Tacrolimus and cerivastatin pharmacokinetics and adverse effects after single and multiple dosing with cerivastatin in renal transplant recipients

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Aims In contrast to cyclosporin, only limited information exists on the interaction potential between the immunosuppressive agent tacrolimus and HMG-CoA reductase inhibitors, which are metabolized via the cytochrome P450 system. The aim of this study was to investigate the pharmacokinetics, and adverse effects of cerivastatin combined with tacrolimus in renal transplant patients.

Methods Ten patients with stable kidney graft functions and LDL-cholesterol serum concentrations $>110 \text{ mg dl}^{-1}$ were included in the study. After an observation period of 3 months, cerivastatin (0.2 mg daily) was administered for an additional 3 months. Tacrolimus steady-state pharmacokinetics and cerivastatin single- and multiple-dose pharmacokinetics were determined. Lipid concentrations, routine laboratory parameters and adverse events were obtained and analysed throughout the study period of 6 months.

Results Blood tacrolimus trough concentrations were not affected by cerivastatin (mean $\pm$ SD $8.6 \pm 2.1 \text{ ng ml}^{-1}$ before, and $8.7 \pm 2.4 \text{ ng ml}^{-1}$ at day 90 of cerivastatin dosing, with a 95% confidence interval on the difference = 0.97, 1.08). The mean area under the blood concentration–time curve to 24 h ($\text{AUC}_{(0,24 \text{ h})}$) for cerivastatin was $14.5 \pm 2.53 \mu\text{g l}^{-1} \text{ h}^{-1}$ at day 1 after starting treatment and $19.02 \pm 3.55 \mu\text{g l}^{-1} \text{ h}^{-1}$ (3 months later), resulting in a 35% higher ($\text{AUC}_{(0,24 \text{ h})}$) compared with the first dose. Total cholesterol, LDL-cholesterol and triglyceride concentrations were significantly lowered by cerivastatin whereas no significant effect of cerivastatin on serum creatininkinase concentrations was observed and no adverse effects were documented.

Conclusions Tacrolimus increased the $\text{AUC}_{(0,24 \text{ h})}$ of cerivastatin by a mean of 35% in renal transplant patients. Cerivastatin had no detectable effect on the pharmacokinetics of tacrolimus.

Keywords: cerivastatin, cytochrome P450, hyperlipidaemia, renal transplantation, tacrolimus

Studies have established a central role of the calcineurin inhibitor tacrolimus in immunosuppressive drug regimens for renal transplantation. Tacrolimus is a lipophilic drug, which is rapidly absorbed, achieving a maximal plasma concentration 0.7–6 h after oral administration and exhibiting an absolute bioavailability of about 20% under fasting conditions. This highly protein-bound agent

(> 98%) is extensively distributed and accumulates in erythrocytes [1]. Almost all of the degradation of tacrolimus (99%) is via demethylation and hydroxylation by the cytochrome P450 3A4 (CYP3A4) enzyme system in the gut and liver. Nine metabolites of tacrolimus have been identified *in vitro*, but only three metabolites have been detected *in vivo*. The 31-O-demethylated metabolite (M-2), which is detectable in humans, is the only metabolite with immunosuppressive activity [1]. Tacrolimus and its metabolites are primarily excreted into the bile with a mean elimination half-life of about 16 h. Renal dysfunction does not alter the pharmacokinetics of tacrolimus

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[1]. These pharmacokinetic properties explain the occurrence of interactions with a number of drugs used in transplant patients, including macrolide antibiotics, several of which are also metabolized by the CYP3A4 [2]. For reasons of safety, monitoring of whole blood trough concentrations of tacrolimus has been established for a number of years to optimize treatment.

To date there is no information concerning the risk of interactions between tacrolimus and statins like cerivastatin in renal transplant recipients. Cerivastatin is absorbed with 60% bioavailability, which is unaffected by food, age or gender [3]. Peak plasma concentration is between 1 and 3 h after oral ingestion. The drug is highly protein bound (> 99%) and predominantly cleared via metabolism in the liver by CYP2C8 and CYP3A4, resulting in two major metabolites with HMG-CoA reductase inhibitory activity comparable to the parent drug. The metabolites are excreted into the faeces (70%) and urine (30%). The elimination half-life of cerivastatin is 2–3 h. Renal dysfunction does not alter the pharmacokinetics of cerivastatin to a significant extent [4]. Although cerivastatin was withdrawn from the market in 2001, at the time of the present study it was widely used as a lipid-lowering drug in renal transplant patients.

