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cardiovascular complications, this difference, if maintained, could prove an advantage of tacrolimus for long-term therapy.

Lower levels of LDL and triglycerides in the tacrolimus- compared to CBIR-treated patients also might lead to less long-term cardiovascular complications in the tacrolimus patients.

Discontinuation for Adverse Events

In the comparative studies performed thus far, discontinuation of study drug citing adverse events as the reason has been more frequent in the tacrolimus- than in CBIR-treated study groups. These discontinuations are disproportionate to the overall comparative incidences of these cited events, especially serious adverse events which were of nearly equal frequency in the CBIR and tacrolimus groups. One possible explanation is that conventional therapy with CBIR was available as an alternative for tacrolimus patients experiencing adverse events (whether or not confirmed as drug related), while there was no corresponding tacrolimus protocol available for CBIR patients experiencing such toxicities.

Pediatric Safety

Adverse events were consistently lower in the pediatric group compared to the adult group of tacrolimus-treated patients. Pediatric and adult CBIR groups had comparable incidences of adverse events. Pediatric tacrolimus patients often had fewer adverse events than pediatric CBIR patients in the FPC-FK506-7 comparative liver transplant study. These findings suggest that tacrolimus may be a preferred immunosuppressive agent for use in pediatric organ transplantation.

8.H.19. Conclusions

A safety profile for tacrolimus can be identified which is similar to that associated with cyclosporine-based therapy. Renal and nervous system toxicities, gastrointestinal side effects, hyperkalemia, and abnormalities in glucose metabolism are clearly evident in both populations. While the overall incidence of adverse events is high in these study populations, the proportion considered serious is generally low and nearly equal in the tacrolimus and CBIR comparative study groups. Most adverse events occur early after transplantation in the primary studies or shortly after conversion to tacrolimus as rescue therapy for refractory rejection. Of the most frequently reported

Fujisawa USA, Inc.**Table 18: Liver Function as Determined by Geometric Mean Total Bilirubin (Serum) in the Two Randomized, Controlled, Primary Liver Transplant Trials**

Time Point Post-Transplant (Days)	Total Bilirubin (mg/dL)			
	FPC-FK506-7		GHBA-157	
	Tacrolimus	CBIR	Tacrolimus	CBIR
1-2	3.2	3.6	3.9	4.9
5-9	2.5	3.8	4.0	6.6
12-16	1.4	3.1	2.7	5.2
21-35	1.0	1.7	1.6	2.4
121-210	0.7	0.9	0.7	1.1
330-390	0.5	0.9	---	---

3.1.4. Summary of Randomized Primary Liver Transplant Trials

A summary of the comparative results of tacrolimus versus CBIR therapy in the randomized, controlled, primary liver transplant studies is presented in Table 19.

Fujisawa USA, Inc.**Table 19: Comparative Summary of Study Endpoints in Randomized, Controlled, Primary Liver Transplant Studies (Tacrolimus vs. CBIR)**

Study Endpoints	FPC-FK506-7	GHBA-157
One-Year Patient Survival	=	=
One-Year Graft Survival	=	=
Incidence of Acute Rejection	tacrolimus <* CBIR	tacrolimus <** CBIR
OKT3 Use	tacrolimus <** CBIR	=
Incidence of Rejection	tacrolimus <** CBIR	tacrolimus <** CBIR

* P = 0.001

** P < 0.001

In two prospective, randomized, CBIR-controlled studies, tacrolimus proved efficacious in the prevention of rejection in patients receiving their first orthotopic liver transplant. Patient and graft survival among tacrolimus-treated patients were comparable to those among CBIR-treated patients in the FPC-FK506-7 study. In the GHBA-157 study, patient and graft survival were six percentage points greater at one year in the tacrolimus group. These differences approached statistical significance (P = 0.078, patient survival; P = 0.073, graft survival). Acute and rejection rates were significantly lower (P ≤ 0.001) among patients in the tacrolimus treatment groups than among patients in the CBIR treatment groups. Liver function, as assessed by laboratory values for total serum bilirubin, showed a trend towards a more rapid decrease in total serum bilirubin levels in the tacrolimus groups compared to the CBIR groups in both the FPC-FK506-7 and the GHBA-157 studies.

-3.1.5. Tacrolimus Publications in Primary Liver Transplantation

An independent, open-labeled, single-center, randomized study comparing the efficacy of tacrolimus as primary immunosuppression to that of standard CBIR in the prevention and treatment of rejection in liver transplant patients has been published.⁸³ Results in 154 patients randomized after liver transplantation (78 tacrolimus, 76 CBIR) were reported. Median follow-up was 611 days in the tacrolimus group and 594 days in the CBIR group. A statistically significant decrease in the incidence of rejection was observed with tacrolimus (56%) compared to CBIR (91%). There were seven deaths and seven retransplants in the tacrolimus group and nine deaths and eleven

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retransplants in the CBIR group. Patient and graft survival rates were similar between treatment groups, with a trend toward higher survival rates in the tacrolimus group. These results are consistent with those from the two multicenter, controlled, liver transplant trials (FPC-FK506-7, GHBA-157).

The University of Pittsburgh published their experience in 399 patients who received a liver transplant under an open-labeled tacrolimus protocol from early 1989 to late 1990.⁸⁴ One-year patient survival in this group was 83.5% and graft survival was 76.2%. This group was compared to 391 patients treated with CBIR from October 1987 to December 1988. One-year patient and graft survival, 74.4% and 68%, respectively, were significantly lower in the historical control group compared to the tacrolimus group ($P < 0.02$).⁸⁴ These results for one-year patient and graft survival are very similar to the GHBA-157 study (see Table 15).

8.G.3.2. *Non-Randomized Historically Controlled Study in Liver Transplantation*

3.2.1. Rescue Study

3.2.1.1. *Introduction*

The third adequate and well-controlled trial evaluated tacrolimus in the treatment of acute rejection. It is estimated that 13% of liver transplant patients will experience acute rejection resistant to treatment with conventional immunosuppressive drugs.¹⁶ The alternatives for the majority of patients experiencing acute rejection are retransplantation, death, or continuing conventional immunosuppressive therapy to which the patient has already evidenced refractory rejection. The risks accompanying re-transplantation are great and further complicated when acceptable donor organs are not readily available. In patients with acute rejection, who are not retransplanted, unremitting rejection and/or drug toxicity may lead to serious morbidity or death. Since patients entered into this study had failed all standard therapies, it was not considered ethical to perform a prospective, randomized study. Therefore, results with tacrolimus are compared to historical controls.

3.2.2.2. Background

Tacrolimus was first used at the University of Pittsburgh as a agent in liver transplant patients experiencing rejection while receiving standard CBIR therapy and in patients intolerant of CBIR.¹¹ Based on the positive results from this treatment experience, Fujisawa USA initiated clinical trials using tacrolimus as an immunosuppressive agent in liver transplant patients.

3.2.2.3. Study Objectives

The Fujisawa-sponsored liver transplant trial was initiated to investigate the safety and efficacy of tacrolimus in patients experiencing liver rejection unresponsive to conventional immunosuppressive therapies.

3.2.2.4. Study Design/Methods

The clinical trial was an open-labeled, multicenter, historically controlled trial, enrolling 125 patients between April 1990 and April 1991.

The primary inclusion criteria included the following:

- ◆ clinical and pathological evidence of rejection despite intensive immunosuppressive therapy;
- ◆ rejection unresponsive to conventional immunosuppression which included, but was not limited to: maximum CyA dosage, two courses of steroids and one course of OKT3 to treat unremitting acute rejection and high doses of steroids and azathioprine to treat chronic rejection;
- ◆ tacrolimus treatment initiation greater than 14 days post-transplant.

The following efficacy parameters are discussed:

- ◆ patient survival
- ◆ graft survival
- ◆ rejection episodes
- ◆ liver function tests

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Patient and graft survival were determined on an intent-to-treat basis. Since graft rejection occurring <21 days after drug conversion could be primarily related to the continuation of the rejection process present at initiation of tacrolimus, only graft rejection occurring >21 days after drug conversion was considered a new rejection episode and, therefore, related to insufficient rejection control by tacrolimus.

Three databases were used as historical controls for comparison with tacrolimus therapy results in the rescue study. To assess the natural history of rejection, an clinical site control was developed. Four of the 11 centers that participated in the study were asked to identify patients who experienced rejection qualifying for entry into the study. These control patients did not receive tacrolimus due to lack of drug availability. Sixty-six patients who fulfilled these criteria were identified as historical controls, of whom 63 were evaluable for analysis.

Since the only alternative for many of these rejection patients would be retransplantation, results of the study were also compared to the results of liver retransplantation in CBIR patients from two historical databases: 1) the UNOS 1991 report of center-specific graft and patient survival rates, and 2) the University of Pittsburgh transplant center. These databases excluded patients who were retransplanted within 14 days of the first transplant to match the inclusion criteria to the trial and to eliminate many of the retransplants for non-immunologic reasons, such as hepatic artery thrombosis and primary non-function.

3.2.2.4.1. Drug and Dosage

Tacrolimus was supplied by a single source (Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan) for the IV formulation and 1 mg and 5 mg hard gelatin capsules. Tacrolimus dosing was initiated no sooner than 24 hours after discontinuing all previous immunosuppressive therapies, except maintenance doses of corticosteroids were permitted. Patients initially received either 0.075 mg/kg intravenously twice daily or 0.15 mg/kg orally twice daily. IV therapy was converted to PO dosing as soon as oral medication was tolerated. Dosing changes were based on plasma trough concentrations and graft rejection or drug toxicity.

3.2.2.5. Results

A total of 125 patients from 11 centers were enrolled in the tacrolimus trial and were included in this study analysis. All patients had undergone transplantation more than 14 days prior to drug conversion. All patients had experienced graft rejection despite receiving extensive conventional CBIR immunosuppressive therapy.

3.2.2.5.1. Patient and Graft Survival

Kaplan-Meier estimates of patient survival rates for tacrolimus rescue patients were 85% at 3 months and 71% at 12 months post-conversion. Graft survival decreased from a 3-month rate of 73% to a 12-month rate of 56%. (See also Appendix-B, Tables B.1 and B.2; Figures 1.3 and 2.3.)

These results are significantly superior for patient and graft survival than those for the UNOS or University of Pittsburgh historical controls. Graft survival was also significantly greater in the tacrolimus-treated patients compared to the site-control rate ($P = 0.021$). Table 20 presents the one-year Kaplan-Meier estimates for patient and graft survival for the historical control groups and tacrolimus group.

Table 20: One-Year Kaplan-Meier Estimates for Patient and Graft Survival for the Trial and its Historical Control Groups

Study	Patient Survival One-year	Graft Survival One-year
UNOS	57% $P < 0.001$	53% $P = 0.031$
U. of Pittsburgh	38% $P < 0.001$	33% $P < 0.001$

P values in comparison to trial results.

