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Optimal FK506 dosage in patients under primary immunosuppression following liver transplantation

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Abstract In a retrospective study, we analysed the FK506 dosage used in primary liver graft recipients enrolled in the European FK506 multicenter trial conducted from September 1990 to January 1992. In addition, a second cohort of patients treated more recently in a single centre was investigated. The impact of different dosing strategies on the clinical course of the patients was analysed with special emphasis on the incidence of rejection episodes and FK506 side-effects. Among the patients enrolled in the European FK506 multicenter trial, those patients enrolled durint the "early" phase of the study received a higher oral FK506 dose [mean oral dosage on day 7 = 0.19 mg/kg body weight (bw) per day, $n = 134$] compared to patients enrolled during the "late" period of the study (mean oral dosage on day 7 = 0.14 mg/kg bw per day, $n = 133$). This lower dosage was the result of several protocol amendments performed to reduce the incidence of FK506 side-effects. Lowering of the FK506 dosage was accompanied by a reduction in the long-term prevalence of side-effects such as diabetes (n.s.) or hypertension ($P < 0.05$), while patient survival and rejection frequency remained constant. Patients treated in centres with online FK506 blood level monitoring experienced significantly less hypertension, less episodes of diabetes and less rejection episodes compared to patients treated in centres without. The clinical course of those patients enrolled in the multicentre trial was compared with the course of a cohort of liver-grafted patients treated with FK506 more recently in a single centre. These patients had a further reduction in the FK506 dosage (0.10 mg/kg bw per day p.o. or less according to whole blood levels, with no intravenous FK506 administration). When compared to patients enrolled in the multicentre trial, these patients experienced less side-effects (nephrotoxicity, hypertension, serious early neurotoxicity) while adaequate immunosuppression was maintained.

Introduction

The new macrolide FK 506 is currently under clinical investigation for baseline and rescue immunosuppression in patients after liver transplantation [7, 8, 11]. Compared to cyclosporin A (CyA), FK 506 has similar but more potent immunosuppressant activity [7, 8]. To establish the usefulness of this new drug for clinical immunosuppression, two large multicenter trials, as well as several other single centre studies have been conducted in Europe and the United States and are currently under final analysis. During the course of both multicentre trials, the FK 506 dosage administered to the patients was reduced to decrease the frequency of drug side-effects. In the present report, we analysed the clinical course of patients treated with these different FK 506 dosing protocols. Most of the data analysed in this study were collected during the European multicentre trial conducted in eight different transplant centres in Europe. In addition, the clinical course of a small cohort of patients treated with low dose FK 506 in a single centre was also analysed.

Patients and methods

As part of the European FK 506 multicentre trial, 267 primary liver graft recipients were treated with FK 506. All patients enrolled in the trial were liver grafted between September 1990 and January 1992 in eight different transplant centres in Europe (Berlin, Birmingham, Cambridge, Hannover, Heidelberg, London, Paris and Stockholm). Exclusion criteria for enrolment into the study were HIV-positive patients, children under the age of 18 years and multiorgan transplants.

The initial FK 506 dosage given to these patients was 0.15 mg/kg body weight (bw) per day i.v. given as 4-h infusions followed by 0.30 mg/kg bw per day p.o. given in two divided doses. This dosage was later reduced to 0.03–0.05 mg/kg bw per day i.v. over a 12-h infusion period followed by 3 times the last intravenous dose orally later on. Oral treatment was commenced as soon as possible. Two cohorts of patients were defined: an "early" cohort of 134 patients (mean oral daily dose on day 7 = 0.19 ± 0.07) and a "late" cohort of 133 patients (mean oral daily dose an day 7 0.14 ± 0.06). In addition, in some centres, online FK 506 blood level monitoring (OLBM) was successfully performed for dose adjustment (blood levels available 1–2 days after blood drawing), in other centres, blood levels could only be measured on a retrospective basis.

In addition, a cohort of 35 patients treated between May and October 1993 in a single centre was also analysed. These patients were treated with a starting dose of 0.06 to 0.10 mg/kg bw per day p.o. ("low dose"); no intravenous FK 506 was given. Some of these patients also received low dose azathioprine (1 mg/kg bw per day). The clinical course of these patients was compared with a historical group of 35 liver-grafted patients receiving primary FK 506. In these patients, dosage was according to the dosing protocol(s) of the multicentre trial. Both groups were comparable for age, sex and underlying disease with the exception of more patients with fulminant hepatic failure in the "low dose" group. The inclusion and exclusion criteria used in this patient group were identical to those used in the patients enrolled in the multicentre trial.

