Published in final edited form as:

Am J Transplant. 2009 June ; 9(6): 1362–1372. doi:10.1111/j.1600-6143.2009.02640.x.

STERIOD-FREE IMMUNOSUPPRESSION SINCE 1999: 129 PEDIATRIC RENAL TRANSPLANTS WITH SUSTAINED GRAFT AND PATIENT BENEFITS

L. Li¹, A. Chang¹, M. Naesens¹, N. Kambham², J. Waskerwitz^{1,3}, J. Martin¹, C. Wong¹, S. Alexander¹, P. Grimm¹, W. Concepcion³, O. Salvatierra^{1,3,*}, and M.M. Sarwal^{1,*}

¹Dept. of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305, USA

²Dept. of Pathology, Stanford University School of Medicine, Stanford, CA 94305, USA

³Dept. of Surgery, Stanford University School of Medicine, Stanford, CA 94305, USA

Abstract

Despite early promising patient and graft outcomes with steroid-free (SF) immunosuppression in pediatric kidney transplant recipients, data on long term safety and efficacy results are lacking. We present our single center experience with 129 consecutive pediatric kidney transplant recipients on SF immunosuppression, with a mean follow-up of 5 years. Outcomes are compared against a matched cohort of 57 concurrent recipients treated with steroid-based (SB) immunosuppression. In the SF group, 87% of kidney recipients with functioning grafts remain corticosteroid-free. Actual intent-to-treat SF (ITT-SF) and still-on-protocol SF patient survivals are 96% and 96% respectively; actual graft survivals for both groups are 93% and 96% respectively; and actual death-censored graft survivals for both groups are 97% and 99% respectively. Unprecedented catch up growth is observed in SF recipients below 12 years of age. Continued low rates of acute rejection, post-transplant diabetes mellitus, hypertension, and hyperlipidemia are seen in SF patients, with sustained benefits for graft function. In conclusion, extended enrollment and longer experience with SF immunosuppression for renal transplantation in low risk children confirms protocol safety, continued benefits for growth and graft function, low acute rejection rates and reduced cardiovascular morbidity.

Keywords

Pediatrics; Kidney transplantation; Steroid-free

INTRODUCTION

Chronic corticosteroid usage, a cornerstone drug for the last five decades in organ transplantation (1), is a major cause of morbidity, ranging from cardiovascular disease, hyperlipidemia, hypertension, cataracts, osteoporosis, weight gain, acne, diabetes mellitus, to bacterial and viral infections. Many of the steroid related cosmetic side effects drive immunosuppression non-adherence, a particular problem in adolescence (2). Additionally, the suppressive effect of chronic, even low dose steroids, on growth velocity in children is a critical concern (3,4). Steroid withdrawal has been attempted in various protocols over the last decade, and though successful in selected patients (5), can result in unacceptably high

Corresponding Authors: Minnie Sarwal, MD, MRCP, Ph.D., G306, 300 Pasteur Drive, Stanford University School of Medicine, Stanford, CA 94305 USA, msarwal@stanford.edu, Phone: (650)723-4517, Fax: (650)498-6762, Salvatierra Oscar, MD., 703 Welch Rd., H2, Stanford University School of Medicine, Stanford, CA 94305 USA, oscars@stanford.edu, Phone: (650)498-5481.

rates of acute rejection and even graft loss (6–10). Steroid minimization does not always eliminate all steroid-related side effects (11–13), which has led to an interest in developing protocols to avoid maintenance steroids in renal transplantation, under the umbrella of more powerful immunosuppressive agents for induction and maintenance therapy (14–18).

Recent single center, non-randomized studies from both the pediatric and adult experience with steroid avoidance have demonstrated reduced morbidity from cosmetic and hemodynamic steroid side effects, reduced viral infection (19), as well as potential benefits for graft function and acute rejection (4,20–30), but these results need to be re-evaluated after the completion of randomized controlled trials. These reported experiences in renal transplantation with steroid avoidance span 5 years in adult renal patients (23,27); and 2 years in pediatric renal patients (24). In this analysis, we present extended enrollment and follow-up of 129 consecutive pediatric and infant recipients treated at a single center since November of 1999. Important questions addressed in this study were: selected comparisons with a concurrent matched steroid-based cohort, long-term tolerability of the steroid avoidance protocol, early and late acute rejection rates, cardiovascular risk factors, growth benefits, graft function, and patient and graft survival.

MATERIALS AND METHODS

Patients

This study reports on a single-center experience for all 129 low immunologic risk (<20% peak panel reacting antibody or PRA) pediatric (0–21 years of age) recipients of a primary kidney allograft at Stanford University transplanted between November 1999 and November 2007, on the Stanford steroid-free (SF) immunosuppression protocol. This previously reported protocol (4) utilizes tacrolimus, mycophenolate mofetil (MMF) and extended Daclizumab induction for 6 months for a total 10mg/kg versus 5 mg/kg for the standard 8 weeks Daclizumab induction used in the steroid-based (SB) comparative group (Fig.1). Extended Daclizumab induction in this protocol is governed by an IND (BB-IND-10127 held by MS until 2004 and since then, by the NIAID at the NIH, when this SF protocol was subsequently tested in an NIH funded randomized multicenter study (SNSO1). Patients have a mean follow-up of 5 years (range from 0.8 to 8.8 years). Patient numbers with complete follow-up at 1, 3, 5, 7, and 8 years are respectively 125, 96, 70, 48, and 29. The first 20 SF patients were maintained on higher tacrolimus target trough levels in the first post-transplant week (17–20ng/mL) and higher dosages of MMF (600mg/m²/dose, twice daily; without drug levels). With early protocol safety, tacrolimus targets were lowered (12–14ng/mL for the first week post-transplantation) and MMF dose has been reduced by 50% to 300mg/m²/dose twice daily (24) (31). In case of MMF intolerance (gastrointestinal or bone marrow suppression) within the first 6 months post-transplant, MMF was temporarily replaced by azathioprine (Imuran®, GlaxoSmithKline) and patients were re-challenged with MMF prior to 6 months. Continued MMF intolerance after 6 months, resulted in MMF being replaced by sirolimus (Rapamycin®, Wyeth® SRL). Sirolimus maintenance dose was 2–8mg/day depended on patient weight and achievement of trough level of 5–8 ng/dL for the first year post-transplantation and 3–5 ng/dL the year after. Overall, 15% patients are on tacrolimus and sirolimus maintenance therapy and selected data sub-analyses have been performed for this patient group.

