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More potent lipid lowering effect by rosuvastatin compared to fluvastatin in everolimus treated renal transplant recipients

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Abstract

Background—Dyslipidemia is a risk factor for premature cardiovascular morbidity and mortality in renal transplant recipients (RTR). Pharmacotherapy with mTOR inhibitors aggravates dyslipidemia thus necessitating lipid-lowering therapy with fluvastatin, pravastatin or atorvastatin. These agents may not sufficiently lower lipid levels and therefore a more potent agent like rosuvastatin maybe needed.

Methods—We have aimed to assess the lipid-lowering effect of rosuvastatin as compared to fluvastatin in RTR receiving everolimus. Safety was assessed as the pharmacokinetic (PK) interaction potential of a rosuvastatin/everolimus combination in RTR. A 12-hour everolimus PK-investigation was performed in twelve stable RTR receiving everolimus and fluvastatin (80 mg/day). Patients were then switched to rosuvastatin (20 mg/day) and a follow-up 12/24-hour PK-investigation of everolimus/rosuvastatin was performed after one month. All other drugs were kept unchanged.

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Results—In RTR already receiving fluvastatin, switching to rosuvastatin further decreased LDL-cholesterol and total cholesterol by 30.2±12.2% ($p<0.01$) and 18.2±9.6% ($p<0.01$), respectively. Everolimus AUC_{0-12} was not affected by concomitant rosuvastatin treatment, 80.3±21.3 μg*h/mL before and 78.5±21.9 μg*h/mL after, respectively ($p=0.61$). Mean rosuvastatin AUC_{0-24} was 157±61.7 ng*h/mL, about 3-fold higher than reported in the literature for non-transplants. There were no adverse events and none of the patients had or developed proteinuria.

Conclusions—Rosuvastatin showed a superior lipid-lowering effect compared to fluvastatin in stable RTR receiving everolimus. The combination of everolimus/rosuvastatin appears to be as safe as the everolimus/fluvastatin combination.

Keywords

Renal transplantation; everolimus; rosuvastatin; lipid lowering; pharmacokinetic; drug-drug interaction

Introduction

Despite a significant improvement in rejection rates and short-term graft survival in renal transplant recipients (RTR), long-term survival of these patients has remained essentially unchanged, and cardiovascular disease continues to be a major cause of death in this patient population (1-4). Hyperlipidemia is one of the major risk factors for developing cardiovascular disease and is a frequent complication post-transplantation, occurring in up to 60% of the patients (5-8). Lipid lowering therapy with the HMG-CoA reductase inhibitors (statins) is generally recommended and may reduce the overall cardiovascular risk (9-11).

The mammalian target of rapamycin (mTOR) inhibitor, everolimus, is a relatively new and increasingly used immunosuppressive drug in RTR. Everolimus provides similar graft survival rates, but has a different cardiovascular risk profile compared to the more commonly used calcineurin inhibitors (CNIs) (12-14). Studies indicate that everolimus may have a favorable effect on renal function and reduce post transplant hypertension (15, 16) but induces a considerable dyslipidemia. Fluvastatin is considered to be a safe statin to use in RTR due to its low interaction potential (9, 17, 18). However, fluvastatin has a modest lipid-lowering effect in patients receiving everolimus, in comparison to those receiving fluvastatin in combination with CNIs (19, 20). Consequently, there might be a need of a more potent lipid-lowering drug in RTR receiving everolimus. In non-transplant patients rosuvastatin has been shown to be a more potent lipid-lowering drug than fluvastatin (21). In addition, rosuvastatin is minimally metabolized and similar to fluvastatin has a low risk for metabolic pharmacokinetic (PK) interactions. However, rosuvastatin has a high affinity for several drug transporters (22-24) and since everolimus has been shown *in vitro* to inhibit various of these drug transporters (25), the possibility of drug-drug interaction between rosuvastatin and everolimus at transporter level cannot be ruled out.

The aims of the present study were to assess the lipid-lowering effect of rosuvastatin in comparison with fluvastatin and to assess the drug-drug interaction potential of the rosuvastatin and everolimus combination in RTR by performing 12/24-hour PK investigations.

Results

Patients

The twelve patients (5 men and 7 women) had a mean age of 61±10 years and all completed the study. Demographic data at inclusion are summarized in Table 1. The patients were treated with 20 mg rosuvastatin per day for an average of 30±4 days with 100% compliance. The rosuvastatin 23- and 24-hour sample was not obtained in six of the twelve patients, while all other everolimus and rosuvastatin concentrations were obtained successfully.

