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Received 6 June 1996.
Accepted 27 August 1996.

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0041-1337/96/6212-1752$03.00/0
TRANSPLANTATION

Vol. 62, 1752–1758, No. 12, December 27, 1996
Printed in U.S.A.

TACROLIMUS IN PEDIATRIC RENAL TRANSPLANTATION[1]

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Tacrolimus was used as the primary immunosuppressive agent in 69 pediatric renal transplantations between December 17, 1989, and June 30, 1995. Children undergoing concomitant or prior liver and/or intestinal transplantation were excluded from analysis. The mean recipient age was 10.3±5.0 years (range, 0.7–17.5 years). Seventeen (24.6%) children were undergoing retransplantation, and six (8.7%) had a panel reactive antibody level of 40% or higher. Thirty-nine (57%) cases were with cadaveric kidneys, and 30 (43%) were with living donors. The mean donor age was 28.0±14.7 years (range, 1.0–50.0 years), and the mean cold ischemia time for the cadaveric kidneys was 27.0±9.4 hr. The antigen match was 2.7±1.2, and the mismatch was 3.1±1.2. All patients received tacrolimus and steroids, without antibody induction, and 26% received azathioprine as well. The mean follow-up was 32±20 months. One- and 4-year actuarial patient survival rates were 100% and 95%. One- and 4-year actuarial graft survival rates were 99% and 85%. The mean serum creatinine level was 1.2±0.8 mg/dl, and the calculated creatinine clearance was 82±26 ml/min/1.73 m^2. The mean tacrolimus dose was 0.22±0.14 mg/kg/day, and the level was 9.5±4.8 ng/ml. The mean prednisone dose was 2.1±4.9 mg/day (0.07±0.17 mg/kg/day), and 73% of successfully transplanted children were off prednisone. Seventy-nine percent were not taking any antihypertensive medications. The mean serum cholesterol level was 158±54 mg/dl. The incidence of delayed graft function was 4.3%. The incidence of rejection was 49%, and the incidence of steroid-resistant rejection was 6%. The incidence of rejection decreased to 27% in the most recent 26 cases (January 1994 through June 1995). The incidence of

[1] Presented at the 15th Annual Meeting of the American Society of Transplant Physicians, May 26–30, 1996, Dallas, Texas.

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new-onset diabetes was 10.1%; six of the seven affected children were able to be weaned off insulin. The incidence of cytomegalovirus disease was 13%, and that of posttransplant lymphoproliferative disorder was 10%; the incidence of posttransplant lymphoproliferative disorder in the last 40 transplants was 5% (two cases). All of the children who developed posttransplant lymphoproliferative disorder are alive and have functioning allografts. Based on this data, we believe that tacrolimus is a superior immunosuppressive agent in pediatric renal transplant patients, with excellent short- and medium-term patient and graft survival, an ability to withdraw steroids in the majority of patients, and, with more experience, a decreasing rate of rejection and viral complications.

Tacrolimus is a relatively new immunosuppressive agent, approved by the FDA in June 1994, for use in liver transplant recipients (*1–6*). It has, however, also been used in adults undergoing renal transplantation, both as a primary and as a rescue agent, in many centers around the world (*7–14*). For the same toxicities, principally nephrotoxicity, neurotoxicity, and diabetogenicity (*15–20*), it has been shown to have more immunosuppressive efficacy than cyclosporine-based therapy (*8, 9, 21*). This has been manifested by improved short- and projected long-term graft survival, and an increased ability to wean steroids completely (*8,9,21,22*).

There has been rather less experience with tacrolimus in pediatric renal transplantation, although the early experience has been encouraging (*23–28*). In this report, our cumulative experience with tacrolimus as the primary immunosuppressive agent in pediatric renal transplant recipients is summarized, and the lessons we have learned and the details of our current strategies for using this agent are described.

