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Neurological complications in the European multicentre study of FK506 and cyclosporin in primary liver transplantation

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Abstract Neurological complications were examined in a multicentre, randomized, parallel-group study of 545 patients undergoing primary liver transplantation to compare the efficacy and safety of FK506- and cyclosporin A-based immunosuppressive regimens (CBIR). In an additional analysis, patients were divided into early and late randomized cohorts to detect the influence of protocol amendements that allowed for FK506 dose reductions. Initial follow-up was for 6 months. Tremor, headache and insomnia were the most frequently reported adverse events involving the neurological system. Whereas these neurological symptoms were observed significantly more often in FK506-treated patients ($P < 0.05$ vs. CsA for the overall population), this was no longer the case for the late FK506 and CBIR cohorts. The risk of FK506-treated patients developing tremor was related to the initial i.v. dose, the rate of administration of the i.v. dose and the daily dose ($P < 0.01$). Headache was significantly correlated with the FK506 dose ($P < 0.05$), and insomnia was not related to any dosing variable. Major neurological symptoms, including psychosis, convulsion, coma, aphasia and intracranial haemorrhage, were reported with a low frequency (0.4–5.2%), and differences between both treatment groups were neither significant for the overall population nor for the early and late cohorts of FK506 and CBIR. Data from the late cohorts showed no differences in the overall incidence of neurological adverse events between FK506- and CBIR-treated patients.

Key words Liver transplantation
Human · Neurotoxicity

Introduction

The introduction of cyclosporin A (CsA) substantially improved the outcome following orthotopic liver transplantation. By the mid-1980s, most maintenance immunosuppression was CsA-based. However, despite over 10 years clinical experience with CsA, treatment regimens continue to be modified, and more potent, but not toxic, immunosuppressive agents were searched for. Preliminary clinical studies commencing in 1989, have indicated that FK 506 is an effective, well-tolerated treatment for the prevention of allograft rejection [1]. However, potent immunosuppressive drugs carry the potential of toxic side-effects and may lead to increased mortality and morbidity following transplantation. CNS toxicity represents a wide spectrum of mild to severe neurological and psychiatric diseases, including epileptic seizures, hemiparesis, dysphasia, cerebellar symptoms and organic brain syndromes (OBS), that have been observed in 6–47% of liver transplant recipients treated with either CsA- or FK 506-based immunosuppression [2–5]. Various perioperative factors, including preoperative hepatic encephalopathy, impaired liver function, hypocholesterolaemia and treatment with high-dose methylprednisolone or OKT3 have been proposed to contribute to CsA- or FK 506-associated neurotoxicity [6–9]. While several studies have evaluated CsA-induced neurotoxicity, little is known about the neurotoxic potential of FK 506. Initial reports have described a similar quality [10], but a considerably lower incidence of neurological symptoms compared with CsA [11]. The present report evaluates the incidence of neurological adverse events within a multicentre, randomized, parallel-group study of 545 patients undergoing primary liver transplantation.

Materials and methods

Study design

This was an open, randomized, parallel-group study conducted between September 1990 and July 1992 in eight centres in four European countries. Patients were randomly assigned to treatment within centres according to predefined inclusion criteria, and stratified for the presence of fulminant hepatic failure. 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.

FK 506-based regimen

Intravenous and oral FK 506 doses administered during the initial phase of this study were selected on the basis of published clinical experience from the University of Pittsburgh [12]. An intravenous infusion of 0.075 mg/kg body weight (BW) was administered over 4 h, repeated every 12 h for 3 days, followed by conversion to oral therapy of 0.3 mg/kg BW per day. However, during the course of the study, clinical experience dictated a number of changes to the FK 506 treatment regimen resulting in the administration of lower doses of FK 506. Intravenous methylprednisolone (10 mg/kg BW) was administered as a single intra- or postoperative dose followed by a daily dose of 20 mg of prednisolone.

Cyclosporin A-based immunosuppressive regimen (CBIR)

CBIR was the most optimal multidrug regimen used in each centre to offer the optimal risk/benefit ratio in the management of allograft rejection. CBIR therapy was standardized for each centre and the duration of the study. The initial dose of each component of the regimen varied between centres: CsA, intravenous 1–6 mg/kg BW per day, oral 8–15 mg/kg BW per day; azathioprine, 1–3 mg/kg BW per day; corticosteroids, 0.5–2.5 mg/kg BW per day. Antilymphocyte or antithymocyte globulins (ALG/ATG) were administered at a dose of 5 mg/kg BW per day for a 1-week induction posttransplantation in three centres.

Management of rejection

The definition of rejection required both histological evidence of rejection and associated biochemical evidence of deteriorating liver function. Patients in both treatment groups received methylprednisolone for treatment of acute rejection and OKT3 monoclonal antibody for steroid-resistant or severe recurrent rejection.

