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FK 506 versus cyclosporin in the prevention of renal allograft rejection – European pilot study: six-week results

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Abstract FK 506 was compared with cyclosporin in a randomised trial in good-risk cadaveric renal transplant recipients. The objective was to evaluate whether oral FK 506 dosing was viable and whether blood concentrations in the range 10–20 ng/ml would prove to be practical. Thirty-one adult patients were randomised to FK 506 and 16 to cyclosporin. Both groups received an identical regimen of azathioprine and corticosteroids. Serum creatinine concentrations decreased rapidly in both groups with mean values below 200 μmol/l within 2 weeks. One graft in the cyclosporin group was lost due to renal vein thrombosis. During the 6-week study period, 19.4 % of patients on FK 506 and 31.3 % on cyclosporin experienced acute rejection. One patient in each group experienced corticosteroid-resistant rejection that responded to anti-lymphocyte therapy. Infections were reported in 51.6 % of the FK 506 group compared with 37.5 % of the cyclosporin group. The spectrum of adverse events was similar in both groups. However, minor neurological disorders were more common in the FK 506 group (54.8 % versus 6.3 %) whereas hypertension was less common (48.8 % versus 75.0 %). The results indicate that oral FK 506 rapidly achieves therapeutic blood concentrations and is an effective immunosuppressant for the initial treatment of renal allograft recipients.

Key words FK 506, cyclosporin, kidney transplantation · Kidney transplantation, FK 506, cyclosporin Cyclosporin, FK 506, kidney transplantation

Introduction

FK 506 is a potent immunosuppressant, both in vitro and in vivo. Following liver transplantation, it appears to be superior to standard cyclosporin-based therapy in reducing the incidence of acute corticosteroid-resistant and refractory rejection [2, 9]. Recent clinical studies have shown that FK 506 is also effective in renal transplantation. Experience from the University of Pittsburgh [7, 8] suggests that FK 506 therapy is associated with patient and graft survival rates equivalent to those from cyclosporin-based regimens, but with improved secondary outcomes. These improvements include a reduced incidence of rejection episodes and corticosteroid requirements, and a lesser need for anti-hypertensive medication. The Japanese FK 506 study group [4, 5] suggested a possible correlation between low whole blood FK 506 trough concentrations and the incidence of rejection, and between high whole blood trough concentrations and adverse events. They recommended FK 506 therapeutic drug monitoring to achieve target whole blood trough concentrations of 15–20 ng/ml.

In previous studies, the administration of FK 506 was based upon an oral dose pre-operatively, followed by intravenous administration until the patient was on a

stable diet. The objectives of the present study were to assess the efficacy and safety of oral FK 506 following renal transplantation and to maintain whole blood trough concentrations of 10–20 ng/ml throughout the 6 weeks of the study. Good-risk adult patients were to be evaluated and an identical immunosuppressive regimen was to be used at each study centre.

Materials and methods

Study design

This was an open, randomised, parallel group study conducted between September 1992 and July 1993 in four European centres. Patients were randomly assigned to treatment within centres in blocks of three, each block containing two patients randomised to treatment with FK 506 and one randomised to cyclosporin. The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the appropriate ethics committees and each patient gave informed consent prior to participation.

Patient selection

Male and female patients, aged 18–70 years, undergoing primary renal transplantation and showing primary renal function (defined as 500 ml of urine output and a clinically significant decrease in serum creatinine concentration within the first 12 h after transplantation) were eligible for entry. Patients were excluded if they had collagen vascular disease, diabetic nephropathy, significant liver disease, HIV positivity, other organ transplants, allo-T-cell antibodies of more than 20 %, ABO blood type incompatibility with the donor, a positive cross-match on the most recent recipient serum specimen, or leukocytopenia (less than 3000 white blood cells per µl). Women who were pregnant or not using adequate contraception were also excluded.