PATIENTS AND METHODS

Between December 17, 1989, and June 30, 1995, tacrolimus was used as a primary immunosuppressive agent in 69 renal transplantations performed in 68 pediatric patients at the Children's Hospital of Pittsburgh (CHP; Table 1). Children who had undergone or were undergoing concomitant liver and/or intestinal transplantation were not included in this analysis. The mean recipient age was 10.3±5.0 years (range, 0.7–17.5 years). Five (7.2%) children were under 2 years of age at the time of transplantation, and another eight (11.6%) were between 2 and 5 years of age. Seventeen (24.6%) children were undergoing retransplantation; eleven (15.9%) received their second, five (7.2%) received their third, and one (1.4%) received his fourth transplant. Nine patients had been transplanted previously elsewhere, and eight had received transplants previously at CHP. Six (8.7%) children had a panel reactive antibody (PRA) level over 40%. The causes of end-stage renal disease are listed in Table 2.

Thirty-nine (57%) transplants were with cadaveric kidneys, and 30 (43%) were with living donors (28 parents, 1 grandmother, and 1 adoptive father; Table 1). The mean donor age was 28.0±14.7 years (range, 1.0–50.0 years). The mean cold ischemia time for the cadaveric kidneys was 27.0±9.4 hr. Eight (20.5%) of the cadaveric cases were with donors less than 5 years of age, and of these, two were with pediatric en bloc kidneys from donors 1 year and 1.2 years of age. All of the recipients of these pediatric kidneys were over 10 years of age. The mean number of antigen matches and mismatches was 2.7±1.2 and 3.1±1.2, respectively.

Immunosuppression was with tacrolimus (*26, 27, 29*); 26% of patients received azathioprine as well. Induction antilymphocyte therapy was not used. Tacrolimus was given orally at a dose of 0.15 mg/kg before surgery. After surgery, it was begun as a continuous intravenous infusion of 0.075–0.10 mg/kg/day. Once patients were able to tolerate a diet, they were started on oral tacrolimus, 0.15 mg/kg twice a day, and the intravenous tacrolimus was gradually tapered off. Plasma levels were followed initially; for the past 2 years, whole blood IMx levels have been used. Current tacrolimus target levels and steroid dosing guidelines are shown in Table 3.

Statistical analysis. The patient survival rate was calculated from the date of kidney transplantation until death, and the graft survival rate was calculated from the date of kidney transplantation until graft failure, retransplantation, or patient death. Survival curves were generated using the Kaplan-Meier (product limit) method and were compared using the log-rank (Mantel-Cox) test. All tests were two-tailed. A P-value less than 0.05 was considered statistically significant.

Until June 1994, when tacrolimus was approved by the U.S. Food and Drug Administration, all transplants were done under a protocol approved by the Human Rights Committee of CHP.

TABLE 1. Recipient and donor demographics: time period 12/17/89–6/30/95

No. of transplants	69
No. of children	68
Recipient age (yr)	10.3±5.0 (range, 0.7–17.5)
<2 years	5 (7.2%)
2–5 years	8 (11.6%)
Retransplants	17 (24.6%)
2nd transplant	11 (15.9%)
3rd transplant	5 (7.2%)
4th transplant	1 (1.4%)
PRA ≥40%	6 (8.7%)
Cadaveric donors	39 (57%)
Living donors	30 (43%)
Donor age (yr)	28.0±14.7
Cold ischemia time (hr)	27.0±9.4
Pediatric donors ≤5 years	8 (20.5%)
Antigen match	2.7±1.2
Antigen mismatch	3.1±1.2
0 Antigen mismatch	2 (2.9%)

TABLE 2. Causes of end-stage renal disease

Obstructive uropathy	12 (17%)
Congenital dysplasia	10 (14%)
Membranoproliferative glomerulonephritis	8 (12%)
Focal segmental glomerulosclerosis	7 (10%)
Hemolytic-uremic syndrome	4 (6%)
Polycystic kidney disease	3 (4%)
Prune belly	3 (4%)
Reflux	3 (4%)
Congenital hypoplasia	2 (3%)
Cystinosis	2 (3%)
Interstitial nephritis	2 (3%)
Other	9 (13%)
Unknown	4 (6%)

RESULTS

The mean follow-up was 32±20 months.

