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Corticosteroids and concomitant medication in the European multicentre study of FK506 and cyclosporin in primary liver transplantation

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Abstract The steroid-sparing effect and the use of concomitant medication during the treatment of liver transplant patients with the novel immunosuppressant FK506 were evaluated within the European multicentre, randomized, parallel-group study in liver transplantation. Patients undergoing primary liver transplantation were randomized to treatment with FK506 ($n = 267$) or with a cyclosporin-based immunosuppressive regimen ($n = 273$). The total cumulative steroid usage was significantly reduced in the FK506 treatment group, which is likely to have resulted from the lower incidence of acute rejection in these patients. The number of patients receiving antidiabetic, diuretic and antihypertensive therapy did not differ between the two treatment groups, even though the incidence of diabetes mellitus and oliguria was significantly higher in the FK506 group. It can, therefore, be assumed that in a number of such cases the severity of these events was very mild necessitating no specific therapy.

Key words FK506
Liver transplantation · Concomitant medication · Steroids

Introduction

Cyclosporin A (CyA) and steroids are the basic immunosuppressive drugs used in organ transplantation. CyA therapy is associated with side-effects, including hypertension, nephrotoxicity and diabetes. In order to treat these side-effects, additional medication is frequently required, especially during the early phase post-transplantation. The frequency and severity, as well as the medication used to treat such side-effects, are major determinants in alternative immunosuppressive regimens. Therefore, the steroid-sparing effect and use of concomitant medication during the treatment of liver transplant patients with the novel immunosuppressant FK506 – i.e. benefit versus risk – were evaluated within the European multicentre, randomized, parallel-group study in liver transplantation.

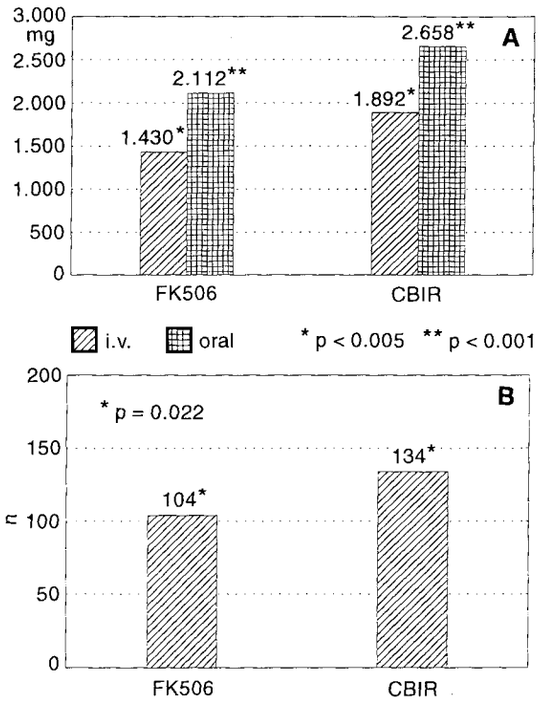

Fig. 1 **A** Total cumulative intravenous and oral dosage of steroids. **B** Number of patients with at least one episode of acute rejection during the first 6 months after liver transplantation with FK 506 and CBIR treatment

Patients and methods

In eight European centres, 267 patients undergoing primary liver transplantation were randomized to treatment with FK 506 and 273 patients to treatment with a CyA-based immunosuppressive regimen (CBIR). According to the protocol, patients randomized to FK 506 treatment originally received an initial intravenous daily dose of 0.15 mg/kg for 3 days. Thereafter, the patients were converted to an oral dose of 0.30 mg/kg per day. After about half of the patients had entered the study, the FK 506 dose was decreased (0.06–0.1 mg/kg i.v. and 0.30 mg/kg orally) in the form of a protocol amendment. Methylprednisolone was administered together with FK 506: 1 g intraoperatively and 20 mg/day beginning on day 1. After the protocol amendment, the intraoperative dose was reduced to 10 mg/kg. CBIR consisted of CyA, azathioprine and steroids with slightly differing regimens in each centre. The German centres used in addition ALG (5 mg/kg per day for 1 week). Data after a follow-up period of 6 months are presented here. Besides steroids, those drugs were also evaluated that were given concomitantly to treat side-effects of FK 506 and CyA. Statistical significance was evaluated by the chi-square test.

