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Conversion from cyclosporine A to tacrolimus after kidney transplantation due to hyperlipidemia

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Abstract As more than 90% of renal grafts retain their function 1 year after renal transplantation, side effects of immunosuppressive therapy gain more and more importance. In a randomised prospective study, we investigated the effects of conversion from cyclosporine A to tacrolimus due to hyperlipidemia in recipients of renal allografts. Fifty-seven patients with stable graft function treated with cyclosporine were randomly assigned to conversion to tacrolimus or continuation of their current therapy and followed for 1 year. Twenty-seven patients were switched and 30 patients remained on cyclosporine A. Cholesterol levels decreased significantly in the tacrolimus group as compared to controls in the intent to treat analysis. When only those patients were evaluated who received cyclosporine or tacrolimus during the whole study, statistical significance was even more pronounced. Triglyceride levels decreased in the tacrolimus group, whereas they increased in controls. Creatinine levels remained stable and no acute rejection was observed. A switch to tacrolimus is a safe alternative in cases of hyperlipidemia after renal transplantation.

Key words Renal transplantation · Hyperlipidemia · Cyclosporine · Tacrolimus

Introduction

In recent years, 1-year graft survival in renal transplantation has reached more than 90% in most centres. Therefore, long-term complications and side effects of immunosuppressive treatment have gained more and more attention [7, 3].

Cardiovascular events are the most frequent cause of death in renal transplant recipients, especially over the long term. Hyperlipidemia and hypertension are known to have a major impact on these events, as well as on long-term graft outcome [1, 13, 16]. Furthermore, there is emerging evidence linking elevated lipid levels to transplant vasculopathy [14].

Recent studies have suggested a beneficial impact of tacrolimus on lipid levels and hypertension after transplantation as compared to cyclosporine [6]. In clinical trials, tacrolimus was associated with a lower degree of hyperlipidemia and hypertension than cyclosporine [6, 11]. Furthermore, in some trials cholesterol and triglyceride levels were lower after conversion from cyclosporine to tacrolimus [9].

In an open, randomised and comparative study, we investigated the effects of conversion from cyclosporine- to a tacrolimus-based immunosuppression in recipients of a renal graft who had stable graft function and suffered from hyperlipidemia.

Patients and methods

Fifty-seven patients (> 18 years of age) who received a cadaveric renal allograft more than 12 months prior to study enrolment and who were being treated with cyclosporine and prednisone were included. They were randomly assigned to one of two regimens (Table 1). Patients were either converted to tacrolimus (conversion, $n = 27$) or remained on their initial cyclosporine-based immuno-

Table 1 Patients characteristics at study entry

	Cyclosporine	Tacrolimus
Number *(n)*	30	27
Age (years)	48 ± 13	48 ± 12
Gender	11 female, 19 male	11 female, 16 male
Time after transplantation (years)	6.2 ± 2.5	6.6 ± 4.0

suppression (controls, $n = 30$). Patients, who were converted received their first tacrolimus dose 12 h after the last cyclosporine dose. Tacrolimus was started at 0.05 mg/kg per day adjusted to trough levels between 4 and 8 ng/ml. Cyclosporine levels were adjusted to trough levels between 100 and 150 ng/ml.

At baseline and after 12 months the following parameters were measured after a 12-h fasting period: cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride levels, blood pressure, antihypertensive and lipid lowering drugs, blood glucose level, body weight and serum creatinine. Cyclosporine and tacrolimus blood levels were routinely measured. All values are given as mean ± SD. For statistical analysis, Wilcoxon and Student's *t*-test were used where appropriate.

