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FK506 conversion for intractable rejection of the liver allograft

Sue V. McDiarmid[1], Goran B. Klintmalm[2], Ronald W. Busuttil[3]

[1] Department of Pediatrics, University of California at Los Angeles Medical Center, MDCC 12-383, Los Angeles, CA 90024-1752, USA
[2] Transplantation Services, Department of Surgery, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, TX 75246, USA
[3] Liver Transplant Program, Department of Surgery, University of California at Los Angeles Medical Center, 10833 Le Conte Avenue, Los Angeles, CA 90024, USA

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Abstract. Twenty-seven liver transplant recipients with intractable, biopsy-proven, acute or chronic rejection (defined as vanishing bile duct syndrome) were converted from cyclosporin to FK506. Successful conversion was achieved in 9 of 15 patients with acute rejection and in 6 of 12 patients with vanishing bile duct syndrome. A normal bilirubin was achieved more quickly in those with acute rejection (within 1 month) than in those with chronic rejection (within 3 months). A preconversion total bilirubin of less than 12 mg/dl was considered significant with regard to a successful outcome ($P = 0.002$). Graft survival was 66.7% and patient survival 73% in the case of acute rejection, and 50% and 66.7%, respectively, in the case of chronic rejection. Nephrotoxicity, neurotoxicity, and gastrointestinal side effects were the most serious complications of FK506 conversion. Six of ten patients had a drop in GFR that was 50% or greater after a minimum of 1 month of FK506 exposure. The mean maintenance dose of FK506 to maintain FK506 serum levels of 0.5–1.5 ng/ml was 0.07 mg/kg per 12 h for adults (half the recommended dose), compared to 0.15 mg/kg per 12 h for pediatric patients. This study demonstrates that FK506 can be used successfully to convert patients with intractable acute and chronic rejection. Careful adjustments of FK506 dosages and levels are required to minimize side effects.

Key words: FK506, liver transplantation, conversion – Liver transplantation, FK506, conversion – Rejection, liver, conversion, FK506 – Conversion, liver transplantation, FK506

Introduction

The first reported clinical use of the new immunosuppressant FK506 in the successful rescue of liver allografts failing due to unremitting rejection [29] provoked intense interest in liver transplantation centers worldwide. For the first time since the seminal breakthrough of cyclosporin in transplantation immunosuppression, a major advance appeared likely. Intriguingly, the macrolide structure of FK506 [15] bears no relationship to the 11-amino-acid ring of cyclosporin; yet, the two drugs share a remarkably similar action, although in vitro FK506 has a potency of the order of one hundred times that of cyclosporin [13]. Both interfere with the cytoplasmic message responsible for gene activation in T cells [31]. As a result, the production of several essential cytokines, including the T-cell-activating cytokine IL2, is blocked. Another commonality between the two drugs has emerged in the spectrum of their toxicities. Such observations have spurred the use of both drugs as probes to unravel the cytoplasmic events involved in T-cell activation. The new knowledge that both agents act through different binding proteins (immunophilins) [23] but share a similar enzyme component (the peptidyl prolyl cis-trans isomerase family) [8, 27] may explain some of the similarities between cyclosporin and FK506, despite their different physical structures.

In the first clinical experiences of FK506 in liver transplantation, important differences between the new drug and cyclosporin were emphasized [7, 29, 33]. Starzl's group reported that the historically poor prognosis of patients with intractable rejection that was recalcitrant to all

Table 1. Pretransplant diagnoses for patients converted to FK506 with intractable acute or chronic rejection

	Acute	Chronic
Sclerosing cholangitis	1	3
α-1 Antitrypsin deficiency	0	2
Cryptogenic cirrhosis	4	1
Fulminant hepatitis	4	1
Chronic active hepatitis (non-C)	2	0
Chronic active hepatitis C	1	0
Biliary atresia	0	1
Hepatocellular carcinoma	1	1
Primary biliary cirrhosis	2	1
San Filipo syndrome	0	1
Alcoholic cirrhosis	0	1

Correspondence to: S. V. McDiarmid

Table 2. Outcome of patients converted to FK506 for acute and chronic rejection. MOF, Multiorgan failure; VBDS, vanishing bile duct syndrome

