One Thousand Consecutive Primary Liver Transplants Under Tacrolimus Immunosuppression: A 17- to 20-Year Longitudinal Follow-Up

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Background. Tacrolimus has proven to be a potent immunosuppressive agent in orthotopic liver transplantation (OLT). The aim of this study is to examine its long-term efficacy and safety.

Methods and Results. One thousand consecutive primary OLTs performed between August 1989 and December 1992 and maintained under tacrolimus-based immunosuppression were followed up until January 2009. Patient and graft survivals with corresponding causes of death and retransplantation, maintenance immunosuppression, and adverse effects were examined. The study population includes 600 males and 400 females comprising 166 children, 630 adults, and 204 seniors. The mean follow-up was 17.83 (range, 16.1–19.50) years. The overall 20-year actuarial patient and graft survivals were 35.8% and 32.6%, respectively. At the last follow-up, 442 patients were alive; 133 (77.1%) children, 265 (34.5%) adults, and 44 (16.1%) seniors ($P=0.0001$). After the first post-OLT year, cardiopulmonary events, recurrence of primary disease, and malignancy were the main causes of death. Overall, 183 recipients underwent retransplants; mainly for primary nonfunction, hepatic artery thrombosis, and recurrent primary disease, 180 required dialysis, and 45 underwent kidney transplant. A total of 97.7% of the survivors were on tacrolimus and 26.2% were also receiving adjunctive immunosuppressants at the last follow-up.

Conclusions. The overall 20-year actuarial patient and graft survivals were 35.8% and 32.6%, respectively, with significantly better survival among children. Age-related complications, recurrence of primary disease, and malignancy were the major causes of late graft loss. Graft loss related to immunologic reasons was rare. The prevention of recurrent disease and newer immunosuppressive regimen will further improve these results.

Keywords: Calcineurin inhibitor, Nephrotoxicity, Rejection, Survival, Tacrolimus.

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Tacrolimus (FK506), a potent in vitro and in vivo immunosuppressive agent, was approved more than a decade ago by the Food and Drug Administration for orthotopic liver transplantation (OLT). Initially, it was used as a rescue treatment for failing liver allografts under cyclosporine A (CsA) (*1–4*). Subsequently, its utility was demonstrated in primary liver transplantation (*5–9*). It reduces the rate and severity of acute rejection episodes demonstrated in several reports (*10*). Later studies showed that it also protects the hepatic allograft from chronic rejection (*11–13*).

The acute toxicity profile of tacrolimus was delineated in several reports (*14–21*). These observations were verified in three prospective randomized trials, which were conducted before Food and Drug Administration approval: the Pittsburgh single-center trial, in which tacrolimus was compared with CsA (*5*), and the United States and European multicenter trials comparing tacrolimus with low-dose steroids with CsA as a part of double, triple, or quadruple induction protocols (*7*, *8*). In these trials, the immediate benefits and limitations of tacrolimus were delineated. Further follow-up of the multicenter trials has demonstrated excellent patient and graft survival rates, with a long-term toxicity profile that has been quite acceptable (*22–24*).

The aim of this study is to evaluate the patient and graft survival for various age populations longitudinally followed up over two decades. The causes of death, retransplantation, maintenance immunosuppression, biochemical and hemato-

