Conversion from Cyclosporine to FK 506 in Liver Allograft Recipients With Cyclosporine-Related Complications

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With the use of CyA for clinical liver transplantation, 1-year survival rates have approached 70%. Nevertheless, allograft rejection continues to be the most common cause of retransplantation and death. Clinical rejection occurs in 70% of liver allograft recipients on CyA and steroid therapy.[1] In addition, nephrotoxicity is the principal and dose-limiting side effect of CyA. Chronic renal damage and functional impairment have been shown to occur in 87.4% of liver transplant patients,[2] and hypertension is an almost universal complication. Antihypertensive therapy is required in the majority of these patients. Alterations in clinical immunosuppression to prevent or reverse these and other side effects have included (1) reduction of CyA dose or (2) addition of azathioprine, antilymphocyte antibodies (ALG), or other agents with concomitant reductions in the CyA dose. These methodologies have their inherent dangers: increasing susceptibility to rejection and increased susceptibility to infection, respectively.

FK 506 is a potent and novel immunosuppressive agent, discovered in Japan less than 4 years ago.[3–5] Much is known about FK 506: in vivo studies of the effectiveness of FK 506 in several allograft models in rats, dogs, and baboons;[6–16] as well as in vitro studies of the properties of FK 506, its mechanisms of action, and its intrinsic cytotoxicity have been documented.[3–6,17,18] Both in vitro and in vivo synergism of FK 506 with other immunosuppressive drugs has been demonstrated and, for this reason, it was planned to give the first human patients a combination of FK 506 and CyA.

A phase I/II trial of FK 506 was conducted with the approval of the University of Pittsburgh Institutional Review Board and the FDA in 1989. The plan was to give FK 506 to patients who were rejecting their liver grafts, in spite of conventional immunosuppression.[19] The protocol was to initially combine low doses of FK 506 with CyA. This was attempted in the first 11 patients. As will be described, this combination was accompanied by a number of adverse reactions. Eventually, a simple switch (clean conversion) was made from CyA to FK 506. The following is an account of the first 40 liver transplant recipients entered into this pilot study.

PATIENTS AND METHODS

Patient Profiles

Nineteen patients were females and 21 were males, ranging from 5 to 74 years of age. The original liver diseases and dates of liver transplants are noted in Table 1.

Indications

All patients had an initial entry diagnosis of uncontrolled liver allograft rejection and/or other complications related to CyA, ie, renal dysfunction or hypertension (Table 1). CyA-related complications were defined as renal failure (a serum creatinine >2.0 mg/dl) and/or postoperative hypertension (diastolic blood pressure > 100 mm Hg despite diuretics) secondary to CyA nephrotoxicity. These patients were therefore considered treatment failures of conventional immunosuppression. Prior to conversion to FK 506, maintenance immunosuppression in all patients was with CyA and prednisone, with or without azathioprine. CyA doses had been maximized to tolerable levels, as limited by renal dysfunction or hypertension.

Diagnostic Evaluations

The cause of liver dysfunction was carefully evaluated prior to enrollment in the study. Ultrasonic determination of vessel patency and radiographic evaluation of the biliary system were used to rule out a technical or mechanical defect. Angiography was performed when indicated.

Liver biopsies were performed in all but three patients prior to entry. An important criterion for entry was the pathologic interpretation of the liver biopsy by a single experienced liver pathologist (A.J.D.), as is discussed elsewhere in this symposium. The histopathologic findings of rejection ranged from periportal accumulations of lymphocytes without obvious duct damage to destruction of the bile ducts with injury to other components of the portal triads.

In 1 patient, an incorrect initial diagnosis of acute cellular rejection was modified to acute hepatitis B infection, after special staining of the liver biopsy for hepatitis B core and surface antigen was positive, 4 days following initiation of FK 506 treatment. Treatment with FK 506 was stopped.

In 6 patients, the clinician's opinion was that the biopsy reading underestimated the severity of the rejection episode. The criteria for rescue therapy in these patients was based primarily on biochemical and clinical parameters, such as elevations of serum transaminases or serum bilirubin to >50% of baseline, clinical signs such as fever, and changes in bile characteristics in those that had T-tubes. In 2 patients, a large element of ischemic injury was noted on biopsy. Two patients had markedly abnormal coagulation parameters, making a liver biopsy unsafe. One patient did not have a biopsy, her entrance criterion being steroid toxicity.

Timing of Therapy

Initiation of treatment with FK 506 was done in the hospital and was given initially as a parenteral dose, followed by conversion to an oral dose. Because of the possibility that FK 506 and CyA would be used together, pharmacokinetic studies were performed with each drug individually, and then in combination, with both intravenous and oral administration. As shown in Table 2, the protocol for conversion from CyA to FK 506 was different for the first 11 patients, after which time a "clean" conversion was performed for the last 29 patients.

