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Conversion from cyclosporin to FK 506 after liver transplantation

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Abstract. Thirty-seven liver-grafted patients with steroid-resistant acute or chronic graft rejection or with cyclosporin-related complications were converted from CyA to FK 506. The clinical outcome of the patients primarily depended on the degree of liver dysfunction present at initiation of FK 506 treatment. In patients switched to FK 506 for treatment of acute or early chronic graft rejection, CyA nephrotoxicity, or CyA malabsorption, the FK 506 therapy was associated with a clear improvement in the clinical course. In contrast, in patients with advanced chronic graft rejection, a lower response rate to the conversion in immunosuppression was observed. The lower response rate was associated with a higher patient mortality. These studies demonstrate that FK 506 represents a valuable alternative immunosuppressant for liver-grafted patients. The conversion from CyA to FK 506 should take place before serious – and potentially irreversible – disturbances in liver function are observed.

Key words: FK 506, liver transplantation – Conversion, FK 506, cyclosporin, liver transplantation – Liver transplantation, conversion

Introduction

FK 506 is a novel macrolide immunosuppressant that is currently under clinical investigation in patients after solid organ transplantation [13, 15]. In vitro, FK 506 has been shown to be ten to one hundred times more potent than cyclosporin (CyA) on an equimolar base. Early reports on the clinical use of FK 506 indicated that the drug could be used for primary as well as rescue immunosuppression in patients after solid organ transplantation [6]. We report here on 37 liver-grafted patients with acute steroid-resistant or chronic graft rejection or with CyA-related complications who were converted to FK 506.

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Patients and methods

Patients

Thirty-seven liver-grafted patients converted from CyA to FK 506 were studied. Thirteen patients were children under 16 years of age and 24 patients were adults between 17 and 66 years of age. Twenty-five patients were switched to FK 506 for treatment of acute steroid-resistant ($n = 6$) or chronic ($n = 19$) graft rejection. Twelve patients were converted for reasons unrelated to rejection, such as CyA nephrotoxicity ($n = 3$), CyA malabsorption ($n = 3$), disturbed CyA metabolism ($n = 4$), or retransplantation after loss of a first graft due to rejection ($n = 2$). The median follow-up time after conversion in all patients was 9 months (range 0.2–30 months).

Histologically, acute graft rejection was diagnosed by the presence of periportal mononuclear infiltrates, endothelialitis, and bile duct lesions [11]. In chronic rejection, destruction of bile ducts associated with vasculopathy was prominent; only a mild periportal infiltrate was observed. In the more serious cases, a progressive loss of bile ducts was seen on repeated biopsies; in some patients a so-called vanishing bile duct syndrome was present.

In all patients with acute graft rejection, one or more courses of steroid bolus therapy had been given prior to initiation of FK 506 therapy. In 17 of 19 patients with chronic rejection, steroids were given prior to FK 506 treatment; 2 patients also received a 7-day course of OKT3 treatment.

Immunosuppression

In most patients, on day 1 of treatment, FK 506 was administered intravenously as two 4-h infusions b.i.d. or as a continuous 24-h infusion. Usually, the patients were switched to oral FK 506 on day 2 of treatment.

In adult patients converted because of intractable graft rejection, the intravenous starting dose was 0.10 mg/kg body weight on day 1, followed by an oral dose of 0.20 mg/kg body weight per day. In the first 15 patients, FK 506 plasma levels (separation at ambient temperature) were aimed at between 2.0 and 5.0 ng/ml in the early treatment course [8, 14, 16]. Later, these levels were reduced to 1.0–3.0 ng/ml. After stabilization of liver function, plasma levels in all patients were maintained below 0.3 ng/ml. In those patients converted because of CyA toxicity or CyA malabsorption, the starting dosage was 0.10 mg/kg body weight per day. In these patients no intravenous FK 506 was given. Target plasma levels were aimed at below 0.3 ng/ml.

In children, FK 506 starting dosages were between 0.075 and 0.15 mg/kg body weight per day i.v. given as a continuous infusion over 24 h, followed by an oral dose of 0.15–0.30 mg/kg per day b.i.d. Target plasma levels were 0.5–1.5 ng/ml in the initial treatment course and below 0.3 ng/ml during the stable, long-term course.