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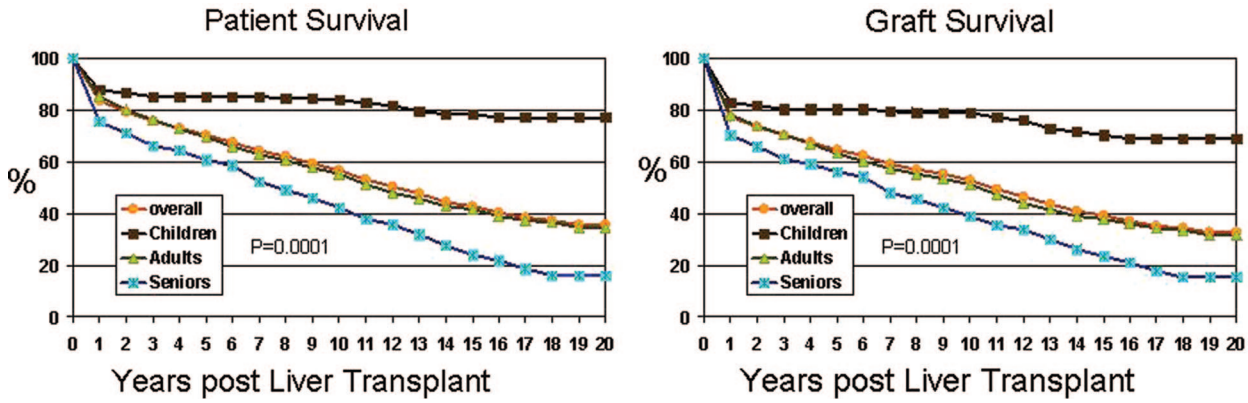

FIGURE 1. Patient and graft survivals among various age groups over time.

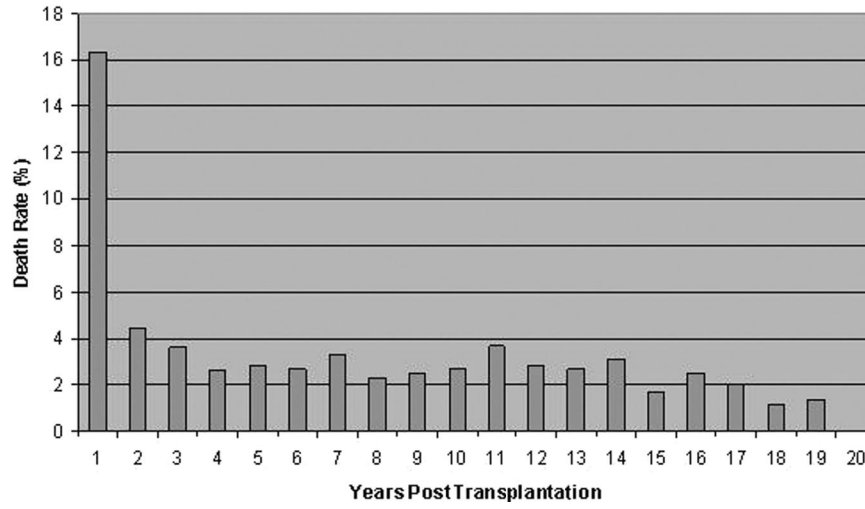

FIGURE 2. Overall death rate per year after liver transplant.

logical functions, and toxicities (renal function, hypertension, and diabetes) were examined among the survivors.

RESULTS

Patient Survival

The overall actuarial patient survival rates at 1, 5, 10, 15, and 20 years were 83.7%, 70.3%, 56.8%, 42.8%, and 35.8%, respectively (Fig. 1). Survival rates for children, adults, and seniors were significantly different. The 1-, 5-, 10-, 15-, and 20-year survival rates were 87.8%, 85.4%, 83.8%, 78.5%, and 77.1% for children, 85.2%, 69.5%, 55.2%, 41.6%, and 34.5% for adults, and 75.5%, 60.7%, 42.3%, 24.1%, and 16.1% for seniors, respectively ($P=0.0001$).

Five hundred fifty-eight (55.8%) patients died during the follow-up period. Overall, the mean death rate was 3.21 ± 3.23 (median, 2.7, range, 0–16.3) percent per year. After the first post-OLT year, the percentage mortality per year reduces significantly for all age groups ($P<0.05$, Fig. 2). The per year mean mortality rates were 0.56 ± 0.67 (median, 0, range, 0–2.2) for children, 2.66 ± 1.1 (median, 2.7, range, 0–5.2) for adults, and 3.15 ± 1.58 (median, 3.2, range, 0–6.6) for seniors.

The causes of death are listed in Table 1. Overall, infectious complications were the most common cause of death, representing 28.6% (n=160) of all deaths. After first post-transplant year, cardiopulmonary events, recurrence of primary disease, and malignancy (including recurrent hepatocellular carcinoma and de novo cancers) constituted the main causes of death. As expected, these events were predominantly seen in the adult and senior recipients.

