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Single-Center Experience with Primary Orthotopic Liver Transplantation with FK 506 Immunosuppression

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Objective

The efficacy for primary orthotopic liver transplantation of a new immunosuppressive agent, FK 506 (tacrolimus, Prograf, Fujisawa USA, Deerfield, IL), was determined.

Summary Background Data

After 3 years of preclinical research, a clinical trial of FK 506 for orthotopic liver transplantation was begun in February 1989, first as a rescue therapy for patients with intractable rejection with conventional immunosuppression, then as a primary drug.

Methods

Between August 1989 and December 1993, 1391 recipients (1188 adult and 203 pediatric) of primary liver allografts were treated with FK 506 from the outset. Results from these patients were analyzed and compared with those of 1212 historical control patients (971 adult and 241 pediatric) given cyclosporine-based immunosuppression.

Results

Actuarial survival at 4 years was 86.2% with FK 506 *versus* 65.5% with cyclosporine in the pediatric patients ($p < 0.0000$) and 71.4% *versus* 65.5% in the adults ($p < 0.0005$). The need for retransplantation was reduced significantly for FK 506 patients. Four-year graft survival was 77.0% with FK 506 *versus* 48.4% with cyclosporine in the pediatric patients ($p < 0.0000$), and 61.9% with FK 506 *versus* 51.4% with cyclosporine in the adult recipients ($p < 0.0000$). Regression analysis revealed that reductions in mortality or graft loss from uncontrollable rejection, sepsis, technical failure, and recurrent original liver disease were responsible for the improved results with FK 506 therapy.

Conclusions
FK 506 is a potent and superior immunosuppressive agent for orthotopic liver transplantation.

FK 506 (tacrolimus, Prograf, Fujisawa USA, Deerfield, IL), the first new baseline immunosuppressive drug to be certified by the FDA in 11 years, has been available in pharmacies in the United States since April 1994. After 3 years of preclinical research in Chiba,[1-6] Pittsburgh,[7-12] Cambridge,[13-15] and elsewhere, the drug was first used clinically in February 1989, to successfully treat patients at our center who were undergoing intractable rejection of their liver allografts despite maximum cyclosporine-based therapy.[16] A few months later, extensive trials were begun with FK 506 as the primary immunosuppressant for recipients of all of the commonly transplanted organs.[17,18]

We report our experience in the 1391 consecutive adult and pediatric recipients of primary liver allografts who were treated from the outset with FK 506 between August 18, 1989, and the end of 1993. The first 120 of these patients were reported at the American Surgical Association in 1990.[17] The subsequent case collection included an internal cohort of 79 optimum risk patients who participated in a randomized trial of FK 506 *versus* cyclosporine, which has been reported elsewhere.[19] However, the current analysis is of all cases, totaling 2.6 times more than the combined number in the recently completed American and European multicenter trials, which have not been published yet. We describe the impact of this drug on our program, and mention some of the management principles that have been found to be applicable to the transplantation of other organs.

METHODS

Case Material

The heterogeneous indications for operation, patient ages, and patient degrees of urgency according to United Network for Organ Sharing (UNOS) criteria are summarized in Table 1. Infants and children accounted for 203 recipients, in whom the most common diagnosis was biliary atresia. Almost ⅔ of the 1188 adults had postnecrotic cirrhosis with various etiologies.

To judge the impact of FK 506 on our program, the patient and graft survivals in our historical experience was reviewed retrospectively to the first case in 1963[20] and stratified according to the principal advances that ultimately made liver transplantation practical: 1) 1963–1979 (n = 168)—immunosuppression was with azathio-

Table 1. INDICATIONS AND UNOS STATUS FOR LIVER TRANSPLANTATION IN 1391 FK506 PATIENTS AND 1212 CYCLOSPORINE PATIENTS*

Patients	FK506	Cyclosporine
No. of patients	1391	1212
No. of transplants	1582	1549
Primary transplantation	1391	1212
Retransplantation	191	337
Median follow-up: mos (range)	29.6 (3–55)	68.3 (25–99)
Pediatric (<18 yrs)		
Number of patients	203	241
Mean age ± SD	5.4 ± 5.5	4.8 ± 4.8
Indications†		
Fulminant failure	13 (6.4%)	18 (7.5%)
Postnecrotic cirrhosis	21 (10.3%)	18 (7.5%)
Biliary atresia	99 (48.8%)	138 (57.3%)
Metabolic disease	27 (13.3%)	31 (12.9%)
Primary malignancy	1 (0.5%)	4 (1.7%)
Other	42 (20.7%)	32 (13.3%)
UNOS Status‡		
1	3 (1.5%)	11 (6.1%)
2	57 (28.1%)	52 (28.9%)
3	72 (35.5%)	47 (26.1%)
4	71 (35.0%)	70 (38.9%)
Adult (>18 yrs)		
No. of patients	1188	971
Mean age ± SD	50.1 ± 12.0	46.7 ± 12.6
Indications		
Fulminant failure	30 (2.5%)	44 (4.5%)
Postnecrotic cirrhosis	749 (63.0%)	508 (52.3%)
Cholestatic disease	200 (16.8%)	229 (23.6%)
Metabolic disease	38 (3.2%)	39 (4.0%)
Primary malignancy	89 (7.5%)	69 (7.1%)
Other	82 (6.9%)	82 (8.4%)
UNOS status‡		
1	5 (0.4%)	56 (6.8%)
2	189 (15.9%)	156 (18.9%)
3	476 (40.1%)	354 (42.8%)
4	518 (43.6%)	261 (31.6%)

* The University of Wisconsin solution was used for graft preservation.
† Indication for primary transplantation.
‡ 1) working, 2) at home (many still working) but requiring close medical supervision and/or sporadic hospital care, 3) hospital-bound continuously or the majority of time, 4) ICU bound. UNOS status of 144 adult patients and 61 children in the cyclosporine group could not be determined.

