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Focus on intractable rejection: 6-month results of the European multicentre liver study of FK 506 and cyclosporin A

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Abstract The incidence of intractable rejection was evaluated during the course of a multicentre, randomised, parallel-group study comparing the efficacy and safety of FK 506 and conventional cyclosporin A-based immunosuppressive regimens in patients undergoing primary liver transplantation. A diagnosis of intractable rejection was made if there was histological evidence of unchanged or worsening acute rejection, or chronic rejection after two discrete courses of antirejection therapy. Antirejection regimens were specific to each centre. Patients who experienced intractable rejection could be withdrawn from the study. Patients who were withdrawn from the cyclosporin A treatment group could subsequently receive FK 506 therapy and vice-versa. Intractable rejection was diagnosed in 32/540 patients (5.9%): 7/267 patients (2.6%) in the FK 506 treatment group and 25/273 patients (9.2%) receiving cyclosporin A therapy ($P < 0.01$). Of these 32 patients, 25 were withdrawn from the study: 3 and 22, from the FK 506 and cyclosporin A treatment groups, respectively. All three patients withdrawn from the FK 506 treatment group are alive: two having undergone retransplantation. Of the 22 patients withdrawn from the cyclosporin A group and converted to FK 506 therapy, 6 were retransplanted, 4 of whom subsequently died. A further two patients died without retransplantation. Thus, in 14 of the 16 patients who were still alive at 6 months, the liver graft was saved after conversion to FK 506 treatment. The reduced incidence of intractable rejection in patients receiving treatment with FK 506, together with the successful rescue of patients developing intractable rejection while receiving cyclosporin A, suggests that FK 506 is an effective immunosuppressive agent following orthotopic liver transplantation.

Key words Liver transplantation
FK 506 · Cyclosporin A

Introduction

The aim of this study was to compare the efficacy and safety of FK 506 and corticosteroids with optimal conventional cyclosporin A based immunosuppressive regimens (triple or quadruple therapy). Traditionally, patient and graft survival have been considered to be the ultimate primary efficacy end-points in studies of new immunosuppressive agents. Graft loss, although often resulting from intractable rejection, can also result from events that are unrelated to the immunosuppressive activity of the agent, such as primary graft failure, recurrence of the underlying disease and hepatic artery thrombosis. Therefore, the incidence of intractable rejection, a direct parameter of immunosuppressive potency, was also considered to be a primary efficacy end-point for this study.

Patients and methods

Patients

Between September 1990 and January 1992, 545 patients, aged 15–68 years, undergoing primary liver transplantation in eight European transplant centres were recruited to this study. Five patients were misrandomised and were excluded from the analysis, leaving a population of 540 patients for the efficacy analysis, 267 of whom were randomised to treatment with FK 506 and 273, to treatment with cyclosporin A. The exclusion criteria were limited to previous liver graft, vasculitis/arteritis, HIV, history of multiple organ transplants, participation in another study within 28 days prior to entry, total lymphoid irradiation the 6-month period before transplantation, metastatic primary liver cancer, other active neoplastic disease and pregnancy.

Study design and definitions

This was a prospectively randomised, open, parallel-group study. Intractable rejection was defined as histological evidence of unchanged or worsening acute rejection, or chronic rejection after two discrete courses of antirejection therapy. Intractable rejection requiring additional rescue therapy was a justifiable reason to withdraw a patient from the study. According to the protocol, patients who were withdrawn from the study were to be further treated and followed according to established medical practice. Thus, patients leaving the cyclosporin A treatment-group could subsequently receive FK 506 for rescue therapy and vice-versa.

Treatment protocols

Patients randomised to cyclosporin A based therapy received the current multi-drug regimen (cyclosporin A, azathioprine, corticosteroids, ± ALG/ATG induction regimen) as used within each centre. The regimen was standardised for each of the eight centres for the duration of the study. The initial cyclosporin A dose varied between centres: intravenous doses ranged from 1–6 mg/kg per day and oral doses from 8–15 mg/kg per day.

For patients randomised to receive FK 506, the initial dose was based on published clinical experience from the University of Pittsburgh [1]: 0.075 mg/kg i.v. over 4 h, repeated every 12 h for 3 days, followed by conversion to oral therapy at a dose of 0.30 mg/kg per day. During the course of the study, clinical experience led to a number of protocol amendments allowing the administration of lower starting doses: 0.03–0.05 mg/kg continuous i.v. over 12 h. The dose for maintenance therapy was adjusted on the basis of individual patient experience. The total oral daily dose remained relatively stable during the 1st month (mean of 0.165 mg/kg on day 7 to 0.159 mg/kg at week 4) and subsequently decreased to a mean of 0.115 mg/kg at 6 months. Corticosteroid treatment in this regimen consisted of 1 g (later amended to 10 mg/kg) methylprednisone on the day of the operation, followed by oral prednisone 20 mg/day thereafter. The protocol allowed subsequent corticosteroid tapering or even discontinuation according to the clinical condition.

