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FK 506 Versus Cyclosporine in Pediatric Liver Transplantation

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No group of patients is likely to benefit more by improvements in immunosuppression than the pediatric transplant recipients who face life-long treatment. The advent of cyclosporine (CyA) has transformed liver transplantation into the preferred treatment modality for chronic liver failure.[1] Its effect on pediatric liver transplantation was profound, allowing for acceptable patient and graft survival when used with steroids at a fraction of the dose necessary under previous immunosuppressive regimens.[2–8] Complications included renal toxicity, hypertension, gum hyperplasia, hirsutism, and an uncommon but very troubling syndrome of facial disfigurement.

FK 506, a new immunosuppressive agent derived from *Streptomyces tsukubaensis*, was first shown to be efficacious in experimental[9] and clinical primary liver transplantation,[10–12] and also in reversing rejection in patients who failed CyA treatment.[13]

Additional indications for use in pediatrics were its apparent simplicity of use, low toxicity, and independence from adjuvant steroid therapy.[9–14]

This report summarizes our clinical experience with FK 506 from a prospective study of children who underwent primary liver transplantation at the Children's Hospital of Pittsburgh between October 1989 and October 1990. Follow-up is provided up to April 1991.

Methods

Patient Selection

Beginning in October 1989, children undergoing first-time liver transplantation at the Children's Hospital of Pittsburgh were eligible to participate in a prospective clinical evaluation of the new immunosuppressant, FK 506. Informed consent was obtained from the parents of all eligible children pretransplant. There were no exclusions. Historical controls who received CyA and matched on age (within 6 months), primary diagnosis, and UNOS severity score were identified for each patient as soon as possible posttransplant. Eligible controls were children who had undergone primary liver transplantation at our center between January 1988, after which time the University of Wisconsin solution was used for organ preservation in all pediatric cases, and October 1989. A single control was randomly selected from all (n = 1 to 12) controls matched for each patient. It was possible to match 50 controls to 59 study patients.

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Data Collection

The charts of both patients and controls were systematically reviewed utilizing standardized datasheets and definitions by a single data collector, and reviewed by a single investigator. Inpatient and outpatient charts were reviewed. Datapoints included patient survival, duration of intensive care and hospital stay, days of fever, results of liver biopsies, liver function tests as measured biochemically and by synthetic function, renal function as measured by BUN and creatinine, hematology, use of immunosuppressants, antimicrobial, and antihypertensive agents.

Immunosuppression

Study Group

FK 506 was given as a continuous infusion of 0.15 mg/kg per day, immediately after transplantation, and converted to 0.3 mg/kg per day in two divided doses postoperatively when oral diet was tolerated. Prednisone or prednisolone were given at doses of 20 mg/d for children >10 kg body weight and 10 mg/d for children <10 kg body weight, respectively, and was reduced gradually after 1 week postoperatively, being discontinued before discharge if a rejection-free state was achieved.

FK 506 serum levels were monitored once or twice weekly. There was no attempt to modify the dose of the drug in order to achieve a certain level.

Control Group

Immunosuppression was given as previously described.[3] Briefly, IV CyA was given (6 mg/kg per day in two divided doses over 4 hours each) immediately after surgery. Oral CyA (17.5 mg/kg per day) was given when oral feedings were well tolerated. The IV CyA was discontinued when whole blood CyA levels of approximately 1000 ng/mL could be maintained on oral CyA alone.

Prednisone was given after reperfusion of the graft as a bolus of 1 g of hydrocortisone for smaller children, or 1 g prednisolone for children larger than 20 kg body weight. Subsequently, a steroid taper over 5 days, starting at 200 mg/d for larger children or 100 mg/d for smaller children was given. The maintenance dose was 20 mg/d initially, and then gradually tapered to the lowest dose necessary to maintain a rejection-free state.

Treatment of Rejection

Study Group

Rejection was treated by augmentation of the FK 506 or prednisone dose, steroid bolus, recycle, or OKT3 as clinically indicated. The dose of FK 506 was not augmented if there was significant impairment of renal function.

Control Group

CyA dose was augmented if whole blood levels were less than 1000 ng/mL. The prednisone schemes used for induction were repeated if necessary. OKT3 was used in steroid-resistant rejections. Azathioprine was added to the regimen if needed to maintain a rejection-free state.

Results

The clinical course of these 109 patients was reviewed. The baseline clinical profile of the patients in the two groups and technical complications were similar (Tables 1 and 2).