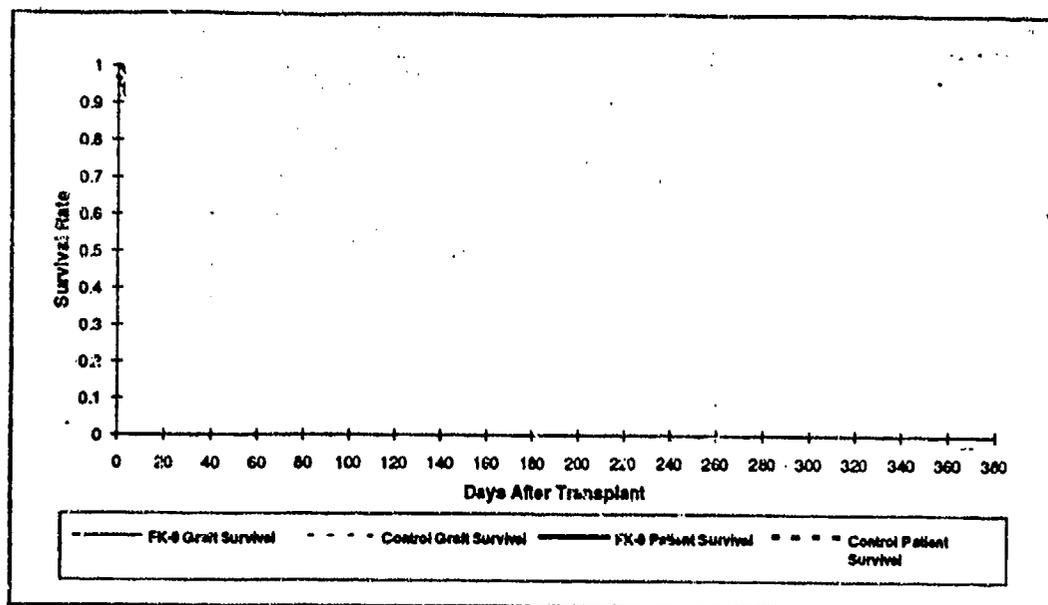


Figure 5. Patient and graft survival to one year, versus UNOS historical control group.

Figure 5 presents the patient and graft survival curves for the study group and the UNOS historical control retransplant group. (See also Appendix B, Tables B.14-B.17.)

3.2.2.5.2. Rejection

The rejection rates reported at >21 days post-conversion in the study group reflect the number of rejection episodes that occurred as a result of insufficient rejection control by tacrolimus; it does not take into account the pre-conversion rejection state.

The tacrolimus rescue patients had an acute rejection rate of 25% at post-conversion day 28. The rate increased to 41% at day 183. Table 21 contains data related to acute rejection rates at specific time points post-conversion. (See also Appendix B, Tables B.3 and B.4; Figures 3.3 and 3.4.)

Fujisawa USA, Inc.**Table 21: Cumulative Acute Rejection Rates in the Trial**

Parameter N=125	28 Days	90 Days	183 Days
Acute Rejection	25%	35%	41%

3.2.2 5.3. Liver Function

All patients who satisfied criteria for study inclusion were allowed to receive tacrolimus therapy regardless of severity of liver dysfunction. Despite dramatic elevations in serum total bilirubin and SGOT at baseline, there was a gradual, but definite, improvement of liver function after conversion to tacrolimus therapy. Table 22 presents the liver function tests results for the trial (See also Appendix B, Tables B.6, B.7, and B.8.)

Table 22: Liver Function Tests Results for Patients in the Study at Selected Time Intervals

	Day 1-2		Day 21-35		Day 121-210		Day 330-390	
	mean	max	mean	max	mean	max	mean	max
Total Bilirubin (mg/dL)	5.1	47.1	3.4	53.0	1.3	38.9	1.0	12.0
	N=91		N=90		N=68		N=18	
SGOT (U/L)	163	1355	92	636	65	489	59	244
	N=87		N=88		N=64		N=18	
SGPT (U/L)	235	999	112	1137	79	800	74	227
	N=84		N=85		N=66		N=17	

* N indicates number of patients for whom LFT values are available at selected time points.

3.2.2.6. Discussion

Tacrolimus demonstrated efficacy in reversing rejection. These effects were seen with both acute and chronic rejection. Analyses of the data from the study demonstrate that most grafts can be salvaged with tacrolimus in combination with small amounts of corticosteroids despite failure of

treatment with large amounts of conventional immunosuppressive agents. The amount of steroid medication and the number of recurrent rejection episodes for these patients subsequent to tacrolimus conversion was dramatically reduced compared to the pre-conversion period. Most patients were maintained on tacrolimus and prednisone for recurrent rejection episodes; only a small number of patients required the addition of azathioprine and/or anti-lymphocyte therapy. As patients were allowed study entry regardless of the severity of liver dysfunction, as measured by liver function tests, it was expected that a significant number of patients would not respond to therapy, a consequence of irreversible damage to the liver caused by the rejection process prior to tacrolimus conversion. The improvements in graft function, as measured by liver function tests, were substantial and dramatic and are self-evident of the efficacy of tacrolimus for therapy of rejection.

Additionally, the graft survival rates in tacrolimus-treated patients were significantly greater in comparison to the three historical control groups. Patient survival was similar in the tacrolimus and in the site-control group, while tacrolimus treatment significantly improved patient survival in comparison to the alternative of retransplantation in the UNOS or University of Pittsburgh historical control groups.

3.2.2. Tacrolimus Publications in Rescue Liver Transplantation

The University of Pittsburgh was the first transplant center in the United States to use tacrolimus as a rescue agent.¹¹ A May 1992 publication⁶¹ describes a retrospective analysis of the effectiveness of tacrolimus when used to rescue liver transplant patients experiencing immunosuppressive-treatment-resistant rejection or treatment toxicity when maintained on standard CBIR.

Between March and December 1989, 96 liver recipients ranging in age from 1 to 74 years (average = 42 years) were converted from CBIR therapy to tacrolimus treatment. All patients had biochemical evidence of graft dysfunction. Eighteen patients showed biochemical signs of graft dysfunction, but were converted primarily for reasons of steroid or cyclosporine toxicity, not because of ongoing graft rejection. The standard initial oral tacrolimus dose was 0.3 mg/kg/day.

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Diagnosis prior to drug conversion was as follows:

<u>Entry Diagnosis</u>	<u># of Patients</u>
Acute Rejection (AR)	18
Chronic Rejection (CR)	33
CR with Hepatitis	20
Hepatitis	7
Other	<u>18</u>
Total	96

At study endpoint, patients had been followed from 9 to 18 months.

The overall patient survival rate (88%) at study endpoint is comparable to the patient survival rate at three months (85%) and is higher than either the 6- or 12-month estimated rates (79% and 71%, respectively) in the trial. The overall graft survival rate from the Pittsburgh publication (69.8%) is higher than either the 6- or the 12-month graft survival rate estimates in the study (66% and 56%, respectively). This difference in survival rates may relate to the difference in the timing of drug conversion.

The Pittsburgh investigators converted CBIR-treated patients experiencing steroid-resistant rejection to tacrolimus treatment after only one course of anti-rejection therapy. Also, while 18 patients had evidence of mild dysfunction, they were converted to tacrolimus therapy primarily for reasons of steroid or cyclosporine intolerance; the study made no provisions for drug conversion due to such intolerance. The participants had received more intensive anti-rejection treatment, including two courses of steroid bolus and recycle and a course of OKT3 for acute rejection and azathioprine for chronic rejection. Therefore, patients in the FPC-sponsored study were in all likelihood experiencing more severe graft dysfunction. Since the patients in the study had more opportunities to improve prior to tacrolimus conversion therapy, only those patients with the most severe graft dysfunction were included in the study.

The published rescue experience from the University of Pittsburgh supports, and is consistent with, the results from the study, further demonstrating the efficacy of tacrolimus in reversing ongoing hepatic rejection.

8.G.3.3. Non-Randomized Uncontrolled Study in Liver Transplantation**3.3.1. Living-Related Donor Liver Transplant Clinical Trial****3.3.1.1. Introduction**

The concept of brain death is not widely accepted in Japan. Therefore, living-related donor liver transplantation is the only means available to successfully treat end-stage liver disease at the present time. In this setting, tacrolimus in combination with corticosteroids was evaluated in an uncontrolled (non-randomized) study (FPC, Japan).

3.3.1.2. Study Objectives

An open-labeled, liver transplant study was conducted to determine the safety and efficacy of tacrolimus in the prevention and treatment of rejection in recipients of living-related donor liver transplants.

3.3.1.3. Study Design/Methods

Between June 1990 and October 1991, 24 patients (ages eight months to 38 years) were recipients of living-related donor liver transplants. All but one of the patients were <16 years of age. The disease leading to transplantation was diagnosed as biliary atresia in 16 patients, hepatitis hepatoma, or protoporphyria in four patients, Budd-Chiari syndrome in two patients, and one case each of intrahepatic obstructive cholestasis and Wilson's disease. There were 12 males and 12 females. A parent served as donor in all cases.

Eighteen patients were treated with cyclosporine and converted to tacrolimus. The remaining six patients were treated with tacrolimus at an initial IV dose of 0.075 mg/kg infused over four to twelve hours and repeated every twelve hours from post-operative day 1. Most patients were converted to PO dosing after several days of IV dosing. As in the controlled study, patients were treated with a bolus injection of methylprednisolone in the operating room, followed by a dose-tapering steroid regimen which resulted in a maintenance dose of 0.5 mg/kg/day by post-operative day 7. Follow-up ranged from 31 days to 414 days after initiation of tacrolimus therapy.

3.3.1.4. Results

3.3.1.4.1. Patient and Graft Survival

Patient survival at three months was 83%. For 6-12 months post-transplant, the survival rate stabilized at 66%. Since none of the patients required a retransplant, the graft survival rate was the same as the patient survival rate at all times. Table 23 contains the patient and graft survival rates for the living-related donor transplant study and Table 24 describes the causes of death for the seven patients who died post-transplant (Appendix B, Tables B.1 and B.2; Figures 1.4 and 2.4).

Table 23 Patient and Graft Survival Rates: Uncontrolled, Living-Related Donor, Primary Liver Transplant Trial

Efficacy Parameter	3 Month	6 Month	12 Month
Patient Survival	83%	66%	66%
Graft Survival	83%	66%	66%

Table 24: Causes of Death for the Seven Patients in the Living-Related Donor Liver Transplant Study (FPC, Japan)

Patient Number	Duration of Tacrolimus Treatment (Days)	Cause of Death
	16	Multi-organ failure
	19	Acute respiratory distress syndrome with renal failure
	22	Congestive heart failure
	26	CMV Infection
	102	Multi-organ failure caused by recurrent porphyria
	154	Respiratory failure caused by fungal pneumonia
	176	Accidental asphyxia

3.3.1.4.2. Rejection

Seventeen percent (4/24) of patients experienced an episode of acute rejection by post-transplant day 28; no patient required OKT3 treatment at any time during the study period. By day 183, no patient had experienced rejection (i.e., discontinued treatment for lack of efficacy). (See Appendix B, Tables B.3, B.4, and B.5; Figures 3.4, 4.4, and 5.4.)

3.3.1.4.3. Liver Function

Liver function, as assessed by laboratory values of total serum bilirubin, SGOT, and SGPT, was monitored at selected time points throughout the study. All laboratory values for liver function tests showed a decrease after day 9 of tacrolimus treatment, as shown in Table 25. (See Appendix B, Tables B.6, B.7, and B.8.)

Table 25: Liver Function Tests Results (Geometric Mean) at Selected Time Points in the Living-Related Donor Liver Transplant Study

	Day 5-9 (N=23)	Day 21-35 (N=21)	Day 121-210 (N=13)
Bilirubin (mg/dL)	3.7	1.0	0.8
SGOT (U/L)	53.0	39.3	45.3
SGPT (U/L)	76.0	39.5	33.1

3.3.1.5. Discussion

Tacrolimus was efficacious in preventing rejection in recipients of living-related donor liver transplants. Patient and graft survival rates were comparable to a previous report of one-year actuarial patient and graft survival rates (82% and 75%, respectively) with CBIR.¹¹⁶ Follow-up in this CBIR publication ranged from 3 to 18 months. The low rejection rate observed in the living-related donor liver transplant trial (FPC,

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Japan) is most likely related to the efficacy of tacrolimus treatment and to the high degree of histocompatibility between donor and recipient.

