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Conversion of Liver Allograft Recipients From Cyclosporine to FK 506-Based Immunosuppression: Benefits and Pitfalls

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CYCLOSPORINE (CyA) has been a major advance in the armamentarium of immunosuppressive agents used in clinical transplantation. The use of CyA and steroids has increased patient and graft survival in human transplantation.[1,2] Rejection continues to be the most common cause of retransplantation, and death is often a sequela of treatment of rejection. A number of adverse effects of CyA have been well defined; these include nephrotoxicity, hypertension, neurotoxicity, hirsuitism, and a number of less well-defined side effects. It has been suggested that this spectrum of side effects are related to a common pathway involving the cyclophyllin receptor.[3] 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, or other agents with concomitant reductions in the CyA dose. These methodologies have their inherent dangers: increased susceptibility to rejection, and increased susceptibility to infection, respectively.

FK 506 is a potent and novel immunosuppressive agent. At the Second International Workshop on FK 506, held in Barcelona, Spain in October 1989, an initial report on the use of FK 506 for conversion of patients with CyA failure to FK 506 was given. This report included the plan to administer FK 506 to 40 patients who were rejecting their liver grafts in spite of conventional immunosuppression.[4] The initial protocol was to combine low doses of FK 506 with CyA, which was attempted in the early experience; however, 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 a detailed account of the first 246 liver transplant recipients converted from CyA, steroids, and/or azathioprine to FK 506 with or without low-dose steroids. The results are analyzed by indications for entrance into the protocol.

PATIENTS AND METHODS

Study Design

This trial was conducted at the University of Pittsburgh, Presbyterian-University Hospital, Children's Hospital, and the Veterans Administration Medical Center (Pittsburgh, PA), with the approval of the respective institutional review boards. Informed consent was obtained from patients or their appointed guardians. The accrual period for this study began on February 28,

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1989, and continued to May 31, 1990. A minimum follow-up period of 2 months was obtained on all patients. The median follow-up period was 240 days.

Patient Profiles

Two hundred forty-six patients were entered in the study. During this period, 15 other patients were converted to FK 506 from CyA at the time of retransplantation, and these results have been reported elsewhere.[5] Of the 246 patients converted to FK 506, 27 patients received their liver allografts at centers other than the University of Pittsburgh, but were subsequently accepted for FK 506 therapy.

Most of the 246 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 previous liver transplant. One patient was carrying his fifth liver transplant at the time of FK 506 conversion (Table 1).

The median time from transplantation to FK 506 conversion was 19 months (range, 0.1 to 78 months). The clinical profiles of the patients are shown in Table 1. The median age was 42 years (range, 1 to 66 years). The sex distribution of the 246 patients was 124 males and 122 females.

Indications

The original diagnoses of the 246 patients are shown in Table 1. Most of the patients had cryptogenic cirrhosis or postnecrotic cirrhosis due to non-A, non-B hepatitis. Cholestatic cirrhosis and alcoholic cirrhosis made up the major remainder of indications.

All patients switched to FK 506-based immunosuppression had an entry diagnosis of liver allograft dysfunction and/or other complications related to CyA, ie, renal dysfunction, hypertension, severe neurotoxicity, or complications related to severe steroid toxicity. Cyclosporine-related complications were defined as renal failure (a serum creatinine >2.0 mg/dL) and/or postoperative hypertension (diastolic blood pressure > 100 despite antihypertensive medications). Steroid toxicity was defined as steroid-induced osteoporosis resulting in multiple bony fractures or morbid obesity. Prior to conversion to FK 506, maintenance immunosuppression in all patients was with CyA and prednisone, with or without azathioprine. Cyclosporine doses had been maximized to tolerable levels, as limited by renal dysfunction or hypertension. Seventy percent of the patients had received at least one course of OKT3 prior to conversion to FK 506. These patients were, therefore, considered treatment failures of conventional immunosuppression.

The indications for FK 506 conversion are shown in Table 1. In several instances, more than one coexistent indication was present. When possible, the indication that most severely affected the patient was used to classify the patient. Rejection was the indication for treatment in 177 patients. Acute rejection was seen in 64 allografts (referred to as “acute rejection”). Chronic rejection was seen in 113 allografts (referred to as “chronic rejection”). A predominantly hepatitic component was seen in 11 patients (referred to as “hepatitis”). Coexistent hepatitis was seen in another 26 patients who also had an element of rejection (eight for “acute rejection/hepatitis” and 18 for “chronic rejection/hepatitis”). Twenty-six liver allograft recipients were converted to FK 506 in the attempt to control the side effects of CyA and steroid therapy (referred to as “nonhepatic indications”). Fourteen of these patients were converted purely for renal failure, seven patients were converted for severe steroid-associated complications, three patients were converted for refractory hypertension related to CyA, and two patients were converted for severe neurotoxicity.

Diagnostic Evaluations

The indications for conversion were based on clinical, biochemical, and histopathologic diagnoses. 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.

