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Glucose metabolism in liver transplant recipients treated with FK 506 or cyclosporin in the European multicentre study

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Abstract From September 1990 to January 1992, 545 liver transplant patients were randomised to treatment with either FK 506 and prednisolone or a conventional cyclosporin-based immunosuppressive regimen (CBIR). Eight European centres participated in the study. Adverse events were reported as defined by each centre. Hyperglycaemia was reported as an adverse event in 30.7% of patients receiving FK 506 compared with 20.5% in the CBIR group ($P < 0.01$). Diabetes mellitus was reported in 17.2% of patients treated with FK 506 and 9.5% of CBIR-treated patients ($P < 0.05$). Treatment with insulin was required in 12.0% of patients in the DK 506 treatment group and in 5% in the CBIR group at 6 months. Initially, higher doses of FK 506 were used. During the study, the protocol was changed to allow a lower dose of FK 506. When the early and late cohorts of patients were compared, the incidence of diabetes mellitus fell from 23.9% to 10.5% in FK 506-treated patients but remained relatively constant in the CBIR group (10.4% to 8.7%). The median cumulative doses of i.v. and p.o. corticosteroids were significantly greater in the CBIR group. Thus, in the overall series, the incidence of diabetes mellitus was significantly greater in the FK 506 group as compared with the CBIR group. However, when a lower FK 506 dose was used during the second half of the study, the difference in the incidence of diabetes mellitus disappeared.

Key words FK 506 · Cyclosporin
Diabetes mellitus · Hyperglycaemia
Glucose metabolism

Introduction

Abnormal glucose metabolism associated with cyclosporin treatment was originally observed in pancreatic transplant recipients that were switched from azathioprine to cyclosporin based immunosuppression [3]. Several subsequent studies have confirmed that cyclosporin is indeed diabetogenic. Hyperglycaemia and overt diabetes in transplant recipients can also be caused by the steroid medication included in the majority of the immunosuppressive protocols used.

FK 506, a macrolide lactone, is a new immunosuppressant with biological proterties remarkably similar to cyclosporin [4]. Also, the side-effects of the two drugs are very similar. Thus, hyperglycaemia and diabetes have been recorded following treatment with FK 506 both in animals and humans. Abnormal glucose metabolism following FK 506 treatment was first noted by Calne et al. in baboons [1] and a similar diabetogenic effect was then seen in untransplanted cynomolgus monkeys [2]. In human transplant recipients treated with FK 506, diabetes requiring insulin treatment was first reported by Todo et al., the incidence of this complication being 8.9% [5].

The efficacy and safety of FK 506 has recently been assessed in a European multicentre study encompassing 545 liver transplant recipients; the patients in the control arm were given cyclosporin-based immunosuppression. The present paper reports on the occurrence of hyperglycaemia and diabetes mellitus during the first 6 months after transplantation in the patients included in this study.

Methods

Patients

Five hundred and forty-five patients were randomised to treatment. Five patients were misrandomised and were excluded. There were 267 patients in the FK 506 group and 273 in the CBIR group. In the present study, the 6-month data are reported. The demography of the patients and the primary diagnosis are given in Tables 1 and 2, respectively. Pretransplant diabetes and antidiabetic therapy were slightly more common in patients in the FK 506 group.

Immunosuppressive treatment protocols

FK 506 was given i.v. initially in a dose of 0.075 mg/kg per 12 h (4 h infusion) during days 0–2. Thereafter, oral FK 506 was given in a dose of 0.15 mg/kg per 12 h. Methylprednisolone was given in a dose of 1 g i.v. (day 0) followed by 20 mg prednisolone daily thereafter. Corticosteroid doses were subsequently tapered and it was acceptable for corticosteroid therapy to be withdrawn. During the course of the study, the protocol was changed as follows: the FK 506 dose was reduced to 0.03–0.05 mg/kg per 12 h (12-h infusion) and oral FK 506 was started as soon as possible in a dose of 0.15 mg/kg per 12 h. Instead of a standard dose of 1 g of methylprednisolone, a dose of 10 mg/kg was given.

Each centre used its own established cyclosporin-based immunosuppressive protocol. Therefore, the dosages of cyclosporin, steroids and azathioprine were different between the centres. Moreover, some centres used ATG (OKT-3) prophylaxis. Thus, 60.1% of the patients were transplanted at centres using a triple drug regimen and 39.9% at centres using quadruple drug regimens.