The steroid dosage under CyA was maintained during the first 3 months following conversion. After this period, steroids were tapered to 5 mg/day; in selected patients, steroids were completely withdrawn.

Results

Actuarial patient and graft survival in the various treatment groups is shown in Table 1. Among the patients converted to FK 506 for treatment of rejection, patient survival varied between 66% (patients converted because of advanced chronic rejection) and 100% (patients treated for acute steroid-resistant rejection). Graft survival was 100% in patients with acute rejection but only 25% in patients with chronic rejection (advanced chronic graft rejection). Among the patients converted for reasons unrelated to rejection, three patients were lost due to infection; the corresponding patient and graft survival figures were 75% each.

Patient mortality primarily depended on the clinical condition of the patients at the time of conversion from CyA to FK 506. Eight patients with advanced chronic graft rejection or severe liver dysfunction unrelated to rejection were in such a disturbed clinical condition that retransplantation was not possible at the time of conversion to FK 506. In these patients FK 506 was the only therapeutic option. Three of these patients (two converted for treatment of graft rejection and one switched for disturbed CyA metabolism) were successfully rescued by FK 506; five others, however, were lost.

In the remaining 29 patients, there was no impairment (for patients converted for treatment of CyA nephrotoxicity) or only moderate impairment (for patients with acute or early chronic rejection) in the clinical status at the time of conversion to FK 506. In this group only four patients were lost, resulting in an actuarial patient survival of 86.3%.

Of the 25 patients converted because of graft rejection, 13 showed a complete normalization in liver function (Table 1). Twelve of these patients are currently well and were discharged from the hospital; one patient died due to pneumonia caused by *L. pneumophilia* during month 5 of FK 506 treatment.

In three patients only a partial response to treatment was observed. In these patients transaminases decreased during the 1st month of treatment. However, in the subsequent months, no further normalization in transaminase levels was detectable and bilirubin levels remained elevated between 400 and 200 μmol/l. One of these three patients died as a result of *Pneumocystis carinii* infection after 4 months of FK 506 treatment. The other two patients were retransplanted after 6 and 8 months of FK 506 therapy, respectively; both patients are well.

In the remaining nine patients, liver function further deteriorated despite initiation of FK 506 therapy. In these patients a worsening in the clinical course was observed that was associated with hepatic coma and respiratory insufficiency. In addition, in some patients, a sudden increase in FK 506 plasma levels (to up to 10 ng/ml) was detectable before the onset of acute liver failure, leading to death or emergency retransplantation. In this group of nonresponders, four patients were retransplanted after 1–3 months of FK 506 therapy. Three of these patients are well; the fourth patient died of *Aspergillus* pneumonia 3 months after retransplantation while on CyA. Two other patients are currently scheduled for retransplantation. The remaining three patients were in a nonretransplantable condition while on FK 506; they died due to end-stage liver failure ($n = 2$) and *Nocardia* infection ($n = 1$).

Depending on the histological type of graft rejection (Table 1), the therapeutic efficacy of FK 506 differed in the various patients. All six patients with steroid-resistant acute graft rejection responded to the FK 506 treatment. In these patients liver function completely normalized (Table 2); no graft or patient was lost in this group. In contrast, among the 19 patients with either chronic or a "mixed" type of acute and chronic rejection, only 10 patients showed a complete or partial response to the FK 506 treatment.

Twelve patients were switched to FK 506 for reasons unrelated to graft rejection. Two patients were treated for baseline immunosuppression following retransplantation. Both patients had lost their first graft due to acute rejection. As expected, in both patients adequate immunosuppression was maintained while under FK 506; no episode of graft rejection was observed.

