Transpl Int (1994) 7 [Suppl 1]: S37–S42

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Neurotoxicity after orthotopic liver transplantation in cyclosporin A- and FK506-treated patients

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Abstract Neurotoxicity is a serious complication following orthotopic liver transplantation leading to increased morbidity and mortality. Neurotoxicity may be evoked by various perioperative factors, or may be due to drug-specific toxicity of immunosuppression. In the present study we evaluated the incidence of central nervous system (CNS) toxicity occurring within the early postoperative period of 121 patients, 61 randomly assigned to FK506- and 60 to CsA-based immunosuppression as part of a multicentre study. The incidence of moderate or severe CNS toxicity was higher in patients treated with FK506 (21.3%) than in patients receiving CsA (11.7%). The duration of symptoms was also greater in patients treated with FK506 than in patients receiving CsA. The incidence of moderate or severe neurotoxicity after retransplantation was markedly greater in patients treated with FK506 (100% of the patients).

Key words Liver transplantation
Neurotoxicity

Introduction

The introduction of cyclosporin A (CsA) and FK506 significantly improved the outcome following orthotopic liver transplantation (LTx). However, potent immunosuppressive drugs carry the potential of toxic side effects and may lead to increased mortality and morbidity following transplantation. Central nervous system (CNS) toxicity presents as a wide spectrum of mild to severe neurological and psychiatric diseases, including epileptic seizures, hemiparesis, dysphasia, cerebellar symptoms and organic brain syndromes (OBS), which have been observed in 6–47% of liver transplant recipients treated with either CsA- or FK506-based immunosuppression [1–3]. Various perioperative factors, including preoperative hepatic encephalopathy, decreased liver function, hypocholesterolaemia and treatment with high-dose methylprednisolone or OKT3 have been suggested as contributing to CsA- or FK506-associated neurotoxicity [4–7]. While several studies have evaluated CsA-induced neurotoxicity, little is known about the neurotoxic potential of FK506. Initial reports have described a similar presentation [8], but a considerably lower incidence, of neurological symptoms compared with CsA [9]. The present study evaluated the incidence of early postoperative neurotoxicity in 121 liver transplant recipients, randomly assigned to either FK506- or CsA-based immunosuppression, transplanted at our institution, as part of a European multicentre study.

Materials and methods

Patients

Between September 1990 and January 1992, 130 LTX were performed at the University Clinic Rudolf Virchow. Of these 130

consecutive transplants, 121 patients with primary liver transplants entered the study according to predefined inclusion criteria. Indications for LTX included 9 patients with acute liver failure due to fulminant HBV and HCV infections, 56 with HBV and HCV cirrhosis, 19 with alcoholic cirrhosis, 14 with primary biliary cirrhosis (PBC), 7 with secondary sclerosing cholangitis (SSC) and 16 with various other indications. Nine patients who were undergoing retransplantation were excluded. All patients were randomized to receive treatment with either FK 506- (61 patients) or CsA-based (60 patients) immunosuppression prior to transplantation. The study was approved by the ethics commitee of the Free University of Berlin and informed consent was received from each patient prior to participation in this study.

Liver transplantation

Surgery was performed according as standard procedures. All grafts were preserved with University of Wisconsin (UW) solution and venovenous bypass was used in all cases. All anastomoses were completed prior to reperfusion. Biliary anastomosis was performed as side-to-side choledochocholedochostomy with a T-tube [10] in all but nine cases; in these cases choledochojejunostomy was necessitated by the primary disease.

Immunosuppressive protocol

FK 506

FK 506 was administered at a dosage of 0.075 mg/kg body weight (BW) intravenously (i.v.) over 8 h commencing on postoperative day (POD) 0 immediately after transplantation. On PODs 1 and 2, 0.075 mg/kg BW FK 506 was administered i.v. twice daily. The FK 506 treatment regimen was reduced following treatment of the first 20 patients to 0.05 mg/kg BW. Commencing on POD 3, 0.15 mg/kg BW FK 506 was given orally twice daily. The oral FK 506 dose was similarly reduced to 0.1 mg/kg BW twice daily. Early dose reductions were performed owing to apparent toxicity, and late dose reductions if graft function was stable and no rejection was suspected. Methylprednisolone was administered by i.v. bolus-injection at a dosage of 500 mg prior to, and 6 h after, reperfusion. Prednisolone treatment was started on POD 1, with 20 mg/day orally and reduced to 15 mg/day after 4 weeks. Thereafter prednisolone was reduced in steps of 5 mg according to graft function and clinical judgement and ideally withdrawn.