8.G.4. Tacrolimus Dosing Analysis**8.G.4.1. Dose Justification for Tacrolimus**

The FPC-FK506-7 protocol mandated initial tacrolimus IV dosing at 0.15 mg/kg/day and oral dosing at 0.3 mg/kg/day in two divided doses. Amendments to this dosing strategy were made due to the renal toxicity seen with the intravenous dose. The final tacrolimus dosing amendment recommended an intravenous dose of 0.1 mg/kg/day as a continuous infusion, with an allowance for a 50% dosage reduction based on post-operative urine output. Oral dosing remained at 0.3 mg/kg/day in two divided doses. Similarly, the GHBA-157 protocol was amended to a final dosing recommendation of 0.06-0.1 mg/kg/day intravenously as a continuous infusion with conversion to oral therapy at 0.15 mg/kg twice daily or three times the last intravenous dose, whichever was less. At day 1 post-transplant, the largest number of patients in both studies were receiving intravenous tacrolimus. The mean dose based on 197 patients in the GHBA-157 study was 0.07 mg/kg/day, whereas the mean dose based on 208 patients in the FPC-FK506-7 study was 0.08 mg/kg/day. At two weeks post-transplant in the GHBA-157 study, 218 patients were receiving oral therapy at a mean dose of 0.15 mg/kg/day in two divided doses. In the FPC-FK506-7 trial, 215 patients were receiving a mean oral dose of 0.20 mg/kg/day in two divided doses at two weeks post-transplant.

To detect any change in the dose response as a result of the dosing amendment change, an analysis of the 286 patients in the FPC-FK506-7 trial who enrolled subsequent to implementation of the dosing amendment was performed. Average IV and oral doses tended to be lower in this subset of patients compared to the overall study population. On day 1 post-transplant, 96 patients were receiving IV tacrolimus at a mean dose of 0.06 mg/kg/day. At two weeks post-transplant, 117 patients were receiving oral therapy at a mean dose of 0.18 mg/kg/day (see Appendix B, Table B.81). One-year patient and graft survival rates in the latter population subset were not significantly different between treatment groups, but tended to be slightly higher than survival rates observed in the overall study population for both the tacrolimus and CBIR groups, as shown in Table 26.

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Table 26: One-Year Patient and Graft Survival Rates for the FPC-FK506-7 Subgroup (Enrolled after April 1991) and the FPC-FK506-7 Overall Study Population

	FPC-FK506-7			
	Subset (post 4/91)		Overall Population	
	Tacrolimus N=140	CBIR N=46	Tacrolimus N=263	CBIR N=266
Patient Survival	92%	89%	88%	88%
	P=0.37		P=0.85	
Graft Survival	84%	83%	82%	79%
	P=0.83		P=0.55	

Statistically significant reductions in rejection, OKT3 use, and rejection in the tacrolimus group compared to the CBIR group, as seen in the overall study population, were also observed in the subset of patients transplanted after the last dosing amendment.

Dose tapering was allowed in the absence of clinical evidence of drug toxicity or rejection. Most rejection episodes occur within the first 1-2 months post-transplant; therefore, it is not uncommon for immunosuppression to be reduced as patients progress in their post-transplant recovery period. This was seen in the FPC-FK506-7 and GHBA-157 trials, where patients were titrated to doses of tacrolimus or cyclosporine based on tolerability and rejection. Consequently, the mean oral dose decreased as time on study drug increased. At six months post-transplant, the average oral dose in the GHBA-157 trial was 0.11 mg/kg/day compared to 0.15 mg/kg/day at two weeks post-transplant. In the adult subgroup of the FPC-FK506-7 study, the mean oral dose decreased from 0.19 mg/kg/day at two weeks post-transplant to 0.14 mg/kg/day at six months post-transplant. (See Appendix B, Table B.69.)

In the historically controlled study of tacrolimus for rejection, the average intravenous dose of tacrolimus on day 1 of therapy was 0.11 mg/kg/day. The average oral dose was 0.28 mg/kg/day 3-7 days post-conversion and 0.22 mg/kg/day six months post-conversion. (See Appendix B, Table B.74.) The higher intravenous and oral doses used in the rescue study may reflect the fact that these patients were studied earlier in the clinical development of tacrolimus, with a larger

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proportion of patients receiving therapy prior to amendments for dosage reduction. It is also possible that higher doses are needed to control on-going rejection.

Based on the last dosing amendments to the two randomized, controlled, primary liver transplant studies, the average intravenous and oral tacrolimus doses in patients from the FPC-FK506-7, GHBA-157, and FPC, Japan studies, and trends in dose reduction based on tolerability and time post-transplant, the following initial doses are recommended for tacrolimus in liver transplantation:

0.05-0.10 mg/kg/day as a continuous intravenous infusion
or
0.15-0.30 mg/kg/day orally in two divided doses.

Liver transplant patients receiving tacrolimus for prevention of rejection and/or patients with increased risk of toxicity (e.g., patients with underlying renal dysfunction) should have therapy initiated at the lower end of the dosing range; whereas patients treated for rejection and/or pediatric patients should have therapy initiated at the higher end of the dosing range. Patients receiving intravenous therapy should be converted to oral dosing as soon as oral therapy is tolerated. Assuming a bioavailability of 20%, patients titrated on IV therapy may be converted to daily oral doses at five times the daily IV dose, if the total daily oral dose is ≤ 0.30 mg/kg/day.

A Fujisawa-sponsored study in primary liver transplant patients comparing the rejection rates and toxicities with two tacrolimus dosing regimens over the first six weeks post-transplant is ongoing. The doses being evaluated in this trial are as follows:

Age (years)		Group 1	Group 2
≤ 6	IV	0.10 mg/kg/day	0.05 mg/kg/day
	PO	0.60 mg/kg/day	0.30 mg/kg/day
>6	IV	0.06 mg/kg/day	0.03 mg/kg/day
	PO	0.30 mg/kg/day	0.15 mg/kg/day

8.G.4.2. Dosing in Pediatric Patients

Tables B.62 and B.65 (in Appendix B) summarize the comparative intravenous and oral doses of tacrolimus in the pediatric and adult populations of the FPC-FK506-7 study. On average, intravenous and oral doses were greater on a

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mg/kg basis in the pediatric population than in the adult population with an increase in the disparity with increased time from transplantation. Additionally, the variability in dosing within the pediatric subgroup is greater than that observed within the adult subgroup. These results are most likely secondary to accelerated metabolism and/or reduced bioavailability of tacrolimus in the pediatric population. In the FPC, Japan study in living-related donor liver transplant, 22 of 24 patients were pediatric (≤ 12 years old). On day 1 of tacrolimus therapy, the average intravenous dose was 0.11 mg/kg/day. The average oral dose was 0.34 mg/kg/day at day 7 of therapy and 0.45 mg/kg/day at three months of therapy. Patients less than three years of age required 2-2.5 times higher doses than patients 3 to 15 years of age to achieve similar plasma concentrations.⁵⁰ A publication from the University of Pittsburgh also supports the requirement for higher doses in pediatric patients.³⁵ A similar phenomenon has been reported with cyclosporine.^{18,19} Although pediatric patients are titrated to higher intravenous and oral doses of tacrolimus, plasma or whole blood concentrations are not increased proportionally, as shown in Tables 27 and 28. The ratios of pediatric to adult mean whole blood and plasma concentrations range from 0.5 to 1.6, whereas ratios of doses range from 1.3 to 3.9. This supports a theoretical difference in pharmacokinetics, but not pharmacodynamics, of tacrolimus between the pediatric and adult populations (see Appendix B, Tables B.62 - B.67).

Table 27 Intravenous (IV) and Oral (PO) Tacrolimus Dosing in Adult and Pediatric Patients in the FPC-FK506-7 Study

		Ratio ^a	Adults Age > 12 years		Pediatric Age \leq 12 years	
			N	Mean \pm SD mg/kg/day	N	Mean \pm SD mg/kg/day
IV	Day 1	1.3	183	0.08 \pm 0.04	20	0.10 \pm 0.03
PO	Day 7	1.3	198	0.20 \pm 0.09	24	0.26 \pm 0.11
	Day 28	2.3	185	0.17 \pm 0.09	22	0.39 \pm 0.18
	Day 180	3.6	166	0.14 \pm 0.07	20	0.50 \pm 0.32
	Day 330	3.9	158	0.12 \pm 0.07	20	0.47 \pm 0.38

^a Ratio represents the mean dose for the pediatric population divided by the mean dose in the adult population

Fujisawa USA, Inc.**Table 28: Plasma and Whole Blood Concentrations of Tacrolimus for Adult and Pediatric Patients in the FPC-FK506-7 Study**

Biological Matrix	Day Post-Transplant	Ratio*	Adults Age >12 Years		Pediatric Age ≤ 12 Years	
			N	Concentration (ng/mL) Mean ± SD	N	Concentration (ng/mL) Mean ± SD
Plasma	Day 1	0.7	61	1.60 ± 1.08	10	1.18 ± 0.69
	Day 7	0.7	99	1.26 ± 0.88	7	0.94 ± 0.63
	Days 21-35	0.5	184	1.16 ± 1.02	21	0.57 ± 0.33
	Days 165-195	1.5	94	0.70 ± 0.59	12	0.90 ± 0.44
	Days 345-375	1.5	34	0.72 ± 1.56	1	1.10
Whole Blood	Day 1	1.2	19	27.77 ± 19.08	2	33.65 ± 39.24
	Days 7	-	33	29.15 ± 20.63	-	-
	Days 21-35	0.6	91	17.41 ± 13.06	6	10.65 ± 3.06
	Days 165-195	1.6	40	11.95 ± 6.89	6	19.58 ± 27.39
	Days 345-375	1.4	19	15.17 ± 15.84	1	21.10

* Ratio represents the mean concentration (plasma or whole blood) for the pediatric population divided by the mean concentration in the adult population.

8.G.4.3. Dose Response Analysis**4.3.1 Animal Studies**

Animal studies (Section 5.B General Pharmacology) have demonstrated dose-response effects of tacrolimus in transplant models including:

- ◆ Rat liver allograft (PVG to LEW rats)
- ◆ Baboon kidney transplant
- ◆ Mouse and rat heart transplant

Serum trough levels of tacrolimus that result in optimal efficacy in a beagle dog model of kidney allotransplantation have been reported as:

0.10-0.40 ng/mL for prophylactic use;
0.28-3.70 ng/mL for treatment of acute rejection.⁸⁸

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These levels are similar to plasma concentrations which produce therapeutic effects in humans; however, higher doses were required in animal models than in humans to achieve similar concentrations.

4.3.2. Clinical Studies

Tacrolimus dose-response analyses for clinical studies were performed for the following efficacy parameters:

- ◆ Patient survival
- ◆ Graft survival
- ◆ Acute rejection
- ◆ OKT3 use
- ◆ Refractory rejection

These efficacy parameters were compared within and between studies for the following tacrolimus dose groups:

<u>IV (mg/kg/day)</u>	<u>PO (mg/kg/day)</u>
< 0.05	< 0.15
0.05 - 0.10	0.15-0.30
> 0.10	> 0.30

The three tacrolimus dose groups include patients treated with the recommended tacrolimus starting dose from the proposed labeling (IV: 0.05-0.10 mg/kg/day, PO: 0.15-0.30 mg/kg/day), and patients treated with greater or lesser doses than the recommended labeled dose.

Phase III protocols had specific recommendations for the initial dose, but allowed for dosage adjustment dependent on clinical evidence of rejection or toxicity, as well as adjustments made to maintain target blood/plasma concentrations. Since patients may have started on a given dose and were subsequently titrated to higher or lower doses, IV dose-response analyses included an evaluation of the first dose and the average IV dose during treatment. Similarly, oral dose-response analyses examined both the initial oral dose (averaged over the first three days of oral dosing) and the average oral dose over the entire treatment period.

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In these exploratory post-hoc analyses, results with a $p < 0.10$ will be described as statistically significant and their clinical importance is discussed.