Table 1. Clinical outcome of patients converted from CyA to FK 506. vbds, Vanishing bile duct syndrome

	Indication for FK 506 treatment			
	Graft rejection			Other[a]
	Acute steroid-resistant	Acute and chronic	Chronic (vbds)	
No. of patients	6	7	12	12
Follow-up (months)	1–14	2–14	1–30	0.2–21
Complete response[b]	6/6	3/7	4/12	8/12
Partial response[c]	0/6	1/7	2/12	1/12
No response	0/6	3/7	6/12	3/12
Actuarial patient survival	100.0%	71.4%[d]	66.6%	75.0%
Actuarial graft survival	100.0%	71.4%	25.0%	75.0%

[a] CyA malabsorption, CyA toxicity, disturbed CyA metabolization
[b] Complete normalization of all liver function tests
[c] Decrease in transaminase levels; bilirubin levels unchanged
[d] One patient died 3 months after retransplantation while on CyA-based immunosuppression

Table 2. Laboratory findings (median) in patients converted from CyA to FK 506. vbds, Vanishing bile duct syndrome

		Indication for FK 506 treatment			
		Graft rejection			Other
		Acute steroid-resistant	Mixed	Chronic (vbds)	
Bilirubin (μmol/l)	Month 0	19	380	343	104
	Month 1	10	310	348	20
	Month 3	10	101	190	11
	Month 6	10	36	209	8
ALAT (U/l)	Month 0	150	124	140	64
	Month 1	49	91	86	27
	Month 3	10	69	42	30
	Month 6	10	32	119	15
AP (U/l)	Month 0	747	800	973	793
	Month 1	780	930	720	320
	Month 3	200	741	711	230
	Month 6	150	504	546	145
Creatinine (μmol/l)	Month 0	62	92	75	106
	Month 1	80	140	128	122
	Month 3	80	100	88	72
	Month 6	80	80	71	97
Glucose (mmol/l)	Month 0	3.9	4.0	4.2	6.0
	Month 1	4.5	5.6	5.4	6.6
	Month 3	4.5	6.2	6.4	5.7
	Month 6	5.0	6.8	6.6	5.5