	Acute $n = 15$	Chronic $n = 12$
Death	4 - 2 Sepsis + MOF - 1 Disseminated lymphoma - 1 Disseminated tuberculosis and aspergillosis	4 - 3 Sepsis + MOF - 1 Brain death
Retransplants	2 - 1 Uncontrolled acute rejection (alive) - 1 Resistant rejection	2 - 2 VBDS (alive)
Graft survival	66.7%	50%
Patient survival	73.3%	66.7%

other conventional therapies could be improved with the substitution of FK506 for cyclosporin [7]. The first trials of FK506 as primary treatment after liver transplantation [33] showed that FK506, unlike cyclosporin, was able to control established rejection and allowed a low dosage, or even discontinuation, of steroids. Overimmunosuppression, evidenced by increased rates of infection or de novo tumor appearance, was not evident. As an added advantage, FK506 appeared to be less nephrotoxic and neurotoxic than cyclosporin [25].

These propitious properties prompted other investigators to petition for the use of FK506, resulting in multicenter trials first aimed at evaluating its efficacy in salvaging liver allografts. The preliminary results [5, 16, 21, 22, 26, 34, 35] confirm the usefulness of FK506 in reversing or ameliorating previously untreatable rejection.

This study reports the early experience shared between two liver transplant centers with previously similar management practices and results, both using FK506 under the same protocol. In reporting this early experience, we have asked four questions: (1) What is the outcome of conversion from cyclosporin to FK506 in OKT3-resistant acute rejection and in vanishing bile duct syndrome? (2) Are there differences in the response to FK506 comparing acute and chronic rejection? (3) Are there predictors of a successful conversion to FK506? and (4) What are the complications after FK506 conversion?

Methods

We studied liver transplant patients at the University of California at Los Angeles Medical Center for the Health Sciences and at Baylor University Hospital. These patients were consecutively enrolled in a shared, institutionally approved protocol developed in conjunction with Fujisawa Pharmaceutical Company for the salvage of liver allografts failing conventional immunosuppression. Both centers followed their previously published standard surgical and immunosuppressive protocols [2, 20].

For patients with intractable acute rejection, the following were required: (1) a liver biopsy confirming the diagnosis within 48 h of planned conversion to FK506, (2) documented adequate cyclosporin levels, (3) two or more treatments of high-dose intravenous methylprednisolone, and (4) a minimum of 7 days of OKT3 or another lymphocyte preparation.

Chronic rejection was defined as the absence of a bile duct in more than half the triads seen on liver biopsy. The biopsy confirming vanishing bile ducts, despite previous optimal cyclosporin levels, high-dose steroids, and azathioprine, must have been obtained within 7 days of conversion to FK506. A trial of an antilymphocyte preparation was considered unnecessary. Further requirements for all patients included a minimum of 14 days of post-transplant care, clinical evidence of ongoing rejection (elevated transaminases and bilirubin), documentation of a patent biliary system, and an intact vascular supply. The pretransplant diagnoses are shown in Table 1.

Exclusion criteria were pregnant or nursing women and patients with uncontrolled concomitant infections; vasculitis or arteritis; other organ transplants; uncompensated cardiovascular, pulmonary, peripheral vascular, or cerebral vascular disease; renal failure requiring dialysis; hepatic stage III or IV hepatic encephalopathy; untreated surgical complications; and positive serologies for hepatitis B, hepatitis C, or HIV infection.

After signing a statement of informed consent, patients were converted to FK506 after a minimum of 24 h following the discontinuation of cyclosporin, azathioprine, high-dose steroids, or any other immunosuppressive agent. At the outset of the study, two doses of FK506 (0.075 mg/kg) were given intravenously 12 h apart, followed 12 h later by FK506 (0.15 mg/kg) given orally every 12 h in conjunction with baseline prednisone (15–20 mg/day for adults and 0.3 mg/kg per day for children). This regimen was quickly modified after early adverse experiences of neurotoxicity and nephrotoxicity forced drastic dose reduction. We adopted a modified protocol allowing for the avoidance of intravenous FK506 whenever possible and a starting oral dose dependent upon the severity of liver dysfunction and renal compromise. As a result, starting oral doses ranged from 0.05 mg/kg per 12 h to 0.15 mg/kg per 12 h. Patients who required intravenous FK506 were given as little as 0.025 mg/kg per 12 h as a continuous infusion.

