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E. Mor
T. Patel
S. Glabman
P. Sheiner
S. Emre
S. Guy
M. Schwartz
C. Miller

Comparison of short and long-term renal function in liver transplant patients receiving cyclosporin or FK506

E. Mor (✉) · T. Patel · S. Glabman
P. Sheiner · S. Emre · S. Guy · M. Schwartz
C. Miller
Department of Surgery, Division of Liver Transplantation, Box 1104,
The Mount Sinai Medical Center,
One Gustave L. Levy Place, New York,
NY 10029, USA

Abstract Long-term renal function was compared in 49 liver recipients [25 patients received cyclosporin (CyA) and 24 patients received FK506] followed for a period of 1 year. Creatinine (CR) and glomerular filtration rate (GFR) pre-transplantation (pre-Tx) and at 1, 3, 5, and 12 months post-Tx were recorded, as well as incidences of hyperkalemia, post-Tx hypertension, and insulin-dependent diabetes mellitus (IDDM) in the two groups. At 1 year post-Tx, the mean Cr had risen from baseline by 56% and 60% in the FK and CyA groups, respectively; the mean GFR had dropped by 32% in FK patients and by 27% in CyA patients. Acute nephrotoxicity occurred in 7/25 CyA patients (2/7 required dialysis) and 9/26 FK patients (7/9 required dialysis; 2/7 were switched to CyA). None remained on dialysis at 3 months. Renal insufficiency persisted at 1 year in 7/16 patients with early toxicity (CyA, 4; FK, 3) and in 3 of the remaining 36 pts ($P < 0.001$). Hyperkalemia occurred in 4/25 CyA, and in 12/24 FK patients ($P < 0.025$), post-Tx hypertension occurred in 15 CyA, and 7 FK patients ($P < 0.05$), and IDDM occurred in 4 CyA and 7 FK patients (P = ns). FK506 and CyA, thus, exerted similar chronic renal effects. Although acute renal insufficiency improved upon dose reduction, renal impairment was permanent in some cases.

Key words Cyclosporin · FK506
Liver transplantation
Renal function

Introduction

FK506 has been successfully employed for primary immunosuppression as well as for treatment of refractory rejection in liver transplant (LTx) recipients. Initial clinical experience with FK506, however, has shown a high incidence of nephrotoxicity, usually occurring during the early postoperative period [1]. Although the effect of chronic administration of FK506 on renal function has not been clearly established, preliminary studies have suggested that this agent causes long-term renal dysfunction, with gradual deterioration in the glomerular filtration rate (GFR), comparable to the chronic nephrotoxicity seen in patients on cyclosporin (CyA) [2–4]. Unlike acute nephrotoxicity, which can often be reversed by dose reduction, the renal dysfunction associated with long-term CyA therapy may be permanent [2]. A similar phenomenon is associated with chronic administration of FK506. In LTx recipients on FK506 who were followed for more than 18 months, creatinine (Cr) was persistently

elevated (> 2 mg/dl) in 20.5% of cases [4]. In our study, we compared the effects of CyA and FK506 on renal function in LTx recipients; we also examined the impact of early nephrotoxicity on subsequent renal function. The incidence of other long-term side-effects and their correlation with renal function were also noted.

Patients and methods

Between February 1991 and October 1991, 64 consecutive LTx recipients were enrolled in a prospective, randomized multicenter trial comparing the efficacy and toxicity of these two agents. Patients with evidence of renal insufficiency (serum Cr < 2 mg/dl or GFR < 30 ml/min per 1.73 m^2) were excluded, as were patients undergoing re-LTx, and patients with a tumor. CyA was administered to 33 patients; 25/33 remained in the CyA group at 1 year post-LTx (2 had been retransplanted, 2 had been switched to FK506 for refractory rejection, 1 had undergone nephrectomy, and 3 had died). FK506 was initially given to 31 patients; at 1 year post-LTx, 24 patients remained in the FK506 group (2 had been retransplanted, 2 were switched to CyA for renal failure, and 3 had died).

