Strategy of FK 506 Therapy in Liver Transplant Patients: Effect of Graft Function

K.M. Abu-Elmagd, J.J. Fung, M. Alessiani, A. Jain, S. Takaya, R. Venkataramanan, V.S. Warty, W. Shannon, S. Todo, A. Tzakis, D. Van Thiel, and T.E. Starzl

IN THE transplant populations and patients with autoimmune diseases, the quality of liver function significantly influences FK 506 doses, drug trough plasma levels, and kidney function. The interrelationship of these variables has been previously discussed in patients with different kinds of organ transplantation.[1] In this report, however, we will concentrate only on liver recipients with different degrees of graft dysfunction, particularly in the perioperative period. From this study, a better understanding has been achieved of FK 506 management strategy in patients with variable quality of liver function.

MATERIALS AND METHODS

Patient Population

Forty-nine adults who were 17 to 69 years old (47 ± 15) received liver transplantation between Dec 16, 1989, and May 5, 1990. Liver transplantation was primary in all patients and FK 506 was the standard immunosuppressive agent. Twenty-three were males and 26 were females. The principal inclusion criterion was sufficient FK 506 plasma trough determinations to permit a reasonably complete reconstruction of events for the first 60 days after transplantation. Cases were excluded if a technically flawed operation was performed or if the patient previously received cyclosporine (CyA).

Patients were stratified into four postoperative categories based on the quality of liver graft function and to a lesser degree on the rapidity of recovery from intensive care support. The pretransplant features of all classes are shown in Table 1. Class I patients (n = 14) became jaundice free with bilirubins less than 2 mg % by 10 days after surgery. They also did not have evidence of major graft ischemia and were ventilator independent within 3 days. Class II cases (n = 17) had less perfect biochemical liver function tests, particularly in the first 5 days, but recovery thereafter was rapid. Five of these patients required ventilator assistance beyond 3 days. Class III (n = 10) and class IV (n = 8) patients had dysfunctional liver grafts with bilirubins above 2 mg % beyond 10 days in class III and throughout the 2-month period of study in class IV individuals. All class III and IV patients required prolonged ventilatory support and total parenteral nutrition.

All included patients were free of intrinsic chronic renal disease. However, at the time of transplantation, 11 patients (22.4%) had hepatorenal syndrome with requirement for pretransplant dialysis in 4 (8.2%). Death due to multiple-organ failure and sepsis occurred in two class IV patients during the study period, giving a total survival rate of 95%.

Immunosuppression

FK 506 therapy began in most patients 2 to 3 hours after revascularization of the graft. It was given initially intravenously in a dose of 0.075 mg/kg to be infused over 4 hours and repeated every 12 hours until oral administration was started. This intravenous (IV) dose is at least 50% greater than the starting IV dose now being recommended. When the conversion was made from IV to oral dosing at 0.15 mg/kg/12 h, administration by both routes frequently was overlapped for one or two doses. The beginning oral dose is the same as that used currently.

Graft biopsies were obtained after 10 to 14 days or before this if there was evidence of graft dysfunction. Dose adjustments were made in most patients on clinical grounds since plasma trough levels of FK 506 were not available until several days later. Revisions of the doses were dictated by suspected adverse effects of FK 506, of which renal and neurologic dysfunction were the most common. Increases in serum creatinine above 2 mg %, BUN above 60 mg %, and changes in the mental status concomitant with significant tremors were the warning parameters for dose reduction, especially if there was significant graft dysfunction. In addition, clinical and/or bacteriological documentation of sepsis was an incentive to temporarily reduce the FK 506 dose. Upward dose adjustments were prompted by a clinical, biochemical,

From the Departments of Surgery (K.M.A., J.J.F., M.A., A.J., S.T., S. Todo, A.T., D.v.T., T.E.S.), School of Pharmacy (R.V., V.S.W.), and the Pittsburgh Cancer Institute (W.S.), University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania.

Supported by research grants from the Veterans Administration and project grant DK 29961 from the National Institutes of Health.

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

0041-1345/91/$3.00/+0

Table 1. Characteristics of All Liver Recipients

Class	Total No.	Age (Mean ± SD)	Sex		Preoperative Biochemical Data				Pre-OLTx Dialysis
			Male	Female	Bilirubin (mg %)	SGPT (IU/L)	BUN (mg %)	Creatinine (mg %)	
I	14	44 ± 17	4	10	6.7 ± 7	103 ± 89	17 ± 8	0.9 ± 0.4	0 (0%)
II	17	49 ± 10	9	8	11.1 ± 12	106 ± 115	23 ± 15	1.1 ± 0.5	1 (6%)
III	10	45 ± 16	5	5	10.2 ± 8	35 ± 20	39 ± 33	1.7 ± 1.3	1 (10%)
IV	8	50 ± 15	5	3	21 ± 12	280 ± 338	46 ± 27	2.7 ± 1.4	2 (25%)

and/or histopathological diagnosis of graft rejection, or sometimes by persistent low plasma FK 506 levels.