The overall 1- and 4-year actuarial patient survival rates were 100% and 95% (Fig. 1, Table 3). Two patients died 3.3 years and 1.3 years after transplantation. The first patient was a 17.4-year-old white female with end-stage renal disease secondary to ureteral reflux who lost her allograft to

* Abbreviations: CHP, Children's Hospital of Pittsburgh; CMV, cytomegalovirus; PRA, panel reactive antibody; PTLD, posttransplant lymphoproliferative disorder.

TABLE 3. Tacrolimus target levels

Time	Level (ng/ml)
First 2 weeks	20–25
1 month	15–20
3 months	10–15
Chronic	<5 to 8–9

Guidelines for steroid dosing

Time	Dose (mg/kg/day)
Intraoperative	15–25
Postoperative day 1–6	3–10 → 0.3–1
Weeks 2–3	0.25–0.75
Weeks 4–5	0.2 to 0.5–0.6
Weeks 6–7	0.17–0.2 to 0.4–0.5
2 months	0.17 to 0.25–0.3
2-1/2 months	0.15 to 0.13–0.2
3 months	0.13–0.1
3-1/2 months	0.13–0.05
4 months	0.08–0
5 months	0.05–0
6 months	0

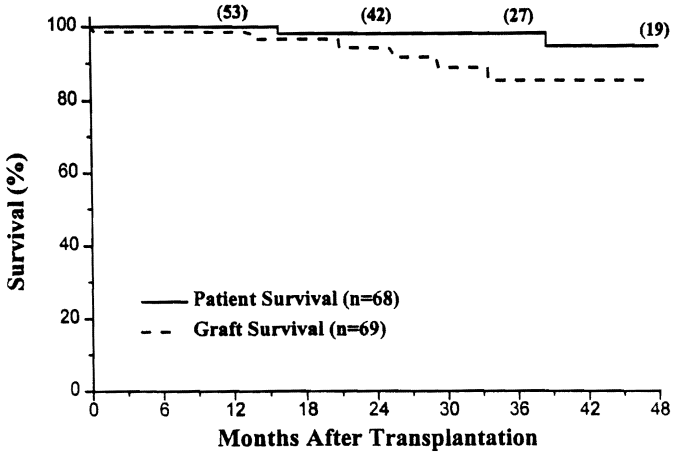

FIGURE 1. Kaplan-Meier patient and graft survival rates for pediatric kidney transplantation from December 14, 1989, to June 30, 1995. The number in parentheses represents the number of patients at risk.

noncompliance 1.8 years after transplantation and died on dialysis (off immunosuppression) 1.5 years later of uncertain causes. The second was a 17.5-year-old black male with sickle cell anemia, who had a difficult course after transplantation, including fungal infection (*Rhizopus*) of his left native kidney, several episodes of rejection, and recurrent sickle crises. He rather suddenly developed fungal sepsis 1.3 years after transplantation, with a mycotic aneurysm of the superior mesenteric artery and associated infarction of his entire gastrointestinal tract.

The overall 1- and 4-year actuarial graft survival rates were 99% and 85% (Fig. 1, Table 4). Eight patients lost their allografts, three to chronic rejection 1.1, 2.8, and 4.2 years after transplantation, three to recurrent disease (hemolytic-uremic syndrome at 0.02 years, membranoproliferative glomerulonephritis type II at 3.4 years, and focal segmental glomerulosclerosis at 2.1 years), one to death at 1.3 years, and one to noncompliance at 1.8 years (Table 4). One- and 4-year actuarial graft survival rates in selected subgroups

TABLE 4. Actuarial patient and graft survival rates[a]

	1 year	4 years
Patient	100%	95%
Graft	99%	85%

[a] Causes of graft loss: disease recurrence, n=3; rejection, n=3; infection/death, n=1; noncompliance, n=1.

