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ORIGINAL ARTICLE

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Impact of changing immunosuppressive monotherapy from Cyclosporin A to Tacrolimus in long-term, stable liver transplant recipients

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Abstract A number of studies have reported a lower atherogenic lipid profile in liver transplant recipients under tacrolimus (FK506) than in those under cyclosporine A (CyA) immunosuppression. This has mainly been attributed to the steroid-saving effect of FK506. However, the effects of converting CyA to FK506 monotherapy on lipid metabolism have not been specifically investigated. In 20 patients with stable graft function, immunosuppressive monotherapy was switched from CyA to FK506 because of CyA-related side-effects (hypertension, nephrotoxicity, hypercholesterolaemia). Serum lipid levels were measured before and 3, 6 and 12 months after conversion. In 5 patients, a modification of immunosuppression became necessary during the study period (4 were reconverted to CyA, 1 to glucocorticoids). In the remaining 15 patients on FK506 monotherapy, 12 months after conversion, a slight decrease in mean serum cholesterol, a slight increase in LDL, but a significant decrease in mean serum HDL were observed, resulting in a significant increase in Chol/HDL and LDL/HDL ratios. Conversion of immunosuppressive monotherapy from CyA to FK506 had no beneficial effect on the atherogenic lipid profile in this selected study population of long-term liver transplant survivors.

Keywords Liver transplantation · Immunosuppressive monotherapy · Lipid metabolism

Introduction

In orthotopic liver transplant patients, an increase in serum lipid levels has been observed postoperatively in the long term [1, 2]. This can, in combination with other factors, lead to a higher atherogenic risk profile after orthotopic liver transplantation (OLT) [3, 4, 5, 6]. It is suspected that, in addition to glucocorticoid administration, calcineurin inhibitor therapy may also play a causative role. Patients receiving CyA-based immunosuppressive treatment show a more pronounced increase in serum lipids than those receiving FK506 [3, 7, 8]. The actual effect of calcineurin inhibitor therapy on lipid metabolism is, however, difficult to determine, since the data reported were obtained mainly in the early postoperative period under continuing glucocorticoid therapy in the presence of known higher cumulative corticosteroid doses and a longer period of glucocorticoid treatment under CyA [3, 9, 10, 11, 12]. The impact on atherogenic lipid profiles of FK506 treatment in comparison with CyA immunosuppression over the long-term in the absence of glucocorticoid administration has not yet been evaluated. The aim of this study, therefore, was to investigate the long-term effect on lipid metabolism of converting immunosuppressive monotherapy from CyA to FK506 in post-OLT patients and to establish whether there is any beneficial effect on the atherogenic risk profile.

Patients and methods

In 20 liver transplant recipients (14 men, 6 women, mean age: 57.6 ± 6.4 years), immunosuppressive monotherapy with CyA (Neoral) was converted to FK506. At this time, the mean daily dose for Cy A was 1.5 ± 0.6 mg/kg body weight, resulting in a mean whole blood trough level of 76.05 ± 15.48 ng/ml (TDx). During the study period, the mean daily dose of FK506 was 0.06 ± 0.02 mg/kg body weight, and the mean FK506 whole blood trough level 6.9 ± 2.32 ng/ml (IMx).

The postoperative interval to conversion was 42 ± 17.56 months. The indications for OLT were: alcoholic cirrhosis of the liver ($n = 8$) Wilson's disease ($n = 1$), haemochromatosis ($n = 1$), autoimmune cirrhosis ($n = 3$), Budd-Chiari Syndrome ($n = 2$), primary biliary cirrhosis ($n = 2$), hepatitis B/C ($n = 2$), and Non-Hodgkin Lymphoma in the liver ($n = 1$). At the time of conversion, none of the patients was receiving glucocorticoids (corticoid-free interval 13.55 ± 4.75 months, cumulative steroid dose 5545 ± 1698 mg) (Table1 1).

The indication for conversion was the presence of at least two of the following CyA-associated side-effects: hypertension (systolic blood pressure≥140 mm Hg, diastolic blood pressure≥90 mm Hg, $n = 12$), impaired renal function (serum creatinine≥1.4 mg/dl, $n = 14$) and elevated serum cholesterol levels (cholesterol≥200 mg/dl, $n = 15$).

The initial dose of FK506 was 0.03 mg/kg body weight, with a target level of 4–6 ng/ml; CyA-based treatment was discontinued 1 day before conversion.

In addition to the recorded basic data (age and sex of the patient, reason for OLT, postoperative interval, steroid-free interval and cumulative steroid dose (mg), antihypertensive medication), the clinical parameters (bilirubin (mg/dl), AST, ALT, GGT, AP (U/L), creatinine, serum glucose (mg/dl) and HbA1C (%)), together with the lipid profiles immediately prior to conversion, and 3, 6 and 12 months thereafter, were obtained.

