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FK506 primary immunosuppression following emergency liver transplantation for fulminant hepatic failure

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Abstract The efficacy and safety of an FK506-compared to a cyclosporin A based immunosuppression regimen was examined in liver recipients who underwent transplantation for fulminant hepatic failure in the European FK506 liver study. A consistent trend towards improved patient and graft survival noted in the FK506-treated patients was apparent from the first postoperative week (e.g. patient survival: day 7, 95.5% vs. 82.1% and month 6, 72.7% vs. 60.7%). Acute (in particular intractable) rejection was less frequent in the FK506 group (e.g. cumulative intractable rejection rate at 6 months, 6.2% vs. 22.6%). In a single centre (Kings College Hospital), 17 patients were studied in more detail. The FK506 treatment group had improved graft function, lower steroid requirments and episodes of infection. Accompanying these benefits, apache 111 and TISS scores were lower in this group in the early posttransplant period. Intensive care discharge was earlier and both treatment groups experienced similar toxicity.

Introduction

The outcome of liver transplantation when carried out for fulminant hepatic failure (FHF) remains inferior to elective transplantation [2, 12]. Selection of patients with liver failure for transplantation is on the basis of biochemical or clinical prognostic criteria indicating an extremely low probability of survival if treated conservatively [3, 4, 13]. These critically ill patients who are at high risk of bacterial and fungal infection receive prophylactic antimicrobial therapy and undergo close infection surveillance following transplantation [15, 16]. Despite these measures, patient loss in the early postoperative period is often related to the development of severe systemic sepsis and multisystem organ failure (MOF) [14]. The risk of these complications in liver recipients is also modified by the immunosuppression regimens used [1, 11]. Conventional regimens based upon cyclosporin A (CyA) and azathioprine include administration of high-dose corticosteroids at substantial dosages in the early postope-

rative period, which is likely to be implicated in the development of sepsis. FK506, a potent immunosuppressant recently the subject of controlled clinical trials allows withdrawal of azathioprine and considerably lower maintenance and supplemental corticosteroids schedules in the control of liver allograft rejection. These modifications in immunosuppression schedules have been proposed as major advances in posttransplant care with the early uncontrolled clinical trials of FK506-based regimens demonstrating both reductions in sepsis and improved patient and graft survival [17]. The advantages of such a regimen may be most readily appreciated in the high-risk patients transplanted for acute liver failure [5].

In this present study, we evaluated the efficacy and safety of an FK506-compared with a conventional CyA-based immunosuppression regimen (CBIR) in 50 recipients undergoing emergency transplantation for FHF in the controlled, European multicentre trial of FK506. In addition, the results from the Kings College Hospital centre are analysed in more detail in relation to the clinical course of the early posttransplant period.

Patients and methods

Study population

Fifty liver recipients transplanted for FHF (as defined by Trey and Davidson [18]) and who were entered into a multicentre, open, prospectively randomised, parallel-group study were studied, comparing primary FK506 immunosuppression ($n = 22$) to a CBIR ($n = 28$) in liver transplantation. Randomisation was performed separately in this subgroup before surgery using a 1:1 randomisation schedule. All patients were followedup for 6 months. Of the total number of patients entered in this study, 17 (34%) were transplanted at Kings College Hospital.

Immunosuppression protocols

In the first part of this study, the initial intravenous (IV) dose of FK506 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 followed by oral FK506 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. Plasma levels in the first phase of the trial were maintained initially between 1–2 ng/ml, with later trial protocol dose reductions allowing levels below this range based on clinical parameters (Sep-pak, room temperature separation, ELISA). 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 FK506 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 CyA (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 in induction schedules additionally in three centres. At Kings College, this regimen in the early postoperative period comprised a triple therapy schedule of CyA (whole blood levels 120–150 ng/ml, monoclonal RIA, Incstar), azathioprine (1 mg/kg per day) and prednisolone 60 mg/day. Maintenance immunosuppression was similarly based, in the absence of drug-related complications, on a triple therapy regimen with CyA levels maintained between 100–150 ng/ml and prednisolone dosage at 0.08–0.10 mg/kg per day.

Supplemental antirejection protocols were similarly centre specific, with this regimen in this centre comprising in initial course of hydrocortisone 1 g bid IV for 2 days followed by 1 g od for 3 days. Rejection episodes resistant to this regimen were treated with an additional course of methylprednisolone 1 g od for 3 days.

