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ANTILYMPHOID ANTIBODY PRECONDITIONING AND TACROLIMUS MONOTHERAPY FOR PEDIATRIC KIDNEY TRANSPLANTATION

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Objective Heavy post-transplant immunosuppression may contribute to long-term immunosuppression dependence by subverting tolerogenic mechanisms; thus, we sought to determine if this undesirable consequence could be mitigated by pretransplant lymphoid depletion and minimalistic post-transplant monotherapy.

Study design Lymphoid depletion in 17 unselected pediatric recipients of live (n = 14) or deceased donor kidneys (n = 3) was accomplished with antithymocyte globulin (ATG) (n = 8) or alemtuzumab (n = 9). Tacrolimus was begun post-transplantation with subsequent lengthening of intervals between doses (spaced weaning). Maintenance immunosuppression, morbidity, graft function, and patient/graft survival were collated.

Results Steroids were added temporarily to treat rejection in two patients (both ATG subgroup) or to treat hemolytic anemia in two others. After 16 to 31 months (mean 22), patient and graft survival was 100% and 94%, respectively. The only graft loss was in a nonweaned noncompliant recipient. In the other 16, serum creatinine was 0.85 ± 0.35 mg/dL and creatinine clearance was 90.8 ± 22.1 mL/1.73 m^2. All 16 patients are on monotherapy (15 tacrolimus, one sirolimus), and 14 receive every other day or 3 times per week doses. There were no wound or other infections. Two patients developed insulin-dependent diabetes.

Conclusion The strategy of lymphoid depletion and minimum post-transplant immunosuppression appears safe and effective for pediatric kidney recipients. *(J Pediatr 2006;148:813-8)*

Until the late 1960s, renal transplantation in pediatric patients was a controversial service that was systematically provided in only a few centers.[1-4] Numerous ethical issues were raised at the outset, including risk to live donors, effects on family unity, mental health of well siblings, and doubts about the long-term prognosis.[5] Some of these anxieties have been relieved with the passage of time. For example, complications associated with heavy steroid use have been progressively circumvented with better adjunct[6] and/or baseline drugs.[7-13] However, chronic immunodepression per se and drug-specific side effects (eg, nephrotoxicity) have remained the principal threats to the quality and duration of life of the pediatric recipient.[14-16]

We report here an experience in 17 pediatric kidney recipients in whom the burden of long-term immunosuppression was lightened with a treatment regimen designed to avoid acute rejection while interfering minimally with natural tolerogenic mechanisms.[17] One principle of the strategy consisted of lymphoid depletion before renal allograft revascularization. In the first eight patients, the lymphoid depletion was done with antithymocyte globulin (ATG; Thymoglobulin®).[18] In the next nine patients, alemtuzumab (Campath-1H®)[19-23] was used. The second therapeutic principle consisted of the use of the least amount of post-transplant immunosuppression consistent with stable graft function. This was accomplished by beginning the postoperative course on tacrolimus monotherapy with subsequent attempts to reduce the frequency of dosing (spaced dose weaning).

METHODS

Populations

Between May 2003 and July 2004, 17 of 18 consecutive kidney-alone recipients at the Children's Hospital of Pittsburgh (CHP) were treated with the tolerogenic strategy. In the single exclusion, the lymphoid depletion was inadvertently omitted. Two subgroups

ATG	Antithymocyte globulin	IRB	Institutional Review Board
CHP	Children's Hospital of Pittsburgh		

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This work was supported by an unrestricted gift from Mr. Robert Eberly.

