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Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients

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Abstract

Background. Hyperlipidaemia is an important risk factor for cardiovascular disease in renal transplant recipients. The aim of this study was to test the efficacy and possible drug–drug interactions of the new HMG-CoA reductase inhibitors (statins) atorvastatin and cerivastatin in cyclosporin A (CsA)-treated renal transplant patients.

Subjects and methods. Thirty patients with stable graft function and LDL cholesterol of 130 mg/dl were randomly assigned to active treatment groups (10 mg atorvastatin or 0.2 mg cerivastatin), or a control group. CsA blood trough levels were controlled on a weekly basis and adapted if they changed more than 25% from baseline values (100–150 ng/ml). Lipid levels and routine laboratory parameters before and after a treatment period of 3 months were compared.

Results. In the group treated with cerivastatin no significant changes in CsA blood trough levels occurred (CsA 116 ± 21 ng/ml *vs* 110 ± 20 ng/ml). In contrast, in the group treated with atorvastatin, four of 10 patients had a rise in CsA blood trough levels of more than 25% within 7–14 days of starting therapy. In the remaining patients no significant changes in CsA drug levels occurred. After therapy with atorvastatin or cerivastatin, total cholesterol, LDL cholesterol, and triglycerides were significantly lower compared with baseline conditions. No changes of CsA or lipoprotein levels were present in the control group.

Conclusion. In our study population both statins were very effective in lowering elevated LDL cholesterol levels. Cerivastatin did not influence CsA blood trough levels, whereas atorvastatin increased CsA levels in four of 10 patients. Further research in a larger study is necessary in order to confirm these results and to investigate the possible reasons for this drug interaction.

Keywords: atorvastatin; cerivastatin; cyclosporin A; cytochrome P450; hyperlipidaemia; renal transplantation

Introduction

High prevalence of combined hyperlipidaemia with elevation of cholesterol and triglycerides contributes substantially to the high morbidity and mortality from cardiovascular disease in patients after renal transplantation [1]. Renal transplant recipients usually have a variety of risk factors causing hyperlipidaemia, including genetic predisposition, obesity, diabetes and immunosuppressive therapy with cyclosporin A (CsA) and corticosteroids [1–3]. Therefore a therapy with HMG-CoA reductase inhibitors (statins) seems to be attractive to reduce the hyperlipidaemia-related cardiovascular risks [3,4]. However, some safety problems in transplant patients treated with CsA were reported, relating to elevated drug levels of statins associated with rhabdomyolysis [5–8] or impairment of renal function due to elevated CsA blood trough levels in single cases [7]. As CsA and many HMG-CoA reductase inhibitors are metabolized by the same cytochrome P450 3A4 enzyme system (CYP3A4) in the liver, possible drug interactions have to be expected during a combination therapy with CsA and statins [6]. Recently two new synthetic statins, atorvastatin and cerivastatin, have been tested in clinical trials in non-transplanted patients and were proven to be effective in decreasing total cholesterol as well as triglycerides [9,10].

Atorvastatin [9] is rapidly absorbed, with a maximum plasma concentration at 1–2 hours after oral administration. Systemic availability is about 30% and absolute bioavailability about 12%. After food intake there is a decrease, whereas in elderly people and females there is an increase in reabsorption of the

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drug. The highly protein-bound agent (>98%) is distributed to liver, spleen, and adrenal glands. The drug is metabolized by the CYP3A4 enzyme in the liver into its pharmacologically active metabolites. The drug and its metabolites are primarily excreted in bile with a mean elimination half-life of about 14 h and an inhibitory activity of about 20 h, due to its active metabolites. Renal dysfunction does not alter the pharmacokinetics of atorvastatin (Table 1).

Cerivastatin [10,11] is rapidly absorbed, with 60% bioavailability unaffected by food, age, or gender. The plasma concentration peak is between 1 and 3 h. The 99% protein-bound drug is predominantly distributed and metabolized in the liver by CYP3A4 and cytochrome P450 2C8 (CYP2C8) enzymes into two major metabolites with less activity than the parent compound. The metabolites are excreted in stool (70%) and urine (30%). The elimination half-life of this drug is 2–3 h. Renal dysfunction does not alter the pharmacokinetics of cerivastatin significantly (Table 1).

In this randomized, open-armed study including 30 renal transplant patients under an immunosuppressive regimen with corticosteroids and CsA, the efficacy, short-term safety, and interaction profile of the new HMG-CoA reductase inhibitors atorvastatin and cerivastatin were monitored [9,10].