The aim of the study was to evaluate the mutual effect of tacrolimus and cerivastatin and their pharmacokinetics in renal transplant patients.

Patients and methods

Subjects

Ten renal transplant patients who had received a kidney transplant more than 6 months ago and who had stable graft functions and serum creatinine concentrations $< 230 \mu\text{mol l}^{-1}$ and LDL-cholesterol concentrations $> 110 \text{ mg dl}^{-1}$ participated in the study. Patients with any clinically significant hepatic, endocrine and gastrointestinal disorders, or who had previously had elevated creatinine phosphokinase (CPK) concentrations were excluded. The immunosuppressive regimen consisted of oral doses of tacrolimus twice daily in combination with corticosteroids once daily. Stable steady-state blood trough concentrations of tacrolimus ($\pm 20\%$) without dosage adjustments had to be achieved 3 months before starting cerivastatin therapy. For patients' details see Table 1.

Drug formulation

Cerivastatin sodium 0.2-mg tablets (supplied by Bayer AG, Leverkusen, Germany) and tacrolimus capsules (supplied by Fujisawa GmbH, München, Germany) were used in this study.

Table 1 Characteristics of patients, immunosuppressive protocols and antihypertensive therapy.

Number of patients (<i>n</i>)	10
Female/male (<i>n</i>)	2/8
Age (years) $\pm$ SD	53 $\pm$ 11 (35–66)
Transplant life (months) $\pm$ SD	36 $\pm$ 29 (9–102)
Body weight (kg) $\pm$ SD	73 $\pm$ 11 (63–85)
Smokers (<i>n</i>)	0

(*n*), Number, other data are means $\pm$ SD and (minimum and maximum range).

Study design

The design of this open, nonrandomized, single-centre, multiple-dose interaction study was approved by the Ethic Committee of the University of Erlangen and written informed consent was obtained from each participant.

The study started with an observation period of 3 months (months 1–3) without cerivastatin therapy, followed by a treatment phase of 3 months (months 4–6). This modified the monitoring of tacrolimus dosage, blood trough concentrations and blood chemistry (haemoglobin, leucocyte count, platelets, CPK, serum creatinine, albumin, AST, ALT, LDH) during months 1–3, and day 1 and day 7 of month 4 and months 5 and 6. All patients were maintained on concomitant individualized steady-state oral doses of tacrolimus (Table 2). The latter was administered at 08.00 h and 20.00 h, whereas cerivastatin was administered at 20.00 h. On the days when cerivastatin pharmacokinetics were studied (day 1 and month 6) cerivastatin was given at 08.00 h p.o. for practical reasons. Cerivastatin and tacrolimus were administered with 120 ml of water, and pharmacokinetics were studied under fasting conditions. The pharmacokinetics of tacrolimus were monitored on day 0, on day 1 of month 4 and after month 6, and those for cerivastatin were analysed on day 1 (first dose) of month 4 and after month 6 to look for possible drug accumulation. Blood samples were taken before and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after administration of the drug. In addition, whole blood trough concentrations of tacrolimus and cerivastatin were determined monthly during the study.

All patients received comedication with methylprednisolone 4 mg day⁻¹, once daily at 08.00 h. Three patients were also treated with mycophenolate mofetil 1 g day⁻¹. Concomitant medication was allowed but had to be started 1 month before the study and had to be continued for the duration of the study, especially if the drug(s) in question interacted with CYP3A4. All patients needed antihypertensive treatment with either AT-1 receptor blockers (*n* = 4), ACE-inhibitors (*n* = 2), loop diuretics

Table 2 Cerivastatin and tacrolimus pharmacokinetics in 10 patients before and after 1 and 3 months of therapy.