CsA

All patients in the CsA group were treated according to our conventional immunosuppressive management, commencing with quadruple therapy for 1 week and subsequently continued as triple therapy. CsA treatment was commenced on POD 1 with 1–2 mg/kg BW CsA as a continuous i.v. infusion over 8 h twice daily and was continued orally after closing the T-tube on POD 5 with 5–7 mg/kg BW CsA, adjusted according to CsA blood level. Early postoperative levels of 600–800 ng/ml (as determined by the nonspecific TDX assay) were aimed at. Azathioprine was administered at a dosage of 25 mg/day for the first 6 postoperative days and thereafter increased to 1–2 mg/kg BW, adjusted according to peripheral leucocyte blood count. Methylprednisolone (500 mg) was administered prior to, and 6 h after, reperfusion. Prednisolone treatement was commenced with 1 mg/kg BW on PODs 1–3 and reduced to 40 mg/day on PODs 4–7. From POD 8 to 13, patients received 25 mg/day, and thereafter were treated with the same dosage of prednisolone as patients in the FK 506 treatment group (20 mg/day until POD 28 and 15 mg/day thereafter). Corticosteroid usage was reduced further according to the same criteria as described for FK 506-based immunosuppression. Anti-thymocyte immunoglobulin (ATG; rabbit ATG; Fresenius, Bad Homburg, Germany) was administered as a continuous i.v. infusion over 8 h at a dosage of 5 mg/kg BW, commencing at the beginning of the operation and continued on PODs 1–6 at the same dose and in the same manner.

Management of rejection

Diagnosis of acute rejection was based on clinical (fever, change of colour and amount of bile production) and laboratory (AST, ALT, bilirubin, γGT and alkaline phosphatase) findings and was confirmed by histological evaluation of graft biopsy specimens. Patients from both treatment groups received methylprednisolone for treatment of acute rejection at a dosage of 500 mg/day for 3 days and OKT 3 monoclonal antibody (Cilag, Sulzbach, Germany) for steroid-resistant or severe recurrent rejection.

Concomitant treatment

Aprotinin administration, i.v. antibiotic treatment, selective bowel decontamination and various other prophylactic procedures were performed perioperatively as previously described [11].

Clinical monitoring and follow up

Prior to transplantation, a medical history and demographic data were obtained from each patient and each was subjected to a physical, clinical laboratory, electrocardiographic and chest radiographic examination. Laboratory tests, including CsA blood levels (nonspecific TDX assay) and FK 506 plasma levels, were carried out, and clinical adverse experiences recorded, on a daily basis for the first month, and then after 3, 6, 9, 12, 18 and 24 months.

Neurological evaluations

Every patient was seen by a neurologist prior to LTX and 1, 3, 6, 9, 12, 18 and 24 months after LTX, routinely. If neurotoxicity was suspected at any time point, the patient was seen by a neurologist and a psychiatrist. Additional diagnostic procedures, i.e. EEG, CCT scan and MRI, were performed as clinically indicated. Encephalopathy was graded on a scale of 0 to 4 according to the classification of Trey et al. [12]. OBS included various degrees of comatose states, as well as disturbances of attention, thinking, concentration, perception, sleeping-waking rhythm, orientation, recent memory and psychomotor activity. Mild OBS included immediate postoperative metabolic encephalopathy of short duration (less then 1 week) and normal EEG findings. Moderate and severe OBS lasted considerably longer, the severity of symptoms was greater, and in most cases EEG abnormalities were observed.

Statistical analysis

All analyses were based on our database rather than the "offical", source-verified audited database of the multicentre study. Kaplan-Meier estimates, Wilcoxon, Chi-squared and Kruskal-Wallis tests were used as indicated. Results were expressed as means ± standard error of the mean.