Initial IV Dose (Appendix B, Tables B.22 - B.26, Figures 12.1-16.4)
The following tacrolimus IV dosing groups were defined for analysis:

First Dose (every 12 hours)	Corresponding Daily Dose
< 0.025 mg/kg	< 0.05 mg/kg
0.025 - 0.05 mg/kg	0.05-0.10 mg/kg
> 0.05 mg/kg	> 0.10 mg/kg

Analyses of the first IV dose showed no significant difference in efficacy parameters among the three tacrolimus dosing groups, for any of the studies, with the exception of discontinuation for lack of efficacy in the study. In this later study, there were significantly more discontinuations for lack of efficacy in the 0.025-0.05 mg/kg group compared to the >0.05 mg/kg group ($p=0.034$). However, only four patients were in the 0.025 - 0.05 mg/kg group. One-year patient and graft survival rates in patients receiving a first IV dose of 0.025 - 0.05 mg/kg (proposed recommended starting dose) in the FPC-FK506-7 study and GHBA-157 study were slightly higher than the overall survival rates in the tacrolimus treatment groups of either study, as shown in Table 29.

Table 29: One-Year Patient and Graft Survival Rates for the 0.025-0.05 mg/kg IV Dosing Group Versus Overall Tacrolimus Treatment Groups in the FPC-FK506-7 and GHBA-157 Studies

	One-Year Patient Survival		One-Year Graft Survival	
	1st IV Dose 0.025-0.05 mg/kg	Tacrolimus Overall	1st IV Dose 0.025-0.05 mg/kg	Tacrolimus Overall
FPC-FK506-7	92% (N=103)	88% (N=263)	83% (N=103)	82% (N=263)
GHBA-157	82% (N=107)	81% (N=270)	78% (N=107)	76% (N=270)

Fujisawa USA, Inc.Average IV Daily Dose (Appendix B, Tables B.27 - B.31; Figures 17.1-21.4)

Significantly higher survival rates were observed in the GHBA-157 0.05 - 0.10 mg/kg/day average IV dose group than in either the lower or the higher dose groups. This observation may partially result from the more seriously ill patients, e.g., patients with multi-organ system failure, receiving lower doses. Analyses of patient and graft survival in the other studies showed no significant differences among dosing groups. In the FPC-FK506-7 study, significantly less acute rejection was seen in patients who received the highest average IV doses (>0.10 mg/kg/day). The acute rejection rate at six months post-transplant in the group receiving 0.05 - 0.10 mg/kg/day (recommended dose) was nearly the same as the overall study population (68% vs 66%, respectively).

In the study, significantly fewer patients were discontinued for lack of efficacy with increasing average IV dose: 67% at <0.05 mg/kg/day, 44% at 0.05 - 0.10 mg/kg/day, and 23% at >0.10 mg/kg/day.

Average Oral Dose - First Three Days (Appendix B, Tables B.32 - B.36; Figures 22.1-26.4)

Table 30 contains the one-year patient and graft survival data by average oral dose over the first 3 days of oral therapy for the GHBA-157 study.

Table 30 One-Year Patient and Graft Survival by First 3-Day Average Oral Dose in the GHBA-157 Study

Tacrolimus Dose mg/kg/day	N	Patient Survival One-Year	Graft Survival One-Year
<0.15	137	81%	76%
0.15-0.30	100	87%	82%
>0.30	10	100%	100%

An increasing survival rate was noted with increasing dose group; however, the number of patients is small in the high-dose group. This trend toward higher survival rates with increased dosage may be the result of the best-risk patients' ability to tolerate the highest doses of tacrolimus. In the study, patient and graft survival were

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significantly greater for the 0.15-0.30 mg/kg/day dose group than for either the higher or lower dose groups. Overall, patient and graft survival rates in all tacrolimus studies were similar or numerically greater for the group receiving an initial 3-day average oral dose of 0.15-0.30 mg/kg/day (the proposed recommended starting dose) compared to the overall study results, as shown in Table 31.

Table 31. Kaplan-Meier One-Year Patient and Graft Survival Estimates for the Initial 3-Day Average Oral Dose Group 0.15-0.30 mg/kg/day Versus Overall Tacrolimus Treatment Group

Study	Patient Survival One-Year		Graft Survival One-Year	
	0.15-0.30 Mg/Kg/Day	Overall	0.15-0.30 Mg/Kg/Day	Overall
FPC-FK506-7	90% (N=134)	88% (N=263)	87% (N=134)	82% (N=263)
GHBA-157	87% (N=100)	81% (N=270)	82% (N=100)	76% (N=270)
FPC, Japan	71% (N=10)	66% (N=24)	71% (N=10)	66% (N=24)

Table 32 presents the rate of OKT3 use by initial 3-day average oral tacrolimus dose group in the FPC-FK506-7 study. The rate of OKT3 use showed a decreasing trend with increasing dose in the FPC-FK506-7 study.

Table 32: OKT3 Use at Six Months Post-Transplant by Initial 3-Day Average Oral Dose in the FPC-FK506-7 Trial

Tacrolimus Dose mg/kg/day	N	OKT3 Use
<0.15	85	25%
0.15-0.30	134	17%
>0.30	15	7%

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The rate of OKT3 use in the 0.15-0.30 mg/kg/day group (recommended starting dose) was similar to the overall FPC-FK506-7 study rate (17% vs 19%, respectively).

In the study, incidence of acute rejection and rejection were significantly different between initial 3-day average oral dose groups, as shown in Table 33. Rejection rates were lowest in the 0.15-0.30 mg/kg/day group.

Table 33: Rejection Rates (%) at Six Months in FPC-FK506-9 Study by Initial 3-Day Average Oral Dose

Tacrolimus Dose mg/kg/day	N	ACUTE REJECTION	REFRACTORY REJECTION
< 0.15	9	44%	73%
0.15-0.30	78	39%	22%
> 0.30	29	52%	28%
		P=0.077	P<0.001

Analyses of rejection rates by initial oral dose reveal significant trends towards lower rates of acute rejection with increasing dose in the FPC, Japan study; however, small sample size precludes definitive conclusions.

Overall Average Oral Dose (Appendix B, Tables B.37 - B.41; Figures 27.1-31.4.)

Patient and graft survival rates did not show clear relationships to the patients' overall average oral dose in the FPC-FK506-7, GHBA-157, or studies, although there is a significant trend in the smaller FPC, Japan study. Again, the small number of patients in each dosing group of the latter study (3, 7, and 11, respectively) prevents a definitive conclusion.

There was significantly less OKT3 use in the 0.15-0.30 mg/kg/day group as compared to the lower or higher dose groups for the FPC-FK506-7 study. In the study, the patients receiving 0.15-0.30 mg/kg/day, as an average dose over the course of the study, had the lowest incidence of acute rejection.

Fujisawa USA, Inc.Tacrolimus Dose-Response Analysis in Pediatric sub-groups

(Appendix B, Tables B.42-B.61; Figures 32.1-51.4.)

To assess whether the observed dose-response relationships were influenced by patient age, the above analyses were repeated for the two studies with adequate number of adult and pediatric patients (FPC-FK506-7,

An overall comparison of efficacy in adult and pediatric groups follows in Section 8.G.5.1. The patients were stratified by age, pediatric ≤ 12 years of age and adult > 12 years of age.

IV Dose

Analyses of first IV dose showed no significant difference by dose group between the adult and pediatric subgroups for any efficacy parameter. Average IV dose evaluation indicated a dose effect for patient and graft survival in the pediatric subgroup of the FPC-FK506-7 trial showing an increase in patient and graft survival with increasing dose groups. Table 34 presents the one-year patient and graft survival rates for the pediatric subgroup in the FPC-FK506-7 trial. (See Appendix B, Tables B.47-B.48; Figures 37.2 and 38.2.)

Table 34: Patient and Graft Survival at One-Year for the Pediatric FPC-FK506-7 Patients by Tacrolimus Dosing Groups

Average IV Dose mg/kg/day	N	Patient Survival	Graft Survival
<0.5	3	33%	33%
0.05-0.10	15	73%	60%
>0.10	9	100%	100%

The small number of patients (N) urges caution in interpretation of these data. As stated previously, this observation may also reflect drug tolerability, which may be best in those patients who are stable and who are most likely to survive. In contrast, patients with multi-organ system failure are less likely to have a favorable outcome and would have doses titrated downward in an attempt to alleviate any potential exacerbating effects of the drug on the other organ systems.

In the pediatric subgroup of the study, discontinuation for rejection was lowest in the >0.10 mg/kg/day average IV dose group, which was similar to results in the overall study population.

Fujisawa USA, Inc.Oral Dose

Evaluation of the initial 3-day average oral tacrolimus dose in the pediatric subgroup reveals significantly greater one-year patient and graft survival in the 0.15 - 0.30 mg/kg/day group ($P < 0.05$). Table 35 presents the one-year patient and graft survival rates for the pediatric subset of the study.

Table 35: One-Year Patient and Graft Survival by Initial 3-Day Average Oral Tacrolimus Dosing Group for the Pediatric Patients

Oral Dose mg/kg/day	N	Patient Survival	Graft Survival
<0.15	2	0%	0%
0.15-0.30	9	89%	49%
>0.30	12	49%	21%

The general clinical practice is to treat either the sickest patients (i.e., those with severe renal dysfunction) with low initial doses and those with the most severe rejection with the highest doses. This may result in having those patients with the greatest chance of survival in the middle-dose group. Small sample size makes the results difficult to conclusively analyze; however, these results support the efficacy of tacrolimus in the group receiving the proposed recommended starting dose (0.15-0.30 mg/kg/day).

Average oral tacrolimus dose evaluation showed an apparent improvement in patient and graft survival in the higher dose group (>0.30 mg/kg/day) in the pediatric group in the FPC-FK506-7 study. Again, the number of patients in the dosing group is relatively small, making conclusive interpretation of results difficult. Patient and graft survival rates in the adult subset of the FPC-FK506-7 study were not significantly different between dose groups and were similar to the overall results for the 0.15 - 0.30 mg/kg/day group.

Summary of Dose Response in Tacrolimus Treated Patients

These dose-response analyses demonstrate that tacrolimus efficacy is maintained in the subset of patients in the FPC-FK506-7, GHBA-157, and studies who have received the recommended starting doses. Overall, there was no substantive evidence of a statistically significant decrease in efficacy in the groups receiving the recommended

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starting dose compared to the high- or low-dose groups considering either initial or average IV or oral doses. However, trends toward differences in efficacy between the dose groups, in general, favored the middle-dose group (recommended starting dose). The results in the pediatric subgroups support the efficacy of the middle-dose group when evaluating patient and graft survival for initial IV and initial oral dosing. When evaluating overall average IV or oral dosing the proportion of pediatric patients receiving the higher doses increased compared to initial dose analyses. Also, there were trends toward increased efficacy of tacrolimus in the higher average oral or IV dose groups. This may reflect the need to titrate pediatric patients to higher doses than adults.

8.G.4.4. *Tacrolimus Plasma/Whole Blood Concentration Analysis*

Whole blood and plasma concentrations were measured to one year post-transplant and available for analyses of the potential relationship of tacrolimus concentration to clinical response in the FPC-FK506-7 study only. Therefore, exploratory analyses were limited to the FPC-FK506-7 study. Cox proportional hazards models were used with plasma or whole blood concentration as a time-dependent variable to evaluate the relationship of concentration (within two weeks prior to the event onset) with the following key efficacy parameters (events):

- ◆ death
- ◆ retransplantation
- ◆ acute rejection
- ◆ OKT3 use

Mean, minimum, maximum, and last concentration within a two-week window prior to the event were assessed. There were, on average, 2-3 times as many plasma concentration values as whole blood concentration values. (See Appendix B, Tables B.69, B.70.) For this reason, the concentration response was first assessed using all available plasma or whole blood concentrations. Subsequently, the analyses were restricted to only those times at which a simultaneous plasma and whole blood concentration level was available. This allowed an assessment of the relative predictability using plasma concentrations compared to whole blood concentrations, while controlling for the bias in sample size. Lastly, analyses were performed using specific cut-off concentrations (ng/ml) to evaluate the relative risk of

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events when plasma concentrations were above or below a specified concentration. Results of these analyses are detailed in Appendix B, Document A.