Drug	mg day ⁻¹	C _{max} (ng mL ⁻¹) (min/max)	t _{max} (h) (min/max)	AUC** (min/max)	t _{1/2} (min/max)
Tacrolimus baseline (day 0)	6.45 ± 3.5	21.7 ± 9.1 ng mL ⁻¹ (10.8/36.1)	2.6 ± 1.5 h (0.75/4.16)	289 ± 76.5 ng mL ⁻¹ h ⁻¹ (204.5/454.6)	12.7 ± 2.2 h (9.51/16.52)
Tacrolimus (day 1)	6.45 ± 3.5	18.7 ± 5.1 ng mL ⁻¹ (11.7/26.2) [CI -3.82, +9.82]	1.9 ± 0.7 h (0.68/2.41) [CI -0.38, +1.78]	276 ± 86.1 ng mL ⁻¹ h ⁻¹ (172.6/427.9) [CI -62.25, +88.25]	11.8 ± 1.45 h (9.3/13.36) [CI -0.82, +2.62]
Tacrolimus (week 12)	6.45 ± 3.5	20.9 ± 8.4 ng mL ⁻¹ (10.1/39.6) [CI -4.22, +8.62]	2.8 ± 1.3 h (1.22/4.05) [CI -0.06, +1.86]	294 ± 71.9 ng mL ⁻¹ h ⁻¹ (218/479) [CI -55.2, +91.29]	13.0 ± 2.4 h (8.89/16.72) [CI -0.63, +3.03]
Tacrolimus metabolite M-2 baseline (day 0)	NA	0.86 ± 0.29 ng mL ⁻¹ (0.51/1.26)	2.37 ± 0.99 h (0.75/4.16)	9.14 ± 3.9 ng mL ⁻¹ h ⁻¹ (2.1/15.9)	8.9 ± 4.48 h (4.2/14.7)
Tacrolimus metabolite M-2 (day 1)	NA	0.85 ± 0.51 ng mL ⁻¹ (0.52/2.3)	2.07 ± 0.97 h (0.68/3.38)	14.7 ± 5.3 ng mL ⁻¹ h ⁻¹ (8.86/27.62)	9.6 ± 3.28 h (3.45/15.77)
Tacrolimus metabolite M-2 (week 12)	n.a.	0.69 ± 0.22 ng mL ⁻¹ (0.4/1.1)	2.34 ± 0.94 h (0.55/3.34)	7.1 ± 2.45 ng mL ⁻¹ h ⁻¹ (3.36/10.5)	9.9 ± 6.7 h (3.47/16.83)
Cerivastatin (day 1)	0.2	3.43 ± 1.48 µg l ⁻¹ (2.0/5.3)	1.49 ± 0.68 h (1.08/2.02)	14.5 ± 2.53 µg l ⁻¹ h ⁻¹ (7.8/26.5)	2.2 ± 1.48 h (1.1/2.9)
Cerivastatin (week 12)	0.2	3.92 ± 1.24 µg l ⁻¹ (1.9/5.45) [CI -0.77, +1.75]	2.33 ± 0.97* h (1.4/3.6) [CI +0.07, +1.61]	22.02 ± 3.055* µg l ⁻¹ h ⁻¹ (10.9/32.19) [CI +10.37, +14.67]	2.93 ± 1.89 h (1.4/4.4) [CI -0.84, +2.3]

Baseline, Values obtained before treatment; day 1 and week 12, values obtained at day 1 and at week 12. Data are arithmetic metric means ± arithmetic SD. (min/max), Minimum and maximum values; NA, not applicable. **P* < 0.05 compared with baseline values. **AUC tacrolimus = AUC₀₋₁₂, AUC cerivastatin AUC₀₋₂₄, CI = 95% confidence interval on the difference.

(*n* = 4), Ca-antagonists (*n* = 6), β-blockers (*n* = 6), α-blockers (*n* = 2) and clonidine (*n* = 3). Adverse events were evaluated by the investigators and registered continuously during the study.

Blood samples were collected through a venous catheter or by direct venepuncture. In order to avoid unused volumes from i.v. lines, the first 3 ml of blood were discarded. Blood samples for cerivastatin analysis were placed in tubes, centrifuged immediately (2000 *g*; 15 min) and separated. Whole blood samples for tacrolimus analysis were collected into EDTA tubes. Serum and blood samples were kept at -20 °C in plastic tubes until analysed.

Assays of tacrolimus and cerivastatin

Cerivastatin plasma samples were analysed by liquid-liquid extraction followed by a specific and sensitive high-performance liquid chromatography procedure using post-column derivatization with UV light and subsequent fluorescence detection [5, 6]. The minimum determinable concentration was 0.5 ng mL⁻¹. The method was validated over a linear range of 0.5–80 ng mL⁻¹, giving a precision and accuracy of <7% (*n* = 14). Tacrolimus analyses were performed by liquid chromatography-tandem mass spectrometry as described elsewhere [7]. Data were validated by the tacrolimus international proficiency testing scheme. The limit of detection of the

method was 0.2 ng mL⁻¹. The coefficient of variation at 4 ng mL⁻¹ was 7.1% (*n* = 14) with an inaccuracy of -3.9%, and that at 25 ng mL⁻¹ was 10.3% (*n* = 14) with an inaccuracy of +9.9%.