Size of the Dose

The initial intravenous dose was 0.15 mg/kg/d on the first day and, on day 2, the daily dose was divided and given every 12 hours. On day 2, oral administration of 0.3 mg/kg/d began, with a 1-day overlap between the parenteral and enteral doses. Adjustments of the FK 506 downward, to 0.15 mg/kg/d, was also made if side effects or other toxicity were encountered.

RESULTS

Response of the Liver Allograft

Of the 40 patients entered in the study, 1 was eliminated from the study because of the incorrect entry diagnosis, which proved to be acute hepatitis B viral infection. Of the remaining allografts studied definitively and in which long-term follow-up of more than 1 month had been obtained, the liver allografts were rescued, as judged by histopathologic criteria and by criteria of liver function, in all but 12 patients. In each case in which histopathologic changes were predominant, the findings of rejection had improved by the first follow-up biopsy, obtained 2 weeks following the start of FK 506 therapy (see Demetris et al, this symposium). These changes were particularly impressive in patients whose pretreatment biopsies contained bile duct lesions that generally progressed to bile duct disappearance and graft loss, in spite of intensive immunosuppression.[1]

The abnormalities in liver function tests were also promptly corrected (Figs 1, 2, and 3). The decline in the bile cannulicular enzymes, alkaline phosphatase, and gamma-guanosine triphosphate in the recipients with bile duct rejection was of special interest, since elevations of these enzymes often premonitor graft loss from chronic rejection (data not shown). In all of the patients who had improvement in histopathologic criteria of rejection, elevations of hepatocellular enzymes, SGTP, and SGOT, which are elevated in cellular rejection, were noted to decline toward normal levels following FK 506 therapy. The median TBIL at the initiation of FK 506 conversion was 3.7 mg/dl, while the median value was 1.2 mg/dl 1 month and later after initiation of FK 506. Similar findings were noted with the median SGOT and SGPT levels, those being 155 IU/ml and 287 IU/ml, respectively, prior to FK 506, and 51 IU/ml and 70 IU/ml, respectively, after FK 506 conversion.

The unmistakable success of FK 506 "rescue" in a patient who had previously received 5 liver transplants over a 5-year-period and who was undergoing further rejection was interrupted by the thrombosis of a previously stenosed hepatic artery on day 100 of FK 506 therapy. Examination of the arterial anastomosis revealed an anastomotic stricture. Microscopically, there was no evidence in the parenchyma of remaining cell-mediated rejection. A sixth liver transplant was placed, and the patient is currently successfully maintained on FK 506 (see Todo et al, this symposium).

Renal Function

Preexisting renal dysfunction was noted in 70% of patients due to primary kidney disease or to CyA. Two of these patients had previously undergone cadaveric renal transplantation in August and December of 1988. In both of these patients, cellular rejection and chronic fibrosis were seen in the kidney allograft biopsies, suggesting that both acute and chronic rejection of the kidney allografts were occurring.

At the time of FK 506 conversion, 9 patients had such severe renal failure, including hyperkalemia, that effective CyA therapy was not possible. All were native kidneys, although 1 patient had previously undergone a native right nephrectomy at the time of the third liver transplantation and had required hemodialysis in the posttransplant period. In 2 patients, who did not require hemodialysis, the creatinine and blood urea nitrogen (BUN) levels were markedly elevated prior to entry on FK 506. Six patients were already on hemodialysis at the time FK 506 therapy was started.

Because of the heterogeneity of the kidneys being studied and the confounding factor or prior treatment with CyA, the nephrotoxicity of FK 506 could not be accurately ascertained. An adverse effect of FK 506 on renal function in these patients appeared to be directly related to the interactions of FK 506 with CyA. It has been found that creatinine clearance is compromised

in patients with CyA, and that FK 506 may augment CyA nephrotoxicity (see McCauley et al, this symposium). With the elimination of CyA and the disappearance of detectable levels of CyA, a fall in BUN and creatinine levels was usually noted. Three of the 6 patients on hemodialysis have actually recovered renal function while on FK 506 and do not require further hemodialysis. One patient on FK 506 required institution of hemodialysis after bilateral renal vein thrombosis was diagnosed by ultrasound, but renal function returned in 3 weeks and the patient is currently off hemodialysis.