Biopsies were performed at the initiation of FK 506 therapy, and at 2 months following FK 506 conversion. Liver biopsies were performed in all but 10 patients prior to entry. Six patients had markedly abnormal coagulation parameters, making a liver biopsy unsafe. Four patients did not undergo biopsy, their entrance criterion being steroid toxicity. An important criterion for entry was the blinded pathologic interpretation of the liver biopsy by a single experienced liver pathologist (A.J.D.). Biopsy specimens were fixed in neutral-buffered formalin and routinely stained with hematoxylin and eosin, trichrome, and reticulin stains.

The following histologic criteria were used for the pathologic diagnosis of acute hepatic rejection:

1. A predominantly mononuclear portal tract infiltrate in which the inflammatory infiltrate consisted of 50% to 60% mononuclear cells intermixed with polymorphonuclear cells and eosinophils.
2. Characteristic localization of the inflammatory cells around and beneath the swollen endothelium of portal capillaries and small veins, with infiltration and damage of the epithelium of small bile ductules. The number of damaged bile ductules and the degree of damage generally increased with time. The most severe changes, with ductular loss, were seen in chronic rejection.
3. Absence of histologic findings suggestive of hepatitis.

A diagnosis of chronic hepatic rejection was made if there was evidence of the following:

1. the obliterative arteriolar lesions that have been found in the liver as well as other solid organs,[1,6]
2. loss of intrahepatic bile ducts, often with only a mild periductal and intraductal chronic inflammatory infiltrate,
3. portal fibrosis, especially if linkage had occurred between portal tracts or central veins, and
4. absence of lobular changes suggesting hepatitis.

A diagnosis of hepatitis was made if there was evidence of

1. Significant panlobular inflammation, piecemeal necrosis, cholangiolar proliferation, disarray with ballooning and spotty individual hepatocyte necrosis, and prominent lymphohistiocytic infiltration of the hepatic lobule with inflammatory cell destruction of hepatocytes. The foregoing are not prominent features of rejection under immunosuppression and suggest a diagnosis of viral hepatitis.
2. Positive staining for viral proteins, or positive growth of virus from liver biopsy specimens. In one 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 appeared positive 3 days following initiation of FK 506 treatment. Treatment with FK 506 was stopped.

When it was the clinician's opinion that the biopsy reading underestimated the severity of the rejection episode, the criteria for rescue therapy was based primarily on biochemical and clinical parameters, such as elevations of serum transaminases or serum bilirubin to greater than 50% of baseline, clinical signs, such as fever, and changes in bile characteristics in those who had T-tubes.

Timing and Details of Therapy

Cyclosporine was discontinued 24 hours prior to the initiation of FK 506 therapy. Initiation of treatment with FK 506 was done in the hospital and was administered 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, administered intravenously over a period of 4 hours. Generally, oral dosages of FK 506 were administered at 0.30 mg/kg in divided doses. Dose adjustments of FK 506 were based on monitoring of serum trough levels by enzyme-linked immunosorbent assay,7 and also by adjustment according to clinical or biochemical parameters. As was previously described, 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 remaining FK 506 conversion patients.[4] The majority of the patients remained in the hospital for 6 days or less following initiation of FK 506, and were followed thereafter on an outpatient basis.

Statistical Analysis

Comparisons of the liver function tests were analyzed using a two-tailed Student's *t*-test with unequal variances. Probability values < .05 were considered statistically significant. All mean values are expressed as mean value ± standard error of mean.

RESULTS

Patient Survival

In this population of 246 patients in which many of the patients were critically ill at the time of FK 506 conversion, 31 deaths were encountered (12.6%) (Table 2). These deaths occurred an average of 74.3 days following FK 506 conversion. 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. Five of the 31 deaths occurred in the 25 patients who underwent retransplantation.

When the mortalities were correlated with the indications for entrance, the highest mortality (six of six) was seen in those patients with pre-existing multi organ system failure related to sepsis. Of the 37 patients in whom significant hepatitis was seen on the pre-FK 506 biopsy, seven deaths (19%) were noted. Twelve (11%) of the 113 patients with chronic rejection died during this period. Only five of the 64 patients (8%) with acute rejection died. while the 26 patients with no evidence of liver dysfunction had the lowest mortality rate, with only two patients (7%) dying in the follow-up period.

Sepsis was the cause of death in 13 patients. Of these, six were overtly septic at the time ofFK 506 rescue. Each of these patients succumbed to mUltiple organ failure from sepsis an average of 13 days after institution of FK 506 therapy (range, 3 to 31 days). These patients were categorized as “multisystem organ failure” because of multisystem failure secondary to sepsis. In five patients, the causes of sepsis after FK 506 conversion were cytomegalovirus pneumonia (one patient), candida pneumonia (one), candida peritonitis following bile duct reconstruction (one), bacterial pneumonia (one), and hemorrhagic pancreatic abscess in a patient with recurrent pancreatitis (one). The final two deaths were in two patients who underwent retransplantation; one developed an aspiration pneumonia and the other developed intra-abdominal sepsis.