To evaluate the lipid profile, the following parameters were applied: total cholesterol (Chol mg/dl), high density lipoprotein (HDL mg/dl), low density lipoprotein (LDL mg/dl), very low density lipoprotein (VLDL mg/dl), serum triglycerides (Trigl. mg/dl), apolipoprotein A1 (ApoA1 mg/dl), and apolipoprotein B (ApoB mg/dl). Using these data, the Cholesterol/HDL and LDL/HDL ratios were calculated. Following the recommendations of the International Task Force for the Prevention of Coronary Heart Disease [13], an increase in the Cholesterol/HDL or LDL/HDL ratio ≥5 was defined as a marker for an elevated atherogenic lipid profile.

Statistical calculations were done using a two-tailed Wilcoxon matched pairs analysis for repeated measurement (GraphPad Prism program version 3.0 for Windows, GraphPad Software, San Diego, Calif., USA). Measured differences were considered statistically significant at $P < 0.05$. Data are expressed as means ± SD.

Table 1 Characteristics of liver transplant patients converted from CyA to FK506 immunosuppression

Age	57.6 ± 6.4 years
Gender	14 males, 6 females
Indications for transplantation	
Alcoholic cirrhosis	8
Hereditary liver diseases	7
Biliary cirrhosis	2
Viral hepatitis	2
Other:	1
Conversion: time after transplantation	42 ± 17.56 months
Conversion: steroid-free interval	13.55 ± 4.75 months
Cumulative steroid dose	5545 ± 1698 mg

Results

FK506-related side-effects after conversion, and clinical parameters

Of the 20 patients, 13 tolerated converting the medication well and experienced no side-effects. Seven patients developed neurological side-effects, although drug levels were within the normal range. Four of the seven patients had to be reconverted to CyA monotherapy (1 to 3 months after beginning of the study). Owing to the need for glucocorticoid treatment of underlying autoimmune hepatitis, one further patient was excluded from the study in the first month following conversion. The remaining 15 patients are the basis for statistical evaluation. During the observation period, the liver function parameters, already within the normal range prior to the switchover, showed further improvement, while glucose metabolism remained unchanged and no de novo diabetes occurred. Also, a significant reduction in serum creatinine levels was observed (Table 2). In all patients, graft function remained stable throughout the entire period under investigation.

Changes in lipid profile

Total serum cholesterol decreased in 10 of the 15 patients with initially elevated levels (Table 3). However, 12 months after changing the immunosuppressive medication, only an insignificant decrease in the mean serum cholesterol level was observed. An analysis of the mean serum triglyceride, LDL and VLDL lipoprotein levels revealed a mild, non-significant increase, while the mean serum concentration of the HDL lipoprotein subfraction, which is considered to be "vascular protective" decreased significantly within the 12-month period, as also did the mean serum level of the apolipoprotein A1, which is mainly associated with HDL. The mean serum level of apolipoprotein B, the major fraction (ApoB100) of which is a constituent of LDL, remained virtually

Table 2 Renal and hepatic function, and glucose metabolism during follow up

	Time after conversion (months)		*P*-value
	0	12	
Creatinine (mg/dl)	1.52 ± 0.61	1.39 ± 0.62	< 0.01
Bilirubin (mg/dl)	0.83 ± 0.23	0.63 ± 0.21	< 0.01
AST (mg/dl)	17.35 ± 11.58	11.40 ± 4.10	NS
ALT (mg/dl)	22.5 ± 14.92	12.33 ± 8.86	< 0.01
GGT (mg/dl)	53.2 ± 55.6	51.67 ± 59.03	NS
AP (mg/dl)	182.2 ± 95.86	123.1 ± 53.14	< 0.01
Blood glucose (mg/dl)	114.6 ± 28.7	110.0 ± 30.20	NS
HbA1C (%)	5.080 ± 0.42	5.087 ± 3.83	NS

Table 3 Lipid metabolism during follow-up

	Time after conversion (months)		*P*-value
	0	12	
Total cholesterol (mg/dl)	194.1 ± 29.67	189.4 ± 29.15	NS
LDL cholesterol (mg/dl)	134.1 ± 28.07	144 ± 34.5	NS
VLDL cholesterol (mg/dl)	9.15 ± 7.48	13.31 ± 14.94	NS
HDL cholesterol (mg/dl)	51.45 ± 14.00	38.77 ± 16.57	< 0.01
Apo A1 (mg/dl)	117.4 ± 24.19	106.8 ± 23.38	< 0.05
Apo B (mg/dl)	99.95 ± 23.06	99.31 ± 25.59	NS
Triglycerides (mg/dl)	83.97 ± 62.28	133.5 ± 139.1	NS
ApoB/Apo A1	0.93 ± 0.29	0.96 ± 0.33	NS
Chol/HDL ratio	4.13 ± 1.47	5.62 ± 2.54	< 0.01
LDL/HDL ratio	2.92 ± 1.33	4.30 ± 2.10	< 0.01