Graft Survival

Patient death and retransplantation were considered as graft loss. The overall graft survival rates at 1, 5, 10, 15, and 20 years were 77.5%, 64.6%, 52.9%, 39.2%, and 32.6%, respectively. At 20 years, graft survival rate was significantly better for children (69%) compared with adults (31.5%) and seniors (15.3%) ($P=0.0001$, Fig. 1).

Overall, 183 retransplants were performed in 154 patients. One hundred fifty-four patients lost their first graft and underwent a second liver transplant, 25 patients received a third, and 4 patients received a fourth transplant.

The causative factors for retransplantation are summarized in Table 2. Primary nonfunction, hepatic artery thrombosis (HAT), and recurrence of disease were the most common reasons for retransplantation. The greatest number of retransplantations was performed in the first year (n=126; 68.8% of total retransplantations). Late retransplantations were mainly performed for recurrent dis-

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TABLE 1. Causes of death in various age groups

Cause of death	n (%)	Children	Adult	Seniors
Infection	160 (16)	13	103	44
Cardiopulmonary	86 (8.6)	2	57	27
Recurrent primary disease	54 (5.4)	5	35	14
Recurrent HCC	29 (2.9)	0	14	15
De novo malignancy	45 (4.5)	0	24	21
Renal failure	22 (2.2)	0	16	6
Cerebrovascular	21 (2.1)	0	14	7
Gastrointestinal	12 (1.2)	1	8	3
MOSF	34 (3.4)	3	25	6
Rejection	5 (0.5)	1	3	1
PTLD	20 (2.0)	3	16	1
Others	17 (1.7)	1	12	4
Unknown	53 (5.3)	4	38	11
Total	558 (55.8)	33	365	160

HCC, hepatocellular carcinoma; MOSF, multiorgan system failure; PTLD, posttransplant lymphoproliferative disorder.

TABLE 2. Causes of first retransplant

Causes of first retransplant	n (%)
Primary nonfunction	63 (6.3)
Hepatic artery thrombosis	46 (4.6)
Recurrence of primary disease	18 (1.8)
Rejection	12 (1.2)
Biliary complications	9 (0.9)
Others	6 (0.6)
Total	154 (15.4)
II: 154 (15.4%); III: 25 (2.5%); IV: 4 (0.4%)	

ease and were mostly confined to the adult and senior group.

Maintenance Immunosuppression

Calcineurin Inhibitors

At the last follow-up, 96.6% (n=427) of survivors were on tacrolimus. The mean dose of tacrolimus was 2.6±1.9 (median, 2) mg/day with a mean whole blood trough concentration of 5.5±4.74 (median, 4.2) ng/mL. Three patients (0.6%) were on CsA and 12 patients (2.7%) were receiving rapamycin to reduce calcineurin inhibitor (CNI)-related nephrotoxicity and due to the recurrence of hepatocellular carcinoma or posttransplant lymphoproliferative disorder (PTLD), respectively. In this cohort, 14 patients were off immunosuppression and had normal liver functions.

Adjunctive Immunosuppression

At the last follow-up, 26.2% (n=116) of survivors were on adjunctive immunosuppressive drugs. Among them, 20.5% (n=91) were on prednisone, 4.75% (n=21) on azathioprine, and 8.8% (n=39) on mycophenolate mofetil (MMF). Among the prednisone group, 75.8% (n=69) patients were on a dose of less than 5.0 mg/day, 18.6% (n=17) on 6 to 10 mg/day, and only 5.4% (n=5) were receiving more than 10 mg/day. The average dose of azathioprine and MMF was 50 mg/day and less than 1.5 g/day, respectively.

Biochemical and Hematologic Functions

Liver Functions

At the last follow-up, the mean total bilirubin was 0.7±1.1 (median, 0.6) mg/dL. The mean aspartate aminotransferase was 37.6±29.2 (median, 28) U/L, mean alanine aminotransferase was 49.3±192.9 (median, 30) U/L, mean alkaline phosphatase was 161.1±150.1 (median, 111.5) U/L, and mean gamma glutamyl transpeptidase was 102.5±209.3 (median, 42) U/L.