are shown in Table 5. Interestingly, cadaveric organ recipients did as well as living donor organ recipients (the numerical superiority in the cadaver group at 4 years, 89% vs. 81%, was not statistically different; four patients in each group lost their kidney). Retransplant recipients were also not statistically worse than first-transplant recipients, but there was an increasing difference in graft survival at 4 years (75% vs. 90%). Patients with high PRA levels did significantly worse than patients with low PRA levels at 4 years (42% vs. 93%; $P=0.0003$), and the 1-year outcomes were also worse (83% vs. 100%). Recipient age had no effect on graft survival, nor did donor age. Of note, all five recipients under 2 years of age and seven of the eight recipients under 5 years of age had functioning allografts. In addition, the 1- and 4-year graft survival rates for the recipients of kidneys from donors 5 years of age or younger were both 100%; one recipient did go on to lose his kidney to chronic rejection at 4.2 years. Rejection was also not associated with statistically worse graft survival, but there was a trend toward worse outcomes at 4 years (78% vs. 97%) in patients who experienced rejection.

The mean serum creatinine level was 1.2±0.8 mg/dl, and the calculated creatinine clearance was 82±26 ml/min/1.73 m^2 (*30*). The mean blood urea nitrogen level was 25±13 mg/dl (Table 6). These values were relatively stable over time (Table 7).

The mean tacrolimus dose was 7.8±6.8 mg/day (0.22±0.14 mg/kg/day), and the mean level was 9.5±4.8 ng/ml (Tables 6 and 7). The mean prednisone dose was 2.1±4.9 mg/day (0.07±0.17 mg/kg/day); for children still on prednisone, it was 7.1±6.8 mg/day (0.3±0.3 mg/kg/day). Seventy-three percent of children transplanted successfully were taken off prednisone (Table 6). Steroids were withdrawn at a mean time of 7.9±5.2 months after transplantation. Ten percent of

TABLE 5. Subgroup actuarial (Kaplan-Meier) graft survival rates

Subgroup	1 year	4 years	P^a
Cadaver	97%	89%	0.804
Living donor	100%	81%	
First transplant	100%	90%	0.114
Retransplant	94%	75%	
PRA <40%	100%	93%	0.0002
PRA ≥40%	83%	42%	
Recipient age			
<2 years	100%	100%	0.807
2–5 years	89%	89%	
>5 years	100%	84%	
Donor age (cadaver)			
≤5 years	100%	100%	0.913
>5 years	98%	83%	
Rejection			
No	97%	97%	0.345
Yes	100%	78%	

[a] Log-rank test.

TABLE 6. Creatine, tacrolimus, and steroid levels

Serum creatinine	1.2±0.8 mg/dl
Calculated creatinine clearance	82±26 ml/min/1.73 ^{2}
Blood urea nitrogen	25±13 mg/dl
Tacrolimus	
Dose	7.8±6.8 mg/day (0.22±0.14 mg/kg/day)
Level	9.5±4.8 ng/ml
Steroids	
Dose (all patients)	2.1±4.9 mg/day (0.07±0.17 mg/kg/day)
Dose (still on prednisone)	7.1±6.8 mg/day (0.30±0.30 mg/kg/day)
Off steroids	73%

patients had to have steroids restarted. Serum creatinine was comparable among patients taken off steroids (1.0±0.4 mg/dl), patients restarted on steroids (1.1±0.7 mg/dl), and patients who were never taken off steroids (1.4±0.4 mg/dl).

Delayed graft function was seen in three (4.3%) patients (Table 8); two required dialysis. All of the delayed graft function was seen in cadaveric cases.