Steroid therapy usually was started at a daily dose of 20 mg, but in a number of the early patients a 5-day steroid cycle was used, starting at 200 mg (four divided doses) and finishing at 20 mg/d. By the end of the 60 postoperative days, 27 (55%) of the patients were completely weaned from steroids. The degree and rate of dose reduction was dictated by the functional status of the graft, biopsy results, evidence of ongoing sepsis, and toxicity from either the FK 506 or the steroids.

The rejection episodes were treated first with an increase in FK 506 doses if this was permitted by the state of the renal function. Steroid boluses with increase in the daily maintenance dose were given to patients with persistent rejection as evidenced by unsatisfactory biochemical and/or histological response. Steroid resistant rejection that required a 3- to 5-day course of OKT3 developed in 9 recipients (18.4%).

FK 506 Plasma Levels

Trough plasma FK 506 levels were determined with the enzyme immunoassay technique of Tamura et al[2] in samples obtained twice per week or more often in complicated cases. However, results from the plasma determinations did not influence the immediate management decision because they were not available until several days later. The optimal 12-hour trough levels were thought to be in the 0.5 to 1.5 ng/mL range. In most of the patients with good graft functions (classes I and II), these trough values were in 12-hour samples. However, in several of the class III or IV patients, FK 506 was given once per day or every other day and consequently the so-called troughs were measured 24 to 48 hours after the last dose.

Statistical Analysis

The 60-day study period was divided into 5-day intervals. For each such interval in each patient, the mean value for all variables was obtained. These means were pooled for all patients in the four classes and the means (±SE) were calculated. Single-variable comparison between two or more of the classes at each time point was done by unpaired Student's t test and Bonferroni's (Dunn) test, respectively. Signed rank comparisons with Bonferroni adjustment were utilized for serial analysis of changes in each parameter at all times of the study period and Kendall tau test for the correlation between two variables with and without a lag time. These were computed using SAS/PC version 6.03 (SAS Institute, Inc, Cary, NC).

RESULTS

Liver Graft Function

During the 60-day study period, serum bilirubin was significantly higher in class IV cases compared to classes I and II. Although the patients in classes III and IV were considered catastrophic with the need for tracheostomy and ventilator dependence for many weeks or months in 12 of the 18 patients, 16 of them survived. The only deaths were from multiple-organ failure at 40 and 47 days in 2 class IV patients. There were no deaths or graft losses among class I, II, or III patients.

FK 506 Plasma Levels and Drug Doses

In class IV patients, plasma FK 506 levels were astonishingly high for most of the first month and up to 60 days. Although the same starting IV doses of FK 506 were used for all patients, the drug plasma trough levels were different in the four recovery classes (Fig 1). In class IV patients, FK 506 plasma levels were significantly higher (P = .0001) than that of class I, II, and III patients at all study points.

The doses of FK 506 were reduced in most of the patients within the first 10 days after transplantation. In class IV patients, the period of IV administration of FK 506 was more prolonged and the acutely reduced dose was significantly lower than in classes I, II, and III. However, by the end of the first 30 postoperative days there was no significant difference in FK 506 doses comparing the four classes. At that time, graft functions were similar for all classes except class IV.

Kidney Function

Daily serum creatinine and blood urea nitrogen (BUN) measurements were used to monitor changes in renal function. Both parameters were significantly elevated at all points of the 60-day study period. In class I and II patients, the maximal increase in serum creatinine occurred 2 to 3 days after the FK 506 plasma level reached its peak. In the undialysed patients, early postoperative serum creatinine and BUN changes were significantly higher in class III and IV patients compared to classes I and II.

There was no new perioperative dialysis requirement in the class I and II recipients and, in fact, a previously dialysis-bound patient in class II had restoration of renal function 21 days after transplant. Renal failure severe enough to require dialysis for the first time was common in classes III (n = 4 of 10) and IV (n = 5 of 8), although this was reversible in most of the cases (Fig 1). At the end of 60 days, five patients were still on dialysis. Four of these five have subsequently recovered from renal failure, leaving only one patient, who died 6 months later of respiratory failure.

Correlation Analyses

Bilirubin, FK 506 Doses, and Drug Plasma Levels. The correlations of serum bilirubin, plasma FK 506 levels drawn on the same day, and the drug dose given are shown in Fig 2 for patients of the combined classes I through IV. There was a significant linear correlation between serum bilirubin (P = .0001) and plasma FK 506 level despite an inverse correlation with FK 506 doses (P = .001). There was also a significant linear correlation between the doses and plasma levels of FK 506. These correlations were especially sharp when patients of class I were compared with those of class IV.

