et al.* Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. *Transpl Immunol* 2008; 20: 32–42
23. Lee SH, Kim CD, Huh KH *et al.* Low-dose mycophenolate mofetil in tablet form or capsule form combined with tacrolimus in the early period after kidney transplantation: a prospective randomized trial. *Clin Nephrol* 2016; 86: 319–327
24. Nashan B, Citterio F. Wound healing complications and the use of mammalian target of rapamycin inhibitors in kidney transplantation: a critical review of the literature. *Transplantation* 2012; 94: 547–561
25. Weiner SM, Sellin L, Vonend O *et al.* Pneumonitis associated with sirolimus: clinical characteristics, risk factors and outcome–a single-centre experience and review of the literature. *Nephrol Dial Transplant* 2007; 22: 3631–3637
26. Stallone G, Infante B, Pontrelli P *et al.* Sirolimus and proteinuria in renal transplant patients: evidence for a dose-dependent effect on slit diaphragm-associated proteins. *Transplantation* 2011; 91: 997–1004
27. Webster AC, Lee VW, Chapman JR *et al.* Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. *Transplantation* 2006; 81: 1234–1248
28. Opelz G, Unterrainer C, Susal C *et al.* Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients. *Nephrol Dial Transplant* 2016; 31: 1360–1367
29. Nashan B, Gaston R, Emery V *et al.* Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. *Transplantation* 2012; 93: 1075–1085
30. Jouve T, Rostaing L, Malvezzi P. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. *J Nephropathol* 2016; 5: 1–7
31. Euvrard S, Morelon E, Rostaing L *et al.* Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med* 2012; 367: 329–339

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Graft survival of pediatric kidney transplant recipients selected for *de novo* steroid avoidance—a propensity score-matched study

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ABSTRACT

Background. Steroid-avoidance protocols have gained popularity in pediatric kidney transplant recipients at low immunologic risk. The long-term safety of steroid avoidance in children with immunologic risk factors remains unknown.

Methods. Pediatric kidney transplant recipients from 2004 to 2014 in the Organ Procurement and Transplantation Network database who received tacrolimus and mycophenolate immunosuppression were investigated. Propensity score matching was used to compare graft survival in 1624 children who received steroid avoidance with 1624 children who received steroid-based immunosuppression. The effect of steroid avoidance on

graft failure among immunologic risk strata was estimated using Cox proportional hazards regression in this propensity score-matched cohort.

Results. It was observed that 5-year graft survival was mildly improved in children receiving steroid avoidance (84.8% versus 81.2%, P = 0.03). This improvement in graft survival occurred in the first 2 years following transplant, when the hazard ratio (HR) for allograft failure in children receiving steroid avoidance was 0.62 [95% confidence interval (CI) 0.45–0.86]. In contrast, steroid avoidance was not associated with improved allograft survival during Years 2–10 following transplant (HR = 0.93; 95% CI 0.75–1.15). During this time period, HRs (95% CIs) for allograft failure within immunologic risk strata were not significantly different from the null value of 1: repeat kidney transplants, 1.84 (0.84–4.05); African-Americans, 1.02 (0.67–1.56); sensitized recipients, 1.24 (0.63–2.43); recipients of deceased donor kidneys, 1.02 (0.79–1.32); recipients of completely human leukocyte antigen-mismatched kidneys, 0.80 (0.47–1.37); and recipients with pretransplant glomerular disease, 0.94 (0.71–1.23).

Conclusions. In pediatric kidney transplant recipients receiving tacrolimus- and mycophenolate-based immunosuppression, steroid avoidance can be safely practiced in children with immunologic risk factors.

Keywords: graft survival, kidney transplantation, pediatrics, propensity score analysis, steroid avoidance

INTRODUCTION

Steroid-avoidance protocols have gained popularity in pediatric kidney transplantation and have shown acceptable outcomes compared to steroid-based regimens [1–10]. However, steroids continue to be prescribed for maintenance immunosuppression in about 65% of pediatric kidney transplant recipients, indicating that hesitancy remains regarding more widespread adoption of steroid-avoidance protocols [11]. Important concerns include appropriate identification of low-immunologic-risk patients amenable to steroid avoidance and the choice of induction agent.

We previously characterized the nationwide practice of steroid avoidance in pediatric kidney transplantation. We reported that children receiving steroid avoidance tended to be low-risk patients who received induction with a lymphocyte-depleting agent. The clinical practice of steroid avoidance, moreover, displayed significant variability among transplant centers: 21% of centers never practice steroid avoidance, while 26% used steroid-avoidance protocols in >60% of transplant recipients [11]. These results indicate a lack of consensus in the transplant community regarding the safe practice of steroid avoidance in pediatric kidney transplantation.

