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LONG-TERM RESULTS AFTER CONVERSION FROM CYCLOSPORINE TO TACROLIMUS IN PEDIATRIC LIVER TRANSPLANTATION FOR ACUTE AND CHRONIC REJECTION

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Abstract

Tacrolimus is beneficial in liver transplantation for reversing steroid-resistant acute rejection, and for controlling the process of chronic rejection in allograft recipients receiving Cyclosporine- (CyA) based regimens.Very little is known about the long-term efficacy of tacrolimus in pediatric transplantation after conversion from CyA. Our study examines the long-term outcome after conversion to tacrolimus for acute or chronic rejection in pediatric liver transplant (LTx) recipients.

Method. Seventy-three children (age < 18 years) receiving their primary LTx under CyA between August 1989 and April 1996 were converted to tacrolimus for ongoing acute rejection (n=22, group I) or chronic rejection (n=51, group II). Mean age at the time of conversion was 10.2±5.5 years with a mean interval from LTx to conversion of 3.5±2.9 (range 0.5–10.1 years). There were 33 boys and 40 girls. All patients were followed until June 1999. Mean follow-up was 97.3±17.4 months (range 62.4–118.9 months).

Results. Overall 5-year actual patient survival was 78.1% and 8-year actuarial survival was 74.6%. Patients converted to tacrolimus therapy to resolve acute rejection (group I) experience significantly better patient and graft survival at 5 and 8 years than those converted to resolve chronic rejection (group II). Eight-year patient survival and graft survival was 95.5 and 90.9% for group I compared to 74.6 and 53.5% for group II, respectively (long rank P =0.035 and 0.01, respectively). Nearly 75% of children were weaned off steroids after conversion. There was a marked improvement in hypertension, gum hyperplasia, hirsutism, and cushingoid appearance. One child in group I (4.5%) and four children in group II (7.8%) developed posttransplant lymphoproliferative disorder after conversion. There was an improvement in growth in children who were less than the age of 12 years at the time of conversion and who were weaned off steroids; more significantly girls responded more favorably than boys.

Conclusion. The benefit of transplantation is maintained long-term after conversion to tacrolimus for acute or chronic rejection. The response rate was significantly better in group I as compared with group II. Marked improvement in growth, hypertension, and reversal of the brutalizing effects of CyA was noted after conversion to tacrolimus. The results suggest that early conversion of pediatric liver transplant patients is warranted for the treatment of acute and chronic rejection, and for improvements in quality of life.

Tacrolimus is a macrolide derived from Streptomyces tsukubaensis found in Tsukuba, Japan in experimental models. Tacrolimus was found to be 10–100 times more potent than Cyclosporine A (CyA) (1). The first clinical trial, performed in 1989 at our center, was a rescue trial for liver allograft failing under CyA therapy due to acute rejection, chronic rejection, or other CyA related complications (2–4). Before this, there was no satisfactory treatment for chronic rejection. The ability of tacrolimus to control, and reverse the process of chronic rejection in some cases was remarkable (3, 5). After reports from our center there were several single center and multi-center reports confirming the same findings in adults as well as in children (6–13). However, very little has been reported on the long-term outcome of pediatric patients rescued by treatment with tacrolimus.

Our purpose was to examine the long-term outcome in children who were converted from CyA to tacrolimus-based immunosuppression for acute or chronic rejection. The results examine

the patient survival, graft survival, causes of death, rate of retransplant, changes in quality of life, and growth and development.

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PATIENTS AND METHODS

Between August 1989 and April 1996, 73 children were converted from CyA based immunosuppression to tacrolimus. There were 33 boys and 40 girls with a mean age of 6.6±5.4 years (range 0.4–17.5 years) at the time of the first liver transplant. Mean age at the time of conversion was 10.2±5.5 years, and the mean interval from the first liver transplant to conversion was 3.5±2.9 years range (range 0.1–10.1years).

The indications for the primary liver transplant are shown in Table 1. Eighteen children (24.7%) received at least two liver transplants. Two children received three liver transplants and one patient received four liver transplants before conversion. Twenty-two children (30.1%) were converted to tacrolimus for ongoing acute rejection (group I). These patients had persistent acute rejection despite of repeated courses of steroids and/or OKT3 within 3 weeks of conversion. Acute rejections were confirmed on liver biopsies in almost all the cases with unresolved biochemical abnormalities. The remaining 51 children (69.9%) were converted for ongoing chronic rejection. Chronic rejections were also confirmed on liver biopsies by a pathologist who had no knowledge of baseline immunosuppression. Fourteen percent of patients received monoclonal antibody OKT3 before conversion and the remaining patients were treated with more then one course of i.v. steroids before conversion. All patients were followed until June 1999; mean follow-up was 97.3±17.4 months (range 62.4–118.9 months). Patient survival, graft survival, cause of death, time of death after conversion, rate of retransplantation, changes in steroids, and immunosuppression-related complications including compromised growth (evaluated using Z score) were followed (14, 15).

Table 1

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Conversion protocol.

