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

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Abstract Nephrotoxicity represents a serious side-effect of immunosuppression following orthotopic liver transplantation. In order to preserve the therapeutic potential of cyclosporin (CsA) and FK506 in human liver transplantation and to differentiate the nephrotoxic action of either drug in a clinical setting, we evaluated the incidence of early and late nephrotoxicity in 121 patients, 60 randomly assigned to CsA- and 61 to FK506-based immunosuppression. Early postoperative renal insufficiency (between POD0 and 30; SCr 1.5–3 mg/dl) was observed to a similar extent in patients treated with CsA (36.7%) and FK506 (42.6%). Early postoperative acute renal failure (ARF; SCr > 3 mg/dl) occurred in 18.3%, regardless of the immunosuppressive management. Approximately 50% of patients with ARF required hemodialysis (CsA: 11.7%; and FK506: 8.3%). Mean onset of hemodialysis in CsA-treated patients was POD1 and in FK506-treated patients, POD6, which demonstrated a different time course of drug-specific nephrotoxicity of CsA and FK506 in early ARF. All patients with early postoperative ARF requiring hemodialysis survived more than 1 year (100% survival). New onset of late ARF (between POD30 and 365), however, occurred in 6.5% under FK506 and in 1.7% under CsA immunosuppression due to severe infections with the multiple organ failure syndrome. This observation was consistent with the assumption of over-immunosuppression rather than a primary nephrotoxic effect. Mortality of patients with late ARF requiring hemodialysis was 100%. Late renal insufficiency appeared in 23.3% of CsA- and in 29.4% of FK506-treated patients, and represented a slowly progressing form of drug-specific nephrotoxicity. These preliminary results demonstrated a similar outcome in terms of early and late nephrotoxicity, but longer follow-up will delineate its overall efficacy and toxicity in humans.

Key words Liver transplantation
Nephrotoxicity

Introduction

New immunosuppressive drugs and amelioration of the perioperative management have significantly improved the outcome after orthotopic liver transplantation. However, immunosuppression in general is associated with a variety of side-effects, on which drug-specific effects may be superimposed. Nephrotoxicity represents one of the most serious side-effects of immunosuppressive treatment, and has been reported to coincide with a high mortality following liver transplantation [1]. Various factors may contribute to early postoperative renal insufficiency or acute renal failure (ARF). Preexisting renal disease, perioperative events such as prolonged hypotension, hemorrhagic shock, and disseminated intravascular coagulopathy may lead to early postoperative ARF. Additional drug toxicity due to antibiotics, antifungal, or virostatic agents have been reported to cause ARF. Elevated bilirubin, as well as increased free hemoglobin, are also proposed to mediate ARF [2]. Impaired postoperative graft function has been reported as a contributing factor to early postoperative nephrotoxicity, since decreased liver function may decrease cyclosporin A (CsA) or FK 506 metabolism and lead to higher blood drug levels [3, 4]. Furthermore, there is evidence of direct toxicity of CsA or FK 506 to tubular or vascular interstitial cells [5], and renal plasma flow (EPRF). Glomerular filtration rate (GFR) is reported to parallel CsA and FK 506 drug levels [6]. Various studies have evaluated CsA-induced nephrotoxicity, but there are few reports about the nephrotoxic potential of FK 506. First reports have described a similar incidence of renal insufficiency and ARF compared to CsA [7]. In the present study, we evaluated the incidence of nephrotoxicity in 121 liver transplant recipients, 60 randomly assigned to CsA- and 61 to FK 506-based immunosuppression.

Materials and methods

Patients

Between September 1990 and January 1992, 130 orthotopic liver transplantations (LTX) were performed at the University Clinic Rudolf Virchow. Of these 130 consecutive transplants, 121 patients with primary liver transplants entered the European FK 506 multicenter study according to predefined inclusion criteria. Indications of LTX were acute liver due to fulminant HBV and HCV infections in 9 patients, HBV and HCV cirrhosis in 56 patients, alcoholic cirrhosis in 29 patients, primary biliary cirrhosis (PBC) in 14 patients, 7 with secondary sclerosing cholangitis (SSC), and various indications in 16 patients. Nine patients with retransplantations were excluded. All patients were randomized either for FK 506- (61 patients) or CsA-based immunosuppression (60 patients) prior to transplantation, and all gave informed consent to the study, which had been approved by the ethics commitee of the Free University of Berlin.