SF recipients were compared with a matched control group (for recipient gender, age, race, and cause of end-stage renal disease, height, weight, donor source, and donor age) of 57 unsensitized recipients of primary transplants, treated with a steroid-based (SB) immunosuppressive protocol utilizing Daclizumab induction for 2 months, tacrolimus and MMF (Table 1). SB patients were those who either did not consent to SF immunosuppression, or those who came to transplantation on low dose steroids for their

primary disease. The incidence of glomerulonephritis (41/129 or 32% in SF vs. 20/57 or 35% in SB) and FSGS (3/57 or 5.3% in SB vs. 7/129 or 5.4% in SF) are equivalent in the both treatment groups. In order to maximize the quality of the control group, the following selection criteria were also included: 1) As the SF protocol started in November of 1999, all SB patients in the control group were selected, on the basis of having received their transplant after this date, concomitant with the start of the SF protocol, making this concurrently transplanted group of patients; 2) peak PRA < 20%, similar to the SF group; 3) primary kidney transplant recipients, similar to the SF group; 4) 100% 1 year graft survival; 5) homogeneity of immunosuppression usage with all patients on tacrolimus, MMF and Daclizumab induction, with the exception that the latter induction utilized the standard 2 month dosing regimen. Within the SB group 57 patients were enrolled with a mean group follow-up of 67 months. Prednisone 10 mg/kg was given peri-operatively followed by 2 mg/kg/day in subjects weighing <40 kg and 1.5 mg/kg/day in subjects weighing >40 kg. The steroid dosing was tapered as follows: by the end of weeks 1, 2, 4, 6, 12, and 16, dosages were 0.5, 0.4, 0.3, 0.2, 0.15, and 0.1 mg/kg/day respectively. There were similar proportions of children ≤ 6 years of age in both groups as recipients of an adult sized kidney (29% in SF and 19% in SB, $p=0.30$).

All SF and SB patients had protocol biopsies at 3, 6, 12, and 24 months after transplantation, and for graft dysfunction. All rejection episodes were biopsy proven and graded by the Banff classification (32). Clinical acute cellular rejection was treated with 3 pulses of intravenous corticosteroid (10mg/kg) with the immediate return to SF maintenance therapy. Vascular rejection was treated with thymoglobulin with steroid premedication (1mg/kg/dose) and consideration of breaking protocol to a SB regimen (24). Subclinical borderline Banff grade rejection was treated with immunosuppression intensification without steroid pulsing. Steroids were introduced as maintenance immunosuppression if a rejection episode recurred within 3 months.

Graft function assessment was based on calculated creatinine clearance by the Schwartz formula (33,34). Height was measured in cm and presented as Z scores (mean height standard deviation scores; mean height SDS), with normative data used for growth from the Center for Disease Control (CDC). Weight was measured in kg and body mass index (BMI) was calculated. Hypertension was defined as present if there was requirement of anti-hypertensive agents for clinical blood pressure control. Hypertriglyceridemia was defined as fasting serum triglyceride levels >140 mg/dl, hypercholesterolemia as fasting serum cholesterol levels >190 mg/dl, and diabetes mellitus as hyperglycemia (fasting plasma glucose > 126 mg/dl, based on the definition used by the American Diabetes Association), requiring treatment with either insulin or hypoglycemia agents. Hospitalizations were captured, with cause. This study was approved by the Institutional Review Board at Stanford University. To determine the effects of SF on nonspecific chronic tubulointerstitial damage, all protocol biopsies performed at one and two years post transplantation were reviewed blindly by the same single pathologist. The extent of interstitial fibrosis/tubular atrophy (IF/TA) was scored on a scale of 0–3 based on the Banff criteria (32) (35).

Statistical Analysis

T test, chi square test, Fisher exact, and ANOVA were used for analysis of continuous or categorical types of data. Linear mixed-effects models were used for evaluation of repeated measures for clinical outcomes comparison such as by adjusting time points categorical variables. For the binary outcomes we used repeated measures Generalized Estimating Equations (GEE) model by adjusting time points categorical variables. Graft and patient death-censored survival analysis were based on Kaplan-Meier survival analysis and chi-square analysis. We used an eGFR based on the Schwartz equation (33,34) of < 10, or return to dialysis as an estimate of graft loss. Cox proportional hazard models were used to analyze

hazard ratios by adjusting patient demographical variables for AR. Multivariate analysis and Pearson/Spearman correlation were used for examining relationship for all parametric or non-parametric variables. Multiple regression and logistic regression models were used to test associations with confounding clinical parameters. P-values ≤ 0.05 were considered statistically significant. Results are reported as mean $\pm$ standard deviation. All statistical analyses were performed using the SAS 9.1.3 (SAS Institute Inc., Cary, NC).

RESULTS

SF Protocol Breaks

At mean follow-up of 5 years after transplantation, 87% of 129 SF patients remain steroid-free. Protocol breaks to steroid-based maintenance therapy occurred in a total of 17 patients, with early breaks in 6 patients between 0–6 months and late breaks in 11 patients, between 6 months to 36 months post-transplantation. Causes for early protocol break were refractory AR (n=3) and recurrent glomerulonephritis (n=3). Causes for late protocol break were refractory AR (n=6), recurrent glomerulonephritis (n=3), PTLN (n=1), and *de novo* reactive arthritis (n=1) (24); these cases have been discussed in detail in a separate manuscript from our group (Sutherland S., *et al*, under review).