For acute rejection CyA was discontinued and tacrolimus was started on the same day. For chronic rejection tacrolimus was started usually 24 hr after discontinuation of CyA. For moderate-to-severe acute rejections, patients were initially treated with i.v. tacrolimus,

aiming for a plasma trough level of 1.5 ng/ml or whole blood trough concentration of 20 ng/ml for about 48±12 hr. The remaining children received oral dose of tacrolimus at 0.2 to 0.4 mg/kg/day, aiming for a trough plasma concentration of 1.0 to 1.5 ng/ml and a whole blood trough concentration of 15 ng/ml. These therapeutic levels could be accomplished within 24 hr of conversion. Other immunosuppressive agents in use at the time of conversion (prednisone and/or azathioprine) were unchanged until the rejection was controlled, then subsequently weaned. After conversion liver biopsies were performed only if clinically indicated; postconversion protocol liver biopsies were not performed.

Patients were monitored in hospital for signs and symptoms of cumulative toxicities of CyA and tacrolimus during the conversion period, including headache, tremor, hypertension, hyperglycemia, and renal dysfunction.

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RESULTS

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Patient Survival

Overall 5-year actual survival for both groups was 78.1% and 8-year actuarial survival was 74.6%. The difference in survival for group I and group II was statistically significant (P =0.035;Fig. 1).

Figure 1

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Group I

Overall 5-year actual and 8-year actuarial survival was 95.5% for this group (Fig. 1). One child (case 20, 7-year-old girl) died 5 weeks after conversion from influenza viral pneumonitis. Another child (case 18, 14.3-year-old girl) died 8.2 years after conversion

from respiratory failure due to cystic fibrosis

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Group II

Five-year actual survival was 70.6% and 8-year actuarial survival was 65.3% for this group (Fig. 1). Seventeen (33%) of the children died during the follow-up period. The causes of death after conversion are shown in Table 2. The most common cause of death was infection (n=9; 52.9%). In four children, the cause of death was determined to be Epstein-Barr virus-related infection resulting in PTLD, two of whom had presented with PTLD before conversion. Candidiasis developed in four patients; two of these presented with a mycotic aneurysm of the hepatic artery resulting in rupture. Two children died from leukemia after failing to respond to chemotherapy. Two additional deaths resulted from intraoperative bleeding at the time of retransplantation. Four children died from (1) primary nonfunction after retransplantation, (2) hemorrhagic pancreatitis, (3) multi-system organ failure, and (4) noncompliance.

Table 2

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Graft Survival

Overall 5-year actual survival for both groups was 67.1% and 8-year actuarial survival was 64.9%. The difference in graft survival for group I and group II was statistically significant long rank P =0.01.

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Group I

Including death as a cause of graft loss, 5-year actual graft survival and 8-year actuarial survival was 90.9% (Fig. 2). One child (case 17; 14.8-year-old boy) required two

Figure 2

retransplants at 30 and 34 months after conversion respectively for liver failure from recurrent acute rejection. He had a documented history of noncompliance after retransplant.

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Group II

Five-year actual graft survival for this group was 56.9% and 8-year actuarial survival was 53.5% (Fig. 2). Fourteen children (27.5%) failed to control progressive chronic rejection and required retransplantation. One patient (Case 68; 18.6-year-old girl) underwent two more retransplants 8 months after conversion both secondary to primary nonfunction of the liver allograft. She died from multi-system organ failure.

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Immunosuppression.

Before conversion the mean CyA trough levels were 273 ng/ml. Thirty children were also on azathioprine with median dose of 25 mg/day.

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Tacrolimus dose.

The mean tacrolimus dose was maintained at 7.5±4.5 mg/day over the first 6 months after conversion. By 2 years, the mean dose stabilized at 5 mg/day for the remainder of the follow-up period. (Fig. 3)

Figure 3

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Tacrolimus trough concentrations.

Initially, tacrolimus trough concentrations were measured in plasma at our institution. After August 1995, concentrations were measured in whole blood, which are approximately 10 times higher than in plasma. The mean trough plasma levels were 0.9±0.6 ng/ml at 6 months and 0.6±0.1 ng/ml at 60 months postconversion. Mean trough whole blood level were 12.0±12.0 ng/ml at 6 month and 6.5±5.0 ng/ml at 72 months postconversion. There was little change in the mean trough concentrations beyond 1 year (Fig. 4). There was no significant difference in tacrolimus dose or concentration between the two groups after the initial conversion period of a few weeks.

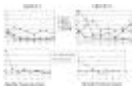

Figure 4

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Prednisone

Before conversion only 3.6% of children were maintained off steroids. After conversion, prednisone dose was lowered gradually on an individual basis, depending on the clinical response and after normalization of liver allograft biochemical changes. This led to a steroid-free population from 31% at 6 months to 78.3% at 72 months (Fig. 3). Furthermore, the proportion of children receiving >10 mg/day declined from 28.6% before conversion to 4.4% at 6 months of follow-up. Overall, the mean prednisone dose before conversion was 10.6±9.4 mg/day. The mean dose was decreased to 4.2±4.5 mg/day at 6 months and 2.5±5.1 mg/day at 6 years after conversion (Fig. 3).