Month 0 = initiation of FK 506 therapy

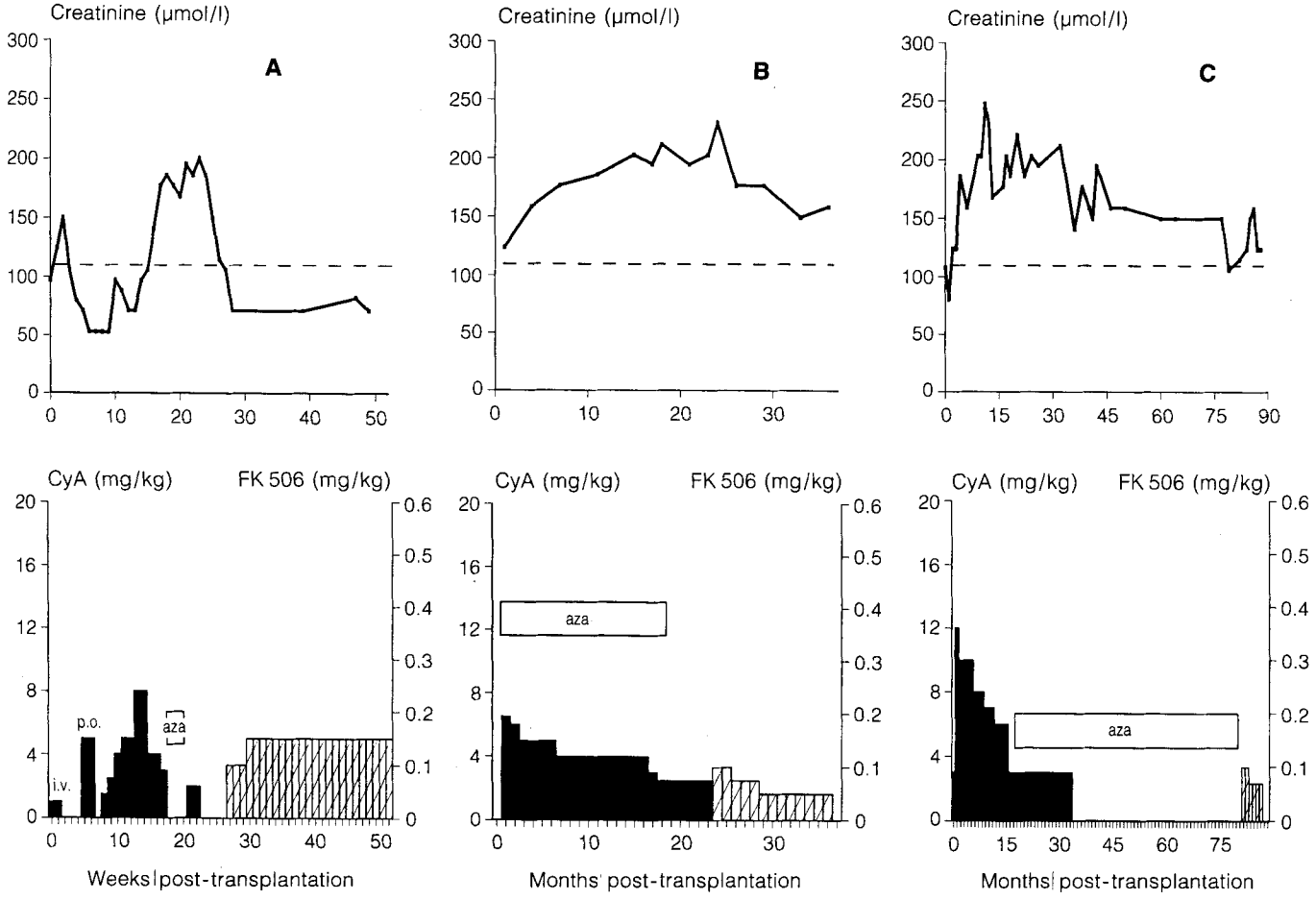

Fig. 1 A–C. Clinical course of three patients converted to FK 506 (▨) because of CyA (■) nephrotoxicity. In all patients azathioprine therapy had been attempted as alternative treatment but had to be withdrawn because of **A** infectious complications or **B, C** pancytopenia. Following conversion to FK 506, kidney function improved or normalized in two patients. In the third patient, a moderate increase in creatinine was observed after initiation of FK 506 treatment. However, following a reduction in FK 506 dosage, the creatinine level declined again

Three other patients were switched to FK 506 for CyA malabsorption that was diagnosed during the stable, long-term course. In these patients also, mild acute graft rejection was observed at the time of conversion to FK 506. In all three patients, the clinical signs of rejection resolved following conversion to FK 506, and adequate immunosuppression was maintained during the subsequent course.

Three other patients were converted to FK 506 when CyA treatment had to be discontinued due to CyA nephrotoxicity (Fig. 1). All three patients had received azathioprine before as alternative treatment; however, azathioprine had to be discontinued due to infection or pancytopenia. Following conversion to FK 506, kidney function completely normalized in one patient (Fig. 1 A). In the second patient (Fig. 1 B), creatinine levels slowly declined following conversion but remain elevated (current creatinine 159 μmol/l). The third patient (Fig. 1 C) was on azathioprine at the time of conversion to FK 506. In this patient CyA had to be discontinued due to CyA nephrotoxicity and severe hypertension 4 years before. She was switched to FK 506 since azathioprine also had to be stopped due to pancytopenia. Following initiation of FK 506 treatment, creatinine levels showed a moderate increase to 150 μmol/l. After reducing the FK 506 dosage, the creatinine levels declined. Her current creatinine is 124 μmol/l; no antihypertensives are being given. In all three patients, adequate immunosuppression was maintained under FK 506 and no signs of graft rejection were observed.

The remaining four patients were converted to FK 506 since a disturbed CyA metabolism made continuation of CyA treatment no longer possible. These patients suffered from severe liver dysfunction unrelated to graft rejection; CyA metabolites were increased to more than 1200 ng/ml on repeated measurements (nonspecific monoclonal RIA). CyA dose reduction was not possible as specific CyA blood levels were below 40 ng/ml. Due to septicemia, all four patients had a very prolonged course after transplantation; three patients were switched to FK 506 while still on respiratory therapy. These patients were in a nonretransplantable clinical condition at the time of conversion to FK 506. Three of the four patients died due to end-stage liver failure complicated by bacterial septicemia 1–3 weeks after initiation of FK 506 therapy; the fourth patient is currently well.