Patient and Graft Survival

Actual patient survival at the current follow-up was equivalent: 96% in ITT-SF patient, 96% in patients maintained on the SF protocol, and 98% in SB patients ($p=0.42$ for ITT-SF versus SB and $p=0.51$ for still on SF versus SB). Four patients in the SF group died (3 in 2005 and 1 in 2002) with functioning grafts (mean serum creatinine for the group at the time of death was 0.8 mg/dl). The causes of death were: bacterial sepsis in a patient with an indwelling intravenous line; pre-transplant diagnosis of severe combined immunodeficiency syndrome; hemophagocytic lymphohistiocytosis; and accidental narcotic drug overdose. One patient died with a functioning graft in the SB group due to recurrent Wilm's tumor. Multivariate analysis was conducted for patient and graft survival across multiple clinical factors (immunosuppression protocol, donor age, donor source, cause of ESRD, recipient age, and recipient gender), using a logistic regression model. There was no significant correlation of any of these confounders with graft or patient survival. Actual graft survival at current follow-up is 93% for all ITT-SF patients, 96% in patients still maintained on the SF protocol, and 91% in SB patients (no differences in graft survival comparisons for on-treatment SF, ITT-SF and SB groups; Figure 2a and Figure 2b). The incidence of death-censored graft survival was better in the still-on-protocol SF versus SB patients (99% versus 93%; $p=0.026$), but not different when ITT-SF death-censored graft survival was compared with SB survival (97% versus 93%; $p=0.25$). The Kaplan Meier survival analysis of these patient groups shows a similar significance for still-on-protocol SF (Figure 2c; $p=0.02$), but no difference for ITT-SF ($p=0.40$). There has been only one re-transplantation in the SF group and this was because of progressive graft injury from drug nephrotoxicity. The patient received a preemptive second transplant from a parent at 8 years following the initial transplant. Despite a non-significant difference in living donor percentage between SF and SB groups (79% vs. 68%) there was no negative impact on graft outcomes in the SB group, based on donor source, as only 1 graft loss in SB group occurred in a patient receiving a kidney from a deceased donor. Also, even though there was an equal incidence of FSGS as a cause of ESRD in both groups, there was no graft loss or patient death due to recurrence of FSGS in either group.

Acute Rejection (AR)

Clinical acute rejection—The incidence of clinical AR in the first post-transplant year did not have any significant difference in patients ITT-SF (12%) versus on SB treatment

(12%) ($p=0.98$) or maintained on SF (7%) versus on SB treatment with $p=0.33$ (Figure 2d); however, the overall incidence of clinical AR at study follow-up (mean of 5 years) was low in an ITT-SF (16%), and also low in patients maintained on SF (11%) (Figure 2d). There was no difference in the mean time to first acute rejection (14 ± 13 months in either maintained on SF or 12 ± 12 months on ITT-SF versus 26 ± 29 months in SB; $p=0.2$ or $p=0.12$), rejection free survival was excellent for the SF group at current follow-up (log rank $p=0.06$, Figure 2e). Multivariate analysis of the characteristics of patients (cause of ESRD, recipient age, donor age, and donor source) using a Cox proportional hazard model showed that the incidence of clinical AR did not associate with any of these adjusting clinical parameters.

Late clinical AR was defined as an acute rejection episode that occurred after the first year post-transplantation. There was a low rate of late AR in SF patients at 4% with a rate of 12% for SB. When stratified by years' post-transplantation, the incidence of late AR (≥ 2 years) in an ITT-SF was 3%, and 10 % in SB (Figure 2d). The mean time for late AR in ITT-SF patient (28 ± 10 months) versus SB (47 ± 29 months) was similar with $p=0.17$, and maintained on SF versus SB was similar (30 ± 8 months) with $p=0.3$.

Sub-clinical acute rejection—Ten percent of ITT-SF patients and 4% of SB patients had sub-clinical AR. There was no difference in the incidence of sub-clinical acute rejection in SF patients based on protocol biopsies alone. Simultaneous with the reduction of maintenance target tacrolimus trough levels (24) (31), the incidence of sub-clinical AR episodes increased (0.75 sub-clinical rejections per year prior to 2002, and 2 sub-clinical rejections per year after 2003).

Graft Function

Graft function, as measured by the Schwartz calculated creatinine clearance in ml/min/1.73m^2 (33,34), was significantly higher at all measured annual time points in the ITT-SF versus the SB group ($F=28.9$, mixed model group effect $p<0.0001$, Figure 3a), regardless of recipient age ($F=17.9$, mixed model group effect $p=0.0001$; Figure 3b). Using a multiple regression model by adjusting clinical AR episodes, donor age, anti-hypertensive agents, serum triglyceride levels, and serum cholesterol levels, the graft function benefit in the SF cohort at 1 year post-transplantation strongly correlates with a lower number of anti-hypertensive agents ($p=0.04$), lower serum triglyceride levels ($p=0.07$), and fewer clinical AR episodes ($p=0.03$) (model $F=4.79$, $p=0.0002$).

Growth

SF recipients ≤ 6 years of age were enrolled in 2001, after safety data was evaluated for the first 10 older children (6–21 years; (4)), thus growth analysis is reported over a 6 years so as to include all age groups. Catch up linear growth trends, represented by Z scores (mean height standard deviation score [SDS]) (Figure 4), were highly significant in the youngest recipients in still-on protocol SF ($n=112$) versus SB immunosuppression ($F=2.8$, mixed model $p=0.01$) (Figure 4a). After 4 years post-transplantation, the youngest SF children show unprecedented catch up growth rates, *greater* than the growth velocity in normal healthy age and gender matched controls (from the CDC). Height benefits were also seen for SF children 6–12 years of age, over the first 6 years post-transplantation ($F=2.9$, mixed model $p=0.01$; Figure 4b). Children ≥ 12 years of age at the time of transplantation, on SF treatment or ITT-SF, demonstrated improved growth trends, which do not reach significance in this study. When comparative growth analysis was performed for the ITT-SF ($n=129$) versus the SB group, all significant differences in growth data persist for the SF group.

Cardiovascular Risk Factors

Diabetes mellitus—The incidence of post-transplant diabetes was lower in the SF group: 0.8% versus 9%; $p=0.0089$). Two African American patients, who were originally on SF immunosuppression, developed PTDM only after breaking to steroid-based maintenance therapy for recurrent rejection in one and recurrence of immunologic disease (Reiter's arthritis) in the other.

Hypertension and Hyperlipidemia—SF patients, maintained on the protocol, had significantly lower requirement for anti-hypertensive agents at all time points post-transplantation (Chi-square=19.86, GEE model group effect $p<0.0001$); with a significantly higher prevalence in SB patients (Table 2). Serum triglyceride levels were also statistically lower in on-protocol SF patients ($F=8.7$, mixed model group effect $p=0.0038$) (Table 2). Irrespective of sirolimus maintenance therapy in 17 SF patients, and the fact that at baseline, SF patients happened to have statistically higher serum cholesterol levels (Table 1), significantly lower serum cholesterol levels were seen in SF patients comparing to SB patients at all time points measured ($F=4.9$, $p=0.0285$) (Table 2). There was a similar incidence of hyperlipidemia in SF patients on tacrolimus and rapamycin (45%) at 1 year post-transplantation when compared to SB patients who were on tacrolimus, MMF, and steroids (40%). In the SF group, hyperlipidemia was mild, even with sirolimus therapy and required treatment with lipid lowering agents in only 2% of SF patients (all on sirolimus), whereas 80% of the SB patients had hyperlipidemia (in the absence of sirolimus maintenance therapy).