Rejection was seen in 34 (49%) patients, and was biopsy proven in over 90% of the cases (Table 8). Over 90% of rejection episodes were seen within the first 2 weeks after transplantation. Steroid-resistant rejection was seen in four (6%) patients; 88% of the rejection episodes were treated with steroids and modification of the tacrolimus dosage. There was a decrease over time in the incidence of rejection; between December 1989 and December 1993, rejection was noted in 63% (27/43) of the patients; between January 1994 and June 1995, the incidence was 27% (7/26; $P=0.004$). This was probably related to maintaining higher tacrolimus levels during the first 2 weeks after transplantation in the more recently transplanted patients (see *Discussion*).

New-onset diabetes was observed in seven (10.1%) patients (Table 8). This was a temporary complication in six children, and normoglycemia off insulin was achieved within several months after gradually reducing both the tacrolimus and steroid dosages. The one patient who remained insulin dependent was the sickle cell patient described above, who had several rejection episodes and required high doses of both tacrolimus and steroids.

Cytomegalovirus (CMV), either asymptomatic infection or symptomatic disease, was observed in nine (13.0%) children (Table 6); in all of these cases, the recipients were seronegative and received kidneys from seropositive donors. All patients received routine prophylaxis with high-dose oral acyclovir; in addition, intravenous ganciclovir and CMV hyperimmune globulin was given to the seropositive donor/seronegative recipient cases. All affected children responded promptly to intravenous ganciclovir and reduction of immunosuppression. In a few cases, it was possible to diagnose CMV infection by antigenemia testing (*31*), before symptomatic disease developed, and treat preemptively with ganciclovir.

Early (4–6 months after transplantation) Epstein-Barr virus-related posttransplant lymphoproliferative disorder (PTLD) was seen in seven (10.1%) patients (Table 8). PTLD was seen in the liver, gastrointestinal tract, and/or allograft. These cases behaved much like viral infections; all disappeared with cessation of immunosuppression and intravenous ganciclovir. Immunosuppression was eventually reintroduced, and none of the children died or lost their allograft. Of note, the incidence of PTLD seemed to decrease as more experience was acquired with tacrolimus. From December 1989 to December 1992, five (17%) cases of PTLD were seen, whereas from January 1993 until June 1995, two (5%) cases were reported. This was probably related both to more aggressive tapering of immunosuppression beginning 6–8 weeks after transplantation and, more recently, monitoring of the Epstein-Barr virus antigenemia to allow for reduction of immunosuppression and preemptive treatment with ganciclovir before PTLD could develop.

In addition, there was one late case of Burkitt's lymphoma in a 11.8-year-old boy, which developed 3.8 years after transplantation and 3 months after his maintenance immunosuppression was increased by 50%. This patient received chemotherapy with cyclophosphamide, vincristine, methotrexate, adriamycin, etoposide, cytosine arabinoside, and prednisone, which was successful in eradicating the lymphoma. His allograft function remains good (serum creatinine, 1.3 mg/dl), and he was recently restarted on tacrolimus, at 1 mg p.o. q.d.

Finally, there was a late case of non-Burkitt's lymphoma in a 16.4-year-old boy who received a transplant in Pittsburgh but was followed elsewhere, which was diagnosed 4.3 years after transplantation. The patient was begun on a chemotherapy regimen identical to that described above and, in addition, he received local radiation therapy to the brain stem. Immunosuppression was discontinued, and renal function has remained normal (serum creatinine, 1.1 mg/dl).

At most recent follow-up, 79% of children with successful transplants were not taking antihypertensive medications. The mean serum cholesterol level was 158±54 mg/dl (Table 9).

Serial heights were reported in all children and were converted to Z-scores. The mean Z-scores were plotted over time for all children and were stratified based on age (under 12 years vs. 12 and over) and steroid dosage (off steroids vs. on) (Figs. 2 and 3 and Table 10). There was enormous variability in growth after transplantation. Clearly, however, children off steroids tended to have more accelerated growth than children on steroids, and children 12 years of age or younger at the time of transplantation tended to achieve better growth than children who received transplants after the age of 12. The most recent Z-score for children 12 and under off steroids was −0.94±1.37; for the five children under 2 years of age (all of whom were off steroids), it was −0.15±0.77.