Patient and Graft Survival

At the end of follow-up (April 1991), 53 (90%) patients are alive in the FK 506 group vs 38 (76%) in the CyA group. Actuarial survival, as shown in Fig 1, was always better in the FK 506 group; 92% vs 80% at 3 months, 90% vs 78% at 6 months, 90 vs 78% at 1 year, and 90 vs 76% at 18 months for each group, respectively (P = .11).

Actuarial graft survival, as shown in Fig 2 is 85% vs 70% at 3 months, 83% vs 68% at 6 months, 83% vs 68% at 1 year, and 83% vs 66% at 18 months, again for each group, respectively (P = .12).

Overall, 7 patients (12%) required a second graft in the FK 506 group vs 9 (18%) in the CyA group (P = NS). One CyA patient required a third graft. An account of the causes of mortality and retransplantation is presented in Tables 3 and 4.

Adjuvant Corticosteroid Therapy

There are significant differences in both the percentage treated and median dose received (Figs 3 and 4). Prednisone was used by all CyA patients throughout the study period, except one patient who was successfully withdrawn at 9 months after transplantation. In contrast, prednisone use in the FK group dropped rapidly to 17% at 3 months, 12% at 6 months, to just under 10% beyond 9 months (P = .001). The induction of prednisone was significantly less in the FK group (see METHODS). The few patients still on prednisone in the FK group received a smaller dose than the CyA patients.

Adjuvant Azathioprine Therapy

None of the FK 506 patients received maintenance azathioprine. Azathioprine was used in about 55% of the CyA patients as adjuvant maintenance immunosuppression.

Drug Levels

CyA levels were highest at 1 week (median 1022 ng/mL). Maintenance levels beyond 6 months were approximately 400 ng/mL. FK 506 levels were highest at 1 day (median 1.65 ng/mL), and were maintained after 6 months at levels below 0.5 ng/mL.

Hematologic and Biochemical Profile

The hematologic and biochemical profiles were similar in both groups (Figs 6 and 7) except for serum BUN which showed a trend favoring FK 506 after 6 months (P = NS).

Complications of Immunosuppression

Rejection

Overall, 45 (76%) of the study patients and 35 (70%) of the control patients experienced at least one rejection during follow-up. There was no difference between groups in the incidence of multiple rejections, as 32% in each group experienced two or more episodes of rejection.

The severity of rejections, judged by the treatment required, was noticeably different between groups. Of the 78 episodes of rejection treated in the FK 506 group, only 1 (1%) required retransplantation, 10 (13%) OKT3, 7 (9%) steroid recycle, 53 (68%) a single steroid bolus, 57 (73%) augmentation of the baseline FK dose, and 41 (53%) augmentation of the baseline steroid dose. The 55 episodes of rejection in the CyA group required 2 (4%) retransplants, 18 (33%) OKT3, 22 (40%) a steroid recycle, 39 (71%) a steroid bolus, 27 (49%) augmentation of CyA dose, and 26 (47%) augmentation of the baseline steroid dose.

OKT3 was used 2.5-fold ($P = .01$) and steroid recycle 4.4 fold ($P < .0001$) more frequently in the CyA group. In contrast, increased FK 506 dosage was 1.5-fold more frequent than increased CyA dosage ($P < .01$).

Infections

The infectious complications occurring during the first 90 days after liver transplantation in children treated with FK 506 and their historical controls are outlined in Table 5. The mean number of infectious episodes was significantly less in patients treated with FK 506 compared to controls (1.4 vs 2.0, $P = .04$). The type and frequency of infection were similar in the two groups, with the exception that catheter-associated infection was seen much more frequently in the historical group. After exclusion of catheter-associated bacteremia, the mean number of infectious episodes per patient seen in patients receiving FK 506 was still less than that of controls, though the difference was no longer significant (1.25 vs 1.54, $P =$ NS).

CMV was the most common viral pathogen seen in both groups of patients. Primary CMV infection occurred in 7 of 14 episodes in patients on FK 506 compared to 5 of 13 episodes in patients in the historical control group. Invasive CMV disease, consisting of enteritis, hepatitis, or pneumonia, was seen in 11 of 14 episodes in patients treated with FK 506 compared to 8 of 13 episodes in control patients ($P =$ NS). Hepatitis was the most common invasive site in both groups.

A trend toward an increase in fatal infections was seen in control patients (2 of 59 vs 7 of 50, $P < .08$). Pathogens associated with a single episode of fatal infection in patients treated with FK 506 included CMV and *Aspergillus fumigatus*. Pathogens associated with a single episode of fatal infection in the control group included CMV, adenovirus, CMV and adenovirus, influenza A, and *Staphylococcus aureus; Enterobacter cloacae* was the pathogen in two fatal infections.