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Liver Function

Before conversion, the mean total bilirubin was 4.9±6.9 mg/dl in group I and 2.9±4.3 in group II. There was wide variation in both groups ranging from 0.1–18.8 in group I and 0.3–14.9 mg/dl for group II. Mean serum bilirubin was normalized by 6 months for group I and by 12 months for group II. However, serum bilirubin levels did not stabilize until the second year in group II. In group I, 5 children (22.7%) had total bilirubin >12 mg/dl and they all responded to conversion. For group II, three patients had a total bilirubin >5 <12 mg/dl, and three patients had a bilirubin >12 mg/dl. One patient with a bilirubin >5 <12 required

retransplantation and the other two responded to conversion. Similarly, two patients with a bilirubin > 12 mg/dl responded, and one required retransplantation. Both retransplants were performed for liver failure from uncontrolled chronic rejection.

It is interesting to note that the mean GGTP level for group I declined from 225 U/liter to less than 100 U/liter at 1 year postconversion and remained at this level for the entire study period. For patients in group II, the mean GGTP level before conversion was 687±782 U/liter. Despite a significant decline over the first 4 years GTTP levels remained relatively high in group II over the entire follow-up period. Changes in liver function for both groups after conversion are shown in Figure 4. Only three patients had biopsy proven acute rejection after conversion that did not require retransplantation.

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Renal Function.

Serial protocol creatinine clearance and or glomerular filtration rate was not performed in these children; although blood urea nitrogen and serum creatinine varies with age and muscle mass these were the only parameters available in medical records. The mean blood urine nitrogen and mean creatinine for both groups remained stable for the entire period. One child received a kidney transplant prior to conversion. There were no new cases of end-stage renal failure, requiring either hemodialysis or kidney transplantation (Fig. 4).

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Additional Risks and Benefits of Conversion

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Posttransplant lymphoproliferative disorder (PTLD).

A summary of the development of PTLD and associated outcomes is presented in Table 3.

Reducing or withdrawing immunosuppressive therapy treated most children who developed de novo PTLD. Table 3

In group I: One child (4.5%; case 10, 17.6-year-old boy) developed PTLD in a cervical lymph node 22 months after conversion. He is alive and free from PTLD with normal liver allograft function at 81 months after the diagnosis of PTLD.

The overall incidence of PTLD was 4 times higher in group II as compared with group I. In group II: nine children (17.6%) developed PTLD, five of them (56%) before conversion. Two children died (case 27 and case 43). One patient (case 27, 5-year-old boy) had PTLD involving lymph node and intestine 1 month before conversion. He died 31 months postconversion. A 6.6-year-old girl (case 43) who developed spindle cell sarcoma of the stomach 2 months before conversion died 19 days after conversion. Both children had chronic rejection with PTLD and were not candidates for retransplantation. Tacrolimus monotherapy was used as a last resort to reverse the on-going chronic rejection and was considered to be the only hope of their survival. Unfortunately, it proved to be fatal on both occasions. Of the four children who developed de novo PTLD, two have died; one at 8 months (case 35) and the other 42 months (case 64) after conversion. The remaining five children (56%) are currently alive and disease-free for 5.5–10 years after the development of PTLD (Table 4). All four children died with PTLD and graft failure.

Table 4

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Hypertension.

Thirty-four children were known to be on antihypertensive medication before conversion. Six patients received two antihypertensive medications and one child was on three antihypertensive medications. Fifteen children (44.1%) were withdrawn from all anti hypertensive medication; in four children (11.8%) the hypertension improved and required reduced amounts of antihypertensive medication. However, two children required more antihypertensive medication after conversion to tacrolimus.

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Hyperkalemia.

Sixteen of 63 children (25.4%) required Fludrocortisone to control hyperkalemia at 1 year. At 5 years 18.5% of children were still on Fludrocortisone. All patients tolerated fludrocortisone without any problem of sodium retention or hypertension in this population.

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Facial appearance.

In addition to the benefits of improvement in liver function after conversion to tacrolimus, we have observed significant improvements in the facial appearance of these young children associated with the reduction in mean dose of steroids and the cessation of CyA therapy. As shown in Figure 5, conversion resulted in a dramatic resolution of steroid-induced cushingoid appearance, and CyA-associated hirsutism. Complete reversal occurred within 3–6 months after conversion to tacrolimus in nearly 90% of children suffering from these brutalizing side effects of CyA and steroids (Table 4).


Figure 5

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Gum hyperplasia.

Gum hyperplasia developed in 78% of CyA-treated children. There was a considerable improvement in 97.4% of children after conversion to tacrolimus as documented in medical records and on inquiry on the phone by coordinators (Table 4).

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Gynecomastia.

Eight boys developed gynecomastia while receiving CyA and steroids; five of them (62.5%) showed resolution after conversion to tacrolimus (Table 4).

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Growth.