DISCUSSION

Tacrolimus has emerged as an efficacious immunosuppressive agent in a wide variety of transplant settings (*4–6, 32–37*). In our pediatric renal transplant recipients, it has been associated with excellent patient and graft survival and an ability to wean steroids and antihypertensive agents in 73% and 79%, respectively, of children with successful transplants. Growth, particularly in preadolescent children who have been weaned off steroids, has improved substantially and has become normal in many cases. The two major complications that had been seen early in our experience with this agent, a moderately high incidence of rejection on the one hand and an alarming incidence of PTLD on the other, seem to have decreased over time. In the 18-month period

TABLE 7. Creatine, tacrolimus, and steroid values over time

	6 months	1 year	2 years	3 years	4 years
Serum creatinine (mg/dl)	1.1±0.6	1.0±0.4	1.1±0.5	1.3±0.7	1.4±1.0
Creatinine clearance (ml/min/1.73 m^2)	81±35	83±23	80±25	79±26	75±30
Blood urea nitrogen (mg/dl)	26±11	24±9	23±9	25±14	26±16
Tacrolimus dose					
mg/day	8.5±5.8	7.2±6.9	6.2±3.3	6.7±3.6	7.8±2.7
mg/kg/day	0.32±0.18	0.23±0.11	0.24±0.13	0.23±0.13	0.26±0.11
Tacrolimus levels (ng/ml)	10.5±3.0	8.8±2.4	8.7±1.9	7.7±2.0	8.0±1.1
Prednisone dose					
All patients					
mg/day	3.3±4.4	1.3±3.2	2.1±5.1	2.2±4.2	3.4±5.0
mg/kg/day	0.11±.14	0.04±.09	0.07±0.18	0.07±0.14	0.12±0.22
Still on prednisone					
mg/day	6.2±4.2	6.7±4.4	9.1±7.1	7.2±4.6	7.9±4.7
mg/kg/day	0.19±0.14	0.20±0.11	0.30±0.28	0.23±0.17	0.29±0.27

TABLE 8. Complications

Delayed graft function	4.3%	(3/69)
Dialysis	3%	(2/69)
Rejection	49%	(34/69)
Dec 1989 to Dec 1993	63%	(27/43)[a]
Jan 1994 to June 1995	27%	(7/26)
Steroid-resistant rejection	6%	(4/69)
New-onset diabetes		
Initial	10.1%	(7/69)
Final	1.4%	(1/69)
Cytomegalovirus	13.0%	(9/69)
PTLD	10.1%	(7/69)
Dec 1989 to Dec 1992	17%	(5/29)
Jan 1993 to June 1995	5%	(2/40)
Lymphoma	2.9%	(2/69)

[a] P=0.004.

TABLE 9. Follow-up data

Off antihypertensive medications	79% (48/61)
Serum cholesterol (mg/dl)	158±54

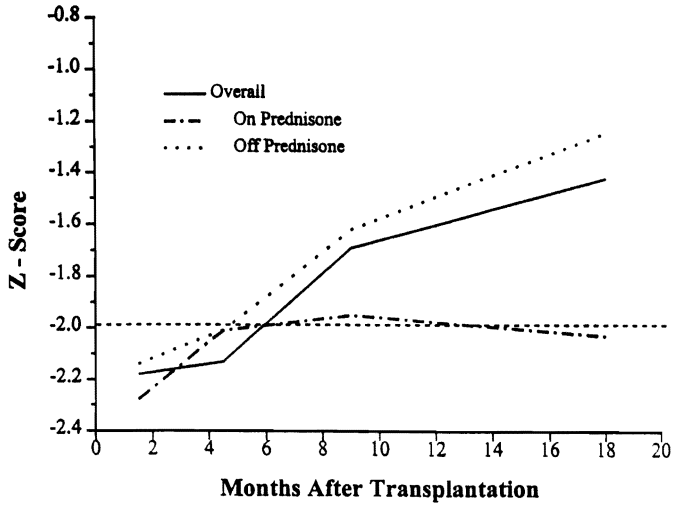

FIGURE 2. Plot of Z-scores over time for patients on and off steroids.