We therefore sought to investigate outcomes of steroid-avoidance protocols in pediatric kidney transplant recipients stratified by immunologic risk factors and by induction agent. To accomplish this, we performed a propensity score-matched cohort analysis of pediatric kidney transplant recipients from July 2004 to June 2014 using data from the Organ Procurement and Transplantation Network (OPTN) database. Our aim was to evaluate whether steroid-avoidance protocols adversely influence allograft survival among high-risk pediatric kidney transplant recipients.

MATERIALS AND METHODS

This study was a retrospective analysis of pediatric kidney transplant recipients (<18 years of age) from July 2004 to June 2014 using data from the OPTN database. In total, there were 8001 children who received a kidney transplant during the study period. Because we sought to adjust for both center- and patient-level characteristics, we included only children who received a kidney transplant at centers that averaged at least one transplant per year ($n = 7769$). Exclusion criteria included multi-organ transplant recipients ($n = 155$), children who did not survive beyond discharge ($n = 104$) with a functioning graft or remained in the hospital for >180 days after transplantation ($n = 5$), and children who were not prescribed both mycophenolate and tacrolimus at discharge ($n = 1271$). An additional 407 subjects did not have a complete set of covariates for analysis, leaving a final cohort of 5827 children.

Patients were classified as receiving a steroid-avoidance protocol if they were discharged from the transplant hospitalization without maintenance steroids, as recorded by transplant professionals on transplant registration forms. This registration form defines maintenance immunosuppression as a drug 'given before, during, or after transplant for varying periods of time which may be either long-term or intermediate term with a tapering of the dosage until the drug is either eliminated or replaced by another long-term maintenance drug'. This does not preclude a short course of steroids post-operatively as an induction agent. Using this definition, 2114 children received steroid-avoidance protocols and 4120 children received steroid-based protocols. Baseline characteristics, including demographic information and immunologic risk factors, were compared between the two groups both before and after propensity score matching. Propensity scores or the probabilities of receiving steroid avoidance upon discharge for individual children were estimated using logistic regression. The scores were then used to match children receiving steroid avoidance with children receiving steroid-based immunosuppression in the same transplant year with similar clinical characteristics. This was accomplished with 1:1 matching without replacement via greedy algorithm matching across centers with a caliper of 10% of the standard deviation of the propensity score. The following covariates were included in estimating propensity scores: age, gender, race, pretransplant dialysis, human leukocyte antigen (HLA) mismatch status, panel reactive antibody (PRA) level, donor type, type of insurance (private versus public), previous kidney transplantation, induction agent (lymphocyte depleting agent and interleukin-2 (IL-2) receptor antagonist), delayed graft function (dialysis within 1 week after transplant), cause of renal failure (glomerular versus non-glomerular disease) and treatment for acute rejection prior to discharge. A center-level covariate, per center pediatric transplant volume, was also included. The primary outcome was graft failure, defined as

Table 1. Baseline characteristics of subjects before and after propensity score matching

Variable	Before matching			After matching		
	Steroid-based ($n = 4120$)	Steroid-avoidance ($n = 2114$)	P-value	Steroid-based ($n = 1624$)	Steroid-avoidance ($n = 1624$)	P-value
Age, median (IQR)	13 (7–16)	12 (6–15)	0.002	12 (7–15)	12 (7–15)	0.56
Male gender	59.0%	60.3%	0.32	60.6%	59.8%	0.64
AA race	21.2%	14.6%	<0.001	18.2%	16.7%	0.27
Pretransplant dialysis	76.2%	68.4%	<0.001	72.0%	71.4%	0.73
Complete HLA mismatch	14.1%	13.9%	0.84	14.4%	14.0%	0.76
PRA level			<0.001			0.55
<10%	83.8%	88.5%		86.8%	87.8%	
10–79%	12.7%	10.3%		11.6%	10.9%	
≥80%	3.4%	1.2%		1.7%	1.3%	
Deceased donor type	63.3%	53.5%	<0.001	61.8%	59.0%	0.11
Private insurance	39.8%	46.5%	<0.001	42.7%	44.0%	0.48
Previous transplant	10.0%	4.1%	<0.001	6.2%	5.0%	0.15
Induction with LDA[a]	35.9%	62.3%	<0.001	56.7%	55.6%	0.52
Induction with IL-2 RA	49.3%	28.0%	<0.001	33.1%	33.2%	0.97
DGF	5.9%	4.0%	<0.001	5.3%	4.8%	0.52
Glomerular disease	36.9%	31.4%	<0.001	33.9%	33.9%	0.97
Acute rejection before discharge	2.4%	1.5%	0.018	2.1%	1.9%	0.71

Categorical variables presented as percentages. Age presented as median (IQR).
AA race, African-American race; DGF, delayed graft function; IL-2 RA, IL-2 receptor antibody; IQR, interquartile range; LDA, lymphocyte depleting agent.
[a]Lymphocyte-depleting agents included antithymocyte globulin, muromonab-CD3 (OKT3) and alemtuzumab.

