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PEDIATRIC LIVER TRANSPLANTATION

A SINGLE CENTER EXPERIENCE SPANNING 20 YEARS[1]

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Background. **Survival after liver transplantation has improved significantly over the last decade with pediatric recipients faring better than adults. The 20-year experience of pediatric liver transplantation at Children's Hospital of Pittsburgh is reported in terms of patient survival; graft survival in relation to age, gender, and immunosuppressive protocols; causes of death; and indications for retransplantation.**

Method. **From March 1981 to April 1998, 808 children received liver transplants at Children's Hospital of Pittsburgh. All patients were followed until March 2001, with a mean follow-up of 12.2±3.9 years (median=12.6; range=2.9–20). There were 405 female (50.2%) and 403 male (49.8%) pediatric recipients. Mean age at transplant was 5.3±4.9 years (mean=3.3; range 0.04–17.95), with 285 children (25.3%) being less than 2 years of age at transplant. Cyclosporine (CsA)-based immunosuppression was used before November 1989 in 482 children (50.7%), and the subsequent 326 recipients (40.3%) were treated with tacrolimus-based immunosuppression. Actuarial survival was calculated using the Kaplan-Meier statistical method. Differences in survival were calculated by log-rank analysis.**

Results. **Overall patient survival at 1, 5, 10, 15, and 20 years was 77.1%, 72.6%, 69.4%, 65.8%, and 64.4%, respectively. There was no difference in survival for male or female patients at any time point. At up to 10 years posttransplant, the survival for children greater than 2 years of age (79.5%, 75.7%, and 71.6% at 1, 5, and 10 years, respectively) was slightly higher than those at less than 2 years of age (72.6%, 66.9%, and 65.3% at 1, 5, and 10 years, respectively). However, at 15 and 20 years posttransplant, survival rates were similar (>2 years=67.3% and 65.8%; <2 years=64.1% and 64.1%). A significant difference in survival was seen in CsA-based immunosuppression (71.2%, 68.1%, 65.4%, and 61%) versus tacrolimus-based immunosuppression (85.8%, 84.7%, 83.3%, and 82.9%) at 1, 3, 5, and 10 years, respectively (P=0.0001). The maximum difference in survival was noted in the first 3 months between CsA and tacrolimus; thus, indicating there may have been other factors (nonimmunological factors) involved in terms of donor and recipient selection and technical issues. The mean annual death rate beyond 2 years posttransplant was 0.47%, with the mean annual death rate for patients who received tacrolimus-based immunosuppression being significantly lower than those who received CsA-based immunosuppression (0.14% vs. 0.8%; P=0.001). The most common etiologies of graft loss were hepatic artery thrombosis (33.4%), acute or chronic rejection (26.6%), and primary nonfunction (16.7%). Of note, retransplantation for graft loss because of acute or chronic rejection occurred only in those patients who received CsA-based immunosuppression.**

Conclusion. **The overall 20-year actuarial survival for pediatric liver transplantation is 64%. Survival has increased by 20% in the last 12 years with tacrolimus-based immunosuppression. Although this improvement may be the result of several factors, retransplantation as a result of acute or chronic rejection has been completely eliminated in patients treated with tacrolimus.**

Over the past 50 years, advances in organ procurement, preservation technology, immunosuppressive management, and perioperative care have contributed to the evolution of liver transplantation as the treatment of choice for end-stage liver disease. Although survival has improved dramatically, acute graft loss, chronic rejection, opportunistic infections, and degenerative diseases have hampered long-term survival. Survival for children is significantly higher than for adults (*1*); however, in the absence of long-term multi-institutional data, such survival outcomes are difficult to elucidate. Consequently, a center-specific 20-year retrospective analysis of all pediatric transplant recipients was implemented to determine patient and graft survival, causes of graft loss, indications for retransplantation, and differences in survival related to age, gender, and immunosuppressive protocols.