Liver transplantation

The surgical procedure was performed in a standardized fashion. All grafts were preserved with University of Wisconsin (UW) solution and veno-venous bypass was used in all cases. All anastomeses were completed prior to reperfusion. Biliary anastomosis was performed as a side-to-side choledochocholedochostomy with a T-tube [8] in all but 9 cases, which required choledochojejunostomy according to the primary disease.

Immunosuppressive protocol

FK 506

FK 506 was administered at a dose of 0.075 mg/kg body weight (BW) intravenously (i.v.) over 8 h, commenced 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 a day. Commencing on POD 3, 0.15 mg/kg BW FK 506 was administered orally twice a day. Due to a high incidence of toxic side-effects, the protocol was amended after treatment of the first 20 patients, and thereafter patients received 0.05 mg/kg BW FK 506 i.v. and 0.1 mg/kg BW orally twice a day. Early dose reductions were performed because of apparent toxicity, late dose reductions, if graft function was stable and no rejections suspected. Methylprednisolone was administered by i.v. bolus injection of 500 mg twice, prior to and 6 h after reperfusion. Prednisolone treatment was commenced on POD 1, with 20 mg/day orally, and reduced to 15 mg/day after 4 weeks. Thereafter, prednisolone medication was reduced in steps of 5 mg according to graft function and clinical judgement, and was ideally withdrawn.

CsA

All patients in the CsA group were treated according to our conventional immunosuppressive management, commencing as quadruple therapy for 1 week and continued as triple therapy thereafter. CsA treatment was started on POD 1 with 1–2 mg/kg BW CsA as a continuous i.v. infusion for 8 h twice a day and was continued orally after closing the T-tube on POD 5 with 5–7 mg/kg BW CsA, adjusted according to CsA blood levels. Early postoperative levels of 600–800 ng/ml by the unspecific TDX assay were aimed for. 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 the peripheral leukocyte blood count. Methylprednisolone (500 mg) was administered prior to and 6 h after reperfusion. Prednisolone treatment was started with 1 mg/kg BW on PODs 1–3 and reduced to 40 mg/day on PODs 4–7. Between PODs is 8 and 13, these patients received 25 mg/day, and thereafter they were treated with the same dosages of prednisolone as patients in the FK 506 group (20 mg/day until POD 28 and 15 mg/day thereafter). Further reductions in corticosteroid medication were performed according to the same criteria as described for KF 506-based immunosuppression. Anti-thymocyte immunoglobulin (ATG; rabbit ATG, Fresenius, Bad Homburg,

Germany) was administered as a continuous i.v. infusion for 8 h at a dosage of 5 mg/kg BW, commencing with the beginning of the operation and continued on PODs 1–6 in the same dose and fashion.

Management of rejection

Diagnosis of acute rejection was based on clinical (fever, change in color, and amount of bile production) and laboratory (AST, ALT, bilirubin, γGT, and alkaline phosphatase) findings and was confirmed by histological evaluation of graft biopsies. Both groups received methylprednisolone for treatment of acute rejection at a dosage of 500 mg/day for 3 following days and OKT3 monoclonal antibody (Cilag GmbH, Sulzbach, Germany) for steroid-resistant or severe recurrent rejection.

Concomitant treatment

Aprotinin administration, i.v. antibiotic treatment, selective bowel decontamination, and various other prophylaxes were perioperatively as previously described [9].

Clinical monitoring and follow-up

Prior to liver transplantation, the medical history, demographic data, physical examination with clinical and laboratory evaluations, electrocardiogram, and chest X-ray were evaluated in all patients. Laboratory evaluations, including CsA blood levels (unspecific TDX assay) and FK 506 plasma levels, as well as clinical adverse experiences, were evaluated on a daily base throughout the 1st months, and subsequently after 3, 6, 9, 12, 18, and 24 months.

Nephrological monitoring

All patients were seen postoperatively by nephrological consultants. If progressive renal insufficiency or acute renal failure was observed, the decision to use hemodialysis was made by nephrologists in cooperation with transplant surgeons.

Statistical analysis

All analyses were based on our database and not the "offical", source-verified, audited database of the 157 study. Kaplan Meier estimates, Wilcoxon, chi-square, and Kruskal-Wallis tests were used as indicated. Results are expressed as means ± standard error of the mean.