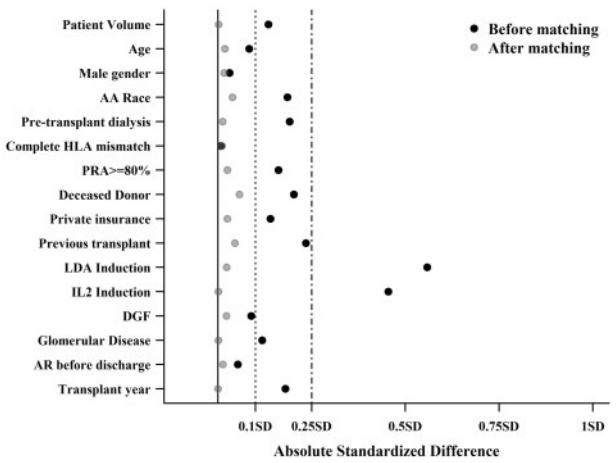

FIGURE 1: Love plot of absolute standardized difference in baseline characteristics before and after matching. AA race, African-American race; AR, acute rejection; DGF, delayed graft function; IL2, IL-2 receptor antibody; LDA, lymphocyte-depleting agent.

return to dialysis or re-transplant. Patients who died with a functioning graft represented a very small number of the entire cohort ($n = 15$). Since the purpose of this analysis was to investigate the effect of steroid avoidance on allograft survival, these subjects were censored as of the patient's death. Graft survival was evaluated for the entire propensity score-matched cohort and among the following immunologic risk strata: repeat kidney transplants, African-Americans, sensitized children (PRA ≥10%), children with pretransplant glomerular disease, and recipients of deceased donor and completely HLA-mismatched kidneys. A stratified analysis was also performed according to the use of a lymphocyte depleting agent for induction.

Statistical analyses were performed using SAS 9.3 and R 3.2.4 statistical software. Chi-square and Wilcoxon rank sum testing were used as appropriate to compare baseline characteristics between treatment groups. Graft survival was compared in the propensity score-matched data using the Kaplan–Meier estimator and the log-rank test. The estimated graft survival curves suggested that the relative hazard of those receiving steroid-avoidance protocols differed in the first 2 years posttransplant compared with long-term follow-up during Years 2–10 posttransplant. Because this violates the constant proportionality assumption of Cox regression modeling, we used a time-varying hazard Cox regression model to examine the long-term relative hazard separately from the short-term hazard over the first 2 years. The long-term effect of steroid-avoidance within immunologic risk was evaluated by including interaction terms with the risk stratum factors in the time-varying hazard Cox regression model. Hazard ratios of graft loss were reported for steroid avoidance among each immunologic risk strata along with Wald 95% confidence intervals (95% CIs).

RESULTS

Cohort characteristics

Demographic and clinical characteristics of the entire cohort and the propensity-score matched cohort are displayed in Table 1. In the propensity score analysis, appropriate matches were identified for 1624 of the 2114 children (77%) who received steroid-avoidance protocols for maintenance immunosuppression. Of these subjects, 1015 (63%) received a short course of steroids as an induction agent [median of 3 days, interquartile range (IQR) of 2–5 days]. Prior to matching, significant differences existed in race, donor type, insurance type,

previous kidney transplant, induction agent, year of transplant, delayed graft function, cause of renal failure and PRA level. In the propensity score-matched cohort, there were no significant differences between children receiving steroid-based and steroid-avoidance protocols. The absolute standardized difference in each demographic or clinical characteristic was <0.1 standard deviation, meeting the generally accepted requirement of well-matched data (Figure 1) [12]. Acute rejection rates were also investigated in the propensity score-matched cohort, as this may influence the effect of steroid avoidance on graft survival. Similar rates of acute rejection were observed at 6 months and 1 year posttransplant. In children receiving steroid avoidance, acute rejection occurred in 8.7% at 6 months and 13.5% at 1 year posttransplant. In those receiving steroid-based immunosuppression, acute rejection occurred in 7.7% at 6 months and 13.1% at 1 year (6-month P-value = 0.33; 1-year P-value = 0.74).

Table 2. Characteristics of subjects receiving *de novo* steroid avoidance, stratified by steroid prescription at 1-year posttransplant

Variable	Remained in steroid-avoidance ($n = 1191$)	Initiated steroids ($n = 283$)	P-value
Age, median (IQR)	12 (6–15)	13 (8–15)	0.098
Male gender	59.0%	63.6%	0.16
AA race	15.8%	18.0%	0.36
Pretransplant dialysis	69.2%	80.6%	<0.001
Complete HLA mismatch	13.1%	16.3%	0.17
PRA level			<0.001
<10%	88.7%	85.5%	
10–79%	10.7%	10.2%	
≥80%	0.7%	4.2%	
Deceased donor type	57.3%	65.7%	0.009
Private insurance	45.6%	37.1%	0.01
Previous transplant	3.8%	9.5%	<0.001
Induction with LDA[a]	57.4%	47.0%	0.002
Induction with IL-2 RA	30.3%	41.7%	<0.001
DGF	4.1%	8.5%	0.002
Glomerular disease	31.7%	44.9%	<0.001
Acute rejection before discharge	1.5%	3.9%	0.01

Categorical variables presented as percentages. Age presented as median (IQR).
AA race, African-American race; DGF, delayed graft function; IL-2 RA, IL-2 receptor antibody; IQR, interquartile range; LDA, lymphocyte depleting agent.
[a]Lymphocyte-depleting agents included antithymocyte globulin, muromonab-CD3 (OKT3) and alemtuzumab.