Prior to the first days's dose of FK506, baseline investigations included a full history and physical examination, blood screen, prothrombin time, partial thromboplastin time, electrolytes, BUN creatinine, glucose, magnesium, amylase, uric acid, SGOT, SGPT, alkaline phosphatase, total bilirubin, direct bilirubin, cyclosporin trough levels, chest x-ray, EKG and, if indicated, a pregnancy test. Whenever possible, a glomerular filtration rate (GFR) was obtained (plasma clearance of indium-DTPA at UCLA, iothalmate at Baylor) and a fasting lipid profile was drawn.

Following FK506 conversion, patients were monitored for toxicity by direct questioning, physical examination, and laboratory tests at weekly outpatient visits for the 1st month. Outpatient visits were then scheduled depending upon the patient's clinical condition. The laboratory evaluation was similar to that of the baseline investigations and was performed weekly for the 1st month and thereafter at every outpatient visit. A repeat liver biopsy was performed after a minimum of 28 days of FK506 therapy, or whenever clinically indicated. Depending upon the patient's proximity to the transplant center, repeat GFRs were obtained after the 1st month of FK506.

Trough plasma FK506 levels were determined every other day for inpatients, weekly for outpatients for the 1st month, and thereafter when clinically indicated. At one central laboratory the FK506 level was determined by ELISA, following a liquid-liquid separation method at 37° [30]. The result was reported between 5 and 12 days afterwards so that FK506 levels could not be used to adjust the dosage meaningfully in response to clinical events. Other clinical tests, such as evaluation for infection, were performed if clinically indicated.

In reporting our results, we distinguish between patients converted to FK506 for acute versus chronic rejection, and we report the outcome, patient survival, and graft survival separately. A successful response to FK506 was defined as an improvement greater than 50% in transaminases and bilirubin, supported by histological improvement on liver biopsy. In patients treated longer than 28 days with FK506, we compared the changes in bilirubin and transami-

nases as acute and chronic rejection resolved. In addition, we analyzed pre-FK506 conversion liver tests retrospectively to determine whether a successful outcome could be predicted. Finally, we assessed toxicities and complications related to FK506 conversion.

Comparisons between groups were made with a two-tailed Student's *t*-test and chi-square analysis. Unless otherwise stated, means are reported with their standard deviation.

Results

Twenty-seven patients were converted from cyclosporin to FK506, 15 because of biopsy-proven acute rejection and 12 because of biopsy-proven chronic rejection, defined as vanishing bile duct syndrome. The pretransplant diagnoses of patients converted to FK506 are shown in Table 1.

Patient and graft survival: acute rejection

Fifteen patients were converted to FK506 because of acute rejection: 13 adults (mean age 44.5 ± 12.8 years) and 2 children (aged 4 and 8 years). FK506 therapy began at a mean of 139 ± 199 days after the last liver transplantation. Actual graft survival was 66.7% and actual patient survival 73.3%.

There were four patient deaths in this group, one occurring after retransplantation. Two patients, who were already in the intensive care unit with multiple complications at the time of conversion to FK506, died within 28 days of progressive multiorgan failure, without any improvement in liver function. One patient died of disseminated lymphoma after two doses of FK506. On review of the preconversion liver biopsy, lymphoma was already present and misdiagnosed as rejection. Another patient was retransplanted after FK506 failed to improve the acute rejection episode, but he died later of disseminated tuberculosis and aspergillosis. He had received FK506 for 21 days prior to retransplantation and died 23 days after the second liver was placed. One other patient received a retransplant after FK506 conversion for acute rejection failed; this patient survived.