Results

Kaplan-Meier estimates for the cumulative number of patients with intractable rejection over time and the associated failure curves are shown in Fig. 1. Kaplan-Meier estimates at 6 months were 2.9% for the FK 506 treatment group and 10.1% for patients receiving cyclosporin A.

Kaplan-Meier estimates of time to first incidence were slightly higher than the actually reported incidence. Intractable rejection was reported in 2.6% of patients (7/267) in the FK 506 treatment group and in 9.2% of patients (25/273) receiving treatment with cyclosporin A. The 32 patients with intractable rejection were divided into three categories as shown in Fig. 2. Twenty-five patients (3 patients treated with FK 506 and 22 patients receiving cyclosporin A) were prematurely withdrawn from the study as a result of intractable rejection. In three patients, intractable rejection was only diagnosed following withdrawal for serious adverse events and in the remaining four cases, both the investigator and the histopathologist considered that the severity of intractable rejection did not warrant withdrawal.

Follow-up

FK506 treatment group (seven patients with intractable rejection)

Three patients were withdrawn from the study as a direct consequence of intractable rejection and converted to cyclosporin A based immunosuppression. All three patients were alive at 6 months, two patients having required retransplantation. In an additional two patients, intractable rejection was diagnosed following withdrawal for serious adverse events, one of whom died on the day of

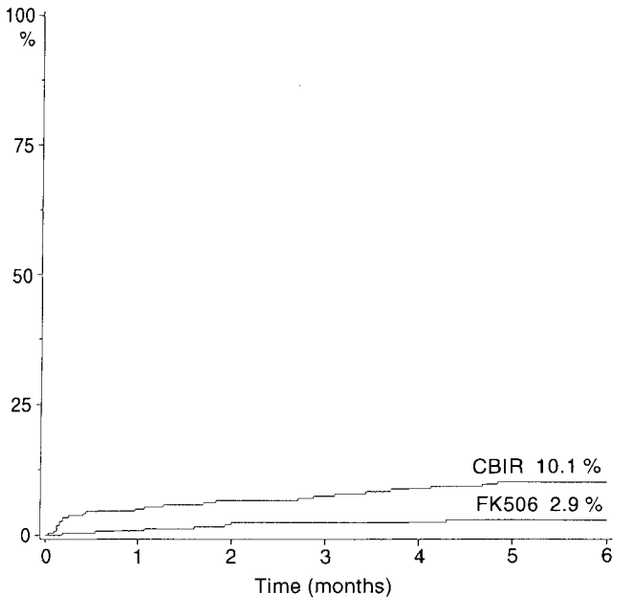

Fig. 1 Kaplan-Meier estimated cumulative rates of intractable rejection ($P < 0.001$)

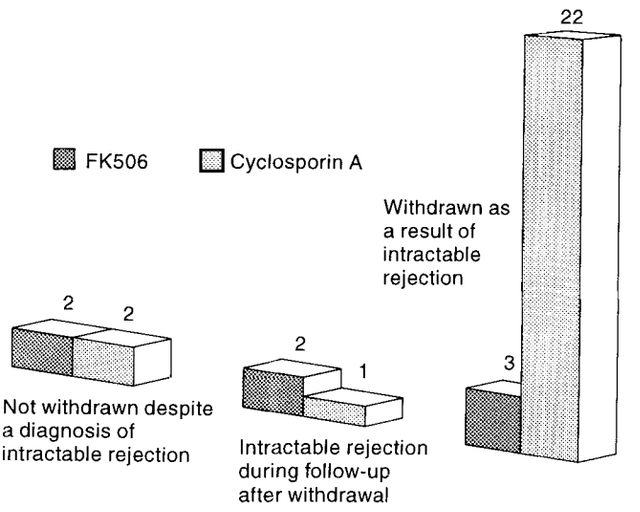

Fig. 2 Number of patients with intractable rejection

withdrawal. The other patient was withdrawn from the study for adverse events on day 9 and died 87 days later. The two remaining patients continued to receive treatment with FK 506, despite a diagnosis of intractable rejection, and were both alive at 6 months.

Cyclosporin A treatment group (25 patients with intractable rejection)

Of the 22 patients withdrawn from the cyclosporin A group and converted to FK 506 therapy, 6 were retransplanted, four of whom subsequently died. A further two patients died without retransplantation. Thus, in 14 of the 16 patients who were still alive at 6 months, the liver graft was saved after conversion to FK 506 treatment. The one patient in whom intractable rejection was only diagnosed after withdrawal for serious adverse events died during the follow-up period while still receiving cyclosporin A therapy. The two patients who were not withdrawn from the study and continued to receive cyclosporin A therapy were both alive at 6 months (Fig. 3).