In the propensity score-matched cohort, steroid prescription was investigated up to 5 years following transplantation. Among patients receiving steroid avoidance at discharge, 85% were steroid-free at 6 months, 81% at 1 year, 75% at 2 years, 74% at 3 years, 70% at 4 years and 71% at 5 years. Conversely, among those receiving steroid-based regimens at discharge, 93% remained on steroids at 6 months, 90% at 1 year, 86% at 2 years, 85% at 3 years, 84% at 4 years and 83% at 5 years following transplantation. Demographic and clinical characteristics of children in whom steroids were initiated at 1 year posttransplant following *de novo* steroid avoidance are presented in Table 2. Transplant recipients who initiated steroids were more likely to have immunologic risk factors, including a higher incidence of sensitization, delayed graft function and previous transplantation. Patients who initiated steroids also were less likely to receive induction with a lymphocyte depleting agent.

Graft survival in children receiving steroid avoidance

In the unmatched data, 5-year death-censored graft survival was improved among children receiving steroid avoidance (85.4% versus 79.4%, P < 0.001). In the propensity score-matched cohort, death-censored graft survival remained improved compared with steroid-based protocols, although this difference was attenuated compared with the unmatched data (Figure 2). Specifically, 5-year allograft survival was 84.8% in children receiving steroid-avoidance compared with 81.2% in steroid-based protocols (P = 0.03).

To evaluate the proportional hazards assumption in the propensity score-matched cohort, the hazard ratio for allograft failure in children receiving steroid avoidance compared with steroid-based protocols was investigated during the study period (Figure 3). The hazard ratio (HR) for allograft failure in children receiving steroid-avoidance was significantly lower

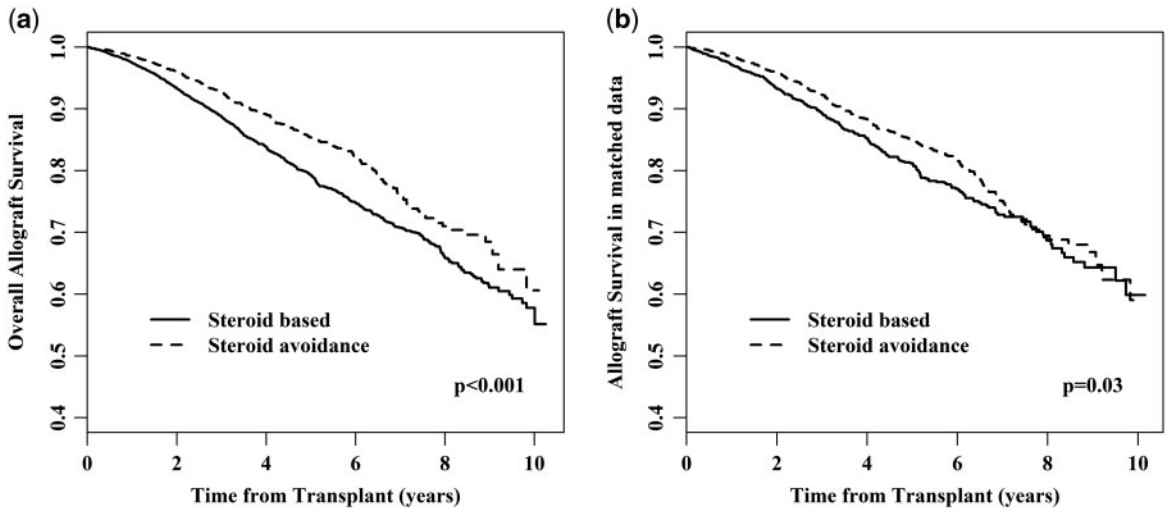

FIGURE 2: Death-censored graft survival in steroid-based versus steroid-avoidance protocols prior to matching (**a**) and after matching (**b**).

immediately following discharge, sharply increasing thereafter to reach a plateau by about 2 years posttransplant. Therefore, outcomes during the first 2 years following transplant were separately investigated from Years 2 to 10 of the study period. In the propensity score-matched cohort, children receiving steroid avoidance had improved 2-year allograft survival, with an HR of 0.62 (95% CI 0.45–0.86; P = 0.004). However, steroid avoidance was not significantly associated with improved long-term allograft survival during Years 2–10 of the study, with an HR of 0.93 (95% CI 0.75–1.15; P = 0.51). In Kaplan–Meier analyses, 2-year allograft survival was improved in children receiving steroid avoidance (95.8%) compared with those receiving steroid-based protocols (93.4%, P = 0.003). However, among children with a functioning graft 2 years after transplant, no difference was observed in death-censored graft survival between children receiving steroid-avoidance and steroid-based protocols (Figure 4). These results indicate that the improved overall graft survival of children receiving steroid avoidance was driven by improved survival during the first 2 years following transplant, when the HR was significantly lower compared with Years 2–10 after transplant.