Results

In the FK 506 treatment arm of the European FK 506 multicentre trial, the overall 6-month patient and graft survival was 83.5% and 79.3%, respectively. A total of 42.0% of all patients experienced at least one episode of biopsy-proven acute graft rejection necessitating antirejection treatment. The most relevant clinical adverse experiences using FK 506 were kidney dysfunction (44.6% of patients with at least one episode), hypertension (33.0% of patients), diabetes mellitus (17.2% of patients) and serious neurological abnormalities such as aphasia, coma, convulsion, intracerebral bleeding or pontine or extrapontine myelinolysis (10.1% of patients).

The mean overall FK 506 dosages given to the patients varied considerably between the different centres (Fig. 1). On posttransplant day 7, the mean oral FK 506 dosage ranged between 0.12 and 0.25 mg/kg bw per day. Further, while in some centres a continuous reduction in FK 506 dosage was performed during the posttransplant period

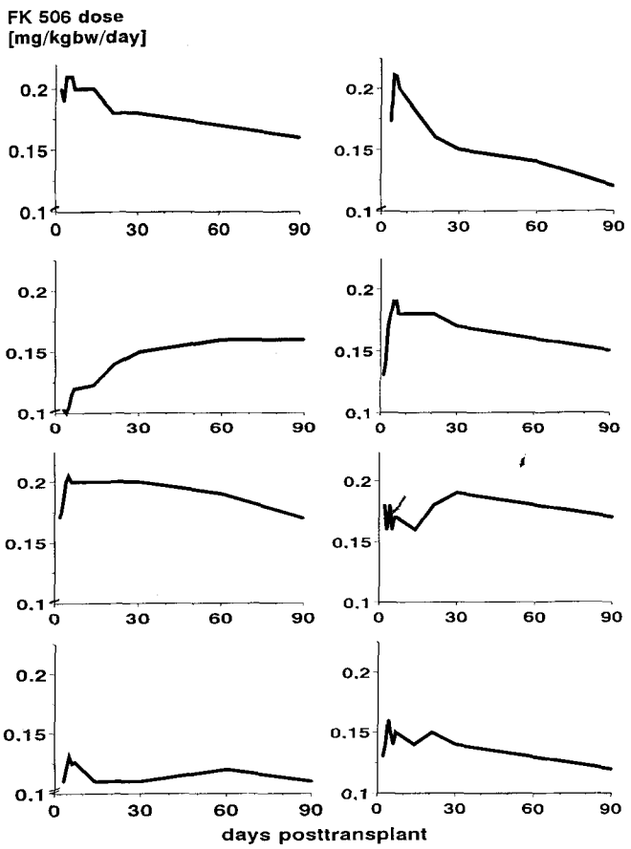

Fig. 1 Mean oral FK 506 dosage in the eight centres participating in the FK 506 multicentertrial

Table 1 Comparison of the clinical course of patients enrolled during the "early" versus "late" phase of the European FK 506 multicenter trial

	"Early" patients	"Late" patients
No. of patients	134	133
Daily oral dose (day 7)	0.19 ± 0.07	0.14 ± 0.06
6-month patient survival	84.3%	82.8%
Patients with rejection (%)	39.6%	44.4%
6-month prevalence of hypertension	24.0%	9.8%[a]
6-month prevalence of diabetes mellitus	24.0%	11.9%

[a] $P < 0.05$ versus early patients (x^2 test)

Table 2 Influence of online blood level monitoring (OLBM) on the clinical course of liver-grafted patients under primary immunosuppression (European FK 506 multicenter trial)

	Patients treated in centres with available OLBM	Patients treated in centres without available OLBM
No. of patients	128	139
Daily oral dose (day 7)	0.16 ± 0.07	0.17 ± 0.06
6-month patient survival	80.2%	86.7%
Patients with rejection (%)	36.5%	47.6%
6-month prevalence of hypertension	9.2%	23.8%[a]
6-month prevalence of diabetes mellitus	12.6%	22.9%

[a] $P < 0.05$ versus patients treated in centres with OLBM (x^2 test)

Table 3 Comparison of liver-grafted patients under primary FK 506 immunosuppression treated with "high dose" vs. "low dose" FK 506 (single centre data)

	"high dose" patients	"low dose" patients
No. of patients	35	35
Enrolment period	9/90–2/92	5/93–10/93
Patients with fulminant hepatic failure	2	6
Male/female ratio	18/17	20/15
Patients with Budd-Chiari syndrome	4	3
Assay used for therapeutic drug monitoring	Plasma EIA	Whole blood EIA/IMX

(e.g. from a mean of 0.20 mg/kg bw per day on day 7 to 0.14 mg/kg bw per day at 3 months, other centres started with low doses and systematically increased the FK 506 dosage in the subsequent period.

