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Glomerular filtration rate after liver transplantation with a low-dose cyclosporin protocol

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Abstract Cyclosporin nephrotoxicity is a well-known complication in organ transplantation. In successful liver transplantation, a moderate degree of renal impairment is accepted. Whether this impairment is continuously progressive, stabilizes with time, or is reversible is not known. We have prospectively evaluated the glomerular filtration rate (GFR) using ^{51}CrEDTA plasma clearance in 29 liver transplant patients (11 males and 18 females) with a mean age of 49 years (range 22–62 years). The ^{51}CrEDTA plasma clearance measurements were performed preoperatively and at 3, 6, 12, 24, and 36 months after the liver transplantation. All but six patients were given sequential, quadruple drug therapy with antithymocyte globulin, azathioprine, steroids, and cyclosporin. Intravenous cyclosporin was avoided and oral cyclosporin started when renal function was stable. Cyclosporin was started in a dose of 8 mg/kg body weight, aiming at whole blood trough levels (specific monoclonal technique) of 200 µg/l in the postoperative period; thereafter, the dosage was rapidly tapered down, aiming at whole blood trough levels of less than 100 µg/l at 3 months (1.5–2 mg/kg body weight). From a mean preoperative GFR of 89 ± 3 ml/min per 1.73 m^2, all patients declined in renal function after transplantation to a mean of 64 ± 4 ml/min per 1.73 m^2 3 months after transplantation, and starting in the 3rd month the renal function was stable at about 70% of the preoperative value. No correlations were found between cyclosporin peak level or accumulated cyclosporin dose and renal impairment. We conclude that liver transplantation with cyclosporin immunosuppression will induce renal impairment even if cyclosporin blood levels are carefully monitored and kept low. However, with a low-dose regimen, a progressive decline can be avoided.

Key words GFR, liver transplantation, cyclosporin · Liver transplantation, GFR, cyclosporin Cyclosporin, GFR, liver transplantation

Introduction

The introduction of cyclosporin as a new immunosuppressive agent has markedly improved the results of liver transplantation [17]. Nephrotoxicity has been a well-known complication of cyclosporin treatment since the beginning of organ transplantation [5, 11]. The degree of nephrotoxicity is reported to correlate with the dose of cyclosporin, the cumulative amount of cyclosporin, and time, but the matter is still the subject of great controversy [1].

Reports of successful orthotopic liver transplantation (OLT) usually include some degree of renal impairment [9], impairment that can generally be attributed to cyclo-

Table 1 Preoperative age, sex, and diagnosis, as well as basal GFR and serum creatinine, in the 29 liver transplant patients included in the study. *PBC* Primary biliary cirrhosis, *CAH* chronic active hepatitis, *SCL.CHOL* sclerosing cholangitis, *ALC* alcohol cirrhosis, *AMYL* amyloidosis, *CA* hepatocellular cancer

Patient no.	Age at transplantation (years)	Sex (M/F)	Diagnosis	Preoperative serum creatinine (μmol/l)	Preoperative GFR (ml/min per 1.73 m^2)
1	49	F	CA	90	74
2	22	M	Hepatitis B	74	89
3	55	M	CA	89	75
4	46	F	SCL.CHOL.	71	102
5	31	M	SCL.CHOL.	64	125
6	35	F	SCL.CHOL.	87	107
7	57	F	PBC	63	75
8	48	F	PBC	63	87
9	51	M	SCL.CHOL.	96	89
10	42	F	CAH	46	60
11	51	F	PBC	56	70
12	51	F	PBC	59	118
13	53	F	PBC	62	106
14	57	F	PBC	65	87
15	62	M	CAH	139	60
16	26	M	SCL.CHOL.	32	110
17	53	F	CAH	91	70
18	30	M	AMYL	61	100
19	57	F	PBC	66	80
20	52	M	ALC	70	75
21	50	M	CAH	96	88
22	59	F	PBC	66	95
23	42	M	SCL.CHOL.	62	95
24	41	F	ALC	31	78
25	46	F	CAH	93	84
26	56	F	PBC	97	112
27	40	M	CAH	64	104
28	59	F	CAH	65	92
29	59	F	PBC	65	92
Mean	49 (Range 22–62)			72 ± 4	89 ± 3

sporin. It is, however, not known whether this renal impairment progresses, stabilizes, or reverse with time [11].

