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Failure of Steroid-Free Immunosuppression in Pediatric Renal Transplantation: Low Conversion Rate to Steroid Based Immunosuppression[3]

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Abstract

Background—Short term outcomes using steroid-free immunosuppression following renal transplantation have been promising. No studies have examined the incidence of and reasons for steroid avoidance protocol failures.

Methods—We present a single center analysis of steroid-free immunosuppression failures amongst 129 pediatric renal transplant recipients with mean follow-up of five years. We analyzed causes for failure and examined reasons for conversion to steroid-based therapy. We compared actual patient and allograft survival and allograft function in the cohort of patients who required conversion to steroid-based immunosuppression with that of the cohort maintaining steroid-free immunosuppression.

Results—13.2% (17/129) of patients failed steroid-free immunosuppression. Actual patient survival was equivalent in the two cohorts, 96.4% for the cohort maintaining steroid-free immunosuppression and 94.1% for those requiring conversion. Actual allograft survival was lower in patients requiring conversion to a steroid-based protocol, 76.5% vs. 95.5% (p=0.004). Estimated GFRs 12- and 24-months post-transplant were greater in patients maintaining steroid-free immunosuppression (p=0.003). Most patients (52.9%, 9/17) who broke the steroid-free protocol did so due to refractory acute rejection. The second most common reason was recurrence of glomerulonephritis (35.3%, 6/17).

Conclusion—The failure rate of steroid-free immunosuppression amongst select pediatric patients undergoing renal transplantation is low. Patients maintaining steroid-free immunosuppression have better allograft survival and function than those requiring conversion to steroid-based therapy. The most common reasons for failure of steroid-free immunosuppression are recalcitrant or recurrent allograft rejection and recurrent glomerulonephritis; the role of conversion to steroid-based immunosuppression following episodes of acute rejection and recurrent glomerulonephritis requires additional analysis.

Keywords

steroid-free; renal transplantation; glomerulonephritis

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Introduction

Corticosteroid therapy has been a cornerstone of immunosuppressive therapy following solid organ transplantation for over 40 years (1,2). Despite their effectiveness, steroids are associated with numerous side effects including glucose intolerance and diabetes, hypertension, hyperlipidemia, cataract formation, osteoporosis and fractures, mood lability, and cosmetic changes (1,3,4). Additionally, in children, steroid therapy is associated with marked growth suppression (2,5,6). Because of these side effects, considerable effort has been focused on withdrawing, minimizing, or avoiding steroid therapy.

Steroid withdrawal was initially associated with an increased incidence of acute allograft rejection, and although some recent studies using more potent immunosuppressive agents have been promising, outcomes remain inconsistent (7-10). However, rapid elimination of steroid therapy, resulting in steroid free maintenance immunosuppression, and complete steroid avoidance protocols have been successfully employed, both in adults and children (2,4, 11-18). Short term outcomes with steroid avoidance are promising, but there are minimal long term data; currently published reports span 5 years for adult renal transplant patients and 4 years for pediatric renal transplant patients (4,15). To date, no studies have addressed failures of steroid free immunosuppression in this population and data regarding conversion of these patients to a steroid based regimen are lacking.

Our experience with steroid avoidance in pediatric and infant renal transplantation recipients began in 1999. We currently present an intention to treat analysis of 129 consecutive pediatric and infant patients transplanted according to our previously published steroid avoidance protocol (2,15), specifically examining steroid free protocol failure rates and indications leading to conversion to a steroid based regimen.

Materials and Methods

Patient Population

This study is an intention to treat analysis of a single-center experience including 129 consecutive, low immunologic risk (<20% peak panel reacting antibody) pediatric (0-21 years of age) recipients of a primary kidney allograft at Stanford University. All patients in this study were transplanted between November 1999 and October 2007. The Stanford steroid-free (SF) immunosuppression protocol, previously reported, utilizes tacrolimus, mycophenolate mofetil (MMF) and an extended daclizumab induction lasting 6 months (2,15). In the case of MMF intolerance within the first 6 months post-transplant, MMF was temporarily replaced by azathioprine (Imuran®, GlaxoSmithKline; AZA) with a MMF re-challenge within 6 months. Continued MMF intolerance after 6 months, resulted in MMF being replaced by sirolimus (Rapamycin®, Wyeth' SRL). All patients had protocol biopsies at 3, 6, 12, and 24 months after transplantation, and in cases of unexplained graft dysfunction. All rejection episodes were biopsy proven and graded by the Banff classification, with Banff grade 1a as the minimum AR criteria (19).