Table 2 Concomittant medication with no direct relation to immunosuppressive regimens (Differences are not statistically significant)

	FK 506	CBIR
Cardiac therapy	81	82
Psycholeptics	70	67
Antihistamines	45	42
Antiepileptics	18	19
Anti-anaemics	18	19
Antiemetics and antinauseants	9	6
Cholesterol reducers	3	2

Results

The administration of FK 506 resulted in a lower cumulative steroid dosage. This effect was obtained due to the administration of a lower maintenance dosage as well as the need for less steroids to control rejection (Fig. 1). Concomitant medication for the treatment of disorders of glucose metabolism, hypertension, renal dysfunction and diarrhoea is listed in Table 1. In Table 2, additional drugs are shown that were given without being directly related to the immunosuppressive regimens. Whilst the incidences of the two main adverse effects – diabetes and oliguria – differed significantly between the two treatment groups, no significant difference was evident in the concomitant medication used to treat these complications. Concerning hypertension, both the incidence of

Table 1 Concomittant medication and adverse effects with FK 506 and CBIR treatment (data is expressed in percentages)

Concomittant medication				Adverse effect			
	FK 506	CBIR	*P* value		FK 506	CBIR	*P* value
Antidiabetics	67	61	n.s.	Diabetes	17	9.5	< 0.05
Diuretics	84	83	n.s.	Renal dysfunction			
				Creat. increase	19	17	n.s.
				Oliguria	18	11	< 0.05
				Kidney failure	9	7	n.s.
Antihypertensives				Hypertension	33	38	n.s.
Total	17	20	n.s.				
Beta-blockers	11	14	n.s.				
Antidiarroeals	34	24	< 0.01	Diarrhoea	33	22	< 0.01

this adverse effect and the medication that was administered to control it did not differ significantly. FK 506 was associated with a significantly higher incidence of diarrhoea that required a significantly higher rate of treatment.

Discussion

Studies with the novel immunosuppressant FK 506 have reported a markedly reduced incidence of acute rejection compared with historical controls treated with CyA [5, 7, 9]. FK 506 therapy is also associated with a reduced incidence of hypertension, although renal impairment and diabetes mellitus have been reported with a similar frequency [4, 5].

The results from two major international, multicentre, randomized clinical studies – conducted in Europe and the US – assessing the efficacy and safety of FK 506 compared with CyA in patients receiving primary liver allografts have shown a significantly reduced incidence of acute rejection [1, 8]. In both studies, the total cumulative corticosteroid dosages administered were significantly reduced for patients receiving FK 506 therapy. However, the results of the European study indicate that the incidence of oliguria, diabetes mellitus and diarrhoea is significantly increased in FK 506-treated patients [2, 3]. Hypertension was diagnosed in a similar number of patients from both treatment groups. The relation of these adverse events to the FK 506 dosage is discussed elsewhere [6]. It has been shown that there is a correlation between diabetes and hypertension, on the one hand and the FK 506 dosage on the other.

It is interesting to note that medication prescribed for the treatment of events such as diabetes and renal dysfunction did not differ between the FK 506 and the CBIR treatment groups. This could result from the fact that the adverse events reported were of mild severity and did not necessitate additional treatment. It is more difficult to evaluate the data concerning the antidiabetic medication, since these included therapy that was administered routinely during the immediate post-transplantation period, along with the insulin given to patients who had diabetes pre-transplant. The difference between the two treatment groups was, however, significant for the administration of antidiarrhoeals.

Conclusions

1. The total cumulative corticosteroid usage was significantly reduced in the FK 506 treatment group in comparison with the cyclosporin A treatment group.
2. The corticosteroid-sparing capacity of FK 506 is likely to have resulted from the reduced incidence of rejection in patients receiving FK 506 therapy.
3. Despite the reduction in corticosteroid usage (and limited or no azathioprine and/or ALG/ATG use), FK 506-treated patients experienced significantly fewer episodes of both acute and intractable rejection.
4. The number of patients receiving antidiabetic, diuretic and antihypertensive therapy did not differ between the two treatment groups, even though the incidence of diabetes mellitus and oliguria was significantly higher in the FK 506 treatment group. It can, therefore, be assumed that in a number of such cases the severity of these events was very mild, necessitating no specific therapy.

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