In one patient, hepatic failure from hepatitis B was the cause of death. The original disease was not related to hepatitis B, and conversion to FK 506 was performed because of suspected rejection. The original diagnosis was incorrect, a fact that was only determined 3 days after FK 506 was started. The patient was taken off FK 506 and emergent retransplantation was performed, but she died 2 days later from suppurative bacterial pneumonia.

Three patients died of metastatic carcinoma. In each of these patients, the metastatic lesions were identical histologically with the tumor removed at the time of transplantation. These deaths occurred at 1, 2.5, and 6 months following FK 506 conversion, and 1,3.5, and 6.5 months after transplantation.

In four patients, retransplantation was not considered an option for the failing liver allograft. Two patients had prolonged liver dysfunction with evidence of chronic rejection, while one had a larger component of biliary stricturing. One patient had intra-abdominal sepsis and required emergent ligation of the hepatic artery. FK 506 was offered as a rescue option, although it was felt that the possibility of success was remote. These four patients died 15.32,81, and 137 days after FK 506 was started.

Three patients died from liver failure related to recurrent non-A, non-B hepatitis. All three patients developed recurrent non-A, non-B hepatitis and were converted to FK 506. The liver dysfunction progressed in all cases, and, in one case, retransplantation was attempted. The new liver developed recurrent non-A, non-B hepatitis, and this patient died of liver failure.

Three patients died of hemorrhagic complications. In one patient, a rupture of a mycotic pseudoaneurysm required ligation of the celiac axis which was complicated by renal failure 9 months following transplantation. The patient was converted to FK 506 and eventually recovered normal renal function. Two months later, a recurrent intra-abdominal hemorrhage occurred from a mycotic aneurysm that formed at the aortic orifice. leading to the patient's death. In another patient, an unsuspected splenic artery aneurysm ruptured 3 days after FK 506 conversion. The patient could not be resuscitated. The third patient died after sustaining a lacerated subclavian artery during an attempt to place a central venous line, causing a massive hemothorax and uncontrollable bleeding.

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

In two deaths, no clear cause of death could be determined. Both of these patients died at home. One patient had been off FK 506 for 4 months at the time of death.

Finally, a complex patient with scleroderma and autoimmune hepatitis developed renal failure after transplantation. FK 506 was started 3 months after the original transplant in hopes of reversing the renal failure. The patient refused further dialysis after 4 months on FK 506, which was discontinued, resulting in the patient's death.

Graft Survival

Of the 246 liver allografts analyzed, 51 grafts were lost from either retransplantation or patient death. This left 196 liver allografts currently functioning. The causes of graft loss are listed in Table 2. Twenty-five grafts failed, requiring retransplantation. Fifteen liver allografts were lost to chronic rejection, unresponsive to FK 506 therapy. Three grafts were lost to hepatic artery thrombosis, and seven were lost to progressive hepatitis affecting the liver allograft. These graft losses occurred a mean of 76.2 days after FK 506 conversion.

When the causes of retransplantation were correlated with the indications for entrance, the highest rate was seen in those patients with pre-existing hepatitis. Of the 37 patients in whom significant hepatitis was seen in the pre-FK 506 biopsy specimen, retransplantation was required in seven (19%). Fourteen of the 113 patients (12%) with chronic rejection required retransplantation during this period. Only three of the 64 patients (5%) with acute rejection required retransplantation, while none of the 26 patients without evidence of liver dysfunction did so.

Biochemical Response of the Liver Allograft

The biochemical response of the liver allografts to FK 506 was broken down into the specific indications for which the patients were switched to FK 506.

Fig 1 shows the total bilirubin and transaminase levels for the 64 patients who were treated for acute rejection, documented on liver biopsy or as judged by biochemical and clinical parameters (acute rejection). The total bilirubin (TBIL), serum glutamic-oxaloacetic (SGOT), and serum glutamate pyruvate transaminase (SGPT) prior to FK 506 were 4.96 ± 0.81 mg/dL, 207 ± 51 IU/L, and 281 ± 47 IU/L, respectively. These values fell, by the sixth month, to 0.46 ± 0.04 mg/dL, 52 ± 6.5 IU/L, and 54 ± 7.5 IU/L, respectively.

Patients with an entrance diagnosis of chronic rejection also had a beneficial response to FK 506. Fig 2 shows the total bilirubin and transaminase levels for the 113 patients treated for this specific indication (chronic rejection). While the total bilirubin fell to normal values (pre-FK 506, 5.08 ± 0.74 mg/dL; 6 months later, 0.81 ± 0.12 mg/dL), the average transaminase values were still slightly elevated above normal values (pre-FK 506, SGOT/SGPT, 198 ± 17.1 IU/L/271 ± 2.7 IU/L; 6 months later, SGOT/SGPT, 69 ± 6.4 IU/L/84.5 ± 11.0 IU/L).