TABLE 10. Z-score (most recent)

Age (yr)	Z-score
<2	−0.15±0.77
2–5	−1.77±0.99
>5	−1.47±1.60
≤12, off steroids	−0.94±1.37
≤12, on steroids	−1.84±1.70
>12, off steroids	−1.81±1.58
>12, on steroids	−2.08±1.46

from January 1994 to June 1995, the incidence of rejection was 27% (7 of 26 cases), in contrast to the 63% (27 of 43 cases) incidence seen from December 1989 to December 1993. Similarly, in the last 40 cases, PTLD was seen in two (5%) patients, in contrast to the five (17%) cases seen in the first 29 patients. Although this is reassuring, the occurrence of two late lymphomas is of concern, and points to the need for continued surveillance and the importance of maintaining low levels of chronic immunosuppression.

Our current practice calls for patients to receive an oral dose of tacrolimus, 0.15 mg/kg, on call to the operating room. On arrival to the intensive care unit after surgery (all of our children go to the intensive care unit after renal transplantation), intravenous tacrolimus is started at a dose of 0.075–0.10 mg/kg/day, as a continuous infusion. When patients are able to tolerate a diet, they are gradually converted to oral tacrolimus, starting at 0.15 mg/kg p.o. twice a day. Intravenous tacrolimus is *not* stopped abruptly, but is tapered over several days. The goal is to maintain whole blood IMx levels of 20–25 ng/ml for the first 2 weeks after surgery. It is our impression that maintaining these high target trough levels has been important in reducing the incidence of early rejection. Tacrolimus dosages are then gradually weaned to maintain levels of 15–20 ng/ml by 1 month, 10–15 ng/ml by 3 months, and less than 5 to 8–9 ng/ml chronically (Table 3).

Steroids are begun in the operating room with a bolus of intravenous methylprednisolone, 15–25 mg/kg. A short steroid recycle is then given during their first postoperative week, tapering from 3–10 mg/kg/day to 0.3–1 mg/kg/day. The wide variability reflects a somewhat higher mg/kg dosage in very small children. In the uncomplicated case, steroid tapering is begun 2–3 weeks after surgery, with the goal of discontinuing steroids altogether by 4–8 months after transplantation. Obviously, the tapering schedule is subject to modification in children experiencing rejection. Whenever possible, however, a consciously aggressive approach to re-

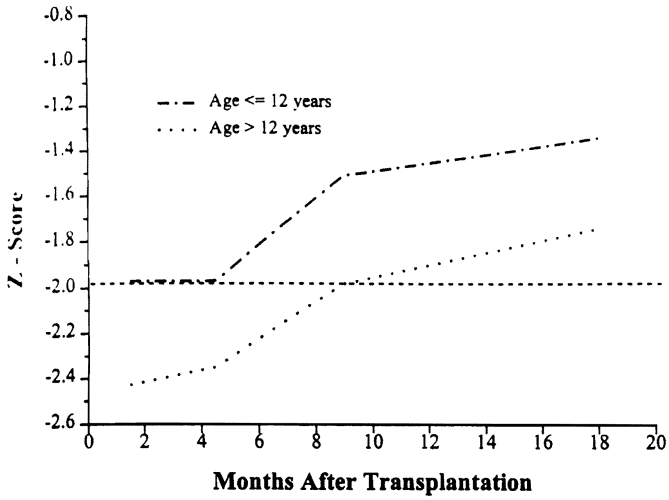

FIGURE 3. Plot of Z-scores over time for patients 12 years and younger vs. patients older than 12 years at the time of transplantation.

ducing immunosuppression, beginning 6–8 weeks after surgery, has, in our view, been instrumental in decreasing the incidence of PTLD. Finally, once steroids have been discontinued and a chronic maintenance dose and level of tacrolimus have been achieved, in the presence of stable renal function, the tacrolimus dose generally should *not* be adjusted upward (it may, however, need to be decreased to the lowest possible dosage consistent with avoiding rejection). Children do not "outgrow" their tacrolimus dosage, and the consequences of an unindicated increase in the dose can be disastrous. In practice, several pediatric patients have been maintained off steroids with tacrolimus levels of less than 5 ng/ml (which generally means a level of 3.0–4.9 ng/ml), with stable, normal renal function.