Growth was determined by using Z scores (14, 15). Information on age and height was available for 17 children before and after conversion to tacrolimus. The Z score before conversion was -2.61±3.12, and improved to -1.7±1.9 at most recent evaluation (at mean follow-up of 4.68 years). The improvement was more in patients who discontinued steroid therapy as compared to those who remained on steroids (Pearson [chi]2 NS). More girls showed improvement in Z score than boys (Pearson [chi]2 square P =0.03.) (Table 5).

Table 5

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DISCUSSION

The first clinical trial of tacrolimus began at our institution in March of 1989 (4) and focused on its use for liver allografts failing CyA-based therapy. Subsequent reports of outcome after conversion from CyA to tacrolimus in both adults and children supported the benefits of its use and guided the development of its use as a primary agent (2, 3, 5–13, 16–20). Initial reports from our institution in 1990 (2) and 1991 (3) showed that conversion from CyA to tacrolimus resulted in a biochemical response in 70% of the patients. Subsequently, Demetris et al. (5) reported a better histopathological response in adults after conversion to tacrolimus in the early stages of chronic rejection; which was sustained in the long term. It was also realized that tacrolimus treatment might not only halt the process of chronic rejection, but also reverse the process in some cases.

In 1991 and1993 we reported the first successful use of tacrolimus in pediatric transplantation both for primary and rescue treatment for all vascularized solid organ transplants (5, 19, 20). Eighty-two percent of the children with LTx could be completely

weaned off steroids after conversion from CyA to tacrolimus with patient and graft survival of 82 and 71%, respectively, reported at 11 to 34 months of follow-up. The kinetic advantages of tacrolimus over CyA, particularly in children were also reported (21–23).

Other studies subsequently reported similar findings (11, 24). It was noted that bilirubin levels normalized more rapidly following conversion for acute rejection than for chronic rejection. Biochemical parameters, such as serum bilirubin >10 mg/dl by Sher et al. (13) and >12 mg/dl by McDiarmid et al. (11) at the time of conversion were identified as poor prognostic factors. Those initial observations are corroborated by the results of our study. Interestingly, a notably poor outcome was reported in pediatric patients rescued for chronic rejection, although it is possible that these patients were at an advanced stage of chronic rejection (12). In our series, the majority of children were in the relatively early stages of disease, based on their biochemical profile. Although three children had serum bilirubin >12 mg/dl, it normalized in two of these children; a third required retransplantation.

Many children are noncompliant to steroids because of appearance. Conversion to Tacrolimus may have a positive impact on these patients. Certainly the positive impact on noncompliance alone would have a direct effect on the incidence of acute and chronic rejection described here.

Observations regarding improvement in hirsutism, growth, and hypertension after conversion from CyA to tacrolimus (25) are strongly substantiated and expanded in this series; the dramatic changes in cushinoid facial appearance are shown in Figure 5. These improvements were accompanied by reversal of gingival hyperplasia and gynecomastia as well as improved growth.

The reported increased incidence of PTLD in children after conversion from CyA to tacrolimus is reflective of the cumulative effect of immunosuppression (26). Approximately, 56% children already had PTLD before conversion, as a cumulative result of chronic efforts to salvage these failing liver allografts. We observed more PTLD in patients

converted for chronic rejection. The overall rate of de novo PTLD was 6.8% in this series. However, death related to PTLD in group II (chronic rejection) was 44.4%, higher than that observed in pediatric transplant patients maintained on tacrolimus as primary therapy. In our primary LTx under tacrolimus, the post-PTLD survival for children was 89% long term with mean follow-up of >6 years after PTLD (27). Such "immunological" complications inevitably impact on long-term survival, and may be another source for the variable success rates (28, 29).

In this study, we have established that the benefits of conversion to tacrolimus are maintained long term, with 8-year patient survival of 95.5% for acute rejection and 65.3% for chronic rejection. Nearly 78% of children remain off steroids. Careful monitoring of the drug at the time of conversion is essential for reduction in toxicity of the drug. In addition, there was a significant improvement in hypertension. The incidence of diabetes in pediatric population is lower as compared to adults under tacrolimus (30). There was no additional nephrotoxicity at long term follow-up.

Based on our findings we conclude that children should be converted to tacrolimus therapy at an early stage of chronic or acute rejection to optimize their long-term outcome. Other indications for conversion should include children with hypertension who are requiring two or more anti-hypertensive medications, children with the brutalizing facial effects of CyA and steroid therapy, steroid dependency, and growth retardation.

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TABLE 1. Indications for liver transplant		
	N	%
Biliary altresia	**32**	**43.8**
Metabolic disease	**14**	**19.1**
[Alpha]-1 antitrypsin def. (10)		
Familial cholestastsis (2)		
Wilson's disease (1)		
Glycogen storage disease (1)		
Hepatitis	**9**	**12.3**
Non-A Non-B (3)		
Autoimmune (2)		
Neonatal (2)		
Giant cell (2)		
Cirrhosis	**9**	**12.3**
Postnecrotic (6)		
Cryptogenic (2)		
Biliary (1)		
Primary sclerosing cholengitis	**2**	**2.7**
Miscellanous	**7**[a]	**9.5**

[a] Homocystin def 1; Budd chiari 1; fulminant hepatic failure 1; congenital hepatic fibrosis 1; carolis 1; intrahepatic cholectasis 1; cystic fibrisis 1.