Lipid parameters

The absolute lipid levels and percent change from baseline are summarized in Table 2. From baseline, while patients were on steady state fluvastatin therapy, to one-month of rosuvastatin treatment LDL-cholesterol and total cholesterol decreased by 30.2±12.2% ($p<0.01$) and 18.2±9.6% ($p<0.01$), respectively. In addition, triglycerides also decreased by 18.2±17.7% ($p=0.01$) and HDL-cholesterol was increased by 5.4±10.4% ($p=0.15$).

Everolimus pharmacokinetics

The mean whole blood concentrations versus time curves of everolimus before and after co-administration with rosuvastatin were superimposable as shown in Figure 1. Everolimus pharmacokinetics fulfilled the bioequivalence criteria when co-administered with rosuvastatin (Table 3). The 90% confidence intervals for AUC_{0-12} and C_{max} after:before-ratio were 0.91-1.05 and 0.96-1.15, respectively.

Rosuvastatin pharmacokinetics

The mean steady state AUC_{0-24} of rosuvastatin was 156±61.8 ng*h/mL and the mean C_{max} was 17.1±6.49 ng/mL. Individual AUC_{0-24} values ranged from 75.3-265 ng*h/mL (3.5-fold range) and values for C_{max} ranged from 6.91-28.9 ng/mL (4.2-fold range). Mean CL/F was estimated to be 148 L/h. The estimated $T_{1/2}$ from the six patients with all concentrations available was 9.5±6.7 hr.

Genotyping

Two of the patients' expressed functional CYP3A5 enzymes (**1/*3*) while the other ten patients were not expressing functional CYP3A5 (**3/*3*). The two patients with functional CYP3A5 did not show altered pharmacokinetics of everolimus ($p=0.67$) or rosuvastatin ($p=0.52$). Only one patient was heterozygote for the variant allele CYP3A5*2, the rest of the patients expressed CYP3A5 (*3/*3). There were no heterozygotes (c.521CT), but two homozygote patients for the *SLCO1B1* c.521CC genotype. Rosuvastatin AUC_{0-24} and C_{max} was 74% ($p=0.09$) and 94% ($p=0.03$) higher, respectively, in the patients with the c.521CC genotype compared with those with the wild-type genotype (c.521TT) (n=10) (Figure 2). For sequence variant *PPARA* (rs4253728) G>A three patients were GG, eight were GA and one AA and for the sequence variant *PPARA* (rs4823616) A>G seven patients were identified as AA, four were AG and one GG. In one patient, homozygote for both *PPARA* (rs4253728 and rs4823616) variant alleles, everolimus AUC_{0-12} and C_{max} was 36 % and 35 % higher, respectively, compared to the average of homozygote and/or heterozygote wild-

type patients. There were no heterozygotes, but three homozygote patients for the *POR*28* allele and no significant association were found between this genotype and everolimus/rosuvastatin pharmacokinetics. Polymorphisms of *ABCB1* did not appear to influence rosuvastatin or everolimus pharmacokinetics. Allele frequencies for all sequence variant investigated, expect *SLC01B1*, did not deviate significantly from Hardy-Weinberg distribution.

Safety

Rosuvastatin was well tolerated, none of the patients experienced any adverse events and laboratory parameters associated with hepatotoxicity or myelotoxicity (CK, ALAT, ASAT, LD and GT) did not change during the study period ($p>0.10$). None of the patients had proteinuria, neither on fluvastatin or after 4 weeks of rosuvastatin treatment. The eGFR was 61±20 mL/min at baseline and did not show any significant change (-2.7±8.6 %, $p=0.12$) during rosuvastatin treatment and no patients experienced any acute rejection episodes during the four-week treatment period.

Discussion

In RTR receiving everolimus based immunosuppression and treated with full dose fluvastatin (80 mg/day), a switch to rosuvastatin (20 mg/day) induced a significant additional lipid-lowering effect. Total cholesterol, LDL-cholesterol and triglycerides were significantly reduced from the fluvastatin treatment values by another 20 to 30% after switching the patients to rosuvastatin. This is the first investigation of this combination in RTR and it appears safe as everolimus pharmacokinetics was unaffected following switch to rosuvastatin, the systemic exposure of rosuvastatin was less than 3-fold higher compared with what is presented for non-transplants in the literature, comparable to what is seen for fluvastatin, and no adverse events were observed (17, 26).

Our results are in agreement with previous findings where rosuvastatin has been consistently found to be the most potent statin in a non-transplant population (27-29). The patients in the current study were already treated with the highest available dose of fluvastatin, and had probably already a LDL-cholesterol reduction of about 38.6 mg/dL (1 mmol/L) from the early post-transplant phase before entering the study (9, 30). Treatment with rosuvastatin reduced LDL-cholesterol further by a mean of 42±21 mg/dL (1.1±0.5 mmol/L). If this effect is due to a more potent drug effect or the increased systemic exposure of rosuvastatin during everolimus treatment remains unanswered. In the Assessment of LEscol in Renal Transplantation (ALERT) study, it was shown that lowering LDL-cholesterol by 38.6 mg/dL (1 mmol/L) reduced cardiac death or myocardial infarction by approximately 30% (30). Implicit this suggests that RTR at high risk for cardiovascular events might benefit from more intensive lipid-lowering therapy. Safely achieving a larger LDL-cholesterol reduction could be of great importance in reducing the cardiovascular risk in these patients. Hence, the additional lipid-lowering effect of rosuvastatin observed in the present study may have a potential to improve long-term outcomes in this population (9, 30).

Pharmacokinetic interactions make immunosuppressive therapy in RTR a challenge and it is important to control potential interactions. Everolimus is extensively metabolized via

CYP3A and is a substrate for P-glycoprotein (P-gp) (31, 32). Rosuvastatin is subjected to a minimal degree of metabolism and has not been reported to be a P-gp substrate (22, 33, 34) and based on this does not seem to be a potential pharmacokinetic risk together with everolimus. However, organic anion-transporting polypeptide 1B1 (OATP1B1) has been shown to be an important transporter when it comes to interactions between other immunosuppressive drugs and statins (17, 35). Previous single dose studies in healthy volunteers investigating the interaction between everolimus and simvastatin, atorvastatin or pravastatin have not shown any evidence of clinically relevant interactions (36, 37). Our results support the previous findings, indicating that rosuvastatin does not influence everolimus pharmacokinetics to any relevant degree in RTR.

Elevated plasma concentrations of statins have been associated with an increased risk of adverse events like myopathies (38). Cyclosporine significantly increases the plasma concentrations of all statins and thus increase the risk of adverse events (17). Recently, Simonsen *et al.* reported a 7-fold increase in the steady state AUC and an 11-fold increase in C_{max} of rosuvastatin in heart transplant recipients on cyclosporine based immunosuppression (39). The marginally higher systemic exposure of fluvastatin (about 2-fold) in combination with cyclosporine is considered safe in RTR and a main reason for it being the most commonly used combination in these patients (17). In the present study, mean rosuvastatin steady state $AUC_{0\text{-}24}$ and C_{max} values were 2.8-fold and 2.5-fold higher, respectively, compared to literature data in non-transplant patients, showing $AUC_{0\text{-}t}$ and C_{max} of 56.8 ng*h/mL and 6.79 ng/mL, respectively (26). Even though a slight increase in risk of statin induced side effects cannot be ruled out, these data indicate that rosuvastatin treatment should be safe in combination with everolimus in RTR. Treatment with high doses (e.g. 80 mg/day) of rosuvastatin has been associated with new onset proteinuria (40). This was not confirmed in the present study and substantiate studies where the frequency of dipstick-positive proteinuria at rosuvastatin doses ≤ 20 mg was comparable to that seen with other statins or with placebo (41). Although none of the patients in the present study developed proteinuria, interpretation of this should be made with caution due to the low number of patients included and the short duration of treatment with rosuvastatin.

Consistent with previous findings, no effect of the presence of functional CYP3A5 enzymes or polymorphisms in *ABCB1* on everolimus disposition was observed (42, 43). The large interindividual pharmacokinetic variability observed with statin therapy has at least in part been associated with altered expression and/or function of OATP1B1 (*SLCO1B1*) (44). The *SLCO1B1* c.521T>C variant is associated with reduced activity of OATP1B1 (45) and the two patients in the present study with c.521CC genotype, had a substantial higher $AUC_{0\text{-}24}$ of rosuvastatin compared to the patients expressing the wild-type genotype. These results mirror previous studies and suggest that patients carrying the c.521CC variant could be more susceptible to adverse events of rosuvastatin. Recent clinical data has identified polymorphisms in *PPARA* (rs4253728 and rs4823613) as potential sources of variability in CYP3A4 activity (46). Interestingly, one patient was homozygote carrier for both *PPARA* variant alleles (rs4253728 and rs4823613) and showed higher systemic exposure of everolimus compared to heterozygote and/or homozygote wild type genotypes. As expected,

polymorphisms in *CYP3A5, ABCB1, POR*28, PPARA* (rs4253728 and rs4823613) had no influence on rosuvastatin pharmacokinetics.