Results

Cholesterol levels at baseline were similar in both groups. During the study, cholesterol levels decreased in the tacrolimus group, whereas they remained stable in controls (Table 2). The difference in the intent to treat analysis 1 year after conversion reached statistical significance ($P < 0.02$). When only those patients were evaluated who received cyclosporine or tacrolimus at 1 year, differences were even more pronounced ($P < 0.01$, Table 3). Differences in low density lipoprotein levels did not reach statistical significance in the intent to treat analysis. Again, when only those patients were evaluated who were on the drug at 12 months, the

Table 2 Metabolic parameters at study entry and after 12 months (intent to treat analysis)

	Cyclosporine		Tacrolimus		*P*
	Entry	12 months	Entry	12 months	
Cholesterol (mg/dl)	260 ± 50	239 ± 60	255 ± 52	206 ± 31	< 0.02
LDL (mg/dl)	158 ± 42	132 ± 43	158 ± 42	119 ± 28	NS
HDL (mg/dl)	49 ± 15	47 ± 12	53 ± 18	53 ± 18	NS
Cholesterol/HDL ratio	5.31 ± 2.1	5.09 ± 2.3	4.81 ± 1.8	3.89 ± 1.4	< 0.05
HDL/LDL ratio	0.31 ± 0.2	0.35 ± 0.2	0.33 ± 0.2	0.45 ± 0.2	NS
Triglycerides (mg/dl)	235 ± 124	243 ± 156	221 ± 107	174 ± 72	< 0.05
Patients on HMG-CoA-inhibitors	69%	69%	54%	54%	
Blood pressure MAD (mm Hg)	109 ± 9	103 ± 9	104 ± 7	101 ± 7	NS
Antihypertensive drugs *(n)*	3.1 ± 0.9	3.4 ± 1.1	2.7 ± 0.8	2.8 ± 1.1	< 0.05
Glucose (mg/dl)	102 ± 26	121 ± 38	105 ± 21	112 ± 26	NS
Body mass index (kg/m^2)	26.1 ± 3.5	26.3 ± 3.2	26.9 ± 2.8	26.4 ± 2.9	NS
Graft loss	0	1	0	0	NS
Creatinine (mg/dl)	1.9 ± 0.6	2.0 ± 1.0	1.7 ± 0.7	1.7 ± 0.8	NS

Table 3 Metabolic parameters at study entry and after 12 months (on drug analysis, only patients who did not change immunosuppression during the whole study were included)

	Cyclosporine		Tacrolimus		*P*
	Entry	12 months	Entry	12 months	
Cholesterol (mg/dl)	258 ± 52	254 ± 62	253 ± 54	200 ± 30	< 0.01
LDL (mg/dl)	155 ± 38	143 ± 34	157 ± 44	118 ± 29	< 0.01
HDL (mg/dl)	52 ± 16	48 ± 14	53 ± 16	51 ± 16	NS
Cholesterol/HDL ratio	4.96 ± 2.0	5.29 ± 2.1	4.77 ± 1.6	3.92 ± 1.4	< 0.05
HDL/LDL ratio	0.34 ± 0.2	0.34 ± 0.2	0.34 ± 0.2	0.43 ± 0.2	NS
Triglycerides (mg/dl)	224 ± 122	266 ± 124	217 ± 102	171 ± 76	< 0.05
Patients on HMG-CoA-inhibitors	72%	72%	57%	60%	
Blood pressure (mm Hg)	111 ± 9	103 ± 9	104 ± 8	101 ± 6	NS
Antihypertensive drugs *(n)*	3.1 ± 1.0	3.4 ± 1.1	2.8 ± 0.8	2.9 ± 1.1	NS
Glucose (mg/dl)	106 ± 25	121 ± 39	102 ± 23	114 ± 27	NS
Body mass index (kg/m^2)	26.5 ± 3.1	26.7 ± 3.0	26.5 ± 2.8	26.1 ± 3.1	NS
Graft loss	0	0	0	0	NS
Creatinine (mg/dl)	1.7 ± 0.4	1.9 ± 0.9	1.9 ± 0.6	1.9 ± 0.8	NS

difference after 12 months was statistically significant ($P < 0.01$, Table 3). Levels of high density lipoproteins did not differ between the groups.