Patient and graft survival: chronic rejection

Twelve patients – eight adults (mean age 43.6 ± 3.8 years) and four children (mean age 5.5 ± 1.0 years) – with vanishing bile duct syndrome were converted to FK506 at a mean of 522 ± 528 days after their last liver transplantation. Although the overall actual graft survival of 50% and actual patient survival of 66.7% for patients with chronic rejection was lower than that of patients with acute rejection, the difference was not statistically significant. The number of deaths and the number of retransplants were the same as those of the acute rejection group. Four patients died and, as in the acute rejection group, the most common cause ($n = 3$) was multiorgan failure in patients already confined to the intensive care unit prior to conversion. In these three patients, the course of FK506 therapy lasted less than 28 days and no improvement in liver function was seen. One patient sustained brain death

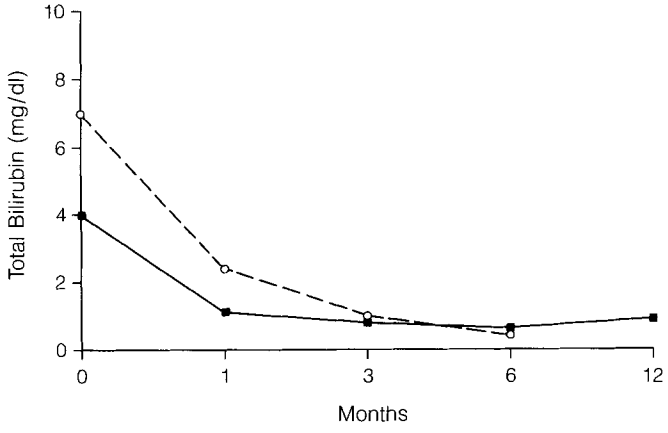

Fig. 1. Comparison of the drop in total bilirubin in patients with acute (—) versus chronic (---) rejection successfully treated with FK506. Patients with acute rejection achieved a normal total bilirubin within 1 month, whereas this took longer than a month in patients with chronic rejection

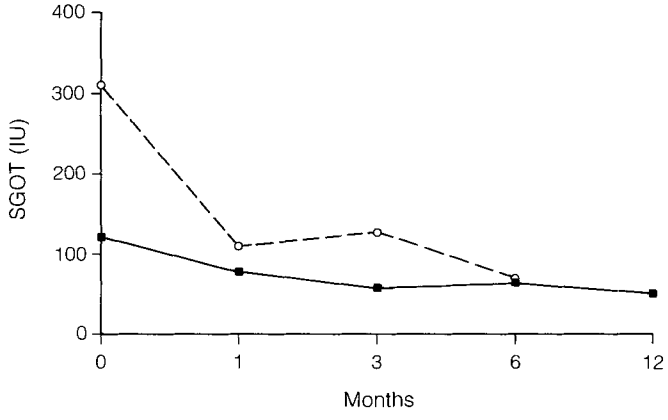

Fig. 2. Comparison of the drop in SGOT in patients with acute (—) versus chronic (---) rejection successfully treated with FK506. The drop in SGOT was slower in patients with chronic rejection

5 days after beginning FK506 subsequent to several hypotensive crises unrelated to FK506. Two patients with vanishing bile duct syndrome did not improve with the switch to FK506 and were successfully retransplanted. Table 2 summarizes the graft and patient outcome of FK506 conversion comparing acute and chronic rejection.

Response to FK506 conversion

Nine of 15 patients with acute rejection were successfully converted to FK506 with a mean follow-up of 328 ± 111 days. FK506 was discontinued in 6 patients because of death ($n = 3$), retransplantation ($n = 2$), and renal failure ($n = 1$). In 6 of the 9 patients remaining on FK506, serum transaminases and bilirubin are presently normal, while in 3 others a mild transaminitis (SGOT and SGPT < 200 IU with a total bilirubin ≤ 2.5 mg/dl) persists. Follow-up biopsies in 7 patients show resolution of rejection while in 2 others histological appearances of the triads show a decrease in the inflammatory infiltrate and bile duct damage.

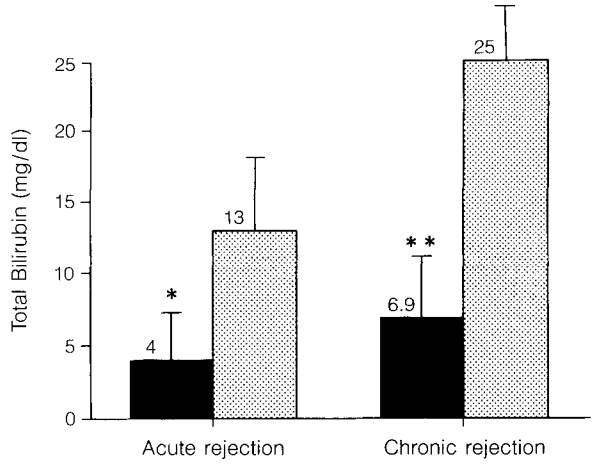

Fig. 3. Comparison of the mean bilirubin between patients successfully converted to FK506 (■) and those who fail conversion (▒). A successful outcome is associated with a significantly lower preconversion bilirubin compared to patients failing conversion. * $P = 0.02$, ** $P < 0.002$

