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Pediatric Kidney Transplantation Using A Novel Protocol of Rapid (6-Day) Discontinuation of Prednisone: 2-year Results¹

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Abstract

Background—There are few prospective studies of prednisone-free immunosuppression (IS) in pediatric kidney transplant (KTx) recipients. We studied outcomes of a protocol using rapid discontinuation of prednisone (RDP, < 1 week) and thymoglobulin induction.

Methods—21 RDP recipients (mean age 14 ± 3 years) received KTx between 5/2002 and 12/2005 and were matched with controls (n=39) for age, race, and donor source. For the RDP group, IS consisted of prednisone tapered off over 6 days, thymoglobulin, mycophenolate mofetil, and cyclosporine (CsA). In controls, IS consisted of thymoglobulin, maintenance prednisone, azathioprine, and CsA.

Results—For the RDP group, graft survival at 1 and 2 years was 90% and 86%; for controls, 92%, and 90% (p=0.86). For the RDP group, the incidence of acute rejection at 1 and 2 years was 14% and 19%; for controls, 23%, and 31% (p=0.17). Of the 18 RDP recipients with functioning grafts, 89% remain prednisone free at follow-up. There was no significant difference between groups in recipient survival rates, incidence of hypertension, chronic allograft nephropathy, or cytomegalovirus disease.

Conclusions—RDP using thymoglobulin, MMF, and CsA in selected pediatric KTx recipients is associated with recipient and graft survival rates and acute rejection incidence comparable to quadruple drug therapy.

Keywords

Prednisone withdrawal; pediatric kidney transplantation; rejection

Introduction

Our center has used a standard quadruple immunosuppression protocol that incorporates prophylactic antibody and corticosteroids since 1968 (1). We, as well as others, have achieved recipient and graft survival rates in infants, young children, and adolescent kidney transplant (KTx) recipients parallel to those in adults (2,3). However, in children, optimal growth and

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minimization of metabolic complications without increased risk of allograft rejection must be considered necessary criteria for determining rehabilitation after kidney transplantation. The adverse effects associated with corticosteroid use are well known and include alterations in carbohydrate, glucose and lipid metabolism, redistribution of body fat, sodium retention, hypertension, cataracts, myopathy, mood and behavioral changes, increased susceptibility to infection, osteoporosis, and growth retardation (4-7). Therefore, new approaches to improving successful rehabilitation such as steroid avoidance/minimization are being explored in pediatric KTx recipients (7-14). However, few prospective studies have been done in pediatric KTx recipients using a protocol of very early steroid avoidance or withdrawal (8-10). The goal of the present study is to determine whether a protocol of rapid discontinuation of prednisone (day 6) with maintenance cyclosporine (CsA) and mycophenolate mofetil (MMF), could achieve infection and growth profiles comparable to those of quadruple therapy without compromise of allograft function (increased acute rejection) in children undergoing kidney transplantation.

Materials and Methods

Recipients

In May 2002, our center began using a prospective, non-randomized protocol of rapid discontinuation of prednisone (RDP) in pediatric KTx recipients that were above 5 years of age, White, not on steroids at the time of KTx, able to take MMF, and Epstein Barr virus (EBV) seropositive. Recipients were selected by their physicians for study entry. Based on outcomes in the initial six recipients, in 2003 the criteria were expanded to include reTx, nonwhites, and EBV seronegativity. Twenty-one pediatric recipients underwent a KTx at the University of Minnesota with this protocol from May 2002 through December 2005. Controls (n=39, Tx between January 2000 and December 2005) were matched for age, race, and donor source. Recipient characteristics are shown in Table 1. Of these, end stage renal disease was due to congenital/obstructive disease in 33% of recipients and 31% of controls. Retransplant recipients were 10% of the RDP group and 46% of controls. The mean age at KTx was 14 ± 3 years (range, 7-18 years) for RDP recipients and 14 ± 3 years (range, 8-18 years) for controls. Body mass index (kg/m², BMI) percentiles and height standard deviation score (HSDS) were calculated using the Baylor College of Medicine growth calculator (15). Hypertension was defined as a systolic or diastolic blood pressure above the 95th percentile for age, height, and sex or use of antihypertensive medication (16). Laboratory data included serum creatinine, blood glucose, white blood cell count, hemoglobin, fasting cholesterol and triglyceride levels. The Schwartz formula was used to estimate glomerular filtration rate (GFR) (17). Anemia was defined as a hemoglobin value < 11 g/dL (18). Our laboratory's elevated values for total cholesterol were > 200 mg/dL and for triglycerides were > 160 mg/dL (19,20). Mean follow-up was 39 months (range, 6 to 66) for RDP recipients and 61 months (range, 12 to 92) for controls. The Institutional Review Board of the University of Minnesota approved our study.