Of interest is a subgroup of FK 506 conversion patients with chronic rejection occurring more than 90 days after trarisplantation, with an entrance total bilirubin of more than 2.5 mg/dL. These parameters define a subgroup of patients with chronic rejection who have done poorly in the past. Fig 3 shows the response of these patients to FK 506. A total of 40 patients were categorized into this subgroup, of which 11 required retransplantation, 10 for persistent chronic rejection and one for hepatic artery thrombosis. Five patients died. This left 24 patients with functioning liver allografts. When this group of 24 patients with functioning chronic rejecting liver allografts were analyzed for their response to FK 506 conversion, it was evident that this group responded favorably. There was a highly significant statistical decline in all liver functions. The mean values were lower at all time points when compared with the baseline values (pre-FK 506: TEIL, 7.52 ± 1.23 mg/dL; SGOT, 280 ± 47.6 IU/L; SGPT, 401 ± 97.1 IU/L; 6 months later: TBIL, 1.07 ± 0.38 mg/dL; SGOT, 96.3 ± 19.5 IU/L; SGPT, 111 ± 24.8 IU/L).

Patients who had indications for FK 506 conversion not related to liver allograft dysfunction were categorized as non-hepatic indications. A total of 26 patients were treated for steroid toxicity (seven patients), renal failure (14), refractory hypertension (three), and neurotoxicity (two). The liver functions remained normal throughout the follow-up period in this subset of patients who were converted for indications other than liver dysfunction (data not shown).

In a group of patients in whom hepatitis was the sole or a major coexistent process prior to FK 506 conversion, the liver function studies were analyzed. As previously mentioned, 12 of the 37 grafts were lost either to retransplantation or to patient death. Hepatitis was a factor in this loss in 10 of the 12 grafts. Of the remaining 25 liver allografts available for analysis, there was less appreciable effect of FK 506 on liver function. As shown in Fig 4, the response of grafts with hepatitis was not as dramatic as that seen with dysfunctional grafts due to rejection alone. There was an initial, statistically significant, improvement in the transaminases by the second

month (SGOT: pre-FK 506, 156 ± 24.5 IU/L; 2 months later, 94.7 ± 11 IU/L; SOPT: pre-FK 506,270 ± 41.8 IU/L; 2 months later, 130 ± 16 IU/L). This may have reflected improvement in the rejection process, which was a component in 15 of the 25 livers analyzed. By the sixth month, there was gradual deterioration in the transaminases such that the SGOT rose to 135 ± 38.8 IU/L and the SGPT rose to 134 ± 28.5 IU/L. In general, this rise was correlated to increased hepatocellular disarray.

Histologic Response of the Liver Allograft

In each case in which 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 biopsy specimens with a diagnosis of rejection showed worsening of the pathology. Thirty-six percent of the liver biopsy specimens showed no pathologic changes between the pre-FK 506 biopsy and the 2-month follow-up biopsy. Forty-seven percent of the remaining biopsy specimens showed improvement between the initial and the follow-up biopsies. These changes were particularly impressive in patients whose pretreatment biopsy specimens contained bile duct lesions that generally progress to bile duct disappearance and graft loss, in spite of intensive immunosuppression. In those liver allografts in which hepatitis was a predominant finding in the pre-FK 506 conversion biopsy, 50% of the follow-up biopsy specimens showed worsening of the hepatitic picture.

Renal Function

On the whole, renal function, as assessed by serum blood urea nitrogen (BUN) and creatinine (Cr), rose during the first few weeks after FK 506 conversion. These values gradually fell during the ensuing follow-up period. The pretreatment BUN and Cr were 37.1 ± 1.47 mg/dL and 1.78 ± 0.11 mg/dL, respectively. These values peaked at 39.7 ± 1.46 mg/dL and 2.27 ± 1.02 mg/dL, respectively, before declining to 31.6 ± 2.01 mg/dL and 2.01 ± 0.20 mg/dL, respectively, by the sixth month.

Pre-existing renal dysfunction was noted in 24.8% of the patients, due to primary kidney disease or CyA. Two of these patients had previously undergone cadaveric renal transplantation with dysfunction of the kidney allograft. In the 244 patients with native kidneys, 59 patients had renal failure as defined by a serum creatinine greater than 2 mgldL (50 of 244), or the requirement for hemodialysis (nine of 244). Because of the heterogeneity of the kidneys being studied and the confounding factor of prior treatment with CyA, the nephrotoxicity of FK 506 could not be accurately ascertained. Three of the nine patients on hemodialysis have actually recovered renal function while on FK 506 and do not require further hemodialysis.