Lymphoproliferative Disease

Lymphoproliferative disease was diagnosed in three patients in the FK group and two in the CyA group, none of them were fatal or required retransplantation. They were all treated with reduction of the immunosuppression and IV acyclovir. One patient in the study group underwent a right hemicolectomy for intestinal lymphoproliferative disease.

Hypertension

Hypertension was seen less often as judged by the use of antihypertensive treatment. Diltiazem was not considered as an antihypertensive in the CyA group because it was frequently given to increase CyA blood levels.

Antihypertensives were given to 17% of the patients at 1 day after transplantation, and decreased gradually to 8% at 15 months in the FK group. In the CyA group, the use of antihypertensives was significantly higher at 1 day (65%), and remained elevated at all time points (45% at 15 months) ($P = .01$).

Discussion

The decision to proceed with this prospective trial for the evaluation of FK 506 in primary pediatric liver transplantation was made with a majority vote of the Institutional Review Board of the Children's Hospital of Pittsburgh. The study takes advantage of a large inventory of historical controls in our program, operated upon and cared for by the same team Using the same preservation and surgical techniques as in the study group. The

controls were matched for age, disease, and medical urgency at the time of transplantation. It was possible to identify such controls for the majority of the study patients.

Comparison of patient and graft survival between the two groups favors the FK 506 group, a difference which did not achieve statistical significance, due to the modest sample size.

Although the number of rejection episodes was similar in the two groups, rejections were easier to manage in the study group. Infections were less common and less severe in the study group. Similarly, hypertension was significantly less common in the study group.

There was a lower requirement for chronic steroid use, with less than 10% of the study patients requiring chronic steroids, versus an almost universal requirement in the control group. Adjuvant azathioprine was only needed in the control group.

Evaluation of hirsutism or facial disfigurement were not included in the study because these side effects are difficult to quantitate, particularly in the control group. Hirsutism or facial disfigurement have not been seen in the study group.

The internal milieu was identical in both groups of patients, at least as judged by blood chemistry and hematology examinations throughout the study period. A sole exception was a decreased serum BUN in the study group starting at 6 months after transplantation, which was not statistically significant.

In conclusion, FK 506 compares favorably to CyA for use in primary liver transplantation. There is a persistent trend for improved patient and graft survival with less frequent antihypertensive treatment and virtual elimination of adjuvant steroid therapy.

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References

1. National Institutes of Health Consensus Development Conferences Statement. Hepatology 1984;4:107s. [PubMed: 6363254]
2. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Hepatology 1982;2:614. [PubMed: 6749635]
3. Starzl TE, Iwatsuki S, Malatack JJ, et al. J Pediatrics 1982;100:681.
4. Esquivel CO, Iwatsuki S, Gordon RD, et al. J Pediatrics 1987;3:1039.
5. Shaw BW, Wood PR, Kaufman SS. J Ped Nutr Gastroenterol 1988;7(part I):157.1989;7(part II):797.
6. Andrews W, Wanek E, Fyock B, et al. J Ped Sur 1989;24:77.
7. Broelsch CE, Emond JC, Thistlethwaite JR, et al. Ann Surg 1988;208:410. [PubMed: 3052326]
8. Busuttil RW, Seu P, Millis JM, et al. Ann Surg 1991;213:48. [PubMed: 1985538]
9. Todo S, Podesta L, ChapChap P, et al. Transplant Proc 1987;19(suppl 6):64. [PubMed: 2445079]
10. Starzl TE, Todo S, Fung J, et al. Lancet 1989;ii:1000. [PubMed: 2478846]
11. Todo S, Fung JJ, Demetris AJ, et al. Transplant Proc 1991;23:1397. [PubMed: 1703340]
12. Tzakis AG, Fung JJ, Todo S, et al. Transplant Proc 1991;23:924. [PubMed: 1703353]
13. Fung JJ, Todo S, Tzakis A, et al. Transplant Proc 1991;23:14. [PubMed: 1703682]
14. Shapiro R, Jordan M, Fung J, et al. Transplant Proc 1991;23:920. [PubMed: 1703352]