Submitted for publication Sep 28, 2005; last revision received Nov 15, 2005; accepted Jan 4, 2006.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2006.01.008

Table I. Donor and recipient population(s)

	All	ATG	Alemtuzumab
n	17	8	9
Case accrual	5/03 to 7/04	5/03 to 12/03	1/04 to 7/04
Mean recipient age (y)	9.4 ± 6.5	8.6 ± 7.3	10.1 ± 6.1
Recipient age range (y)	1 to 18	1 to 18	1 to 18
Primary graft	15 (88%)	7 (87.5%)	8 (89%)
Live donor	14 (82%)	6 (75%)	8 (89%)
Donor age (y)	36.2 ± 9.0	37.0 ± 7.6	35.6 ± 10.5
HLA mismatch (of 6)	2.6 ± 1.2	2.3 ± 1.7	2.9 ± 0.6
Deceased donor CIT (HR)	23.4 ± 9.3	18.1 ± 1.8	34

were defined by the agent used for lymphoid depletion, ie, ATG (n = 8) or alemtuzumab (n = 9). There were no differences between the two groups in the donor and recipient demographics and risk factors (Table I). All 17 grafts functioned well at the outset.

Immunosuppression

LYMPHOID DEPLETION. The first eight patients were infused with 5 mg/kg rabbit ATG. In the six recipients of live donor kidneys of this group, the ATG dose was divided. The first 3 mg/kg were infused slowly throughout the night preceding operation, whereas an additional 2 mg/kg were given after the induction of anesthesia. The two cadaveric organ recipients had a single 5 mg/kg infusion. For the nine patients treated after December 2003, 0.4 to 0.5 mg/kg alemtuzumab (Campath-1H®) were substituted for the ATG. The alemtuzumab was infused over a 2- to 4-hour interval that included periods following the induction of anesthesia.

In all 17 patients, two doses of 10- to 15-mg/kg intravenous methylprednisolone were administered to prevent ATG- or alemtuzumab-induced cytokine reactions. The first steroid infusion coincided with the antibody infusion, and the second was given during performance of the arterial anastomosis.

TACROLIMUS. Twice daily monotherapy was started orally on postoperative day 1, with tacrolimus target trough levels of 10 ng/mL. Approximately 4 to 6 months after transplantation, the twice daily dosage was consolidated to a single daily dose, eg, 2 mg in the morning and evening were given as a 4-mg morning dose. Three to 6 months after this initial step, the interval between tacrolimus doses was lengthened to every other day or 3 times per week (Figure 1).

All subsequent decisions about tacrolimus doses were based on what already had transpired in the individual case, with particular weight given to serum creatinine concentration and urinalysis. Steroids or other agents were not added to baseline monotherapy unless there was evidence of acute rejection (n = 2), or in two cases, for the treatment of

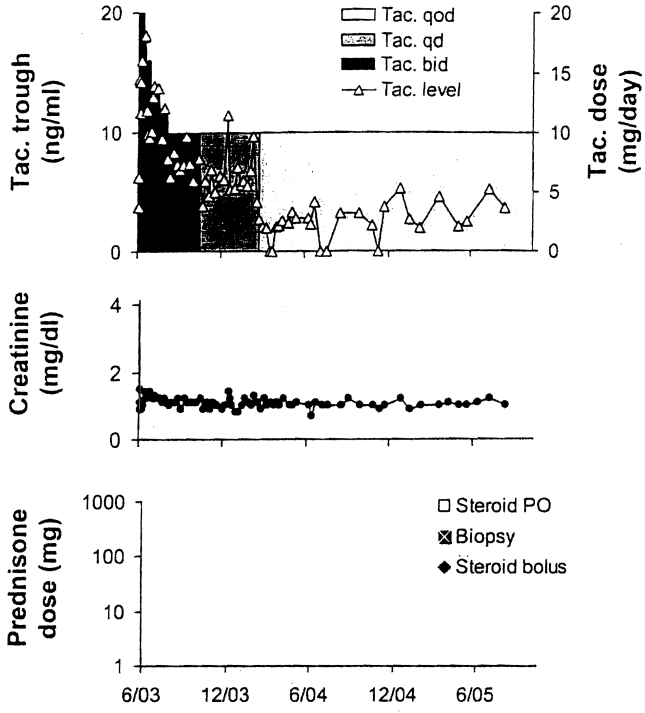

Figure 1. Course of a 15-year-old recipient of a maternal kidney. The patient was pretreated with ATG. The twice daily tacrolimus (Tac.) dose of 5 mg was consolidated to one 10 mg per day after 4 months. At 8.5 months, the dose was spaced to every other day and has remained at that frequency for 20 months (top panel). Because serum creatinine and creatinine clearance have been stable throughout, there have been no biopsies or additional treatment (bottom two panels).

hemolytic anemia. When necessary, steroid therapy was temporary, eg, a single bolus of methylprednisolone, or a 3- to 5-day course of high-dose steroids that was rapidly weaned thereafter. Biopsies were obtained only for specific indications such as an increase in serum creatinine.