Immunosuppressive protocol

The patients were assigned to receive either FK 506 or cyclosporin therapy as part of a triple drug immunosuppressive regimen within 24 h of transplantation. The administration of azathioprine and corticosteroids was identical in both groups. Azathioprine was given as an intravenous bolus of 2 mg/kg on the day of transplantation and subsequently as an oral dose of 1–2 mg/kg. Corticosteroids were given as 500 mg methylprednisolone intravenously on the day of transplantation, followed by 125 mg on day 1. Corticosteroid therapy was subsequently reduced to 20 mg of oral prednisolone daily for the first 2 weeks, 15 mg daily during weeks 3 and 4, and 10 mg daily during weeks 5 and 6. FK 506 was initiated at 0.30 mg/kg per day in a twice daily dosing schedule and the dose was adjusted to establish a whole blood trough concentration of 10–20 ng/ml (Abbott IMx specific assay [3]). Cyclosporin was administered orally to maintain plasma trough concentrations of 150–300 ng/ml (monoclonal specific assay) or 300–600 ng/ml (polyclonal specific assay).

Definition and management of rejection

Acute rejection was defined as a deterioration in renal function as assessed by serial serum creatinine determinations and a renal biopsy confirming the presence of acute rejection requiring additional immunosuppressive therapy. Significant renal deterioration was defined as an increased serum creatinine concentration of at least 20 % above baseline. Rejection was treated with the local rejection treatment protocol at each individual centre.

Statistical analysis

Kaplan-Meier estimates of the time to first acute rejection were obtained; differences between treatment groups were compared using the generalised Wilcoxon test. The incidence of rejection was assessed using chi-square methods.

Student's t-test was used to assess differences in demographic characteristics (age, height and weight) between the two treatment groups whilst Fischer's exact test was used to compare sex and race.

Results

Forty-seven patients were recruited for the study. Thirty-one were randomised to receive FK 506 and 16 to receive cyclosporin. The two groups were well matched for recipient age (mean 46.1, SD 12.5 versus 45.1, SD 12.3 years), duration of dialysis (mean 2.9, SD 2.1 versus 4.2, SD 3.2 years), donor age (mean 38.1, SD 14.8 versus 34.5, SD 16.4 years) and cold ischaemic time (mean 23.5, SD 7.4 versus 22.5, SD 4.2 h).

Patient and graft survival

There were no deaths in either group. One graft in the cyclosporin group was lost due to renal vein thrombosis 41 days post-transplant.

Acute rejection

During the 6-week study period, no graft was lost from rejection. Six patients in the FK 506 group (19.4 %) and five patients in the cyclosporin group (31.3 %) experienced single episodes of acute rejection (Table 1). One patient from each group experienced corticosteroid-resistant rejection, but both responded to anti-lymphocyte therapy.

Renal function

Renal function improved rapidly in both groups as assessed by serial serum creatinine measurements (Fig. 1). In both treatment groups, the mean serum creatinine concentration was below 200 µmol/l within

Table 1 Incidence of rejection

	FK 506 ($N = 31$)		Cyclosporin A ($N = 16$)	
	n	%	*n*	%
Number of patients with an acute rejection episode	6	19.4	5	31.3
Number of patients with a corticosteroid-sensitive acute rejection episode	5	16.1	3	18.8
Number of patients with a corticosteroid-resistant acute rejection episode	1	3.2	1	6.3
Other treatment	0	0.0	0	0.0

[a] One patient received combined treatment with ATG and corticosteroids as primary rejection treatment

2 weeks of transplantation. Subsequent increases in creatinine were attributed to drug nephrotoxicity in two patients from the FK 506 group (6.5 %) and in one patient from the cyclosporin group (6.3 %) and responded to dose reduction.

Hypertension

Prior to transplantation, 29 patients (93.5 %) randomised to FK 506 were receiving treatment for hypertension compared with 13 patients (81.3 %) randomised to cyclosporin. By 6 weeks post-transplant, 15 patients on FK 506 (48.8 %) and 12 patients on cyclosporin (75.0 %) remained on anti-hypertensive medication, although this difference was not statistically significant. The median blood pressure at 6 weeks was similar for both treatment groups (140/82 mm Hg for the FK 506 group and 140/80 mm Hg for the cyclosporin group).

Neurological disorders

No serious neurological or psychiatric disorders were reported in either group. However, minor neurological symptoms were predominantly reported by patients in the FK 506 group. Adverse neurological events in patients on FK 506 consisted of mild tremor in eight (25.8 %), paraesthesia in six (19.4 %), headache in five (16.1 %), insomnia in two (6.5 %) and mild depression in two (6.5 %). One patient (6.3 %) in the cyclosporin group reported headache, but no other adverse neurological disorders were reported.

