i301

Retransplantation of Liver: A Comparison of FK 506- and Cyclosporine-Treated Patients

S. Takaya, O. Bronsther, S. Todo, K. Abu-Elmagd, A. Jain, M. Alessiani, J. Madariaga, I.R. Marino, R. Selby, J.J. Fung, R.D. Gordon, and T.E. Starzl

DESPITE improvements in operative techniques, organ preservation, and the introduction of OKT3, the incidence of retransplantation (RETx) under cyclosporine (CyA)-based therapy has changed little since our initial report.[1-3] Approximately 15% to 20% of all CyA-treated recipients require RETx, with a 1-year mortality rate of 50%.

The purpose of this study was to evaluate the impact of FK 506 on the incidence of RETx and on the cause of graft loss.

CASE MATERIALS

CyA Group

Between October 25, 1987 and September 5, 1989, 631 adult patients (18 years or older) received their first orthotopic liver transplantation (OLTx) under CyA–steroid therapy at the University Health Center of Pittsburgh. Within the first 6 months following the OLT, 97 adults patients had required 118 retransplantations (RETx) (97 second, 19 third, and 2 fourth). Median follow-up in this group was 27 months.

Four patients initially treated with CyA had unsuccessful attempts at rescue with FK 506 before RETx. Following RETx, 18 patients were switched to FK 506. For the purpose of analysis, these patients were included in the CyA group.

FK 506 Group

Between August 19, 1989 and September 30, 1990, 409 adults received primary liver grafts under FK 506 and low-dose steroid therapy. Thirty-five patients required 39 RETxs (35 second, 4 third) within the first 6 months following the primary transplantation. Median follow-up in this group was 13 months.

Organ Preservation

All of the liver allografts in this study were preserved with the University of Wisconsin solution.

Patient Survival, Follow-Up, and Statistics

The indication for RETx from clinical and pathologic evidence was classified as: 1—technical, 2—rejection, 3—primary nonfunction, 4—infection, and 5—miscellaneous. A diagnosis of primary nonfunction was made if a graft never demonstrated evidence of initial function following transplantation. Clinical findings and examinations strongly associated with primary nonfunction included stage 4 coma, sluggish or no bile flow, progressive jaundice, uncorrectable coagulopathy, metabolic acidosis, renal failure, and cardiodynamic shock. The pathology of such grafts usually showed massive or submassive ischemic necrosis, or severe cholestasis without evidence of rejection. A technical classification was assigned to all grafts failing from vascular thromboses, complications of biliary reconstruction, or other errors in operative technique. The miscellaneous category included grafts lost from causes such as ruptured splenic aneurysm and recurrence of original disease.

The patient survival was calculated from the date of second transplant. The minimum observation periods were 14 months in the CyA group and 9 months in the FK 506 group. The survival rates were calculated by the Kaplan-Meier method, and statistical analysis were performed by Breslow method using BMDP statistical software. Other statistical methods used were the Mann-Whitney U rank-sum test, Kruskal-Wallis test, and Yates corrected chi-square analysis. $P < .05$ was considered statistically significant.

RESULTS

The Incidence of and Survivals After Retransplantation

The incidence of RETx within 6 months of primary transplantation was 15.4% (97 of 631) in the CyA group, and 8.6% (35 of 409) in the FK 506 group (Table 1). The lower incidence in the FK 506 group was significant ($P < .005$).

One and 6 months patient survival rates after RETx were 69.1% and 54.6%, respectively, in the CyA group, and 85.7% and 62.9% in the FK 506 group (Fig 1). The differences in the two groups were not significantly different ($P = .49$ by Breslow method).

Table 1. The Incidence of Liver Retransplantation in the First 6 Months

	CyA Group	FK 506 Group	P Value
No. of Patients	631	409	
Age (y)	18.1–73.9	18.1–67.9	
Second transplant	97 (15.4%)	35 (8.6%)	<.005
Third transplant	19	4	
Fourth transplant	2	0	
Total RETx in the first 6 months	118 (18.7%)	39 (9.5%)	<.005

From the Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

Supported by research grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Thomas E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Avenue, Falk Clinic, Pittsburgh, PA 15213.

0041-1345/91/$3.00/+0

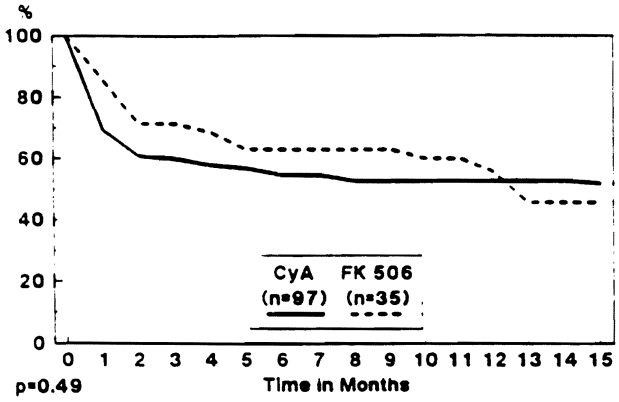

Fig 1. Patient survivals in the CyA and FK 506 groups following retransplantation. The survival was calculated from the date of second liver transplant. No statistical significance was observed in these two groups (P = .49).