Infection Prophylaxis and Monitoring

The following long-standing practice on the kidney transplant service at the CHP was not modified. Prophylaxis with trimethotrim sulfamethoxazole, nystatin, and oral valgancyclovir was administered for a minimum of 6 months. With transplantation from an Epstein Barr Virus (EBV) or Cytomegalo virus (CMV)-seropositive donor to an EBV- or CMV-negative recipient, the valgancyclovir prophylaxis was extended to 12 months and a single 100-mg/kg dose of CMV immune globulin was administered on postoperative day 1. Quantitative EBV testing with polymerase chain reaction was done monthly for the first 6 months and every other month for the subsequent 6 months. Assays of CMV antigenemia were performed weekly for 3 months, every other week during months 3 to 6, then monthly out to 1 year. Screening for polyoma (BK) virus was done as clinically indicated.

Institutional Review

The immunosuppression strategy applied in the pediatric renal recipients reported here was accepted in 2001

Table II. Results in the 16 patients with functioning grafts*

	All (n 16)	ATG (n 7)	Alemtuzumab (n 9)
Follow-up months	22 ± 4.9	26 ± 2.8	18 ± 2.6
Creatinine	0.85 ± 0.35	0.96 ± 0.30	0.77 ± 0.38
Creatinine clearance	90.8 ± 22.1	75.6 ± 12.5	102.5 ± 21.0
Spaced dose weaning	14 (88%)	5 (71%)	9 (100%)
Months to spaced dosing	11.1 ± 3.5	11.7 ± 3.8	9.9 ± 2.3
Months since spaced dosing	10.5 ± 5.1	14.3 ± 5.4	8.4 ± 3.6
Received post-transplant prednisone	3†	2†	1‡
Acute rejection	1 (6%)	1 (14%)	0
Delayed graft function	0	0	0
Patients biopsied	6 (38%)	3 (43%)	3 (33%)
PTLD	0	0	0
CMV	0	0	0
Polyoma (BK) virus	0	0	0
Post-transplant diabetes	2 (13%)‡	0	2 (22%)‡
Autoimmune hemolytic anemia	2 (13%)	1 (14%)	1 (11%)

*A 17th patient who lost her graft to noncompliance is described separately in the text. Including all 17, patient/graft survival is 100%/94%: 100%/88% in the ATG subgroup (n = 8) and 100%/100% in the alemtuzumab subgroup (n = 9).
†Includes one patient treated for rejection in the ATG group and two patients (one in each group) treated with steroids for autoimmune hemolytic anemia.
‡Includes one patient with voracious post-transplant appetite and obesity.

as standard of care for adult kidney and other kinds of organ recipients by the University of Pittsburgh Institutional Review Board (IRB), and by the Innovative Practices Committee and the Pharmacy and Therapeutics Committees of the University of Pittsburgh Medical Center. The strategy was approved by the foregoing committees as the standard of care for pediatric recipients of liver, intestinal, or multivisceral allografts as of July 2001.[24] The institutional approvals were extended to pediatric kidney recipients in 2003 after extensive experience in adult renal recipients.[25-27] The off-label use of alemtuzumab, an FDA-approved drug, and of the doses of ATG, were sanctioned by the IRB and the other aforementioned oversight committees. Informed consent that included a full description of the regimen(s) was obtained from the parent(s) or legal guardian(s).