Immunosuppression

No immunosuppression was given immediately pretransplant. Thymoglobulin was given at 1.5 mg/kg intravenously (IV) per day for 5-7 days in the RDP recipients and for 6-15 days in the control recipients and the first dose was given intraoperatively. For the RDP group, prednisone was given as follows: 10 mg/kg IV intraoperatively, 1 mg/kg IV on day 1, 0.5 mg/kg IV days 2 and 3, 0.25 mg/kg IV days 4 and 5, and 0 mg/kg on day 6. Mycophenolate mofetil was given at 600 mg/m²/dose twice a day. The first dose was given IV intraoperatively. Cyclosporine A (Neoral) was begun PO on day 1 and dosed to achieve target levels in both groups as follows: zero to three months: 175-200 ng/mL; four to six months: 150-175 ng/mL, seven to nine months: 125-150 ng/mL, nine months to one year: 100-125 ng/mL. For controls, prednisone was started at 2 mg/kg/day orally, then tapered to 0.45 mg/kg/day at 1 month

posttransplant, and then to 0.25 to 0.3 mg/kg/day at 1 year. Azathioprine was started at 5 mg/kg/day orally on the day of the KTx, and then tapered to 2 to 2.5 mg/kg/day over the 1st week posttransplant.

Antimicrobial, antifungal, and antiviral (cytomegalovirus [CMV], EBV) prophylaxis

Our prophylaxis protocols have been previously described (2). Oral trimethoprim-sulfamethoxazole was given daily as prophylaxis against urinary tract infection (UTI) and *Pneumocystis carinii* infection. Fungal prophylaxis was provided with oral nystatin for 6 months posttransplant. All recipients received intravenous ganciclovir (5 mg/kg every 12 hours) while receiving thymoglobulin followed by oral valganciclovir (10 to 15 mg/kg per day) for 12 weeks. All recipients were monitored monthly for EBV infection by polymerase chain reaction (PCR). If the EBV PCR test result became positive, the valganciclovir dose was doubled to 20 to 30 mg/kg per day and continued until the EBV PCR became negative. All doses of ganciclovir and valganciclovir were adjusted as needed for degree of renal function.

Rejection and infection

All rejection episodes were confirmed by percutaneous renal biopsy and characterized as previously described (21,22). Acute tubulointerstitial (TI) rejection was defined by the presence of tubular mononuclear infiltrates, interstitial mononuclear infiltrates and edema, erythrocyte extravasation, and tubular damage. Acute vascular rejection was defined by subendothelial mononuclear infiltrates and endothelial sloughing. Chronic allograft nephropathy was characterized by interstitial fibrosis, tubular atrophy, fibrointimal thickening and obliteration of arteries and arterioles. In RDP recipients mild acute rejection (Banff grade 1, n=3) was treated with Solumedrol for 3 doses followed by a rapid steroid taper to a low maintenance prednisone dose. OKT3 was also given for 5-7 days for more severe acute rejection (Banff grade 2, n=1). All RDP recipients that developed acute rejection were subsequently placed on maintenance steroids. In control recipients, the first episode of acute rejection (Banff grade 1, n=10) was treated with 2 mg/kg/day of prednisone followed by a steroid taper to a maintenance dose. OKT3 was given for 5-7 days for more severe acute rejection (Banff grade 2, n=2). Bacterial infections were diagnosed by culture results. Viral infections were diagnosed by culture results, rapid antigen detection tests, changes in serology, PCR, and cerebral spinal fluid abnormalities. Diagnosis of EBV-associated posttransplant lymphoproliferative disorder (PTLD) or lymphoma was based on histopathology and classified according to the 1997 Society for Hematopathology workshop recommendations.

Statistical analysis

Groups were analyzed by intention to treat. Data are expressed as the mean $\pm$ standard deviation (SD) and range. Statistical analyses were performed using the Wilcoxon rank-sum test, chi-square test, Fisher exact test, and Kruskal-Wallis test. Time to acute rejection, to chronic allograft nephropathy, and to PTLD, as well as actuarial graft and recipient survival rates, were calculated using Kaplan-Meier survival methods. Graft loss was defined as a return to chronic dialysis, a graft nephrectomy, a reTx, or death. Graft and recipient survival rates and the incidence of acute rejection and chronic allograft nephropathy at 2 years posttransplant are shown because of small numbers in the RDP group beyond 2 years. A P value ≤ 0.05 was considered statistically significant.