Relevant clinical side effects of FK 506 observed in this group of patients were tremor, nephrotoxicity, hypertension, and diabetes mellitus. Tremor, possibly related to the FK 506 treatment, was detectable in 70 % of the patients and usually responded to FK 506 dose reduction. The incidence of FK 506 nephrotoxicity, defined as an increase in serum creatinine above 140 μmol/l, was 60.0 %. All episodes of FK 506 nephrotoxicity responded to dose reduction. The incidence of new onset hypertension (requiring antihypertensive medication) and insulin-dependent diabetes mellitus was 23.3 % and 20.0 %, respectively.

Not only the incidence but also the long-term prevalence of FK 506 side effects was analyzed. After 6 months of therapy, 3 of 21 patients presented with new onset hypertension. FK 506 nephrotoxicity was not observed in any of the 21 patients after 6 months of FK 506 therapy. However, one patient treated for baseline immunosuppression after retransplantation presented with kidney dysfunction (an increase in creatinine to > 200 μmol/l) after 12 months of FK 506 therapy. Following dose reduction, creatinine values slowly decreased; the current creatinine is 150 μmol/l. At 6 months after initiation of FK 506 therapy, glucose tolerance was impaired in 3 of 21 patients; two of these patients are currently on insulin. The third patient was placed on a diet in month 6; following dose reduction in this patient, glucose metabolism normalized again.

One patient developed intra-abdominal malignant lymphoma (centroblastic, B-non-Hodgkin's lymphoma of monoclonal type) during month 6 of FK 506 therapy. This 7-year-old patient required very high i. v. and oral FK 506 doses for control of acute steroid-resistant graft rejection (up to 2.0 mg/kg body weight per day). While on FK 506 she was also treated with azathioprine and high-dose steroids. After 3 months of therapy, graft rejection was successfully controlled; however, in month 5 the patient developed EBV infection. In month 6, malignant non-Hodgkin's lymphoma was diagnosed. Following a profound reduction in FK 506 dosage, a slow regression of lymphoma was observed; the patient has since been discharged from the hospital.

Discussion

Currently, CyA is the immunosuppressant of choice for liver-grafted patients. The clinical introduction of CyA in the early 1980s has resulted in a clear improvement in the overall results of liver transplantation. However, the use of CyA can be associated with long-term side effects such as hypertension, nephrotoxicity, or diabetes mellitus [2]. Moreover, even with triple or quadruple therapy, in some patients severe graft rejection may occur which, if not effectively controlled, can only be treated by retransplantation. The present study has proven that FK 506 is a valuable alternative immunosuppressant for patients with acute steroid-resistant or early chronic graft rejection, as well as for patients with CyA-related complications. Especially in patients with early stage graft rejection that does not respond to conventional antirejection treatment, conversion to FK 506 represents an excellent alternative to retransplantation.

In contrast to earlier reports [6, 13], however, we have also found that in patients with advanced chronic graft rejection (histologically, vanishing bile duct syndrome) FK 506 treatment is only of limited clinical benefit. In this patient group the actuarial graft survival was only 25 %; in addition, a high mortality rate (4 of 12 patients lost) was observed. Several factors may be responsible for the increased mortality in these patients. In general, patients with advanced liver dysfunction are known to have an increased risk for infection under immunosuppressive treatment. In fact, two of the four patients lost in this group died due to infectious complications that coincided with their end-stage liver failure. In addition, some of these patients had received excessive immunosuppressive therapy

prior to conversion to FK 506. This also results in an increased risk for infection. Finally, because of their disturbed liver function, FK 506 parent drug and metabolites might have accumulated in the blood of these patients after conversion. This can also be associated with overimmunosuppression [1], resulting in an increased susceptibility to serious infections.