Table 1 . Indications for liver transplanta Homocystin def 1; Budd chiari 1; fulminant hepatic failure 1; congenital hepatic fibrosis 1; carolis 1; intrahepatic cholectasis 1; cystic fibrisis 1.

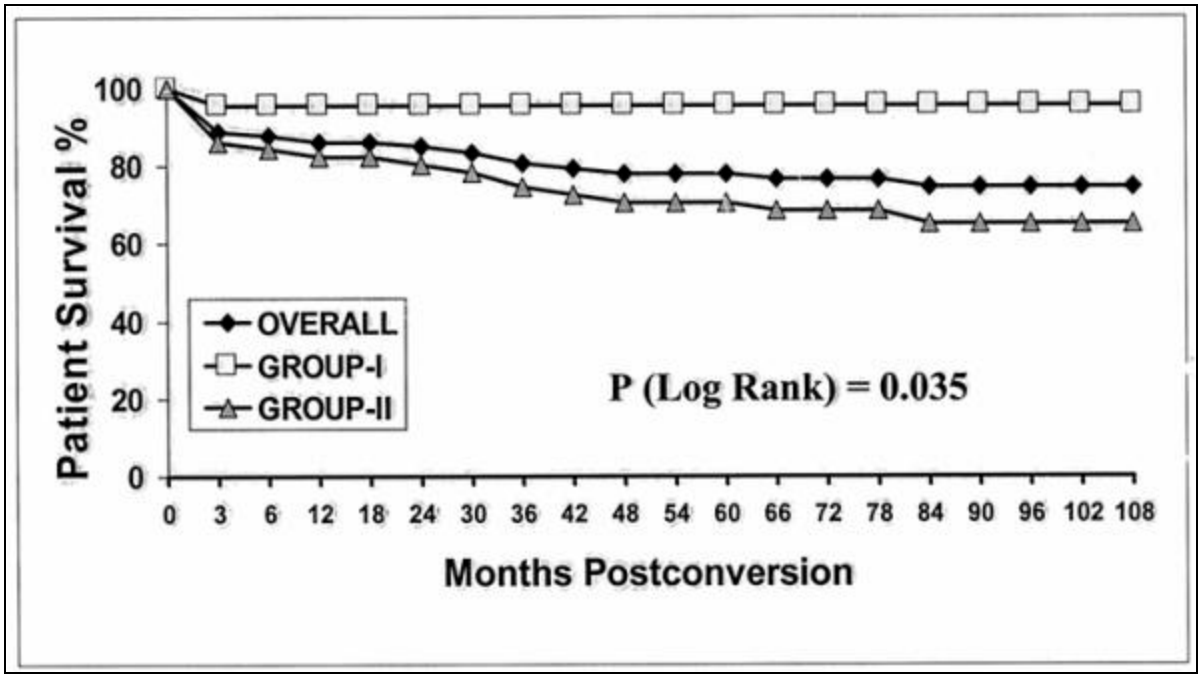


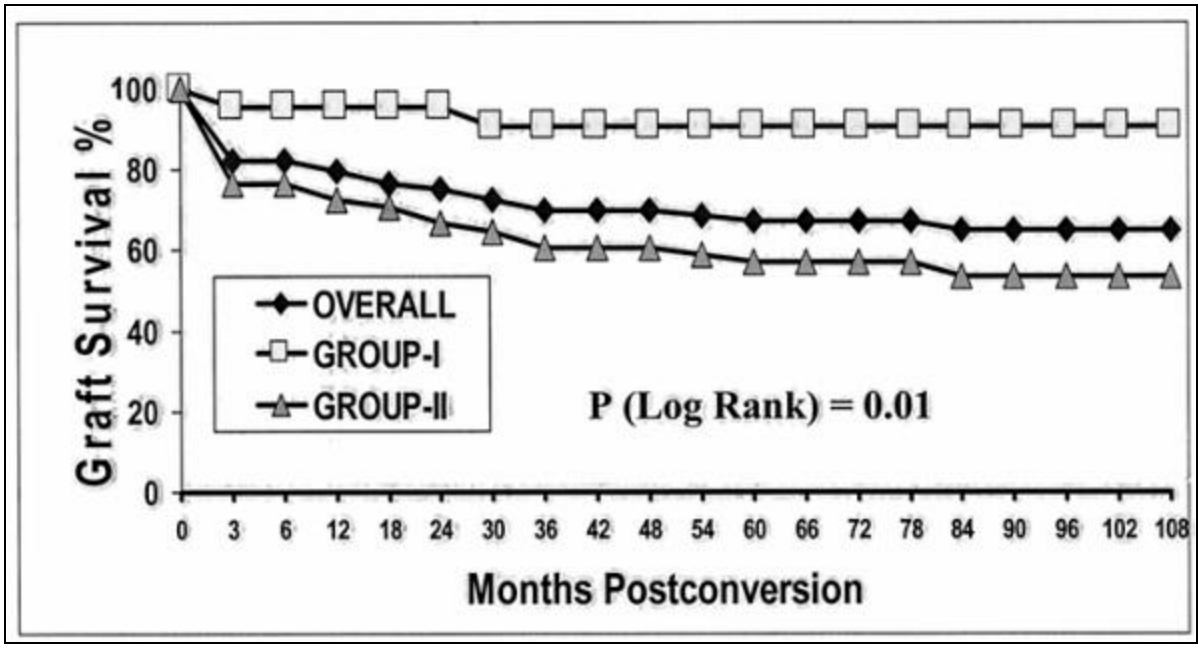
Figure 1 . Patient survival overall and for group I (acute rejection) and group II (chronic rejection).