Previous estimates of renal damage after organ transplantation have been hampered by the fact that inadequate tools for measurement of renal function have been used [15]. Serum creatinine is most often used, but this parameter is affected by age, sex, diet, and body-muscle mass and is not a true filtration marker because of the simultaneous tubular secretion and reabsorption of creatinine [16]. True filtration markers, like inulin and ^{51}CrEDTA, give appropriate measurements of renal function, i.e., glomerular filtration rate (GFR) [3, 9].

The aim of the present study was to prospectively evaluate whether the cyclosporin-induced loss in renal function following OTL is progressive with a low-dose regimen of cyclosporin immunosuppression.

Patients and methods

Patients

Renal function was monitored in 29 OLT patients. Their preoperative diagnosis, age, and sex are shown in Table 1. The median follow-up time was 2 years (range 1–4 years). Preoperative GFR measurements were performed in all patients included in the study, and inclusion criteria were a preoperative GFR ≥ 60 ml/min per 1.73 m^2 and stable liver graft function at 3 months.

Operative procedure

All donor livers were harvested in a similar manner using University of Wisconsin solution. No venovenous bypass was used, except in the first five cases. The anhepatic time was 47 ± 2 min and the peroperative blood loss was comparable with a median transfusion of 9 units (400 cc) of blood (range 1–38 units).

Immunosuppression

All patients except patients nos. 1–6 received sequential, quadruple drug immunosuppression with antithymocyte globulin, (Thymoglobulin, Mérieux, France), azathioprine (Imurel, Wellcome, London, UK), cyclosporin (Sandimmun, Sandoz, Basel, Switzerland) and steroids (Prednisolon, KabiVitrum, Stockholm, Sweden). Antithymocyte globulin (5 mg/kg body weight) was given for 5–7 days, together with azathioprine (2 mg/kg body weight) and steroids beginning with 100 mg/day and decreasing with time. Intravenous cyclosporin was avoided and oral cyclosporin started when the patient was able to eat, provided renal function was stable, usually on the

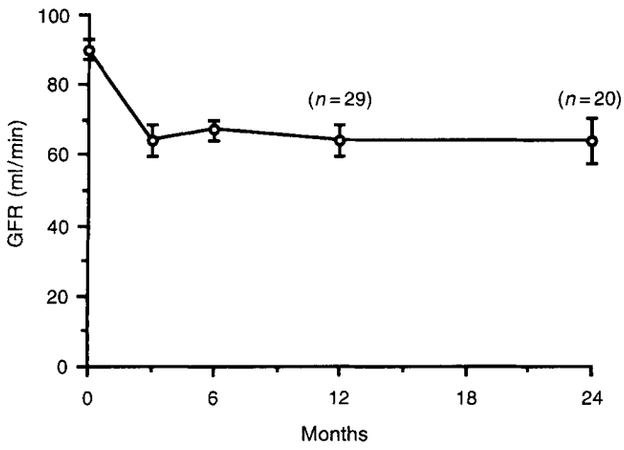

Fig. 1 GFR in 29 patients before and after orthotopic liver transplantation

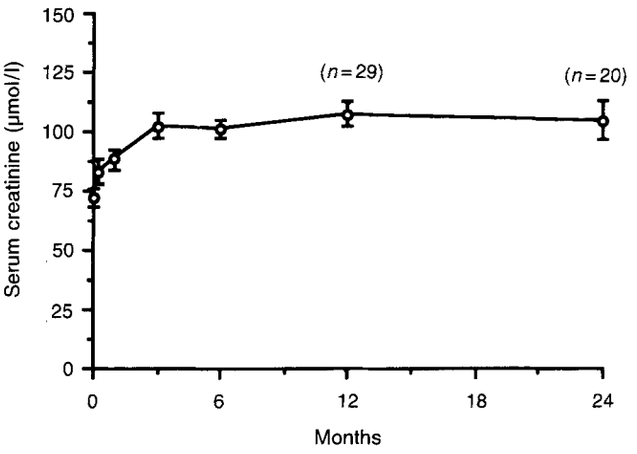

Fig. 2 Serum creatinine in 29 patients before and after orthotopic liver transplantation