Renal Functions

Overall, 180 (18%) recipients required renal replacement therapy after liver transplantation including 36 (3.6%) patients within the first year of transplant. Among them, 45 (4.5%) patients underwent 51 kidney transplants including 7 children, 23 adults, and 16 seniors. Five patients received a second and one patient received a third kidney transplant. Four of the seven children underwent kidney transplant for primary hyperoxaluria. At the last follow-up, the mean serum creatinine level was 1.56±1.53 (median, 1.2) mg/dL with mean blood urea nitrogen of 23.6±14.5 (median, 20) mg/dL including 20 patients with kidney transplant. A total of 86.8% (n=384) of survivors had a serum creatinine level less than 2.0 mg/dL.

Hematologic Functions

The mean hematocrit was 39.6%±16.3% (median, 39.1%). The mean white blood cell count was 6.7±3.7 (median, 6.2)$\times 10^9$ per liter and the mean platelet count was 204.8±95.6 (median, 188.5)$\times 10^9$ per liter.

Adverse Effects

Hypertension

Fifty-four percent (n=238) of the survivors are currently receiving antihypertensive medications. In 57.2% (n=136) of patients, hypertension was controlled with small dose of a single antihypertensive agent, usually a calcium channel blocker.

Diabetes

Twenty-four percent (n=106) of the survivors were diagnosed with diabetes and 68.8% (n=73) of them were on insulin.

Hyperkalemia

Hyperkalemia requiring treatment was observed in 9.3% (n=41), and all cases was controlled with fludrocortisone.

Posttransplant Lymphoproliferative Disorder

PTLDs were observed in 43 recipients, 18 (10.8%) children and 25 (3%) adults/seniors. PTLD accounts for 3 (9.1%) deaths among pediatric recipients, 16 (4.3%) among adults, and 1 (0.6%) among the seniors.

De Novo Malignancy

The rate of de novo cancers in adults continued to increase since we last reported 5 years ago with mean follow-up

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of 13.4±0.92 years. Nonmelanotic skin cancers were reported in 35 (4.2%) adult patients, and melanotic skin cancers with other noncutaneous cancers occurred in 65 (7.8%) adult patients. De novo malignancies account for 45 (8.5%) deaths among adults and seniors.

DISCUSSION

This study is the largest series of OLT recipients from a single center with this length of follow-up. We believe that this type of review is helpful not only for informing patients about their survival chances but also in improving the long-term results by understanding the factors that relate to late graft loss and complications from the immunosuppressive regimens.

The data presented here showed that the 20-year actuarial patient and graft survival was 35.8% and 32.6%, respectively. These results are somewhat different from those reported by Busuttil et al. (*24*). In the later study, overall 1-, 5-, 10-, and 15-year patient and graft survival rates were 81%, 72%, 68%, and 64%, and 73%, 64%, 59%, and 55%, respectively. An important difference from our series is that the study by the University of California, Los Angeles, has reported a slightly shorter follow-up (15 years vs. 17–20 years) and had a higher percentage of pediatric patients (21.7% vs. 16.6%) in their series along with different cutoff limits for age groups compared with our study. However, the conclusions were somewhat similar that the long-term benefits of OLT were greatest in pediatric patients. In our series, 77.1% of the pediatric patients were alive compared with 34.5% of adults and 16.1% of seniors.

Deaths account for a major proportion of late graft loss. The three most common causes of death were cardiopulmonary diseases or events, recurrence of primary disease, and malignancy (recurrent and de novo) (*25*). The mean time of late graft loss due to cardiovascular diseases was longer than all the other causes. Because of this late occurrence, cardiovascular disease may be considered as a natural cause of death. Late mortality and late graft loss are infrequent among pediatric OLT recipients (*26–31*). Among pediatric recipients, late graft loss is uncommon in part because most children do not undergo OLT for diseases that recur in the allograft. In contrast, primary liver diseases with the potential of recurrence (hepatitis C, primary sclerosing cholangitis, alcoholic liver disease, hepatobiliary malignancy, etc.) are the commonest indication for OLT in adults and seniors. This is startling because it underscores the efficacy/longevity of the transplanted liver among adults and seniors as the age-related cardiopulmonary events and recurrence of the "primary disease" were the most common reason for late graft loss/mortality among them.