In 3 patients with poor renal function at the onset of FK 506, cadaveric renal transplantation was undertaken during the course of FK 506 therapy for persistent renal failure. One patient had a serum creatinine of 2.4 mg/dl and hyperkalemia of 6 mEq/L. She underwent transplantation on day 24 of FK 506 therapy, 10 days after discontinuation of CyA, using an en bloc set of kidneys from a 22-month-old donor. The kidneys functioned immediately, and the creatinine level has been between 1.4 and 1.8 mg/dl for more than 7 months. In the second patient, in whom renal function was markedly diminished at the onset of FK 506 therapy, renal transplantation was performed for symptoms of uremia. This patient received a kidney transplant from a 52-year-old donor. Both kidneys from this donor experienced acute tubular necrosis, necessitating hemodialysis following transplantation in both recipients (the mate recipient being transplanted under standard CyA and steroids). The recipient receiving the mate kidney had hemorrhage from the arterial suture line during the second postoperative week and succumbed to a myocardial infarction. The cause of the hemorrhage was thought to be due to a mycotic aneurysm. In the patient on FK 506, prolonged ATN was also experienced, but renal function returned, liberating the patient from hemodialysis. Thirty-one days after renal transplantation, and 79 days after FK 506 therapy, she had a bleed from a mycotic aneurysm and required emergency allograft nephrectomy. The removed kidney had no evidence of cellular rejection and appeared normal. This patient is currently being maintained on hemodialysis. The third patient, with a baseline creatinine clearance of 20 ml/hr, received a cadaveric kidney for symptoms of uremia. Her serum creatinine has been 0.7 mg/dl on FK 506.

Adverse Reactions

The details of FK 506-associated side effects are discussed elsewhere (Shapiro et al, this symposium). The most common side effect of intravenous FK 506 administration was headache, occurring in 70% of patients. The headaches responded to symptomatic treatment and did not require a reduction in dosage. Switching to oral administration relieved the headache in all patients.

The next most frequent side effects of intravenous therapy were nausea (65%) and vomiting (35%). Treatment consisted of antiemetics. Spontaneous resolution of these symptoms occurred in all but one patient, in whom persistent symptoms were attributed to uremia. With intravenous therapy, anorexia was mild and seen in all but two patients, generally associated with the nausea. Oral intake was adequate in all patients.

No adverse hemodynamic changes, such as hypotension or cardiac changes, were noted during the oral or intravenous administration of FK 506 (see Kang et al, this symposium). In all patients who had hypertension while on CyA alone, antihypertensive medications were eliminated or reduced.

Other side effects seen with intravenous FK 506 were a feeling of warmth (61%) and flushing (16%). Less frequent side effects were rash (10%), chest pain (without electrocardiographic changes) (10%), anxiety (10%), and abdominal cramping, night sweats, fatigue, photophobia, and blurred vision (all less than 5%). These symptoms were also markedly reduced following oral conversion of FK 506. A total of 74% of patients experienced no further side effects.

Hyperkalemia was seen in 35% of patients following administration of FK 506. Treatment was initiated with potassium-binding resins and potassium-restricted diets. Investigation into the cause of hyperkalemia suggested that the mechanism is similar to that seen in CyA hyperkalemia, with adrenal suppression of mineralocorticoid synthesis. Addition of a synthetic mineralocorticoid, fludrocortisone, relieved the hyperkalemia in all of these patients (see McCauley et al, this symposium).

Mortality

In this population of compromised patients, a total of 6 deaths was encountered (15%). In 1 patient, who was removed from the study, fulminant hepatic failure from hepatitis B progressed. Emergency retransplantation was performed, but she died 2 days later from suppurative bacterial pneumonia. At autopsy, there was no evidence of vasculitis, and her renal allograft did not appear to have any toxicity related to FK 506.

The second patient was started on FK 506 with pathologic findings of late chronic rejection. These changes could not be reversed with FK 506. She died of technical causes during an attempted retransplantation.

Four patients had systemic sepsis at the time of entry into the FK 506 rescue protocol. Each of these patients succumbed to multiple organ failure from sepsis. One patient was a 56-year-old man with a diagnosis of Laennec's cirrhosis. He underwent his first liver transplant, but required retransplantation on the third day. His posttransplant course was complicated by drainage of intraabdominal abscesses and renal failure. He was started on FK 506 on the 15th day following his initial transplant. Despite further drainage of abscesses, he died 15 days following institution of FK 506.

The second patient was a 52-year-old woman with non-A-non-B chronic active hepatitis. She was febrile at the time of transplantation, and pancytopenic with a marked coagulopathy. Postoperatively, she continued to be febrile and remained intubated, eventually requiring a tracheostomy. She remained pancytopenic, with renal failure. She was started on FK 506 on the 12th posttransplant day and, 6 days later, she died from multiorgan failure. At autopsy, the liver was normal, and no specific cause of death was identified. No vasculitis was found.