Using all available plasma or whole blood values (i.e., 2-3 times greater number of plasma than whole blood values), the following relationships were found:

- ◆ Higher plasma concentrations (mean, minimum, or maximum within the two-week window) were related to lower risk of acute rejection.
- ◆ High last plasma concentration within the two-week window prior to the event was related to a lower rate of OKT3 use.
- ◆ No relationship of acute rejection or OKT3 use with whole blood concentrations.
- ◆ Higher whole blood or plasma concentrations associated with a greater risk of death.
- ◆ No significant relationships with plasma or whole blood concentrations and rejection or retransplant.

When the analyses were restricted to only simultaneous plasma and whole blood values, there was no longer a relationship of plasma concentration to acute rejection or OKT3 use. This may indicate the lack of a relationship of whole blood concentration to these events is due to the smaller number of whole blood samples compared to plasma. Using only simultaneous plasma or whole blood values, the relationship of both higher plasma and higher whole blood concentration to increased risk of death remained.

Using various cut-off plasma concentrations (0.5, 1.0, 1.5, and 2.0 ng/mL), the risk of acute rejection appeared to decrease in a linear fashion with increasing plasma concentration. The relationship was strongest using the minimum plasma concentration in the two-week window prior to the event. This trend was not as apparent using the endpoint of OKT3 use. Only a minimum plasma value of ≥ 0.5 ng/mL was related to a reduced risk of OKT3 use. Table 36 summarizes the concentration-response results for plasma and whole blood values.

Fujisawa USA, Inc.**Table 36: Concentration-Response Relationship for Plasma or Whole Blood Levels in FPC-FK506-7 Study**

Outcome	All Samples Analyzed	Simultaneous Plasma & Whole Blood Analyzed
Death	Positive Relationship with Plasma & Whole Blood**	Positive Relationship with Plasma & Whole Blood**
Retransplant	None	None
Acute Rejection	Inverse Relationship with Plasma Only**	None
OKT3 Use	Inverse Relationship with Plasma Only**	None
Refractory Rejection	None	None

** Significant relationship $P < 0.05$

Based on these analyses, there appears to be a relationship between tacrolimus plasma concentration and risk of acute rejection and OKT3 use, a risk which declines with increasing tacrolimus plasma concentration. This, again, is not seen with whole blood concentrations, nor is it seen with plasma levels when the plasma sample size is made identical to that of whole blood sample size. High tacrolimus plasma and whole blood concentrations are positively related to risk of death. This relationship is most likely the result of the clinical condition of these patients and liver failure which can lead to increased tacrolimus concentrations through decreased metabolism. A minimum tacrolimus plasma concentration of ≥ 0.50 $\mu\text{g/mL}$ within two weeks prior to event was positively related to a reduced risk for rejection and OKT3 use.

8.G.4.5. Summary of Dose Response/Concentration Response

There appear to be dose- and plasma-concentration response relationships for tacrolimus. These relationships indicate that there may be a dose or concentration below which the risk of lessened immunosuppressive efficacy exists. Results in patients treated with doses within the recommended starting doses in the proposed labeling are similar, or better, than the overall study results in the controlled clinical trials.

Fujisawa USA, Inc.**8.G.5. Analysis of Response in Subsets of Overall Population****8.G.5.1. Subset Analysis by Age**

The FPC-FK506-7, and FPC, Japan studies included pediatric (≤ 12 years) and adult patients. The GHBA-157 study enrolled adult patients only. The numbers of pediatric and adult patients enrolled by study are shown in Table 37.

Table 37: Enrollment of Pediatric and Adult Patients by Study

Study	Drug	Adult	Pediatric
FPC-FK506-7	Tacrolimus	233 (38.6%)	30 (11.4%)
	CBIR	245 (92.1%)	21 (7.9%)
GHBA-157	Tacrolimus	270 (100%)	0 (0%)
	CBIR	275 (100%)	0 (0%)
FPC, Japan	Tacrolimus	2 (8%)	22 (92%)

The FPC-FK506-7 and pediatric and adult populations were analyzed to compare the relative efficacy of tacrolimus therapy in these two population subsets. Since the FPC, Japan study included only two adult patients and the GHBA-157 study excluded pediatric patients, a meaningful comparison between population subsets in these studies could not be made.

5.1.1. Patient Survival

The pediatric FPC-FK506-7 patients treated with tacrolimus tended to have lower patient survival rates than the tacrolimus-treated adult patients. At 3 months post-transplant, the tacrolimus-treated pediatric patients had a survival rate of 87% versus 92% for the adult tacrolimus-treated patients. The pediatric survival rate dropped to 80% at six months post-transplant where it remained for the duration of the study. The adult patient survival rate declined slightly to 91% at six months and 89% at 12 months post-transplant. Likewise, at all time points, the adult CBIR-treated patients had higher patient survival rates than their pediatric counterparts. The three-month CBIR-treated pediatric survival rate of 86% decreased to a 12-month rate of 81% compared to

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the adult rates of 93% and 88%, at three and 12 months, respectively. Survival for the pediatric tacrolimus-treated patients was not significantly different than the pediatric CBIR-treated patients. In addition, none of the differences in patient survival rates between population subsets were statistically significant.

Similar to the FPC-FK506-7 results, the patient survival rate in the pediatric population of the study tended to be lower than that for the adult population. The differences in survival rates between adult and pediatric patients in the study were not as great as those observed in the FPC-FK506-7 study. This may be related to technical complications common in pediatric patients immediately post-transplant (e.g., hepatic artery thrombosis) which occurred in the FPC-FK506-7 study, but would be uncommon in a study, such as

Table 38 presents the patient survival rates by age for the FPC-FK506-7 and studies. (See Appendix B, Tables B.90 and B.95; Figures 53.1-53.4 and 58.1-58.3.)

Table 38. Patient Survival Rates in Pediatric and Adult Subgroups of the FPC-FK506-7 and Studies

Study	Patient Survival					
	3 Months		6 Months		12 Months	
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
FPC-FK506-7						
Tacrolimus	87%	92%	80%	91%	80%	89%
CBIR	86%	93%	81%	91%	81%	88%

Figure 6 presents the patient survival curves to one year for the FPC-FK506-7 pediatric and adult subgroups treatment group.

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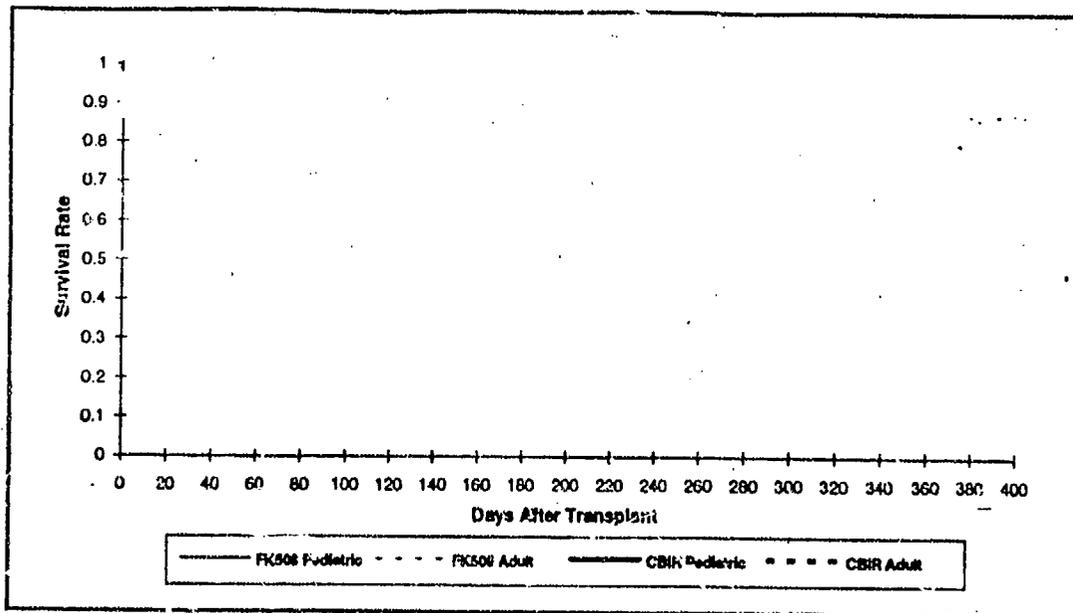


Figure 6. Patient survival, tacrolimus (FK506) versus CBIR in pediatric and adult patients (FPC-FK506-7 study).

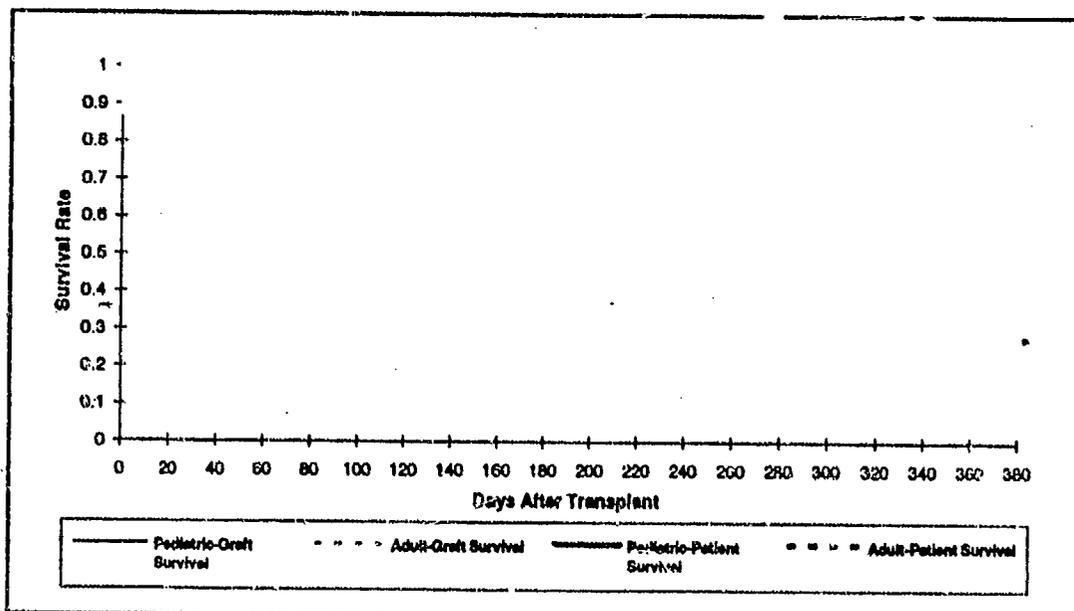


Figure 7. Patient and graft survival rates for the FPC-adult and pediatric patients.

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The Kaplan-Meier estimates of patient and graft survival to one year for the pediatric and adult patients by treatment group are presented in Figure 7.

5.1.2. Graft Survival

Table 39 presents graft survival rates by treatment groups for pediatric and adult subgroups of the FPC-FK506-7 and studies. (See Appendix B, Tables B.91 and B.95; Figures 54.1-54.4 and 59.1-59.3.)

Table 39: Graft Survival Rates by Treatment Group for Pediatric and Adult Populations in the FPC-FK506-7 Studies

Graft Survival						
Study	3 Months		6 Months		12 Months	
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
FPC-FK506-7						
tacrolimus	77%	88%	70%	87%	70%	83%
CBIR	71%	87%	71%	84%	71%	80%

Figure 8 presents graft survival curves for pediatric and adult patients in the in FPC-FK506-7 study by treatment group.

In the FPC-FK506-7 study, pediatric patients treated with tacrolimus tended to have lower graft survival rates than the adult tacrolimus treatment group. This difference (70% vs 83% at one year) approached statistical significance ($P=0.062$). Pediatric CBIR patients also tended to have lower graft survival rates than did adult CBIR patients, although the magnitude of the difference was smaller than that in the tacrolimus treatment group (9 percentage points at one year in the CBIR group; 13 percentage points at one year in the tacrolimus group). Graft survival rates were similar when comparing tacrolimus to CBIR in either the pediatric or the adult subgroups.