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prine (or cyclophosphamide), prednisone, and usually antilymphocyte globulin; this original series 1 had 170 patients,[21] 2 of whom were excluded from the current analysis because they underwent simultaneous renal transplantation; 2) 1980–1987 (n = 623)—immunosuppression was with cyclosporine and prednisone, to which azathioprine, antilymphocyte globulin (or OKT3) were added as clinically indicated; Eurocollins solution was used for organ preservation; 3) 1987–1989 (n = 1212)—same as the previous advance (2), but organ preservation was with University of Wisconsin (UW) solution; 4) 1989–1993 (n = 1391)—same as the previous advance (3), but with FK 506 instead of cyclosporine.

For a more detailed comparison between the previous and current regimens, the 1212 patients in Group 3 were analyzed in the same detail as the 1391 patients in Group 4. The collective case profiles were comparable except for trends in the later period for older age candidates, a higher percentage of postnecrotic cirrhosis, and more extremely ill patients (Table 1).

Immunopathologic and Surgical Procedures

With rare exceptions, ABO identical donors were used. Human lymphocyte antigen matching was random. Because lymphocytotoxic results became available after the fact, 10% of livers were transplanted across positive crossmatches.[22] The panoply of variations used for the donor operations and transplant operations has been described elsewhere.[23] Needle biopsies were taken frequently to determine the cause of graft dysfunction or routinely during the early part of the study. The histopathologic criteria of rejection have been standardized thoroughly.[23]

Immunosuppression

FK 506

The general policies were the same as reported to the American Surgical Association in 1990[17] and were similar to those developed previously for cyclosporine.[21] The nephrotoxicity, neurotoxicity, and diabetogenicity of FK 506 were delineated and shown to be dose related from the outset.[17,18,24] In addition, it was promptly learned that defective metabolism of the drug when there was hepatic graft dysfunction necessitated downward dose adjustments.[17,25,26] Consequently, dose revisions were guided by the balance between rejection control, toxicity, and trough plasma levels of FK 506, which were measured with an enzyme immunoassay technique[27] and targeted to 1 ng/mL. For the first cases, the initial

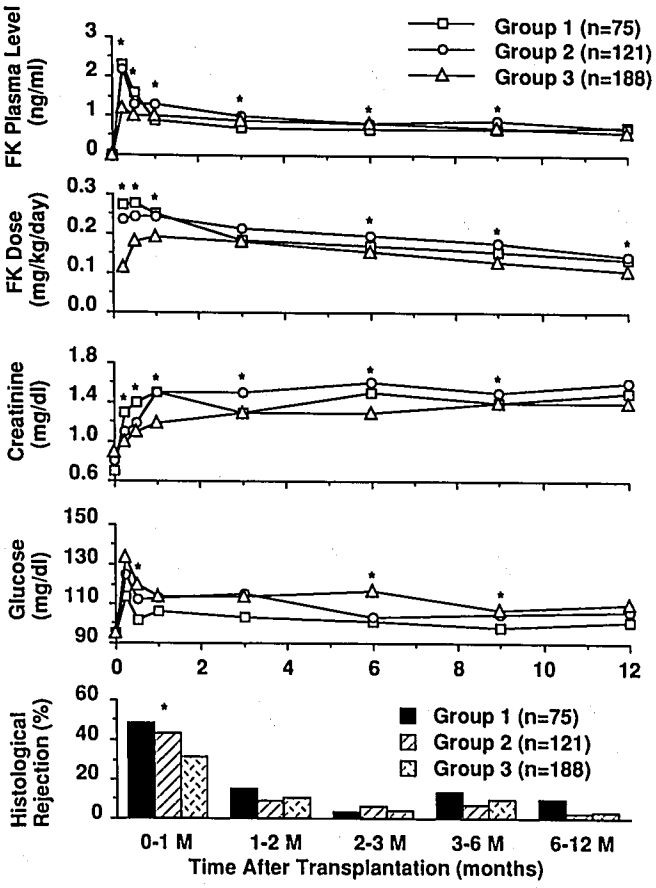

Figure 1. Effect of three different perioperative dosing schedules of FK 506 in patients selected for analysis because they did not have pre-existing renal dysfunction or glucose intolerance, and because their hepatic grafts functioned promptly. Intravenous induction doses were 0.15, 0.10, and 0.05 mg/kg/day in Groups 1, 2, and 3 respectively, and starting oral doses were 0.3, 0.2–0.3, and 0.2 mg/kg/day. *p < 0.05 means group differences were significant.

intravenous doses were 0.15 mg/kg/day given in divided 4-hour boluses; however, in May 1990, these were reduced to 0.10 mg/kg/day and administered by continuous infusion until oral alimentation was resumed. When these doses still were found to be toxic for a significant number of patients, intravenous induction was further reduced in August 1991 to 0.05 mg/kg/day. The oral doses that originally were 0.3 mg/kg/day also were scaled down commensurately.

The drift to more conservative dosing is illustrated in Figure 1 in subgroups of high-, medium-, and low-dose recipients who were selected for special study because they were free of confounding factors. Conditions for inclusion were preoperative serum creatinine < 1.5 mg%, preoperative fasting blood sugar < 150 mg%, and good early hepatic graft function. The results of such studies improve management policies for more complex cases.

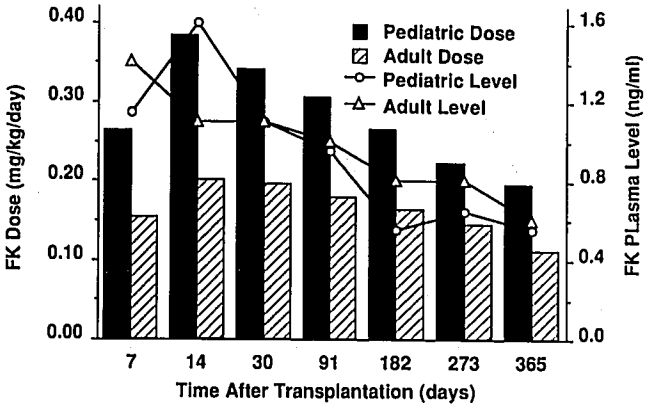

Figure 2. Average FK 506 doses/kg and 12-hour trough plasma concentrations in pediatric and adult liver recipients during the first postoperative year.