The third septic patient was a 33-year-old woman with a diagnosis of fulminant hepatitis A. She was noted to have developed severe hemorrhagic pancreatitis at the time of transplantation and was taken back to the operating room on the fourth posttransplant day for debridement of a pancreatic abscess. She was oliguric throughout the posttransplant period, requiring hemodialysis. She was placed on FK 506 on the fifth posttransplant day, but remained ventilator dependent, with thrombocytopenia requiring platelet transfusions until she developed a intrapulmonary hemorrhage and died on the 31st postoperative day.

The last septic patient was a 43-year-old woman with end-stage lung disease. She underwent double lung transplantation and was ventilator-dependent. She was found to have chronic end-stage liver disease after her lung transplantation and, 1 month later, she underwent liver transplantation. During the fourth week after the liver transplantation, she developed severe cytomegalovirus colitis, requiring total colectomy. She became oliguric, requiring hemodialysis and, on the 39th day following liver transplantation (10 weeks after the double lung transplantation), she was started on FK 506. Her deteriorating liver function stabilized but she was found to have a clotted portal vein when a routine ultrasound was performed during the second week of FK 506 therapy. She died on the 23rd day of FK 506 therapy.

Pharmacologic Monitoring

Pharmacokinetic data of FK 506 are being presented elsewhere in this symposium (see Jain et al and Venkat et al). A prolongation of the half-life of CyA elimination was noted in patients who received both FK 506 and CyA. In effect, this increased serum trough levels of CyA and subsequently enhanced the toxicity of both drugs, even when CyA had been discontinued.

DISCUSSION

The phase I/II trials began in a population of patients with refractory complications due to CyA, including rejection, hypertension, nephrotoxicity, and steroid toxicity. In this high-risk group of patients, many who have received azathioprine, OKT3, and high doses of steroids, the beneficial effect of FK 506 was not expected to be a major one. Yet, over 70% of patients treated by conversion to FK 506 had both clinical and histopathologic responses. Marked improvement in biochemical parameters was noted in a majority of patients. Those patients who did not respond to FK 506 conversion had histopathologic evidence of end-stage chronic rejection, with obliteration of vascular lumen and total disappearance of intrahepatic bile duct structures. Nevertheless, a number of patients with marked liver function abnormalities responded by returning to normal levels. This phenomenon, not seen before with patients on CyA, OKT3, or azathioprine, may be related to a hepatotrophic effect of FK 506 on the liver (see Francavilla et al and Mazzaferra et al, this symposium). While it is tempting to speculate on the possible role of FK 506 on reparative processes following control of rejection, further investigations in this area are necessary.

The nature of the high-risk patients in this study was exemplified by 6 deaths (4 of whom were in intensive care unit settings) in patients who were dependent on respiratory support and were also septic at the time of FK 506 initiation. Yet, in other patients who were equally disadvantaged, FK 506 was able to reverse renal failure and maintain normal liver function.

The several side effects seen among the first human subjects were related to the intravenous infusion, and promptly ceased with oral conversion. Many patients also commented on a sense of well being, noting that they felt better after stopping CyA and beginning FK 506 therapy. Side effects of chronic CyA administration, hirsutism, gingival hyperplasia, and tremors, were eliminated or minimized by FK 506 therapy. It is noted elsewhere in this symposium that FK 506 also lowered serum cholesterol levels, and was not associated with elevation of serum uric acid levels (see Van Thiel et al, this symposium). Other side effects reported in animals but not seen in humans are vasculitis, elevations in blood sugar, and cataracts.

Other side effects are possible in humans, but only long-term follow-up will address this question. Side effects related to any potent immunosuppressive agent include susceptibility to opportunistic infections (see Alessiani et al, this symposium), lymphoproliferative diseases, and other de novo malignancies.

Finally, detailed pharmacokinetics enabled us to determine that combination immunosuppression with FK 506 and CyA was accompanied by elevations in serum creatinine and serum urea nitrogen, which fell after elimination of cyclosporine (see McCauley et al, this symposium). We had hoped that FK 506 and CyA would be synergistic, but the synergism proved to be toxic reactions, making these agents incompatible.

In conclusion, this study was performed to evaluate the efficacy, safety, and side effects of FK 506 in patients who had CyA-related complications, including a failure to control rejection. Patients were maintained on FK 506 for periods up to 7 months with minimal side effects, providing CyA was not continued.

This trial has had a major effect in liver transplantation. The qualities of FK 506 in this clinical trial, in which FK 506 was used as a "rescue" drug, have demonstrated marked clinical efficacy. Information gathered regarding dosage schedules, routes of elimination, and other pharmacokinetic data have enhanced the value of this drug in clinical practice. Untoward side effects were carefully looked for, and occurred at a low frequency.