Subjects and methods

Patients

Thirty stable renal transplant recipients participated in this open-armed, randomized clinical study. All subjects were in good condition as assessed by means of physical examination, vital signs, and laboratory tests, and all patients gave their written, informed consent for participation in the study. Inclusion criteria were: stable graft function (serum creatinine <3 mg/dl for more than 6 months after renal transplantation), first or second renal transplantation, no changes in CsA dosage or co-medication, and constant CsA blood trough levels between 100 and 150 ng/ml, (Abbott assay using monoclonal antibodies) within 3 months before study entry (Table 2). Low-density lipoprotein (LDL) cholesterol levels had to be ⩾130 mg/dl. Patients with coronary heart disease or those who had had a myocardial infarction within the last 6 months were excluded. All patients received a low-cholesterol diet when starting the therapy. Patients participating were allocated at random to the three groups of the study. In group A 10 mg atorvastatin and in group B 0.2 mg cerivastatin were administered once a day in the evening for 3 months. Group C was the control group without drug treatment. All 30 subjects had a similar immunosuppressive regimen (including CsA and corticosteroids) and antihypertensive therapy (Table 2). According to the pre-fixed criteria, CsA blood trough levels were not allowed to rise more than 25% above baseline values (100–150 ng/ml) during the treatment with statins, otherwise the dosage of CsA had to be reduced. The clinical characteristics, co-medication, and pretrial lipid profile of all patients are listed in Tables 2 and 3. In both treatment groups there was a preponderance of male patients (two females *vs* eight males), whereas in the control group the gender distribution was the opposite (eight females *vs* two males). As the problem with uneven gender distribution was identical in the drug treatment groups, it did not seem to be important for a comparative study between both statins for their potential drug interaction with CsA.

In all patients a routine clinical evaluation including the measurement of body weight and vital signs (blood pressure, heart rate) was performed before, and on days 7, 14, and 28, and at 3 months after starting the therapy. At the same time points blood samples were drawn after at least a 12-h fasting period to measure the following parameters: red and white blood cell count and thrombocyte count, liver enzymes, creatine phosphokinase (CPK), serum creatinine, urea and electrolytes, total cholesterol and triglycerides, LDL-cholesterol, high-density lipoprotein (HDL) cholesterol, and CsA blood trough levels. In addition standardized, tolerability and safety assessments were included.

Table 1. Pharmacokinetics of atorvastatin and cerivastatin (revised in [9,10])

	Atorvastatin	Cerivastatin
Absorption	Rapid	Rapid
Maximum plasma levels (h)	1–2	2–3
Systemic availability (%)	12	60
Protein bound (%)	98	99
Metabolism	CYP3A4	CYP3A4, CYP2C8
Elimination	Bile	70% Bile, 30% Urine
Elimination half-life (h)	14	2–3

Statistical analysis

Statistical differences were determined by the Mann–Whitney U test, differences were considered significant at $P \leqslant 0.05$.

Results

According to our study design the pretreatment lipid profile of all patients was abnormal, without any statistically significant differences between the groups (Table 3). In the control group without any therapy (group C) no significant changes in the lipid profile, CsA blood trough levels or serum creatinine occurred (Table 3).

In contrast, in patients treated with cerivastatin (group B), after 3 months of therapy total serum cholesterol (−32%), LDL cholesterol (−38%) and triglyceride levels (−23%) were significantly lower than at the beginning of the study ($P \leqslant 0.05$), whereas HDL cholesterol remained unchanged (Table 3). CsA blood trough levels were constant over the whole study period (changes <25%) and CsA dosage did not have to be adapted in any patient of group B (Table 3).

In the atorvastatin group (group A) total serum cholesterol (−30%), LDL cholesterol (−42%) and triglycerides (−23%) were significantly lower after therapy ($P \leqslant 0.05$) and in addition an increase in HDL cholesterol (+10%) was documented (Table 3). A rise in CsA blood trough levels ⩾25% of baseline values occurred in four of 10 patients, all male (26–54%, Figure 1a–d), requiring a reduction of the CsA daily dosage according to the study protocol. All four patients had significantly elevated CsA blood trough levels on day 7, the first time-point CsA blood levels

Table 2. Characteristics of patients, immunosuppressive protocols, and antihypertensive therapy