Discussion

It has been reported that an estimated 13% of liver transplant patients experience rejection that does not respond to therapy with conventional immunosuppressive drugs [2]. The data presented in this study confirmed this: intractable rejection affected 9.2% of cyclosporin A treated patients within the first 6 months of primary liver transplantation. Only 2.6% of patients receiving treatment with FK 506 experienced intractable rejection. In view of the clinical importance of intractable rejection, leading to retransplantation or death if no effective rescue therapy is available [3], its low incidence in this study was remarkable.

Of the 22 patients withdrawn from cyclosporin A treatment and converted to FK 506 therapy, 19 did not require immediate retransplantation. The fact that 15 of these patients were alive at 6 months, all but one still having their first graft, showed that FK 506 was also capable of salvaging grafts in patients with intractable rejection. These results were comparable to those recently reported, where 11 of 18 patients with intractable rejection were successfully rescued with FK 506 treatment [4].

It can, therefore, be concluded that FK 506 is an effective immunosuppressive agent for the prevention of intractable rejection following orthotopic liver transplantation and is also effective for rescue therapy.

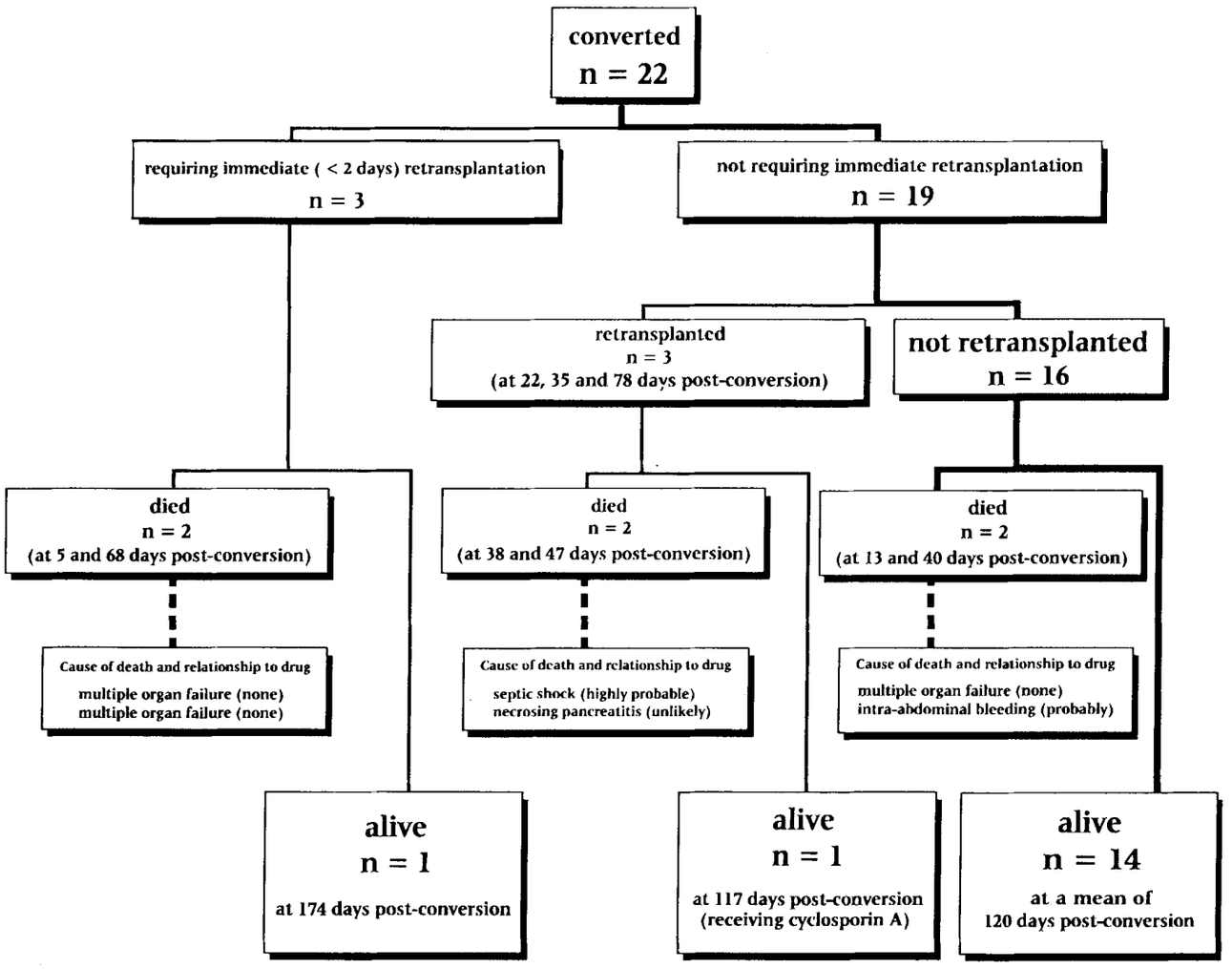

Fig. 3 Follow-up of 22 patients converted from cyclosporin A to FK 506 treatment following intractable rejection

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