Graft survival rates were comparable at three months post-transplant between the pediatric and adult population in the study, 77% versus 72%, respectively. Both groups showed a decline in graft

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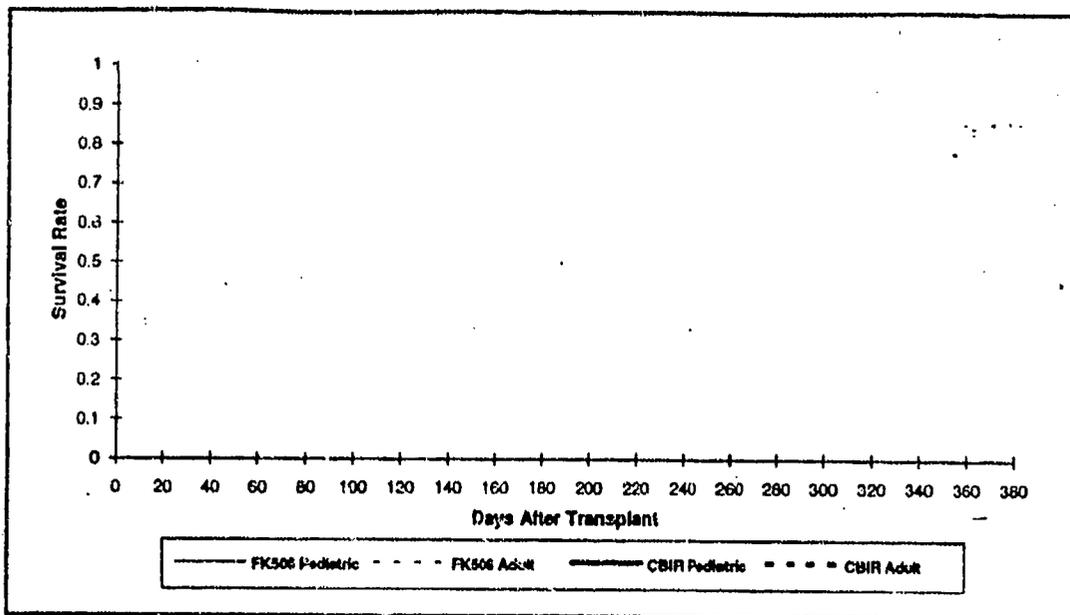


Figure 8. Graft survival for pediatric and adult FPC-FK506-7 patients, tacrolimus (FK506) versus CBIR.

survival over time, with the pediatric population showing the greatest decline. At six months post-transplant, the pediatric graft survival rate was 68% and declined to 39% at 12 months. Adult graft survival rates at six and 12 months post-transplant were 65% and 60%, respectively. While the difference in graft survival rates between population subsets was not statistically significant, the small sample sizes must be taken into account.

5.1.3. Rejection

Pediatric patients receiving tacrolimus in the FPC-FK506-7 study had the lowest acute rejection rate compared to all other groups. Table 40 presents acute rejection rates for the controlled liver transplant studies for pediatric and adult subsets. (See also, Appendix B, Tables B.92 and B.97; Figures 55.1-55.4 and 60.1-60.3.)

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Table 40 Rates of Biopsy-Confirmed Acute Rejection Episodes for Pediatric and Adult Subpopulations in the FPC-FK506-7 and the Clinical Trials

Acute Rejection Rate						
Study	28 Days		90 Days		183 Days	
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
FPC-FK506-7 Tacrolimus	36%	57%	47%	65%	52%	67%
CBIR	79%	66%	79%	72%	79%	73%

Although not statistically significantly different, the pediatric subset of the FPC-FK506-7 study had a reduced rate of acute rejection compared to the adult group. Differences in acute rejection rates between pediatric and adult tacrolimus groups were 15 percentage points at 183 days post-transplant. In contrast, acute rejection rates in the FPC-FK506-7 pediatric CBIR group were higher than the adult CBIR patients at 28, 90, and 183 days post-transplant, although the difference was not statistically significant.

The advantage of tacrolimus compared to CBIR in reducing rejection rates was evident when comparing the two pediatric groups or the two adult groups. Although the absolute difference was greater in the pediatric population (27 percentage points at six months in pediatric vs six percentage points in adults), statistical significance ($P = 0.005$) was evident only in the adult population due to the larger number of adult patients compared to pediatric patients.

Figure 9 presents the rate of the cumulative incidence of acute rejection in FPC-FK506-7 adult and pediatric patients.

The use of OKT3 was similar in adult and pediatric patients in the FPC-FK506-7 trial. The decreased use of OKT3 in the overall tacrolimus population compared to the CBIR population remained for both the pediatric and adult subsets. At six months post-transplant, the rate of OKT3 use was 17 percentage points lower in tacrolimus-treated adults and 11 percentage points lower in tacrolimus-treated pediatric patients compared to CBIR. This difference was statistically significant in the

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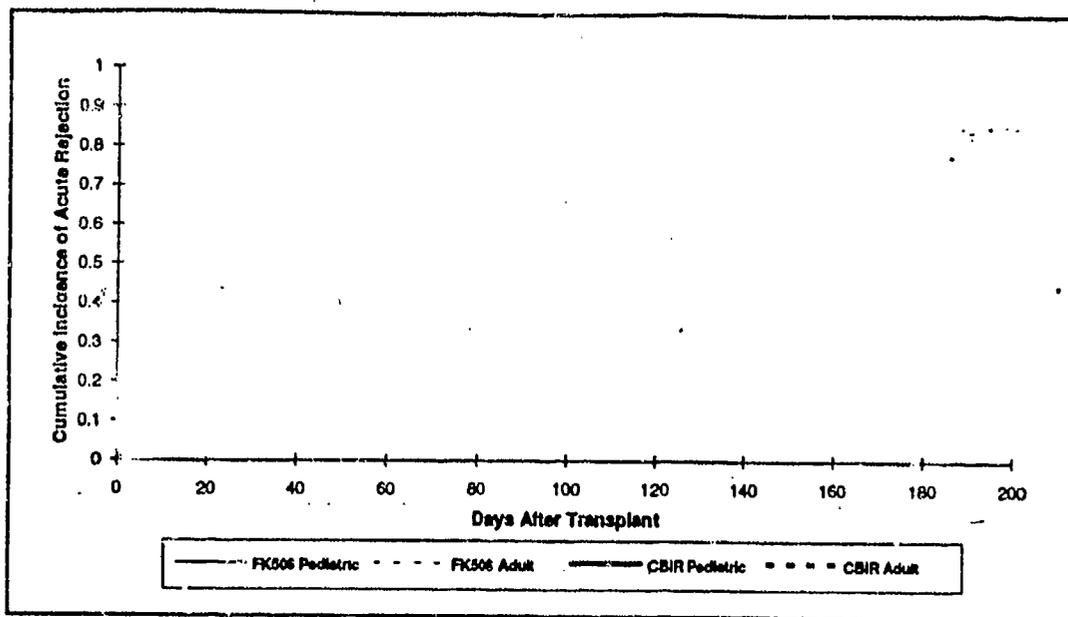


Figure 9. Cumulative incidence of acute rejection in FPC-FK506-7 pediatric and adult patients, tacrolimus (FK506) versus CBIR.

adult population only ($P < 0.001$). (See Appendix B, Tables B.93 and B.98; Figures 58.1-58.4 and 63.1-63.3.)

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Table 41 presents OKT3 use rates at selected time points for the pediatric and adult subgroups in the FPC-FK506-7 study.

Table 41: OKT3 use Rates for Pediatric and Adult Populations in the FPC-FK506-7 Clinical Trial

OKT3 Use						
Study	28 Days		90 Days		183 Days	
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
FPC-FK506-7 tacrolimus	16 %	15%	21 %	19%	21 %	19%
CBIR	32%	28%	32%	34%	32%	36%

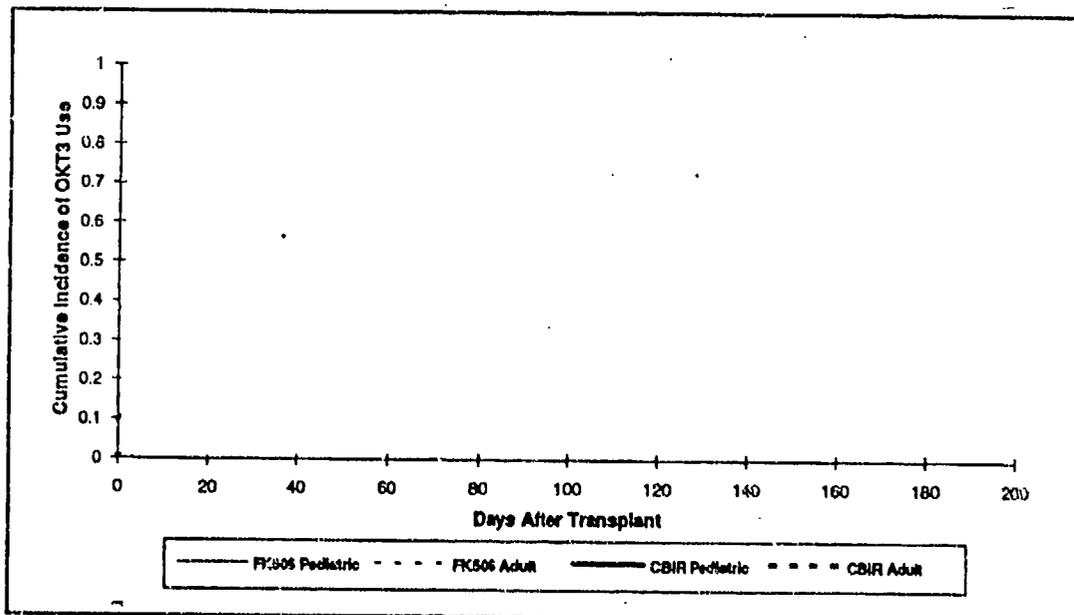


Figure 10. Cumulative OKT3 use in FPC-FK506-7 pediatric and adult patients, tacrolimus (FK506) versus CBIR.

Figure 10 presents the rate for the cumulative incidence of OKT3 use for treatment of rejection in the FPC-FK506-7 pediatric and adult subgroups.

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5.1.4. Refractory Rejection

There was no incidence of rejection among FPC-FK506-7 pediatric patients in either the tacrolimus or CBIR treatment groups by day 183; while 3% of tacrolimus-treated adults and 14% of CBIR-treated adults had experienced rejection by day 183 ($P < 0.001$). In the study, 29% of pediatric patients and 26% of adult patients experienced rejection and discontinued for lack of efficacy by day 183 post-conversion to tacrolimus. (See also Appendix B, Tables B.94 and B.99; Figures 57.1-57.4 and 62.1-62.3.)

5.1.5. Summary of Adult versus Pediatric Comparison

A trend toward lower patient and graft survival rates was seen in the pediatric CBIR and tacrolimus groups in the FPC-FK506-7 study and the study compared to adult patients. This decrease is consistent with reported literature describing greater risk for death or graft loss, particularly in pediatric patients less than three years of age.⁸² Early death or graft loss is more common among pediatric liver transplant patients than among adult patients. The differential survival rates between pediatric and adult liver transplant patients can be attributed to the increased difficulty in the surgical procedure, the high rate of thrombosis, and the underlying cause of liver dysfunction necessitating liver transplantation in pediatric patients. Finding a size-matched donor for pediatric liver transplantation is difficult, particularly in patients less than three years of age. Consequently, the use of reduced-size liver transplants (RLT) and living-related donor transplants (LRT) has increased. Thrombosis of the hepatic artery is a serious complication following liver transplantation which usually occurs within the first several weeks of transplantation. It is estimated that 4% of adult patients will experience hepatic artery thrombosis; however, 12% of pediatric patients (<18 years of age) are expected to develop hepatic artery thrombosis and an estimated 30% of patients under the age of one will experience hepatic artery thrombosis.⁸⁶

The underlying cause of liver disease or dysfunction is another contributing factor to the high mortality and morbidity rates early after transplantation among pediatric patients. Children presenting with liver dysfunction are often more critically ill than adults awaiting transplantation. The reasons for liver dysfunction (e.g., metabolic

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disorders, congenital conditions) often place pediatric patients in a medically more urgent state than adult patients.