Table 2 Analysis of renal function (GFR) following orthotopic liver transplantation in patients with a preoperative GFR ≤ 90 ml/min per 1.73 m^2 and patients with a preoperative GFR > 90 ml/min per 1.73 m^2

	Group 1 GFR ≤ 90 ml ($n = 17$)	Group 2 GFR > 90 ml ($n = 12$)
Preoperative GFR	77 ± 2	105 ± 3
GFR 1 year postoperatively	56 ± 5	76 ± 6
Reduction (%)	27	27

5th–7th postoperative day. Cyclosporin was given initially in a dose of 8 mg/kg body weight, aiming at a concentration of 200 µg/l (whole blood levels) postoperatively and a concentration of 100–150 µg/l at 3 months [18]. The first six patients did not receive any antithymocyte globulin but were still on a similar cyclosporin dosage protocol.

Measurements of renal function

Serum creatinine was measured daily, when the patients were in the ward, and then at each outpatient visit. GFR measurements were performed shortly before transplantation and at 3 months, 6 months, 1 year, 2 years, and 3 years post-transplantation. GFR was measured using ^{51}CrEDTA plasma clearance with a single injection of the isotope [2]. The plasma clearance was calculated as the ratio between the dose of ^{51}CrEDTA injected and the area under the curve determined by four blood samples [2].

Calculations and statistics

Results are given as means ± SE. An ANOVA followed by the Scheffé F test was used to compare means, and a least square regression analysis was used to test correlations.

Results

GFR

All patients showed a decline in renal function after transplantation. From a preoperative value of 89 ± 3 ml/min per 1.73 m^2, GFR was reduced to 64 ± 4 ml/min per 1.73 m^2 at 3 months ($P < 0.01$). After 2 years the mean GFR was reduced ($P < 0.01$) to 70 % of the preoperative value (Fig. 1).

When the patients were divided into two groups depending on their preoperative GFR (> 90 ml/min per 1.73 m^2 or ≤ 90 ml/min per 1.73 m^2), the reduction in GFR was 27 % in both groups at 1 year (Table 2).

In ten patients GFR was followed for 3 years. From a preoperative GFR value of 86 ± 5 ml/min per 1.73 m^2, renal function was reduced to 57 ± 7 ml/min per 1.73 m^2 at 3 months. After 2 years the mean GFR was 55 ± 6 ml/min per 1.73 m^2, and after 3 years it was 54 ± 6 ml/min per 1.73 m^2.

One patient required dialysis in the postoperative phase. That patient had an initial GFR of 60 ml/min per 1.73 m^2. Two years after OLT, GFR seems to be stable (59 ml/min per 1.73 m^2) and no further reduction has occurred.

Serum creatinine

Serum creatinine showed a corresponding rise with a preoperative value of 72 ± 4 µmol/l, 102 ± 5 µmol/l at 3 months, and 104 ± 8 µmol/l at 2 years (Fig. 2).

In ten patients serum creatinine was followed for 3 years. From a preoperative value of 71 ± 5 µmol/l, the serum creatinine value rose to 119 ± 10 µmol/l at 3 months. After 2 years the mean serum creatinine value was 116 ± 8 µmol/l, and after 3 years it was 122 ± 8 µmol/l.

Table 3 Mean daily cyclosporin dose (mg/kg body weight) and mean cyclosporin concentration (μg/l) in 29 liver transplant patients on a low-dose cyclosporin protocol

Postoperative time	Daily dose (mg/kg body weight)	Cyclosporin concentration (μg/l)
1 week	6.2 ± 0.5	123 ± 12
2 weeks	8.9 ± 0.5	188 ± 12
3 weeks	8.3 ± 0.6	200 ± 14
4 weeks	6.8 ± 0.5	212 ± 21
3 months	4.3 ± 0.3	182 ± 18
6 months	3.6 ± 0.3	132 ± 14
1 year	3.2 ± 0.2	117 ± 10
2 years	2.4 ± 0.3	113 ± 17

Table 4 Blood pressure at 1 and 2 years after liver transplantation

Postoperative time	Systolic (mm Hg)	Diastolic (mm Hg)
1 year (n = 29)	136 ± 3 (range 110–170)	84 ± 2 (range 60–100)
2 years (n = 20)	139 ± 4 (range 120–190)	88 ± 2 (range 75–100)

Cyclosporin

The average dose of cyclosporin given and the mean concentration of cyclosporin are listed in Table 3. There was no correlation between the impairment of renal function and the amount of cyclosporin given when measured as top concentration, mean concentration per week, or at 3, 6, 12, and 24 months after transplantation (data not shown).