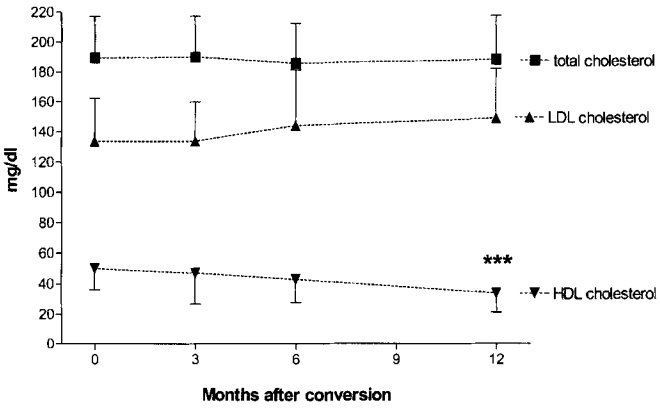

Fig. 1 Cholesterol, LDL and HDL lipoproteins in liver transplant recipients after conversion of immunosuppressive monotherapy: Means ± SD of cholesterol, HDL and LDL subfractions before (0) and 3, 6 and 12 months after conversion

constant throughout the period under observation (Fig. 1). The calculated cholesterol/HDL ratio increased over the period under observation to a mean value significantly in excess of 5 (Chol/HDL ratio: 5.62 ± 2.54 vs. 4.13 ± 1.47, $P = 0.01$), that of the LDL/HDL ratio to figures significantly in excess of 4 (4.30 ± 2.10 vs. 2.92 ± 1.33, $P = 0.01$) (Fig. 2), which is indicative of an increase in the atherogenic risk 12 months after conversion.

Discussion

In liver transplant recipients with stable graft function, the investigation of the long-term side-effects of immunosuppressive treatment is becoming an ever more important focus of attention. In addition to hypertension, diabetes mellitus, overweight, and other factors, hyperlipidaemia also appears to play a major role in raising the cardiovascular risk [3]. Comparative studies have shown that elevated serum lipid levels are more

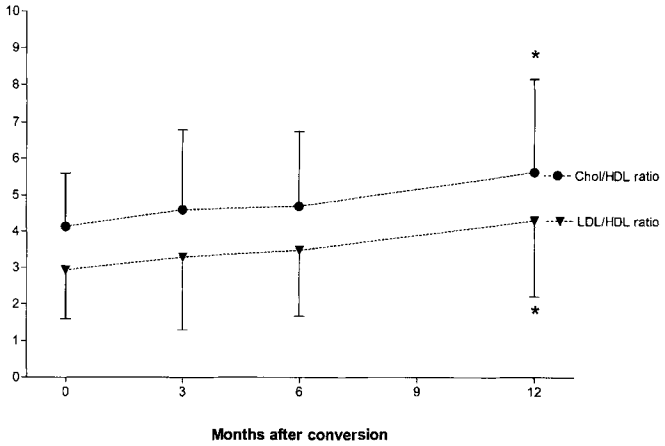

Fig. 2 Cholesterol/HDL and LDL/HDL ratio in liver transplant recipients after conversion of immunosuppressive monotherapy: Means ± SD of cholesterol/HDL and LDL/HDL ratio before (0) and 3, 6 and 12 months after conversion

frequently observed in CyA-associated immunosuppression than in FK506-based treatment [1, 2, 7, 8, 10, 12, 14, 15]. After adjuvant glucocorticoid withdrawal, evaluated serum lipid levels have been reported to decrease, and this applies also to CyA medication [16, 17]. Elevation of serum lipid levels is thus attributed mainly to adjuvant glucocorticoid treatment [18, 19], and, in the presence of high serum lipid levels, conversion of immunosuppression from CyA to FK506 with the aim of lowering the steroid dose has been recommended [2]. The actual influence of the calcineurin inhibitors on the lipid metabolism is thus unclear.

In the present study, steroid-free patients receiving relatively low dose immunosuppression were investigated 42 ± 17.45 months after OLT, prior to and after conversion. In this way, we were able to investigate the effect of FK506 on lipid metabolism while eliminating the steroid effect. In accordance with results reported in earlier publications, we found an improvement in liver function parameters [20, 21], creatinine and hypertension after conversion [1, 7, 18, 22, 23, 24, 25, 26, 27], whereas glucose metabolism remained stable before and after substitution [3, 15].

Neurological side-effects are more frequently observed under FK506 than under CyA [25, 28, 29, 30, 31, 32], and—as in the present study—may be an indication for reconversion to CyA [33, 34, 35].

Switching from CyA monotherapy to FK506 did not improve the lipid profile in our patient population. In conformity with earlier studies [1, 3, 4, 9, 12, 14, 18, 36, 37, 38, 39, 40], we also observed a small decrease in serum cholesterol levels. However, the overall lipid status under FK506 deteriorated, as indicated by the Chol/HDL and LDL/HDL ratios, which, when increased to values > 5, reflect an increased atherogenic risk [13, 41]. With regard to posttransplant hyperlipidaemia,

therefore, conversion of immunosuppressive monotherapy from CyA to FK506 monotherapy did not positively alter the lipoprotein subfractions.

We can summarize that converting immunosuppressive monotherapy from CyA to FK506 because of CyA-related side-effects can successfully be accomplished with few side-effects. The marked decrease in HDL overcomes the weak cholesterol-lowering effect and therefore does not lead to an improvement in atherogenic lipid profile in liver transplant recipients.

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