In the "late" patients, a reduction in the long-term prevalence of side-effects, such as diabetes and hypertension [$P < 0.05$ (x^2-test)], was observed, while patient survival and rejection frequency remained constant (Table 1). Patients treated in centres with OLBM available experienced less side-effects such as diabetes or hypertension [$P < 0.05$ (x^2-test)]. This benefit was not due to a decreased overall dosing in centres with OLBM as the mean dosage given to the patients on day 7 was nearly equal in both groups (Table 2). There was also a reduction in the frequency of rejection episodes observed in patients treated in centres with OLBM, suggesting that at least a subgroup of patients in these centres had their dosages increased according to low blood levels.

Using single centre data obtained from the Hannover group (Table 3), the clinical course of a "low dose" cohort of liver-grafted patients was analysed. As shown in Fig. 2, the lower FK 506 starting dose in the "low dose" group resulted in a lower overall mean FK 506 dose administered to these patients when compared to a historical "high dose" group (those patients who had been enrolled in the European multicentre trial in that single centre). There was a tendency to less episodes of kidney dysfunction during the early course after transplantation; this was accompanied by a lower overall creatinine level (Fig. 3). In parallel to the reduction in the incidence and severity of nephrotoxic episodes, the incidence of episodes of hypertension was also reduced in the "low dose" patients (P = n.s.); there was no difference in the incidence of diabetes mellitus in both groups.

In patients receiving the lower FK 506 dosage, the frequency of episodes of serious early neurological abnormalities, such as aphasia, cramps, intracerebral bleeding, coma and pontine or extra-pontine myelinolysis, was reduced compared to patients receiving "high dose" FK 506. With "high dose" FK 506, this serious early

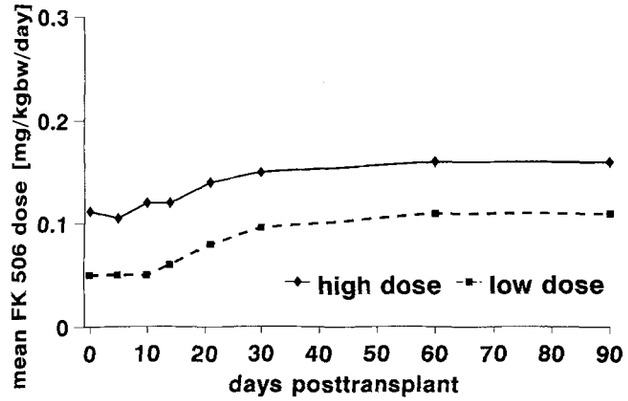

Fig. 2 Course of the mean oral FK 506 dosage in two groups of patients treated with "high dose" or with "low dose" FK 506 (single centre experience)

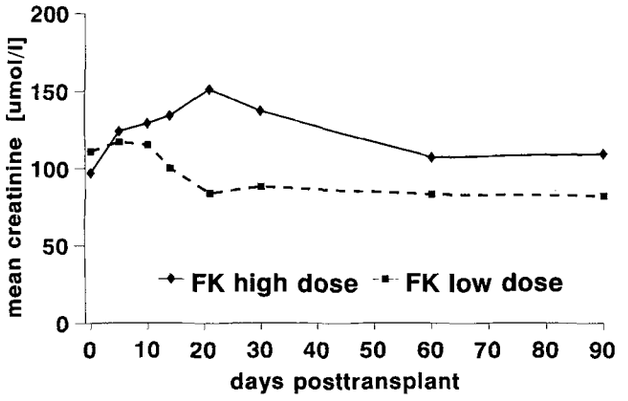

Fig. 3 Course of mean creatinine in two groups of patients treated with "high dose" or with "low dose" FK 506 (single centre experience)

postoperative complication was observed in 6 out of 35 patients, with low dose FK 506, this complication was seen in 4 out of 35 patients (n. s.; Table 4). The frequency of biopsy-proven acute graft rejections requiring treatment (increase in FK 506 dose or steroid boluses) was comparable; 23 % and 26 % of patients in the "high dose" and "low dose" groups, respectively, had experienced at least one episode of graft rejection at 6 months. No chronic graft rejection was seen during the first 6 months posttransplantation. Six of nine patients experiencing acute graft rejection in the low dose group had been started with FK 506 dosages of less than 0.10 mg/kg bw per day due to initial liver dysfunction [1, 5, 10]. These patients had not had their FK 506 dosages increased in the later course and were on FK 506 dosages below 0.05 mg/kg bw per day at the onset of rejection. Most of the whole blood levels measured at the onset of rejection were below 5.0 ng/ml.

Discussion

The clinical use of FK 506 for immunosuppression in primary liver transplantation is characterised by a "learning" curve on the optimal use of this potent new drug. While in the so-called late patient group in the European multicentre trial, the safety profile of the drug was substantially improved by the lower FK 506 dosing, the safety profile remained unsatisfactory compared to CyA, with equal or even higher frequencies of some side-effects. Apparently, the patients enrolled during the "late" phase of the European multicentre trial were still overtreated. We showed here that a further reduction in FK 506 dosage to 0.10 mg/kg bw per day is possible without losing drug efficacy. Using this low FK 506 dosage, the FK 506 side-effect profile was equal or superior to a historical CyA group (e. g. the control arm of the European FK 506 multicentre trial). The higher immunosuppressive potency of FK 506 was maintained. This observation, however, awaits more substantial confirmation. A multicentre trial investigating the impact of low oral FK 506 dosing on the side-effect profile of the drug has just finished in Europe and awaits final statistical evaluation.