Efficacy and safety parameters

Patient and graft survival was analysed using Kaplan-Meier methods and the survival times were compared between the treatment groups using the generalised Wilcoxon test. As a large proportion of clinical events where in the early posttransplant period, this test, which is more sensitive for early events in life-table analysis, was employed. Patients who died or underwent retransplantation were defined as having graft failure. The same conventions were employed for the time to first rejection/intractable rejection with distribution of events between the study groups compared with the Cochran-Mantel-Haenszel procedure. Protocol liver biopsies were performed on day 7 and whenever a rejection episode was clinically or biochemically suspected. In the separate Kings College Hospital analysis, outcome of the study population was determined by measurement of routine clinical and biochemical parameters, in addition to prognostic scoring systems [apache 111 and therapeutic intervention scoring system (TISS)] used in the assessment of critically ill patients [10]. These results are expressed as median (mean) and compared using chi-squared methods or the Fisher exact test.

Results

A consistent trend towards improved patient survival was detected in favour of FK506-treated patients with this pattern apparent from week 1 (95.5% versus 82.1% in the CBIR group) and continuing to the 6-month follow-up period [72.7% and 60.7%, respectively (ns); see Fig. 1]. A similar benefit was also noted for primary graft survival in the FK506 group, with a survival at 6 months of 72.7% compared to 53.6% in the CBIR group (ns; see Fig. 2).

A significantly lower cumulative risk of an acute rejection episode was observed in the FK506 group compared to the CBIR patients at 1 week (19.3% versus 59.1%), with considerably lower overall rejection frequency in the early postoperative period (see Fig. 3).

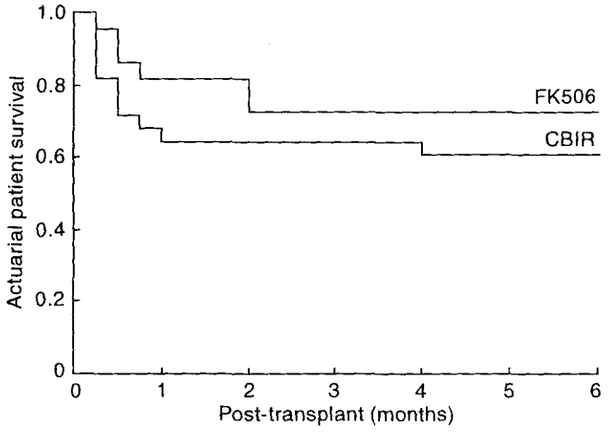

Fig. 1 Cumulative actuarial patient survival to 6 months in the whole study population for FK 506 ($n = 22$) and CyA ($n = 28$) based immunosuppression regimens

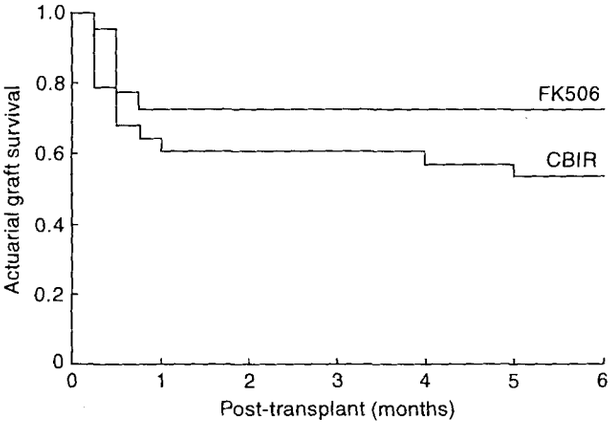

Fig. 2 Cumulative actuarial graft survival to 6 months in the whole study population for FK 506 ($n = 22$) and CyA ($n = 28$) based immunosuppression regimens

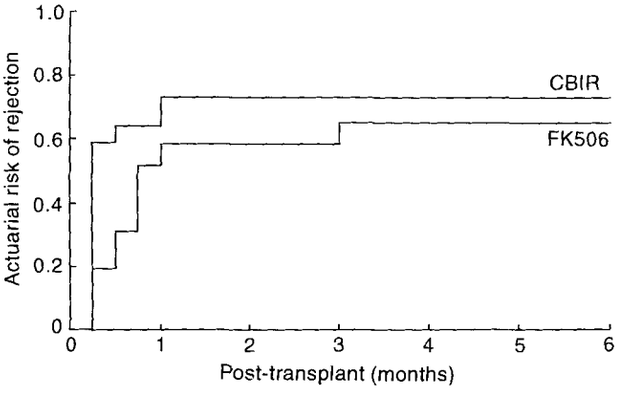

Fig. 3 Cumulative risk of an acute rejection episode to 6 months in the whole study population for FK 506 ($n = 22$) and CyA ($n = 28$) based immunosuppression regimens

Similarly, there was a marked reduction in the intractable rejection rate between the groups. The intractable rejection rate of 22.6% at 6 months in the CBIR group was compared to a rate of 6.2% in the FK 506 group in this study population (see Table 1). Notably, the rates of rejection, particularly intractable episodes, were considerably higher in fulminant patients than elective recipients irrespective of immunosuppression, although these rates were always lower in the FK 506-treated patients.