17 of the 129 patients broke the steroid free protocol and were converted to steroid based therapy. This cohort of 17 patients was reviewed in its entirety with a focus on events leading to conversion and outcome following conversion. Additionally, this cohort was compared with the 112 patients that maintained a steroid free immunosuppressive protocol. We examined patient and allograft survival and allograft function amongst patients in each cohort. Patient and allograft survivals are actual survival rates for the respective cohorts through September of 2008. In addition, death censored allograft survival was also calculated. Allograft loss was defined as a return to dialysis or death with a functioning graft. Unless otherwise noted, all

acute rejection rates include both clinical and subclinical AR. Estimated glomerular filtration rates (GFR) were calculated according to the method described by Schwartz et. al. (20).

This study was approved by the Institutional Review Board at Stanford University.

Conversions to a Steroid Based Immunosuppressive Protocol

Acute Rejection—Patients with biopsy proven AR were converted to a steroid based immunosuppression protocol for the following predetermined protocol indications: 1) AR occurring in the first three post-transplant months, 2) AR not fully responsive to either pulse dose (10mg/kg/dose for three doses) methylprednisolone therapy or anti-thymocyte globulin, 3) recurrent AR, defined as a second biopsy consistent with AR within three months of the initial biopsy. Receiving intravenous corticosteroids briefly (once daily for three days) to treat an episode of acute rejection was not considered a failure provided the patient fully responded to therapy with a return to baseline allograft function and continued to receive steroid free immunosuppression after the rejection event.

Recurrence of Primary Disease—The majority of patients with recurrence of primary glomerulonephritic disease, as diagnosed by biopsy, with concomitant allograft dysfunction were converted from steroid free to steroid based immunosuppression. This decision was, at times, necessarily an arbitrary one. Early in our steroid free experience all recurrences were converted to a steroid based regimen, which was considered the standard of care. As our experience expanded, patients with mild, biopsy proven recurrence were closely followed and converted to steroid based therapy only if the recurrence demonstrated progression, both clinically and on biopsy. All patients with recurrence of disease known to have a poor prognosis, such as FSGS and MPGN, were converted to a steroid based regimen, again considered the standard of care, to optimize their outcome.

Other Causes of Conversion—One patient developed a disease state known to respond to corticosteroid therapy. He was converted to a steroid based regimen as the disease was expected to be long standing in nature. One patient developed a hematologic complication associated with over-immunosuppression. This necessitated replacement of MMF with a less potent antimetabolite, azathioprine; the combination of tacrolimus and azathioprine was inadequate, resulting in AR, and low dose prednisone was added.

Statistical Analysis

T test, chi square test, and Fisher exact test were used for analysis of continuous or categorical types of data. P-values ≤ 0.05 were considered statistically significant. Results are reported as mean ± standard error. All statistical analyses were performed using the SAS 9.1.3 (SAS Institute Inc., Cary, NC).

Results

Initial Steroid Free Cohort

A total of 129 pediatric kidney transplant recipients, by intention to treat analysis, were placed on a steroid avoidance immunosuppressive protocol. Mean age at transplant was 11.1 ± 0.6 years. More than half of the recipients were male (61.2%) and the majority of allografts were from a living donor (76.7%). Actual patient and allograft survivals were 96.1% and 93.8%, respectively, at a mean of 59.9 ± 2.4 months of follow up. In the entire cohort, five patients died with normal functioning grafts, resulting in a death censored allograft survival of 97.7%. The most common causes of end stage renal disease (ESRD) prior to transplant were glomerulonephritis (GN) at 21.7% (28/129), renal dysplasia at 20.2% (26/129), and obstructive uropathy at 16.3% (21/129). The overall one year incidence of clinical AR was 11.6% (15/129).

Nine of 129 patients had early, recurrent, or recalcitrant AR and were converted to a steroid based regimen. The overall incidence of recurrent glomerulonephritis was 28.6% (8/28). All eight recurrences were clinical; none were diagnosed on surveillance biopsy. Six of the eight patients experiencing recurrence were converted to a steroid based protocol.

