Incidence and Treatment of Rejection Episodes in Primary Orthotopic Liver Transplantation Under FK 506

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FOLLOWING the demonstration of the potent immunosuppressive effect of FK 506 on human T lymphocyte activation[1,2] and the prolongation of graft survival on experimental models,[3-6] FK 506 has been applied successfully in clinical settings.[7-10] In this report, we present our experience with 125 primary liver transplant patients treated with FK 506 as a primary immunosuppressive agent.

This analysis focuses on the incidence of rejection, management of rejection episodes, and the role of concomitant use of prophylactic steroid in FK 506 treated patients.

MATERIALS AND METHODS

This study, which was done at the University of Pittsburgh, included patients who underwent primary liver transplantation between August 18, 1989, and February 16, 1990. A prospective randomized trial of cyclosporine (CyA) and FK 506 was initiated afterwards. The 110 adults were between 18 and 69 years of age and the 15 children were between 4 months and 17 years of age. Seven children were ≤1 year of age. Primary causes of hepatic failure are summarized in Table 1. All the patients were followed up for 180 to 355 days (mean duration 242 days). There were 10 deaths in the follow-up period. Eleven patients required a second transplant and four patients required a third transplant. Subsequent episodes of rejection in retransplants were not included for analysis. All patients received one dose of FK 506 (0.15 mg/kg/d) IV on the first day and 0.075 mg/kg twice a day as a constant infusion over 2 to 4 hours. Oral doses were introduced as soon as patients could tolerate oral fluids with a variable period of overlap with IV FK 506.[11] Subsequent adjustments in FK 506 dosage were made depending on hepatic graft function, adverse effects from the drug, and the drug's plasma trough levels. The first 63 patients received 1-g doses of prophylactic methylprednisone after perfusion of liver and then 200 mg in four divided doses on the first postoperative day and then reduced by 40 mg everyday until 20 mg/d of maintenance was reached. (Doses were scaled down for infants and children. Most children below the age of 8 years received half the adult doses.) The remaining 62 patients received only 20 mg/d (10 mg/d children) of methylprednisone as prophylaxis. Steroids were reduced postoperatively on an individualized basis.

The clinical diagnosis of rejection was made by rises in serum bilirubin and hepatic enzymes in the absence of biliary complications, ischemic damage, or development of hepatitis (hepatitis B, non-A, non-B, or cytomegalovirus [CMV]). In addition, the adult patients had protocol biopsies at 10 to 14 days posttransplantation and subsequently if clinically indicated.

Table 1. Indications of Primary Liver Transplant (n = 125)

Nonalcoholic cirrhosis	45 (36%)
Alcoholic cirrhosis	28 (22%)
Cholestatic disease	29 (22%)
Biliary atresia	8 (7%)
Fulminant failure	4 (3%)
Tumor	4 (3%)
Miscellaneous	8 (7%)

RESULTS

In this group of 125 patients, 115 (92.0%) are well at the present time. One hundred nine patients (87.2%) have their original grafts (Fig 1). Three patients are alive with second transplants and the other three with third transplants.

Rejection episodes were considered to be early when they occurred within 90 days and late when they occurred after 90 days (Table 2). Forty-five patients (36%) experienced one episode of rejection, 6 patients (4.8%) two episodes, and 1 patient (0.8%) experienced three episodes of rejection within the first 90 days, whereas 73 patients (58.4%) remained free from any episode of rejection and did not require additional immunosuppression in the first 3 months. Only 11 patients of 113 (9.7%) patients who were alive with primary grafts at 90 days experienced one episode of rejection and one patient (0.9%) experienced

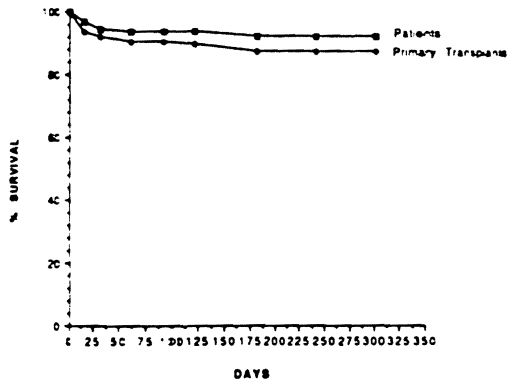

Fig 1. Percentage survival of patients and primary transplants on FK 506 over the follow-up period (n = 125).

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Supported by research grants from the Veterans Administration and project grant no. DK 29961 from the National Institutes of Health, Bethesda, MD.