Given the excellent patient and graft survival rates obtained under tacrolimus-based immunosuppression, the ability to wean steroids and antihypertensive agents in a high percentage of cases, and the decreasing incidence of both rejection and PTLD as more experience with the agent has been acquired, we believe that tacrolimus is the immunosuppressive drug of choice in children undergoing renal transplantation.

Acknowledgments. **We thank Regina Fenton, RN, BSN, Loraine Kaminski, RN, BSN, Jennifer Ovesney, RN, M.J. Grosso, RN, MSN, Deborah Good, RN, BSN, Holly Woods, RN, Jareen Flohr, RN, BSN, Sue Bauder, RN, Sharon Orlofske, RN, and Mark Paynter, RN, BSN, for their help with patient care; Janet Schmelzer for her help with data entry and organization; Kate Carr for her help with slide preparation; and Susan Shandor for her help with typing the manuscript and with table and slide preparation.**

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Received 25 April 1996.
Accepted 13 September 1996.

0041-1337/96/6212-1758$03.00/0
TRANSPLANTATION

Vol. 62, 1758–1762, No. 12, December 27, 1996
Printed in U.S.A.

CLINICAL HEPATITIS AFTER TRANSPLANTATION OF HEPATITIS C VIRUS–POSITIVE KIDNEYS

HLA-DR3 AS A RISK FACTOR FOR THE DEVELOPMENT OF POSTTRANSPLANT HEPATITIS[1]

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Background. **Exposure to hepatitis C virus (HCV) and subsequent infection after renal transplantation lead to significant clinical hepatitis in approximately 50% of graft recipients.**

Methods. **One hundred thirty-two consecutive renal allotransplant patients, who underwent transplantation of kidneys from HCV-positive cadaveric donors, were studied to investigate the relationship between donor and recipient HLA type and the risk of developing clinical hepatitis. Specific attention was directed toward the DR3 and DR4 alleles, as these had previously been associated with worse prognoses in autoimmune and viral hepatitis.**

Results. **Overall, 42% of patients receiving kidneys from donors seropositive for HCV developed clinical hepatitis. This was unrelated to preoperative recipient HCV serum reactivity ($P=0.65$). Patients receiving kidneys from seropositive donors with HCV RNA as detected by PCR were more likely to develop hepatitis than those receiving kidneys from PCR-negative donors (56% vs. 11%; $P=0.005$). The presence of the DR3 allele was associated with a significant risk of clinical hepatitis ($P=0.025$); 80% of DR3-positive recipients (n=34) progressed to hepatitis compared with 42% of DR3-negative patients. No other recipient HLA type was significantly related to prognosis. All patients receiving a donated kidney that expressed the B41 allele developed hepatitis, compared with 55% of recipients of non-B41 grafts ($P=0.039$). No association between the development of clinical hepatitis and HLA compatibility was found.**

Conclusions. **These results suggest that both HLA type and viral presence as assayed by polymerase chain reaction, influence the risk of disease progression after transplantation of HCV-positive kidneys. Application of these associations may decrease the relative risk of a recipient contracting HCV hepatitis after cadaveric renal transplantation.**

Kidneys from donors infected by the hepatitis C virus (HCV*) have been shown to function after allotransplantation as well as kidneys from noninfected donors. Their use has increased the sparse supply of donor organs and has

[1] Presented at the 15th Annual Meeting of the American Society of Transplant Physicians, May 26–30, Dallas, Texas.

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* Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction.