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## Current Status of FK 506 in Liver Transplantation

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In 1987 Ochiai and coworkers presented a report on the immunosuppressive qualities of a new immunosuppressive agent, FK 506, isolated from the fermented broth of a soil fungus, *Streptomyces tsukubaensis*.<sup>1</sup> Extensive in vitro studies demonstrated the effectiveness in suppressing mixed lymphocyte cultures, presumably by inhibiting IL-2 synthesis following alloactivation.<sup>2</sup> The receptor for FK 506 has been identified and has been characterized as a peptidyl-prolyl *cis-trans* isomerase.<sup>3</sup>

The background for the clinical development of FK 506 was well documented by Starzi in the opening remarks of a satellite symposium on FK 506, held in Barcelona, Spain, in November 1989 as part of the European Society of Organ Transplantation.<sup>4</sup> In vivo studies using a number of animal models have shown a marked ability to prevent rejection following various types of organ transplants.<sup>5-7</sup> More interestingly, FK 506 possesses the ability to reverse ongoing rejection in animal models.<sup>7,8</sup> This characteristic is unique, since it is well known that cyclosporine (CyA) will not reverse established ongoing rejection. These properties served as the initiative to pursue clinical testing of FK506.

The objective of this report is to update the reader on the current status of the use of FK 506 in liver transplantation at the University of Pittsburgh. One phase of the study consists of the “rescue” with FK 506 of liver allografts undergoing rejection with CyA-based immunosuppression.<sup>9</sup> The second phase of the report consists of the results of primary liver transplantation using FK 506.<sup>10</sup>

## METHODS

### Study Design

The trials in liver transplantation were conducted at the University of Pittsburgh, Presbyterian University Hospital, Children’s Hospital of Pittsburgh, and the Veterans Administration Medical Center, with the approvals of the respective institutional review boards, informed consent was obtained from patients or their appointed guardians.

### Patient Profiles

In the rescue therapy study, 173 patients admitted for hepatic rejection were converted from CyA to FK 506. Fifty-seven patients were diagnosed with acute rejection, and 116 patients were diagnosed with chronic rejection. Most of the 173 rescue patients were bearing their first liver allograft at the time of the conversion from CyA to FK 506. A smaller number of patients had previously undergone more than one liver transplantation; one patient was carrying his

fifth liver transplant at the time of FK 506 conversion. In the primary FK 506-treated study, 125 patients received FK 506 and low-dose steroids as the baseline immunosuppression therapy after liver transplantation.

### Diagnostic Evaluations

For patients who were experiencing liver dysfunction, the final categorization of the dysfunction was based on clinical, biochemical, and histopathologic findings. For all patients, in both the primary and rescue therapy groups, the cause or causes of liver dysfunction were carefully sought. 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. Appropriate viral cultures and stains were used to detect viral infections. Protocol biopsies were employed to evaluate the efficacy of FK 506 therapy. All biopsies were blinded and interpreted by a single experienced liver pathologist (A.J.D.). Biopsy specimens were fixed in neutral buffered formalin and stained with hematoxylin-eosin, trichrome, and reticulin stains. The criteria used for pathologic diagnosis have been clearly defined in previous reports.<sup>11</sup>

### Timing and Details of Therapy

Treatment with FK 506 was begun in the hospital and was given initially as a parenteral dose, followed by conversion to an oral dose. The initial parenteral dose of FK 506 was 0.075 to 0.15 mg/kg, given intravenously over a period of 4 hours. This treatment was continued until the patient was able to ingest the oral form of FK 506. Generally, oral dosage of FK 506 was 0.30 mg/kg, divided into two doses. Doses of FK 506 were adjusted on the basis of serum trough levels monitored by ELISA<sup>12</sup> as well as clinical or biochemical variables.

### Evaluation of Response

Periodic liver function tests, including total bilirubin (TBIL), serum glutamic transaminases (SGOT and SGPT), and alkaline phosphatase levels were performed. All values are expressed as the mean  $\pm$  SD. Protocol biopsies were obtained after initiation of FK 506 therapy.

## RESULTS

### Rescue Therapy

In this population of 173 patients, many of whom were critically ill at the time of FK 506 conversion, a total of 14 deaths were encountered (8.1%). The causes of death were numerous, but the incidence of mortality was directly correlated with the medical condition of the patient at the time of FK 506 conversion. Sepsis was the cause of death in four patients. Three patients died from metastatic carcinoma following transplantation. In two patients, retransplantation was not considered an option for the failing liver allograft. Three patients died with hemorrhagic complications. One patient with pathologic findings of late chronic rejection died from technical causes during an attempted retransplantation. In one death, no clear cause could be determined. This patient died at home and had been off FK 506 for 4 months when she died.

The biochemical response of the liver allografts to FK 506 is reported by classification of patients as having either acute or chronic rejection. Figure 1 shows the total bilirubin and Fig 2 shows the transaminase levels for the 57 patients who were treated for acute rejection. These levels were documented by liver biopsy or as judged by biochemical and clinical variables. The TBIL, SCOT, and SGPT levels prior to FK 506 were  $4.68 \pm 5.91$  mg/dL,  $240 \pm 431$  IU/L, and  $292 \pm 383$  IU/L, respectively. By the sixth month these values dropped to  $0.76 \pm 1.41$  mg/dL,  $98 \pm 163$  IU/L, and  $90 \pm 128$  IU/L, respectively.

Patients with an entrance diagnosis of chronic rejection also had a beneficial response to FK 506. Figure 3 shows the total bilirubin and Fig 4 shows the transaminase levels for the 116 patients treated for this specific indication. The total bilirubin decreased to normal values (pre-FK 506,  $5.07 \pm 8.16$  mg/dL; after 6 months,  $0.99 \pm 1.47$  mg/dL) while the average transaminase values were still slightly above normal values (pre-FK 506, SGOT/SGPT,  $200 \pm 175/275 \pm 223$  IU/L; after 6 months, SGOT/SGPT,  $44 \pm 72/101 \pm 68$  IU/L).

In each case where histopathologic changes were predominant, the influence of FK 506 on the initial findings of rejection or hepatitis could be evaluated in serial follow-up biopsies. Overall, 17% of the biopsies with a diagnosis of rejection showed worsening of the pathology; 36% of the liver biopsies showed no pathologic changes between the pre-FK 506 biopsy and the 2-month follow-up biopsy; and 47% of the remaining biopsies showed improvement between the initial and follow-up biopsies. These changes were particularly impressive in patients whose pretreatment biopsies contained bile duct lesions that generally progress to bile duct disappearance and graft loss, despite intensive immunosuppression.

### Primary FK 506 Treatment After Liver Transplantation

Ten of the 125 patients died, for a survival rate of 92% after 6 to 12 months. When compared with 325 sequential liver transplantations during the preceding year before FK 506, the results are significantly better statistically in terms of patient and graft survival (Fig 5). This trend was seen in both the adult population (110 patients) and the pediatric population (15 patients), although the number of pediatric patients in the trial was too small to achieve statistical significance. Of the 10 deaths, 5 were due to sepsis, 1 to heart failure, 1 to a cerebral vascular accident, 2 to nonreversible hepatic coma, and 1 to technical complications.

During the follow-up period, 50% of all recipients were taken off steroids and were maintained on single-drug immunosuppression with FK 506. Yet 52.8% of all patients were rejection-free during the entire period of study. Most of the rejection episodes were mild and easily controlled with a single dose of bolus steroids (either methylprednisolone or hydrocortisone). Only 17.8% of the rejection episodes required further steroid treatment in the form of a steroid taper or additional steroid boluses. In addition, only 11.2% of the patients required OKT3. The incidence of serious infections, despite the potency of FK 506, has not appeared to be alarming. The incidence of serious infections was about 50% less than seen in a historical group of patients given CyA. Of note is that the incidence of cytomegalovirus infections did not appear to be increased when compared with patients on CyA.

## DISCUSSION

Cyclosporine-based immunosuppression significantly enhanced both patient and graft survival, when compared with the era of azathioprine and steroids.<sup>13</sup> Nevertheless, most centers experience a 40% to 50% 1-year graft loss and 25% to 30% patient within the first-year loss. The most common complicating factor has been the development of rejection, occurring in over 70% of all CyA-treated patients. In addition, the sequela caused by overimmunosuppression, such as the excessive use of steroids or anti-lymphocyte preparations, have a high incidence of infectious complications. It stands to reason that a baseline immunosuppressive agent that allows a lower incidence and easier treatment of rejection would decrease both graft and patient loss. From the results of our preliminary studies presented here, the use of FK 506 in liver transplantation has these advantages. The use of FK 506 appears not only to decrease the absolute incidence of rejection episodes, allowing a marked reduction in steroid doses, but also to make the treatment of rejection much simpler. The requirement for OKT3 in liver transplantation has decreased by 50%.

The ability of a new immunosuppressive agent to be dose-adjustable for treatment of acute and chronic rejection would represent an important facet, ascribed only to steroids in the past. Thus, FK 506 can be used in this manner. In fact, the first response to a developing rejection is to increase the baseline dose of FK 506. In rescue therapy, the marked ability of FK 506 to reverse both acute and chronic rejection has not been seen with any immunosuppressive agent in the past. While the mechanism by which FK 506 is able to do this is not known, it would appear that it would entail mechanisms other than simply inhibition of IL-2 synthesis. FK 506 has been shown to be a potent hepatotropic agent.<sup>14,15</sup> Liver allografts in end-stage chronic rejection can be rescued in 60% to 70% of the cases.<sup>9</sup>

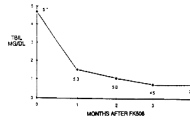
The Food and Drug Administration will require further substantiation of the efficacy of FK 506 in multicenter trials. Prospective, randomized trials comparing FK 506 therapy with CyA-based immunosuppression are currently underway. These studies will help identify areas in which FK 506 may be more advantageous, or more disadvantageous, than current methods of immunosuppression. A well-defined endpoint, other than patient or graft loss, should be utilized, since the data presented here also suggest that a conversion to FK 506 might salvage liver allografts in danger of being lost to rejection. Future trials examining the role of FK 506 in liver allograft rejection are being devised either separately from the primary trials or, perhaps, as part of the primary trials.