FK 506 can be used to decrease or eliminate CyA-related complications while preserving adequate immunosuppression. In the long run, this may delay or prevent the necessity for retransplantation, and/or greatly reduce complications of CyA. FK 506 and CyA cannot be used together, at least with the dose schedules followed in this trial.

Acknowledgments

References

1. Starzl TE, Demetris AJ, Van Thiel D. N Engl J Med 1989;391:1014, 1092. [PubMed: 2674716]
2. McCauley, J.; Van Thiel, DH.; Starzl, TE., et al. Nephron. (in press)
3. Goto T, Kino T, Hatanaka H, et al. Transplant Proc 1987;19(suppl 6):4. [PubMed: 2445072]
4. Kino T, Hatanaka H, Hashimoto M, et al. J Antibiot 1987;40:124. [PubMed: 3558113]
5. Kino T, Hatanaka H, Miyata S, et al. J Antibiot 1987;40:1256. [PubMed: 2445722]
6. Ochiai T, Nakajima K, Nagata M, et al. Transplant Proc 1987;19:1284. [PubMed: 2484094]
7. Todo S, Demetris AJ, Ueda Y, et al. Transplant Proc 1987;19(suppl 6):57. [PubMed: 2445076]
8. Todo S, Podesta L, ChapChap P, et al. Transplant Proc 1987;19(suppl 6):64. [PubMed: 2445079]
9. Murase N, Todo S, Lee PH, et al. Transplant Proc 1987;19(suppl 6):71. [PubMed: 2445081]
10. Ochiai T, Nagata M, Nakajima K, et al. Transplantation 1987;44:729. [PubMed: 2447688]
11. Ochiai T, Nakajima K, Nagata M, et al. Transplantation 1987;44:734. [PubMed: 2447689]
12. Collier DS, Thiru S, Calne R. Transplant Proc 1987;19:62. [PubMed: 2445077]
13. Calne R, Collier DS, Thiru S. Transplant Proc 1987;19:63. [PubMed: 2445078]
14. Starzl, TE.; Makowka, L.; Todo, S., editors. Transplant Proc. Vol. 19. 1987. p. 3
15. Todo S, Ueda Y, Demetris JA, et al. Surgery 1988;104:239. [PubMed: 2456627]
16. Todo S, Demetris A, Ueda Y, et al. Surgery 1989;106:444. [PubMed: 2474865]
17. Zeevi A, Duquesnoy R, Eims G, et al. Surg Res Comm 1987;1:315.
18. Zeevi A, Duquesnoy R, Eiras G, et al. Transplant Proc 1987;19:40. [PubMed: 2445073]
19. Starzl TE, Todo S, Fung J, et al. Lancet 1989;2:1000. [PubMed: 2478846]
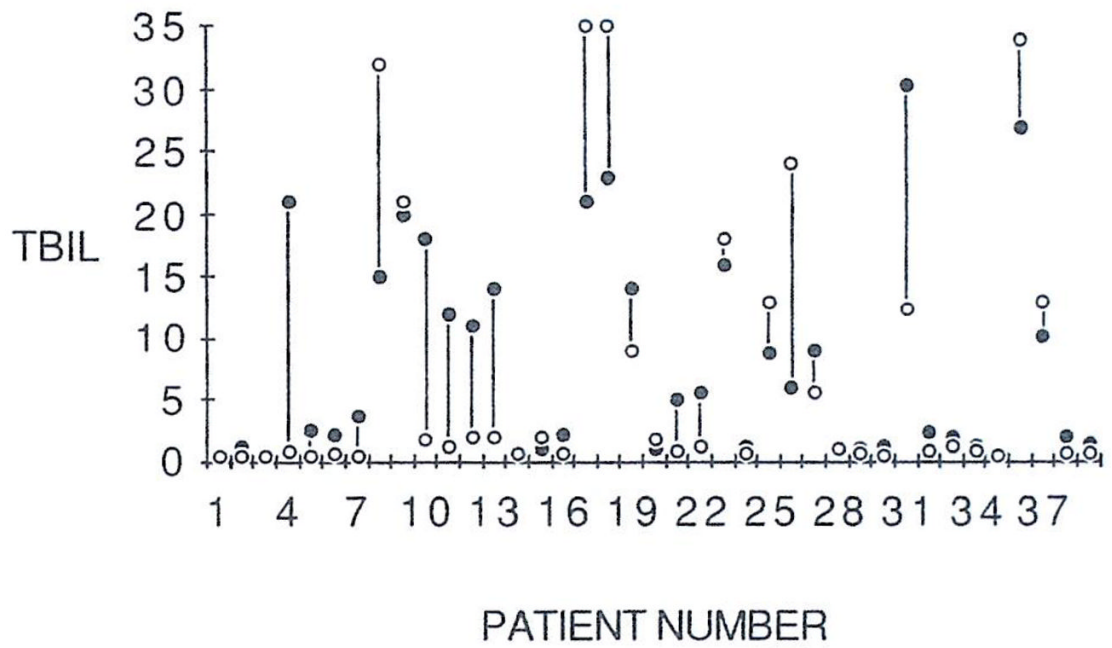
Fig 1.
Pretreatment and posttreatment values of total bilirubin in the 39 patients are shown. Closed circles indicate pretreatment values and open circles indicate posttreatment values.