MATERIALS AND METHODS

From March 1981 to April 1998, 808 children received liver transplants at Children's Hospital of Pittsburgh. All patients were followed until March 2001, with a mean follow-up of 12.2±3.9 years (median=12.6; range=2.9–20). There were 405 female (50.2%) and 403 male (49.8%) pediatric recipients. Mean age at transplant was 5.3±4.9 years (mean=3.3; range 0.04–17.95), with 285 children (25.3%) less than 2 years of age at transplant. Cyclosporine (CsA)-based immunosuppression was used before November 1989 in 482 children (50.7%), and the subsequent 326 recipients (40.3%) were treated with tacrolimus-based immunosuppression as previously described (*2, 3*). Indications for liver transplantation are listed in Table 1. Patients received cadaveric grafts, and living-related grafts were not included in the study. Split or reduced-size adult livers were

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TABLE 1. Indications for liver transplantation

Indications for liver transplantation	CsA n(%)	Tacrolimus n(%)
Biliary atresia	264 (54.7)	153 (46.9)
Metabolic	77 (15.9)	46 (14.1)
A-1-A	45	18
GSD-I	1	0
GSD-IV	7	5
Hemochromatosis	2	1
Hyperlipidemia-II	1	0
Carbamylphosphatase deficiency	1	1
Oxalosis	0	7
Ornithine transcarbamyl deficiency	0	3
Criglar Najjar syndrome	0	1
Erythropoetic porphyria	0	1
Tyrosinemia	10	3
Wilson's disease	10	6
ALF	25 (5.1)	25 (7.6)
NANB hepatitis	24 (4.9)	9 (2.7)
Cryptogenic	15 (3.1)	15 (4.6)
Familial cholestasis	17 (3.5)	10 (3.0)
Primary hepatic malignancy	11 (2.3)	12 (3.6)
Neonatal hepatitis	13 (2.6)	7 (2.1)
Secondary biliary cirrhosis	11 (2.2)	6 (1.8)
Congenital hepatic fibrosis	5 (1.0)	10 (3.1)
AI hepatitis	4 (0.8)	4 (1.2)
PSC	4 (0.8)	3 (0.9)
HCV	0	2 (0.6)
Budd-chiari	2 (0.4)	3 (0.9)
HBV	1 (0.2)	1 (0.3)
Others	8 (1.6)	20 (6.1)
Cystic fibrosis	0	7
TPN liver failure	2	3
Nodular regenerative hyperplasia	0	3
Adenoma	1	0
Focal nodular hyperplasia	1	0
Mesenchymal hematoma	1	0
Pseudoinflammatory tumor	1	0
Incidental hepatoma	1	0
Trauma	1	0
Hemangioma	0	1
Indian childhood cirrhosis	0	2
Adrenoleucodystrophy	0	1
Histiocytosis X	0	1
Unknown	0	1
Biliary Dysgenesis	0	1
Total	482	326

A-1-A = alpha 1 antitrypsin deficiency; GSD = glycogen storage disease; ALF = acute liver failure; NANB = Non-A Non-B; AI = autoimmune; PSC = primary sclerosing cholangitis; HCV = hepatitis C Virus; HBV = hepatitis B virus; and TPN = total parenteral nutrition.

transplanted in 17 pediatric recipients, all of whom received tacrolimus-based immunosuppression.

Statistical Analysis

Actuarial survival was calculated with the Kaplan-Meier statistical method. Differences in survival were calculated by log-rank analysis. The incidences of various events were compared between two groups with the Pearson chi-square. Differences in mean values between both groups were compared using the equality of variance and independent sample Student t test. The Statistical Package for Social Sciences 10.0 software (SPSS, Inc., Chicago, IL) was used for generating statistical data. Multiple time points were analyzed to study the statistical significance of differences occurring at various times during the follow-up period. $P<0.05$ was considered significant.