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0041-1345/91/$3.00/+0

Table 2. Frequency of Rejection

Episode	No. of Patients	Percentage
Early within 90 days (n = 125)		
1	45	36.0
2	6	4.8
3	1	0.8
Rejection free*	73	58.4
Late rejection after 90 days (n = 113)		
1	11	9.7
2	1	0.9
Rejection free*	101	89.4

*Cumulative rejection free 66 patients (52.8%).

two episodes of rejection. Sixty-six patients (52.8%) had no rejection throughout the entire follow-up period.

In 110 adult patients, the results were compared between the 54 who received initial high prophylactic doses of methylprednisone (group 1, Table 3) and the 56 patients who received low doses of methylprednisone (group 2, Table 3).

In group 1 patients, 17 of the 54 (31%) patients experienced a first episode of rejection at mean of 18.3 (±10.3 SD) days after transplantation. In group 2, 27 of 56 (48%) patients experienced a first episode of rejection at a mean time of 13.9 (±10.7 SD) days. The apparent differences in episodes of rejection or timing of rejection were not statistically significant by chi-square *t* test analysis. The children were excluded from the foregoing analysis because they were not systematically biopsied.

Treatment of rejection was catalogued for all recipients, adults as well as children. There were a total of 73 episodes of rejection (early, late, recurrent). The majority of the rejection episodes were mild and were easily controlled with a single dose of 1 g IV methylprednisone (28 episodes, 38.4%) or a single dose of 1 g IV hydrocortisone (17 episodes, 23.3%) (Table 4). Thirteen (17.8%) episodes of rejection required further bolus steroid therapy to control the rejection. Short courses of OKT3 (3 to 5 days, 5-10 mL) were used to treat 15 episodes of rejection in 14 patients. In six patients, this therapy was used as primary treatment to control rejection while in the other 7 patients, it was used in conjunction with additional steroids. One patient was given two courses of OKT3. All the episodes of rejection were reversed completely except in two patients who required retransplantation due to persistent

Table 3. Frequency of Rejection During the First 90 Days (Adults Only)

	Episodes/Patient (%)	Day on Onset (mean ± SD)
High dose of prophylactic steroid (group 1)	17/54 (31)	18.3 ± 10.3
Low dose of prophylactic steroid (group 2)	27/56 (48) P:NS	13.9 ± 10.7 P:NS

Table 4. Treatment of Rejection

Drug	Episode (%)
Hydrocortisone (1 g)	28 (38.2)
Methylprednisone (1 g)	17 (23.3)
OKT3 (3-5 d, 5-10 mL)	15 (20.5)

rejection. OKT3 treatment was not considered in these two patients since the first patient was in the early part of the trial and the second patient had a primary nonfunction and received a second transplant 2 days later when a suitable donor was found.

DISCUSSION

The episodes of rejection under FK 506 were less frequent than in our past experience,[10] the intensity of the rejection was milder, and nearly two-thirds (62%) of these were reversed easily with a single dose of IV hydrocortisone or methylprednisone.

As time passed during the trial, side effects were delineated. Also, it was shown how effectively FK 506 could be used with other agents. A modified short course of 5-10 mg of OKT3 was given for 3 to 5 days and this was effective but associated with infectious morbidity.[12] In six cases, OKT3 was used to control moderate rejection as the first choice of antirejection treatment, and in eight more patients it was used in conjunction with steroid bolus therapy. In this series, there were only two transplants lost directly to uncontrollable rejection. OKT3 treatment was not used in either case. OKT3 might be considered a course of last appeal, but a dangerous one.

We evaluated the policy of high dose steroid prophylaxis in the first week for the first half of our patients vs limitation of steroids for the second half. There was an increase in the incidence of rejection from 31% to 48% and the first episode of rejection appeared to be earlier in the low steroid cohort. However, this was not statistically significant (chi-square *t* test). Since the rejection episodes are so readily reversible, the appeal of high dose prophylactic steroids is limited in any case.

SUMMARY AND CONCLUSIONS

FK 506 therapy with low doses of steroids was adequate to control rejection in most liver recipients. Rejection episodes were readily reversed with single IV doses of methylprednisone or hydrocortisone. Short courses of OKT3 (3 to 5 days 5-10 mL) controlled severe rejections. The rate of retransplantation directly due to rejection was low (1.6%). There was a limited need for steroids either early or out to 6 to 12 months.

ACKNOWLEDGMENTS

The assistance of René J. Duquesnoy, PhD in the analysis of data and preparation of the manuscript is gratefully acknowledged.

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