Fig 2.
Pretreatment and posttreatment values for SQOT (IU/ml) are shown for the 39 patients. Closed circles indicate pretreatment values and open circles indicate posttreatment values.

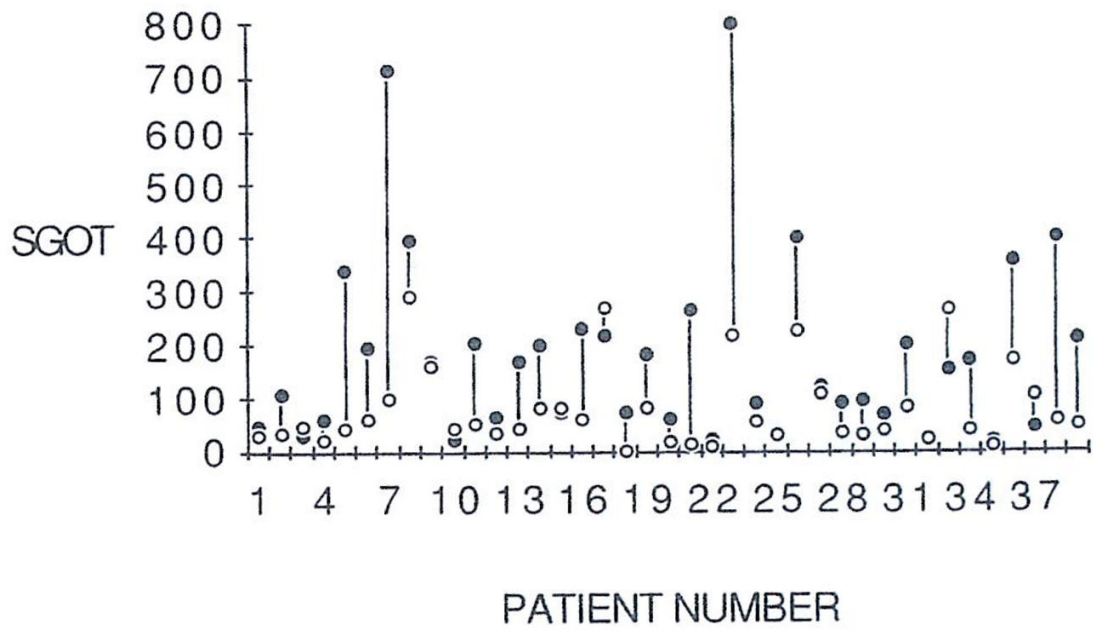**Fig 3.**
Pretreatment and posttreatment values for SGPT (IU/ml) are shown for the 39 patients. Closed circles indicate pretreatment values and open circles indicate posttreatment values.
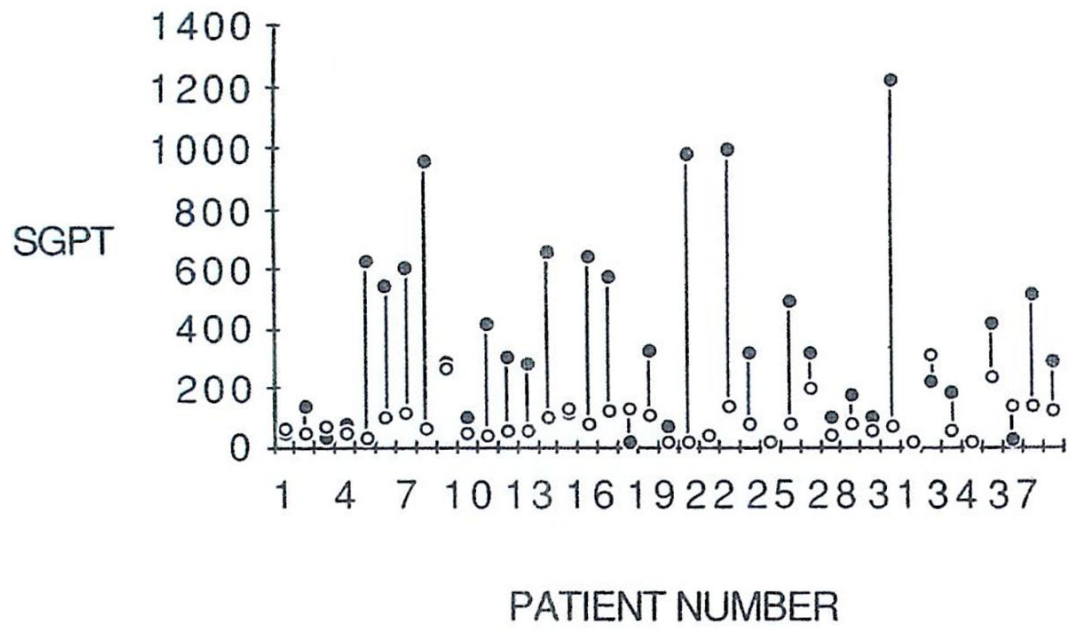
Table 1