## Acknowledgments

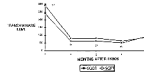
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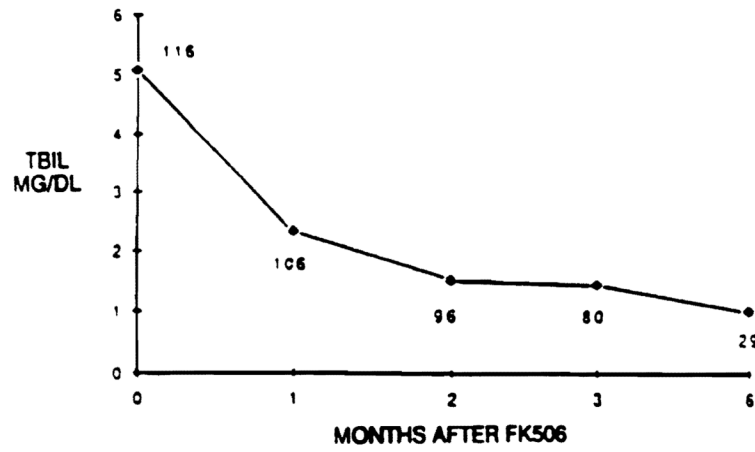
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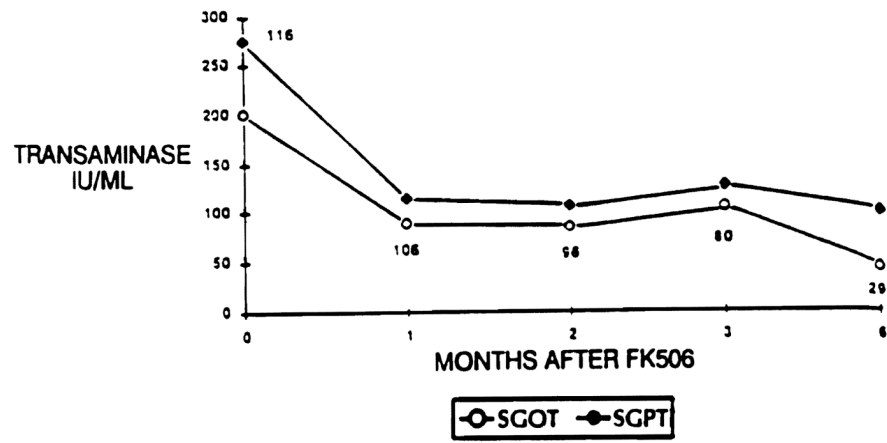
**Fig 1.**  
Total bilirubin values in 57 liver transplant recipients with acute rejection who were switched to FK 506 from cydosponne.



**Fig 2.**  
SGOT and SGPT values In 57 liver transplant recipients with acute rejection after conversion to FK 506.

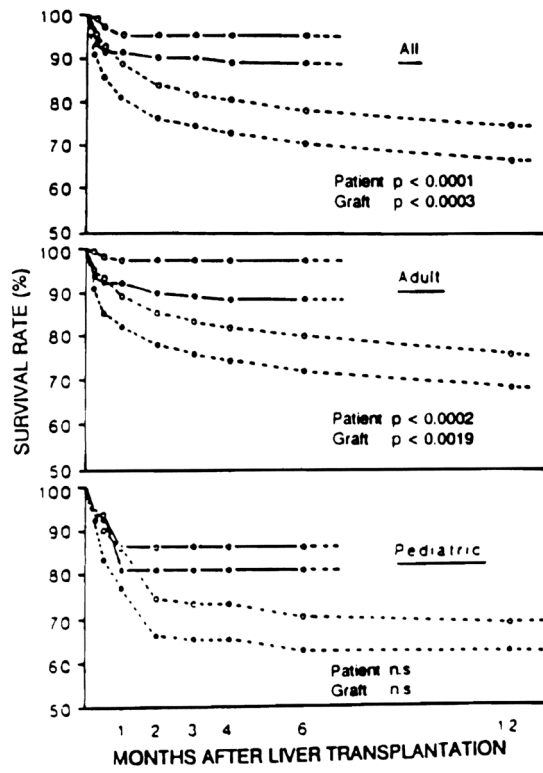


**Fig 3.** Total bilirubin values in 116 liver transplant recipients with chronic rejection who were switched to FK 506 from cyclosporine.



**Fig 4.** SGOT and SGPT values in 116 liver transplant recipients with chronic rejection after conversion to FK 506.





**Fig 5.** Life survival curves for primary liver transplantation recipients given FK 506 and cyclosporine.