A further reduction in FK 506 starting dosage to below 0.10 mg/kg bw per day does not seem possible without adding other immunosuppressants such as mono or polyclonal antibodies. Therefore, we currently recommend that reduced the starting dosage should not be below this limit. An exception should be in patients with serious early liver dysfunction; these patients are known to develop high blood levels with subsequent episodes of toxicity in the immediate postoperative period if the dosage is not reduced (Table 5) [1, 5, 10].

Table 4 Incidence of FK 506 side-effects in patients on "high dose" or "low dose" FK 506 (single centre data)

	"high dose" patients	"low dose" patients
Hypertension (requiring medication)	34.3 %	17.1 %
Diabetes mellitus (requiring medication)	8.6 %	8.6 %
serious early neurotoxicity (aphasia, coma, intracerebral bleeding, cramps, pontine myelinolysis)	17.1 %	11.4 %

Table 5 Recommended FK 506 dosage in liver-grafted patients

	FK 506 dosage (mg/kg bw per day)	FK 506 blood level (ng/ml)
Early postoperative course		
Good graft function	0.10 p.o.	5–10
Impaired graft function	0.05–0.07 p.o.	5–15
Maintenance course	0.10 oral	3–8
Rescue (graft rejection)	Day 1 = 0.10 i.v. Subsequent days = 0.20 p.o.	5–15

Blood level monitoring to adjust FK 506 dosage to target levels between 3.0 and 15.0 ng/ml in whole blood [2, 12] is a mandatory; in centres with OLBM, the frequency of both side-effects and rejection episodes was reduced [6, 9].

While according to the study protocol, the FK 506 starting dose was relativly fixed, an alteration in FK 506 dose according to clinical events such as rejection or toxicity was allowed. In addition, in some centres, doses were adjusted to maintain target blood or plasma levels. Therefore, a profound heterogeneity in FK 506 dosing was found between the various centres. This variability not only reflected random centre differences in the use of a new drug but also reflected the individual centres experience regarding the incidence and severity of infection as well as graft rejection. While in some centres, an initial large dosage of immunosuppression was given that was later reduced, in other centres, the initial immunosuppression was low and was then slowly increased. With FK 506 immunosuppression – compared to conventional immunosuppression – there is a stronger relationship between drug dosage and resulting immunosuppressive effect over a broad dosage range [7, 8, 10]. Conversion from CyA- to FK 506-based immunosuppression can be performed in patients with CyA toxicity (using a low initial FK 506 dose) as well as in patient on CyA with intractable graft rejection (high initial FK 506 dose) [11]. Thus, irrespective of the underlying immunosuppressive strategy in a given centre or in a given patient, flexible immunosuppression with FK 506 can be performed only by increasing or reducing the dosage. The addition of other immunosuppressants in, e. g. high risk patients, in most cases is not necessary. This results in a more easy handling of FK 506.

Currently available data indicate, that – compared to CyA – there is a somewhat higher overall frequency of serious neurological abnormalities in primary liver immunosuppression. Interestingly, during both European liver studies, the European multicentre study and the subsequent "dose finding" study, there was considerable centre variation as to the frequency of serious neurological abnormalities using FK 506. While some centres reported an incidence of up to 20% of adverse events, in other centres the frequency was negligible. In addition, in contrast to liver-grafted patients under primary FK 506 immunosuppression, in liver rescue immunosuppression [11], as well as in kidney primary immunosuppression [7, 8], neurological symptoms are extremely rare. One can, therefore, speculate that (a) liver-grafted patients during the early posttransplant course are more prone to the development of neurological complications and (b) different centres utilise different non-immunosuppression-related strategies to minimise the incidence of posttransplant neurological abnormalities.

While there are several advantages of FK 506 compared to CyA such as better patient and graft survival (McMaster et al., this issue), higher immunosuppressive potency (Bismuth et al., this issue; Calne et al., this issue), less hypertension-inducing effects and the steroid-sparing effect (Otto et al, this issue), the frequency of serious neurological abnormalities seems to be somewhat (although not significantly) higher with FK 506 than with CyA. Irrespective of the unsolved question of whether FK 506 is, in fact, causative of this kind of serious posttransplant complication, other non-immunosuppression-related therapeutic strategies such as radical fluid restriction during the perioperative course or strict albumin substitution (Undre et al., this issue) should be utilised to minimise the incidence and severity of neurological complications after liver transplantation.

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