Results

Demographic data, including preoperative encephalopathy, physical health according to the WHO performance score and preexisting neurological diseases were not significantly different between the two treatment groups. Irrespective of the immunosuppressive management, approximately two-thirds of all patients were restricted in physical activity, but were able to care for themselves and to do light work for more than 50% of their waking hours prior to LTX. The remaining one-third were either limited to self-care and confined to bed and chair for more than 50% of their waking hours or completely disabled and confined to bed and chair. Preoperatively, no or only mild encephalopathy was observed in 86.9% of patients in the FK 506-treated group and in 83.3% of patients treated with CsA. The remaining patients in both groups had either moderate or severe encephalopathy. Preexisting major neurological diseases were not observed in either group.

Survival

Actual 3-month and 1-year patient survival was similar in both groups with 100% and 90.2% for FK 506-treated patients and 98.3% and 96.6% for CsA-treated patiens, respectively.

Incidence of early postoperative neurotoxicity

Moderate or severe neurotoxicity early (within the first months) following TLX occurred in 21.3% of FK 506-treated patients compared with 11.7% of CsA-treated patients and included coma, OBS, hemiparesis, dysphasia, epileptic seizures and cerebellar dysfunction (Table 1). The mean day of onset of neurological symptoms was similar in both treatment groups with POD 4 (range POD 1–14) in FK 506-treated patients and with POD 4.3 (range POD 1–8) in CsA-treated patients. In FK 506-treated patients the duration of symptoms varied between several weeks to months or never resolved completely in three cases (4.9%), while in CsA-treated patients the duration of symptoms varied between 1 week and 2 months.

A further 9.8% of FK 506-treated patients and 13.3% of CsA-treated patients experienced mild neurological symptoms, which included mainly mild OBS including short-duration immediate postoperative metabolic encephalopathy. Regardless of the immunosuppressive management, the mean day of onset of mild neurological symptoms was earlier than in those patients experiencing moderate and severe neurotoxicity, with POD 2.5 (range POD 0–4) in FK 506-treated patients and with POD 1.4 (range POD 0–3) in CsA-treated patients. The duration of symptoms was considerably shorter than in patients experiencing moderate or severe neurotoxicity (2 days to 1 week).

Table 1 Neurological symptoms in the early postoperative period (*OBS* organic brain syndrome). Symptoms of patients with mild neurotoxicity were summarized as mild OBS, the remaining symptoms were observed either alone or in various combinations in patients with moderate or severe neurotoxicity

Symptom	FK 506-treated patients	CsA-treated patients
OBS (mild)	6/61 (9.8%)	8/60 (13.3%)
OBS (moderate)	8/61 (13.1%)	4/60 (6.7%)
OBS (severe)	4/61 (6.6%)	3/60 (5.0%)
Hemiparesis	3/61 (4.9%)	1/60 (1.7%)
Dysarthria	3/61 (4.9%)	2/60 (3.3%)
Seizures	1/61 (1.6%)	2/60 (3.3%)
Depression	1/61 (1.6%)	–
Cerebellar symptoms	1/61 (1.6%)	1/60 (1.7%)
Acinetic mutism	1/61 (1.6%)	–

Additional treatment and clinical course

In most cases transient pharmacological treatment with haloperidol, diazepam or valproate was necessary. FK 506 medication was reduced in all cases of moderate and severe toxicity, and was withdrawn for variable periods of time in six patients. In five patients FK 506 medication was discontinued owing to severe neurotoxicity and the patients were switched to CsA. Three of these patients recovered completely, while neurological deficits persisted in two patients. CsA medication was adapted to a lower therapeutic range in most cases, and in one case CsA was withdrawn and the patient switched to FK 506. However, severe neurotoxicity was not the main reason for conversion, as this patient experienced steroid-resistant rejection, followed by OKT3 treatment. Neurological symptoms persisted following conversion and the patient recovered partially after 1 year. The remaining patients recovered completely.