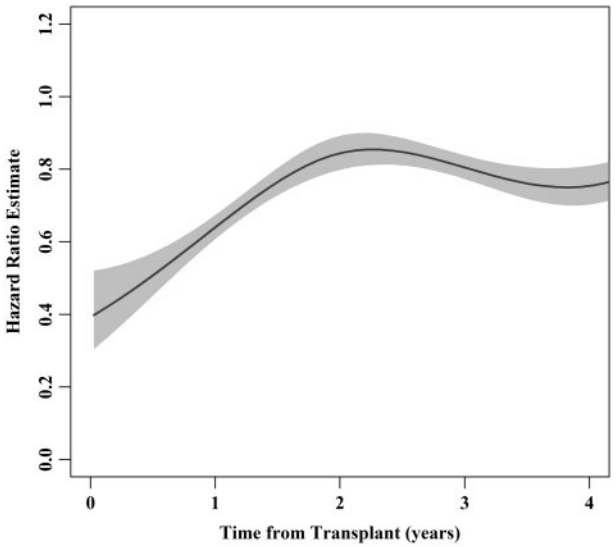

FIGURE 3: Plot of hazard ratio for allograft failure in children receiving steroid avoidance during the follow-up period.

Graft survival stratified by immunologic risk factors and induction agent

Long-term graft survival during Years 2–10 after transplant, when the constant proportionality assumption was supported, was evaluated when stratified by immunologic risk factors and by induction agent. Steroid avoidance did not show any effect on death-censored graft failure when stratified by induction agent. Within immunologic risk strata, the HRs (95% CI) for allograft failure for children receiving steroid avoidance were not significantly different from the null value of 1, similar to the overall analysis (Table 3). Specifically, among sensitized recipients and African-Americans, there was no significant association of steroid avoidance with allograft failure. Steroid avoidance in children with a pretransplant diagnosis of glomerular kidney disease was not associated with an increased risk of allograft failure. Among repeat transplant recipients, a trend was evident toward a higher risk of allograft failure in those receiving steroid avoidance (HR = 1.8), although this did not reach statistical significance (P = 0.08).

DISCUSSION

We demonstrated that steroid-avoidance protocols are safely practiced in pediatric kidney transplant recipients receiving tacrolimus- and mycophenolate-based immunosuppression. In this propensity score-matched cohort analysis, children receiving steroid-avoidance protocols comprised a significant number of high-risk transplant recipients, including 59% who received deceased donor kidneys, 17% African-Americans, 12% who were sensitized (PRA >10%) and 5% who received a repeat kidney transplant. Importantly, long-term allograft survival of steroid-avoidance protocols was similar to steroid-based

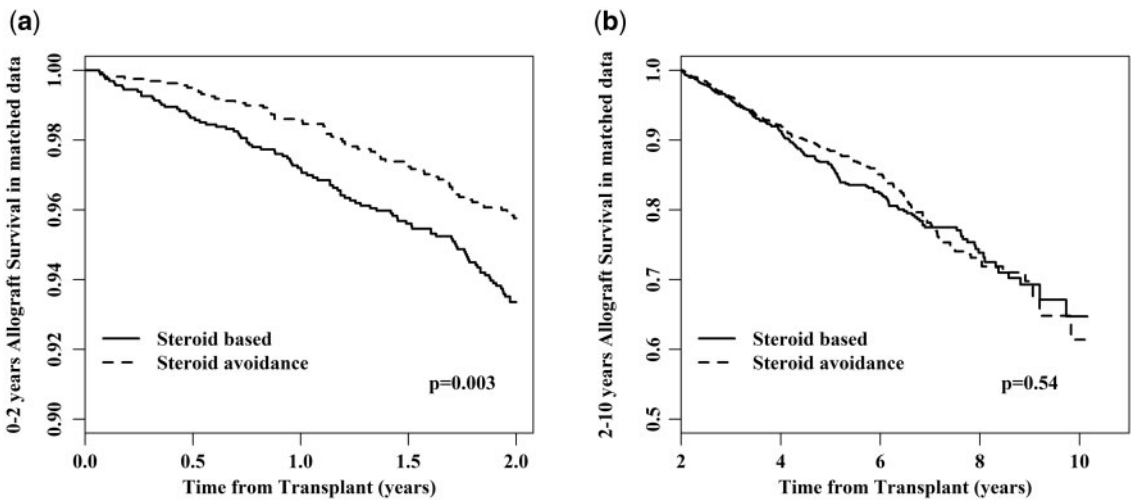

FIGURE 4: Death-censored graft survival during Years 0–2 (**a**) and Years 2–10 (**b**) following transplant in the propensity score-matched cohort.