Of the 37 patients treated, 9 died, 8 of them while on FK 506; one patient died 3 months after retransplantation while on CyA. Three patients died who were in a retransplantable condition at initiation of FK 506 treatment but who did not respond to the conversion in immunosuppression. The clinical condition of these patients deteriorated under FK 506 in such a way that they finally presented with end-stage liver failure that did not allow retransplantation. One can argue that in these patients the therapeutic option of retransplantation was lost due to the FK 506 treatment. Therefore, it is of utmost importance not to miss the right moment for retransplantation in patients who fail FK 506 treatment but who are still in a retransplantable condition. Retrospective analysis of the clinical course of these patients revealed a constant increase in serum bilirubin despite conversion from CyA to FK 506. Furthermore, in most of these patients, a sudden increase in FK 506 plasma levels (to up to 10 ng/ml), indicating the disturbed metabolizing capacity of the liver [1, 3, 4, 7, 9], was detectable before the onset of acute liver failure that led to death or retransplantation. Therefore, emergency retransplantation should always be considered if there is such a sudden rise in FK 506 levels in a patient who obviously does not respond to FK 506 rescue treatment.

It is interesting that three of the eight patients who were lost while on FK 506 died due to opportunistic infection that was related to overimmunosuppression (*L. pneumophila, P. carinii* and *Nocardia brasiliensis*). In these patients high plasma levels were aimed at (2.0–5.0 ng/ml); in fact, in two patients, even higher plasma levels (8–10 ng/ml) were detectable before the onset of infection. In none of the three patients was evidence for FK 506 toxicity, such as nephrotoxicity or tremor, observed while they were obviously overimmunosuppressed. Therefore, also in patients without clinically manifest FK 506 side effects, a regular FK 506 plasma level monitoring strategy seems mandatory in order to avoid overimmunosuppression. As a consequence of the fatal outcome in these three patients, the FK 506 target plasma levels aimed at in patients with cholestatic graft rejection were reduced to 1.0–3.0 ng/ml; since then, in this institution, no further opportunistic infection has been seen in patients under FK 506 treatment.

The development of malignant lymphoma is another well-known potential consequence of overimmunosuppression that is usually observed in patients treated with monoclonal or polyclonal antibodies. In our series, one 7-year-old child developed EBV-associated malignant lymphoma. Interestingly, in this child, FK 506 plasma levels were not elevated; in contrast, very high oral dosages (up to ten times the normal dosage) were necessary to maintain plasma levels around 0.5 ng/ml and to control rejection. It is not clear whether the lymphoma in this patient was a direct consequence of these high FK 506 dosages or whether it was influenced by the additional administration of azathioprine and high-dose steroids. Lymphoma developed despite the fact that no antibodies (ATG, OKT3) were given to the patient; this points again to the potential hazard to overimmunosuppression mediated by FK 506.

The toxicity profile of FK 506 observed in this group of patients was comparable to that found in patients under primary FK 506 immunosuppression [5, 12]. Predominantly tremor, hypertension, and passager nephrotoxicity were observed. In contrast to patients under primary FK 506, however, we observed an increased frequency in new onset diabetes mellitus (20.0 % incidence and 14.5 % prevalence after 6 months of FK 506 treatment). FK 506 administered at a high dosage is known to be potentially diabetogenic [10]. The increased frequency of diabetes mellitus that we observed might have been due to the fact that higher FK 506 dosages were given to our patients. Moreover, most of the patients who were switched to FK 506 because of acute steroid-resistant or chronic graft rejection had received multiple boluses of high-dose steroids prior to the switch to FK 506, and this could have aggravated the potential diabetogenicity of the drug.

In conclusion, conversion from CyA to FK 506 represents a valuable alternative for patients with CyA-related complications or with acute or early stage chronic graft rejection. However, irrespective of the indication for FK 506 therapy, conversion should take place before serious disturbances in liver function and/or clinical status (i.e., a serum bilirubin >300 µmol/l) are observed. Finally, measures must be taken to ensure that one does not miss the right moment for retransplantation in patients with advanced liver dysfunction who do not properly respond to the change in immunosuppressive treatment.

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