Cohort Maintaining Steroid Avoidance Protocol

The demographics of the 112 patients in the cohort that remained on the steroid avoidance protocol are described in Table 1. There were no significant difference between this cohort and the cohort that required a break in protocol with respect to age, gender, donor source, or follow up. Actual patient survival was 96.4%, actual allograft survival was 95.5%, and given the four patient deaths with a functional allograft in this cohort, death censored allograft survival was 99.1%. Mean estimated GFRs at 12 and 24 months post transplant were 111.0 ± 2.8mL/min/1.73m^2 and 105.7 ± 2.8mL/min/1.73m^2, respectively. Clinical AR occurred during the first 12 post transplant months in 7.1% of patients (8/112). Subclinical AR occurred during the first 12 post transplant months in 8% (9/112). Of the 17 patients with AR, actual patient and allograft survivals were 100% and 100%; mean estimated GFRs at 12- and 24-months were 105±8.1mL/min/1.73m2 and 103±7.4mL/min/1.73m2, respectively. Recurrent GN occurred in 2/112 (1.8%) patients who remained steroid free; both patients had ESRD due to IgA nephropathy and received intensification of MMF therapy along with initiation of fish oil therapy.

Cohort Requiring Conversion to a Steroid Based Protocol

In total, 17 patients broke the steroid avoidance immunosuppression protocol, a failure rate of 13.2%. The demographics of these patients are described in Table 1. The 17 patients failed the protocol at a mean 10.0 ± 2.2 months (range 0.2 – 36 months) after transplantation. 35.3% of the patients (n=6) were converted early, less than six months after transplantation. Actual patient survival was 94.1%, which was not significantly different than the cohort that maintained steroid avoidance immunosuppression. Actual allograft survival was 76.5%, and given the one patient death with a functional allograft in this cohort, death censored allograft survival was 82.4%; both values were significantly lower than the cohort that maintained steroid free immunosuppression ($p<0.005$ and $p<0.005$). Mean estimated GFRs at 12 and 24 months post transplant were 89.5 ± 5.3mL/min/1.73m^2 and 81.6 ± 8.6mL/min/1.73m^2, respectively. Both of these values were significantly lower than those in the cohort maintaining steroid free immunosuppression ($p<0.005$ and $p<0.005$). The reasons for breaking protocol are shown in Table 2. The most common reason for breaking protocol was early or refractory AR (52.9%). The second most common event necessitating conversion was recurrence of primary glomerulonephritic disease (35.3%); two patients developed recurrent IgA nephropathy, two developed recurrent FSGS, one patient developed recurrent MPGN, and one patient developed recurrent Wegener's granulomatosis. One patient was converted due to development of a de novo autoimmune disease (reactive arthritis) and one patient was converted due to development of PTLD with the requisite reduction in immunosuppression.

Discussion

To the best of our knowledge, this study is the first to characterize patients who fail steroid free immunosuppression. Overall, our failure rate of 13.2% is similar to the 17% rate reported by Kandaswamy et. al. (21). Our results suggest that failure to tolerate a steroid free immunosuppressive regimen portends a worse prognosis; patients who required transition to a steroid based protocol had lower actual allograft and death censored allograft survival rates. Additionally, at 12 and 24 months post transplant, patients who broke the steroid free immunosuppressive protocol had significantly lower estimated GFRs. Much of the difference in allograft survival and function can be explained by the fact that the most common reason for breaking protocol was early or refractory acute allograft rejection (AR); AR is a well known

risk factor for worse allograft survival and has been associated with reduced GFR (22-24). Ultimately, the clinical implication of these patients who were converted after AR is uncertain. Considering that the overall one year incidence of clinical AR amongst all 129 patients was only 11.6%, it is conceivable that they represent the expected stronger immune responders seen even with steroid based protocols. Additionally, although estimated GFRs at 12 and 24 months post transplant were lower in the patients with AR who were converted to a steroid based immunosuppressive regimen when compared with patients who experienced AR but remained steroid free, this difference failed to reach statistical significance (Table 3).

The second most common reason for failing steroid free immunosuppression was recurrence of primary glomerulonephritic renal disease. These recurrences were clinically relevant as all were diagnosed by a biopsy performed in the setting of new onset proteinuria or unexplained allograft dysfunction; none of the recurrences were diagnosed by surveillance biopsy.

Recurrent GN is a long-term concern with a prevalence that increases over time; it is the third most common cause of allograft loss at 10 years post transplant, behind chronic rejection and death with a functioning allograft (25). Recurrence rates for IgA nephropathy, FSGS, MPGN, and membranous nephropathy have been estimated at 13-46%, 20-50%, 20-25% (MPGN type I) 80-100% (MPGN type II), and 10-30%, respectively (26).