FK 506 Plasma Levels and Serum Creatinine. There was no statistically significant correlation between serum creatinine and FK 506 plasma levels in the patients who

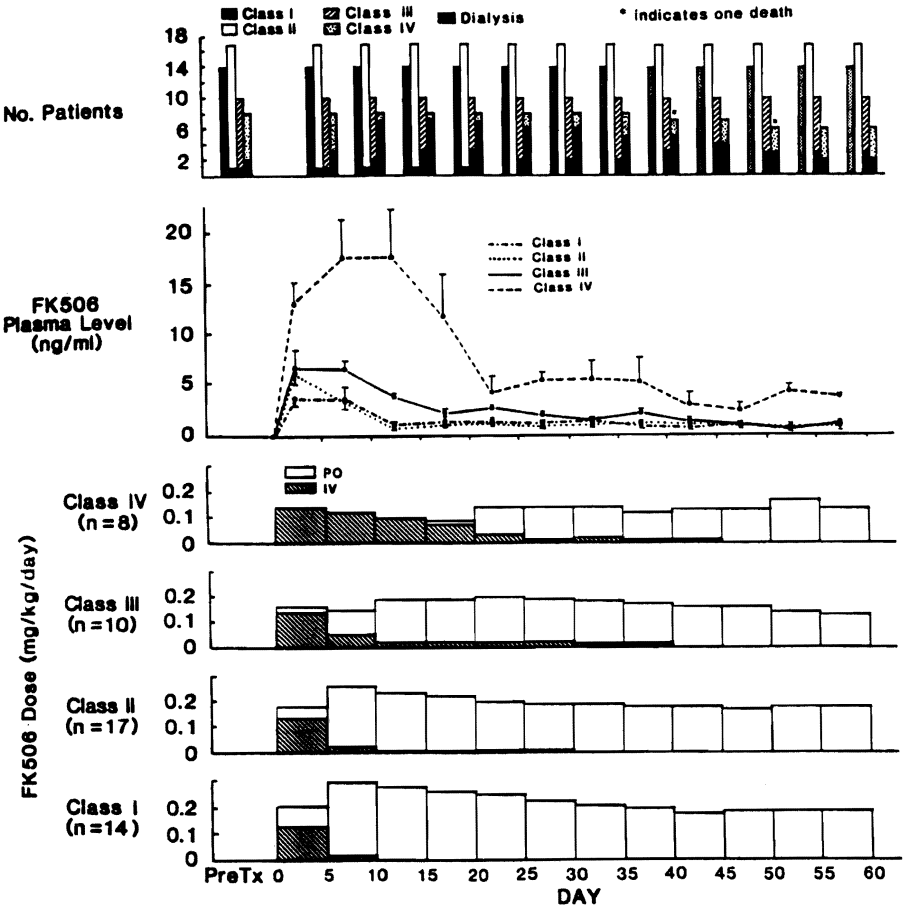

Fig 1. Effect of postoperative liver function on FK 506 doses, plasma levels, and kidney function. Note that the highest plasma levels despite the lowest doses were in the patients with early unsatisfactory graft function. Meanwhile, four class III patients and five class IV patients required postoperative dialysis for some time.

did vs those who did not require dialysis. However, the mean FK 506 plasma levels were significantly ($P < .05$) higher in patients who required hemodialysis than that of the patients who maintained adequate kidney function.

Steroid Therapy

The maintenance steroid dose was more significantly reduced ($P < .05$) in class IV patients compared to the other classes, particularly in the early postoperative period. The early graft dysfunction with the coexistence of life-threatening sepsis dictated the early reduction of steroid doses in many of these cases. By the end of 20 days, there was no significant difference in the mean steroid doses for the four classes. Collectively, 55% of these patients ($n = 27$) were weaned from steroids at the end of the 60-day study period.

DISCUSSION

The pharmacokinetics of the new immunosuppressive drug FK 506 are reasonably well understood in large animals and humans.[3,4] FK 506 is metabolized mainly by the liver and its terminal half-life after a redistribution phase is about 9 hours.[3] The drug clearance, however, is high and actually exceeds total hepatic blood flow, indicating significant extrahepatic metabolic pathways. In contrast, the clearance rate of CyA is low.[5] Also, the nature of oral FK 506 absorption and timing of peak plasma levels appear to differ from CyA. In contrast to CyA, FK 506 does not need bile to be absorbed from the gastrointestinal tract.[6] The oral formulation of FK 506 also seems to have "slow release" qualities with blunted peak plasma levels and modest fluctuations in plasma concentrations.