They showed that avoidance of the early postoperative FK 506 plasma spike essentially eliminated the toxicity problems that bedeviled our first patients and those subsequently entered into the early multicenter trials. Importantly, the incidence of rejection was not increased as the FK 506 doses were diminished (Fig. 1). The penalty, however, was the need for compensatory increases in prednisone doses and a consequent statistically greater incidence of hyperglycemia (Fig. 1, second panel from bottom) until these doses could be weaned.

On a body weight basis, children required average FK 506 doses 1.52 times greater than those of adults to achieve equivalent plasma trough levels. In both age groups, progressive weaning to lower doses throughout the first year and subsequently of FK 506 (Fig. 2) and prednisone made management easier, reduced toxicity, and assured a high quality of life.

Other Drugs

In the first cases, 1 g of methylprednisolone was given intravenously to adults during operation, followed by a 5-day burst of methylprednisolone, which was started at 200 mg on the first day and reduced daily in 40 mg steps until 20 mg/day was reached on postoperative day 6. Appropriately lower doses were given to infants and children. During a second phase, treatment was begun with 20 mg/day methylprednisolone, a policy still followed on a discretionary basis with some fragile recipients. However, the high-dose steroid burst at the beginning has been shown to be effective prophylaxis in the event of a positive lymphocytotoxic crossmatch[28] and is our current routine standard because the results of the immunologic tests usually are not available at the time of operation. With either kind of induction, prednisone doses were weaned over several months and eventually stopped if there was no evidence of rejection.

Clinical diagnoses of rejection episodes were confirmed by needle biopsy. If they were unresponsive to increasing the maintenance doses of FK 506, the rejections were treated with a single 1-g bolus of methylprednisolone or hydrocortisone for adults or with smaller quantities for children. If rejection persisted, additional steroids were given, a 3- to 5-day course of 5 or 10 mg/day OKT3 was considered, and in a few cases, azathioprine was added.

The Cross-Over Phenomenon

With the first clinical use of FK 506, it was noted[16,29] and soon widely confirmed that the drug had a remarkable ability to halt and reverse liver rejection that was intractable, despite optimal cyclosporine-based therapy. After rescue, most of these patients were liberated from dependence on high doses of steroids. This *prima facie* evidence of superiority raised troubling ethical issues about randomized trials in such a high-risk population. These same questions of propriety had been raised in 1980, when cyclosporine replaced azathioprine,[30] and a decade later, patient demand for FK 506 and the determination of the physicians and surgeons to give what they believed to be optimal treatment generated tumultuous conflict with the Institutional Review Board, which had mandated such a trial. As a compromise, a trial was begun, but only for low-risk patients.[19,31] In the meantime, a large scale switch was occurring from cyclosporine to FK 506. The crossover eventually totalled 437 patients in our program alone, with an estimated 1000 examples elsewhere in the United States. In 1991, an interinstitutional advisory group, impaneled by the University of Pittsburgh as a watchdog safeguard for patients' rights, recommended discontinuance of the randomized trial, and with the concurrence of the Institutional Review Board and the Food and Drug Administration (FDA), this was done. With freedom of patient choice in effect, FK 506 replaced cyclosporine (Fig. 3).

Data Analysis

Patient survival was calculated from the date of transplantation until patient death, and graft survival was calculated from the date of transplantation until retransplantation or patient death. Survival curves were generated using the life table method and were compared using the log rank (Mantel-Cox) test. Cox's proportional hazards model was used to analyze different causes of mortality and different causes of graft failure in the patients from Group 3, who received cyclosporine, com-

pared with those of Group 4, who received FK 506. Differences in group means were tested using the one-way analysis of variance; differences in proportions were tested using Pearson's chi square test of association. A p value < 0.05 was considered statistically significant.

RESULTS

Survival

Patient survival during the 30-year history of clinical liver transplantation improved in leaps rather than steps (Fig. 4). The greatest single increment was the advent of cyclosporine,[21,32] which was first given to a liver recipient by Calne et al.[33] A small additional gain (NS, $p = 0.18$) came with the introduction of UW solution (Group 3). Further improvement relative to what had been achievable previously already was evident at the time of our presentation in 1990, at the American Surgical Association, of the first 120 liver recipients who represented our learning curve. With >4 years follow-up, 13 (86.7%) of the 15 original pediatric recipients and 81 (77.1%) of the 105 adults remain well. All of the survivors are working, in school, or fully functional in home life. The more than tenfold expansion of this experience has confirmed the initial conclusions.

Pediatric Recipients

Infants and children of all ages, with all diagnoses, and of all urgency categories, including the high-risk UNOS 4, had an improved prognosis (Table 2).

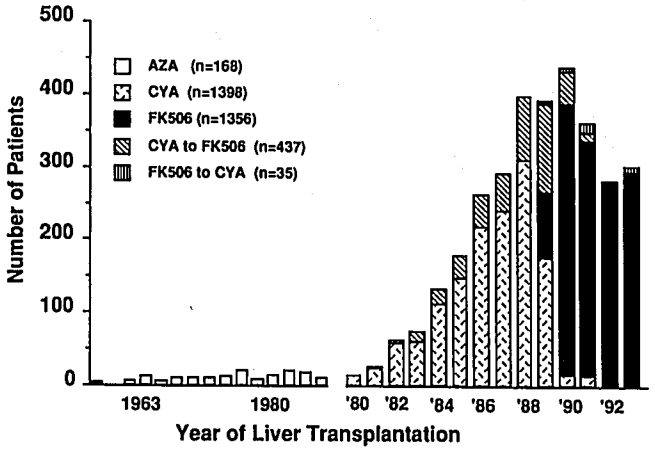

Figure 3. Baseline immunosuppressive drugs used during the 30-year history of our continuously functioning liver transplant program. A few patients in 1971–1972 had cyclophosphamide instead of azathioprine (not shown).