Disorders of glucose metabolism

Three patients (9.7 %) in the FK 506 group developed transient hyperglycaemia, but no patient in either group required long-term therapy for diabetes mellitus.

Infections

Twenty-five infections were reported in 16 patients (51.6 %) in the FK 506 group, compared with 15 infections in six patients (37.5 %) in the cyclosporin group. The majority were urinary tract infections, reported in 25.8 % of FK 506-treated patients and 25.0 % of cyclosporin-treated patients. Viral or fungal infections were recorded in 16.2 % of patients on FK 506 compared with 18.8 % of patients on cyclosporin. These consisted of herpes simplex ($n = 2$) and cytomegalovirus ($n = 3$)

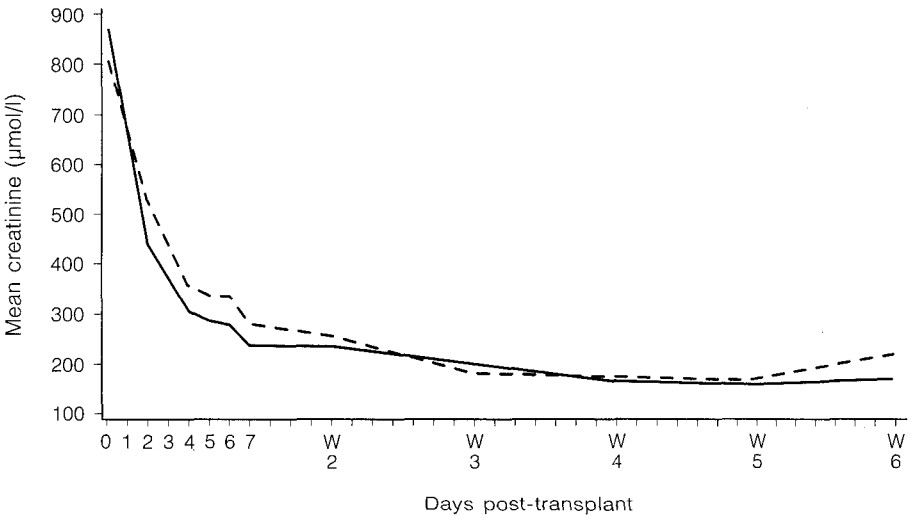

Fig. 1 Mean daily plasma creatinine concentrations in patients receiving FK 506 (—, $n = 31$) and cyclosporin A (----, $n = 16$)

Table 2 FK 506 oral dosage and trough whole blood concentration

	Median dose		Median trough concentration	
	mg/kg per day	Q1–Q3	ng/ml	Q1–Q3
Week 1	0.30	0.20–0.36	14.0	11.6–19.0
Week 2	0.30	0.22–0.37	13.6	11.5–16.2
Week 3	0.30	0.21–0.40	14.0	12.1–16.7
Week 6	0.30	0.21–0.36	17.7	13.5–21.0

for the FK 506 group and candida ($n = 2$) and cytomegalovirus ($n = 1$) for the cyclosporin group.

FK 506 dosage and whole blood trough concentrations

The median total daily dose of FK 506 required to maintain whole blood trough concentrations between 10 and 20 ng/ml was 0.30 mg/kg per day during each of the 6 weeks of the study. For individual patients, however, there was a wide variation in dosage in order to maintain blood concentrations within the target range (Table 2). One patient on FK 506 developed small bowel obstruction due to an incarcerated hernia and required intravenous medication. The remaining patients received oral medication only throughout the study. The median whole blood concentration ranged from 13.6 to 17.7 ng/ml from week 2 to week 6.

Discussion

This study reports the first European experience with FK 506 therapy in renal transplantation. In order to evaluate the safety and the efficacy of the drug, we elected to confine the study to good-risk patients receiving grafts that exhibited immediate renal function. The study had three main objectives. Firstly, we wanted to know whether a triple immunosuppressive regimen incorporating FK 506, low-dose corticosteroid therapy and azathioprine was equivalent in efficacy and safety to a similar triple therapy regimen based upon cyclosporin. Secondly, we wanted to determine whether initial FK 506-based therapy could be administered orally and successfully prevent early acute transplant rejection. Thirdly, we sought to determine whether the recommended target concentrations for therapeutic drug monitoring were appropriate and whether these concentrations could be easily achieved with acceptable safety and efficacy.

