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Renal complications and development of hypertension in the European study of FK506 and cyclosporin in primary liver transplant recipients

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Abstract We examined the occurrence of renal complications and hypertension in 540 primary liver recipients entered into the European liver trial comparing primary FK506 to a cyclosporin A based immunosuppression regimen (CBIR). No difference in serious renal impairment or mean creatinine levels was observed with similar rates of "kidney failure" (FK506 9.4% vs. CBIR 7.3%) and dialysis requirements (FK506 12% vs. CBIR 11%). "Abnormal kidney function", a less serious parameter of renal impairment, was reported in 89 recipients (33%) in the FK506 group versus 58 (21%) in the CBIR group ($P < 0.01$). Development of this complication was associated with elevated intravenous FK506 dosing schedules, with the mean cumulative dose 43% higher than treated patients with unaffected kidney function. In a later cohort of patients where intravenous dosing was lower, no significant difference in renal complications was detectable. The 6-month prevalence rate of systemic arterial hypertension was noted to be lower in the FK506-treated patients compared to the CBIR group [33 (17.2%) vs. 47 (25.7%)].

Key words Immunosuppression
Nephrotoxicity · Transplantation

Introduction

The clinical usefulness of a proposed immunosuppressant in organ transplantation is determined not only by the agent's efficacy but also by its toxicity profile. In liver transplantation, conventional immunosuppression protocols at present are based around cyclosporin A (CyA) in both induction and maintenance regimens. However, the main dose-limiting factor of this agent is its systemic toxicity profile that includes an acute and chronic detrimental effect on renal function [2, 6]. The development of renal dysfunction before and following liver transplantation is associated with increased rates of sepsis and lower patient and graft survival [3, 8]. FK506, a clinically new immunosuppressant agent, has recently been proposed to possess a superior therapeutic index in liver transplant recipients in relation to both efficacy and drug-related toxicity [10]. However, further controlled data are re-

quired before the precise clinical role of this agent in immunosuppression protocols is determined.

In this present study, we examined the occurrence of renal complications and hypertension in the European multicentre study of primary liver transplant patients receiving either FK 506 or a CyA-based immunosuppression regimen (CBIR). The influence of FK 506 dosage protocols on these complications was also determined.

Patients and methods

Study population

A total of 540 patients (15–68 years, 294 male: 251 female) from a multicentre, open, prospectively randomised, parallel-group study comparing primary FK 506 immunosuppression ($n = 267$) to a CBIR ($n = 273$) in liver transplantation were studied. Randomisation was performed before surgery using a 1:1 randomisation schedule. No patients were excluded on the basis of comorbid medical conditions (including renal impairment/failure) or the presence of fulminant hepatic failure, with this latter group stratified separately. All patients were followed up for a minimum of 6 months. In an attempt to determine the influence of dosage schedules on FK 506-related nephrotoxicity, we also examined the occurrence of renal complications in two patient cohorts [so-called early ($n = 134$) and late ($n = 133$) cohorts] divided on the basis of the FK 506 dosage protocol amendments outlined below.

Immunosuppression protocols

In the first part of this study, the initial intravenous (IV) dose of FK 506 of 0.075 mg/kg (4-h infusion) was administered within 6 h after closure of the abdominal wall. This dose was repeated every 12 h for 3 days and was followed by oral FK 506 therapy at a dose of 0.30 mg/kg per day in two divided doses. Subsequently, this regimen was modified to 0.03–0.05 mg/kg (12-h infusion) repeated every 12 h for 3 days with the same oral dosing schedule. Investigators were allowed to perform dose modifications on the basis of graft function, efficacy, drug monitoring and drug-related toxicity. Corticosteroid administration in this treatment group was standardised with initial doses of prednisolone (or equivalent) commenced at 20 mg/day with reductions as clinically indicated. Azathioprine was not routinely administered in this group except if desired during FK 506 interruption or withdrawal.

The CyA-based regimens were centre specific, with each programme maintaining their preferred optimal immunosuppression regimen at the time of protocol design (1989) throughout the study period. All induction maintenance regimens included cyclosporin A (2–6 mg/kg per day), azathioprine (1–3 mg/kg per day) and corticosteroids (0.2–10 mg/kg per day) with antilymphocyte globulin administered additionally in three centres. Supplemental antirejection protocols were similarly centre specific.

Renal function/statistical methods

Adverse experiences in relation to renal dysfunction were summarised using the COSTART coding system with incidence rates compared between the groups using chi-square methods. In addition (due to variable follow-up and exposure to the test drugs), renal function was also examined using cumulative rates and Kaplan-Meier methods. Finally, in the FK 506 group only, the effects of various dosing parameters on renal function (initial IV dose, rate of initial IV dose, total days of IV dosing, total cumulative IV dose, the average dose in the week before occurrence of renal dysfunction and the cumulative dose to the occurrence of renal dysfunction) were examined. For the latter two dosing parameters, the method of Robins and Tsiatis was used to analyse the relationship between the parameter and the time to occurrence of the renal complication. The complications examined were 'kidney failure' and haemodialysis requirements, 'abnormal kidney function', 'oliguria' and 'increased creatinine'. Hypertension was defined by the investigators using their own standard clinical criteria.