Body mass index—SF patients showed smaller changes in BMI after transplantation, compared to SB, but significant changes occurred only in the first 2 years post-transplantation (Δ BMI at 1 year 1.5 ± 3.5 in SF versus 3.3 ± 3.7 kg/m² in SB; $p=0.0034$, and Δ BMI at 2 years 1.6 ± 6.1 in SF versus 3.8 ± 3.9 kg/m² in SB; $p=0.02$). Approximately 20% of patients were overweight (BMI > 25 kg/m²) in SF arm and 30% in SB arm at 1 and 2 years of follow-up, and approximately 10% were obese (BMI > 30 kg/m²) patients in both arms at 1 and 2 years of follow-up.

Bone Marrow Suppression

In the first year post-transplantation, 18% of SF patients required usage of granulocyte colony-stimulating factor (GCSF) to support their white blood cell counts (WBC) within the normal range ($4.0\text{--}11.0 \times 10^9/\text{L}$), while SB patients maintained their WBC counts without GCSF requirement ($p=0.0025$). Most of the SF patients (82%) who required GCSF were transplanted earlier in the study, prior to 2002, when higher doses of MMF were used in the protocol (24). When stratifying the effect of higher MMF usage on bone marrow suppression in the first 20 patients (receiving 1200 mg/m²/day MMF) versus the last 20 patients enrolled (receiving 600 mg/m²/day MMF) with at least one year follow-up, there was less GCSF usage (60% versus 8%; $p=0.004$), with similar WBC counts (7.4 ± 2.7 in the first 20 versus $7.4\pm1.9 \times 10^9/\text{L}$ in the last 20; $p=0.98$) when lower MMF doses were used. The hematocrit was higher in SF group in the first post-transplant year ($37\% \pm 5\%$ versus $34\% \pm 4\%$; $p<0.0001$), without more erythropoietin (EPO) usage in SF patients early post-transplantation (25% versus 18%; $p=0.34$). After 2 years post-transplant, there were no significant differences in HCT, WBC counts, EPO and GCSF usage.

Infection

There was no increased incidence of bacterial infections or hospitalizations in the SF group (32% in SB versus 36% in SF, $p=0.6$). Subclinical EBV viremia, measured by peripheral blood quantitative PCR, was detected in 22% of SF patients and 57% of SB patients

($p < 0.05$), but there were no differences in the incidence of subclinical CMV viremia (12% in SF versus 17% in SB; $p = 0.1$). We have previously reported on the time to detection of subclinical EBV and CMV viremia and its clinical impact in SF and SB patients (19). There was a low incidence of CMV disease (2 SF patients versus 1 SB patient), 1 nodal PTLN in SF and 4 nodal PTLN in SB ($p = 0.17$), and 2 SF patients were diagnosed with BK nephritis.

Protocol biopsy results and incidence of chronic graft injury

Within the SF group, 76 protocol biopsies at one year and 47 biopsies at two years were reviewed and compared with the SB group with 34 biopsies at one year and 17 biopsies at 2 years. The IF/TA score in all the groups ranged from 0–3 and there was no significant difference in the IF/TA score between the two immunosuppression groups either at one ($p = 0.1$) or two years post transplantation ($p = 0.46$).

DISCUSSION

We have herein reported on an extended experience with SF immunosuppression in pediatric renal transplantation. This single center study provides the largest experience and the longest outcome data following transplantation without any planned steroids in children. Eighty-seven percent of patients were able to be maintained on SF immunosuppression at a mean of 5 years (0.8–8.8 years) of study follow-up. The most important observation of this study is that steroid- avoidance with maintenance tacrolimus and MMF, and extended induction with Daclizumab for 6 months, is safe, without increased risk of infections and malignancies, and is effective, with an increased tendency to stay rejection-free, slower decline in graft function and potentially improved long-term graft survival. Additional long term benefits of dramatic catch-up growth trends are seen in young children, supporting the transplantation of children with renal failure before 12 years of age, accompanied by simultaneous avoidance of maintenance steroids. The important benefits of steroid avoidance on mitigating diabetes and cardiovascular risk factors are also appreciated.

An unexpected initial finding of this study, which persists on longer follow-up, is that the occurrence of acute clinical rejections was low in the milieu of complete steroid avoidance, with no planned pre-, intra- or post-operative steroid exposure. In the NAPRTCS 2007 report data (36), where data was collected on pediatric renal transplant outcomes between 2001 to 2006, the clinical acute rejection rate is 20.7% for deceased donor recipients and 24.7% for living donor recipients. The low immunological risk with this protocol may relate to many reasons. Low acute rejection rates have also been reported in the adult renal transplant experience from Matas et al (27), where steroids were rapidly discontinued by the 6th post-operative day and in the CARMEN study (37) where there was complete steroid avoidance. Some studies employing steroid discontinuation many months after transplantation have reported a higher incidence of acute rejection (7,8). It has been hypothesized that as steroids suppress the release of many cytokines (38,39) and may inhibit peripheral tolerance via a Fas-dependant mechanism (40), continuation of steroids months after transplantation may result in “steroid dependency”, with an increased incidence of acute rejection on late steroid withdrawal. The FREEDOM (41) study, on the other hand, utilizing early steroid discontinuation or avoidance in adult renal transplantation, reports higher rejection rates with 2 doses of Basiliximab induction and cyclosporine based maintenance immunosuppression, suggesting that effective induction and maintenance immunosuppression are both important for successful steroid avoidance. In addition, a recent randomized double blind trial of early steroid cessation also shows the biopsy confirmed AR approached significance for steroid withdrawal comparing with chronic steroid therapy (42). Secondly, our study is restricted to low-risk, unsensitized recipients (PRA < 20%), with the vast majority (69%) receiving living donor organs, while the deceased donors generally accepted at Stanford have short cold ischemia times (< 18 hours).