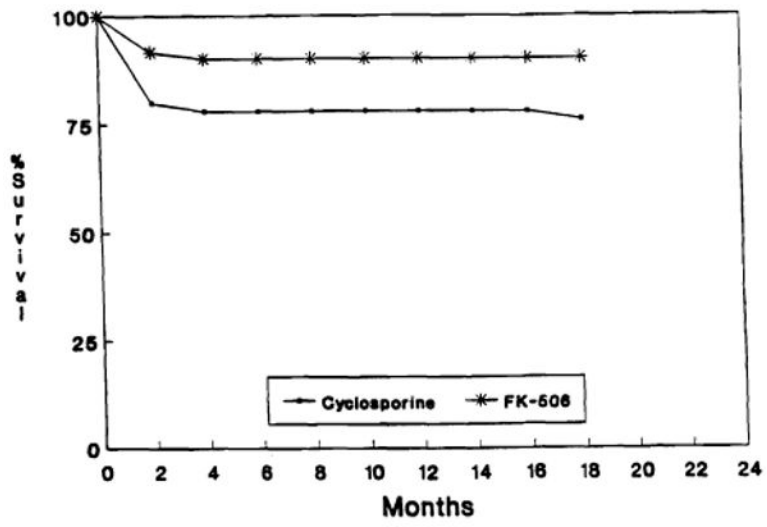

Fig 1.
Actuarial patient survival in pediatric liver Tx.

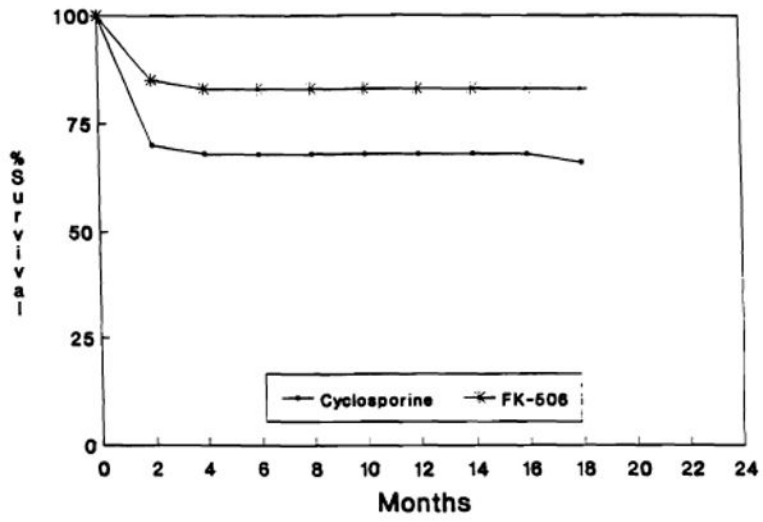

Fig 2.
Actuarial graft survival in pediatric liver Tx.

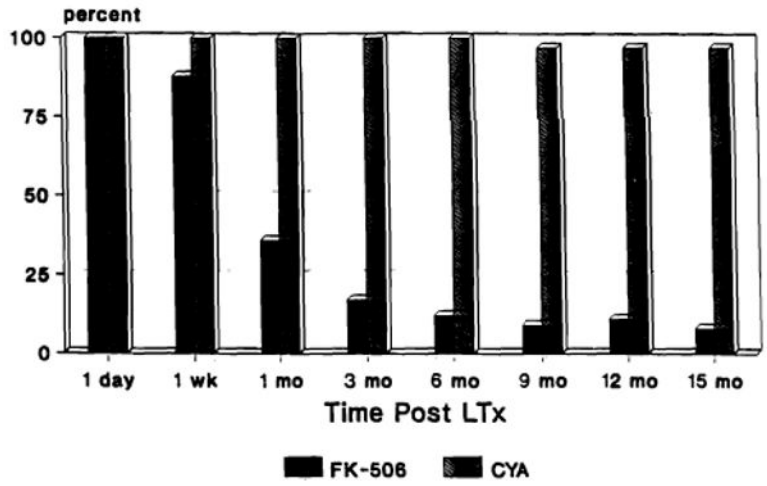

Fig 3.
Percentage of patients on adjuvant steroid therapy.