Table 3. Long-term allograft survival of steroid avoidance stratified by immunologic risk factors in the propensity score-matched cohort

Immunologic risk factor	*n* (%)	HR (95% CI)	P-value
Transplant history			0.08
Repeat transplant	140 (5.8)	1.84 (0.84–4.05)	
Primary transplant	2258 (94.2)	0.89 (0.72–1.11)	
Donor type			0.26
Deceased	1408 (58.7)	1.02 (0.79–1.32)	
Living	990 (41.3)	0.79 (0.54–1.15)	
Race			0.70
African-American	395 (16.5)	1.02 (0.67–1.56)	
Non-African-American	2003 (83.5)	0.93 (0.73–1.18)	
Sensitization			0.39
PRA ≥10%	2673 (11.4)	1.24 (0.63–2.43)	
PRA <10%	2125 (88.6)	0.90 (0.72–1.13)	
HLA matching			0.56
Complete HLA mismatch	326 (13.6)	0.80 (0.47–1.37)	
HLA mismatch <6	2072 (86.4)	0.95 (0.76–1.20)	
Induction agent			0.62
LDA induction	1265 (52.8)	0.89 (0.67–1.19)	
No LDA induction	1133 (47.2)	0.99 (0.73–1.35)	
Cause of ESRD			0.85
Glomerular disease	1595 (66.5)	0.9 (0.64–1.26)	
Non-glomerular disease	803 (33.6)	0.94 (0.71–1.23)	

P-value represents the P-value for the interaction term. Estimates represent the HR for patients receiving steroid-avoidance compared with steroid-based protocols.
LDA, lymphocyte-depleting agent; ESRD, end-stage renal disease.

protocols among children with these risk factors for inferior graft outcomes.

Steroid avoidance has become a major goal in pediatric kidney transplantation during the past decade and has been safely practiced in select transplant recipients [9, 13]. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that steroids can be discontinued during the first week of transplant in patients at low immunologic risk [14]. However, marked variability exists in the practice of steroid avoidance among transplant centers, and selection criteria for steroid avoidance remains an important clinical concern [11]. Sensitized patients have routinely been excluded from steroid avoidance in previous studies [2, 3, 6]. Also, African-Americans have been consistently underrepresented, with the largest study including only 34 African-American participants [3]. Only one small trial of 13 children demonstrated acceptable short-term outcomes in high-risk pediatric recipients, including African-Americans, sensitized recipients and those with zero HLA matching [7]. In this nationwide analysis, a comparatively larger number of African-Americans ($n = 272$), sensitized patients ($n = 198$) and recipients of complete HLA-mismatched kidneys ($n = 228$) received steroid-avoidance protocols. Among these children considered to be at high risk in our cohort, long-term allograft survival was similar in those receiving steroid-avoidance compared to steroid-based protocols. Our results, therefore, extend the findings of previous studies by showing that steroid avoidance can be safely practiced in children with immunologic risk factors, including African-Americans and sensitized children.

Repeat transplant recipients represent a distinct group at high immunologic risk, who are frequently allosensitized and at increased risk for allograft failure [15]. Furthermore, in adult patients receiving steroid avoidance, repeat transplant recipients are at increased risk of acute rejection [16] and return to steroid therapy [17]. In a previous nationwide analysis of the clinical practice of steroid avoidance [11], we reported that children with a previous transplant were the least likely to receive steroid avoidance, and many published studies of steroid avoidance have excluded these patients from participation [1–3]. To our knowledge, this is the first study to evaluate the effect of steroid avoidance on allograft outcomes in this patient population compared with primary transplant recipients. In our cohort, repeat transplant recipients receiving steroid avoidance did not have significantly worse long-term outcomes. However, the HR for long-term allograft failure in repeat transplant recipients was 1.84 and approached significance ($P = 0.08$). Limited power may have played a role, as repeat transplants represented only 5% of the entire propensity score-matched cohort. Our results should, therefore, be interpreted with caution in this particular high-risk group of transplant recipients.

The choice of induction agent remains an important clinical decision when practicing steroid avoidance. The primary benefit of lymphocyte depleting agents is a reduced risk of acute rejection, especially in high-risk patients [18, 19]. However, these agents have been associated with increased risk of cytomegalovirus infection and posttransplant lymphoproliferative disorder [19–21], and the long-term benefit on graft survival is uncertain [22]. Prior to matching, 62% of transplant recipients in steroid-avoidance protocols received a lymphocyte-depleting agent. The preferential use of lymphocyte-depleting agents in steroid avoidance may represent an effort to mitigate the risk of acute rejection in these patients. The type of induction agent, however, did not influence the long-term outcomes of steroid avoidance, which was equally safe in patients receiving lymphocyte-depleting agents and IL-2 receptor antibody induction. Although lymphocyte-depleting agents may have some benefit in high-risk recipients irrespective of steroid use, our results indicate that the choice for induction agent should not be significantly influenced by concurrent use of steroids for baseline immunosuppression. In patients receiving steroid avoidance who are otherwise at low immunologic risk, standard induction with an IL-2 receptor antibody is a reasonable option.