Results

Whole study population

There were no significant differences in baseline pretransplant demographics or clinical characteristics between the two treatment groups. Additionally, no difference in subjective organ assessment or intra-operative events that could have influenced postoperative renal function, such as ischaemia time, use of veno-venous bypass, duration of surgery or blood loss, were demonstrated. Similarly postoperatively, there was no detectable difference in exposure to nephrotoxic agents including aminoglycoside antibiotics, systemic amphotericin B or non-steroidal anti-inflammatory drugs.

The overall incidence of adverse experiences affecting the urogenital system was significantly higher in the FK 506 treatment group (71.1%) compared to the CBIR treatment group (55.3%; $P < 0.05$), with the largest proportion of these events attributed by investigators to the immunosuppressive therapy. Severe renal impairment was not significantly different overall between the groups, with an incidence of 'kidney failure' in the FK 506-treated group of 25 (9.4%) vs. 20 (7.3%) in the CBIR-treated patients, and similarly there was no difference in the requirements for a period of haemodialysis [FK 506-treated patients, 33 (12%) compared to 31 (11%) CBIR-treated patients].

Abnormal kidney function (COSTART term that includes renal insufficiency) was second only to tremor as the commonest adverse experience reported by investigators in the FK 506-treated patients. This complication was seen in 89 recipients (33%) in this group versus 58 (21%) in the CBIR group ($P < 0.01$). This complication resulted in a dose reduction and/or interruption in 36 (13%) and 35 (13%) FK 506-treated patients, respectively, versus 21 (8%) and 17 (6%), respectively in the CBIR group. The prevalence of abnormal renal function,

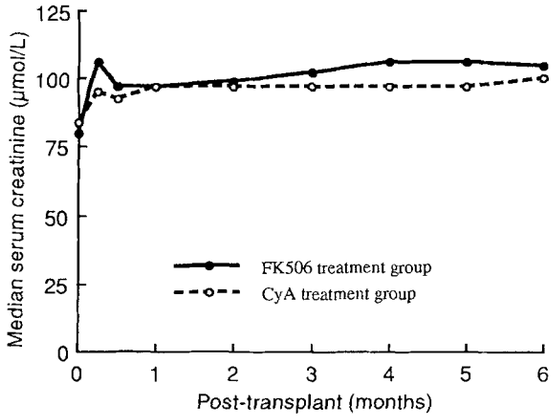

Fig. 1 Serum creatinine (median) levels in the FK 506 and CBIR treatment groups at several study time-points in the 6-month follow-up period. With the exception of day 7, no statistical difference was detected

which initially declined at 23 months compared to the early postoperative period, rose again by 6 months in both treatment groups with no significant difference detected between them at this time (FK 506 group, 12% vs. CBIR, 9% at 6 months). A similar pattern was also observed in relation to the other COSTART terms of 'oliguria' and 'increased creatinine'. However, with the exception of the first few days post-transplantation, there was no significant difference in serum creatinine levels between the groups (see Fig. 1). Significant centre variations in relation to the incidence of abnormal renal function were detected in the CBIR-treated patients, with the centre using the highest CyA dosing regimen (initial IV dose 6 mg/kg per day) experiencing the most frequent renal complications.

Several parameters of the dosage protocols of FK 506 administration only were examined in relation to the occurrence of episodes of renal dysfunction (see Table 1). As can be seen from this table, a strong association existed between higher IV dosing schedules and the development of episodes of renal dysfunction. It is apparent that the rate, daily dosage and total period of IV administration were implicated in these events. In particular, the total cumulative IV dose was significantly higher in patients experiencing these different indices of renal dysfunction, with the mean dose 30–51% higher compared to those recipients with unaffected kidney function.

Electrolyte abnormalities following transplantation were also studied. The risk of developing hyperkalaemia was similar in both groups [FK 506, 12 patients (4.49%) vs. 11 (4.03%)]. Hypomagnesaemia, which is a recognised complication of CyA-related renal tubular toxicity, was more frequently seen in FK 506-treated patients [40 (15%)] compared to the CBIR-treated group [23 (8%); $P < 0.05$)]. Interestingly, the development of this complication was associated with significantly lower FK 506 dosages in the FK 506 patients, probably reflecting the absence of renal failure that would secondarily increase circulating magnesium levels.

Systematic arterial hypertension, which is a further recognised complication of CyA, was also evaluated. No overall significant difference in cumulative rates of this complication were demonstrated. However, it is important to differentiate episodes of temporary hypertension occurring in the early postoperative period [related incidentally to cumulative IV dose of FK 506 (0.32 vs. 0.22 mg/kg)] from sustained development of this complication requiring antihypertensive agents. Notably, the 6-month prevalence rate was reduced in the FK 506-treated patients at this time compared the CBIR group [33 (17.2%) vs 47 (25.7%)].