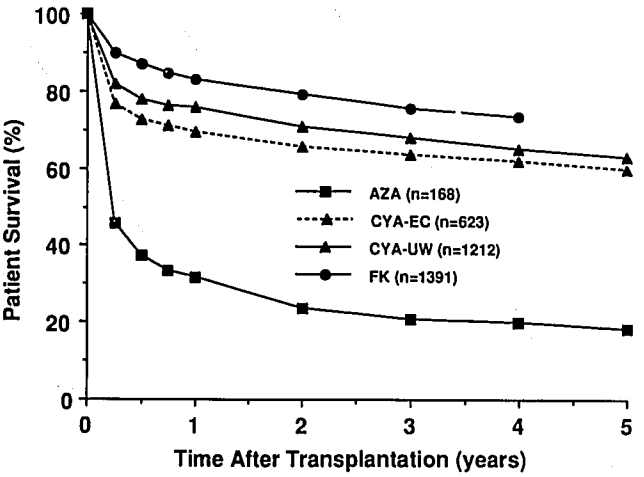

Figure 4. Patient survival during the 30-year history of the program at the Universities of Colorado (1963–1980) and Pittsburgh (1981–1993). The eras were defined by major improvements (see text). The dates of case accrual from bottom to top curves were 1963–1979 (Group 1), 1980–1987 (Group 2), 1987–1989 (Group 3), and 1989–1993 (Group 4). Groups 3 and 4 had significantly different survival ($p < 0.0000$). AZA = azathioprine, CyA-EC = cyclosporine, Eurocollins solution for preservation, CyA-UW = cyclosporine, University of Wisconsin solution for preservation, FK 506 = tacrolimus, University of Wisconsin solution for preservation.

Adult Recipients

An improvement also was observed in the adults that was significant overall ($p < 0.0005$), evident in all eight subgroups, and significant in four of the eight (Table 3). However, the large survival gap in the patients with hepatitis B virus was primarily a result of avoidance of hepatitis E antigen-positive recipients in the FK 506 era.

Graft Survival

The survival slopes in the different eras and their degree of separation from each other were parallel to those of patient survival, but approximately 10% lower (Fig. 5). The higher patient survival reflected the benefit of retransplantation. The improvement of graft survival when UW solution was added to cyclosporine-based immunosuppression (Group 2 *vs.* Group 3) was significant ($p = 0.0057$), as was the further improvement with FK 506 (Group 3 *vs.* Group 4; $p < 0.0000$).

Causes of Death

The first 3 months after liver transplantation has long been known to be the period of principal mortality (Fig. 4). During this time, the same kinds of lethal complications were seen in the cyclosporine and FK 506 groups, but they occurred less frequently with FK 506 in all

Table 2. SURVIVAL OF PEDIATRIC PATIENTS UNDER FK506 *VS.* CYCLOSPORINE AFTER LIVER TRANSPLANTATION

		Survival (%)					
	N	3 Mo	6 Mo	1 Yr	2 Yr	4 Yr	p Value*
All patients							
FK506	203	91.1	89.6	88.5	88.5	86.2	0.0000
CYA	241	74.2	72.2	71.3	68.0	65.5	
Age							
0–2 yrs							
FK506	86	88.3	85.9	85.9	85.9	82.4	0.0003
CYA	98	67.3	64.2	62.2	59.1	58.1	
2–12 yrs							
FK506	76	90.7	89.4	88.0	88.0	85.9	0.0418
CYA	115	79.1	78.2	78.2	75.6	71.3	
12–18 yrs							
FK506	41	97.5	97.5	94.9	94.9	94.9	0.0024
CYA	28	78.5	75.0	75.0	67.8	67.8	
Indication							
Biliary atresia							
FK506	99	91.9	88.8	88.8	88.8	87.3	0.0004
CYA	138	73.1	71.7	70.2	68.8	66.6	
Metabolic disease							
FK506	27	96.3	96.3	91.8	91.8	—	0.1763
CYA	31	80.6	80.6	80.6	80.6	77.4	
UNOS 4							
FK506	71	84.5	83.0	83.0	83.0	78.0	0.0132
CYA	70	68.5	65.7	64.2	60.0	60.0	

* Log-rank test between FK group and cyclosporine group.

seven of the cause of mortality categories of both pediatric and adult cohorts (Table 4). The three categories in which the differences were statistically significant were technical failure (most commonly hepatic artery thrombosis or bile duct complications), sepsis, and the umbrella of immunologic reason, which included rejection, graft *versus* host disease, and post-transplant lymphoproliferative disorders.

In the 4-year postoperative perspective, the same three factors were identified. By Cox regression analysis, the relative risk of fatal technical complications or sepsis in children was more than four times higher with cyclosporine (Table 5). For adults, immunologic reason, sepsis, and disease recurrence (most commonly malignancies or hepatitis) ranged from 1.56 to 1.95 times higher with cyclosporine than with FK 506 (Table 5).

Incidence and Causes of Retransplantation

With FK 506, retransplantation was required in 9.9% of the pediatric recipients treated with FK 506 compared with 22.8% in those treated with cyclosporine. The lower rate with FK 506 was accounted for mainly by decreased rates of technical failure and irreversible rejection (Table 6). In the 4-year perspective, the Cox regression analysis showed the same thing (Table 7).

In adults, the retransplantation rate during the first 3 months with FK 506 compared with cyclosporine was 9.8 *versus* 13.7%, with technical failure and rejection accounting for most of the difference. By Cox regression analysis, the risk of retransplantation because of rejection over a 4-year follow-up was 2.4 times greater with cyclosporine than with FK 506. Retransplantation for recurrent disease had a 3.5 times greater risk with cyclosporine than with FK 506; however, this was due to the same avoidance of E antigen-positive candidates described under cause of mortality (Table 3).