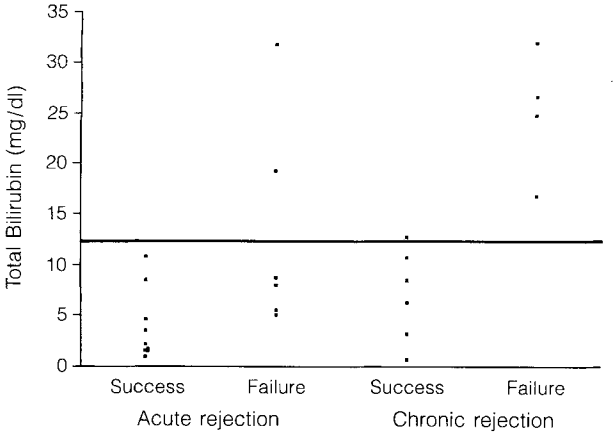

Fig. 4. Graphic illustration of how the total preconversion bilirubin predicts the outcome of FK506 treatment. The total preconversion bilirubin of each patient is plotted, depending on the outcome of treatment and the nature of rejection. A line differentiating success from failure with FK506 treatment can be drawn at a total bilirubin of 12 mg/dl. * $P = 0.002$ for bilirubin < 12 mg/dl (chi-square)

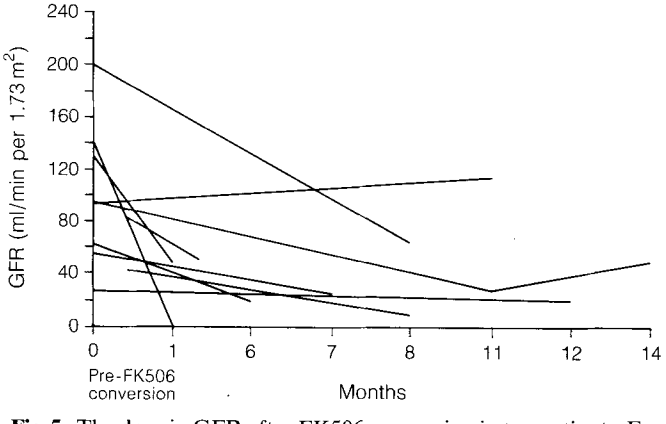

Fig. 5. The drop in GFR after FK506 conversion in ten patients. For six of the ten patients, the GFR dropped 50% or more compared to their preconversion value after a minimum of 1 month of FK506 treatment

Six of 12 patients with vanishing bile duct syndrome remain on FK506 with a mean follow-up time of 181 ± 77 days. In 4 of the 6 other patients, FK506 has been stopped because of death and in 2 because of retransplantation.

Of the 6 patients successfully converted to FK506, 3 patients have normal transaminases and bilirubin while 3 others still show mildly elevated transaminases and bilirubin (SGOT and SGPT < 200 IU, bilirubin < 2.5 mg/dl).

Repeat biopsies show that one patient now has a normal number of bile ducts, while in four others the bile duct number is increasing. In one patient it has not been possible to obtain repeat biopsies.

Rate of liver function improvement compared for acute and chronic rejection

Figures 1 and 2 compare the changes in mean bilirubin and SGOT over time for patients successfully converted to FK506 for acute versus chronic rejection. After 1 month of FK506 therapy, patients with acute rejection had a normal bilirubin (mean 1.1 ± 0.54 mg/dl), whereas in patients with chronic rejection the mean bilirubin was 2.4 ± 1.7 mg/dl at 1 month. In patients with chronic rejection, bilirubin became normalized after 3 months (mean 1.0 ± 0.91 mg/dl). We noted a similar lag in the decrease in SGOT in these patients. Alkaline phosphatase measures proved to be highly variable in both groups. Persistent elevations were common, and in several patients an increasing alkaline phosphatase was noted despite improvement in other liver test parameters.