Support from federal granting agencies or commercial sources was neither sought nor accepted. There were no blood drawings from pediatric recipients for any purpose other than patient care. No attempt was made to use blood, biopsy, or other specimens to elucidate tolerogenic mechanisms or other matters. Adverse events, including those related to medication were recorded according to existing practices of the CHP organ transplantation services. In compliance with federal statutes, data were extracted for retrospective analysis from the clinical records using an IRB-approved honest brokering system. The institutional oversight policies of the CHP, the University of Pittsburgh, and the University of Pittsburgh Medical Center are fully compliant with all legal statutes and with the regulations of the United States Department of Health and Human Services.[28]

RESULTS

Survival

With a mean follow-up of 22 ± 4.9 months (range 16 to 31), patient survival is 100% and graft survival is 94%. The one graft loss was of a cadaver kidney in an 18-year-old pre-sensitized female (25% Panel Reactive Antibody [PRA], negative crossmatch) who was pretreated with ATG before undergoing retransplantation and who never underwent spaced weaning. Because of a slowly rising serum creatinine (to 1.6 mg/dL), the patient had a biopsy at 6 months that was diagnosed as pylonephritis (gram negative rods) and was treated with intravenous antibiotics. Two other late biopsies revealed rejection. She did not comply with subsequent follow-up, was exposed to pregnancy risk while truant from her family and healthcare team, and lost her kidney after 20.5 months. Further analysis (Table II) was confined to the other 16 cases.

Weaning

As of November 2005, all 16 patients with functioning kidneys (Table II) are being treated with a single immunosuppressive drug: tacrolimus (n = 15) or sirolimus (n = 1). Fourteen of the 16 are on spaced doses (Figure 2). Five (71%) of the seven ATG-treated patients have been on every other day or 3 times per week doses of tacrolimus monotherapy for 14.3 ± 5.4 months following the post-transplant institution of spaced dose schedules 11.7 ± 3.8 months postoperatively. The other two ATG-treated patients are on daily tacrolimus (n = 1) or sirolimus (n = 1).

All nine alemtuzumab-treated patients have been on every other day or 3 times weekly tacrolimus doses for 8.4 ±

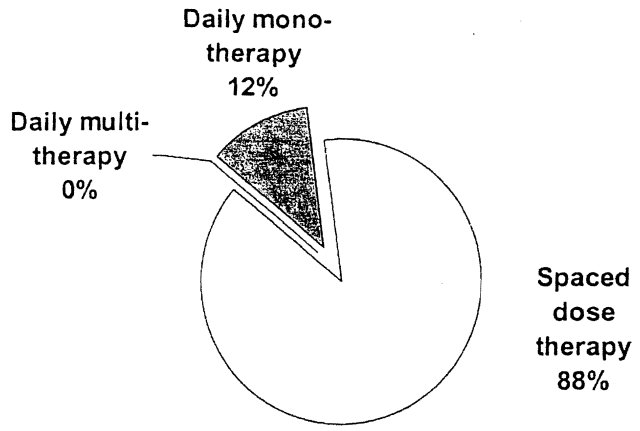

Figure 2. Current immunosuppression at a mean follow-up of 22 ± 4.9 months in 16 patients with functioning kidneys. Of the 14 patients on spaced-weaning (88%), 11 have doses every other day and three are on a 3 times per week (Monday, Wednesday, Friday) schedule.

3.6 months following the institution of dosing 9.9 ± 2.3 months post-transplantation.

Rejection and Graft Function

The incidence of rejection before weaning was higher with the use of ATG compared with alemtuzumab (Table II). All of the six biopsies from the 16 patients with currently functioning grafts (one per each patient after 7 to 240 days after transplant, mean 73 ± 100) were obtained before the onset of spaced weaning. One of the biopsies had mild rejection that was treated with a bolus of prednisone. Two of the six specimens had unequivocal evidence of tubular vacuolization, connoting drug toxicity. There were no examples of the focal segmental glomerulosclerosis described by Bartosh et al[29] in one of their four pediatric recipients treated with alemtuzumab in a different strategy, nor was there any early or late evidence of a nephrotic syndrome.

The incidence of clinical rejection after the start of weaning has been zero in both the ATG and alemtuzumab groups. In the 16 patients with functioning kidneys, the mean serum creatinine is 0.85 ± 0.35 mg/dL, with a mean calculated creatinine clearance of 90.8 ± 22.1 mL/1.73 m^2 (Table II). Only two of the 16 patients are receiving any hypertensive drugs; both were 18 years of age and had been on multiple agents for several years before transplantation. One of these patients is currently receiving twice daily doses of nifedipine (extended release). The other is receiving twice daily doses of 60 mg nifedipine and one 0.1-mg dose per day of clonidine.