RESULTS

Patient Survival

Overall patient survival at 1, 5, 10, 15, and 20 years was 77.1%, 72.6%, 69.4%, 65.8%, and 64.4%, respectively (Fig. 1). There was no difference in survival for male or female patients at all time points (Fig. 2, top). At up to 10 years posttransplant, the survival for children greater than 2 years of age (79.5%, 75.7%, and 71.6% at 1, 5, and 10 years, respectively) was slightly higher than those at less than 2 years of age (72.6%, 66.9%, and 65.3% at 1, 5, and 10 years, respectively) (Fig. 2, bottom). However, at 15 and 20 years posttransplant, survival rates were similar (>2 years=67.3% and 65.8%; <2 years=64.1% and 64.1%). A significant difference in survival was seen in CsA-based immunosuppression (71.2%, 68.1%, 65.4%, and 61%) versus tacrolimus-based immunosuppression (85.8%, 84.7%, 83.3%, and 82.9%) at 1, 3, 5, and 10 years, respectively ($P=0.0001$) (Fig. 3, top). The maximum survival difference was observed in the first 3 months posttransplant (22.8% with CsA vs. 9.5% with tacrolimus). After 3 months, the survival at 10 years was 78.6% with CsA versus 91.5% with tacrolimus, a difference of 12.9% (Table 2)

Causes of Death

A total of 258 children (32%) died during the follow-up period with 55.4% of deaths occurring within the first 3 months posttransplant. Of the mortalities, 203 recipients (42.1%) received CsA-based immunosuppression and 55 recipients (16.8%) were treated with tacrolimus. Causes of death are listed in Table 2 with the most common cause of death being infection (43%).

The mean annual death rate beyond 2 years posttransplant was 0.47% with the mean annual death rate for patients who received tacrolimus-based immunosuppression being significantly lower than those who received CsA-based immunosuppression (0.14% vs. 0.8%; $P=0.001$) (Table 2). The annual death rate for patients using CsA and tacrolimus-based immunosuppression is shown in Figure 4. The difference in the death rate between the immunosuppressive protocols was observed at all time points. The cumulative death rate at 1, 3, and 12 months posttransplant for CsA-treated patients was 16.3%, 22.6%, and 28.8%, respectively, and for tacrolimus-treated patients was 6.4%, 9.5%, and 14%, respectively.

Graft Survival

Patient deaths or retransplantations were considered as graft loss. Graft survival at 1, 5, 10, 15, and 20 years was

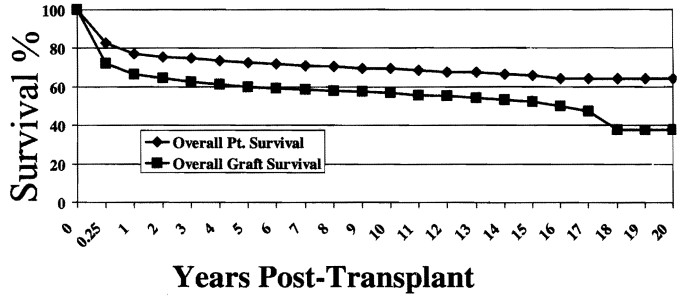

FIGURE 1. Patient and graft survival over time.