Pre-FK506 conversion predictors of successful outcome

We first considered whether the total bilirubin prior to FK506 conversion could predict a successful outcome. In Fig. 3 the mean total bilirubin of patients successfully converted to FK506 is compared with those who failed to improve after FK506 therapy. For acute rejection successful converters had a significantly lower starting total bilirubin (mean 4.0 ± 3.2) compared to the mean total bilirubin (13.0 ± 9.7) of those who failed conversion ($P = 0.02$; Fig. 3). The same analysis pattern occurred for chronic rejection. By constructing a scattergram (Fig. 4) of preconversion FK506 total bilirubin levels, a line differentiating those with a successful or an unsuccessful outcome could be drawn at a total bilirubin of approximately 12.0 mg/dl. Chi-square analysis confirmed that a total bilirubin of less than 12 mg/dl prior to conversion to FK506 was significantly associated with a successful outcome ($P = 0.002$).

Current immunosuppression

The mean maintenance oral FK506 dose for adult patients (0.07 ± 0.04 mg/kg per 12 h) was half of the recommended starting dose. However, the mean pediatric maintenance dose (0.15 ± 0.04 mg/kg per 12 h) is considerably higher

than that for the adult population. The average maintenance prednisone dose is low (6.6 ± 1.8 mg/day for adults and 0.18 ± 0.08 mg/kg per day for pediatric patients). Only two patients, both converted to FK506 for acute rejection, have required a single course of high-dose, intravenous steroid therapy. OKT3 has not been needed for any patient following FK506 conversion.

Complications

Nephrotoxicity. Pre- and post-FK506 conversion GFRs from 10 of the 15 patients who were treated with FK506 for more than 28 days were available for comparison and are shown in Fig. 5. Six of the 10 patients had a 50% or greater reduction in GFR after a minimum of 1 month of FK506 exposure. Overall, the mean decrease in GFR was 48 ml/min per 1.73 m^2.

Two patients required dialysis after starting FK506; in one patient kidney failure resolved only after FK506 was discontinued, whereas the other patient responded to drastic lowering of the FK506 dose and is now free of dialysis.

New-onset hypertension occurred in one patient. One other patient could be weaned off previously needed antihypertensives. The new onset of electrolyte disturbances was also noted. One patient developed new-onset hyperkalemia, one patient hyperchloremic acidosis, and two patients hypomagnesemia.

Neurotoxicity. The symptoms of neurotoxicity could be broadly divided into those indicating central nervous system upregulation or downregulation, as listed in Table 3. Of considerable concern were the neurological complications of one patient with chronic rejection who had been fully functional as an outpatient prior to FK506 conversion. He developed an unexplained coma beginning after the 1st week of FK506. FK506 levels ranged between 19.0 and 26.8 ng/ml prior to and during the onset of coma. Shortly thereafter, despite first lowering and then discontinuing the FK506 dose without improvement in mental functioning, the patient developed pancreatitis, which led to progressive multiorgan deterioration and death. Three other patients were affected to a lesser degree, with reactions ranging from hypoactivity to somnolence. This was seen at FK506 levels ranging from 1.1 to 5.4 ng/ml. This behavior reversed after dose adjustment. Also worrisome were the hallucinations experienced by two patients; they did not resolve until the dose of FK506 was reduced.

Other adverse events. Other adverse events possibly related to the use of FK506 are shown in Table 4. Predominant were gastrointestinal side effects ranging from anorexia to gastric paresis. New-onset insulin-dependent diabetes has developed in one patient. The patient with pancreatitis had already been described in detail above.

Infectious complications. Patients treated with FK506 for more than 28 days have generally remained free of infection. One patient has developed new-onset hepatitis B, but no patient has developed CMV disease. The patient who died of disseminated tuberculosis and aspergillosis after FK506 withdrawal has been discussed previously.