Infections

There were no wound or systemic infectious complications in the 17 patients (including the noncompliant patient). Despite transplantation from CMV-positive donors to seronegative recipients in nine patients (53%), there were no examples of CMV disease. Although transplantation was from EBV-positive donors to EBV-negative recipients in 11 (65%) of the 17 cases, the incidence of post-transplant lymphoproliferative disorder (PTLD) was zero. Polyoma (BK) virus infection, the importance and treatment of which in kidney recipients has been recognized only in the last 10 years,[30,31] was not observed.

Nonrenal Adverse Events

One alemtuzumab-treated recipient developed insulin-dependent diabetes mellitus after retransplantation that has improved but not fully reversed with spaced weaning of tacrolimus to every other day. This patient also had developed diabetes after the previous transplantation. A second alemtuzumab-treated recipient, who developed diabetes associated with rapid weight gain, is receiving dietary advice.

Two patients, one each treated with ATG and alemtuzumab, were diagnosed with autoimmune hemolytic anemia that was not associated with deterioration of renal function. This complication was successfully managed with a course of adrenal corticosteroids. Both patients are currently steroid-free. The ATG-conditioned patient was switched from tacrolimus to cyclosporine, and then from cyclosporine to sirolimus, and remains on sirolimus monotherapy. The alemtuzumab-conditioned patient has been weaned to one dose every other day of tacrolimus.

Growth

The growth retardation associated with chronic immunosuppression described 35 years ago[32] and many times subsequently[14] was avoided as shown in Figure 3 for the 16 patients with current graft function. On the average, these recipients were below normal before transplantation, with mean age- and gender-adjusted height Z scores of −1.53 ± 1.86. The current height Z score has improved to −0.74 ± 1.46 for a mean gain of 0.79 ± 0.67. The weight Z score improved from −0.90 ± 1.79 to the present score of −0.28 ± 1.63 for a gain of 0.62 ± 0.96. The improvement in both Z scores was most notable in the short-stature or light-weight recipients of young age.

DISCUSSION

The strategy applied in these patients was reminiscent of that employed in 1962 to 1963 for 16 consecutive pediatric recipients of live donor kidneys at the University of Colorado. Recipient pretreatment with azathioprine had been shown to improve canine kidney allograft survival compared with survival with postoperative therapy only. Consequently, daily azathioprine in the pioneer patients was started 1 to 4 weeks[33] before transplantation, a far less effective pretreatment than the antibody infusion of the current recipients. Instead of tacrolimus, post-transplant monotherapy was with azathioprine, to which prednisone was added only to treat rejection.[1,33] At the time of a 1966 report,[34] 12 of the 16 historical recipients were alive with functioning grafts after follow-ups of 21 to 36 months. Now, after 41.4 to 42.2 post-transplant