Results

Demographic data were not significantly different in both groups. The incidence of preexisting diseases such as diabetes, hyperpertension, or renal diseases, which may predispose to postoperative ARF, was not significantly different in both groups. Physical status prior to transplantation was also similar. Regardless of the immunosuppressive management, approximately two-thirds of all patients were restricted in physical activity, but were able to take care of themselves, and to do light work more than 50% of waking hours, whereas the remaining third were either limited in their ability to take care of themselves and were confined to bed and chair more than 50% of waking hours or were completely disabled and completely confined to bed and chair. Preexisting hepatorenal syndromes were observed in 4.9% of FK 506- and 6.7% of CsA-treated patients. Prior to transplantation, insulin-requiring diabetes was evident in 1.7% of FK 506- and in 5% of CsA-treated patients, while preexisting hypertension was not observed in either group.

Survival

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

Early postoperative nephrotoxicity

Early postoperative renal insufficiency [within 1 month; serum creatinine (SCr) > 1.5 but < 3 mg/dl] was observed in 38.3% of patients treated with CsA and in 42.6% of patients treated with FK 506 (P = n.s.; Table 1). Acute renal failure (ARF) was observed to the same extent (FK 506: 18.0% and CsA 18.3%) in patients treated with either drug, and approximately 50% of these patients required hemodialysis (11.7% of patients treated with CsA and 8.2% of patients treated with FK 506). Three patients, who were retransplanted and dialyzed 5 days prior to re-LTX or immediately following re-LTX were not included in the statistical analysis. One patient treated with CsA had an increased serum creatinine prior to LTX, the remaining patients had normal kidney function preoperatively. The mean onset of hemodialysis on POD 6.4 (range: POD, 4–13) was considerably later in FK 506-treated patients compared to a mean onset on POD 1 (range: POD: 0–2) for CsA-treated patients, while the duration was similar in both groups (CsA, 5 and 61 days; mean 20.6 days, and FK 506, 1 and 74 days; mean, 16.8 days). The frequency varied between 3–48 hemodialyses (mean frequency of 14 dialyses) for CsA-treated patients, and 1–41 (mean 10) hemodialyses for FK 506-treated patients.

Additional treatment and clinical course

Regardless of the immunosuppressive management, patients with renal insufficiency and ARF were treated with

Table 1 Incidence of nephrotoxicity of patients randomly assigned to FK 506 or cyclosporin A (CsA). Early nephrotoxicity was observed within the 1st month following liver transplantation. Onset of late nephrotoxicity after the 1st month following liver transplantation up to 1 year. Differences between CsA- and FK 506-based immunosuppression were not significant. Major differences in 1-year survival were observed between patients with early and late hemodialysis. Late hemodialysis occurred in all cases in connection with severe infection and multiple organ failure syndrome (*ARF* acute renal failure)

Severity and onset	FK 506	CsA	Survival
Renal insufficency – early	26/61 (42.6%)	23/60 (36.7%)	91.8%
ARF – early	11/61 (18.3%)	11/60 (18.3%)	90.9%
Hemodialysis – early	5/61 (8.3%)	7/60 (11.7%)	100%
Renal insufficiency – late	18/61 (29.4%)	14/60 (23.3%)	96.9%
ARF – late	4/61 (6.5%)	1/60 (1.7%)	40%
Hemodialysis – late	2/61 (3.7%)	1/60 (1.7%)	0%

continuous i.v. infusion of frusemide and low dose dopamine (beyond the routinely treated 48 h) to improve diuresis. In CsA-treated patients, four patients recovered completely with a kidney function within the normal range, while three patients still had mildly impaired kidney function with serum creatinine levels of 1.7–1.8 mg/dl. Early withdrawal of FK 506 medication and additional treatment with ATG was performed in three patients. One patient was switched to CsA on POD 26 due to nephrotoxicity. A second patient was converted to CsA due to nephrotoxicity on POD 1 after early retransplantation due to initial non-function (INF). In one patient with ARF, FK 506 withdrawal and the conversion to CsA was performed on POD 12, mainly due to severe neurotoxicity. Within 1 year, all but one patient recovered completely. One patient continued to have mildly impaired kidney function and a serum creatinine of 2 mg/dl. No patient with early postoperative ARF developed ARF again during the later follow up, or required permanent hemodialysis.