The CyA group received CyA, azathioprine (1 mg/kg), and prednisone (tapered to 10 mg/day at 1 year posttransplantation). Target through blood levels were 800–1000 ng/ml (TDX polyclonal assay) during the first 8 weeks after LTx, and 400–600 ng/ml thereafter. The FK506 induction dose was 0.15 mg/kg per 24 h i.v. and then 0.15 mg/kg per 12 h p.o. Patients were maintained on FK506 and prednisone (tapered to 5 mg/day at 3 months post-LTx), with the FK506 dose adjusted to maintain therapeutic plasma levels (0.5–2.0 ng/ml) as measured by enzyme immunoassay [5]. In patients who developed acute toxicity from either agent, the dose was reduced until symptoms subsided. Episodes of acute rejection were treated with steroid pulse followed by tapering doses; for steroid-resistant rejection, a 10- to 14-day course of OKT3 was given.

Renal function was assessed on the basis of serum creatinine levels and GFR prior to LTx and at 28, 90, 150, and 360 days afterward. The GFR was estimated by technetium 99 clearance but was not done in all patients at all intervals after transplantation.

Each patient's age, gender, and UNOS status were recorded, as were development of other toxic effects related to chronic administration of CyA or FK506, including episodes of hyperkalemia (serum K > 6.0 mEq/ml) requiring treatment, post-LTx hypertension, and insulin-dependent diabetes mellitus (IDDM).

The CyA and FK groups were compared for renal function and for percentage changes in mean creatinine and GFR from baseline to intervals after LTx. The incidence of other postoperative chronic drug-related toxicities was also compared between the groups. The relative risk for developing chronic renal insufficiency (persistently elevated Cr > 2 mg/ml at 1 year post-LTx) was calculated in patients with and without early nephrotoxicity. Statistical analysis was performed by SPSS/PC+ software (SPSS, Inc., Chicago) using Student's paired *t*-test and chi-square analysis. A *P* value of less than 0.05 was considered statistically significant.

Results

Mean ages, male to female ratios, and severity of liver disease as assessed by UNOS score were comparable between the two groups. There were three children (< 2 years) in the FK group and none in the CyA group. Pre-LTx mean Cr levels and GFR were 1.0 ± 0.5 mg/dl and 71 ± 25 ml/min, respectively, in the CyA group and 0.9 ± 0.4 mg/dl and 75 ± 20 ml/min, respectively, in the FK506 group. Post-LTx, there were no significant differences in serum Cr (Fig. 1) or GFR (Fig. 2) between the groups. The percentage change in mean Cr from baseline was 100% on postoperative day (POD) 7 and 25% on POD 28 for patients on FK, and 40% on POD 7 and 56% on POD 28 for patients on CyA. At 1 year post-LTx, the percentage change in mean Cr was 56% and 60% in the FK and CyA groups, respectively. The mean GFR fell from 75 ± 19 ml/min at baseline to 52 ± 22 ml/min on POD 28 in the FK group and 51 ± 19 ml/min at 1 year. A similar decrease in mean GFR was noted in the CyA group: baseline, 70 ± 26 ml/min; POD 28, 56 ± 19 ml/min; 1 year, 51 ± 21 ml/min.

Seven of the 25 patients in the CyA group and 9 of the 26 patients who started on FK506 developed acute

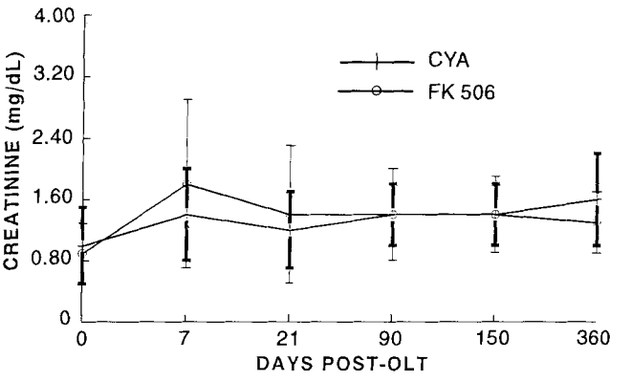

Fig. 1 Creatinine levels after liver transplantation in patients receiving cyclosporin (CyA) or FK506