Although rejection rates were similar or higher in the pediatric CBIR group compared to the adult CBIR group, pediatric patients receiving tacrolimus had the lowest rates of rejection compared to either the adult tacrolimus treatment group or either subset population in the CBIR treatment group. However, use of OKT3 was similar in adult and pediatric tacrolimus patients with both rates lower than the CBIR subgroups. rejection was not seen in the pediatric patients in the FPC-FK506-7 study.

In summary, tacrolimus-treated pediatric patients had lower rejection rates than their adult counterparts. These data suggest superior immunosuppressive efficacy of tacrolimus in pediatric patients. There is clearly great benefit to pediatric rescue patients; such patients, having failed intensive anti-rejection therapy with standard immunosuppressants, would be expected to have the greatest degree of liver dysfunction. Also, there appears to be great benefit to pediatric patients undergoing primary liver transplant, including living-related donor graft recipients, who survive the early post-transplant technical complications common to this group.

Overall, tacrolimus appears to be an effective immunosuppressant in the pediatric and adult populations with potential advantages over and above CBIR therapy in acute rejection and steroid-resistant rejection rates. The lower survival rates in the pediatric population compared to the adult population are similar and consistent with publications describing CBIR therapy in pediatric patients. Tacrolimus appears to be particularly effective in preventing acute rejection in pediatric patients.

8.G.5.2. Subset Analysis by CBIR Control Regimen

In the FPC-FK506-7 and GHBA-157 studies, centers used different CBIR treatments (double, triple, or induction); whereas, tacrolimus was used with low-dose steroids only. Subset analyses were performed to evaluate the efficacy of tacrolimus compared to the various CBIR control regimens in both studies. These analyses were subdivided based on double therapy (cyclosporine plus corticosteroids), triple therapy (cyclosporine, azathioprine, and

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corticosteroids), and induction therapy (anti-lymphocyte globulin, followed by cyclosporine, azathioprine, and corticosteroids).

5.2.1. Patient and Graft Survival by CBIR Control Regimen

Table 42 presents the one-year patient survival rates by study for investigational sites using the various CBIR treatments compared to tacrolimus treatment at these sites. Table 43 presents one-year graft survival rates for the CBIR control regimen and tacrolimus treatment by study. (See also, Appendix B, Tables B.100 and B.101; Figures 63, 64, 68, 69, 73, and 74.)

Table 42: Patient Survival (%) at One Year Post-Transplantation by CBIR Control Regimen in the FPC-FK506-7 and GHBA-157 Studies

Control Regimen	FPC-FK506-7		GHBA-157	
	Tacrolimus + steroids (n)	CBIR (n)	Tacrolimus + steroids (n)	CBIR (n)
Double CBIR	85% (27)	81% (31)	-	-
Triple CBIR	87% (210)	87% (208)	78% (157)	73% (164)
Induction CBIR	100% (26)	96% (27)	86% (113)	80% (111)
Overall	88% (263)	88% (266)	81% (270)	75% (275)

Fujisawa USA, Inc.**Table 43: Graft Survival (%) at One Year Post-Transplantation by CBIR Control Regimen in the FPC-FK506-7 and GHBA-157 Studies**

Control Regimen	FPC-FK506-7		GHBA-157	
	Tacrolimus + steroids (n)	CBIR (n)	Tacrolimus + steroids (n)	CBIR (n)
Double CBIR	81% (27)	77% (31)	-	-
Triple CBIR	80% (210)	78% (208)	72% (157)	65% (164)
Induction CBIR	96% (26)	89% (27)	81% (113)	76% (111)
Overall	82% (263)	79% (266)	76% (270)	70% (275)

CBIR Induction Therapy

In the FPC-FK506-7 study, one center used induction therapy with an anti-lymphocyte globulin in the CBIR control arm. Twenty-six patients at that center were randomized to tacrolimus and 27 to CBIR. Patient survival at one year post-transplant was 100% in the tacrolimus group and 96% in the CBIR group with corresponding graft survival rates of 96% and 89%, respectively. In the GHBA-157 study, three centers used an anti-lymphocyte induction in the cyclosporine-based immunosuppressive regimen (CBIR) control arm. A total of 224 patients were randomized at these centers: 113 patients to tacrolimus therapy and 111 patients to CBIR. Kaplan-Meier estimates of one-year patient survival were 86% in the tacrolimus group and 80% in the CBIR group; corresponding one-year graft survival rates were 81% in the tacrolimus group and 76% in the CBIR group.

CBIR Triple Therapy

Five centers in the GHBA-157 trial used a triple therapy regimen in the CBIR group. One hundred fifty-seven tacrolimus patients and 164 CBIR patients were randomized at these sites. One-year Kaplan-Meier estimates of patient survival were 78% in the tacrolimus group and 72% in the CBIR group with corresponding graft survival at one year of 72% and 65%, respectively. In the FPC-FK506-7 trial, 10 of 12 sites used a triple therapy regimen in the CBIR arm. Two hundred-ten patients

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were enrolled in tacrolimus treatment and 208 in CBIR. One-year Kaplan-Meier estimates of patient survival were 87% in the tacrolimus treatment group and 87% in the CBIR treatment group with corresponding one-year graft survival rates of 80% and 78%, respectively.

CBIR Double Therapy

One center in the FPC-FK506-7 study used double therapy in the CBIR control arm. There were 27 patients randomized to tacrolimus and 31 randomized to CBIR at this center. Kaplan-Meier estimates of one-year patient survival were 85% in the tacrolimus group and 81% in the CBIR group; one-year graft survival was estimated at 81% and 77%, respectively.

In summary, tacrolimus (plus low-dose steroids) treatment demonstrated comparable or improved patient and graft survival rates to each of the CBIR control regimens at liver transplant centers in the US and Europe.

Overall, centers using induction CBIR therapies had higher patient and graft survival in both the CBIR and tacrolimus groups compared to other centers. In both the FPC-FK506-7 and the GHBA-157 studies, patient and graft survival were greater in the tacrolimus group than in the CBIR group at induction centers. Centers using triple therapy had lower overall patient and graft survival than the induction centers. The tacrolimus and CBIR survival was similar in triple therapy centers in the FPC-FK506-7 study; however, in the GHBA-157 study, tacrolimus graft survival was seven percentage points greater than the CBIR graft survival at one year post-transplant. The one FPC-FK506-7 center using double therapy had overall slightly lower survival rates than centers using either triple or induction therapy. At this center, the survival rate in the tacrolimus group was four percentage points greater than the CBIR survival for both patient and graft survival at one-year post-transplant.

5.2.2. Acute Rejection

The rate of acute rejection in the CBIR arm of the FPC-FK506-7 was highest with double therapy and lowest with induction therapy, as shown in Table 44. The rate of rejection with tacrolimus was six and nine percentage points less, respectively, than the double or triple therapy CBIR but six percentage points higher than that at the centers

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using an induction regimen. In GHBA-157, the induction centers had overall lower rejection rates than the centers using triple therapy. Tacrolimus rates were lower than CBIR rates with or without induction therapy; however, the difference was greater with triple therapy (17 percentage points) than CBIR induction therapy (8 percentage points). (See Appendix B, Table B.102; Figures 65, 70, and 75.)

Table 44: Acute Rejection Rates at Six Months Post-Transplantation by Treatment Group for the Randomized, Controlled, Primary Liver Transplant Studies

Control Regimen	FPC-FK506.7		GHBA-157	
	Tacrolimus + steroids (n)	CBIR (n)	Tacrolimus + steroids (n)	CBIR (n)
Double CBIR	77% (27)	83% (31)		
Triple CBIR	64% (210)	73% (208)	46% (157)	63% (164)
Induction CBIR	70% (26)	64% (27)	35% (113)	42% (111)
Overall	66% (263)	73% (266)	41% (270)	54% (275)

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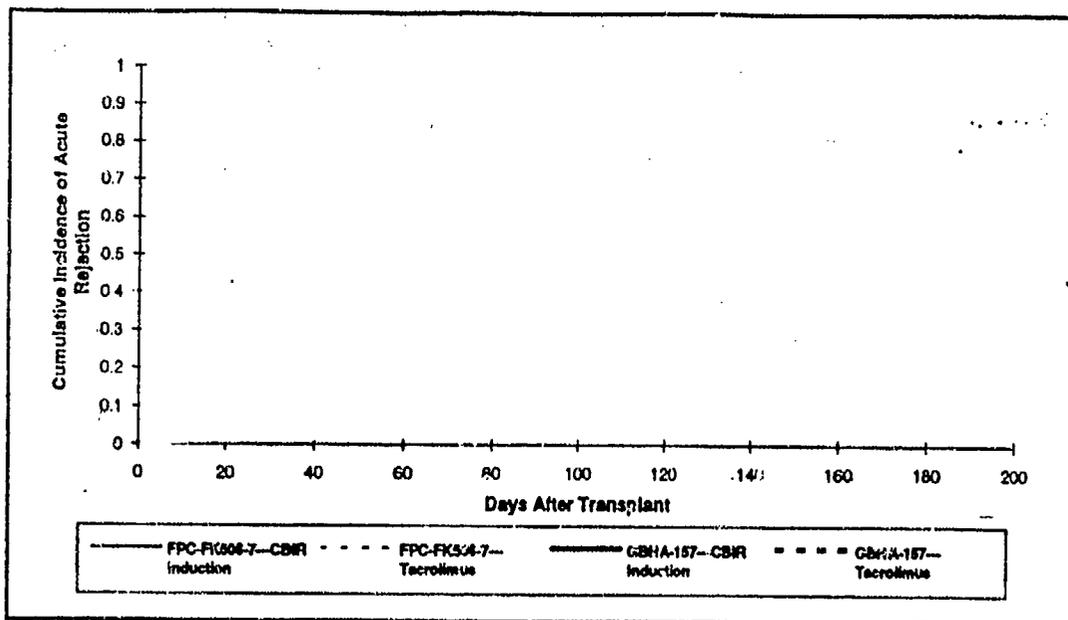


Figure 11. Acute rejection rates at induction therapy sites.

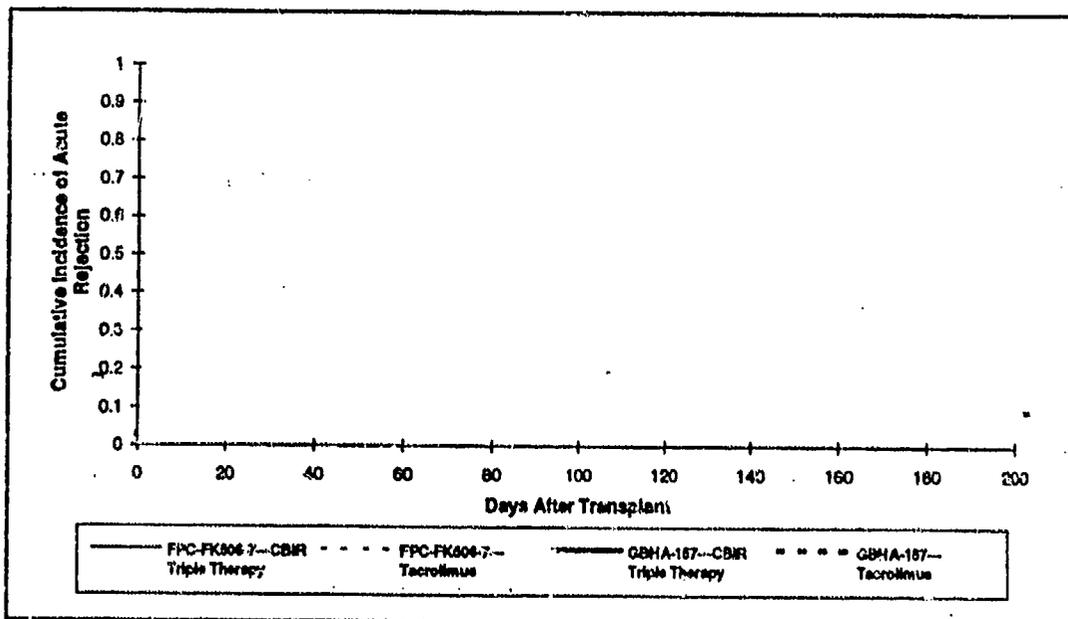


Figure 12. Acute rejection rates at triple therapy sites.