Table 3. Neurological complications associated with FK506 treatment (salvage therapy) are separated into those downregulating and upregulating the central nervous system (CNS)

Neurotoxicity	
CNS downregulation	
Coma	1
Somnolence	2
Hypoactivity	1
Lower extremity weakness	2
CNS upregulation	
Insomnia	4
Hallucinations	2
Headache	6
Tremor	4
Parasthesiae	3
Itch	3

Table 4. Miscellaneous complications associated with FK506 treatment (salvage therapy)

Miscellaneous	
Gastric paresis	3
Anorexia	6
Alopecia	3
Diabetes	1
Pancreatitis	1
Arthralgia/myalgia	3

De novo malignancy. One patient developed a nondisseminated B-cell polyclonal lymphoma 3 months after FK506 therapy was stopped. He had received FK506 for 24 days at the time of retransplantation after an extended course of OKT3 and two courses of high-dose steroids failed to control acute rejection. He has been successfully treated with irradiation and reduced immunosuppression.

Discussion

The barrier to successful immunosuppression of the liver transplant patient with rejection that is recalcitrant to conventional methods has, until now, appeared insurmountable. Such patients frequently came to retransplantation, further diminishing an already inadequate resource, suffered severe infectious complications, or developed de novo malignancy as a result of repeated salvos of broad-spectrum, but ineffective, immunosuppressants. The detrimental impact on graft and patient survival is common knowledge in any experienced liver transplant program but has not been clearly described in the literature. The lack of a control group creates an inherent difficulty in interpreting the results of a study such as this. A prospective, randomized trial comparing FK506 for rejection that has failed to respond to all conventional therapies with prolonged, additional conventional management poses unacceptable ethical dilemmas, particularly as the consequen-

ces to the patient whose liver graft has failed are either death or urgent retransplantation. The second option is to compare the results of FK506 salvage with a historical control group. The major drawback of this approach is the establishment of criteria by which patients are selected. The analysis of a historical control group is, by definition, retrospective, the outcome is known, and selection bias is inevitable.

We also recognize that subtle changes in the criteria for patient selection existed within this study, perhaps favorably biasing our results. As our positive experience with FK506 increased so did our willingness to convert patients to FK506 earlier. It can be argued that spontaneous improvement may have occurred in some patients with acute rejection who did not respond to OKT3. Similarly, "reversible" vanishing bile duct syndrome has been reported [9]. We confirmed the observation of Demetris et al. [6] that in cases where conventional therapy was ineffective, early conversion to FK506 resulted in a better prognosis than delaying the use of FK506. In our study a preconversion bilirubin of less than 12 mg/dl was significantly associated with a successful outcome. It seemed, therefore, unjustified to withhold FK506 and risk further deterioration once there was established biopsy evidence of vanishing bile duct syndrome or ongoing acute rejection after the failure of OKT3 treatment.

The potency of the immunosuppressant and the toxic effects of this drug were quickly apparent. The initial recommendation of intravenous FK506 at a dose of 0.075 mg/kg per 12 h proved to be associated with unacceptable nephrotoxicity and neurotoxicity [10]. This may well have been related to the poor liver function of these patients at the time of conversion. Abu-Elmagd and colleagues [1] recently emphasized that poor liver function, by affecting both the absorption and the elimination of the drug, was associated with increasing FK506 levels.

We found that much of this early toxicity could be avoided by beginning with oral FK506. One clear advantage of FK506 over cyclosporin is that its absorption appears to be independent of bile present in the intestinal lumen [11]. However, we again found that the recommended oral dose of 0.15 mg/kg per 12 h was frequently excessive and necessitated reduction to a dose as low as 0.03 mg/kg per 12 h. Our current practice is to initiate FK506 therapy by the oral route whenever possible, and to decrease the dosage if the liver function is impaired and the creatinine level elevated (> 1.5 mg/dl). Furthermore, the calculated lean body weight of the obese patient is used to determine the dosage. For adults the oral dose range is now 0.03–0.1 mg/kg per dose. The intravenous dose range is 0.015–0.05 mg/kg per 12 h given as a continuous infusion. Children, however, appear to exhibit a different pharmacokinetic profile compared with adults, and dosage requirements need to be higher in order to achieve similar blood levels. This difference is reflected in our study by a pediatric maintenance dose twice that of the adult patients. Recent evidence suggests that pediatric patients have an increased clearance of FK506 and more erratic gastrointestinal absorption than adults, a scenario reminiscent of cyclosporin [12]. In general, we therefore initially give pediatric patients oral cyclosporin at a dose of 0.15 mg/kg per 12 h and intravenous FK506 at a dose of 0.05–0.075 mg/kg per 12 h.