Early and late patient cohorts

It is clear from the above data that much of the renal toxicity associated with FK 506 was related to increased

Table 1 Relationship between several intravenous FK 506 dosing parameters and the presence of impairment in renal function. The consistently higher dosage schedules in FK 506-treated patients experiencing renal dysfunction supports the dose-dependency of this phenomenon, which has already been established for cyclosporin A

Dosing parameter (mean)	Renal function					
	Kidney failure		Abnormal kidney function		Increased creatinine	
	Present	Absent	Present	Absent	Present	Absent
Initial IV dose (mg/kg)	–	–	–	–	0.0514***	0.0378
Initial rate IV (mg/kg/hr)	–	–	0.0077**	0.0056	0.0102***	0.0053
Cumulative IV dose (mg/kg)	0.484**	0.235	0.314*	0.219	0.357**	0.221
Total IV dosing days (days)	7.33*	4.03	5.36*	3.65	–	–

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2 Analysis of influence of lower FK 506 dosing schedules on the occurrence of episodes of renal dysfunction. The intravenous dose reduction in this later patient cohort was up to 60% less than the initial schedules, in addition to being infused over a 12-h period (compared to a previous 4-h period). Data are presented as n(%)

		Renal function			
		Kidney failure	Abnormal kidney function	Increased creatinine	Oliguria
FK 506	Early cohort ($n=134$)	15 (11.2)	49 (37)	32 (23.9)	25 (19)
	Late cohort ($n=133$)	10 (7.5)	39 (29)	19 (14.3)	24 (18)
CyA	Overall ($n=273$)	20 (7.3)	58 (21)	49 (18)	30 (11)

dosage. Due to these toxicity considerations, there was a significant study protocol dosage reduction for patients entered into the latter half of this study. A major reduction in renal adverse experiences was detected in this group, with the incidence of all the indices of renal function examined diminishesd to levels similar to and, on occasion, less than the CBIR-treated group (see Table 2). However, a slightly increased tendency to oliguria may continue with IV dosing of FK 506, with all the episodes of oliguria occurring in the first 28 days following transplantation presumably related to early IV administration of the major immunosuppressant agent. Of particular interest, the frequency of 'increased creatinine' was lower in the late FK 506 cohort compared to the CyA recipients, with this index of renal function detecting the more clinically important chronic nephrotoxicity. Similarly, the cumulative 6-month incidence of hypertension was significantly reduced in the late [36 (27.07%)] compared to the early cohort [52 (38.81%); $P < 0.05$].

Discussion

The results of this study, which provides controlled clinical data on the nephrotoxic properties of both the major immunosuppressants, indicated that use of FK 506 has a broadly similar toxicity profile to CyA. Although many comorbid clinical events can lead to post-transplant renal failure, immunosuppressant-related nephrotoxicity often contributes to this event. Development of severe renal impairment in the early post-transplant period was associated with an inferior overall outcome and it was, therefore, reassuring that FK 506 administration was not associated with an increased incidence of this complication with approximately equal rates of 'kidney failure' and dialysis requirements as the conventional CyA -based regimens. In the event of significant early renal dysfunction, most centres reduce or interrupt the dose of CyA and compensate for this by administering increased dosages of corticosteroids or by introducing OKT_3, although both these therapeutic responses are accompanied by increased risk of sepsis [1, 5, 7].

In the indices of less significant renal damage examined, a consistent trend towards increased frequency of these complications in the FK 506-treated patients was noted. Although this pattern was present in the overall study population, the frequency of complications in the patients representing the early 'high-dose' cohort accounted for the majority of the differences. It is clear that the dosage of FK 506 administered to this early patient cohort was too high, with the accompanying levels of toxicity necessitating frequent dose modifications. Notably, however, despite increased rates of early renal dysfunction, there was no detectable differences by 6 months. The importance of dosage in the renal toxicity associated with intravenous administration of FK 506 was clearly demonstrated both in the examination of several dosing parmaters and in the separate study of the later patients entered into the study with lower intravenous and oral dosing protocols. Significantly, no differences in renal complications were detectable in this latter group compared to the control population. These patients, despite the FK 506 dose reduction, continued to benefit from superior control of rejection (personal communication European FK 506 liver study group) with this combined data, supporting the proposal that this agent may possess a superior therapeutic index to CyA. Although no differences in circulating potassium levels were detected, lower magnesium levels were more frequently associated with FK 506 administration and clinicians should beware of this complication as hypomagnesaemia has been implicated in increased neurological adverse events following liver transplantation [4].

The previously described lower frequency of systemic arterial hypertension in FK 506-treated patients was confirmed in this study [9]. It remains unclear whether this reduction reflects the lower corticosteroid doses which may contribute to this complication, administered alongside this agent or represents an intrinsic benefit of FK 506. The reduction in concomitant antihypertensive

medication and the absence of possible hypertension-related complications is a significant advantage of this agent over CyA. This benefit is particularly important in the paediatric population, as this group suffer disproportionately from severe hypertension.

With a large proportion of the nephrotoxicity of FK 506 associated with intravenous administration, the proposal that oral dosing reduces overall toxicity without loss of efficacy requires to be studied. This preliminary observation has recently been formally tested in a more recent European controlled trial in liver recipients with initial results suggesting that this route of administration achieves satisfactory drug levels and may lead to a reduced overall systemic toxicity profile (personal communication, European FK 506 liver study group).

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