The decision to use steroid avoidance in children with end-stage renal disease secondary to glomerulonephritis presents a unique challenge. Among patients with a pretransplant diagnosis of primary glomerular disease, recurrence occurs in up 10–50% [23] and is the third leading cause of allograft failure [24]. There are limited data in children regarding the association steroid avoidance with posttransplant recurrence of glomerular disease. In a cohort of 129 children receiving *de novo* steroid-free immunosuppression, Sutherland *et al.* reported that recurrence of glomerulonephritis was the second most frequent cause for initiation of steroids [25]. However, many studies have shown that the risk of allograft loss due to disease recurrence is not affected by steroid-free immunosuppression [26–28]. Likewise in our cohort, allograft survival in children with pretransplant glomerulonephritis was not adversely affected by steroid avoidance, indicating that this approach is a safe option in children with glomerular disease.

Steroid avoidance was associated with improved short-term allograft survival in our propensity score-matched cohort. This is consistent with a previous analysis by Luan *et al.*, who investigated allograft survival of steroid-avoidance protocols in adult kidney transplant recipients using OPTN data [29]. They reported that steroid-avoidance protocols were associated with improved 1-year allograft survival compared with steroid-based protocols. We suspect that improved short-term outcomes in children receiving steroid avoidance, which was most prominently observed immediately following transplant, reflected clinical judgment that is not accounted for by pre-transplant variables included in the propensity score analysis. For example, it is possible that children with slow recovery of renal function after transplant or peri-transplant complications, such as disease recurrence, were preferentially kept on maintenance steroids.

The strengths of this study include the large sample size, extended follow-up period and the comprehensive nature of the OPTN database, which provided a large number of variables to include in the propensity score model and minimize confounding. Nevertheless, the findings and conclusions of this study should be interpreted within the framework of inherent limitations of observational studies. First, although we adjusted for known risk factors of poor outcomes, the possibility of residual unmeasured confounding must be considered, which likely accounted for improved short-term allograft survival in patients receiving steroid avoidance. Patient compliance, which is not captured in registry data, is another variable that may influence the clinical decision to use steroid avoidance and may also affect allograft outcomes. A second limitation is a lack of granularity in data regarding steroids and concomitant immunosuppression. For example, the dose of immunosuppressive medications is not reported, and variation in tacrolimus levels could have existed between treatment groups. Finally, patients were classified according to steroid prescription at discharge, and this changed in a small percentage of patients at follow-up. Our results should, therefore, be interpreted as the overall safety of *de novo* steroid-free immunosuppression, although this does not preclude the subsequent initiation of steroids if clinically indicated.

Given these limitations, the findings of this study should be interpreted with some caution, as steroid avoidance is not without some risk. Adult meta-analyses of randomized controlled trials have shown increased risk of acute rejection in patients receiving steroid avoidance, the long-term consequences of which remain uncertain [30–32]. In an analysis of OPTN data by Schold *et al.* high-risk transplant recipients, including repeat transplants and sensitized patients, demonstrated an increased risk to start steroids after initial steroid avoidance [17]. In our cohort, patients with immunologic risk factors were also more likely to initiate steroids at 1 year posttransplant, although this occurred in only 19% of those selected for *de novo* steroid avoidance. Furthermore, steroid avoidance did not adversely affect long-term allograft survival in those with immunologic risk factors, indicating that steroid avoidance can be safely attempted with a reasonable chance of success in these higher-risk patients. Benefits of steroid avoidance include decreased cardiovascular morbidity and improved growth posttransplant [3, 4, 6, 10, 33]. Therefore, the decision to use steroids should not be based strictly on race, sensitization or other risk factors for inferior outcomes. Rather, immunosuppression should be tailored to individual patients considering both the potential benefits and morbidity associated with steroid use.

In conclusion, steroid avoidance can be safely practiced in children receiving tacrolimus- and mycophenolate-based immunosuppression, including those with risk factors for inferior graft outcomes. Steroid avoidance is, therefore, a reasonable option to avoid steroid-associated morbidity in pediatric kidney transplant recipients.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract form.