Results

Recipient and graft survival

Recipient and graft survival rates at 6 months, 1, and 2 years posttransplant did not significantly differ between the two groups (P=NS, Table 2). Graft survival rates were 100%, 90%, and 86%

at 6 months, 1, and 2 years for RDP recipients; 95%, 92%, and 90% for control recipients ($P=0.86$, Figure 1) with and without censoring for death, recurrent disease, technical and vascular complications. Sixteen of eighteen eligible RDP recipients (89%) remain steroid free at follow-up.

Rejection and graft function

The overall incidence of acute rejection did not significantly differ between the two groups. The incidence of acute rejection at 6 months, 1, and 2 years posttransplant is shown in Table 2. The incidence of delayed graft function did not significantly differ between the two groups (0% RDP vs. 13% controls, $p = 0.15$). We found no statistically significant difference in the incidence of chronic allograft nephropathy, serum creatinine values, or estimated GFR values at 6 months, 1, and 2 years posttransplant between the RDP and control groups ($P=NS$, Table 2).

Laboratory and growth data

The mean white blood cell count was lower in RDP recipients at 6 months and 2 years posttransplant compared to control recipients ($p=0.03$ for both) (Table 3). The difference in the incidence of elevated total cholesterol and triglyceride levels at follow-up did not achieve statistical significance (Table 2). There were no significant differences between groups for mean blood glucose, hemoglobin, cholesterol, or triglyceride levels (Table 3). Mean height standard deviation scores were significantly improved in RDP recipients compared to control recipients pre- and posttransplant (Table 2). There was no significant difference in BMI percentiles between groups.

Infections and other complications

Infections posttransplant are shown in Table 4. The incidence of symptomatic EBV infections (excluding PTLD or lymphoma) was significantly lower in RDP versus control recipients (0% vs. 20%, $P=0.04$). The incidence of other infections did not significantly differ between the two groups ($P=NS$, Table 4). There were no cases of PTLD in the RDP group and one case in the control group ($P=NS$). No cases of diabetes mellitus developed in RDP recipients and 2 (5%) cases developed in control recipients ($P=NS$). The incidence of hypertension and anemia did not differ significantly between the two groups at follow-up ($P=NS$, Table 3). At 1 and 2 years posttransplant the incidence of leukopenia was 30% and 6% in RDP recipients compared to 23% and 9% in control recipients ($P=NS$ for both). Leukopenia was managed by transiently decreasing the dose of MMF and 11 (52%) RDP recipients received granulocyte colony stimulating factor for treatment of leukopenia compared to 4 (10%) control recipients ($p = 0.001$). Eleven (52%) RDP recipients and 24 (62%) control recipients received an erythropoietin-stimulating agent for treatment of anemia ($p = 0.59$).

Causes of graft failure and death

Grafts were lost in 3 (14%) RDP recipients and 11 (28%) control recipients ($P=0.85$). The causes of graft failure in RDP recipients were acute rejection ($n=1$), chronic allograft nephropathy ($n=1$), and death ($n=1$); in control recipients were acute rejection ($n=1$), chronic allograft nephropathy ($n=4$), death ($n=2$), recurrent disease ($n=1$), technical/vascular ($n=1$), unknown ($n=1$), and urologic complication ($n=1$). The difference in the causes of graft failure between groups was not statistically significant ($P=0.85$). One recipient (cerebrovascular accident, 5%) died in the RDP group and 2 (sudden death at home, respiratory failure; 5%) in the control group.

Discussion

To our knowledge, this is the first prospective study to show that corticosteroids can be rapidly discontinued in pediatric KTx recipients using thymoglobulin induction combined with maintenance CsA and MMF immunosuppression. Recipient and graft survival rates and acute rejection incidence for RDP recipients are comparable to those in control recipients during the 2 year follow up period. However, the incidence of chronic allograft nephropathy in RDP recipients suggests possible subclinical acute rejection episodes may have occurred, as recipients were biopsied for elevation of serum creatinine levels.

In addition to a low incidence of acute rejection in RDP recipients, this study found a low incidence of acute EBV infection and PTLN. These data compare favorably to a prospective pediatric study of steroid avoidance in 57 recipients that used a protocol of prolonged 6 month administration of prophylactic antibody therapy with Daclizumab (humanized, monoclonal IL2R antibody) and maintenance immunosuppression with tacrolimus and MMF (9). The study reported that at 1 year follow-up the incidence of acute rejection was 8%, EBV positivity 12%, and PTLN incidence was 2%.