Clinical monitoring and follow-up

Prior to transplantation, the medical history, demographic data, physical examination and clinical laboratory evaluations, electrocardiogram, and chest X-ray were obtained from all patients. Laboratory evaluations, including CsA blood levels and FK 506 plasma levels, and clinical adverse experiences were evaluated on a daily basis for the first 2 weeks, and subsequently after predefined time intervalls.

Neurological evaluations

Neurological evaluations were performed preoperatively and at predefined postoperative time intervals. If neurotoxicity was suspected, patients were seen by a neurologist or psychiatric consultant, according to the management of each centre. Additional diagnostic procedures, i.e. EEG, CCT-scan and MRI were performed as clinically indicated.

Statistical analysis

Kaplan Meier estimates, Wilcoxon and chi-square tests were used as indicated. Results are expressed as the mean ± standard error of the mean.

Results

Survival

Kaplan-Meier estimates for 6-month patient survival were similar in both groups, with 83.5% for the FK 506-treated patients and 79.3% for the CBIR treatment regimen.

Neurological adverse events within the first 6 months following liver transplantation

Major neurological adverse events including coma, psychosis, convulsion, neuropathy and aphasia were observed with a frequency between 1.5 and 5.2% in patients treated with either immunosuppressive regimen (Table 1). None of these adverse events were significantly different between the two treatment regimens, for the overall population, for the early or late cohorts.

Further disturbances in cerebral vigilance, attention, thinking concentration, perception, sleeping-waking rhythm, orientation, recent memory and psychomotor activity were reported as various neurological symptoms as outlined in Table 1. Except for confusion, no differences between both treatment groups were observed. Tremor, headache and insomnia were the most frequently reported adverse neurological events. In the overall population, all three symptoms were observed significantly more often in patients receiving FK 506 therapy (Table 1). However, this was no longer the case for the late FK 506 and CBIR cohorts.

Neurological adverse events were most frequently reported within the first 4 weeks following transplantation (Table 2). One or more neurological symptoms were observed in 163 patients (61.1%) treated with FK 506 compared with 132 patients receiving CBIR treatment (48.4%), while the total number of neurological events increased to 77.9% (208 patients) in patients treated with FK 506 and to 68.5% (167 patients) in patients treated with CBIR. Psychosis, confusion and delirium, also frequently observed after major surgical interventions, though to a lesser extent, occurred mainly within the 1st 4 postoperative weeks, irrespective the immunosuppressive treatment. Convulsions, including grand mal convulsions, were also observed mainly within the early postoperative period, with the exception of grand mal convulsions in CBIR-treated patients, which occurred in approximately 50% of the cases after the 1st postoperative months. Encephalopathy, as a liver disease associated syndrome, was observed exclusively within the 1st 4 postoperative weeks. However, somnolence and coma occurred in 50% of the cases after the 1st postoperative month, and may, according to our experience, be preferably related to severe infection and the multiple organ failure syndrome (MOFS). Depression, headaches, tremor and peripheral neuropathy and hypesthesia were

Table 1 Neurological adverse events observed within the first 6 months following liver transplantation. Total number of patients = number of patients reporting one or more neurological adverse experiences

Neurological symptoms	FK 506 ($n=267$)	CsA ($n=273$)
Coma	6 (2.2%)	3 (1.1%)
Somnolence	10 (3.8%)	6 (2.2%)
Encephalopathy	2 (0.8%)	4 (1.5%)
Convulsion	13 (4.9%)	8 (2.9%)
Grand mal convulsion	4 (1.5%)	8 (2.9%)
Aphasia	4 (1.5%)	1 (0.4%)
Dysarthria	3 (1.1%)	4 (1.5%)
Psychosis	14 (5.2%)	13 (4.8%)
Confusion	23 (8.6%)[a]	11 (4.0%)
Delirium	4 (1.5%)	8 (2.9%)
Paranoid reaction	2 (0.7%)	2 (0.7%)
Insomnia	78 (29.2%)	55 (20.2%)
Depression	11 (4.1%)	13 (4.8%)
Headache	84 (31.5%)[b]	58 (21.3%)
Tremor	116 (43.5%)[b]	81 (29.,7%)
Neuropathy	10 (3.8%)[b]	14 (5.1%)
Miscellaneous	138 (51.6%)	95 (34.9%)
Total number of patients	208 (77.9%)	167 (68.5%)

[a] $P < 0.05$; [b] $P < 0.01$

Table 2 Neurological adverse events observed within the first 4 weeks following liver transplantation. Total number of patients = number of patients reporting one or more neurological adverse experiences