REFERENCES

1. Bhakta N, Marik J, Malekzadeh M *et al.* Can pediatric steroid-free renal transplantation improve growth and metabolic complications? *Pediatr Transplant* 2008; 12: 854–861
2. Delucchi A, Valenzuela M, Ferrario M *et al.* Early steroid withdrawal in pediatric renal transplant on newer immunosuppressive drugs. *Pediatr Transplant* 2007; 11: 743–748
3. Sarwal MM, Ettenger RB, Dharnidharka V *et al.* Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. *Am J Transplant* 2012; 12: 2719–2729
4. Sarwal MM, Vidhun JR, Alexander SR *et al.* Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. *Transplantation* 2003; 76: 1331–1339
5. Silverstein DM, Aviles DH, LeBlanc PM *et al.* Results of one-year follow-up of steroid-free immunosuppression in pediatric renal transplant patients. *Pediatr Transplant* 2005; 9: 589–597
6. Grenda R, Watson A, Trompeter R *et al.* A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transplant* 2010; 10: 828–836
7. Li L, Chaudhuri A, Chen A *et al.* Efficacy and safety of thymoglobulin induction as an alternative approach for steroid-free maintenance immunosuppression in pediatric renal transplantation. *Transplantation* 2010; 90: 1516–1520
8. Oberholzer J, John E, Lumpaopong A *et al.* Early discontinuation of steroids is safe and effective in pediatric kidney transplant recipients. *Pediatr Transplant* 2005; 9: 456–463

9. Nehus E, Goebel J, Abraham E. Outcomes of Steroid-avoidance protocols in pediatric kidney transplant recipients. *Am J Transplant* 2012; 12: 3441–3448
10. Webb NJA, Douglas SE, Rajai A *et al.* Corticosteroid-free kidney transplantation improves growth. *Transplantation* 2015; 99: 1178–1185
11. Nehus E, Liu C, Hooper DK *et al.* Clinical practice of steroid avoidance in pediatric kidney transplantation. *Am J Transplant* 2015; 15: 2203–2210
12. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46: 399–424
13. Zhang H, Zheng Y, Liu L *et al.* Steroid avoidance or withdrawal regimens in paediatric kidney transplantation: a meta-analysis of randomised controlled trials. *PLoS One* 2016; 11: e0146523
14. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; 9 Suppl 3: S1–155
15. Magee JC, Barr ML, Basadonna GP *et al.* Repeat organ transplantation in the United States, 1996–2005. *Am J Transplant* 2007; 7: 1424–1433
16. Woodle ES, Alloway RR, Buell JF *et al.* Multivariate analysis of risk factors for acute rejection in early corticosteroid cessation regimens under modern immunosuppression. *Am J Transplant* 2005; 5: 2740–2744
17. Schold JD, Santos A, Rehman S *et al.* The success of continued steroid avoidance after kidney transplantation in the US. *Am J Transplant* 2009; 9: 2768–2776
18. Brennan DC, Daller JA, Lake KD *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; 355: 1967–1977
19. Webster AC, Ruster LP, McGee R *et al.* Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev* 2010; 20: CD003897
20. Bustami RT, Ojo AO, Wolfe RA *et al.* Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. *Am J Transplant* 2004; 4: 87–93
21. Kirk AD, Cherikh WS, Ring M *et al.* Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. *Am J Transplant* 2007; 7: 2619–2625
22. Hill P, Cross NB, Barnett AN *et al.* Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. *Cochrane Database Syst Rev* 2017; 1: CD004759
23. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. *Am J Transplant* 2006; 6: 2535–2542
24. Briganti EM, Russ GR, McNeil JJ *et al.* Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002; 347: 103–109
25. Sutherland S, Li L, Concepcion W *et al.* Steroid-free immunosuppression in pediatric renal transplantation: rationale for and [corrected] outcomes following conversion to steroid based therapy. *Transplantation* 2009; 87: 1744–1748
26. Mulay AV, van Walraven C, Knoll GA. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. *Am J Transplant* 2009; 9: 804–811
27. Ibrahim H, Rogers T, Casingal V *et al.* Graft loss from recurrent glomerulonephritis is not increased with a rapid steroid discontinuation protocol. *Transplantation* 2006; 81: 214–219
28. Boardman R, Trofe J, Alloway R *et al.* Early steroid withdrawal does not increase risk for recurrent focal segmental glomerulosclerosis. *Transplant Proc* 2005; 37: 817–818
29. Luan FL, Steffick DE, Gadegbeku C *et al.* Graft and patient survival in kidney transplant recipients selected for *de novo* steroid-free maintenance immunosuppression. *Am J Transplant* 2009; 9: 160–168
30. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation* 2010; 89: 1–14
31. Pascual J, Royuela A, Galeano C *et al.* Very early steroid withdrawal or complete avoidance for kidney transplant recipients: a systematic review. *Nephrol Dial Transplant* 2012; 27: 825–832
32. Pascual J, Zamora J, Galeano C *et al.* Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009; 21: CD005632
33. Li L, Chang A, Naesens M *et al.* Steroid-free immunosuppression since 1999: 129 pediatric renal transplants with sustained graft and patient benefits. *Am J Transplant* 2009; 9: 1362–1372

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