The Cause of Graft Failure in RETx

The causes of graft loss were grouped in five categories (Fig 2). Primary nonfunction (PNF) was the most common cause for RETx in both groups. Nonetheless, the incidence of PNF was significantly lower in the FK 506 group when compared to the CyA group (4.1% vs 7.4%, $P < .05$). Cold ischemic times were 14.5 ± 6.2 hours in the FK 506 group, and 15.7 ± 7.1 hours in the CyA group (P = .65). Percentages of grafts whose cold ischemic times were more than 18 hours were not significantly different (31.3% vs 33.3%).

Rejection was the third leading cause of graft failure with an incidence of 2.9% (18 of 631) in the CyA group. Ten of these primary grafts failed from acute cellular rejection within 8 to 31 days (median 11 days). One graft failed from antibody-mediated rejection with partial portal vein thrombosis. Another graft failed from antibody-mediated rejection due to ABO incompatibility. Six grafts were lost to chronic rejection with prominent bile duct damage or bile duct loss within 49 to 165 days after transplantation (median 125 days). Although three of those six patients were switched to FK 506 for attempt to rescue at 22, 88, and 128 days after the primary transplantation, they required RETx 9, 26, and 60 days later and two patients survived.

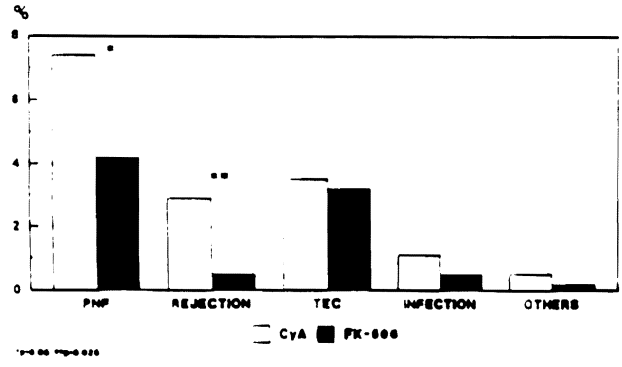

Fig 2. The cause of graft failure in liver RETx. The incidence of rejection and primary nonfunction decreased significantly in the FK 506 group ($P < .025$ and $P < .05$, respectively) when compared to the CyA group. PNF, primary nonfunction; TEC, technical problems; other, miscellaneous causes.

The incidence of rejection was significantly decreased in the FK 506 group (0.5%, 2 of 409) when compared with the CyA group (2.9%, 18 of 631, $P < .025$). In the FK 506 group, two grafts failed from antibody-mediated rejection. The lymphocytotoxic crossmatch tests of both patients were strongly positive, and both of these grafts were lost at 3 and 38 days, respectively. No acute cellular rejection was observed as the cause of graft loss. Furthermore, no chronic rejection was observed in the FK 506 group within the first 6 months.

There was no significant difference in the incidence of technical problems or infections in these two groups of patients.

DISCUSSION

Successful RETx of the liver was first accomplished as early as 1967.[1] However, the morbidity and mortality from such efforts were so overwhelming that RETx was a highly questionable undertaking until the advent of CyA.

During our first 5 years of CyA use (1980 to 1984), 18.6% of patients required RETx.[2] This incidence has changed little in the ensuing years. In the present study of CyA cases (1987 to 1989), in which the basic immunosuppressive therapy was with CyA and steroids supplemented by OKT3 and/or azathioprine, the rate of RETx was 15.4%. Interestingly, rejection as the cause for graft loss declined from 8.7% to 2.9%.

The introduction of the new immunosuppressant FK 506 decreased the need for RETx from 15.4% to 8.6% ($P < .005$). One reason for this significantly lower incidence of RETx was a further decrease in grafts lost to rejection to 0.5%. Only two grafts were lost to rejection, and in both cases, the lymphocytotoxic crossmatch test was strongly positive. These patients required RETx within 3 and 38 days, even though high-dose steroids and OKT3 therapy were used. RETx rates in all positive crossmatch patients were 23.6% in the CyA group, and 24.2% in the FK 506 group, respectively. The need for RETx appeared to be higher in positive crossmatch patients, regardless of the immunosuppression.[4,5]

The incidence of primary nonfunction, although reduced in both groups from our initial reports, was reduced even more in the FK 506 group (4.2% vs 7.4% in CyA group, $P < .05$). The reason for this is not clear. There was no significant difference in cold ischemic times between the CyA and FK 506 groups, and the difference might be related to the hepatotrophic activity of FK 506[6] and/or more complete restortion of hepatic ATP after reperfusion in FK 506-treated patients.[7]

REFERENCES

1. Starzl TE, Iwatsuki S, Van Thiel DH, et al: Hepatology 2:614, 1982

2. Shaw BW Jr, Gordon RD, Iwatsuki S, et al: Transplant Proc 17:264, 1985

3. Furukawa H, Todo S, Imventarza O, et al: Transplantation 51:1000, 1991

4. Takaya S, Duquesnoy R, Iwaki Y, et al: Transplant Proc 23:396, 1991

5. Takaya S, Bronsther O, Iwaki Y, et al: Transplantation (in press)

6. Francavilla A, Barone M, Todo S, et al: Lancet ii:1248, 1989

7. Sakr MF, Zetti GM, Farghali H, et al: Transplant Proc 23:340, 1991