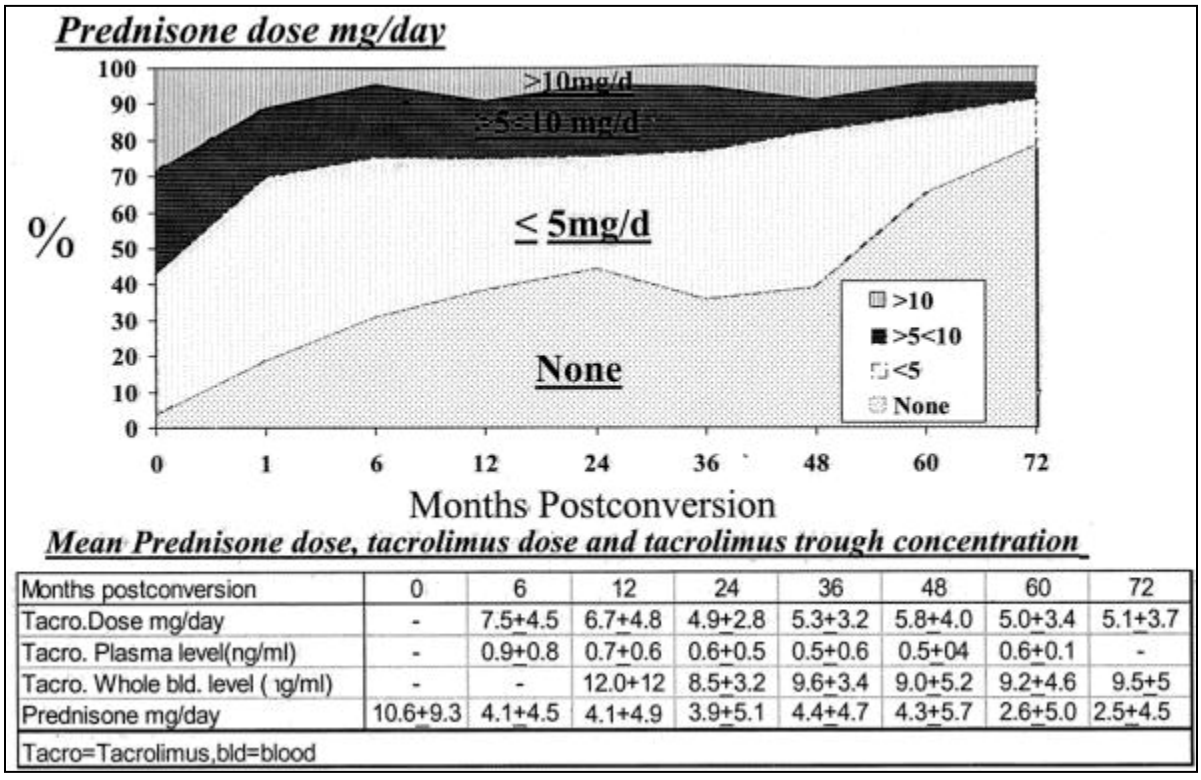
TABLE 2. Causes of death

Months postconversion	≤3	>3 to ≤6	>6 to ≤12	>12 to ≤24	>24 to ≤36	>36 to ≤48	>48 to ≤60	>60 to ≤72	>72 to ≤84	>84 to ≤96	Total
Causes											
EBV/PILD	1		1		1	1					4
Fungal				1		1[a]	1[a]		1		4
Adenovirus				1							1
Influenzavirus	1[b]										1
Intraoperative				1				1			2
Leukemia				1				1			2
PNF						1					1
Multisystem failure						1					1
Pancreatitis										1	1
Noncompliance								1			1
Total											18

[a] Mycotic-aneurism rupture.
[b] From group I, PNF, primary nonfunction.

Table 2 . Causes of death a Mycotic-aneurism rupture.b From group I, PNF, primary nonfunction.





Mean Prednisone dose, tacrolimus dose and tacrolimus trough concentration

Months postconversion	0	6	12	24	36	48	60	72
Tacro.Dose mg/day	-	7.5±4.5	6.7±4.8	4.9±2.8	5.3±3.2	5.8±4.0	5.0±3.4	5.1±3.7
Tacro. Plasma level(ng/ml)	-	0.9±0.8	0.7±0.6	0.6±0.5	0.5±0.6	0.5±04	0.6±0.1	-
Tacro. Whole bld. level (ıg/ml)	-	-	12.0±12	8.5±3.2	9.6±3.4	9.0±5.2	9.2±4.6	9.5±5
Prednisone mg/day	10.6±9.3	4.1±4.5	4.1±4.9	3.9±5.1	4.4±4.7	4.3±5.7	2.6±5.0	2.5±4.5

Tacro=Tacrolimus,bld=blood

Figure 3 . Shows percentage of children off prednisone, 510 mg/day before conversion and up 72 months postconversion. Also shown are mean daily dose of tacrolimus, trough concentration of tacrolimus, and mean daily prednisone dose.