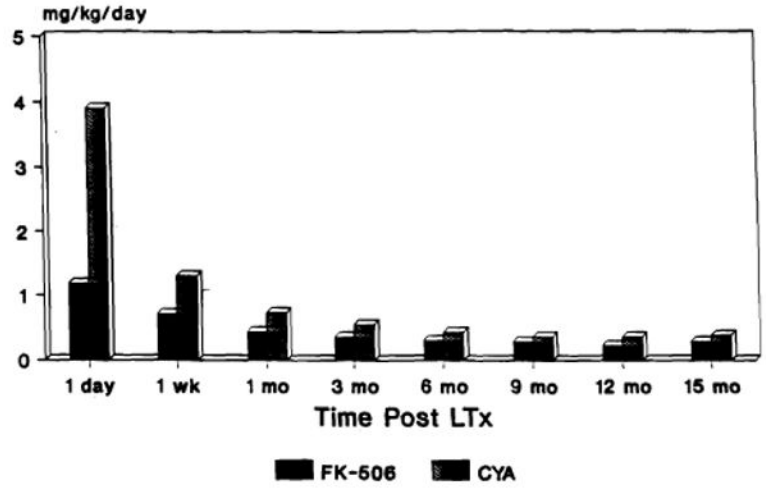

Fig 4.
Prednisone dose per patient receiving adjuvant steroid therapy in the two groups.

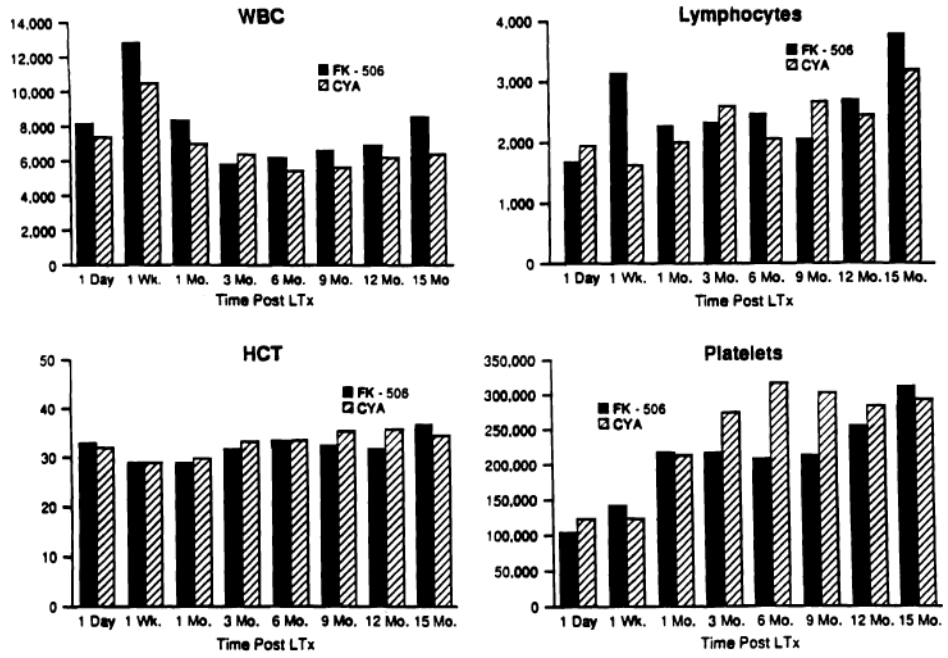

Fig 5.
Hematologic profile: study vs control group.

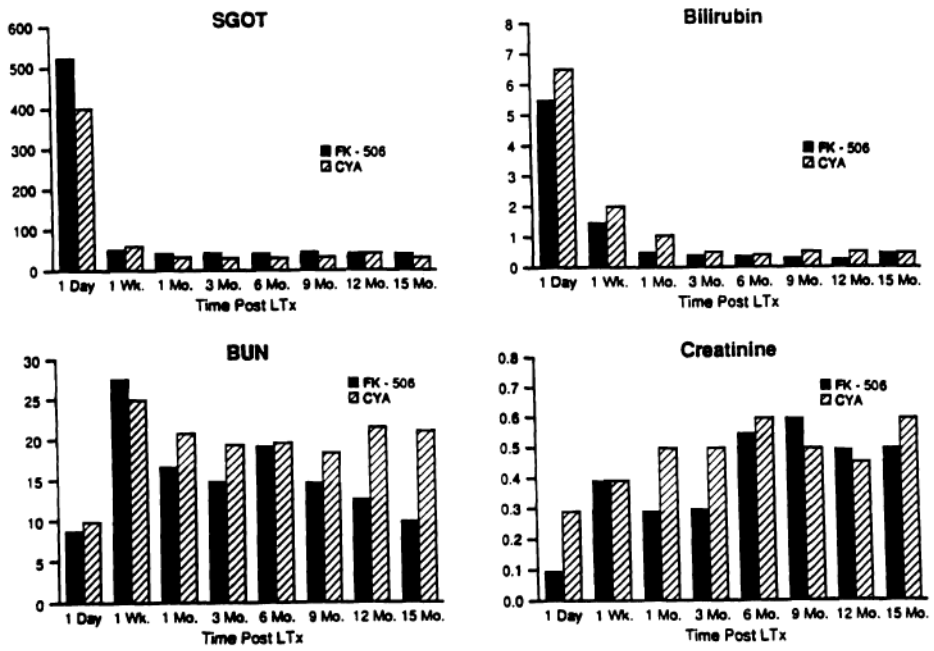

Fig 6.
Biochemical profile: study vs control group. Liver/kidney function labs.