The unavailability of timely FK506 levels forced reliance on clinical manifestations of toxicity to regulate the FK506 dose. The most useful laboratory parameter indicating toxicity was a rise in serum creatinine. Increasing tremor, severe headache, mental status changes such as insomnia or somnolence, nausea, and evidence of intestinal ileus were common clinical manifestations of toxicity prompting drastic dose reduction in the order of 30%–60%.

With the increasing use of FK506 in multiple transplant centers, it is important that an agreement soon be reached on a common methodology to measure FK506 levels so that comparisons between centers are valid. As in cyclosporin level measurements, differences in FK506 levels can be expected depending upon the temperature of separation, whole blood versus serum measures, and the ELISA method itself [14]. Current research is now being focused on methods to distinguish FK506 from its metabolites and to determine the function of such metabolites [4, 36].

The range of toxicities reported in this study is remarkably similar to that of cyclosporin [24]. The early hope that FK506 might be less nephrotoxic now seems unfounded. Preliminary results from this single center of serial measurements of GFR in the randomized, control trial of FK506 versus cyclosporin as a primary immunosuppressant after liver transplantation suggest that both drugs are equally nephrotoxic [18]. Our report is the first to report changes in the GFR after conversion to FK506, and this early experience is one of concern. We found a reduction greater than 50% in GFR in the majority of patients studied. Further studies will be required to determine whether this effect persists, improves, or progressively deteriorates with time. Two patients with an impaired GFR as a consequence of chronic cyclosporin use showed a further reduction in GFR to less than 20 ml/min per 1.73 m^2 after FK506 conversion that placed them in jeopardy of kidney failure. Both of these patients have maintenance FK506 levels of less than 1.5 ng/ml, and although both have shown a significant improvement in liver function on FK506, neither has a normal liver test or a normal liver biopsy that would allow a more drastic reduction in dosage. These two patients illustrate how narrow the therapeutic window may be for FK506 in certain individuals.

The manifestations of neurotoxicity, tremor, headache, insomnia, and paresthesiae (including a troublesome itch) were common, but generally controllable with a reduction in the FK506 dose. Severe neurotoxicity, including seizures and expressive dysphagia, attributed to FK506 has been reported by others [28]. In this study we describe one patient with unexplained coma and three others with decreased mental activity. A recent finding (personal communication) of MRI changes in a patient treated with FK506 highlights the need to assess neurologic dysfunction meticulously in patients under FK506 treatment.

Considering earlier reports, the severity of anorexia, sometimes progressing to frank gastric paresis, was somewhat unexpected, but brought to mind previous concerns

of the FK506 gastrointestinal toxicity profile in baboon and dog studies [3].

Consistent with early reports, we also noted sporadic examples of hyperkalemia, a low incidence of hypertension [17], and new-onset diabetes [19]. Hypomagnesemia has not been previously emphasized and occurred in two patients. Pancreatitis, a toxicity concern in the dog model [32], occurred in one patient and could not be attributed to any other cause. Several patients reported some loss of luxuriant hair growth induced by previous use of cyclosporin.

In summary, this study confirms that FK506 deserves its reputation for accomplishing what no other immunosuppressant has done before, i.e., the ability to turn back the advancing tide of irrepressible rejection despite optimal conventional treatment. A successful outcome is more likely if conversion to FK506 is initiated before the total bilirubin rises above 12 mg/dl. However, the spectrum of toxicities observed did not appear to offer any advantage over cyclosporin, and significant nephrotoxicity and neurotoxicity can be expected. In fact, the balance between the therapeutic benefit of FK506 and its toxicity may be even more delicate than that of cyclosporin. The initially recommended doses of FK506 now appear to be too high (with the possible exception of the FK506 doses for pediatric patients) and the dosage and route of administration should be individually tailored, depending upon liver function and pre-existing renal or neurological impairment. Further studies are urgently needed to determine the relationship between FK506 levels, doses, immunosuppressive efficacy, and toxicity.

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