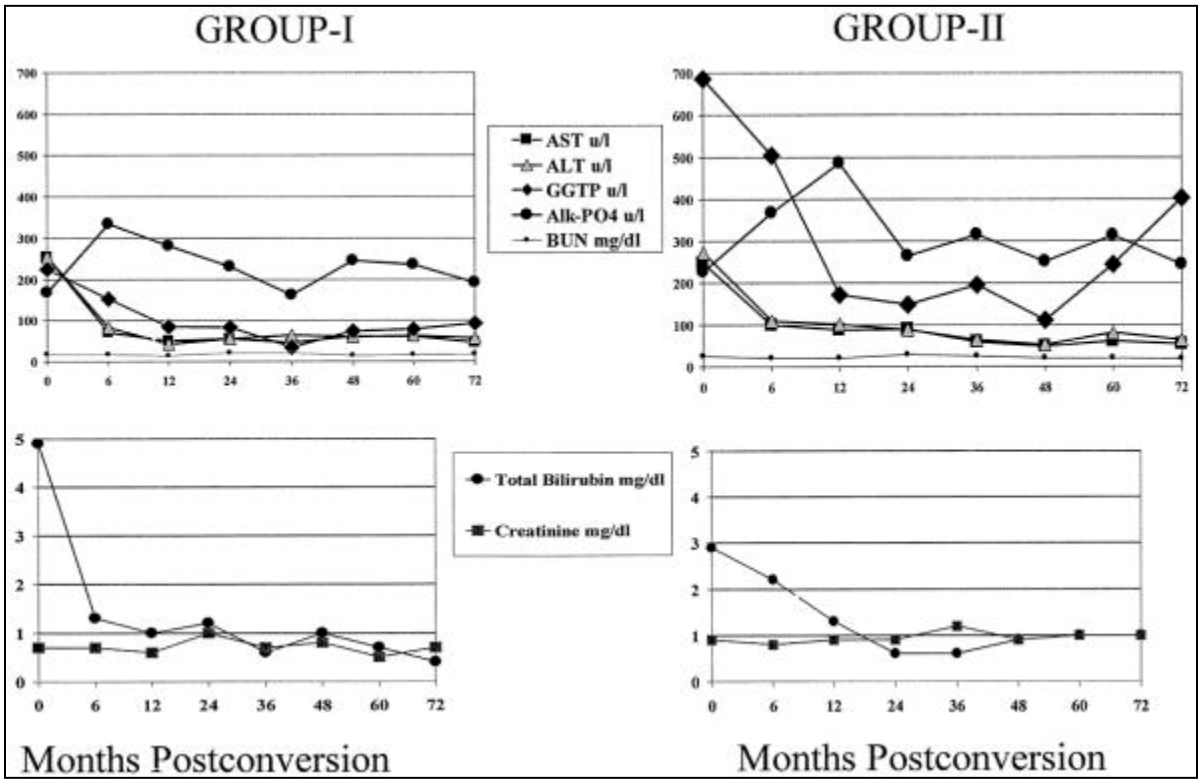


Figure 4 . Liver and renal function at conversion and up to 72 months after conversions, for group I and group II all are mean values.

TABLE 3. Posttransplant lymphoproliferative disorder (PTLD)

Case	Gender	Age at Ltx (yr)	Age at Switch (yr)	Group	Site of ptld	Months to PTLD from switch[a]	Survival post-PTLD (mo)	Survival from switch (mo)	Pt. surv. from Ltx (mo)	Current status
10	M	13	17.61	I	cervical node	22.01	80.56	102.57	157.96	Alive
27	M	5	8.50	II	lymph node, intestine	(−1)[b]	32.10	31.10	72.80	Deceased
28	M	2.5	9.02	II	adenoid	(−51.58)	110.95	59.38	137.63	Alive
34	F	7	14.26	II	para tracheal mass	(−52.76)	120.76	67.99	155.20	Alive
35	M	5.9	9.19	II	submandibular mass	7.70	0.56	8.26	47.76	Deceased
36	F	6.2	6.30	II	gastric antrum	6.78	97.37	104.14	105.33	Alive
43	F	1	6.57	II	spindle cell gastric	(−2.14)	2.76	0.63	67.47	Deceased
46	F	2.24	11.58	II	tonsil, lymphnodes	(−109.57)	166.35	56.78	168.88	Alive
61	F	2	2.17	II	liver	0.20	65.95	66.15	68.19	Alive
64	F	0.6	1.33	II	tonsils, adenoid, cervical node	37.80	4.21	42.01	50.72	Deceased
	Mean	*3.60*	*7.66*			*13.12*	*66.78*	*48.49*	*97.11*	
	SD	*2.42*	*4.14*			*16.79*	*60.54*	*32.08*	*46.27*	

LXa Liver transplant.
[a] Mean; SD, and median calculation excludes the patients with PTLD pre conversion. PTLD was four times higher in group II comp.
[b] PTLD months before conversion to tacrolimus.