DISCUSSION

Although FK 506 and cyclosporine are chemically unrelated, each with a specific cytosolic binding site of different molecular weight,[34,35] both drugs block the immune response by preventing the transcription of early T-cell activation genes.[36] Both also are nephrotoxic, neu-

Table 3. SURVIVAL OF ADULT PATIENTS UNDER FK506 *VS.* CYCLOSPORINE AFTER LIVER TRANSPLANTATION

		Survival (%)					
	N	3 Mo	6 Mo	1 Yr	2 Yr	4 Yr	p Value*
All patients							
FK506	1188	89.7	86.6	82.1	77.7	71.4	0.0005
CYA	971	83.7	79.4	76.8	71.8	65.3	
Age							
18–60 yrs							
FK506	899	91.6	88.5	84.4	79.9	74.1	0.0003
CYA	837	84.4	80.5	77.9	73.0	66.7	
>60 yrs							
FK506	289	83.9	80.6	75.1	70.9	61.2	0.1219
CYA	134	79.1	72.3	70.1	64.9	56.7	
Indication							
Non-A, non-B cirrhosis							
FK506	225	89.1	86.7	80.5	74.3	73.3	0.5972
CYA	179	84.9	79.8	77.6	75.4	72.0	
Alcoholic cirrhosis							
FK506	268	90.9	87.4	84.5	81.3	72.4	0.1344
CYA	169	83.4	80.4	79.2	75.1	66.3	
HB cirrhosis							
FK506	95	91.5	90.4	83.3	77.8	68.9	0.0030
CYA	68	75.0	67.6	63.2	52.9	48.5	
Primary biliary cirrhosis							
FK506	108	88.7	86.8	84.7	83.5	83.5	0.4656
CYA	137	87.5	85.4	83.2	81.7	76.3	
Primary sclerosing cholangitis							
FK506	88	100.0	98.8	97.5	96.0	91.4	0.0158
CYA	86	91.8	89.5	87.2	83.7	76.4	
UNOS 4							
FK506	518	86.5	83.3	77.5	73.9	68.1	0.0002
CYA	261	77.7	72.0	67.4	62.4	55.2	

* Survival rates were computed using the life table method, and p value by the log-rank test.

rotoxic, and diabetogenic.[17,18,24] In addition, the two drugs are powerful growth factors. They are hepatotrophic because they augment hepatic regeneration,[37,38] and they prevent the hepatocyte atrophy and organelle injury caused by Eck's fistula.[39,40] However, the growth effects of gingival hyperplasia, facial brutalization, and hirsutism of cyclosporine are not caused by FK 506, and the drug is associated with a lower incidence of hypertension and hypercholesterolemia.[17,18]

Although the preceding profiles were not identical, the similarity of effects of two such diverse agents was perplexing until their mechanisms of action were clarified with molecular studies. These revealed that cyclosporine and FK 506 are essentially inactive "prodrugs" whose cytosolic binding immunophilins (cyclophilin and FKBP12, respectively) also are inert in isolation.[39] However, the cyclosporine-cyclophilin and FK 506-FKBP complexes activate a common target, phosphatase calcineurin, which modifies the transduction of calcium dependent signals from the surface T-cell receptor to the nucleus.[39–41] The immunophilins are found in all cells and are suspected by related mechanisms to participate in the modulation of multiple immunologic, endocrinologic, growth control, and chaperone-mediated pathways.[41–43] Thus, there was an explanation for the common pattern of the pleotropic effects.

Similar mechanisms notwithstanding, the clinical performance of FK 506 has been superior to cyclosporine. In our aborted randomized liver transplantation trial,[19,31] as in randomized trials conducted in multiple European and American centers, crossover from cyclosporine to FK 506 because of intractable rejection (but not vice versa) was a common event that frequently prevented death or the need for retransplantation of the patients begun on cyclosporine. With analyses by "intent to treat," patient and graft survival was similar on both

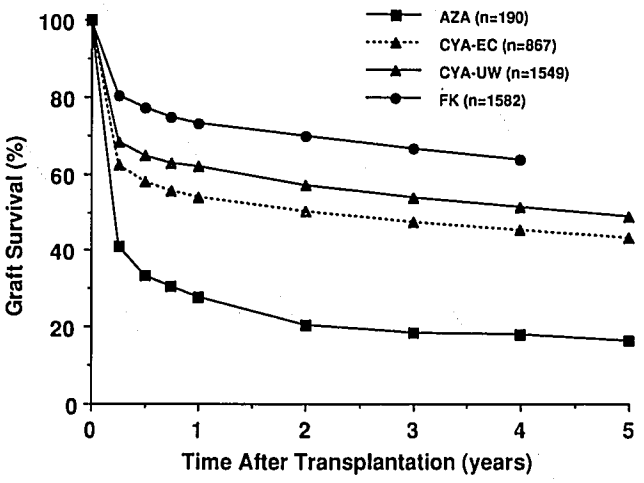

Figure 5. Graft survival in same patients as Figure 4.

treatment limbs but never inferior with FK 506. However, this parity reflected the rescue of a significant number of patients classed for analysis as cyclosporine "successes," in whom treatment had been changed permanently to FK 506. The superiority of FK 506 in randomized single-center trials of renal[44] and lung transplantation[45] also was obscured by minimizing the crossover factor. Rather than perpetuate this artifact of interpretation, we have analyzed the effect that the drug has had on the welfare of the patient population in our program.

