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Patient and graft survival in the European Multicentre Liver Study – FK506 vs cyclosporin A

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Abstract A prospective randomised study was conducted to evaluate the efficacy and safety of FK506 administered with corticosteroids compared with a cyclosporin A-based immunosuppressive regimen in patients undergoing primary liver transplantation. 545 patients were recruited in eight European centres, of whom 267 were randomised to FK506 therapy and 273 to cyclosporin A-based therapy. The estimated Kaplan-Meier patient and graft survival figures of 82.9% and 77.5% respectively in the FK506 group were higher than the comparable figures in the cyclosporin A group (77.5% and 72.6%, respectively). These differences did not reach statistical significance. Retransplantation rates, time to first rejection episode and number of rejection episodes were all lower ($P < 0.001$) in the FK506 group. The infection rates were comparable between the two groups. During the study, the dose of FK506 was reduced; this did not compromise efficacy and reduced the associated toxicity. FK506 provides effective immunosuppression in patients undergoing primary liver transplantation and is associated with a lower incidence of rejection.

Key words FK506 · Cyclosporin A
Liver transplantation · Human

Introduction

Patient and graft survival are the clearest endpoints of liver transplantation. These endpoints are influenced by choice of donor and recipient, surgical events and rejection episodes. However, only rejection episodes can be influenced by an immunosuppressive regimen.

The incidence of intractable rejection and the feasibility of the salvage of patients with intractable rejection, who normally require retransplantation, are also important.

To prevent graft failure and prolong patient survival after solid organ transplantation, triple conventional the therapy usually consists of with cyclosporin A (CSA), azathioprine and corticosteroids. However, a novel immunosuppressive agent, FK 506, has shown promise in clinical practice over the last 4 years [1–5], and its efficacy was therefore investigated in a European multicentre study in liver transplant recipients.

The European FK506 Multicentre Liver Study commenced in September 1990 with the objective of evaluating the efficacy and safety of FK506, administered in

conjunction with corticosteroids, as compared with an individual best local conventional CSA-based immunosuppressive regimen in patients undergoing primary liver transplantation.

Patients and methods

Study population

A total of 545 patients, aged between 15 and 68 years, were enrolled in this prospective randomised parallel group study in eight European centres (Paris, France; Berlin, Hannover and Heidelberg, Germany; Birmingham, Cambridge and London, UK; and Stockholm, Sweden). The exclusion criteria were limited, since one of the objectives of the study was to evaluate FK 506 in the type of patients seen in everyday clinical practice. Patients were excluded from the study only if they had a previous liver allograft, advanced malignancy, recent total lymphoid irradiation, known or suspected pregnancy, and other well established absolute contraindications to liver transplantation.

Treatment regimens

Of the 545 patients recruited, 5 patients were misrandomised, and thus 540 were included in the efficacy analysis; 267 were randomised to FK 506 treatment and 273 to CSA-based therapy. The primary diagnoses were comparable between the two treatment groups (Table 1). Transplantation was considered urgent in approximately 15% of FK 506 and CSA patients, and an intermediate or high patient risk score was reported in approximately 20% of patients in both treatment groups.

The CSA-based regimen consisted of each centre's optimal conventional protocol of CSA, azathioprine and corticosteroids. In addition, the German centres administered 5 mg/kg daily antilymphocyte or antithymocyte globulin (ALG/ATG) for 1 week. The treatment regimen was standardised for each of the eight centres for the duration of the study. However, the initial dose of CSA varied between centres: the intravenous dose ranged from 1 to 6 mg/kg daily and the oral dose from 8 to 15 mg/kg daily.

Based on early experience [1], the initial dose of intravenous FK 506 was administered over 4 h. During the trial this dose was reduced to ameliorate toxicity, and the latter half of both patient groups recruited received a mean intravenous dose of 0.032 mg/kg per 24 h by continuous infusion; this dose was administered for a median time of 2 days. These patients received a mean oral dose of 0.141 mg/kg per day on day 7 and 0.105 mg/kg per day by month 6.

Corticosteroid therapy in the FK 506 group consisted of 1 g methylprednisolone intraoperatively (later amended to 10 mg/kg), followed by an oral dose of 20 mg/day thereafter. The protocol allowed subsequent tapering or discontinuation of the corticosteroids, depending on the patients' clinical condition. However, patients in the CSA arm continued with the corticosteroid therapy recommended by the individual participating centres.

Significantly fewer corticosteroids were administered in the FK 506 group. The mean cumulative intravenous dose of corticosteroids was 1430 mg compared with 1893 mg for the FK 506- and CSA-treated patients, respectively ($P = 0.005$). The mean oral dose was 2112 mg compared with 2658 mg, respectively ($P < 0.001$).