Sixty-three percent of U.S. pediatric KTx recipients transplanted between 2002 and 2006 received tacrolimus and MMF as part of their immunosuppression protocol compared to 10% of recipients that received CsA and MMF as used in our protocol (23). The present study shows that steroids can be rapidly discontinued in pediatric KTx recipients receiving maintenance CsA immunosuppression in combination with MMF without an increased risk of clinical acute rejection. Although this is the first study to report follow-up data out to 2 years, a 2 year follow up period should still be considered short term in pediatric KTx recipients. The results of this study are especially important for centers that include CsA as part of their maintenance immunosuppression protocol and for recipients intolerant of tacrolimus.

A previous report from this center found a 58% incidence of hypercholesterolemia at 3 years posttransplant in CsA treated KTx recipients (20). The data in the present study suggest that the risk of hypercholesterolemia is less in CsA treated recipients in the absence of steroids. Similar to studies in recipients treated with tacrolimus, the present study found no increased incidence of diabetes mellitus in RDP recipients treated with CsA. There was no decrease in the incidence of hypertension or medication usage in RDP recipients compared to control recipients. The incidence of leukopenia was high in RDP recipients during the first year posttransplant and was managed by decreasing the dose of MMF and by the use of granulocyte colony stimulating factor.

There are some limitations to this study. First, protocol biopsies were not done and episodes of subclinical acute rejection may have led to chronic allograft nephropathy. Second, RDP recipients were selected based on physician choice. It is possible that lower risk recipients were rapidly discontinued from prednisone. At a minimum these data show that selected recipients can achieve good outcomes on steroid-free, CsA based immunosuppression protocols.

In conclusion, rapid discontinuation of prednisone in the setting of a short course of induction therapy with Thymoglobulin and maintenance immunosuppression with CsA and MMF can be used in pediatric kidney transplant recipients resulting in recipient and graft survival rates comparable to those seen in steroid based IS protocols. This can be achieved in selected recipients (above 5 years of age and not on steroids at the time of transplant) without an increased incidence of acute rejection. The study RDP protocol was associated with a low incidence of acute EBV infection, a lower incidence of hyperlipidemia, and good height growth. Additional studies and longer patient follow-up are warranted.

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Abbreviations

GFR	Glomerular filtration rate
KTx	Kidney transplant
RDP	Rapid discontinuation of Prednisone
IS	Immunosuppression
PTLD	Posttransplant lymphoproliferative disorder

Figure.

Actuarial censored and uncensored graft survival rates by type of steroid therapy, Rapid discontinuation of prednisone (RDP) recipients (n=21) or Control recipients (n=39). P= 0.86, Wilcoxon rank-sum test.

Table 1
Recipient Characteristics by Steroid Protocol

Characteristic	RDP	Control	p value
Age (years, mean $\pm$ SD) (range)	14 $\pm$ 3 (7.8-18)	14 $\pm$ 3 (8.1-18)	NS
Race N (%)			NS
<i>White</i>	17 (81)	32 (82)	
<i>Nonwhite</i>	4 (19)	7 (18)	
Gender N (%)			0.01*
<i>Female</i>	5 (24)	23 (59)	
<i>Male</i>	16 (76)	16 (41)	
Transplant type N (%)			NS
<i>Deceased donor</i>	6 (29)	10 (26)	
<i>Living donor</i>	15 (71)	29 (74)	
Transplant number N (%)			0.01**
<i>Primary</i>	19 (90)	21 (54)	
<i>Retransplant</i>	2 (10)	18 (46)	
Cause of ESRD N (%)			NS
<i>Congenital anomalies</i>			
<i>Obstructive or reflux nephropathy</i>	7 (33)	12 (31)	
<i>Glomerulonephritis</i>	4 (19)	13 (33)	
<i>Focal segmental glomerulosclerosis</i>	2 (10)	2 (5)	
<i>Cystic kidney disease</i>	4 (19)	2 (5)	
<i>Other</i>	4 (19)	10 (26)	
Cytomegalovirus antibody at transplant (%)			0.38*
<i>Positive</i>	25	41	
<i>Negative</i>	75	59	
Epstein Barr virus antibody at transplant (%)			0.78*
<i>Positive</i>	62	55	
<i>Negative</i>	38	45	
Panel Reactive antibody at transplant (%)			0.13**
<i>0</i>	90	64	
<i>1-10</i>	0	13	
<i>>10</i>	10	23	
Body mass index (kg/m ²) percentile at transplant			0.054**
< 5%	5%	3%	
5% - <85%	67%	78%	
85% - <95%	5%	16%	
$\geq$ 95%	24%	3%	
Height SDS	-0.9 $\pm$ 1.6	-1.9 $\pm$ 1.6	0.003 [†]