Previous experience has shown that by week 6 the majority of acute transplant rejection episodes will have occurred. Thus, the Japanese FK 506 study group [5] demonstrated that 80 % of all rejection episodes occurred in the first 6 weeks. In a large cohort of patients, Cecka [1] reported that an early rejection episode, occurring within the first 30 days following transplantation, is the strongest predictor, of subsequent graft survival. Our study showed that by week 6 there was an 11.9 % difference in rejection rates in favour of FK 506 therapy. Because of small numbers, this difference was not statistically significant; a large phase III comparative trial between FK 506 and cyclosporin is required to provide a conclusive answer.

The starting dose of 0.30 mg/kg per day proved to be a satisfactory recommendation to achieve target trough whole blood concentrations between 10 and 20 ng/ml. There was, however, a wide variation in dose and in whole blood concentrations throughout the study. This indicates a large inter- and intra-patient variability in absorption and clearance of FK 506. The Abbott automated immunoassay (IMx) was successful in providing same day results of whole blood concentration, facilitating patient management [3].

With this interim report following 6 weeks of treatment, long-term safety was never an objective of the study. Long-term follow-up of these patients will be reported in due course. There have been three main areas of concern with regard to FK 506 therapy: neurological, nephrological and glucose metabolic disorders.

Twenty-seven adverse neurological events were reported in 17 of the 31 patients receiving FK 506 (54.8 %). Tremor was the most common event, occurring in 25.8 % of FK 506 patients. The tremor was fine in nature and did not interfere with daily life or necessitate withdrawal of the patient from the study. Persistent tremor was reported in seven of the eight patients, whereas other neurological events (paraesthesia, headache, insomnia and depression) tended to remit despite continuation of therapy.

Nephrotoxicity was only reported in two patients on FK 506 and one patient on cyclosporin. The serum creatinine concentrations in both groups were similar at the end of 6 weeks. Clearly, long-term follow-up studies are required to determine whether FK 506 confers any advantage for chronic nephrotoxicity.

FK 506 appeared to show a benefit with regard to hypertension. At 6 weeks, over half of the patients on FK 506 (51.6 %) did not require anti-hypertensive medication compared with 25.0 % of the patients randomised to cyclosporin. This difference may have an impact on long-term patient and graft survival.

Disorders of glucose metabolism and diabetes have been reported to be more common in liver transplant recipients treated with FK 506 than in comparable patients receiving cyclosporin, although both drugs probably induce tissue insulin resistance [6]. Transient hyperglycaemia was reported in three patients on FK 506. However, all three were receiving corticosteroids, which confound the interpretation of metabolic data.

Impaired glucose tolerance is a well-recognised feature of patients with liver disease, and further studies in renal transplant recipients are necessary to establish whether FK 506 has a long-term diabetogenic effect.

Urinary tract infection was the most commonly reported adverse event in the study, occurring in 25.8 % of the FK 506 group and 25 % of the cyclosporin group. Fungal and viral infections are the hallmark of over-immunosuppression. These occurred infrequently with a similar incidence in both groups.

In conclusion, this study has demonstrated that a triple immunosuppressive regimen based upon FK 506 is effective and has an acceptable safety profile when compared with cyclosporin. FK 506 can be administered orally and at an initial dose of 0.30 mg/kg per day in order to achieve a target range of 10–20 ng/ml. Therapeutic drug monitoring is required because of the large variability in dose and blood concentration effects. No patient suffered from life-threatening infection. Mild tremor was the principle adverse effect but did not cause any patient to withdraw from the study. Nephrotoxicity was rarely reported with either drug, but FK 506 appeared to confer an advantage with respect to hypertension. There was an 11.9 % improvement in the prevention of rejection episodes in the FK 506 group, but a larger cohort of patients is required to evaluate this finding. Such a study is now underway as a multicentre European trial.

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