Neurotoxicity following retransplantation

Between September 1990 and December 1992, 6 of the 121 patients were retransplanted – 5 patients within 1 year

and 1 patient after 1 year. Three of six patients had no neurotoxicity following primary transplantation, while the remainder showed mild signs of neurotoxicity. Four patients were initially treated with CsA and two with FK506. Two patients were switched to FK506 after retransplantation owing to intractable and chronic rejection, while one patient was switched to CsA owing to nephrotoxicity. CsA-treated patients developed mild or no signs of neurotoxicity after retransplantation, while three patients treated with FK506 experienced moderate or severe neurotoxicity. The spectrum of neurological symptoms was similar to those seen in patients after primary LTX. All patients but one recovered completely. One patient died following hypoxic brain injury.

Neurotoxicity and immunosuppression

FK506

FK506 medication was reduced early postoperatively in patients with moderate or severe neurotoxicity. These reductions are mainly the result of toxicity (neuro- and nephrotoxicity), since on-line monitoring of FK506 levels was not available. Patients with moderate or severe neurotoxicity received significantly less FK506 within the first 30 days (8.4 ± 0.3 mg/day; $P \leqq 0.01$) compared with patients with mild or no neurotoxicity (12.5 ± 0.3 and 12.3 ± 0.2 mg/day, respectively). However, FK506 plasma levels in patients with moderate or severe neurotoxicity were in a similar range to FK506 levels in patients without neurotoxicity (0.8 ± 0.1 and 0.7 ± 0.1 ng/ml, respectively), whereas FK506 levels of patients with mild neurotoxicity were significantly higher during the first month following LTX (1.2 ± 0.2 mg/ml; $P \leqq 0.01$). After LTX, the mean oral FK506 medication for patients with moderate or severe neurotoxicity remained significantly lower with 7.9 ± 0.1 mg/day compared with 11.1 ± 0.2 and 10.2 ± 0.2 mg/day for patients with mild or no neurotoxicity ($P \leqq 0.01$), but FK506 plasma levels were in a similar range in all groups. All except one patient with moderate or severe neurotoxicity had maximal FK506 levels within the normal or low therapeutic range within several days prior to the onset of symptoms (range of maximal FK506 levels 0.2–1.7 ng/ml, mean 0.7 ng/ml). In one patient the peak FK506 level reached 4.4 ng/ml.

CsA

Whithin the first postoperative month patients with moderate or severe neurotoxicity received significantly less oral CsA (441 ± 8 mg/day) compared with patients with mild or no neurotoxicity (616 ± 14 and 544 ± 6 mg/day, respectively; $P \leqq 0.01$). CsA levels were adapted to a lower therapeutic range (419 ± 5 vs. 520 ± 7 ng/ml and 528 ± 3 ng/ml in patients with mild or no neurotoxicity; $P \leqq 0.01$). To achieve CsA levels with the therapeutic range, patients with mild neurological symptoms required higher CsA dosages than patients with no neurotoxicity. Within the first year, oral CsA dosages per day were similar in all groups (420–470 mg), and CsA levels were within a similar range (470–510 ng/ml). As in FK506-treated patients, high CsA blood levels were not observed prior to, or at the onset of, neurotoxicity. All patients with moderate or severe neurotoxicity had maximal CsA levels within the normal or low therapeutic range (mean maximal CsA level 490 ng/ml, range 347–600 ng/ml).

Discussion

Early postoperative CNS toxicity was observed in 25.0% of CsA-treated patients and 31.3% of FK506-treated patients, which lie within the ranges reported in the literature [1–3]. We observed a similar quality of neurotoxicity, i.e. diagnosis and symptoms of neurological diseases were the same in patients treated with either drug, which conforms with the observations of Freise et al. [8]. However, we found a higher incidence of moderate and severe neurotoxicity in patients treated with FK506 compared with patients receiving CsA, in contrast to previous reports from the Pittsburgh group [9, 13]. However, it needs to be emphasized that two unequal immunosuppressive regimens were being compared: FK506 plus corticosteroids versus CsA-based quadruple therapy. CsA therapy alone in connection with prednisone would require higher CsA dosages to be administered with the possibility of increased toxicity. Regarding nephrotoxicity, withdrawal of FK506 medication and ATG application for several days can avoid the need for a haemodialysis, as has been shown in several patients. A similar approach may be promising for patients experiencing neurotoxicity. Furthermore, initial FK506 dosages were rather high according to the protocol, and were only reduced if toxicity was observed. Our results are at variance with the total population of 545 patients recruited into the European FK506 multicentre study (to be published). This may result from being only a single-centre experience, or from re-evaluation of COSTART-coded adverse events. Using FK506 over the last 3 years, we have experienced a learning curve in the handling of