RDP, Rapid discontinuation of prednisone; SD, Standard deviation; ESRD, End-stage renal disease; SDS, Standard deviation score; NS, not significant;

* Fisher's exact test,

** Chi-square test,

[†]Wilcoxon rank-sum test

Table 2

Transplant Outcomes by Steroid Protocol

Characteristic	RDP	Control	p value
Recipient survival (%)			0.61
6 Months	100	100	
1 Year	95	97	
2 Years	95	97	
Graft survival (%)			0.86
6 Months	100	95	
1 Year	90	92	
2 Years	86	90	
Mean serum creatinine (mg/dL)			
6 Months	1.5 ± 0.9	1.1 ± 0.4	0.08
1 Year	1.5 ± 0.6	1.3 ± 0.7	0.09
2 Years	1.6 ± 0.6	1.4 ± 0.8	0.12
Mean glomerular filtration rate (mL/min/1.73m ²)			0.81
6 Months	77 ± 25	82 ± 29	
1 Year	73 ± 24	76 ± 22	
2 Years	73 ± 25	73 ± 24	
Incidence of acute rejection (%)			0.17
6 Months	14	21	
1 Year	14	23	
2 Years	19	31	
Incidence of chronic allograft nephropathy (%)			0.76
6 Months	9	5	
1 Year	25	8	
2 Years	35	30	
BMI (kg/m ²) % at 2 years postTx			0.33
<5%	0%	6%	
5%-<85%	60%	59%	
85%-<95%	7%	19%	
≥95%	33%	16%	
Height SDS			
6 Months	-1.0 ± 1.6	-2.0 ± 1.6	0.006*
1 Year	-0.6 ± 1.1	-2.0 ± 1.5	0.001*
2 Years	-0.6 ± 1.1	-1.9 ± 1.5	0.002*
Hypertension at 2 years	82%	77%	1.00
Anemia (Hgb < 11 g/dL) at 2 years	18%	14%	1.00
Elevated triglycerides at 2 years	36%	61%	0.26
Elevated cholesterol at 2 years	9%	42%	0.10

RDP, Rapid discontinuation of prednisone; BMI, Body mass index (kg/m²); postTx, Posttransplant; SDS, Standard deviation score; Hgb, Hemoglobin

* Wilcoxon rank-sum test

Table 3

Laboratory Data by Steroid Protocol

Laboratory Value (Mean $\pm$ Standard Deviation)	RDP	Control	p value
Blood glucose (mg/dL)			
6 Months	88 $\pm$ 15	93 $\pm$ 15	0.46
1 Year	95 $\pm$ 14	95 $\pm$ 26	0.50
2 Years	98 $\pm$ 13	107 $\pm$ 82	0.06
White blood cell count ($10^9/L$)			
6 Months	4.5 $\pm$ 2.1	6.0 $\pm$ 2.4	0.03*
1 Year	5.1 $\pm$ 1.7	5.4 $\pm$ 1.8	0.44
2 Years	5.7 $\pm$ 1.6	7.3 $\pm$ 3.5	0.03*
Hemoglobin (g/dL)			
6 Months	11.7 $\pm$ 2.0	11.7 $\pm$ 1.6	0.43
1 Year	12.2 $\pm$ 1.6	12.0 $\pm$ 1.9	0.63
2 Years	12.6 $\pm$ 1.3	12.4 $\pm$ 1.6	0.73
Total Cholesterol (mg/dL)			
6 Months	184 $\pm$ 39	237 $\pm$ 104	0.27
1 Year	188 $\pm$ 53	222 $\pm$ 56	0.052
2 Years	166 $\pm$ 59	229 $\pm$ 126	0.11
Triglycerides (mg/dL)			
6 Months	170 $\pm$ 145	229 $\pm$ 173	0.43
1 Year	183 $\pm$ 120	221 $\pm$ 135	0.41
2 Years	169 $\pm$ 116	203 $\pm$ 123	0.29

RDP, Rapid discontinuation of prednisone

* Wilcoxon rank-sum test

Table 4
Overall Infections and PTLD Posttransplant, by Steroid Therapy

Type	RDP N (%)	Control N (%)	p value
Epstein-Barr virus	0 (0)	8 (21)	0.04 [*]
Cytomegalovirus disease	3 (14)	5 (13)	1.00
Polyoma (BK) virus	0 (0)	2 (5)	0.54
Urinary tract infection	0 (0)	2 (5)	0.54
Line sepsis	3 (14)	6 (15)	1.00
PTLD	0 (0)	1 (3)	1.00

RDP, Rapid discontinuation of prednisone; PTLD, posttransplant lymphoproliferative disorder/lymphoma

^{*} Fisher's exact test