Triglyceride levels decreased in the tacrolimus group, whereas they increased in controls ($P < 0.05$). Only HMG-CoA-inhibitors were used as lipid lowering drugs (lovastatin, pravastatin and simvastatin). Sixty-nine percent of patients in the cyclosporine group received antihyperlipidemic treatment at study entry as well as after 12 months. In the tacrolimus group, 54% of patients were on antihyperlipidemic treatment at baseline and at 12 months the dose of statins per patient was higher in controls.

At study entry, blood pressure did not differ between the groups (Table 2). Blood pressure was even lower in both groups 1 year after inclusion, without a significant difference. However, there was a difference regarding the number of antihypertensive drugs. While the number remained stable in tacrolimus treated patients, it increased in cyclosporine treated ones ($P < 0.05$, Table 2).

At study entry, cyclosporine trough levels were 131 ± 29 ng/ml. After 12 months, trough levels were 7.1 ± 2.2 ng/ml in tacrolimus-treated patients (cyclosporine level in controls: 128 ± 32 ng/ml). After 12 months, tacrolimus dose was 0.05 ± 0.02 mg/kg per day (cyclosporine 2.5 ± 0.94 mg/kg per day).

Body mass index remained unchanged in both groups (Table 2). Blood glucose levels increased slightly in both groups.

One patient on cyclosporine lost his graft due to chronic graft deterioration and had to be treated with hemodialysis. In all other patients, renal function was stable during the study. Acute rejection periods were not observed in the tacrolimus group or in controls.

Six patients in the cyclosporine group were switched to tacrolimus during the first months of the study due to other well-known side effects of cyclosporine, e.g. gum hyperplasia or hypertrichosis. Two patients in the tacrolimus group were switched to cyclosporine. One patient developed severe itching which persisted after reconversion; another patient developed increasing blood glucose levels which decreased to baseline after reconversion.

Discussion

In patients with stable graft function, life quality and side effects of immunosuppression gain more and more importance. Hyperlipidemia and hypertension are thought to have a major impact on arteriosclerosis, cardiovascular morbidity and mortality, and chronic graft deterioration [3, 5].

Treatment with cyclosporine is associated with hyperlipidemia, arterial hypertension and glucose tolerance deterioration [7, 8, 15]. Up to 90% of patients treated with cyclosporine after renal transplantation suffer from hyperlipidemia and/or arterial hypertension [12]. Elevated serum lipid levels are linked to later graft failure and arteriosclerosis [12]. Cyclosporine is associated with elevation of lipid levels after renal transplantation [4]. Although there are other factors such as corticosteroids and graft dysfunction, cyclosporine is clearly associated with hyperlipidemia and hypertension. The importance of hypertension for long-term outcome after kidney transplantation has often been highlighted [12, 13].

Recently, some authors have reported a lower incidence of arterial hypertension and a reduced need for antihypertensive medication in renal transplant recipients treated with tacrolimus [10, 11]. They also reported reduction of other typical cyclosporine-associated side effects such as hyperlipidemia, gum hyperplasia and hypertrichosis [6, 7]. Although the patients in our study were 6–7 years after renal transplantation when included in the study, we observed a statistically significant decrease in serum cholesterol, LDL-cholesterol and triglyceride levels after conversion to tacrolimus. Furthermore, in our study a smaller number of antihypertensive drugs was necessary to control blood pressure in the tacrolimus group. Thus, our study supports a mild beneficial effect of a conversion from cyclosporine to tacrolimus on arterial blood pressure.

Our study, as well as others, has demonstrated that conversion from cyclosporine to tacrolimus is safe. In this study, we observed no acute rejection periods in either group and only one graft loss in the cyclosporine group due to chronic graft deterioration. The improvements in hyperlipidemia and hypertension may increase long-term graft survival and reduce the incidence of cardiovascular morbidity and mortality.

In conclusion, a conversion to tacrolimus may be considered in patients with hyperlipidemia or a high number of antihypertensive agents treated with cyclosporine. In the case of tacrolimus-related side effects, reconversion to cyclosporine will ameliorate these side effects. Further prospective studies are necessary to assess possible beneficial effects of a conversion from cyclosporine to tacrolimus on graft survival and cardiovascular morbidity and mortality over the long term.

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