Table 4. CAUSE AND INCIDENCE OF MORTALITY IN FK506 PATIENTS AND CYCLOSPORINE PATIENTS WITHIN 3 MONTHS AFTER LIVER TRANSPLANTATION

	FK506	Cyclosporine	p Value
Pediatric patients			
No. of patients	203	241	
No. of mortalities	18 (8.9%)	62 (25.7%)	0.0001
Causes			
Technical failure	6 (3.0%)	27 (11.2%)	0.0010
Sepsis	1 (0.5%)	11 (4.6%)	0.0080
Immunosuppression related	1 (0.5%)	8 (3.3%)	0.0350
Extrahepatic event	3 (1.5%)	7 (2.9%)	0.3130
Disease recurrence	0	1 (0.4%)	0.3580
Graft failure	7 (3.4%)	8 (3.3%)	0.9400
Other	0	0	—
Adult patients			
No. of patients	1188	971	
No. of mortalities	119 (10.1%)	158 (16.3%)	0.0010
Causes			
Technical failure	22 (1.9%)	42 (4.3%)	0.0007
Sepsis	33 (2.8%)	41 (4.2%)	0.0660
Immunosuppression related	9 (0.8%)	15 (1.5%)	0.0830
Other	1 (0.1%)	4 (0.4%)	0.1150
Graft failure	33 (2.8%)	35 (3.6%)	0.2740
Disease recurrence	1 (0.1%)	2 (0.2%)	0.4500
Extrahepatic event	20 (1.7%)	19 (2.0%)	0.6350

Based on our participation and observation in all previous transitions in the field, and influenced by the experience reported here, we believe that FK 506 will supplant cyclosporine as the principal baseline drug for transplantation of the liver and other organs. Aside from the quality of life issues favoring FK 506 that have been reported in detail elsewhere—most hinging on the associated lower need for steroids and fewer cosmetic side effects—it has permitted a reduction in global mortality, either when used up front or to rescue therapeutic failures of the previous best regimen. The dramatic way in which better immunosuppression changes the mortality and "need for retransplantation" profiles also was seen in 1980, with the advent of cyclosporine. The three categories most affected then were the same as with the later transition from cyclosporine to FK 506—rejection, sepsis, and technical failure.

The rubric of technical failure can mean different things to different people. The best example is hepatic artery thrombosis, which we have categorized for 30 years as "technical failure" because the surgeon's poor performance always is a theoretical possibility. However, Makowka et al.,[46] Samuel et al.,[47] and many others have shown that this complication is associated with multiple nontechnical factors, of which incompletely controlled rejection is thought to be a major one. Furthermore, most mechanical complications can be indirectly attributable to or aggravated by excessive immunosuppression (particularly prednisone). Once a seam is opened in the fabric of the finished transplant product by rejection or by the drugs used to control it—whether this be in the graft vasculature, drainage system, or any other component of the operation—the deadly handmaid of sepsis in the associated triad is close by.

As FK 506 diffuses into general use, the same practical matter will be faced as during the change from azathioprine to cyclosporine concerning the difficulty of changing from a familiar therapeutic regimen to a new one. This time around, there will be a better understanding of what is involved. The prevention of organ rejection by various immunosuppressive agents has been described increasingly in terms of the molecular site of disruption of the alloactivated T-cell response.[48,49] Recent evidence, however, suggests that the control of rejection and, ultimately, graft acceptance depend on a permissive effect of these drugs on a mutual host-graft leukocyte migration that leads in successful cases to mixed, long-term microchimerism in the recipient and the transplant.[50,51]

Table 5. COX REGRESSION ANALYSIS OF CAUSE OF DEATH AFTER LIVER TRANSPLANTATION

	FK506	Cyclosporine	RR*	p Value
Pediatric patients	203	241		
No. of mortalities	26 (12.8%)	90 (37.3%)		
Cause of mortality				
Technical failure	6 (3.0%)	33 (13.7%)	4.1998	0.0019
Graft failure	7 (3.4%)	9 (3.7%)		
Immunosuppression-related	6 (3.0%)	16 (6.6%)		
Disease recurrence	1 (0.5%)	3 (1.2%)		
Extrahepatic event	3 (1.5%)	9 (3.7%)		
Sepsis	3 (1.5%)	13 (5.4%)	4.5424†	0.0203
Other	0 (0.0%)	7 (2.9%)		
Adult patients				
No. of patients	1188	971		
No. of mortalities	267 (22.5%)	372 (38.3%)		
Cause of mortality				
Technical failure	47 (4.0%)	58 (6.0%)		
Graft failure	36 (3.0%)	36 (3.7%)		
Immunosuppression-related	21 (1.8%)	43 (4.4%)	1.9532	0.0173
Disease recurrence	54 (4.5%)	84 (8.7%)	1.5942‡	0.0108
Extrahepatic event	34 (2.9%)	49 (5.0%)		
Sepsis	58 (4.9%)	74 (7.6%)	1.5627†	0.0431
Other	17 (1.4%)	28 (2.9%)		

* Relative risk of death for patients on CYA compared to patients on FK506.
† Relative risk adjusted for etiology of original disease, age >60 yrs, and UNOS status.
‡ Relative risk adjusted for etiology of original disease.

Many of the enigmas of transplantation immunology can be explained by the recent discovery of this chimerism. The events with immunosuppression leading to the ubiquitous persistence of donor leukocytes in recipient tissues imply that there is a widespread engagement, activation, and inactivation of the immunocytes of both donor and recipient cell populations, and ultimately, the development of various degrees of donor specific nonreactivity. Of critical importance for transplantation of leukocyte-rich organs, such as the liver and intestine, recipient-specific nonreactivity of the chimeric donor cells also must evolve if the patient is to escape the complication of graft versus host disease graft *versus* host disease. This fresh insight into the fundamental mechanism of allograft acceptance as a two-way immunologic transaction makes comprehensible the characteristic cycle of recovery that was first observed in kidney recipients treated with azathioprine and prednisone[20] and soon after in recipients of livers and other kinds of organs. Rejection that typically occurred in the first few days or weeks could be reversed with adrenal cortical steroids, and in successful cases, most frequently represented in the liver recipient population, immunosuppression can be reduced and occasionally, stopped.[52]

With this fresh insight into mechanisms, it has become

Table 6. CAUSE AND INCIDENCE OF RETRANSPLANTATION OF THE PRIMARY GRAFT IN FK506 PATIENTS AND CYCLOSPORINE PATIENTS WITHIN 3 MONTHS AFTER LIVER TRANSPLANTATION