Immunosuppressive therapy for long duration leads to an increased risk of developing lymphoproliferative disorders and de novo malignancies. Lymphoproliferative disorders developed in 43 patients in this series in which higher doses of tacrolimus were initially used; the predominance in the pediatric population (10.8%) was significantly higher than in adults and seniors (3%). The risk factors for the higher incidence in pediatric patients have been previously reported (*32*, *33*). Fortunately, with better understanding, earlier diagnosis, and development of better antiviral agents, survival after PTLD has improved (*34–36*). De novo malignancy accounts for 8% of deaths in our study population. This has two possible explanations. Eighty-three percent of the recipients in this study were older than 18 years at the time of transplant. With increases in age, these patients may increase the proportion of patients who are at risk of developing cancers that are more common in that age group, mainly lymphoma, squamous cell carcinoma, lung carcinoma, and colon carcinoma. An increased incidence in aerodigestive malignancies may be associated with the risk factors of a long history of smoking and chronic alcohol use in this patient population. De novo malignancies are a risk factor for long-term survival in adult and senior OLT recipients, whether the incidence is increased or not, compared with age-adjusted general population cohorts (*37–42*). Second, cancers that develop in organ allograft recipients frequently have a more aggressive course than similar tumors in patients who have not undergone transplantation (*43*, *44*).

Graft loss and death from immunologic causes (acute or chronic rejection) remain extremely rare under tacrolimus (*11–13*, *45–49*). The lower rate of rejection under tacrolimus may be in part due to the ability of reversing early acute rejection by increasing levels of tacrolimus (*2*, *46*). A meta-analysis of 16 randomized trials comparing CsA with tacrolimus for liver transplanted patients showed that tacrolimus is superior to CsA in improving survival (patient and graft) and preventing acute rejection after liver transplantation (*48*). Tacrolimus reduced the acute rejection and steroid resistant rejection by 18% and 43%, respectively, in the first year compared with CsA-treated recipients. Late acute rejection is often associated with noncompliance; a lower rate of discontinuation was noted with tacrolimus than CsA (*48*).

Nephrotoxicity is always a concern with the use of CNIs. In this long-term follow-up study, 4.4% of recipients underwent kidney transplantation for end-stage renal disease including four pediatric patients with hyperoxaluria. These figures are comparable with the findings of early (*7*, *8*, *48*, *50*, *51*) and long-term (*22*, *52*) nephrotoxicity reported after OLT using CsA or tacrolimus. The cumulative increase in the development of end-stage renal failure in tacrolimus-treated patients is consistent with other reports in CsA-treated patients (*53*, *54*). Early withdrawal of CNIs may be the best option by delivering CNIs during the early period of immunologic graft injury and then converting to less nephrotoxic agents before significant renal damage occurs (*55–57*). In this context, various newer immunosuppressive agents including MMF, rapamycin, and interleukin-2 inhibitors have been tried in combination with CNIs or as monotherapy and showed encouraging results with reduction in perioperative and long-term nephrotoxicity (*57–62*).

The incidence and management of hyperkalemia and hypertension seem to be stable with long-term follow-up (*63*). Twenty-four percent of the survivors were diagnosed with diabetes and two thirds were on insulin. Tacrolimus increases the risk of new-onset diabetes (*48*); however, we lack data on pretransplant diabetes among these patients; steroids may also be contributory. The increasing use of early weaning of steroid or steroid-free immunosuppressive regime may improve the diabetes profile.