Additionally, only 6% of SF recipients were African-American. We wish to emphasize that comparisons regarding acute rejection rates were conducted with a steroid-based group of similarly low immunologic profile. Thirdly, the low acute rejection rate in this study may be due to the immunosuppression combination employed by the protocol: dual maintenance immunosuppression, rather than monotherapy (43), which is tacrolimus based (27,44,45), and employs a novel prolonged IL-2 receptor blockade. The extended Daclizumab usage in this protocol is likely a critical anchor in providing good immunologic protection at antigen presentation and the ensuring early months following transplantation. We and others have previously shown that the double pre-transplant dose of 2 mg/kg provides serum Daclizumab levels of > 5 mcg/ml in all recipients ages (4,24,46), which may be crucial for suppressing IL2 dependant proliferative responses, independent of the saturation of the IL2-receptor (47). Finally, SF patients have a lower rate of CMV and EBV sub-clinical viremia (19), which could also reduce the immunologic risk of acute rejection.

The Canadian multi center transplant study groups have expressed some concern for late allograft loss (22) with steroid avoidance, but the immunosuppression protocols in the study group vary considerably from the one used in this study. In an analysis of the subclinical histological evolution of the protocol biopsies, without any subclinical or clinical acute rejection, performed within the SF group, we reported on a significant increase in chronic tubulo-interstitial injury in the first 2 years after transplantation unrelated to rejection (48). Donor organ-recipient size discrepancy appeared to be the most important determinant of this chronic tubulo-interstitial damage, even in the absence of acute rejection. Comparisons of chronic graft injury scores between the SF and the SB group in this study showed a progressive increase in chronicity, but there were no differences in the incidence or extent of chronic graft injury in the 2 protocol groups. As the pathologist was blinded with regards to patient steroid usage, this analysis suggests that, rather than use or avoidance of steroids, other factors such as maintenance therapy with a calcineurin inhibitor, may be driving the progression of chronic graft injury after transplantation. The low rates of late acute rejection argue against increased long-term graft damage by the omission of steroids from the immunosuppressive protocol. This hypothesis appears to be validated in the comparative benefit for graft function and projected long-term graft survival for the SF over the SB groups. In addition, the mitigation of cardiovascular risk factors, such as hypertension, hyperlipidemia and diabetes in the SF group, will likely result in long-term patient benefits and also contribute to some observed long-term graft survival benefits. Notable amongst these, is the continued excellent overall graft function during the extended period of follow-up, showing that the steroid avoidance protocol is safe after discontinuation of immunologic support from the extended Daclizumab induction. Importantly, the hyperlipidemia in the SF recipients was mild, even when the protocol utilized sirolimus maintenance therapy, whereas concomitant administration of sirolimus and steroids often resulted in significant hyperlipidemia in SB patients, even with low dose maintenance steroids of 0.05–0.1 mg/kg/day. Similarly, the diabetogenic effect of tacrolimus and other patient risk factors such as race may be greatly accentuated by concomitant steroid exposure. Thus the patient tolerability of both tacrolimus and sirolimus may be improved in steroid-avoidance protocols.

An important patient benefit from this study is the demonstration of significant catch-up growth potential in children 1–12 years of age, after successful transplantation, previously masked by chronic steroid usage. We now observe that children from 1–6 years of age at the time of transplantation, in particular, start to show catch-up growth rates, even greater than their age and gender matched peers. This signals that with steroid avoidance regimes, young children may be able to realize their final adult growth potential, but this would be influenced by the residual effects of uremia in childhood prior to transplantation. This catch up growth benefit has not been previously reported in any other pediatric transplant study on

steroid minimization. The absence of steroids is also important to realize the post-pubertal growth potential in children transplanted at 6–12 years of age. However, children with renal transplantation over the age of 12 years, with sometimes important and long-standing growth failure from longer duration of chronic renal insufficiency prior to transplantation, do not show the same significant growth benefits as children from 1–12 years of age. Thus preemptive transplantation in young children and infants prior to the age of 12, and avoiding steroids after transplantation, may provide the best window of opportunity to achieve full growth potential in children.

The early SF immunosuppressive protocol experience induced more bone marrow suppression than the SB protocol which was likely related to the fact that in this phase of the protocol, higher MMF doses were used. In addition, the use of corticosteroids leads to leucocyte demargination, which could mask the effect of MMF use on the bone marrow. MMF doses are better tolerated at lower doses in SF patients, and can likely be safely lowered, as seen in this study, perhaps because of previously reported increased bioavailability of MMF in the absence of steroids has been previously reported (49).

A limitation of this study is that it is a single-center, non-randomized analysis on a selected group of patients with low sensitization risk. Recognizing this and to assure as best as possible, a robust control group, all control patients were required to have a functioning graft at 1 year post-transplantation. Our study benefits from being protocolized by a small and consistent physician group. As the early results of the study were encouraging (4,24), the protocol was rapidly accepted as standard of care at our center and randomization could not be done. However, the protocol was adopted as part of a multicenter US and Canadian NIH funded study (SNSO1), including 130 patients randomized to the Stanford SF protocol with extended Daclizumab induction versus “classic” SB immunosuppression with standard 2 months Daclizumab induction. Both arms were maintained on long-term tacrolimus and MMF therapy. We await the future report of the results of this study, which will also provide direct comparison of clinical results and chronic graft injury scores from protocol biopsies in both the SF and SB cohorts.

The adult renal transplant experience has also reported successful prednisone-free maintenance immunosuppression in higher-risk groups—for example, African- Americans, those with high PRA levels and those with DGF (50) (51), suggesting that steroid elimination may possibly be applicable to most pediatric recipient groups. However, additional study with larger numbers of African-American and deceased donor recipients, as well as repeat transplants, are necessary to test extension of this protocol to all pediatric recipient groups. The SNSO1 study will also be able to address this issue as it incorporates a larger number of African-American and deceased donors.

In summary, this study demonstrates the safety of using a SF immunosuppressive regimen for kidney transplantation in low-risk pediatric recipients. This protocol demonstrates that the incidence of acute rejection is no higher than that seen in steroid-based protocols. Steroid avoidance appears to result in a growth advantage in recipients less than 12 years of age at time of transplantation. In addition, there appears to be a mitigation of hypertension, hyperlipidemia, post-transplant diabetes and subclinical CMV and EBV viremia, which may be critical in driving excellent graft function observed in the SF patients. The apparent diminution of steroid-related side effects, in combination with a low acute rejection rate and good graft survival, suggest that transplant programs could consider eliminating steroids from immunosuppressive protocols for low-risk pediatric recipients.

Acknowledgments

We are grateful to the help from our pediatric transplant nephrology team, especially Dr. Scott Sutherland, Dr. Lauren Weintraub, the transplant nephrology fellows, and for the invaluable and persisting efforts of all people involved in the pediatric kidney transplant program at Stanford University, namely, the clinicians, renal nurses, transplant coordinators, children and their families.