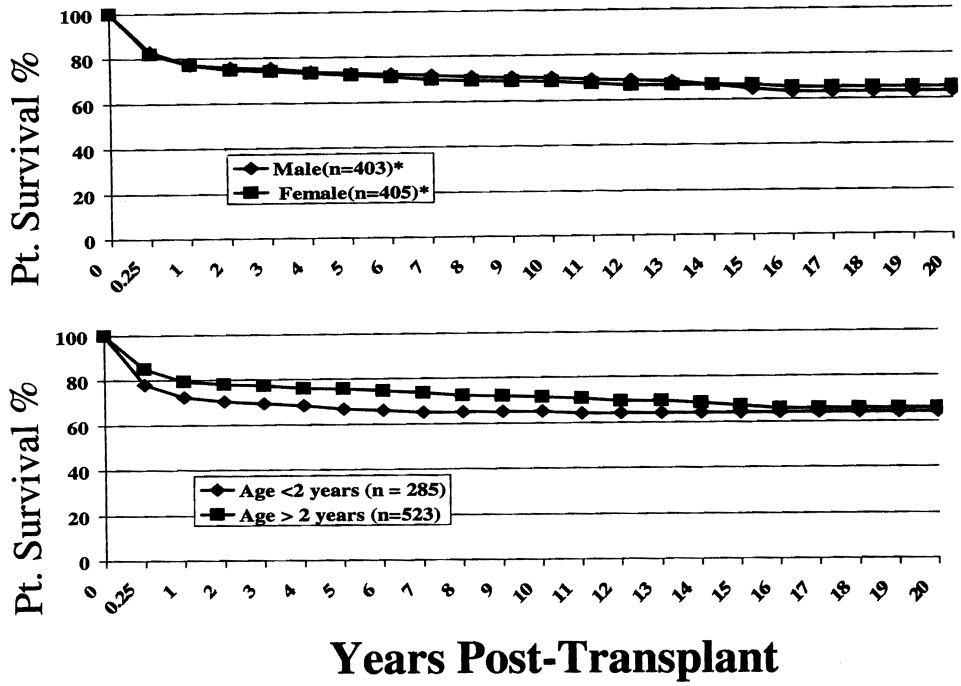

FIGURE 2. Patient survival by gender (top) and by age (bottom).

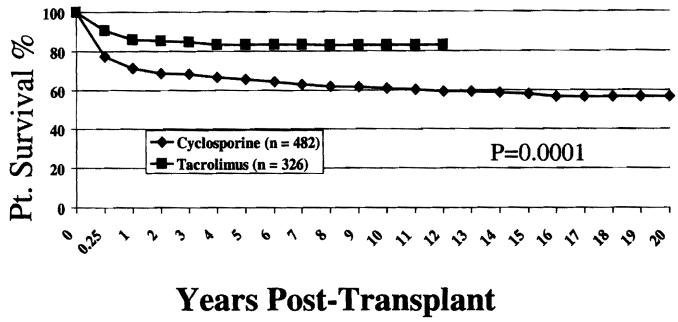

FIGURE 3. Patient survival under cyclosporine and tacrolimus immunosuppression.

66.6%, 60%, 57%, 52.3%, and 37.9%, respectively (Fig. 1). There was no difference in graft survival by gender (Fig. 5, top). Graft survival for children less than 2 years of age at the time of transplant and for those greater than 2 years of age at the time of transplant was not significantly different (Fig. 5, bottom). Two children under CsA-based immunosuppression required late retransplantation for chronic rejection at 16.5 years and 18 years posttransplant. Graft survival under CsA versus tacrolimus-based immunosuppression was similar to patient survival with a highly significant difference (P=0.0001) at 12 years posttransplant (Fig. 6).

Indications for Retransplantation

Two hundred three children (25.1%) required a second liver transplant. Additionally, 40 children required a third graft, six children received four grafts, and one child received five liver transplants. All seven children who received four or more grafts died. Hepatic artery thrombosis was the most common indication for a second allograft under both CsA and tacrolimus-based immunosuppression with an incidence of 33.4% (n=68) (Table 3). The second most common reason for retransplantation was rejection, both acute and chronic, with 54 patients (26.6%) who required another graft. Retransplantation was required in six patients (2.9%) with acute rejection and in 46 patients (22.6%) with chronic rejection. Interestingly, all retransplantations for acute or chronic rejection were performed in patients who were treated with CsA-based immunosuppression and none under tacrolimus.

Primary nonfunction was the third most common indication for retransplantation and was seen in 34 patients (16.7%). Of these patients, 19 (9.3%) were treated with CsA and 15 (7.3%) were treated with tacrolimus. Additional reasons for retransplantation included biliary stricture, posttransplant lymphoproliferative disease (PTLD), and others. Long-term survival after one retransplantation or ≥2 retransplantations was significantly inferior compared to those who retained their original allograft (Fig. 7).