In conclusion, we have noted that overall survival after liver transplantation has improved over the last two decades. Pediatric recipients continue to have significantly better survival compared with adults and seniors. In the long term, age-related

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TABLE 3. Indications of primary liver transplant

Indications	n (%)
Postnecrotic cirrhosis	341 (34.1)
Alcoholic cirrhosis	188 (18.8)
Biliary atresia	86 (8.6)
Primary biliary cirrhosis	83 (8.3)
Primary sclerosing cholangitis	60 (6)
Primary hepatic malignancy	79 (7.9)
Acute fulminant failure	34 (3.4)
Autoimmune liver disease	33 (3.3)
Alpha 1-antitrypsin deficiency	22 (2.2)
Budd-Chiari syndrome	12 (1.2)
Metastatic carcinoma	10 (1.0)
Alagille syndrome	9 (0.9)
Hemochromatosis	8 (0.8)
Cystic fibrosis	7 (0.7)
Neonatal hepatitis	6 (0.6)
Familial cholestasis	6 (0.6)
Hyperoxaluria	4 (0.4)
Criggler–Najjar syndrome	2 (0.2)
Trauma	2 (0.2)
Tyrosinemia	2 (0.2)
Congenital hepatic fibrosis	2 (0.2)
Urea cycle defect	1 (0.2)
Histiocytosis	1 (0.2)
Sarcoidosis	1 (0.1)
Polycystic liver disease	1 (0.1)
Total	1000 (100)

complications, recurrence of primary disease, and malignancy were the major causes of late graft loss. Graft loss from acute or chronic rejection was rare under tacrolimus-based immunosuppression. The prevention of recurrent disease and better immunosuppression may further improve the outcome.

MATERIALS AND METHODS

The study subjects include 1000 consecutive primary OLTs performed at our institution between August 1989 and December 1992. We reported their first follow-up of 39.5 months (range, 18–59 months) in 1995 (*64*). This was subsequently updated in September 1999 (*65*) and March 2005 (*66*) with a mean follow-up of 93 months (range, 72–113 months) and 13.4 years (range, 11.7–15 years) respectively.

The study population includes 600 males and 400 females, with a mean age of 42.6±20.2 years. There were 166 children (younger than 18 years), 630 adults (older than 18 years to younger than 60 years), and 204 seniors (older than 60 years). Eight hundred forty-one (84.1%) patients were hospital bound at the time of OLT; 382 patients (38.2%) were class 3 (in the hospital), 328 (32.8%) were class 4 (in intensive care unit), and 131 (13.1%) were United Network for Organ Sharing class 4 signal transducer and activator of transcription (life expectancy <2 days in the intensive care unit). One hundred fifty-nine patients (15.9%) were United Network for Organ Sharing class 1 and 2 (out of hospital with limited working capacity). Two hundred seventy donors were younger than 18 years (mean, 9±2 years), 347 were 18 years or older but younger than 35 (mean, 25±2) years, 242 were 35 years or older but younger than 50 (mean, 42±4) years, and 141 were older than 50 (mean, 57±4) years at the time of donation.

Indications for primary transplant are illustrated in Table 3. The details of the population and the primary diagnoses have been described previously (*64–66*). All patients were followed up until January 2009 with a mean follow-up of 17.83 (range, 16.1–19.5) years.

Perioperative Immunosuppression

Tacrolimus was started parenterally on the day of transplant and converted to oral dosing once bowel function returned. The intravenous dose ranged from 0.1 to 0.4 mg/kg per day. The starting oral doses averaged 0.2±0.1 mg/kg per day. However, dose adjustments were made continuously, guided by plasma trough levels of tacrolimus (targeted at 1.0 ng/mL) and above all by the balance of rejection control, signs of nephrotoxicity, neurotoxicity, and diabetogenecity (*64*).

Tacrolimus doses steadily declined with time in all age groups (except in infants). By 3 months, 53% of surviving patients were steroid free. At 3 months, doses were low, only 10% of the patients were requiring more than 10 mg/day. Infants and children were weaned off steroids much faster than adults and seniors (*64*).

Statistical Analysis

Values are presented as mean±SD. Kaplan–Meier analysis (SPSS Window version 11.5; SPSS Inc., Chicago, IL) was used to estimate the patient and graft survival. Log-rank test was used to compare the difference in survival. For all analyses, a P value of 0.05 or less was considered significant.

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