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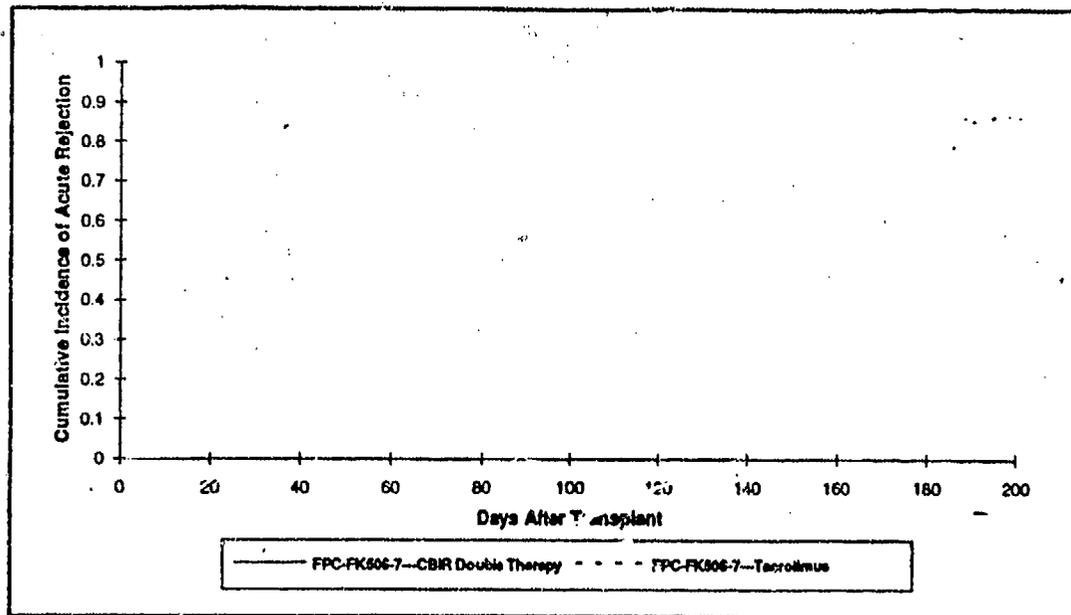


Figure 13. Acute rejection rates at double therapy sites.

Figures 11, 12, and 13 present the cumulative incidence of acute rejection episodes for patients treated at investigational sites using induction, triple, and double CBIR, respectively.

OKT3 use was highest in the double therapy CBIR groups and lowest in the induction CBIR groups, as shown in Table 45. In the FPC-FK506-7 study, rates of OKT3 use with tacrolimus were lower than rates of OKT3 use with any of the CBIR control regimens. In the GHBA-157 study, OKT3 was used infrequently. Similar rates were seen at triple therapy centers and induction therapy centers of GHBA-157; the rates of OKT3 use among tacrolimus patients were slightly lower than those in CBIR patients at either triple therapy or induction sites. (See Appendix B, Table B.103; Figures 66, 71, and 76.)

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Table 45: Six Month Post-Transplant Rate (%) of OKT3 Use for Treatment of Rejection for the Controlled, Primary Liver Transplant Studies by CBIR Treatment

Control Regimen	FPC-FK506-7		GHBA-157	
	Tacrolimus + steroids (n)	CBIR (n)	Tacrolimus + steroids (n)	CBIR (n)
Double CBIR	23% (27)	44% (31)		
Triple CBIR	18% (210)	35% (208)	8% (157)	10% (164)
Induction CBIR	21% (26)	30% (27)	8% (113)	11% (111)
Overall	19% (263)	36% (266)	8% (270)	10% (275)

Rates of discontinuation for lack of efficacy were similar across CBIR therapy types in both the FPC-FK506-7 and the GHBA-157 studies. The rejection rates ranged from %.

rejection rates were substantially lower among tacrolimus-treated patients, except at the FPC-FK506-7 induction center, where the tacrolimus group rate was uncharacteristically high (11%) and two percentage points higher than the CBIR group rate. Table 46 presents rejection rates at six months post-transplant by treatment type for the FPC-FK506-7 and the GHBA-157 studies. (See Appendix B, Table B.104; Figures 67, 72, and 77.)

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Table 46: Rejection Rates (%) as Measured by Discontinuance for Lack of Efficacy at Six Months Post-Transplantation by Treatment Group for each CBIR Control Regimen in the FPC-FK506-7 and GHBA-157 Studies

Control Regimen	FPC-FK506-7		GHBA-157	
	Tacrolimus + steroids (n)	CBIR (n)	Tacrolimus + steroids (n)	CBIR (n)
Double CBIR	4% (27)	12% (31)		
Triple CBIR	1% (210)	14% (208)	3% (157)	11% (164)
Induction CBIR	11% (26)	9% (27)	3% (113)	10% (111)
Overall	3% (263)	13% (266)	3% (270)	10% (275)

5.2.3. Summary-CBIR Control Regimens

Based on these data, tacrolimus, which is a double therapy regimen consisting of tacrolimus plus small doses of corticosteroids, showed comparable to improved patient and graft survival rates when compared to the three most commonly used CBIR treatment types (double, triple, and induction therapies). Additionally, rates of acute rejection, OKT3 use, and rejection were lower among tacrolimus-treated patients than among patients in any of the CBIR-type treatments for both the FPC-FK506-7 and the GHBA-157 studies, with the exception of the one FPC-FK506-7 center using induction therapy. This center reported higher than typical rejection rates in the tacrolimus-treated patients and reported a slightly higher rejection rate for the tacrolimus treatment group than for the CBIR treatment group.

Overall, tacrolimus was shown to have superior efficacy when compared to various cyclosporine-based regimens despite the use of significantly fewer concomitant immunosuppressive agents in the tacrolimus regimen.

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8.G.5.3. Subset Analysis by Gender

Patient and graft survival rates were analyzed to compare the efficacy of tacrolimus in males and females in the FPC-FK506-7, GHBA-157, and FPC, Japan studies. (See Appendix B, Tables B.105-B.114; Figures 78.1-87.4.) There were no differences in the survival rates of male versus female tacrolimus-treated patients for any study, with the exception of a higher one-year graft survival rate for females in the study. The Kaplan-Meier estimates of one-year graft survival rates were 65% for females and 46% for males, a difference approaching statistical significance ($P = 0.074$).

The incidence of acute rejection at six months post-transplant was compared between males and females within the tacrolimus-treated patients. Differences in acute rejection rates between the genders were evident only in the GHBA-157 study; six-month Kaplan-Meier survival estimates of the rate of acute rejection were higher in females (47%) than in males (36%), a difference approaching statistical significance ($P = 0.059$). Rejection rates were higher with CBIR treatment compared to tacrolimus treatment when evaluating male and female patients in the FPC-FK506-7 and GHBA-157 studies. There were no significant differences in OKT3 use between males and females in the four tacrolimus studies. Lower rates of OKT3 use with tacrolimus as compared to CBIR in FPC-FK506-7 study were demonstrated within the male and female subgroups; the difference was statistically significant in each group ($P = 0.002$). Similarly, the rates of rejection in the tacrolimus-treated patients remained comparable between males and females for the four tacrolimus clinical trials. Moreover, lower rates of rejection for tacrolimus-treated patients compared to CBIR-treated patients were noted within the male and female subgroups of the FPC-FK506-7 and GHBA-157 studies.

8.G.5.4. Subset Analysis by Race

Patient and graft survival rates in the FPC-FK506-7, GHBA-157, and studies were analyzed by race. Since all patients in the FPC, Japan study were Oriental, subset analyses by race were not feasible for this study.

There were no statistically significant differences in patient and graft survival rates among the different races within the CBIR or tacrolimus treatment groups in these studies. An analysis of tacrolimus versus CBIR survival rates in the FPC-FK506-7 and GHBA-157 studies grouped by Caucasian and Non-Caucasian was performed. Patient and graft survival in tacrolimus-treated patients was superior to CBIR-treated patients in the Caucasian subgroup in

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the GHBA-157 study ($P = 0.081$, patient survival; $P = 0.048$, graft survival) as shown in Table 47. (See Appendix B, Tables B.115-B.118.)

Table 47: Patient and Graft Survival by Race for the FPC-FK506-7 and GHBA-157 Studies

		Patient Survival One-Year		Graft Survival One-Year	
		Tacrolimus	CBIR	Tacrolimus	CBIR
FPC- FK506-7	Caucasian Tacrolimus=208 CBIR=203	90%	86%	84%	79%
	Non-Caucasian Tacrolimus=55 CBIR=63	82%	92%	75%	81%
GHBA- 157	Caucasian Tacrolimus=260 CBIR=260	82%	76%	77%	70%
	Non-Caucasian Tacrolimus=7 CBIR=10	71%	70%	57%	70%

8.G.6. Long-Term Effectiveness, Tolerance, and Withdrawal

8 G.6.1. Long-term Effectiveness

The FPC-FK506-7 and GHBA-157 studies demonstrate the efficacy of tacrolimus in preventing rejection and maintaining patient and graft survival for at least one year post-liver-transplantation. This is despite a decrease in the dose of concomitant corticosteroids relative to CBIR and a general lowering of the tacrolimus dose over time post-transplant. Less experience is available from non-randomized Fujisawa-sponsored studies in liver rescue, but these data support the efficacy of tacrolimus for at least one year post-conversion compared with historical control groups treated with CBIR.

Published studies support a longer period of effectiveness for tacrolimus. Investigators at the University of Pittsburgh have described a randomized study of tacrolimus versus CBIR in liver transplantation⁸³ with median follow-up of 611 days for the tacrolimus group and 594 days for the CBIR group.

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Additionally, results in pediatric liver transplant patients with follow-up to 34 months have been published.⁸⁷

8.G.6.2. Tolerance

There is no evidence of the development of tolerance to the effects of tacrolimus in any Fujisawa-sponsored study or reports in the published literature. Most events, including rejection and patient death or graft loss, occur early post-transplantation with stabilization of rates over time post-transplant.

8.G.6.3. Withdrawal

Discontinuation of an immunosuppressive agent in transplant patients may lead to rejection or graft loss, but no other withdrawal effects were noted in the study populations. In general, if tacrolimus therapy is discontinued, conversion to alternative immunosuppression is necessary to maintain graft function.

8.G.7. Conclusion

Fujisawa has performed three adequate and well-controlled studies of tacrolimus in the prevention and treatment of rejection after liver transplantation. The two randomized, multicenter, CBIR-controlled studies (FPC-FK506-7 and GHBA-157) performed to investigate the efficacy and safety of tacrolimus in the prevention of rejection after liver transplantation, have shown tacrolimus to be:

- ◆ Equivalent to cyclosporine-based regimens in one-year patient survival;
- ◆ Equivalent or slightly better than CBIR regimens in one-year graft survival;
- ◆ Superior to CBIR in reducing the cumulative incidence of acute rejection;
- ◆ Superior to CBIR in reducing the severity of rejection (discontinuations for lack of efficacy rejection);
- ◆ Superior to CBIR in the rate of normalization of liver function post-transplant as measured by total serum bilirubin concentration.