Posttransplant Lymphoproliferative Disease

PTLD developed in 79 children (9.7%). Of these patients, 40 children (8.3%) received CsA-based immunosuppression and 39 children (11.6%) received tacrolimus-based immunosuppression. No significant difference was demonstrated between groups (P=0.08). The most common site of PTLD was in the lymph nodes. Sites of PTLD under CsA and tacrolimus are shown in Table 4.

Because most cases of PTLD occur after the first 2 months posttransplant, outcomes of patients at risk beyond 2 months posttransplant were investigated to further examine the incidence of PTLD. At 2 months posttransplant, 426 patients under CsA and 312 patients under tacrolimus were considered at risk. Of these patients, the incidence of PTLD was 9.4% in the CsA group and 12.5% in the tacrolimus group. The difference was not significant (P=0.177). Interestingly, survival after PTLD was significantly higher in patients who received tacrolimus-based immunosuppression than those patients who received CsA (P=0.001) (Fig. 8).

TABLE 2. Causes of Death

Causes	Months after transplantation													
	0 to 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	96 to 108	108 to 120	>120	Total n(%)
Infections	67	14	7	4	3	5	2	4	1	2			1	110 (42.6)
Cyclosporine	55	10	4	3	1	5	2	4	1	2			1	
Tacrolimus	12	4	3	1	2									
Cardiovascular	6	2							1					9 (3.4)
Cyclosporine	3	1							1					
Tacrolimus	3	1												
Respiratory	6	2	2	1										11 (4.2)
Cyclosporine	5	1	1	1										
Tacrolimus	1	1	1											
Gastrointestinal	5	1	2	1						1				10 (3.8)
Cyclosporine	2	1	2	1						1				
Tacrolimus	3													
Central nervous system	5													5 (1.9)
Cyclosporine	4													
Tacrolimus	1													
Hemorrhage	25			3		1	2							31 (12)
Cyclosporine	21			3		1	2							
Tacrolimus	4													
Recurrent disease	3		1	4		1		1						10 (3.8)
Cyclosporine	3		1	3		1		1						
Tacrolimus														
Other	16	2	4	1		3	1	2	1	1			2	33 (12.7)
Cyclosporine	12	1	4	1		3	1	2	1	1			2	
Tacrolimus	4	1												
Unknown	10	7	4	2	2	1	1		2	1	1	2	6	39 (15.1)
Cyclosporine	7	3	3	2	2	1			2	1		2	6	
Tacrolimus	3	4	1				1				1			
Total														258

Mean death rate per year beyond 2 years: overall = 0.47%; under tacrolimus = 0.14%; and under CsA = 0.8%.

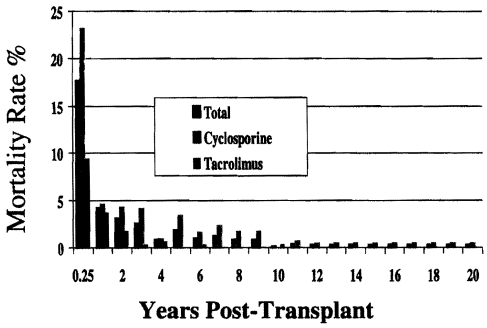

FIGURE 4. Overall morality rate over time under cyclosporine and tacrolimus immunosuppression.