Kings College Hospital experience

There was no significant difference in the clinical characteristics of the two limbs of the study population, with both groups having similar pretransplant status and donor organ characteristics (Table 2). All donors and recipients were ABO compatible. The median grade of encephalopathy in the FK 506 (2.5) and the CyA recipients (3) was similar, with evidence of cerebral oedema present in two of eight and in three of nine patients, respectively. Renal replacement therapy was required in three of eight of the FK 506 recipients and in four of nine CyA recipients prior to transplantation. The actuarial 1-year patient and graft survival at 6 months post-transplantation or at retransplantation was 87% (seven of eight) in the FK 506 group and 53% (five of nine) in our CyA-treated patients (ns). Current follow-up of the population reveals an actuarial patient survival of 75% (six of eight) in the FK 506 and 44% (four of nine) in the CyA group (ns). The causes of the two deaths in the FK 506 recipients were segmental hepatic infarction leading to retransplantation and subsequent sepsis/MOF and primary sepsis/MOF. In the CyA-treated patients, patient loss ($n = 5$) was due to graft versus host disease/MOF, chronic rejection requiring retransplantation and subsequent development of haemorrhagic pancreatitis/MOF and primary sepsis/MOF (three cases).

Table 1 Cumulative incidence of acute (including intractable) rejection rates at 6 months in both the emergency and elective patient groups under the FK 506- and CyA-based immunosuppression regimens (CBIR)

Recipients	Rejection	FK 506 (%)	CBIR (%)
FHF	Acute	65.5	73.2
	Intractable	6.2	22.6
Low risk	Acute	40.5	53.7
	Intractable	3.1	9.4
All	Acute	42.0	54.7
	Intractable	2.9	10.1

Table 2 Clinical and demographic data of the patients entered into the european FK 506 primary liver transplant study at the Kings College Hospital site prior to transplantation, showing donor organ ischaemia times and intra-operative blood loss

	FK 506 ($n=8$)	CyA ($n=9$)
Age (years)		
Median	34	35
Range	18–53	17–64
Sex		
M/F	2/6	3/6
Aetiology		
Acetaminophen	2	2
Non A–non B	3	2
Hepatitis A/B		4
Wilsons	2	
Drug	1	1
Apache 111		
Median	53	62
Range	19–91	19–78
Infection		
Suspected	3/8	4/9
Confirmed	3/8	2/9
Donor organ		
Total ischaemia time (hours)	12.6	9.5
Surgery		
Intra-operative blood loss (mls)	2617	3250

Apache 111 and TISS scores were lower in the FK 506 recipients, particularly in the first posttransplant week and five of eight (63%) FK 506-treated patients were discharged the intensive care unit by the end of the 1st week compared to three of nine (33%) CyA-treated recipients (Table 3). The median period to self-ventilation in survivors was 3 days in the FK 506 group and 5 days in the CyA recipients (ns). Early graft function was superior in the FK 506 limb as assessed by routine clinical measurements of serum levels of aspartate aminotransferase (AST) and bilirubin (Table 4). In the FK 506-treated patients, levels of AST were significantly reduced in the 1st week following transplantation in comparison to those on CyA, with the largest difference between the

Table 3 Critically ill prognostic scores (apache 111 and TISS) in the early posttransplantation period in the Kings College Hospital series

Day	Apache 111			TISS		
	CyA	FK 506	*P* value	CyA	FK 506	*P* value
1	71	58	ns	37	35.5	ns
3	67	55	0.05	37	28	0.02
7	53	45	0.08	14	7.5	ns
14	46	40	ns	8.5	4	N/A

regimens noted on the 7th postoperative day (78 vs. 326 IU/l, $P < 0.05$). Similarly, the serum bilirubin did not rise significantly in the FK 506 patients in comparison to the CyA patients, with levels lower in FK 506 recipients throughout the early posttransplant period (e.g. postoperative day 7: 188 vs. 352 μmol, $P < 0.05$; Table 4). Reflecting the clinical parameters above, the median period in the intensive care unit (either discharge or death) was lower in the FK 506 group compared to the CBIR group (median period: 6 vs. 11 days).

Thirteen episodes of histologically confirmed acute rejection occurred in the CyA recipients, with all patients experiencing at least one episode (1.38 episodes per patient). Control of rejection was achieved following one cycle of supplemental corticosteroids in nine episodes, with a further four episodes requiring an additional cycle of steroids. Two patients developed intractable rejection and were switched to rescue therapy with FK 506. In one patient, rejection was successfully reversed, while the other patient was unresponsive to FK 506 salvage therapy and required retransplantation. In the FK 506 group, only four episodes of rejection occurring in four patients were documented, all of which were reversed by one cycle of supplemental corticosteroids (0.5 episodes per patient; $P < 0.02$). The total steroid requirements in the 1st 30 days following transplantation (prednisolone equivalent dose/day graft survival) was 150 mg/day in the CyA limb and 69 mg/day in the FK 506 limb ($P < 0.01$).