	FK506	Cyclosporine	p Value
Pediatric patients			
No. of patients	203	241	
No. of retransplantations	20 (9.9%)	55 (22.8%)	0.0003
Causes			
Technical failure	6 (3.0%)	32 (13.3%)	0.0001
Rejection	0	6 (2.5%)	0.0240
Graft infection	1 (0.5%)	5 (2.1%)	0.1500
Graft failure	13 (6.4%)	12 (5.0%)	0.5170
Disease recurrence	0	0	—
Other	0	0	—
Adult patients			
No. of patients	1188	971	
No. of retransplantations	116 (9.8%)	133 (13.7%)	0.0040
Causes			
Technical failure	28 (2.4%)	37 (3.8%)	0.0490
Rejection	7 (0.6%)	13 (1.3%)	0.0950
Graft failure	76 (6.4%)	80 (8.2%)	0.1000
Other	2 (0.2%)	0	0.2010
Graft infection	3 (0.3%)	3 (0.3%)	0.8040
Disease recurrence	0	0	—

Table 7. COX REGRESSION ANALYSIS OF CAUSE OF PRIMARY GRAFT RETRANSPLANTATION

	FK506	Cyclosporine	RR*	p Value
Pediatric patients				
No. of patients	203	241		
No. of primary graft retransplantations	22 (10.8%)	72 (29.9%)		
No. of primary graft mortalities	16 (7.9%)	51 (21.2%)		
Cause of primary graft failure				
Technical failure	6 (3.0%)	35 (14.5%)	4.6803	0.0008
Graft failure	13 (6.4%)	12 (5.0%)		
Rejection	0 (0.0%)	16 (6.6%)	†	
Graft infection	3 (1.5%)	7 (2.9%)		
Disease recurrenc e	0 (0.0%)	1 (0.4%)		
Other	0 (0.0%)	1 (0.4%)		
Adult patients				
No. of patients	1188	971		
No. of primary graft retransplantations	153 (12.9%)	203 (20.9%)		
No. of primary graft mortalities	197 (16.6%)	246 (25.3%)		
Cause of primary graft failure				
Technical failure	42 (3.5%)	52 (5.4%)		
Graft failure	77 (6.5%)	80 (8.2%)		
Rejection	18 (1.5%)	40 (4.1%)	2.4431	0.0023
Graft infection	4 (0.3%)	4 (0.4%)		
Disease recurrence	8 (0.7%)	24 (2.5%)	3.5397‡	0.0022
Other	4 (0.3%)	3 (0.3%)		

* Relative risk of death for patients on CYA compared to patients on FK506.
† Relative risk could not be determine because no events occurred in FK group.
‡ Relative risk adjusted for etiology of original disease, age >60, and UNOS status.

possible to understand the empirically evolved therapeutic dogma on which successful whole organ transplantation is based. The dogma calls for baseline treatment with a maintenance drug or drugs plus trial-and-error intervention with the highly dose-maneuverable adrenal cortical steroids to whatever level is required to maintain stable graft function. This dogma has been able to accommodate increasingly potent new agents with variable sites of action, of which FK 506 is merely the latest example. The ease with which FK 506 could be assimilated into the established strategy was illustrated by our own start-up experience[17] and by experience in the multicenter trials in which the 28 participating teams (10 in Europe and 18 in the United States) were not permitted to have a familiarizing pilot experience with the new agent. However, the requisite management skills followed a well-worn trail and were acquired so quickly that the learning curve was scarcely demonstrable in the better centers.

Armed now with a drug as potent as FK 506, the same generic treatment formula should be applicable to further improvements in organ transplantation. If our contention is valid that the migration and grafting of "passenger leukocytes" of bone marrow origin is the seminal explanation for allograft acceptance, the next steps will involve manipulation of this process. In a direct extension of the concept,[53] we currently are augmenting leukocyte traffic in unconditioned recipients of cadaver livers, kidney, heart, and lungs by the concomitant intravenous infusion of donor bone marrow cells under exactly the same conditions of FK 506-prednisone treatment used for the patients of the current report.

All 16 of the first organ/bone marrow recipients have had good clinical course with follow-ups of 5 to 16 months, and all have easily demonstrable chimerism of blood mononuclear leukocytes, estimated to 1000 times or greater than the naturally occurring low-level chimerism. The astonishing ease with which this was accomplished without the occurrence of significant clinical graft *versus* host disease has been verification of the new paradigm in transplantation immunology and provides the first realistic hope that transplantation may become feasible, with the ultimate objective of deliberate drug discontinuance.

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Discussion

DR. GORAN B. KLINTMALM (Dallas, Texas): You just heard another presentation of a monumental piece of work from the University of Pittsburgh and the group of Dr. Starzl. We have to recall that this drug was discussed at the special meeting in Gothenburg in the fall of 1987. Some findings from animal experiments by one of the major investigators, Dr. Roy Calne, suggested to us all present that this was too toxic to be used and was about to be dropped from the investigator's table. From that meeting Dr. Starzl went home to Pittsburgh and actually redid most of the trials that had been presented. Dr. Todo was one of the collaborators in the core group and they proved the drug to be very potent and very effective, both in the laboratory and in the clinical setting.

The drug is now poised to be launched as an FDA-approved immunosuppressant for liver transplantation in the United States. There are other trials going on in kidney transplantation as well as in heart and lung transplantation, and hopefully, with those concluded we'll see the indications for this drug expanded. Its use for autoimmune disease is a very interesting question that will remain to be elucidated.

The early pilot trials of Pittsburgh called for two large multicenter trials to be started, one in Europe and one here in the United States. These multi-center trials were done as prospective open-label randomized trials and showed the following results: with a minimum of one-and-a-half-year follow-up of all the patients, the graft and patient survival are the same in the FK506 and in the cyclosporine arms in the U.S. trial. The incidence of rejection is down significantly in the FK group, and the use of the rescue agent OKT3 for steroid unresponsive rejection is significantly reduced.