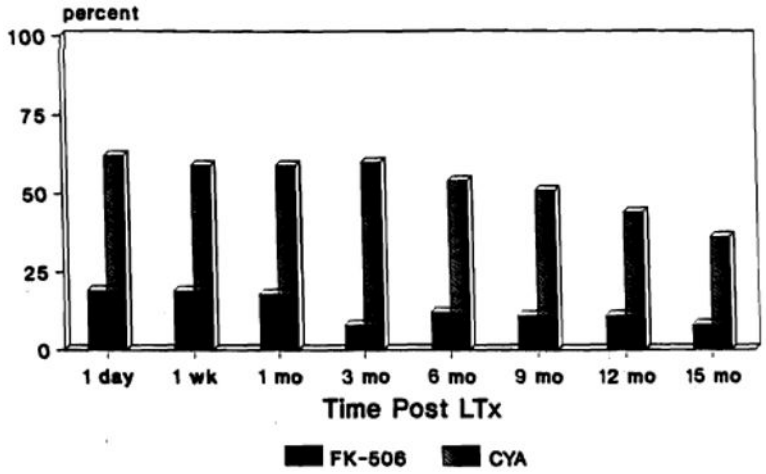

Fig 7.
Incidence of hypertension requiring treatment in study vs control group.

Table 1
Pretransplantation Clinical Profile of the Patients in the Study and Control Group

	FK 506	CyA
Number	59	50
Median age	2.7 years (0.2 to 16.5)	1.8 years (0.3 to 15.2)
Male/female	31/28	22/28
Cholestatic liver disease	38	36
A-1-A	3	3
Neonatal hepatitis	5	2
Cystic fibrosis	3	2
Fulminant hepatitis	2	2
Hepatoblastoma	2	2
All others	6	2
Previous Kasai	30	28
PRA > 10%	4	4
Gross × (+)		
Strongly	1	4
Weakly	10	4

Table 2
Technical Complications Posttransplantation

Complications	FK 506	CyA
Postoperative bleeding	8	4
Hepatic artery thrombosis	6	8*
Portal vein thrombosis	0	2
Cava thrombosis stricture	0	0
Rupture of pseudoarithm of PV	0	1
Biliary stricture	4	5
Retention of stent	1	1
Biliary leakage	1†	0
Intra-abdominal abscess	2‡	0
Bowel perforation	0	1

*ln 3 of these patients, the diagnosis was made by repeat ultrasound examinations. The hepatic artery was visualized later and they presented no complications.

†From accessory bile duct of a liver segment.

‡On the raw surface of liver fragment.

Table 3

Causes of Death After Transplantation

	FK 506	CyA
Fatal infections	2	7
Operative	1	2
Tumor recurrence	—	1
Portal vein thrombosis	—	1
Rejection	—	1
Primary nonfunction	2	—
Intracerebral hemorrhage	1	—
Total	6	12

Table 4
Causes of Retransplantation in the Study Versus Control Group

	FK 506	CyA
Hepatic artery thrombosis	2	3
Primary nonfunction	3	2
Rejection	2	3
Adenovirus hepatitis	—	1
Total	7	9

Table 5

Infectious Complications During the First 90 Days After Pediatric Liver Transplantation: FK 506 Versus Controls

	FK 506	Control
Total episodes infection	82	100*
Episodes/patients	1.4	2.0†
Fatal infections	2	7
Bacterial infections	42	60
Fatal	0	3
Bacteremia	13	35
Line-associated	5	22
Other source identified	3	9
Intra-abdominal without bacteremia	7	6
Wound	4	1
Other	18	19
Viral Infections	33	32
Fatal	1	4
CMV	14	13
Adenovirus	4	7
Other	15	12
Fungal	8	10
Fatal	1	0

*$P = .04$ by Student's t test for unequal variances.

†$P < .08$ by Fisher's Exact Test.