	Atorvastatin group	cerivastatin group	control group
Patients (*n*)	10	10	10
Female/male (*n*)	2/8	2/8	8/2
Age (years) ± SD	52 ± 14	51 ± 11	49 ± 14
Transplant life (months) ± SD	55 ± 34	42 ± 30	72 ± 38
Body weight (kg) ± SD	71.7 ± 13*	50.7 ± 10*	70.3 ± 14*
Smokers (*n*)	0	1	0
Methylprednisolone (mg/day) (*n*)	4	4	4
CsA (mg/day)	190 ± 60	150 ± 57	202 ± 48
CsA (mg/kg body weight/day)	2.7 ± 0.9	3.0 ± 0.8	2.9 ± 0.9
Artrial hypertension (*n*)	10	10	10
AT_1 receptor blockers (*n*)	3	1	4
ACE inhibitors (*n*)	3	3	4
Loop diuretics (*n*)	7	8	4
Ca antagonists (*n*)	6	7	6
Beta blockers (*n*)	5	7	7
Alpha blockers (*n*)	2	1	1
Clonidine (*n*)	2	2	2

AT1-receptor blocker, angiotensin II receptor blocker; ACE inhibitors, angiotensin converting enzyme inhibitors; Ca antagonists, calcium channel blocker; *n*, number of patients in group A, B or C. Other data are means ± SD.
*$P < 0.05$ comparing the atorvastatin group (A), cerivastatin group (B), and control group (C).

Table 3. Biochemical profile in 30 kidney-transplanted patients before and after 3 months of therapy (statins/diet or diet only)

	Atorvastatin group Dose (10 mg/day)		Cerivastatin group Dose (0.2 mg/day)		Control group	
	Before	After	Before	After	Before	After
Total cholesterol (mg/dl)	275 ± 46	192 ± 28*	305 ± 23	207 ± 39*	245 ± 37	249 ± 39
LDL cholesterol (mg/dl)	185 ± 47	106 ± 28*	200 ± 17	129 ± 37*	169 ± 51	172 ± 57
HDL cholesterol (mg/dl)	44 ± 12	51 ± 13	47 ± 12	50 ± 8	55 ± 12	60 ± 10
Triglycerides (mg/dl)	205 ± 73	158 ± 83*	264 ± 95	204 ± 78*	156 ± 51	163 ± 57
Serum creatinine (mg/dl)	1.2 ± 0.6	1.22 ± 0.5	1.8 ± 0.5	1.55 ± 0.4	1.4 ± 0.6	1.4 ± 0.6
CsA dosage (mg/day)	190 ± 60	178 ± 60	150 ± 57	150 ± 57	202 ± 0.9	202 ± 0.9
CsA blood level (ng/ml)	112 ± 11	121 ± 28	116 ± 21	110 ± 20	121 ± 18	133 ± 23
CPK (U/l)	35.7 ± 15	41.7 ± 16	23.4 ± 4.4	28.6 ± 7	36.5 ± 14	34.7 ± 8.5
AST (U/l)	8.8 ± 1.2	9.8 ± 1.7	7.0 ± 0.9	7.1 ± 0.8	8.9 ± 1.2	8.0 ± 1.0
ALT (U/l)	12.8 ± 4.0	12.9 ± 6.0	6.25 ± 1.0	7.1 ± 1.0	9.0 ± 2.2	7.7 ± 1.9

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatinine phosphokinase. Before, value obtained before the treatment; After, value obtained after 3 months of treatment. Data are means ± SD.
*$P < 0.05$ as compared to baseline values.

were controlled after starting statin therapy. In these four patients mean CsA daily dosage was reduced from 211 ± 40 mg before to 177 ± 33 mg after starting atorvastatin therapy, and accordingly CsA dosage per kg bodyweight (bw) was lowered from 3.1 ± 0.8 mg/kg bw before to 2.7 ± 0.7 mg/kg bw after starting therapy. The other six patients showed no relevant increase in CsA blood trough levels and remained on a mean daily dosage of 2.4 ± 0.9 mg CsA/kg bw. (Table 4). Co-medication in the artorvastatin treated-patients was very similar in both subgroups. However, three of the six patients not showing any changes in CsA blood trough levels were on AT1-receptor blockers and only two patients on calcium antagonists, whereas characteristically all four patients of the atorvastatin group that required reduction of CsA daily dosage received calcium antagonists. On the other hand, seven of ten cerivastatin-treated patients also received different calcium-antagonists without showing any changes of CsA blood trough levels.

In both groups treated with statins, serum creatinine levels remained stable and further side-effects or changes in laboratory parameters did not occur. The hypolipidaemic response of LDL cholesterol and total cholesterol was similar to patients on atorvastatin and cerivastatin (Table 3).