A higher incidence of episodes of infection was noted in the CyA limb [2 (2.11 per patient)] compared to the FK 506 limb [1 (0.88 per patient); $P < 0.01$], with sepsis a

Table 4 Early graft function in the Kings College Hospital patients as assessed by serial liver function tests [serum bilirubin and aminoaspartatetransferase (AST)] in the 1st month following transplantation

Day	AST (IU/L)			Bilirubin (μmol)		
	CyA	FK 506	*P*	CyA	FK 506	*P*
3	303 (106)	152 (40)	<0.05	193 (31)	184 (64)	NS
7	326 (100)	78 (23)	<0.05	352 (64)	188 (48)	<0.05
14	105 (17)	70 (31)	NS	357 (60)	182 (77)	<0.05
28	119 (43)	74 (20)	NS	70 (10)	35 (7)	<0.05

major contributing factor to all deaths in the study population. The majority of these infectious episodes were either of confirmed or suspected bacterial sepsis, with the number of viral infections insufficient for analysis. Two patients in the CyA limb additionally developed systemic/cerebral nocardiosis at 6 and 8 months posttransplantation. There were no protozoal infections in the FK 506 limb.

Major neurological complications were infrequent in this study population despite the severity of pretransplantation hepatic encephalopathy. There were no episodes of seizures in either group; one patient in the FK 506 group experienced a possible episode of central nervous system toxicity (aphasia persisting until the 2nd posttransplant week). No significant psychiatric or confusional episodes were seen. Renal impairment was common in these patients and dialysis was required in three of eight FK 506 recipients and four of nine CyA recipients (the same patients who required pretransplant dialysis) with creatinine clearance rates similar between the groups. The clearance rates were 53 ml/min at day 7, 70 ml/min at 3 months and 82 ml/min at 12 months in the FK 506 group and 58 ml/min, 81 ml/min and 85 ml/min in the CyA group, respectively (ns).

Discussion

The postoperative course of patients who undergo emergency liver transplantation for FHF remains particularly hazardous, with 1-year survival rates reported at between 50–60% [2, 4, 12]. Candidates for transplantation are critically ill, with a wide spectrum of organ dysfunction and a high frequency of organ system failures. The outcome of transplantation is significantly determined by appropriate patient selection, with exclusion of patients who have either evidence of irreversible brainstem dysfunction, pharmacological-resistant haemodynamic disturbance or severe systemic sepsis. Despite increasing experience in the management of these patients, the development of severe postoperative sepsis still accounts for a considerable proportion of early graft and patient loss. The increased frequency of bacterial and fungal sepsis in patients with FHF reflects impaired neutrophil and Kupffer cell function and acquired defects in opsonisation [4]. These patients, who should be considered to be immunodeficient, are at particular risk from the nonspecific immunological effects mediated by high-dose corticosteroid schedules that constitute a major component of induction immunosuppression regimens in the early posttransplant period [7].

This present study demonstrated the potential benefits available with an FK 506-based immunosuppression regimen in those high-risk recipients transplanted for FHF. In the FK 506-treated patients, we showed an improvement in a range of standard clinical and biochemical parameters in relation to both graft function and systemic illness. Easier control of allograft rejection and a reduction in the prevalence of severe systemic sepsis are the main explanations for the superior graft function and outcome in this group. The potent immunosuppression available with this agent permitted a substantial reduction in total steroid requirements, which may have been a major contributing factor to the reduction in systemic sepsis. Liver function can be severely affected by systemic sepsis with the development of a prolonged cholestatic syndrome and it is, therefore, interesting to note the lower level of bilirubinaemia in the FK 506-treated compared to the CyA-treated patients [6]. Other possible explanations for the differences in graft function may be the hepatotoxic and hepatotrophic profiles of these major immunosuppressants. CyA has well-documented cholestasis effects, a phenomenon not reported with FK 506 [9]. This latter agent also appears to have significant hepatotrophic properties with an early report suggesting that this may be considerably superior to CyA [8]. It is of interest that the rates of rejection (including intractable) were higher in the patients in this population of FHF-transplanted patients compared to elective recipients emphasising the requirement for potent immunosuppression in this group. The mechanisms underlying this phenomenon require to be determined. Excellent long-term graft function in those recipients immunosuppressed with FK 506 monotherapy supports the withdrawal of corticosteroids and azathioprine from maintenance regimens and thereby removing the serious long-term complications of these agents.

The absence of any major neurological complications or long-term renal impairment in these patients was reassuring. These patients who were all encephalopathic and had a high prevalence of renal dysfunction were at particular risk from immunosuppressant-related neurotoxicity and/or nephrotoxicity. In this present study, no significant difference in the toxicity profile of the major immunosuppressants was detected.

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