Blood pressure

In order to explore the possibility of hypertension developing in these patients, blood pressure was measured at 1 and 2 years after liver transplantation (Table 4). In the patients followed for 2 years, no difference in blood pressure was found between the 1- and 2-year check-up, and only 4 patients out of 20 followed up to 2 years were receiving antihypertensive drug treatment.

Discussion

In this prospective study, the impact of cyclosporin on renal function was studied in patients receiving a low-dose cyclosporin protocol after liver transplantation. We found a 28% reduction in GFR after 3 months, but no progression after that time was seen.

Since the introduction of cyclosporin in the early 1980s, the results of organ transplantation have further improved [6, 13, 15]. Compared with conventional immunosuppression, i.e., steroids and azathioprine, immunosuppression with cyclosporin has improved allograft survival and reduced both morbidity and mortality [4]. Cyclosporin has since been the main immunosuppressive agent, in spite of its several serious side effects, nephrotoxicity being the most frequent and clinically important [7, 10, 12]. The problem of acute nephrotoxicity has been diminished with increased experience handling the drug, including the measurement of drug concentration with specific monoclonal techniques [18] and identification of other drug interactions [8]. In contrast to the often reversible acute toxic effects, chronic nephrotoxicity is irreversible and, in kidney transplantation, the main reason for the poorer renal function when compared to kidney recipients immunosuppressed with steroids and azathioprine [6]. Neither the mechanism behind cyclosporin's chronic effect nor the extent of permanent renal damage is understood, and when studying renal allograft recipients it can be difficult to differentiate between allograft rejection and cyclosporin nephrotoxicity [4, 6]. Transplantation of other organs, such as the heart and liver, allows assessment of cyclosporin nephrotoxicity in a more selective fashion.

Previous studies of renal function after OLT using GFR measurements are few. Wheately and coworkers [19] showed an initial reduction in GFR by 60%, which then stabilized at a level of 50% of the preoperative GFR 1 year after transplantation. In a group of pediatric patients, Mc Diarmid et al. were able to show a slightly progressive reduction in the GFR after 1 year [10]; they suggested that the fall in GFR could be progressive and implemented serial measurements in long-term cyclosporin-treated patients. Poplawski and coworkers retrospectively analyzed GFR in 52 OLT adults, where a reduction of 43% in GFR was noted 1 year after transplantation [14]. In their series GFR stabilized at that level at 2 years, although only 13 of the 52 patients were followed for 2 years.

Cyclosporin-induced renal insufficiency is a major concern in all transplant recipients, and reports indicating a progressive decline is both a major concern and the rationale for the use of a low-dose cyclosporin protocol in the present series. The presently used immunosuppressive protocol does not enhance the frequency of graft rejection, and in this prospective analysis we were able to show that the reduction in kidney function in our patients was less than that previously reported. This was not due to a selection of patients with normal GFR since we included patients with GFRs as low as 60 ml/min. Our mean preoperative GFR of 90 ml/min is less than the Dallas group reported (98 ml/min per 1.73 m^2) [14]. A different method was, however, used to measure GFR.

The reduction in kidney function in our patients was not accompanied by any severe hypertension, and only 4 out of 20 patients were receiving antihypertensive treatment 2 years postoperatively. Proteinuria was not measured in all of our patients, but we did not find any significant amount in any of the patients measured and, thus,

there were no indications of other renal diseases leading to the observed decrease in kidney function in our patients. Our present results also indicate that, using a low-dose cyclosporin protocol, the reduction in renal function will be moderate and, more important, not progressive. Additional follow-up is, however, essential to disclose the real long-term effects.

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