Funding Sources: NIAID (R01 AI61739)

Abbreviations

AR	Acute Rejection
BMI	Body Mass Index
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
EPO	Erythropoietin
ESRD	End-Stage Renal Disease
FK	Tacrolimus
GCSF	Granulocyte Colony Stimulating Factor
ITT-SF	Intent-to-treat steroid free
MMF	Mycophenolate Mofetil
NAPRTCS	North American Renal Transplant Cooperative Study
SDS	Standard Deviation Scores

REFERENCES

1. Delucchi A, Valenzuela M, Ferrario M, Lillo AM, Guerrero JL, Rodriguez E, et al. Early steroid withdrawal in pediatric renal transplant on newer immunosuppressive drugs. *Pediatr Transplant*. 2007; 11(7):743–748. [PubMed: 17910651]
2. Shaw RJ, Palmer L, Blasey C, Sarwal M. A typology of non-adherence in pediatric renal transplant recipients. *Pediatr Transplant*. 2003; 7(6):489–493. [PubMed: 14870900]
3. Vidhun JR, Sarwal MM. Corticosteroid avoidance in pediatric renal transplantation. *Pediatr Nephrol*. 2005; 20(3):418–426. [PubMed: 15690189]
4. Sarwal MM, Yorgin PD, Alexander S, Millan MT, Belson A, Belanger N, et al. Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. *Transplantation*. 2001; 72(1):13–21. [PubMed: 11468528]
5. Tonshoff B, Hocker B, Weber LT. Steroid withdrawal in pediatric and adult renal transplant recipients. *Pediatr Nephrol*. 2005; 20(3):409–417. [PubMed: 15650883]
6. Starzl TE, Marchioro TL, Terasaki PI, Porter KA, Faris TD, Herrmann TJ, et al. Chronic survival after human renal homotransplantation. Lymphocyte-antigen matching, pathology and influence of thymectomy. *Ann Surg*. 1965; 162(4):749–787. [PubMed: 5319400]
7. Hricik DE, O'Toole MA, Schulak JA, Herson J. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. *J Am Soc Nephrol*. 1993; 4(6):1300–1305. [PubMed: 8130356]
8. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol*. 2000; 11(10):1910–1917. [PubMed: 11004223]
9. Ahsan N, Hricik D, Matas A, Rose S, Tomlanovich S, Wilkinson A, et al. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil--a prospective randomized study. Steroid Withdrawal Study Group. *Transplantation*. 1999; 68(12):1865–1874. [PubMed: 10628766]

10. Pascual J, Quereda C, Zamora J, Hernandez D. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. *Transplantation*. 2004; 78(10):1548–1556. [PubMed: 15599321]
11. Lo Cascio V, Bonucci E, Imbimbo B, Ballanti P, Tartarotti D, Galvanini G, et al. Bone loss after glucocorticoid therapy. *Calcif Tissue Int*. 1984; 36(4):435–438. [PubMed: 6435841]
12. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med*. 1993; 119(10):963–968. [PubMed: 8105737]
13. Rueggsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. *European journal of clinical pharmacology*. 1983; 25(5):615–620. [PubMed: 6662161]
14. Starzl TE. FK 506 versus cyclosporine. *Transplant Proc*. 1993; 25(1 Pt 1):511–512. [PubMed: 7679820]
15. The U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med*. 1994; 331(17):1110–1115. [PubMed: 7523946]
16. Khwaja K, Asolati M, Harmon JV, Melancon JK, Dunn TB, Gillingham KJ, et al. Rapid discontinuation of prednisone in higher-risk kidney transplant recipients. *Transplantation*. 2004; 78(9):1397–1399. [PubMed: 15548981]
17. Garcia R, Pinheiro-Machado PG, Felipe CR, Park SI, Silva LA, Franco MF, et al. Conversion from azathioprine to mycophenolate mofetil followed by calcineurin inhibitor minimization or elimination in patients with chronic allograft dysfunction. *Transplant Proc*. 2006; 38(9):2872–2878. [PubMed: 17112853]
18. Sollinger HW U.S. Renal Transplant Mycophenolate Mofetil Study Group Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 1995; 60(3):225–232 [PubMed: 7645033]
19. Li L, Chaudhuri A, Weintraub LA, Hsieh F, Shah S, Alexander S, et al. Subclinical cytomegalovirus and Epstein-Barr virus viremia are associated with adverse outcomes in pediatric renal transplantation. *Pediatr Transplant*. 2007; 11(2):187–195. [PubMed: 17300499]
20. Birkeland SA. Steroid-free immunosuppression after kidney transplantation with antithymocyte globulin induction and cyclosporine and mycophenolate mofetil maintenance therapy. *Transplantation*. 1998; 66(9):1207–1210. [PubMed: 9825819]
21. Birkeland SA. Steroid-free immunosuppression in renal transplantation: a long-term follow-up of 100 consecutive patients. *Transplantation*. 2001; 71(8):1089–1090. [PubMed: 11374407]
22. Cole E, Landsberg D, Russell D, Zaltzman J, Kiberd B, Caravaggio C, et al. A pilot study of steroid-free immunosuppression in the prevention of acute rejection in renal allograft recipients. *Transplantation*. 2001; 72(5):845–850. [PubMed: 11571448]
23. Khwaja K, Asolati M, Harmon J, Melancon JK, Dunn T, Gillingham K, et al. Outcome at 3 years with a prednisone-free maintenance regimen: a single-center experience with 349 kidney transplant recipients. *Am J Transplant*. 2004; 4(6):980–987. [PubMed: 15147433]
24. Sarwal MM, Vidhun JR, Alexander SR, Satterwhite T, Millan M, Salvatierra O Jr. 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(9):1331–1339. [PubMed: 14627912]
25. ter Meulen CG, van Riemsdijk I, Hene RJ, Christiaans MH, Borm GF, van Gelder T, et al. Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor alpha therapy: a prospective, randomized, multicenter study. *Am J Transplant*. 2004; 4(5):803–810. [PubMed: 15084178]
26. Kandaswamy R, Melancon JK, Dunn T, Tan M, Casingal V, Humar A, et al. A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients--an interim analysis. *Am J Transplant*. 2005; 5(6):1529–1536. [PubMed: 15888064]
27. Matas AJ, Kandaswamy R, Gillingham KJ, McHugh L, Ibrahim H, Kasiske B, et al. Prednisone-free maintenance immunosuppression-a 5-year experience. *Am J Transplant*. 2005; 5(10):2473–2478. [PubMed: 16162197]