Table 1 Patient demography (*CBIR* cyclosporin-based immunosuppressive regimen)

		FK 506 ($n=267$)	CBIR ($n=273$)
Age (years)	Mean	45.6	45.6
	Range	18.0–66.0	15.0–68.0
Sex (n)	Male	136	158
	Female	134	117
Total ischemia time (h)	Mean	12.2	12.2
Surgical procedure (h)	Mean	7.2	7.4
	Range	3.3–17.3	3.3–18.0

Table 2 Primary diagnosis

	FK 506 ($n=267$)	CBIR ($n=273$)
Cirrhosis[a]	195	191
Acute hepatic failure	22	28
Carcinoma	27	42
Miscellaneous	23	12
Pre-transplant diabetes	26	21
Antidiabetic therapy	14	9

[a] Including 23 patients from each transplant group with sclerosing cholangitis

Adverse events monitoring and statistical methods

In order to assess the safety and tolerability of the study medication, the investigators were responsible for reporting any untoward clinical event experienced by the patient or any clinically significant adverse changes in laboratory data. These events had to be recorded, irrespective of their causality in relation to the study drug. A clinical adverse event was defined as any unintended change in signs or symptoms of the body. Worsening of a pre-existing condition was considered to be an adverse event, as was any new event experienced by any patient. The incidence of adverse events for both clinical and laboratory events were combined and summarised using the COSTART coding system.

Hyperglycaemia and diabetes mellitus were reported as defined by each centre. The incidence rates were compared between treatment groups using chi-squared methods or the Fisher exact test. The Mann-Whitney U test was used to compare total daily corticosteroid doses between treatments.

Table 3 Actual FK 506 dosages in the early and late subgroups of patients. Values are mean mg/kg

FK subgroup	Initial i.v.	Initial p.o.
Early	0.05	0.18
Late	0.03	0.14

Results

Immunosuppressive drug usage

The change in the recommended initial dosages of FK 506 during the study resulted in a late subpopulation of patients who had a lower maintenance treatment with FK 506 (Table 3).

The total cumulative corticosteroid usage for maintenance immunosuppression was significantly less in patients receiving FK 506 therapy (intravenous: 1430.0 mg and 1892.5 mg, $P = 0.005$; oral: 2112.0 mg and 2658.0 mg, $P < 0.001$ for the FK 506 and CBIR treatment groups, respectively). The amount of corticosteroids used for the treatment of rejection were not different between the two treatment groups.

Glucose metabolism

Blood glucose levels pre- and post-transplant are given in Table 4. Eighty-two out of 267 patients (30.7%) in the FK 506 treatment group and 56 out of 273 patients (20.5%) receiving CBIR therapy were diagnosed as having hyperglycaemia ($P < 0.01$). Diabetes mellitus was reported to occur in 17.2% of the patients treated with FK 506 and in 9.5% of patients in the CBIR group ($P < 0.05$). When patients with pre-transplant antidiabetic drugs were excluded, the percentage of patients with ongoing insulin treatment at 6 months was 12.0% and 5.0% in the FK 506 and CBIR groups, respectively. If both insulin and oral antidiabetic treatment taken into account, the corresponding figures were 15.6% and 6.6%, respectively.

When the early and late (lower dosages of FK 506) cohorts of patients were compared, the incidence of diabetes mellitus fell in FK 506-treated patients but remained relatively constant in the CBIR group, the difference between the FK 506 and CBIR groups no longer being significantly different (Table 5). The corresponding data for hyperglycaemia is also given in Table 5.

Discussion

The diabetogenic effect of FK 506, reported in previous experimental and clinical studies, was confirmed in the present multicentre study. The incidence of diabetes mellitus reported for the FK 506 patients was significantly higher than for the patients on cyclosporin based immunosuppression. This difference was not related to the steroid medication, indeed, the cummulative dose of steroids was somewhat lower in the FK 506 group.

When this study was initiated, most participating centres had essentially no experience with FK 506 in patients. Furthermore, therapeutic drug monitoring of FK 506 was hampered by the fact that the ELISA technique available was time consuming and not very reliable. Moreover, the optimal plasma levels were not known. Therefore, dose adjustments were often guided by clinical monitoring of effects and side-effects – i.e. the dose was reduced when side-effects occurred. When the study had been in progress for some time, it was felt that drug toxicity was a significant problem, and the dosage of

Table 4 Median blood glucose levels (mmol/l) before and after liver transplantation in FK 506 and CBIR patients

	Pre-transplant	Post-transplant immediately	1 month	3 months	6 months
FK 506	5.90	13.40	6.30	5.80	5.30
CBIR	5.70	14.20	5.70	5.60	5.20

Table 5 Incidence of hyperglycaemia and diabetes mellitus in the overall series and in early and late subgroups of patients. The dose of FK 506 was lowered between the early and the late subgroups

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

	Overall		Early subgroup ($n = 269$)		Late subgroup ($n = 271$)	
	Hyperglycaemia	Diabetes mellitus	Hyperglycaemia	Diabetes mellitus	Hyperglycaemia	Diabetes mellitus
FK 506	30.7 **	17.2 *	33	23.9 **	29	10.5
CBIR	20.5	9.5	23	10.4	18	8.7

FK 506 was reduced. For the analysis, the case material was divided into two subpopulations, the early subgroup with a higher mean dose of FK 506, and a late subgroup with a lower mean dose of FK 506. When the incidence of diabetes mellitus was investigated in the latter subgroup there was no longer any difference between the FK 506 and the cyclosporin-treated patient groups. Thus, following optimisation of the FK 506 protocol, the incidence of abnormal glucose metabolism was similar to that seen with cyclosporin.

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