FK 506 Patient Data

Patient No.	Date of Entry	Age (yr)	Sex	Type of Treatment	Date of Treatment	Original Disease, Cause of Graft Loss, and Indication for FK 506	Graft Function?	Cause of Graft Loss or Patient Death
1	3/1/89	27	F			Cryptogenic cirrhosis		
				OLTX#1	7/2/85	Chronic rejection	No	
				OLTX#2	12/28/87	Chronic rejection	No	
				OLTX#3	6/29/89	Acute rejection	Yes	
				CRT#1	3/27/89	Primary	Yes	
2	3/25/89	38	M			Sclerosing cholangitis		
				OLTX#1	11/9/83	Primary nonfunction	No	
				OLTX#2	11/14/83	Chronic rejection	No	
				OLTX#3	12/6/85	Hepatic artery thrombosis	No	
				OLTX#4	2/16/86	Chronic rejection	No	
				OLTX#5	1/1/89	Acute rejection	No	Hepatic artery thrombosis
				OLTX#6	7/2/89	Primary	Yes	
3	4/4/89	31	F			Autoimmune lupoid hepatitis		
				OLTX#1	6/26/84	Chronic rejection	No	
				OLTX#2	11/18/87	Acute rejection	Yes	
						Lupus nephritis		
				CRT#1	8/18/88	Chronic rejection	No	Chronic rejection
				CRT#2	5/21/89	Primary	No	Mycotic aneurysm
4	4/8/89	43	F			Polycystic liver/kidney disease		
				OLTX#1	11/22/88	Fulminant hepatic failure	No	Death, liver failure
				CRT#1	11/22/88	Chronic rejection	No	
5	6/3/89	42	M			Cryptogenic cirrhosis		
				OLTX#1	4/30/89	Acute/chronic rejection	Yes	
6	6/30/89	31	F			Cryptogenic cirrhosis		
				OLTX#1	12/2/82	Acute rejection	Yes	
				CRT#1	10/19/89	Primary	Yes	
7	7/1/89	44	M			Sclerosing cholangitis		
				OLTX#1	6/15/86	Chronic rejection	Yes	

Patient No.	Date of Entry	Age (yr)	Sex	Type of Treatment	Date of Treatment	Original Disease, Cause of Graft Loss, and Indication for FK 506	Graft Function?	Cause of Graft Loss or Patient Death
8	7/8/89	18	F	OLTX#1	5/13/86	ESLD secondary to toxic shock / Chronic rejection	No	
				OLTX#2	7/8/86	Acute rejection	Yes	
9	7/30/89	63	F	OLTX#1	5/8/89	Cryptogenic cirrhosis / Chronic rejection	No	Death, operative
10	8/2/89	36	M	OLTX#1	7/10/89	Sclerosing cholangitis / Chronic rejection	No	Chronic rejection
				OLTX#2	8/29/89	Primary	Yes	
11	8/10/89	45	F	OLTX#1	7/28/89	Sclerosing cholangitis / Acute rejection	Yes	
12	9/8/89	26	M	OLTX#1	8/27/89	Budd-Chiari / Acute rejection	Yes	
13	9/14/89	60	M	OLTX#1	9/10/89	Laennec's cirrhosis / Acute rejection	Yes	
14	9/16/89	64	F	OLTX#1	9/14/89	Non-A–non-B hepatitis / Primary nonfunction	No	
				OLTX#2	9/16/89	Primary/renal failure	Yes	
15	9/16/89	64	M	OLTX#1	9/16/88	Laennec's / Primary nonfunction	No	
				OLTX#2	9/18/88	Acute rejection	Yes	
16	9/20/89	56	M	OLTX#1	8/29/87	Primary biliary cirrhosis / Primary	Yes	
17	9/20/89	30	M	OLTX#1	9/16/88	Non-A–non-B hepatitis / Primary nonfunction	No	
				OLTX#2	9/25/88	Chronic rejection	Yes	
18	9/21/89	61	F	OLTX#1	5/29/89	Non-A–non-B hepatitis / Chronic rejection	No	Chronic rejection
				OLTX#2	10/1/89	Primary	Yes	
19	9/21/89	56	M	OLTX#1	9/6/89	Laennec's cirrhosis / Primary nonfunction	No	
				OLTX#2	9/8/89	Rejection, renal failure	No	Death, sepsis