28. Woodle ES, Alloway RR, Buell JF, Alexander JW, Munda R, Roy-Chaudhury P, et al. Multivariate analysis of risk factors for acute rejection in early corticosteroid cessation regimens under modern immunosuppression. *Am J Transplant.* 2005; 5(11):2740–2744. [PubMed: 16212635]
29. Kumar MS, Heifets M, Moritz MJ, Saeed MI, Khan SM, Fyfe B, et al. Safety and efficacy of steroid withdrawal two days after kidney transplantation: analysis of results at three years. *Transplantation.* 2006; 81(6):832–839. [PubMed: 16570004]
30. Rajab A, Pelletier RP, Henry ML, Ferguson RM. Excellent clinical outcomes in primary kidney transplant recipients treated with steroid-free maintenance immunosuppression. *Clin Transplant.* 2006; 20(5):537–546. [PubMed: 16968478]
31. Naesens M, Salvatierra O, Li L, Kambham N, Concepcion W, Sarwal M. Maturation of dose-corrected tacrolimus predose trough levels in pediatric kidney allograft recipients. *Transplantation.* 2008; 85(8):1139–1145. [PubMed: 18431234]
32. Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int.* 1999; 55(2):713–723. [PubMed: 9987096]
33. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J Pediatr.* 1984; 104(6):849–854. [PubMed: 6726515]
34. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr.* 1985; 106(3):522–526. [PubMed: 3973793]
35. Solez K, Colvin RB, Racusen LC, Sis B, Halloran PF, Birk PE, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant.* 2007; 7(3):518–526. [PubMed: 17352710]
36. NAPRTCS. NAPRTCS 2007 Annual Report. 2007
37. Rostaing L, Cantarovich D, Mourad G, Budde K, Rigotti P, Mariat C, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation.* 2005; 79(7):807–814. [PubMed: 15818323]
38. Almawi WY, Melemedjian OK, Rieder MJ. An alternate mechanism of glucocorticoid anti-proliferative effect: promotion of a Th2 cytokine-secreting profile. *Clin Transplant.* 1999; 13(5): 365–374. [PubMed: 10515216]
39. Satterwhite T, Chua MS, Hsieh SC, Chang S, Scandling J, Salvatierra O, et al. Increased expression of cytotoxic effector molecules: different interpretations for steroid-based and steroid-free immunosuppression. *Pediatr Transplant.* 2003; 7(1):53–58. [PubMed: 12581329]
40. Baumann S, Dostert A, Novac N, Bauer A, Schmid W, Fas SC, et al. Glucocorticoids inhibit activation-induced cell death (AICD) via direct DNA-dependent repression of the CD95 ligand gene by a glucocorticoid receptor dimer. *Blood.* 2005; 106(2):617–625. [PubMed: 15802531]
41. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transplant.* 2008; 8(2):307–316. [PubMed: 18211506]
42. Woodle ES. A Randomized Double Blind, Placebo-Controlled Trial of Early Corticosteroid Cessation Versus Chronic Corticosteroids: Five Year Results. *American Journal of Transplantation.* 2008; 8 Supplement 2:300.
43. Sinclair NR. Four decades of glucocorticosteroid immunosuppression. *CMAJ.* 1993; 148(8):1277–1278. [PubMed: 8462048]
44. Gallon L, Perico N, Dimitrov BD, Winoto J, Remuzzi G, Leventhal J, et al. Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression comparing sirolimus vs. MMF. *Am J Transplant.* 2006; 6(7):1617–1623. [PubMed: 16827862]
45. Gallon LG, Winoto J, Chhabra D, Parker MA, Leventhal JR, Kaufman DB. Long-term renal transplant function in recipient of simultaneous kidney and pancreas transplant maintained with two prednisone-free maintenance immunosuppressive combinations: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. *Transplantation.* 2007; 83(10):1324–1329. [PubMed: 17519781]
46. Stock PG, Ascher NL, Osorio RW, Tomlanovich S, Lake JR, Nikolai B, et al. Standard sequential immunosuppression with Minnesota antilymphoblast globulin and cyclosporine vs FK 506: a

- comparison of early nephrotoxicity. *Transplant Proc.* 1993; 25(1 Pt 1):675–676. [PubMed: 7679838]
47. Chang GJ, Mahanty HD, Vincenti F, Freise CE, Roberts JP, Ascher NL, et al. A calcineurin inhibitor-sparing regimen with sirolimus, mycophenolate mofetil, and anti-CD25 mAb provides effective immunosuppression in kidney transplant recipients with delayed or impaired graft function. *Clin Transplant.* 2000; 14(6):550–554. [PubMed: 11127307]
48. Naesens M, Kambham N, Concepcion W, Salvatierra O Jr, Sarwal M. The evolution of nonimmune histological injury and its clinical relevance in adult-sized kidney grafts in pediatric recipients. *Am J Transplant.* 2007; 7(11):2504–2514. [PubMed: 17725681]
49. Cattaneo D, Perico N, Gaspari F, Gotti E, Remuzzi G. Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. *Kidney Int.* 2002; 62(3):1060–1067. [PubMed: 12164891]
50. Anil Kumar MS, Moritz MJ, Saaed MI, Heifets M, Sustento-Reodica N, Fyfe B, et al. Avoidance of chronic steroid therapy in african american kidney transplant recipients monitored by surveillance biopsy: 1-year results. *Am J Transplant.* 2005; 5(8):1976–1985. [PubMed: 15996248]
51. Alloway RR, Hanaway MJ, Trofe J, Boardman R, Rogers CC, Buell JF, et al. A prospective, pilot study of early corticosteroid cessation in high-immunologic-risk patients: the cincinnati experience. *Transplant Proc.* 2005; 37(2):802–803. [PubMed: 15848537]

Figure 1. Stanford Steroid-free immunosuppression protocol

Steroid-free immunosuppression usage is marked with the solid black line; steroid-based immunosuppression is marked with the hashed grey line. Protocol biopsies (denoted by stars) were performed at baseline (prior to reperfusion of the kidney), 3 months, 6 months, 12 months and 24 months post-transplantation. Extended Daclizumab induction was given for 6 months post-transplantation in SF patients (black solid line) versus standard usage of 2 months Daclizumab induction in SB patients (gray dashed line).