In the subgroup of patients with pre-existing renal failure as the sole indication for FK 506 conversion, the BUN and Cr values prior to FK 506 were 46.9 ± 4.3 mg/dL and 3.11 ± 0.19 mg/dL, respectively. Renal function improved in this group of patients and, at the end of 6 months, the BUN and Cr values were 32.5 ± 5.8 mg/dL and 2.33 ± 0.24 mg/dL, respectively (data not shown).

In six patients who had either poor renal function or who were on hemodialysis at the onset of FK 506 therapy, cadaveric renal transplantation was undertaken during the course of FK 506 therapy for persistent renal failure. Two kidney allografts failed; one was from a patient who required an allograft nephrectomy 1 month following kidney transplantation for a mycotic aneurysm. The recipient (who was on CyA) receiving the mate kidney also hemorrhaged from a mycotic aneurysm. The second patient was a sensitized recipient and received a kidney that never functioned. He remains dialysis-dependent. In the remaining four patients, with a mean follow-up of 11 months, renal function remains excellent, with the average serum creatinine being 1.2 mg/dL (range, 0.7 to 1.8 mg/dL).

Adverse Reactions

A detailed questioning of patients was performed for all patients converted to FK 506 from CyA. The overall incidences of side effects from FK 506 given to this group of patients are listed in Table 3. The most common side effect of FK 506 administration was insomnia, occurring in 31% of all patients at some time after FK 506 conversion. This was followed by tremors, primarily in the upper extremities, which were seen in 26% of the patients. Headaches occurred in 22% of the patients. Hyperesthesias of the feet were noted in 21% of the patients. Photophobia was seen in 15% of all questionnaires.

FK 506 therapy was also associated with a number of transient gastrointestinal complaints. Ten percent of the patients noted nausea or vomiting, 12% noted diarrhea, 10% noted increased appetite, and 14% noted decreased appetite. Gas pains were reported in 17% of the patients.

Hyperkalemia was seen in 35% of patients following administration of FK 506. Treatment was initiated with potassium-binding resins and potassium-restricted diets. Addition of a synthetic mineralocorticoid, Florinef, relieved the hyperkalemia in all of these patients.

One case of lymphoproliferative disease was found in this group of patients. This was seen in a 5-year-old girl with an original diagnosis of biliary atresia. She received one course of OKT3 during the second posttransplant week. She had persistent rejection and was converted to FK 506 1 month following transplantation. She did well until an episode of gastrointestinal bleeding was noted 7 months after FK 506. Upper endoscopy revealed a gastric ulcer that was interpreted as showing a polyclonal lymphoma of the stomach. Treatment consisted of the administration of intravenous acyclovir and the lowering of FK 506 doses. A repeat endoscopy 1 month later revealed healing of the ulcer.

DISCUSSION

This report confirms our initial report[4] on the usefulness of FK 506 conversion for patients with refractory complications due to CyA, including rejection, hypertension, nephrotoxicity, and steroid toxicity. However, we have also defined circumstances in which FK 506 conversion is not beneficial and, perhaps, deleterious.

In the high-risk group of patients with chronic rejection, many of whom had received previous azathioprine, OKT3, and/or high doses of steroids, over 70% of the 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 whose values were abnormal prior to conversion to FK 506. Even with a group of patients with end-stage liver disease from chronic rejection with marked liver function abnormalities, liver functions responded favorably. 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.[8, 9] Unlike CyA, which also possesses hepatotrophic qualities in the liver,[9] FK 506 is able to reverse the pathologic findings of chronic rejection, including small bile ductular damage and loss.[10] The limitation in the ability to rescue a chronically rejecting liver allograft is likely to be the arterial inflow and the requirement for some residuum of portal biliary structures. Those patients with a diagnosis of chronic rejection who did not respond to FK 506 conversion had histopathologic evidence of end-stage chronic rejection with obliteration of the vascular lumen and total disappearance of intrahepatic bile duct structures.

FK 506 has been shown to reverse ongoing acute cellular rejection in animal models when started early in the rejection episode.[11] This study demonstrates a marked ability of FK 506 to reverse ongoing acute cellular rejection. Liver functions stabilize and revert toward normal, usually within several days of starting FK 506. The quality of dose adjustability in the treatment

of rejection has always been considered to be limited to steroids. The consideration that an agent which, theoretically, acts in a manner similar to CyA (but is able to reverse ongoing rejection) will force those studying transplant immunobiology to re-examine the effect of FK 506 on the immune response. It should be suspected that the biologic effect that FK 506 is able to achieve is more than merely affecting the genesis of rejection. This phenomenon may account for the successful use of FK 506 in primary liver transplantation, and the low rates of rejection seen in those patients.[5]

Patients with hypertension, nephrotoxicity, steroid toxicity, or neurotoxicity have responded to FK 506 conversion. All patients with steroid toxicity were able to stop steroids. The number of patients treated for the indications of hypertension or neurotoxicity are too small to make a generalization; however, conversion to FK 506 affords maintenance of adequate immunosuppression. Some patients with nephrotoxicity related to CyA have also benefited from FK 506. However, we have not yet been able to prospectively identify those patients in whom this conversion will fail.