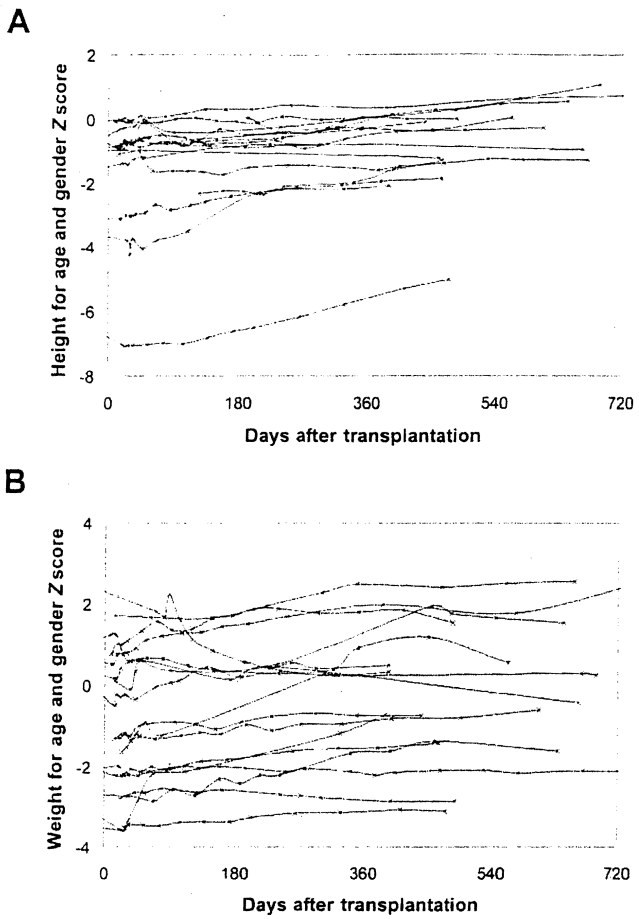

Figure 3. Height (Panel A) and weight (Panel B) for age and gender *Z* scores for the 16 patients who bear functioning grafts. Reference population data is from the 2000 Centers for Disease Control, growth data available online at www.cdc.gov/growthcharts.

years, six still bear their original grafts, all but one with a normal serum creatinine. Moreover, four of the six have been off all immunosuppression for 5 to 21 years.[35]

By 1964, the original strategy was modified in two ways in Colorado and worldwide.[35] Because 15% to 20% of the rejections had proved to be irreversible, large doses of prednisone were given from the time of operation instead of being added to azathioprine as needed. The second modification was de-emphasis or omission of pretreatment. These changes were carried forward after cyclosporine and tacrolimus became available, using the new drugs as one component of multi-agent regimens. Reliable prevention of acute rejection resulted, as well as reduction in the use of steroids.[8-13] However, the drastic weaning from immunosuppression accomplished in the early cases was almost never accomplished. Efforts to improve the complex protocols were frustrated for many years because the mechanisms of organ engraftment, and the effect of immunosuppression on these mechanisms, were unknown.

After donor leukocyte microchimerism was discovered in 1992 in our long-surviving kidney and liver recipients, including the survivors from the bellwether 1962 to 1963 pediatric renal series,[36,37] it was concluded that exhaustion-deletion of the antidonor response initiated by migration into the recipient of the graft's migratory passenger leukocytes is the seminal mechanism of alloengraftment and of acquired tolerance (reviewed[17,37-40]). It also was suggested that strong prophylactic post-transplant immunosuppression could narrow the one-time-only window of opportunity for efficient acute clonal deletion.[17,39] To avoid this, the therapeutic principles employed in the cases reported here were proposed.[17,25] The purposes of lymphoid depletion were to reduce the anticipated donor-specific clonal response into a more easily controllable and deletable range before arrival of the graft, and to permit the safe use of light post-transplant immunosuppression. Because of its relative freedom from infusion reactions, greater potency, and longer effect,[22,23,41] alemtuzumab is our current preferred antilymphoid antibody.

After the strategy was shown to be effective for adult renal transplantation,[25-27] it was adopted in 2003 as the optimal standard of care for pediatric kidney recipients at the CHP. Spaced weaning was initiated later than in the adults and was stopped at every other day or 3 doses per week. Further spacing is not planned until the third post-transplant year unless specifically indicated. Complete immunosuppression discontinuance is not contemplated except for life-threatening reasons, eg, an uncontrollable post-transplant lymphoproliferative disorder. Similar to the experience of 1962 to 1963, normal growth patterns that are part of a happy childhood appear to have resumed in the current recipients while there has been a paucity of drug-associated complications (eg, drug-specific side effects, opportunistic infections, and virus-associated malignancies). The hemolytic anemia in two of our current patients also was a déjà vu observation. Similar puzzling early hematologic abnormalities were seen in the historical recipients, and they were readily controlled by temporary treatment with steroids.[1]

Although we emphasize that the kidney recipients reported here had a short follow-up to date (mean 22 months, range 16 to 31), the continued well-being of these patients is presaged by observations still being made of their analogous predecessors of 40 years ago.

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