Discussion

Efficacy and short-term safety of atorvastatin and cerivastatin in CsA-treated renal transplant recipients

Cerivastatin and atorvastatin were very effective in reducing total cholesterol, LDL cholesterol and triglycerides in renal transplant recipients [9,10], with-

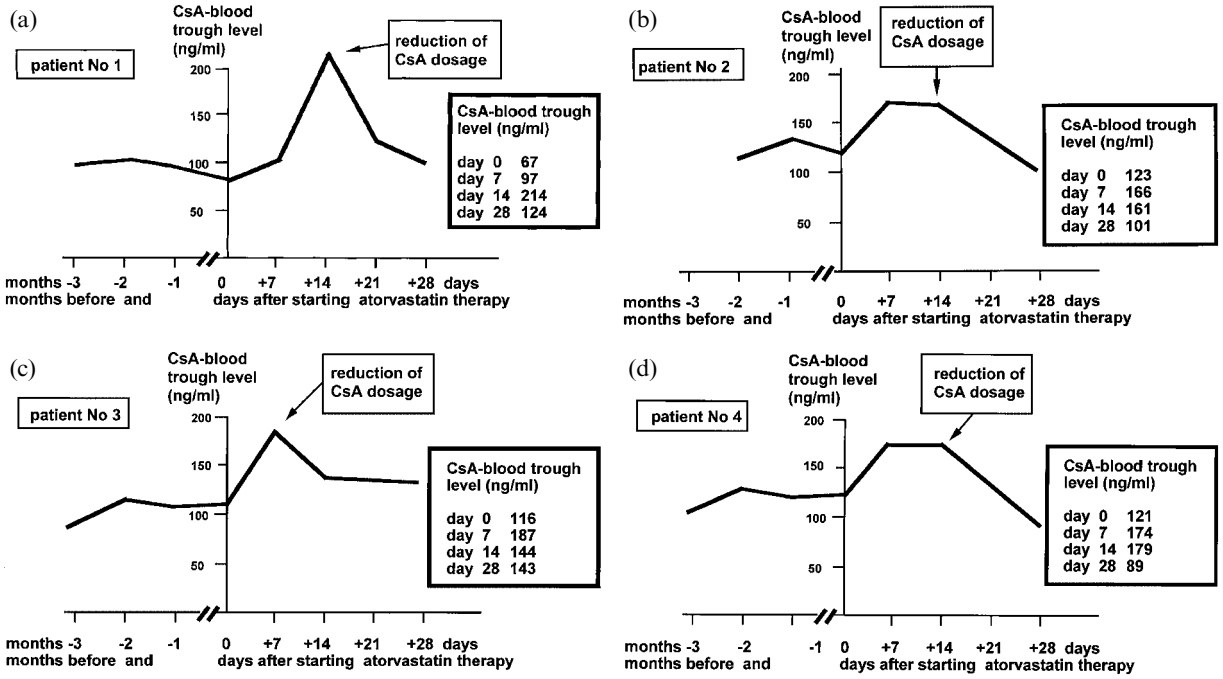

Fig. 1. (a–d) Increase of CsA blood trough level and reduction of CsA dosage in patients Nos 1–4 after atorvastatin therapy. Shown are CsA blood trough levels 3 months before until 28 days after starting atorvastatin therapy.

Table 4. CsA dosage (mg/day and mg/kg body weight/day) and CsA blood trough levels in the atorvastatin-treated patients (including subgroups) before and 3 months after therapy

	Atorvastatin group 6/10 patients (no drug interaction)		Atorvastatin group 4/10 patients (drug interaction)	
	Before	After	Before	After
CsA dosage (mg/day)	179±75	179±75	211±40	177±33
CsA dosage (mg/kg body weight/day)	2.4±0.9	2.4±0.9	3.1±0.8	2.7±0.7
CsA blood level (ng/ml)	109±15	124±28	114±9	122±27*

*After reduction of baseline CsA dosage (−17%).

out any difference between these two compounds. The trend for atorvastatin in elevating HDL cholesterol could be a drug effect itself [9] or due to possibly elevated drug levels of atorvastatin caused by concomitant CsA therapy. Elevated atorvastatin levels have been described earlier for a combination therapy of atorvastatin with other CYP3A4 substrates like itroconazol or erythromycin [9,12]. In our study, both statins were administered in a reduced dosage because of safety concerns.