Late nephrotoxicity

Late nephrotoxicity was defined as renal insufficiency or ARF between POD 30 and POD 365. Renal insufficiency (SCr > 1.5 < 3 md/dL) was observed to a similar extent in patients treated with either drug. Renal insufficancy was observed in 23.3% of CsA- and in 29.4% of FK 506-treated patients (P = n.s.). Late ARF (SCr > 3 mg/dL) was observed in 5% of CsA-treated patients compared to 9.9% of FK-506-treated patients (P = n.s. vs. CsA). Of these patients, hemodialysis was necessary in all cases treated with CsA and in four out of six cases treated with FK 506. In CsA-treated patients, 2 hemodialyses were still performed due to early postoperative ARF, while one patient (1.7%) developed a new onset of ARF within the later follow-up due to severe infection with multiple organ failure syndrome (MOFS). In FK 506-treated patients, two patients also required hemodialysis for more than 1 month postoperatively, one patient after re-LTX. New onset of late ARF was observed in four patients (6.6%). In all cases, the cause of ARF was severe infection, and in two cases, that required hemodialysis, infection was accompanied by MOFS with a lethal outcome.

In all patients, immunosuppression was reduced and in two patients, FK 506 medication was intermittantly or permanently withdrawn. Neither CsA nor FK 506 levels were increased above the therapeutic range prior to the onset of infection.

Nephrotoxicity and immunosuppression

CsA

CsA medication was reduced to achieve CsA levels within a lower therapeutic range in patients with ARF. Mean oral CsA dosages in patients requiring hemodialysis were significantly lower within the 1st month as well as within the 1st year following transplantation (500 ± 19 mg/day and 375 ± 11 mg/day, respectively) compared to patients without hemodialysis (598 ± 19 mg/day and 423 ± 7 mg/day, respectively; $P \leq 0.01$ at both time points). As intended, CsA levels were significantly lower within the first 30 days, with mean CsA levels in patients receiving hemodialysis of 542 ± 20 ng/ml vs. 703 ± 9 ng/ml in patients without hemodialysis ($P \leq 0.01$). Trough levels remained significantly lower within the 1st year following transplantation in patients requiring hemodialysis (456 ± 17 ng/ml) compared to patients without dialysis (548 ± 6 ng/ml; $P \leq 0.01$).

FK 506

FK 506 dosages were reduced in all patients with ARF according to nephrotoxicity and not according to FK 506 plasma levels, since on-line monitoring was not available. Oral FK 506 dosages in patients requiring hemodialysis were significantly lower within the 1st month (9.5 ± 0.4 mg/day) compared to patients without hemodialysis (12.1 ± 0.2 mg/day; $P \leqq 0.01$). Thereafter, oral FK 506 dosages were kept slightly lower. Trough levels of FK 506 were significantly lower in patients requiring hemodialysis within the 1st month as well as within the 1st year following LTX (0.58 ± 0.1 ng/ml and 0.3 ± 0.1 ng/ml, respectively) compared to patients without hemodialysis (0.86 ± 0.2 ng/ml and 0.56 ± 0.1 ng/ml, respectively; $P \leqq 0.01$ at both time points).

Discussion

New approches to immunosuppressive treatment that will increase the immunosuppressive potency but decrease the incidence of drug-specific toxicity are desirable. Using the protocol of the European multicenter study, we found a similar incidence of early postoperative renal insufficiency, with 36.7% for CsA treated patients and 42.6% for FK 506-treated patients. Early ARF occurred in 18.3% of patients regardless of the immunosuppressive management. Approximately 50% of patients with ARF required hemodialysis, which conforms with previous reports in the literature [1, 10]. In contrast to what has been observed by others, our data did not support an increased mortality in dialyzed patients or patients with early postoperative ARF [11, 12]. In the present study, we confirmed our previous observation that early hemodialysis does not coincide with increased mortality [13]. Actual 1-year survival was even higher in patients dialyzed early, with 100% for both immunosuppressive managements compared with the overall 1-year survival. Since only 50% of patients with early ARF were dialyzed in either group, early postoperative hemodialysis was neither performed prophylactically nor intensively, but when indicated, i.e., if conservative treatment failed.