FK 506 is remarkably well tolerated. Yet, FK 506 and CyA share many similar biologic properties. Both immunosuppressive agents have specificity toward T cells. Both drugs inhibit interleukin-2 synthesis and, therefore. T-cell proliferation.[12, 13] The mechanism whereby these drugs inhibit T cell function is thought to be in an inhibition of their respective receptors, which are peptidyl-prolyl *cistrans* isomerases,[14,15] and is considered to be important in a number of protein-folding events.[16] While some of the neurotoxicity, nephrotoxicity, and diabetogenic effects of both drugs are similar, there are marked differences. The incidence of hypertension is less, while gingival hyperplasia and hirsuitism is virtually nonexistent.

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. Of special interest is the possibility of using FK 506 in disease processes in which biliary structures are targets of immune destruction. Two patients have been treated with FK 506 for control of chronic graft-versus-host disease following bone marrow transplantation. Both patients manifested liver disease related to destruction of the portal biliary structures, similar to that seen in chronic liver allograft rejection. Indeed, both histologically and immunopathologically, the mechanism of liver injury is similar in both disease processes. Both patients have had dramatic responses to FK 506. The serum bilirubin profiles in the patients treated are shown in Fig 5. The canalicular enzymes have also shown a marked response to FK 506 (data not shown). It will be of great interest to determine the possibility of rescuing failing livers in patients with chronic graft-versus-host disease.

The ultimate role of FK 506 in the treatment of immuneregulated diseases is not clear; however, the ability of FK 506 to affect diverse target systems will make it attractive to study.

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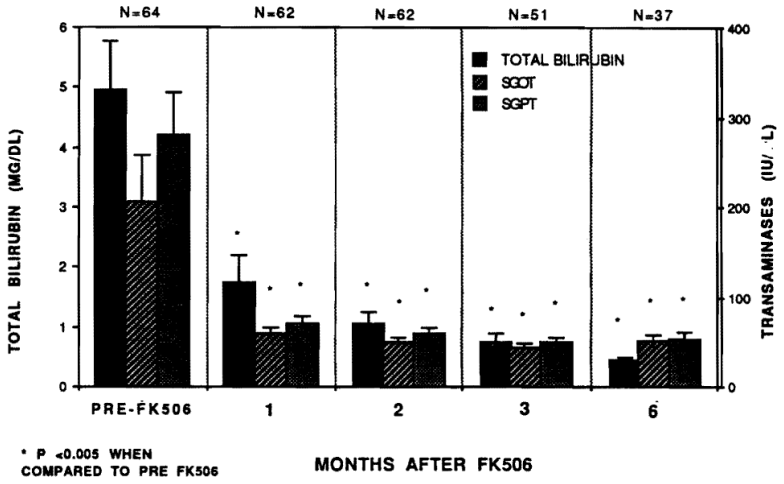

Fig 1.

Improvement in liver function studies in patients with chronic rejection who have been switched to FK 506.