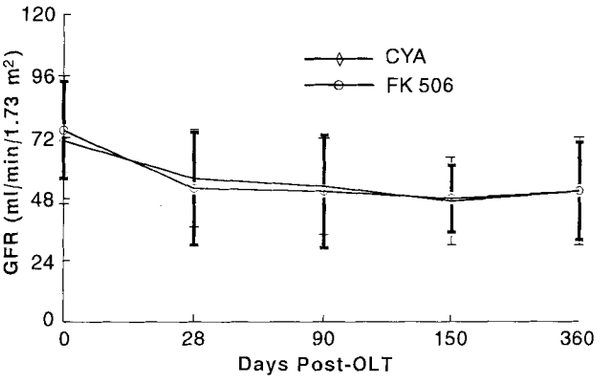

Fig. 2 GFR after liver transplantation in patients receiving CyA or FK506

nephrotoxicity; the latter figure includes two FK 506 patients who were eventually changed to CyA. Two patients in the CyA group and seven in the FK group required postoperative dialysis, but none required dialysis at 3 months post-LTx. Renal insufficiency persisted at 1 year in 7/16 patients with early nephrotoxicity (CyA, 4 patients; FK, 3 patients) and in 3 of the remaining 36 patients ($P < 0.001$).

Hyperkalemia was noted in 4/25 patients in the CyA group, compared to 12/24 patients in the FK group ($P < 0.025$). Post-LTx hypertension developed in 15 patients in the CyA group and in 7 in the FK group ($P < 0.05$). Four patients in the CyA group and seven in the FK group developed IDDM ($P =$ ns). These complications were not associated with early or late nephrotoxicity.

Discussion

One of the major drawbacks of long-term use of CyA is the development of chronic renal dysfunction, which has been reported to occur in more than 70% of cases [6]. In early studies of FK 506 in liver recipients, renal function was reportedly preserved in 81% of patients [7, 8]. More recently, however, it has become clear that FK 506 imposes a risk for chronic renal dysfunction similar to that of CyA [4, 9]. Accordingly, in our study, the decrease in Cr and GFR from baseline to 1 year was comparable in patients maintained on CyA and in those receiving FK 506. Interestingly, we found that, although the renal failure occurring early after LTx was usually reversible, suggesting functional impairment, some degree of renal dysfunction persisted in 43.8% of affected patients.

The intravenous FK dose for induction was high in this study, causing a relatively high incidence of severe early nephrotoxicity requiring dialysis (23%). In accordance with another report [10], our more recent experience suggests that therapeutic FK levels can be achieved with oral FK 506 induction, with a lower incidence of acute nephrotoxicity. The relatively high incidence of FK nephrotoxicity in our study may also be explained by our learning curve with a new agent, by the lack of availability of daily FK blood levels, and by the narrow therapeutic range of plasma FK levels. More recently, we have been able to lower FK toxicity by adjusting the dose according to daily FK levels measured by a whole blood assay, aiming at a lower therapeutic range (between 10 and 15 ng/ml).

This study also confirmed previous findings of a lower incidence of hypertension and higher incidence of hyperkalemia in patients receiving FK 506 compared to those on CyA [4]. These complications, however, were equally distributed among patients with and without renal toxicity, and in the majority of cases did not correlate with FK levels. A distinct pattern of FK tubulopathy has been described, with degeneration of mitochondria and vacuolization of the proximal tubules, which may explain the impaired ion transport and the development of hyperkalemia [11].

In summary, long-term renal function was similar in LTx recipients receiving FK 506 and CyA; both agents imposed a 30% drop in GFR at 1 year after transplantation. Although acute renal insufficiency improved in all patients once the dose was reduced, some suffered permanent renal impairment. Prevention of early FK nephrotoxicity by use of oral induction, with careful monitoring of blood levels, as well as the use of Imuran with lower doses of FK 506, may help reduce the incidence of chronic renal damage.

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