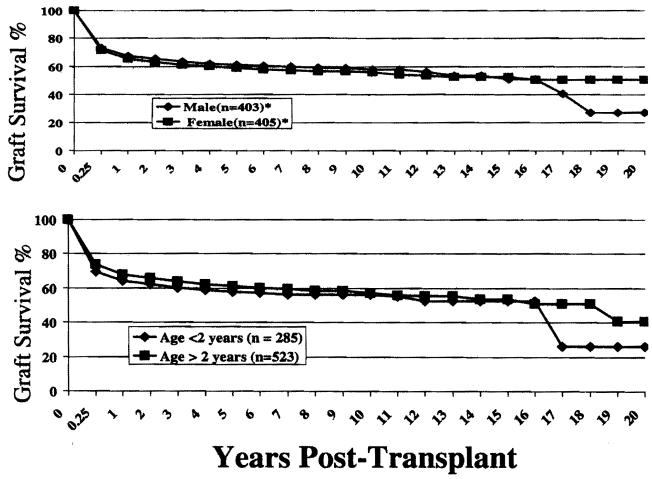

FIGURE 5. Graft survival by gender (top) and age (bottom).

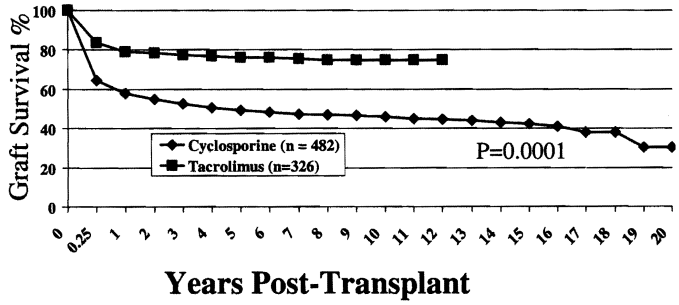

FIGURE 6. Graft survival under cyclosporine and tacrolimus immunosuppression.

TABLE 4. Site of PTLD

Site of PTLD	CsA	Tacrolimus
Lymph node	17	18
Tonsil and adenoid	7	
Liver	3	5
Gastrointestinal	2	12
Multiple	9	3
Lung	2	
Spleen		1
Total (%)	40 (8.3%)	39 (11.65%)

DISCUSSION

Long-term survival data from other transplant centers report increased survival over time, which suggested an increase in earlier patient referrals, improvements in surgical techniques, improved operative and perioperative patient management, and an increased understanding of more po-

TABLE 3. Indications for retransplantation

Causes	Months after transplantation													
	0 to 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	96 to 108	108 to 120	>120	Total n(%)
Hepatic artery thrombosis	68	5	1		3	1								78 (38.4)
Cyclosporine	56	3	1		3	1								
Tacrolimus	12	2												
Primary nonfunction	34													34 (16.7)
Cyclosporine	19													
Tacrolimus	15													
Acute rejection	5											1		6 (2.9)
Cyclosporine	5											1		
Tacrolimus							None							
Chronic rejection	10	5	5	6	7	3	2	0	2		1		7	48 (23.6)
Cyclosporine	10	5	5	6	7	3	2		2		1			
Tacrolimus							None							
Other*	12	3			3		1		1				1	21 (10.3)
Cyclosporine	10	2			1		1						1	
Tacrolimus	2	1			2				1					
Unknown	10			2	1	1		1					1	16 (7.8)
Cyclosporine	9							1					1	
Tacrolimus	1			2	1	1								
Total														203

* = Bilary-3, PTLD-3 Rec-1, and Technical-14.