Various factors, such as preoperatively impaired kidney function, intra- or postoperative hypertension, impaired liver function, or liver failure have been proposed to mediate early ARF [1–3]. Preoperative creatinine levels were within the normal range in more than 90% of patients requiring postoperative hemodialysis and mean SCr levels were similar in dialyzed patients and in patients developing ARF compared to the remaining patients.

In CsA-treated patients, mean onset of hemodialysis was POD1 with a range from POD0 to POD2. Severe coagulopathy and increased preservation injury may have had an impact on the incidence of early postoperative hemodialysis in CsA-treated patients, since the incidence of relaparotomies due to severe coagulopathy and diffuse intraabdominal hemorrhage was significantly higher in CsA-treated patients requiring hemodialysis compared to FK 506-treated and dialyzed patients as well as compared to patients without hemodialysis (data not shown). Furthermore, the cold ischemic time was slightly prolonged.

In FK 506-treated patients, the onset of hemodialysis was considerably later compared to CsA-treated patients with a mean of 6.4 days and a range of 4 to 13 days. This finding indicated that, in this group, hemodialysis occurred, not due to perioperative events, which should have at least partially recovered by that time, but as a result of drug-specific side-effect of FK 506. Various mechanisms have been proposed. FK 506 may act as a vasoconstrictor, and has been reported to decrease the renal blood flow, possibly by increasing endothelin secretion, or it may have a direct cytotoxic action on renal tubular cells [14, 15]. All mechanisms may require several days for the developement of acute nephrotoxicity. The use of other nephrotoxic drugs, including antibiotics, was similar in both groups.

Neither increased CsA levels nor increased FK 506 levels were responsible for the onset of early postoperative nephrotoxicity. Maximal trough levels of both drugs were well within the therapeutic range, and mean CsA and FK 506 levels were significantly lower within the 1st month of transplantation. The observation that toxicity may occur despite low or normal drug levels has been previously reported [16].

Late renal insufficiency (between POD 30 and 365), with an increase in serum creatinine between 1.5 and 3.0 mg/dl, was observed to a similar extent in CsA- (23.3%) and FK 506- treated patients (29.4%), and may represent the drug-specific nephrotoxicity of CsA and FK 506. Interstitial fibrosis, vacuolization of renal tubules and chronic damage of the vascular endothelium were most likely responsible for the rise in serum creatinine [17]. Within the 1st year of LTX, increases in SCr were rather slow, but longer observation periods are necessary to evaluate progressive and chronic changes.

Late ARF with or without hemodialysis always occurred in connection with severe acute infections and was not evoked by increased levels of either CsA or FK 506. Furthermore, late ARF was strongly associated with FK 506 medication. Over-immunosuppression may be

postulated, despite drug levels being within the normal range. The incidence of late ARF was relatively small, with 1.7% for CsA-treated patients and 6.5% for FK 506-treated patients, but mortality of patients with late ARF requiring hemodialysis was 100%, regardless of the immunosuppressive therapy. All three patients died due to severe infections with MOFS. In these cases, nephrotoxicity may not have resulted from a drug-specific side-effect of immunosuppression on the kidneys, but may have occurred due to infections with MOFS, which most likely developed due to over-immunosuppression. Over-immunosuppression may now be avoided by measuring whole blood FK 506 levels instead of plasma levels, which have been shown to be more reliable in the case of CsA. The number of cases was small, but the incidence was markedly higher in FK 506-treated patients, in contrast to what has been observed previously by the Pittsburgh group [18]. These results suggested that early postoperative ARF and hemodialysis has to be sharply distinguished from new onset of late ARF requiring hemodialysis. Etiologies for both seem to be completely different and the outcome varies between 0% and 100%.

In conclusion, early postoperative renal insufficiency and ARF were observed to a similar extent in patients treated with CsA and FK 506. All patients with early postoperative ARF requiring hemodialysis survived at least for 1 year (100% survival). Therefore, early hemodialysis did not coincide with increased mortality. New onset of late ARF, however, occurred due to severe infections with MOFS. Mortality of patients with late ARF requiring hemodialysis was 100%. Long-term drug-specific nephrotoxicity, represented by mildly impaired kidney function, was observed in 23.3% (CsA) to 29.4% (FK 506) of the patients. Severity and outcome of late nephrotoxicity remains to be evaluated after longer observation periods.

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