In addition, azathioprine was given to 24% and 93% of patients in the FK 506 and CSA treatment groups, respectively, and ALG/ATG was administered to 9% of the FK 506 and 42% of the CSA-treated patients. In the majority of cases, azathioprine and ALG/ATG were given during interruptions of FK 506 therapy, while they formed part of the main immunosuppressive regimen in the CSA group.

Table 1 Primary diagnosis

	FK 506 ($n = 267$)	Cyclosporin A ($n = 273$)
Post-hepatitic cirrhosis	62	64
Alcoholic cirrhosis	21	29
PBC	53	47
PSC	23	23
Other cirrhosis	36	28
Fulminant hepatitis	22	28
Carcinomas	27	42
Miscellaneous	23	12

Results

Patient survival

The estimated Kaplan-Meier overall patient survival rates at 6 and 12 months were higher in the FK 506 group than in the CSA group (Fig. 1), although the difference

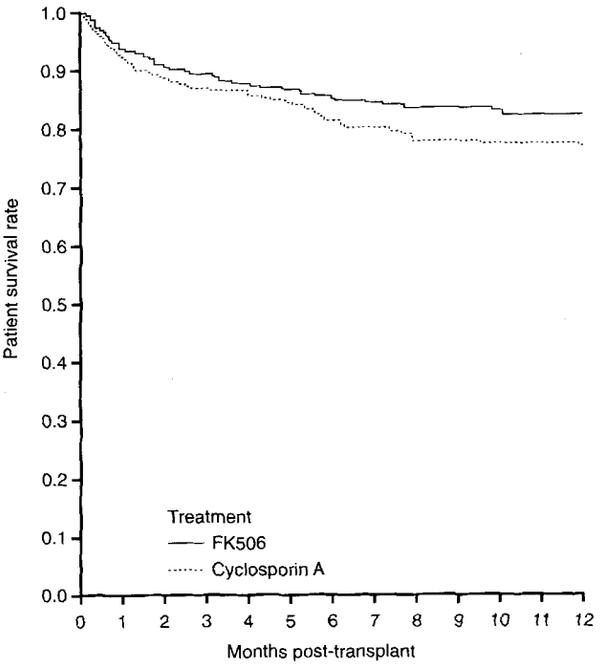

Fig. 1 Estimated cumulative patient survival rate (Kaplan-Meier)

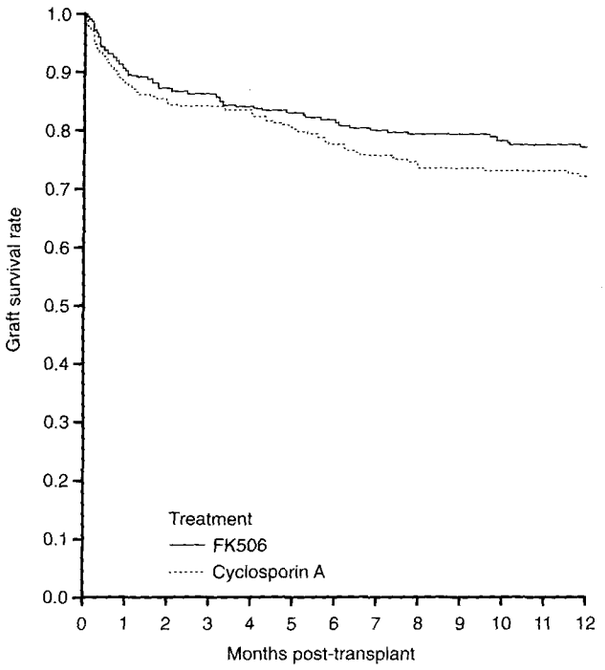

Fig. 2 Estimated cumulative graft survival rate (Kaplan-Meier)

did not reach statistical significance. Overall patient survival at 6 months was 83.5% in the FK 506 group compared with 79.3% in the CSA group. This analysis was based on the intention-to-treat population and therefore included patients who died intraoperatively and did not receive either of the treatment regimens. At 12 months, the estimated overall patient survival was 82.9% and 77.5% for the FK 506 and CSA, respectively.

The patient survival rate was also dependent on whether patients were classified as "high" or "low" risk. In the low-risk group, the patient survival rate was 87.4% and 83.3% in the FK 506 and CSA groups, respectively, while in the high-risk group, patient survival was lower at 69.9% and 69.3%, respectively.

Graft survival

Graft survival is an important endpoint in studies of immunosuppressive agents, since it not only reflects the number of deaths, but also the number of patients who require retransplantation. The estimated Kaplan-Meier overall graft survival rate was higher in the FK 506 group than in the CSA group (Fig. 2). Overall graft survival at 6 months was 79.3% and 74.9% in the FK 506 and CSA groups, respectively. At 12 months, the estimated graft survival was 77.5% and 72.6%, respectively.