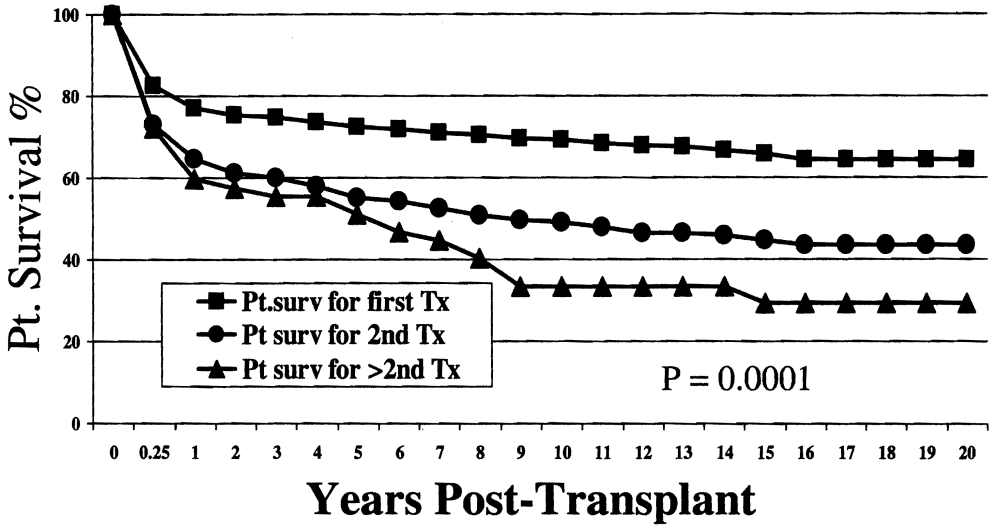

FIGURE 7. Patient survival by number of transplants.

tent immunosuppressive agents (*1, 4, 5*). Data that reflect increased survival after pediatric liver transplantation have been reported from the comprehensive European (*6*) and United States (*7*) registries as well as from individual centers including the University of California at Los Angeles (*8*), Dallas (*9*), Wisconsin (*10*), and Spain (*11*) (Table 5). A 20-year overall actuarial patient survival of 64.4% is reported here, representing the largest pediatric liver transplant experience with the longest follow-up from a single center.

The most significant factor that affects an increased survival in this experience was a change in immunosuppressive protocols from CsA-based immunosuppression in the 1980s, with a survival of 61% at 10 years, to tacrolimus-based immunosuppression resulting in an 83% survival at 10 years. The highest number of deaths occurred within the first 3 months posttransplant in each group, but more so in the CsA group. Beyond this time, technical and donor/recipient selection differences are not expected to contribute to the overall survival. However, the difference in survival beyond 3 months posttransplant was 13% and still significant, which suggests a direct effect of new immunosuppressive agents. Another contributing factor was the conversion of several

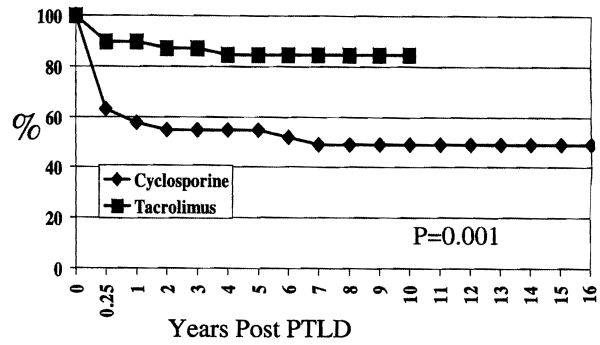

FIGURE 8. Survival after PTLD under cyclosporine and tacrolimus immunosuppression.

TABLE 5. Improvement in survival over time in other centers

Transplant centers (ref-year)	No. of Patients	Years follow-up	Survival (%) early phase*	Survival (%) late phase*
European (ref. 6)	2554	10	58 at 5 years	78 at 5 years
United States (ref. 7)	261	15	66.7 at 5 years	
University of California at Los Angeles (ref. 8)	569	14	75 at 5 years	85 at 5 years
Dallas (ref. 9)	202	12	72 at 2 years	87 at 2 years
Wisconsin (ref. 10)	76	8	77.3 at 8 years	
Spain (ref. 11)	198	14	74 at 5 years	82 at 5 years
Pittsburgh (present)	808	20	61 at 10 years	83 at 10 years

* Early phase = in the initial phase of liver transplant; late phase = current results at the time of publication.

patients who received CsA-based immunosuppression with persistent acute cellular rejection or chronic rejection to tacrolimus-based therapy (*23*).