this new agent. FK 506 therapy can be commenced orally instead of intravenously at lower dosages than recommended in the current study without loss of potency. Monitoring has been optimized by measuring whole-blood FK 506 levels instead of plasma levels, which have been proven to be more reliable in the case of CsA. Thus it seems that the incidence and severity of neurotoxicity can be reduced without loss of the superior immunosuppressive potency of FK 506.

Mild neurotoxicity was observed either immediately after LTX, or the onset of symptoms was within the first 2 postoperative days, indicating that severely compromised liver function may have an impact on early neurotoxicity, as previously reported [4, 14]. However, the onset of moderate severe neurotoxicity was several days postoperatively, which provides evidence that moderate and severe neurotoxicity may be CsA- or FK 506-associated, and that these immunosuppressive agents require several days to induce neurotoxicity. This hypothesis is supported by the observation that most patients recovered after withdrawal or dose reduction of FK 506 and regulation of CsA dosages to a lower therapeutic range.

Patients undergoing retransplantation experienced moderate or severe neurotoxicity significantly more often in the early postoperative period compared with the incidence in these patients following their first LTX, and compared with the overall incidence of early postoperative neurotoxicity of patients treated with either drug. A significantly higher frequency of neurological symptoms following the first retransplantation has previously been observed by Lopez et al. [15]. Whether the incidence and severity of neurotoxicity in these patients was greater because of the more severely compromised condition of these patients, or if other factors such as over-immunosuppression were responsible for this phenomenon remains speculative. The number of retransplantations was small ($n = 6$); however, differences between the two immunosuppressive managements were apparent. None of the three patients treated with CsA following retransplantation experienced moderate or severe neurotoxicity, while this was the case in all three patients treated with FK 506.

The precise mechanism of CsA- and FK 506-mediated neurotoxicity remains unknown. Intravenous administration and high levels of FK 506 or CsA have been suggested as contributing to drug-associated neurotoxicity, but our results did not confirm either hypothesis. FK 506 and CsA levels were within the low therapeutic range prior to, and after the onset of, neurological symptoms, and the onset of symptoms in several cases was associated with oral and not intravenous FK 506 or CsA medication.

The general perioperative condition as well as the perioperative severity of encephalopathy also had a significant impact on the incidence of neurotoxicity (data not shown). However, the operative procedure per se as evaluated by the duration of the recipient operation and utilization of red packed cells, and early relaparotomies due to coagulopathy and diffuse intra-abdominal haemorrhage did not contribute to early postoperative neurotoxicity (data not shown). Neither did the duration of preservation. Various other factors, such as high-dose methylprednisolone, OKT3 and electrolyte disturbances, have been suggested as mediating or coinciding with neurotoxicity following LTX [6, 7]. However, we found that acute rejection occurred in all cases after the onset of neurological symptoms, possibly owing to a reduction in immunosuppression (data not shown). Treatment with high-dose methylprednisolone and OKT3 initiated after the onset of neurotoxicity does not seem to play a major role in the development of neurotoxicity.

Neurotoxicity represents a serious side effect of immunosuppression following LTX. Neurotoxicity within the early postoperative period was observed to a similar extent in patients treated with either drug. However, the incidence of moderate and severe neurotoxicity was higher in patients treated with FK 506 than in patients receiving CsA. Moderate and severe neurotoxicity required several days to develop, indicating a contributory role for both immunosuppressive agents, while mild neurotoxicity occurred considerably earlier, and may be more likely to be associated with impaired liver function. After retransplantation, the incidence of neurotoxicity was increased if patients were treated with FK 506. Whether a reduction or withdrawal of FK 506 in critically ill patients, or whether lower dosages of FK 506, as presently recommended, combined with other immunosuppressive agents, at least in the early phase following LTX, would reduce severe neurological complications remains to be evaluated in additional studies.

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