Table 2 Episodes of infection in FK 506 and cyclosporin A treated patients

	FK 506 ($n=267$)	Cyclosporin A ($n=273$)
Total patients treated with antibiotics	156	172
Total number of confirmed infections	287	355
Specific confirmed infections:		
Pneumonia	22	35
Cytomegalovirus	25	43
Sepsis	38	49

The retransplantation rate was lower in the FK 506-treated than in CSA-treated patients (6.4% compared with 10.3%, respectively). Furthermore, the incidence of acute rejection was significantly lower at 6 months in the FK 506 group compared with the CSA group (38.6% vs 49.1%, $P < 0.001$), and there was also a lower incidence of intractable rejection (2.6% vs 9.2%, $P < 0.001$).

Incidence of infection

Infection in immunosuppressed patients is one of the main concerns of clinicians, since these can often prove to be life-threatening. A trend towards a decreased incidence of overall and specific infections was reported in the FK 506 treatment group, and the total number of patients requiring treatment with antibiotics throughout the 6-months study period was lower in patients receiving FK 506 (Table 2), although no indices of infection reached statistical significance.

There were no significant differences in the death rate or causes of death between the groups. There were 43 deaths reported in the FK 506 group compared with 56 deaths in the CSA group. All deaths in the FK 506 arm were attributed to adverse events, while in the CSA arm 39 deaths were related to adverse events and 6 to intractable rejection. The main causes of mortality in both groups were infection and organ failure, with bleeding, graft vs host disease and recurrence of cancer accounting for the remainder.

Early/late subgroup analysis

Survival

FK 506 treatment was associated with increased patient and graft survival in the early FK 506 subgroup (i.e.

Table 3 Early/late subgroup analysis (6 months)

	FK 506 (%)	Cyclosporin A (%)
Patient survival		
"Early"	84.3	76.1
"Late"	82.8	82.5
Graft survival		
"Early"	82.0	73.9
"Late"	76.7	76.0
Patients with acute rejection		
"Early"	39.6	51.5
"Late"	44.4	58.3
No. of treated infections		
"Early"	79.1	82.0
"Late"	75.9	79.0

patients receiving the higher dose of FK 506) compared with the early CSA subgroup at 6 months post-transplantation (Table 3). Comparable patient and graft survival rates were reported in patients who received a reduced dose of FK 506 (late subgroup) compared with CSA.

Rejection

In the FK 506 group there were 39.6% and 44.4% rejection episodes in the early and late subgroups, respectively, compared with 51.5% and 58.3%, respectively, in the CSA-treated patients (Table 3).

Infections

The total number of treated infections was comparable in the CSA-treated patients and those receiving FK 506 in both the early and late subgroups (Table 3).

Discussion

The European FK 506 Multicentre Liver Study was significant in that the study population was representative of the types of patients requiring primary liver transplantation in everyday clinical practice and therefore did not exclude patients who were considered at high risk of death or graft failure. Indeed, with the exception of children, the exclusion criteria were only limited to those patients in whom it would normally have been unwise to perform liver transplantation. The FK 506-treated patients and those randomised to CSA-based therapy were comparable with regard to demographic data, primary diagnosis, and fulminant hepatic failure, the latter being a well known risk factor for sepsis, multi-organ failure and death.

The treatment protocols at each centre involved in the study were standardised for the individual centres for the duration of the study to allow for effective comparison. The FK 506 protocol amendments were essentially driven by the need to reduce the dose and increase the duration of intravenous therapy in order to reduce acute toxicity. Importantly, the reduction in dose did not result in a reduction of efficacy or an increase in the number or type of infections experienced by the patients. The toxicity of the FK 506 regimen in the latter half of the study was comparable to that of the CSA-based regimen. These results have been supported by recent reports [6].

Acute and chronic rejection are the main causes of graft loss in transplanted patients. Furthermore, the effects of immunosuppressive treatment itself can result in an increased likelihood of infection including life-threatening complications such as pneumonia, cytomegalovirus infection, and sepsis. In the European FK 506 Multicentre Liver Study, FK 506 treatment resulted in a trend to increased patient and graft survival, decreased numbers of infectious episodes, fewer cases of retransplantation and fewer episodes of acute and intractable rejection than a CSA-based regimen. It is also worthy of note that in the FK 506 protocol a smaller amount of corticosteroid was used, which may have resulted in less overimmunosuppression and therefore influenced the incidence of infection and the rate of patient and graft survival. Similar results have been reported from the comparable US multicentre study [2].

The dosage reduction did not compromise efficacy in the late patient subgroup, and the difference in rejection rates was maintained. The late patient subgroup demonstrated a reduced incidence of adverse events compared with the early patient subgroup. An important finding was that the reduced dose of FK 506 did not result in an increased incidence of infection compared with the early phase FK 506 patients.

From the results of the European FK 506 Multicentre Liver Study it can therefore be concluded that FK 506 provides effective long-term immunosuppression in patients undergoing primary liver transplantation.

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