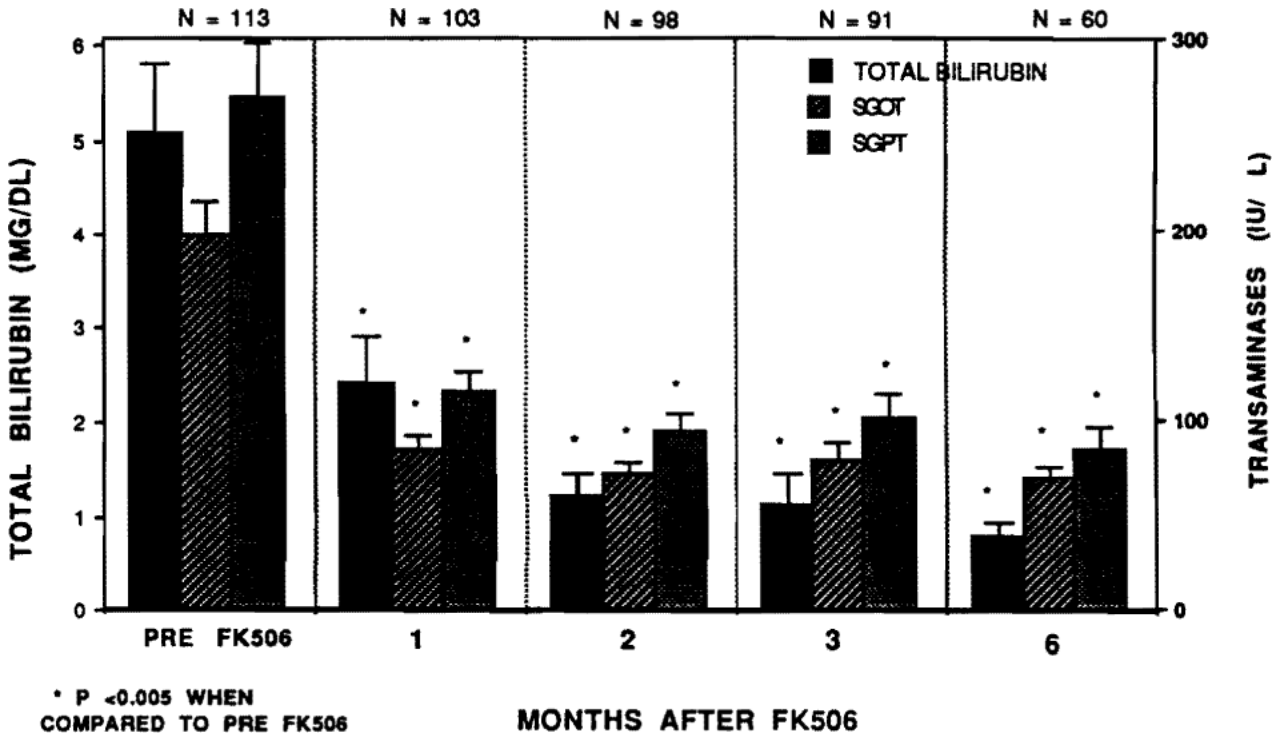

Fig 2.
Treatment response of chronically rejecting, end-stage liver allografts with FK 506.

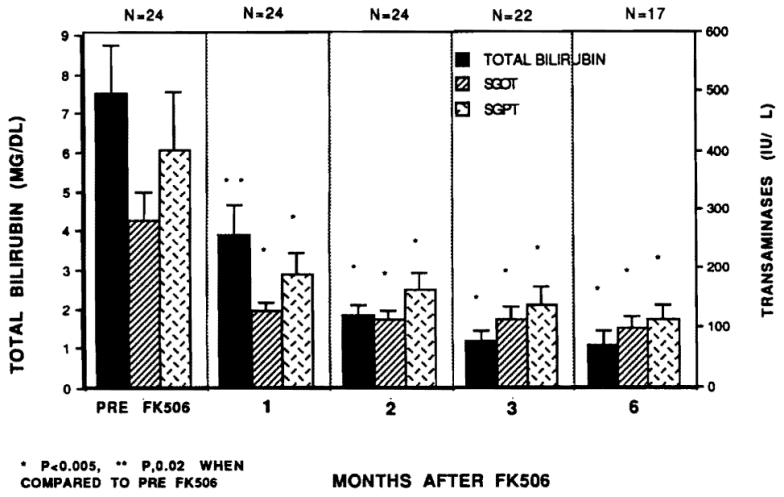

Fig 3.
Influence of pre-existing hepatitis in the response of liver allografts to conversion to FK 506.