Fig 2a

Fig 2b

Fig 2c

Fig 2d

Fig 2e

Figure 2. Graft survival and Acute Rejection results for SF and SB patients

a: Graft survival for SF and SB patients Kaplan-Meier survival analysis curves are shown for patients currently maintained on SF (n=112; black line) and concurrently transplanted SB (n=57; gray line) patients until current follow-up.

b: Graft survival for ITT-SF and SB patients Kaplan-Meier survival analysis curves are shown for patients with ITT-SF protocol (n=129; black line) and concurrently transplanted SB (n=57; gray line) patients until current follow-up.

c: Death-Censored Graft survival for SF and SB patients Kaplan-Meier survival analysis curves are shown for patients currently maintained on SF (n=112; black line) and concurrently transplanted SB (n=57; gray line) patients until current follow-up.

d: Incidence of Acute Rejection in ITT-SF, maintained on SF, and SB patients This figure shows a comparison of the percentage of clinical acute rejection, late clinical AR (occurring after 1 year post-transplantation), early clinical AR (occurring within 1 year post-transplantation) among ITT-SF, (black color bar), maintained on SF (darker gray color bar), and only the SB (dark gray color bar) patients. P values were listed either between ITT-SF versus SB or maintained on SF versus SB.

e: Probability of remaining free from AR in SF and SB patients This Kaplan-Meier analysis curves are shown for probability of remaining free of clinical rejection, between SF (black color bar), and the SB (dark gray color bar) patients at current follow-up.

Fig 3a

Fig 3b

Figure 3. Comparison of Graft function between ITT-SF and SB protocols

a: For overall age of patients, calculated creatinine clearance (ml/min/1.73m²) (Y axis) is plotted against months of follow-up post-transplantation (X axis) for ITT-SF (black line) and SB (gray line) protocols. Each dot with the solid vertical lines (up/down) represents mean $\pm$ standard deviation. $F=28.9$, mixed model group effect $p<0.0001$ was derived from linear mixed model by repeated measures.

b: For children (age ≤ 6 years), calculated creatinine clearance (ml/min/1.73m²) (Y axis) is plotted against months of follow-up post-transplantation (X axis) for ITT-SF (black line) and SB (gray line) protocols. Each dot with the solid vertical lines (up/down) represents mean $\pm$ standard deviation. $F=17.9$, mixed model group effect $p=0.0001$ was derived from linear mixed model by repeated measures.

Fig 4a

Fig 4b

Figure 4. Growth comparisons between SF and SB protocols

a: Mean height Z score were shown for children (age ≤ 6 years) for SF (black bar) and SB (gray bar) protocols. The values are shown under the figure. $P=0.01$ was derived from the linear mixed model by repeated measures.

b: Mean delta height Z scores are shown for young patients (age 6–12 years) for SF (black bar) and SB (gray bar) protocols. $P=0.01$ was derived from the linear mixed model by repeated measures.

Table 1

Patient demographics of SF and SB patients in this study

Baseline Patient Characteristics & Immunosuppression			
	Steroid-free	Steroid-based	<i>P</i> value
Before Transplantation	129	57	
Recipient			
Mean age (yrs)	11.0 ± 6.7	12.5 ± 6.1	0.18
Mean age (yrs) males	10.7 ± 6.8	12.6 ± 6.8	0.23
Mean age (yrs) females	11.7 ± 6.5	12.4 ± 5.7	0.65
Gender: females	39%	55%	0.07
Mean height (cm)	130.5 ± 35.9	136.2 ± 35.0	0.34
Height Z-score	-1.2 ± 1.5	-1.1 ± 1.5	0.72
Mean weight (kg)	38.2 ± 23.2	39.5 ± 20.8	0.74
Mean BMI (kg/m ²)	20.3 ± 4.7	19.6 ± 4.2	0.35
Mean BSA (m ²)	1.2 ± 0.5	1.2 ± 0.5	0.54
Race (1,2,3,4,5) [†]	54%, 21%, 9%, 8%, 8%	52%, 24%, 12%, 4%, 8%	0.85
Cause of ESRD (1,2,3,4,5,6,7) [‡]	32%, 10%, 16%, 13%, 18%, 5%, 6%	35%, 6%, 2%, 8%, 12%, 5%, 32%	0.1
Dialysis pre-transplant	70%	80%	0.13
PRA < 20%	100%	100%	1
Mean Hematocrit (%)	33.7 ± 6.6	33.7 ± 7.0	0.99
Mean white cell count(ul)	8.4 ± 3.9	8.0 ± 3.5	0.54
Mean serum cholesterol (mg/dl)	161.5 ± 48.6	135.9 ± 43.6	0.01
Mean serum triglyceride (mg/dl)	170.6 ± 95.0	182.1 ± 91.0	0.57
Hypertension (%)	52%	61%	0.37
Donor			
Mean donor age	34.4 ± 11.2	33.9 ± 10.5	0.84
Donor age range (yr)	2.3 – 57	0.6 – 50	
Donor Type (LRD)	79%	68%	0.12
Mean HLA match LRD	2.8 ± 1.4	2.8 ± 1.3	0.99
Mean HLA match CAD	1.6 ± 0.9	2.0 ± 1.7	0.87

[†] Race: 1=Caucasian; 2= Hispanic; 3=Asian; 4=African American; 5=Other

[‡] ESRD= End-stage Renal Disease: ESRD categories: 1= Glomerulonephritis; 2= Polycystic Kidney Disease; 3=Dysplasia; 4=Reflux Nephropathy; 5=Obstructive Uropathy; 6=FSGS; 7=Others

PRA= Panel reacting antibody levels

Table 2

Post transplantation hypertension and hyperlipidemia

Post transplantation hypertension and hyperlipidemia			
	Steroid-free	Steroid-based	<i>P</i> value
Hypertension (%) *			
1 year	31%	55%	
3 year	12%	70%	<0.0001
5 year	14%	50%	
7 year	8%	56%	
Hypercholesterolemia (%) **			
1 year	15%	40%	
3 year	18%	26%	0.0285
5 year	20%	50%	
7 year	25%	75%	
Hypertriglyceridemia (%) ***			
1 year	45%	60%	
3 year	32%	65%	0.0038
5 year	26%	50%	
7 year	8%	80%	

* Hypertension was defined as present if there was requirement of anti-hypertensive agents for clinical blood pressure control

** Hypercholesterolemia was defined as fasting serum cholesterol levels >190 mg/dl

*** Hypertriglyceridemia was defined as fasting serum triglyceride levels >140 mg/dl