Patient No.	Date of Entry	Age (yr)	Sex	Type of Treatment	Date of Treatment	Original Disease, Cause of Graft Loss, and Indication for FK 506	Graft Function?	Cause of Graft Loss or Patient Death
20	9/21/89	48	F	**OLTX#1**	4/3/87	Non-A–non-B hepatitis / Chronic rejection	Yes	
21	9/22/89	31	M	**CLUS#1**	12/1/88	Cholangiocarcinoma / Renal failure	Yes	
22	9/22/89	56	M	**OLTX#1**	9/9/89	Laennec's cirrhosis/hepatoma / Acute rejection	Yes	
23	9/22/89	59	F	OLTX#1	8/27/89	Primary biliary cirrhosis / Primary nonfunction	No	
				OLTX#1	8/29/89	Rejection, renal failure	Yes	
24	9/22/89	64	M	**OLTX#2**	9/15/89	Non-A–non-B hepatitis / Acute rejection	Yes	
25	9/22/89	6	F	**OLTX#1**	12/9/89	Alagille's syndrome / Acute rejection	Yes	
26	9/23/89	52	F	**OLTX#1**	9/12/89	Non-A–non-B hepatitis / Renal failure	No	Death, sepsis
27	9/23/89	33	F	**OLTX#1**	9/19/89	Hepatitis A / Rejection, renal failure	No	Death, sepsis
28	9/25/89	20	F	**OLTX#1**	6/7/89	Hepatitis B / Chronic rejection	Yes	
29	9/26/89	46	F	OLTX#1	6/20/89	PBC/scleroderma / Acute rejection	No	
				OLTX#2	7/17/89	Renal failure	Yes	
30	9/26/89	31	M	**OLTX#1**	5/5/84	Non-A–non-B hepatitis / Chronic rejection	Yes	
31	9/27/89	44	M	**OLTX#1**	12/9/85	Non-A–non-B hepatitis / Acute rejection	Yes	
32	9/27/89	63	M	**OLTX#1**	9/13/89	Laennec's cirrhosis / Chronic rejection	Yes	
33	9/27/89	34	M	**OLTX#1**	1/22/89	Laennec's cirrhosis / Rejection, HUS	Yes	
34	9/27/89	62	F			Cryptogenic cirrhosis		

Patient No.	Date of Entry	Age (yr)	Sex	Type of Treatment	Date of Treatment	Original Disease, Cause of Graft Loss, and Indication for FK 506	Graft Function?	Cause of Graft Loss or Patient Death
35	9/28/89	31	M	**OLTX#1**	9/23/89	Acute rejection	Yes	
						Sclerosing cholangitis		
36	9/28/89	64	F	**OLTX#1**	6/21/88	Chronic rejection	Yes	
						Primary biliary cirrhosis		
37	9/28/89	74	M	**OLTX#1**	3/13/89	Steroid toxicity	Yes	
						Non-A–non-B hepatitis		
				OLTX#1	5/11/89	Primary nonfunction	No	
				OLTX#2	5/14/89	Chronic rejection	Yes	
38	9/29/89	43	F			Laennec's cirrhosis		
				OLTX#1	8/21/89	Acute rejection	No	Death, sepsis
				LUTX#1	7/12/89	Chronic rejection	No	
39	9/29/89	40	M			Non-A–non-B hepatitis		
				OLTX#1	12/11/87	Chronic rejection	Yes	
40	9/29/89	5	F	**OLTX#1**	8/24/89	Acute rejection	Yes	
						Biliary atresia		

OTLX, orthotopic liver transplant; CRT, cadaveric renal transplant; LUTX, lung transplant; ELSD, end-stage renal disease; PBC, primary biliary cirrhosis; HUS, hemolytic uremic syndrome.

Table 2

Conversion Protocol for Patients on CyA to FK 506

		Dose		
First 11 patients				
FK 506	0	.15 mg/kg/d IV × 3 d	.30 mg/kg/d PO × 11 d	.30 mg/kg/d PO
CyA[*]	100%	50%	30%	0%
Next 29 patients				
FK 506	0		.15 mg/kg/d IV × 1 d	.30 mg/kg/d PO
CyA	100%	0%	0%	0%

[*] Expressed as a percentage of baseline CyA dose.