Although there has been no evidence of hepatic or cardiac toxicity in different organ recipients, it is clear that liver function influences all postoperative pharmacokinetic variables. In patients with relatively normal liver graft function (class I) and those with significantly damaged but quickly recovered grafts (class II), the starting IV and oral doses were well tolerated. Plasma FK 506 trough levels rose during IV administration, but the levels quickly receded once oral dosing was started. Since FK 506 augments liver regeneration, its presence actually may have facilitated recovery of the graft from perioperative ischemic damage.[7,8]

In class III and IV patients with significant perioperative graft dysfunction, the plasma FK 506 levels rose astronomically and stayed high for several days in spite of dose reduction or even discontinuance. This was most evident

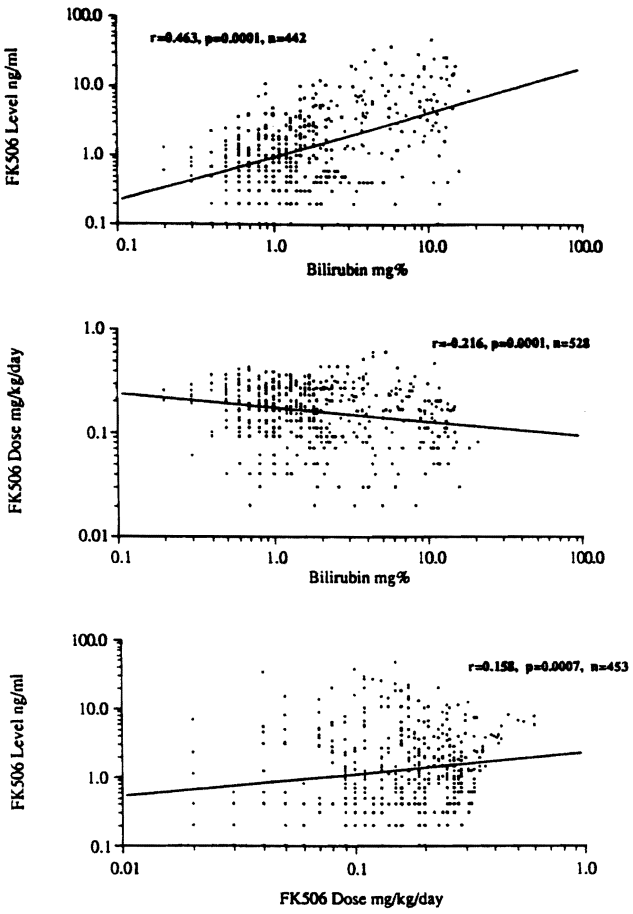

Fig 2. Scatter plots for the actual values of simultaneously determined serum bilirubin, FK 506 plasma level, and drug dose on $\log_{10}$ scale for all recipients. Serum bilirubin has a significant positive correlation with FK 506 plasma levels and inverse correlation with FK 506 doses. With r value of 0.158, there was a significant (P = .0007) correlation between FK 506 doses and levels.

during the period of FK 506 IV therapy. The high levels appeared to be associated with a high incidence of dialysis. Increases in renal function indices were noticed 2 to 3 days following the high peaks of FK 506 plasma levels. Clearly, FK 506 was not the only nephrotoxic factor. Most of these class III and IV patients had variable degrees of multiple-organ failure before transplantation or perioperatively. Hypotension, sepsis, and the need for nephrotoxic antibiotics were almost invariable. These are known to be independent or collaborating factors in the development of renal failure following liver transplantation, no matter what the drug therapy.[9,10]

However, the nephrotoxic effect of FK 506 could be clearly analyzed in class I and II patients who did not have significant liver graft dysfunction or coexistent systemic sepsis. The temporary rises in plasma FK 506 levels during IV therapy and the concomitant rises in BUN and creatinine were partly reversed when the FK 506 doses were lowered or changed to the oral route. In these patients, the deterioration in renal function did not correlate significantly with plasma FK 506 levels. Yet, dose reduction of FK 506 appeared to be a beneficial adjustment.

This study, which has been reported earlier in greater detail,[1,11] has led to inescapable conclusions. First, patients with defective drug metabolism caused by hepatic dysfunction are more vulnerable to acute or prolonged overdose of FK 506, toxic blood levels of FK 506, and the development of renal dysfunction. Second, the IV FK 506 doses used in these early trials were too high, even for patients with good liver graft function. Our current practice is to give IV FK 506 by constant infusion at a dose of 0.1 mg/kg/d or even lower instead of the 4-hour bolus infusion twice a day used in this study. In contrast, the oral doses every 12 hours were appropriate if good graft function was achieved.

With either IV or oral dosing, the demonstration that FK 506 kinetics are markedly affected by hepatic dysfunction is a clear warning against overdosage in patients with failing liver grafts under primary FK 506 therapy or in those under conventional immunosuppressive therapy who are switched to FK 506. Failure to frequently monitor plasma FK 506 levels in these patients with quick and appropriate dose adjustments can lead to serious drug toxicity.

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