Despite four patients developing elevated CsA blood trough levels after treatment with atorvastatin, no further relevant side-effects were documented with either of the two statins. No significant changes in liver enzymes, CPK, or serum creatinine levels occurred. There was no evidence of myalgia or myopathy after 3 months of therapy, although according to the literature there should be a higher risk for this specific side-effect of statins especially in transplant recipients [6,13]. The undesirable side-effect of rhabdomyolysis in transplant patients has been described for the liphophilic statins simvastatin and lovastatin, and very recently for atorvastatin [6,7,13], but the experience with new agents such as atorvastatin or cerivastatin is still very limited. Despite the lack of severe side-effects of atorvastatin and cerivastatin in our patient population, our results about the safety profile of these drugs should still be interpreted with caution because of the small number of patients and the short treatment periods.

Drug–drug interactions of atorvastatin or cerivastatin with CsA in renal transplant recipients

Several different mechanisms of drug–drug interactions between CsA and statins affecting the metabolism or excretion of each of these drugs have been discussed in the literature [6,19]. First of all biliary excretion, an important way for elimination of statins, could be reduced by concomitant CsA treatment [6,18]. Perhaps

more relevant are the drug interactions due to the intestinal and hepatic CYP3A4 enzyme system, as both statins and CsA are metabolized in the cells by CYP3A4 and therefore compete for this enzyme system in different tissues [9,10]. In addition, atorvastatin and CsA, have another common pathway of detoxification, namely the transport *via* the multidrug resistance gene product (MDR1), P-glycoprotein. Both drugs are extruded out of intestinal, bile duct and hepatic cells by this transmembrane efflux pump [14,15,21].

The data of this study do not show any elevation of CSA blood trough levels after a 3-month therapy with cerivastatin, which could be explained by the fact that cerivastatin in comparison with CsA has a very low binding affinity to CYP3A4 and was administered in a low dosage. Our results are in agreement with those of other drug–drug interaction studies using different CYP3A4 substrates (itraconazole, erythromycin, or mibefradil) together with cerivastatin [10,16,17]. Although serum levels of cerivastatin were not measured in our study, they are also not expected to be significantly higher, because cerivastatin can be metabolized by CYP3A4 and alternatively by CYP2C8, which is not involved in the metabolism of CsA [16].

Drug interaction studies with atorvastatin and other CYP3A4 substrates showed moderate to severe elevated drug levels of atorvastatin and, in some cases, of the concurrent drug as well [6,9,12]. Although the affinity of atorvastatin to CYP3A enzymes is similar to that of cerivastatin, it has to be considered that the therapeutically effective serum levels of atorvastatin are 50-fold higher than the average cerivastatin serum levels. It should be noted that rhabdomyolysis in a patient treated with atorvastatin and CsA was reported very recently [13]. Most case reports describing severe rhabdomyolysis in patients receiving statins show co-medication with other CYP3A4 substrates, such as macrolide antibiotics, ketoconazole or calcium antagonists (mibefradil) [25–27]. Drug–drug interactions in transplant recipients receiving CsA are very complex, as these patients are often treated simultaneously with multiple drugs, which are metabolized by the cytochrome P450 enzyme system. In our study, all patients with elevated CsA blood trough levels after atorvastatin therapy received calcium antagonists as co-medication. These drugs are well-known substrates of CYP3A enzymes and elevated CsA drug levels have been described before [28]. Interindividual variability of the cytochrome P450 enzyme activity due to genetic polymorphism in this enzyme system should also be considered as a possible cause of elevated drug levels [19,29].

At the present time there is very little information about drug–drug interactions with regard to MDR1 P-glycoprotein, an important membrane transporter for lipophilic xenobiotics such as anticancer drugs, CsA, or atorvastatin [14,15,20,21]. MDR1 P-glycoprotein is expressed in many excretory epithelia like the bile ducts, the intestinal cells, or the proximal tubules, and functions as an efflux pump for lipophilic drugs by eliminating them from cells [22]. P-glycoprotein may play an important role in net drug absorption and drug–drug interactions of shared CYP3A4/P glycoprotein substrates [23].

In conclusion atorvastatin and cerivastatin are both highly effective drugs for the treatment of post-transplant hyperlipidaemia. Due to the different pharmacokinetic properties of atorvastatin and cerivastatin, renal transplant patients treated with CsA and atorvastatin seem to have an increased risk of drug-interaction-induced variations in CsA blood trough levels, compared with patients receiving CsA and cerivastatin. Especially if co-medication with other CYPP3A4 substrates such as antibiotics or calcium antagonists is necessary, CsA-treated transplant recipients should be monitored carefully for CsA blood trough levels and possible toxic side-effects of the different drugs. As the treatment of renal transplant recipients with statins is necessary in many cases and might be even beneficial for the prophylaxis of chronic rejection [24,29,30], long-term effects of atorvastatin or cerivastatin should be investigated in a larger population of kidney transplant patients.

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