Table 3 . Posttransplant lymphoproliferative disorder (PTLD)LXa Liver transplant.a Mean; SD, and median calculation excludes the patients with PTLD pre conversion. PTLD was four times higher in group II comp.b PTLD months before conversion to tacrolimus.

TABLE 4. Secondary benefits of conversion from CyA to tacrolimus

	Cushingoid	Hirtutism	Gingival hyperlasia	Gynecomastia[a]
No. of children affected	46	39	35	8
% Improvement	98.1	97.4	94.3	62.5
% No improvement	1.9	2.6	5.7	27.5

[a] Male patients.

Table 4 . Secondary benefits of conversion from CyA to tacrolimusa Male patients.

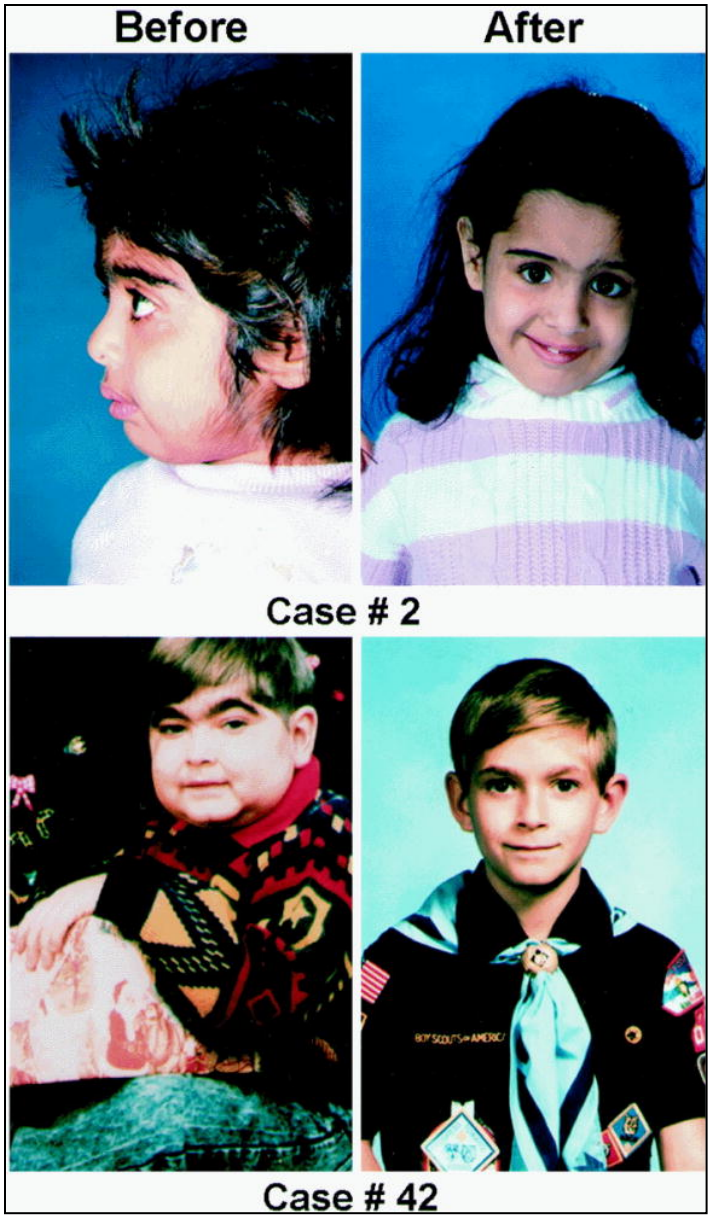


Figure 5 . Photographs of two patients before and after conversion to tacrolimus, showing marked improvement in the facial cushingoid appearance and hirtutism.

TABLE 5. Age/height Z score

	n	Mean ± Z Score			Male	Female	Age > 12	Age < 12	On steroid	Off steroid
		Before	After	Change	n (%)	n (%)	n (%)	n (%)	n(%)	n(%)
Overall	17	−2.84 ± 3.08	−1.89 ± 2.5	0.96 ± 3.2	8 (47)	9 (53)	4 (24)	13 (76)	7 (41)	10 (59)
Improvement	9	−4.25 ± 2.9	−2.8308	2.78 ± 3.55	2 (22)[a]	7 (78)[a]	2 (22)	7 (78)	2 (22)	7 (78)
No Improvement	8	−1.27 ± 2.5	−2.35 ± 2.26	−1.82 ± 0.77	6 (75)[a]	2 (25)8[a]	2 (25)	6 (75)	5 (63)	3 (37)

[a] Significant: Pearson χ^2: P = 0.03.

Table 5 . Age/height Z scorea Significant: Pearson [chi]2: P = 0.03