In the present report, survival after a second or third liver transplant is significantly inferior when compared to those pediatric recipients who retained their original graft. This finding has been supported by other large patient series with long-term follow-up (*12*, *13*). Survival for children who received a transplant at less than 2 years of age was slightly inferior initially when compared to children who received a transplant at more than 2 years of age, but survival was almost the same in the long term. Comparable results in infants have been cited (*14–16*), although there is an increased risk of hepatic artery thrombosis in this group.

In previous reports from this center, female liver transplant recipients had an increased survival compared to males (*1*, *17*) when the total sample of children and adults was analyzed. However, this difference was not observed when only the pediatric population was analyzed.

There are several reports that suggest an immunological advantage with tacrolimus compared to CsA (*9*, *18*, *19*). This analysis reports the complete absence of graft loss from either acute or chronic rejection under tacrolimus, which is remarkable considering the incidence under CsA is 11% in a 20-year follow-up. Migliazza et al. (*11*) and Asfar et al. (*20*) independently found chronic rejection as a significant cause of graft loss. Dunn et al. (*12*) reported that 4% of pediatric deaths after transplantation were directly related to rejection. More than a decade ago, observations from this institution supported the findings of a reduced rate of acute rejection as well as a decreased severity of rejection in patients who received tacrolimus (*3*, *21*). Additionally, the ability of tacrolimus to reverse acute and chronic rejection and act as a rescue agent for patients who fail treatment with CsA provided a better understanding of the process of rejection and its treatment and the clinical limits of failure (*2*, *22*). Consequently, a significant number of children under CsA-based immunosuppression were converted to tacrolimus for ongoing steroid-resistant acute and chronic rejection. Many of these children have been maintained on much lower doses of steroids (*23–25*). At this institution, nearly 25% of children under CsA-based immunosuppression have been converted to tacrolimus with many of the graft rescued from acute and chronic rejection during the last decade (*23*). Nearly 80% of pediatric patients are now maintained only on low-dose tacrolimus. This accomplishment initiated the clinical application of steroid-free monotherapy with tacrolimus after pediatric liver transplantation (*26*), which has resulted in fewer long-term complications related to steroid use and polypharmacological immunosuppressive therapy.

The virtual absence of chronic rejection in adult liver transplant recipients after a review of over 5000 liver biopsies from more than 1200 patients with a mean follow-up of 6 years has been previously reported (*27*). Hepatitis B and C viruses, primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis were found to be risk factors for the development of chronic rejection after liver transplantation. Fortunately, these liver diseases as indications for transplantation are extremely rare in the pediatric population. Chronic rejection in pediatric liver transplant recipients is usually a result of treatment for life-threatening infection and PTLD or noncompliance. Chronic rejection, as defined by the Banff criteria (*28*, *29*), has not been detected in a subset of tacrolimus-treated patients (n=166) with an 8- to 12-year follow-up of 500 liver biopsies (Abstract to be presented at ILTS 2001).

PTLD continues to be a complication in pediatric liver transplantation. However, the ability to reverse acute rejection after PTLD coupled with early diagnosis of PTLD through serial monitoring of the Epstein Barr viral load in high-risk pediatric liver transplant recipients has effectively improved survival after PTLD (*29*).

The 20-year actuarial survival for pediatric liver transplant recipients is 64% in a series of 808 children. Infection remains the most common cause of death. Retransplantation is most commonly indicated for hepatic artery thrombosis and primary nonfunction. Survival after the introduction of tacrolimus-based immunosuppression has increased by 14% to 21% at 1 year (85% vs. 71.2%) and 12 years (82.9% vs. 61%) posttransplant. The increased survival rate of our program may reflect improvements in surgical techniques, better donor/recipient selection, and advance in posttransplant medical management. However, in our experience, increased survival can be attributed to the total absence of graft loss as a result of acute or chronic rejection by 12-year follow-up, which reflects the immunological advantage of tacrolimus-based immunosuppression.

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