Data analysis

All pharmacokinetic evaluations were performed by non-compartmental methods. Maximum concentrations (C_{max}) and time to peak concentration (T_{max}) were taken immediately from the plasma or blood concentration-time profiles. C_{trough}, the concentration directly before the next dose was used to evaluate tacrolimus whole-blood concentrations during the first 3 months of the study. Terminal elimination half-life (T_{1/2}) values were obtained by linear regression analysis after log-transformation of the last data points using Akaike's information criterion. Areas under the curve (AUC) extrapolated to infinity and AUC at steady state within the dosage interval (AUC₍₀₋₁₂₎ for tacrolimus and metabolite M-2, AUC₍₀₋₂₄₎ for cerivastatin) were calculated using the log-linear trapezoidal rule. All parameters are expressed as arithmetic means (m) ± arithmetic standard deviation (SD) and minimum-maximum ranges are demonstrated. Tacrolimus trough concentrations, cerivastatin pharmacokinetics (AUC, C_{max}, T_{max}, T_{1/2}), LDL-cholesterol, triglyceride and HDL-cholesterol concentrations predose and after starting 3 months' cervastalin were compared using a

paired *t*-test following logarithmic transformation, with $P < 0.05$ as the minimum level of significance

Results

Tacrolimus and tacrolimus metabolite pharmacokinetics before and after single and multiple dosing with cerivastatin

Mean tacrolimus blood trough concentrations did not change more than 10% over the whole study period {baseline 8.6 ± 2.1 (6.2/9.1), day 1 8.4 ± 1.7 (5.9/9.3) and week 12 8.7 ± 2.2 (6.5/9.3) [mean $\pm$ SD (min–max range)]} and tacrolimus dosage did not have to be changed in any patient after initiation of cerivastatin treatment (Table 2). The mean ratio of post/predose tacrolimus concentration was 1.01 with a 95% confidence interval of 0.97, 1.08. Tacrolimus pharmacokinetics were not altered by co-administration of cerivastatin (Table 2).

Cerivastatin pharmacokinetics after single and multiple dosing

The pharmacokinetics of cerivastatin on day 1 and day 90 after daily dosing with 0.2 mg day^{-1} are shown in Table 2. During the 90-day period we observed statistically significant increases in the T_{max} ($14.3 \pm 1.5\%$) and AUC ($35.3 \pm 2.7\%$) of cerivastatin (Table 2).

Lipid-lowering effects of cerivastatin

The pretreatment lipid profiles of kidney transplant patients and the effects of cerivastatin on lipid profiles are outlined in Table 3. The tacrolimus-treated patients included in the study without any prior lipid-lowering therapy showed moderately elevated concentrations of

total serum cholesterol, LDL-cholesterol and triglycerides, whereas HDL-cholesterol was in the normal range. After 90 days of therapy with cerivastatin total serum cholesterol (-18%), LDL-cholesterol (-25%) and triglyceride concentrations (-35%) were significantly lower than at the beginning of the study ($P < 0.05$), whereas HDL-cholesterol showed elevated concentrations ($+15\%$, Table 3).

Adverse events

In one patient increased CPK concentrations with a maximum of 240 U l^{-1} after 2 weeks of cerivastatin therapy were observed. Cerivastatin therapy was continued in that patient and CPK concentrations decreased to normal range without further intervention. Serum myoglobin concentrations remained in the normal range in this patient. In all patients serum creatinine concentration did not change and there were no effects on their biochemical and haematological profiles (Table 3).

Discussion

To date, the effect of combination therapy with tacrolimus and statins has not been investigated in renal transplant patients. In contrast to cyclosporin A [8–11], no safety concerns related to elevated drug concentrations of statins associated with rhabdomyolysis or impairment of renal function have been reported for tacrolimus, which was introduced as an immunosuppressive agent in 1994. The present study has to evaluate the potential mutual drug–drug interaction between the statin cerivastatin and tacrolimus over a treatment period of 90 days.

Table 3 Biochemical profile of 10 kidney-transplant patients before, 1, 4 and 12 weeks after starting cerivastatin therapy.