Recently, Ibrahim et. al., published data regarding rates of allograft loss due to recurrent GN in their steroid avoidance protocol (3). Recurrence was a common cause of allograft dysfunction in their study; over 20% of biopsies performed for appearance of proteinuria or an unexplained rise in creatinine demonstrated recurrent GN. Furthermore 20% of patients with recurrence went on to lose their allograft. Recurrence rates of GN were compared with a historical control group who received transplants for ESRD due to GN, but were managed with a steroid based maintenance regimen. No statistical analysis was provided, however, recurrence rates were routinely higher in the steroid free group: IgA nephropathy 7% vs. 4.5%, FSGS 19% vs. 12.2%, MPGN 20% vs. 9.7%, and membranous nephropathy 28% vs. 16.7%.

It is important to note that the role of corticosteroid therapy and/or the conversion to a steroid based immunosuppressive protocol in both early/recalcitrant acute rejection and recurrent glomerulonephritic disease following renal transplantation is unknown. It is not clear whether conversion to a steroid based regimen following AR may result in better graft survival and less recurrent AR (27). Furthermore, although corticosteroids are commonly used to treat primary glomerulonephritic diseases, the literature is mixed as to their effectiveness in this role, and there are minimal data regarding their use to treat recurrent GN following transplantation (26,28). Clearly, before stronger conclusions can be drawn, more robust data are required.

In conclusion, failure of steroid avoidance immunosuppression in low immunologic risk pediatric patients undergoing renal transplantation occurs in approximately 13% of cases. Patients who maintain steroid free immunosuppression have a better prognosis than those who require conversion to steroid based immunosuppression, regardless of cause. Failure is most commonly due to recalcitrant AR and secondarily is due to recurrence of glomerulonephritis. Clearly, the effect of recurrent GN following renal transplantation warrants further study and the role of corticosteroid therapy in these recurrences needs to be better elucidated.

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Abbreviations

MMF
: mycophenolate mofetil

ESRD
: end stage renal disease

GN
: glomerulonephritis

FSGS
: focal segmental glomerulosclerosis

MPGN
: membranoproliferative glomerulonephritis

PTLD
: post transplant lymphoproliferative disorder

GFR
: glomerular filtration rate

AR
: acute rejection

Table 1

Comparison of Patients Maintaining Steroid Free Immunosuppression and Patients Failing Steroid Free Immunosuppression

	Steroid Free w/o Protocol Break (n=112)	Break of Steroid Free Protocol (n=17)	p-values
Age at Transplant (Years)	10.9 ± 0.6	12.5 ± 1.3	0.33
Gender			0.45
Male	62.5%	52.9%	
Female	37.5%	47.1%	
Donor Source			0.21
Living Donor	78.6%	64.7%	
Deceased Donor	21.4%	35.3%	
Follow Up (Months)	59.2 ± 2.6	64.2 ± 6.4	0.36
Time Post Transplant Protocol Broken (Months)	N/A	10.1 ± 2.1	
Patient Survival	96.4%	94.1%	0.65
Allograft Survival	95.5%	76.5%	0.004
Death Censored Allograft Survival	99.1%	82.4%	0.0002
GFR at 12mo post transplant (mL/min/1.73m2)	111.0 ± 2.8	89.0 ± 4.7	0.003
GFR at 24mo post transplant (mL/min/1.73m2)	105.7 ± 2.8	81.6 ± 8.6	0.002

Table 2

Indications for Break of Steroid Avoidance Immunosuppression

Indication for Protocol Break	Number of patients	% of total cohort (n=17)
Refractory acute rejection	9	52.9
Banff 1a	*2*	
Banff 1b	*5*	
Banff 2a	*1*	
Banff 2b	*1*	
Steroid Refractory	*6*	
Recurrent GN	6	35.3
de Novo autoimmune disease	1	5.9
PTLD	1	5.9

Table 3

Allograft Function Following AR in the Two Cohorts

	AR with Maintenance of Steroid Free Regimen	AR with conversion to a Steroid Based Regimen	P-value
Patients with AR	17	9	
GFR 12 mo post transplant (mL/min/ 1.73m2)	105.2±8.1	91.3±8.6	0.29
GFR 24 mo post transplant (mL/min/ 1.73m2)	103.3±7.4	79.6±12.8	0.10