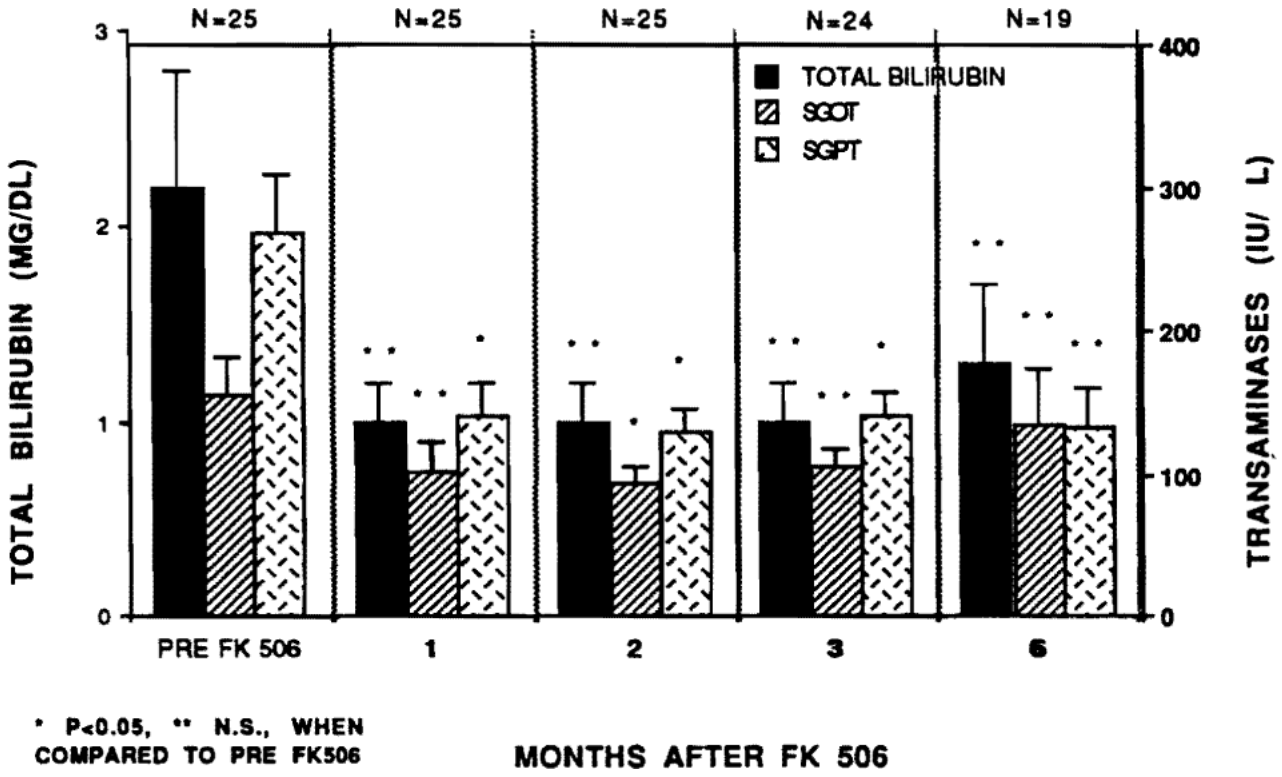

Fig 4.
Examples of recovery of end-stage liver disease in two patients with chronic graft-versus-host disease following bone marrow transplantation.

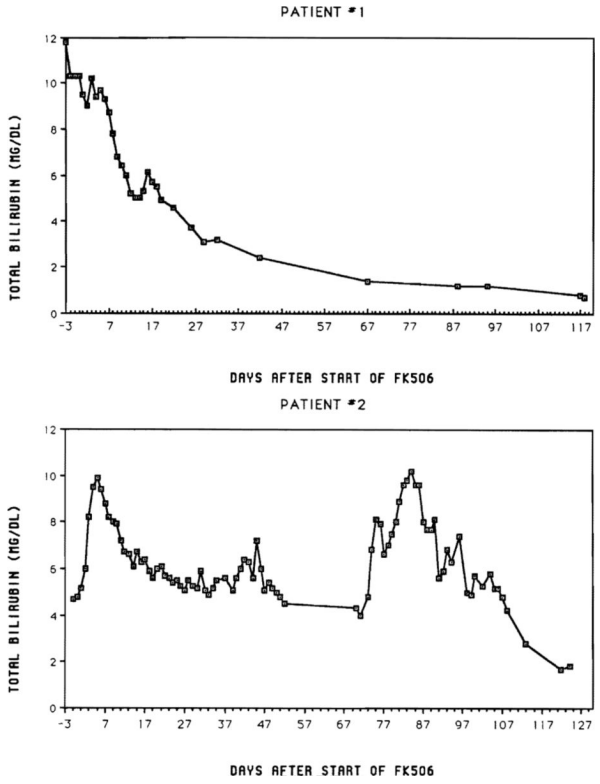

Fig 5.
Improvement in liver function studies in patients with chronic rejection who have been switched to FK 506.

Table 1

Clinical Profile of FK 506 Conversion Patients

Median age (y):	42
Sex (M/F):	124/122
Liver allograft treated	
No. 1:	203
No. 2:	32
No. 3:	9
No. 4:	1
No. 5:	1
Original diagnosis	
Cryptogenic cirrhosis:	79
Laennec's cirrhosis:	34
Primary biliary cirrhosis:	32
Sclerosing cholangitis:	25
Hepatitis B:	14
Biliary atresia:	13
Autoimmune cirrhosis:	10
Malignancies:	10
Miscellaneous:	39
Indications for FK 506	
Acute rejection:	64
Acute rejection/hepatitis:	8
Chronic rejection:	113
Chronic rejection/hepatitis:	18
Hepatitis:	11
Non-hepatic indications:	
Steroid toxicity:	7
Renal failure:	14
Hypertension:	3
Neurotoxicity:	2
Multiorgan system failure:	6

Table 2

Causes of Graft and Patient Loss

Patient loss	
Liver failure	
Non A-Non B hepatitis:	3
Fulminant hepatitis B:	1
Non-retransplantable:	4
Metastatic carcinoma:	3
Sepsis:	13
Renal failure:	1
Hemorrhage:	3
Operative death:	1
Unknown causes:	2
Graft loss	
Chronic rejection:	15
Hepatic artery thrombosis:	3
Hepatitis:	7

Table 3

Incidence of Side Effects[a]

Side Effect	Incidence (%)
Insomnia	31
Tremors	26
Headache	22
Hyperesthesia	21
Musculoskeletal	20
Blurred vision	19
Itching	18
Fatigue	17
Gas pain	17
Hair loss	16
Photophobia	15
Decreased appetite	14
Diarrhea	12
Nausea	10
Increased appetite	10
Sweating	9
Tinnitus	9
Dizziness	7
Nightmares	7
Hair growth	6
Chest Pain	3

[a]Represents a cumulative frequency based on 1,515 patient interviews.