	Baseline	Day 7	Week 4	Week 12
Total cholesterol (mg dl^{-1})	226 ± 36	Not done	Not done	$186 \pm 28^*$ [CI +10.2, +69.8]
LDL-cholesterol (mg dl^{-1})	129 ± 39	Not done	Not done	$93 \pm 22^*$ [CI +6.8, +65.3]
HDL-cholesterol (mg dl^{-1})	51 ± 13	Not done	Not done	59 ± 17 [CI -6.0 , +22.1]
Triglycerides (mg dl^{-1})	189 ± 89	Not done	Not done	$123 \pm 59^*$ [CI +3.5, +108.8]
Serum creatinine (mg dl^{-1})	1.4 ± 0.46	1.42 ± 0.5	1.44 ± 0.4	1.47 ± 0.49
CPK (U l^{-1})	33 ± 18	35 ± 28	28 ± 10	40 ± 39
AST (U l^{-1})	9.7 ± 3.2	12.3 ± 9.7	9.8 ± 4.1	11 ± 3.8
ALT (U l^{-1})	12.3 ± 6.9	16.5 ± 16	14.2 ± 10	15.7 ± 10.2

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatinine phosphokinase; baseline, value obtained before starting treatment with cerivastatin. Day 7, weeks 4 and 12: values obtained after day 7, week 4 and week 12 after starting cerivastatin treatment. Data are means $\pm$ SD, CI = 95% confidence interval on the difference between baseline and week 12. $^*P < 0.05$ compared with baseline values.

Tacrolimus pharmacokinetics were not altered by single and multiple doses of cerivastatin (0.2 mg), suggesting that no additional tacrolimus blood trough concentrations needed to be measured after initiating cerivastatin therapy. These findings are in line with the lack of interaction of cerivastatin with other drugs metabolized by CYP3A4, such as nifedipine, itraconazole and mibefradil [12]. Cyclosporin steady-state blood concentrations are also unaffected in kidney transplants receiving cerivastatin [5, 13]. Our data suggest that of the tacrolimus metabolites, M-2 does not contribute to the clinical effect of the drug, because of its low $C_{\max}$ and AUC compared with those of the parent compound.

The AUC of cerivastatin after a single dose was comparable to published values obtained in healthy subjects [3, 14]. After 3 months of therapy, there was about a 15% increase in $C_{\max}$ and 35% in AUC of cerivastatin. Similar observations after single-dose administration of cerivastatin have recently been reported for tacrolimus-treated liver transplant patients. Thus tacrolimus steady-state trough concentrations remained unaltered and the mean cerivastatin AUC and $C_{\max}$ were approximately 50% higher compared with data obtained in healthy subjects [14]. Those and our results contrast with those from cyclosporin A-treated patients, where fourfold increases in cerivastatin AUC and in the AUCs of other statins (twofold and 23-fold) have been reported [5, 11]. The mechanism of this interaction between cyclosporin and cerivastatin A is still under discussion [5, 11]. Our data indicate that tacrolimus caused a smaller increase in AUC compared with cyclosporin A. Although the concomitant use of these drugs proved to be well tolerated in the study by Mück *et al.* [5], this finding must be interpreted cautiously because of the recent problems associated with cerivastatin.

The pretreatment lipid profile in our study group was abnormal, but values were not as high as reported for cyclosporin A-treated renal transplants. Our data confirm results reported by McCune *et al.* [15] and demonstrate that tacrolimus has only a moderate influence on post-transplant hyperlipidaemia, with a maximum increase in total cholesterol of only 30% [16]. To reduce cardiovascular risk in renal transplant patients, we decided to treat with statins with the aim of lowering LDL-cholesterol values to $<100 \text{ mg dl}^{-1}$, according to the official National Cholesterol Education Programme (NCEP) guidelines [17] for patients with cardiovascular disease and the recommendations for the outpatient surveillance of renal transplant recipients [18]. The use of cerivastatin in our patients resulted in the desired reduction in LDL-cholesterol concentrations. Long-term studies of hyperlipidaemia and its treatment are needed to provide further data for treatment recommendations in renal transplant patients. In comparison with cyclosporin A-treated renal

transplant patients who experienced a decrease in total cholesterol (-32%) and LDL-cholesterol (-38%) during treatment with cerivastatin (0.2 mg) [13], patients in the present study exhibited a smaller decrease of 20% (total cholesterol) and 25% (LDL-cholesterol). This may have been due to a greater effect of cyclosporin on cerivastatin metabolism leading to a higher systematic exposure to the latter drug [5].

Although cerivastatin was withdrawn from the market in 2001 because of severe cases of rhabdomyolysis, the present study provides valuable insights into its interaction with tacrolimus in renal transplant patients mediated by cytochrome P450. Our data suggest a different interaction profile for cerivastatin in combination with tacrolimus compared with that with cyclosporin, which may be of clinical relevance.

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