Neurological symptoms	FK 506 ($n=267$)	CsA ($n=273$)
Coma	4 (1.5%)	–
Somnolence	5 (1.9%)	1 (0.4%)
Encephalopathy	2 (1.1%)	4 (1.5%)
Convulsion	11 (4.1%)	7 (2.6%)
Grand mal convulsion	3 (1.1%)	2 (0.7%)
Aphasia	4 (1.5%)	–
Dysarthria	1 (0.4%)	1 (0.4%)
Psychosis	13 (4.9%)	11 (4.0%)
Confusion	21 (7.9%)[a]	9 (3.3%)
Delirium	3 (1.1%)	8 (2.9%)
Paranoid reaction	1 (0.4%)	1 (0.4%)
Insomnia	69 (25.9%)	49 (18.0%)
Depression	3 (1.1%)	3 (1.1%)
Headache	33 (12.4%)	20 (7.3%)
Tremor	43 (16.1%)	27 (9.9%)
Neuropathy	7 (2.6%)	5 (1.8%)
Miscellaneous	78 (27.3%)	63 (23.1%)
Total number of patients	163 (61.1%)	132 (48.4%)

[a] $P < 0.05$

reported more frequently during the later follow-up (beyond 1 months after transplantation). The pattern of neurological symptoms was similar in patients treated with either immunosuppressive management at both time points: early and late postoperatively. The severity of neurological symptoms may be somewhat higher in FK 506-treated patients than in patients receiving CBIR therapy, as assessed by a higher frequency of conversions from FK 506 to CBIR therapy owing to neurotoxicity. Sixteen patients (6%) were converted from FK 506 to CBIR therapy, while two patients (0.7%) were converted from CBIR to FK 506 within the first 6 months following transplantation.

The risk of FK 506-treated patients developing tremor was related to the initial i. v. dose ($P < 0.01$), the rate of administration of the initial i. v. dose ($P < 0.01$) and the mean daily total dose ($P < 0.01$). Headache was significantly correlated with the FK 506 dose at the time of occurrence ($P < 0.05$). Insomnia was not correlated with any dosing variable.

Discussion

The incidence of adverse neurological events observed within the 1st 6 months following liver transplantation in this multi-centre, randomized, parallel-group study of 545 patients compared very well with reports in the literature for both the FK 506 and the CBIR treatment regimen [2–4]. The incidence of seizures following CsA treatment has been reported to approach 42% of liver-transplanted patients [2]. Major neurological complications, including seizures, cerebrocerebellar symptoms, coma, cortical blindness, psychosis, visual hallucinations and intracranial hemorrhage, are observed in 8.4–47% of CsA-treated patients [3, 7, 13]. Initial reports from the Pittsburgh group have described a lower incidence of neurotoxicity, with 6.0 and 8.4% in FK 506-treated patients [5, 11, 14]. In the present study, neurological symptoms were similar in patients treated with either drug, which was in agreement with the observations of Freise et al. [10].

Various perioperative factors, including preoperative hepatic encephalopathy, impaired liver function, hypocholesterolaemia, hypomagnesaemia, electrolyte disturbances and treatment with high-dose methylprednisolone or OKT3, have been found to contribute to CsA- or FK 506-associated neurotoxicity [6–9, 15]. Furthermore, we found that increased bilirubin, impaired liver and kidney function and imbalances of glucose metabolism also had a significant impact on the incidence and severity of neurotoxicity within the early postoperative period (Berlin single centre experience, to be published). Severe infections, most likely due to over-immunosuppression, combined with the multiple organ failure syndrome including the CNS, was mainly responsible for late neurotoxicity.

To evaluate various contributing factors apart from the purely FK 506- or CsA-associated neurotoxicity, re-evaluation of COSTARD-coded adverse events in single centres seems desirable. Data from the Berlin single centre experience were at variance with the total population of 545 patients recruited to the European FK 506 multicentre study regarding the cumulative data of neurological adverse experiences that showed a similar incidence for most neurological symptoms. The number of patients experiencing neurological symptoms seemed rather high, but only a few symptoms were serious in nature. Therefore, various symptoms either occurring with a low frequency or regarded as less impotant were summarized as miscellaneous (Tables 1 and 2). A considerably higher incidence of major neurological adverse events was found in Berlin, but still compared very well with the literature. Furthermore, the incidence of moderate and severe neurotoxicity was even markedly higher in FK 506-treated patients in Berlin (to be published). This may result from being only a single-centre experience, or from the reevaluation of COSTARD-coded adverse events. However, as those patients who were converted from one immunosuppressive agent to the other due to neurotoxicity also experienced the most serious neurological complications, then there is the same trend for a somewhat higher severity of FK 506-associated neurotoxicity, similar to that seen in our single centre experience.

Further improvements in the FK 506 regimen, including immediate postoperative oral FK 506 administration and optimized monitoring by measuring whole blood instead of plasma FK 506 levels, may further reduce the neurotoxic potential of FK 506, without affecting its superior potency.

In conclusion, neurological adverse events area common feature following liver transplantation. Tremor, headache and insomnia were the most frequently reported neurological adverse events. These adverse events were rarely considered to be serious in nature. Major neurological adverse events, including coma, psychosis, confusion, convulsion, aphasia, hemiparesis and intracranial hemorrhage were observed with a low frequency (0.4%–5.2%), irrespective of the immunosuppressive agent used.

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