However, what was not anticipated at the onset of the trial was that the nephrotoxicity is as serious with FK as with cyclosporine. There's also question about the higher incidence of serious neurotoxicity with this drug. This is presently receiving further analysis. Finally, FK506 seems possibly more diabetogenic than cyclosporine. Similar results have been shown in the European trials.

Again, this drug is a major step forward and I think what you have seen here on the screen is what happens with improved immunosuppression. It allows the patients to survive the complications that they encounter after liver transplantation. And this is virtually the same result we saw in 1979 and 1980 when we first started using cyclosporine in Denver.

If I have any critique, it is why did the Pittsburgh group not do a randomized trial in 1991 and have this drug FDA-approved years ago? You have the patient material and the experience that equals the rest of the world combined.

I have, however, a couple of questions for Dr. Todo. First, what do you see as the FK506 future role, as a rescue agent, as a maintenance immunosuppressant, and in other organ transplantation? And secondly, are there any subgroups of patients where you would not use FK506 as the primary maintenance immunosuppression—for example, patients in acute renal failure or in patients with hepatic coma prior to transplantation?

DR. JOSHUA MILLER (Miami, Florida): I would like to congratulate Dr. Todo and the group headed by Dr. Starzl for introducing this wonderful new agent in transplantation. Dr. Todo probably knows that we in Miami have the second biggest population of patients converting to FK506. We have dealt with Pittsburgh since 1990 with this agent. I actually do have a few points that I would like him to comment on.

We have noted that when we have referred patients who are kidney transplant recipients with refractory rejection for conversion to FK506, there is uniformly a stabilization of their function and amelioration of what we have termed refractory rejection after OKT3 or other agents. These patients have stabilized, yet there appear to be in the primary treatment with FK506 in Pittsburgh a number of patients who have lost their grafts due to rejection.

It is a difficult thing to bring into balance, because one might think that there would even be a group of our patients that would prove to be refractory to FK506 therapy because of their previous refractory rejection. I think it is almost statistically significant now that this is not the case.

Is there some kind of enzyme induction that might go on that might make patients who are refractory to Cyclosporine more sensitive to FK506 therapy and vice versa? I think this is an interesting biological question and I would like to have your comments on it.

The other question that I had was on the use of FK506 in children who, in transplants of other organs, are quite subject to rejection, even perhaps more so than adults, yet apparently your FK506 therapy in children is more effective than in adults. Can you give us a reason for this?

Again I would like to congratulate Dr. Todo, one of the pio-

neers in the use of this drug both in the experimental animal and then in the clinic, for being a major reason why it is now virtually on our pharmacy shelves.

DR. JOHN TERBLANCHE (Cape Town, South Africa): Could you tell us what the relative costs are going to be vis-a-vis the previous agents? The problem we have outside the United States—and I think you may actually have it here as well—is cost.

Our cardiac transplants in Cape Town are limited by the cost of the current drugs, our liver transplants are limited in the same way, and we in fact convert the kidney transplants to Imuran after 6 months, because cost is a problem. What will the cost of FK506 be? Is it going to be a problem? Or has the company kept the cost a secret?

DR. CHARLES MILLER (Mount Sinai Hospital, New York): I would like to congratulate Dr. Todo on a beautiful piece of work.

I noticed one point of real interest, that part of the improved survival was due to a decrease in recurrence of primary disease. And one question would be, are these primary diseases autoimmune-type disease such as autoimmune hepatitis, primary biliary cirrhosis or sclerosing cholangitis, or is it in fact a decrease in recurrent infectious disease such as hepatitis C or hepatitis B?

We have found that there has been a correlation between recurrent viral disease and the amount of rejection and/or immunosuppression you need to use, and I wonder if FK506 by preventing rejection has reduced those recurrent infections that are so problematic?

I congratulate you again on a beautiful presentation.

DR. SATORU TODO (Closing discussion): Thank you very much for your comments, Dr. Klintmalm and Dr. Joshua Miller, Dr. Terblanche and Dr. Charlie Miller.

Regarding the first question from Dr. Klintmalm, whether FK506 should be used for rescue therapy or for primary immunosuppression, I believe it should be both. From our experience, as I have shown in this paper, patients on this agent have a much greater chance of survival after liver transplantation than with any other conventional treatment. It is particularly so with pediatric recipients. Infants and children are greatly benefitted by the use of FK506 in terms of patient survival, graft survival, rejection episodes, and the need for other anti-rejection drug usage, especially steroids. This means that FK506 should be used as a baseline immunosuppressive agent. In addition, as shown by us and others, many of the recipients who developed intractable rejection or side effects with conventional therapy were successfully rescued by FK506. Thus, this agent should also be used as a rescue therapy. The potent immunosuppressive effect of FK506 is readily ascertained by the fact that intestinal transplantation in humans, which has never been satisfactory with conventional treatment, has become a practical reality with the advent of this agent.

I don't believe that any subgroup of patients should be eliminated from treatment with FK506, since most of the side effects of FK506 are equal to or less than conventional agents, and, I believe, liver recipients should be offered a better chance of survival after life-saving surgery.

Dr. Joshua Miller, we are not sure why pediatric patients have much better results than adult recipients. Since they can tolerate higher doses of FK506, the higher initial concentration of this agent in plasma may permit better control of graft rejection.

Regarding the question from Dr. Terblanche about the cost of FK506, I hear from the Fujisawa Pharmaceutical Company that it would be similar to conventional agents. However, in a clinical setting, since this agent allows earlier discharge of the recipient after liver transplantation, a lower incidence of rejection episodes, less frequent use of other anti-rejection agents, and fewer retransplantations and lower mortality rates, it offers better cost-performance.

Finally, in answer to the question from Dr. Charlie Miller why FK506 was associated with a lower incidence of recurrent liver disease, as described in this paper, strict selection for liver transplantation of patients who have hepatitis B virus related liver disease is a major reason for the reduction.