Even though the sample size is adequate for the investigation of the drug-drug interaction, it is a limitation to only investigate twelve patients for one month when it comes to assessing side effects. Another potential weakness is the lack of washout period between the discontinuation of fluvastatin and the introduction of rosuvastatin. It was however considered unethical to take these patients off statin treatment and due to the short half-life of fluvastatin (2.3 h) no residual lipid-lowering effect of fluvastatin is anticipated after 4 weeks on rosuvastatin. In addition, the use of literature data for comparison of systemic exposure of rosuvastatin is obviously not an optimal study design. We believe however that it is an informative comparison considering the ethical and practical difficulties to obtain data from transplanted patients with and without their main immunosuppressive drugs.

In conclusions, rosuvastatin showed a superior lipid-lowering effect to fluvastatin in everolimus treated RTR. The combination of everolimus and rosuvastatin seems to be safe, but a slightly increased risk of statin-induced side effects cannot be ruled out.

Patients and Methods

Patients and study design

Twelve RTR receiving everolimus, mycophenolate acid and steroid-based immunosuppression were included in this open label, single-center prospective study. Inclusion criteria included >18 years of age, stable renal function (plasma creatinine <200 μmol/L and <20 % change in the last two weeks) and having received both everolimus and fluvastatin (80 mg/day) for a minimum of three months. Everolimus was subjected to therapeutic drug monitoring (TDM), aiming for trough concentrations in the range 4-8 μg/L. Doses of all concomitantly used drugs, including everolimus, were to be kept unchanged from at least two weeks prior to the first 12-hour PK investigation and throughout the study. Patients with a known hypersensitivity to rosuvastatin were excluded.

At the first PK investigation day, baseline measurement of fasting plasma lipid levels and a 12-hr pharmacokinetic investigation of everolimus were performed. The following day the patients were switched from fluvastatin therapy (80 mg/day) to 20 mg rosuvastatin daily. After one month of concomitant everolimus and rosuvastatin treatment, measurement of plasma lipid levels was repeated and the second 12-hr pharmacokinetic investigation of everolimus was performed. In addition, a 24-hr pharmacokinetic investigation of rosuvastatin was performed. An EDTA whole blood sample was also drawn during the study, for determination of the recipients' genotypes (*CYP3A5, ABCB1, POR*28, PPARA* and *SLCO1B1*). Proteinuria was examined by urine dipstick before and after treatment with rosuvastatin. Tablet count was performed after four weeks of rosuvastatin treatment.

The study was performed in accordance with the Declaration of Helsinki, local laws and other relevant regulation and written informed consent was obtained from all patients prior to inclusion. The study was approved by the Regional Committee for Medical and Health

Research Ethics and by the Norwegian Medicines Agency (EudraCT nr: 2011-005212-29). The study is registered on ClinicalTrials.gov (NCT01524601).

Pharmacokinetic investigations

Patients fasted overnight and a standard hospital breakfast was served 2 hr after drug intake. Samples for the PK profiles were collected before administration of everolimus/fluvastatin or rosuvastatin (C_0) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12-hr following drug intake. Two additional samples were collected 23-hr and 24-hr after administration of the rosuvastatin dose on the follow-up PK-investigation, after four weeks of rosuvastatin treatment.

Bioanalytical methods

Whole blood concentrations of everolimus—Concentrations of everolimus were determined in EDTA blood with a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay as previously described (47). Briefly, the analyte was extracted by protein precipitation with zinc sulfate and acetonitrile. Everolimus was separated chromatographically on a C18 column before MS/MS detection of ammoniated ions using electrospray ionization interface in a positive mode. Stable isotope-labeled ($^{13}C_2D_4$) everolimus was used as internal standard. The validated analytical range was between 2.8 and 35 μg/L with coefficients of variation (CV; precision) less or equal to 10% during analyzes of the study samples. Assay accuracy was in agreement with external quality controls from the Analytical Services International proficiency testing program.

Plasma concentrations of rosuvastatin—Rosuvastatin was analyzed with a validated LC-MS/MS method as previously described ((48); see Supplemental Digital Content, Patient and methods).

Genotyping

A 6 mL EDTA blood sample was obtained for each patient and stored at -20°C prior to DNA extraction. Genomic DNA was extracted from the EDTA whole blood using the QIAmp® DNA blood Minikit (Qiagen®, Hilden, Germany).

Genotyping of *SLCO1B1* and *CYP3A5* was carried out using validated and certified TaqMan®-based real-time PCR methods at Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. Designed primers and probes for the detection of *SLCO1B1*5* (rs4149056; *521T>C*), *CYP3A5*2* (rs28365083; *27289C>A*), and *CYP3A5**3 (rs776746; *6986G>A*), were purchased from Applied Biosystems, Foster City, CA. Absence of variant alleles was interpreted as presence of the wild-type allele (**1*).

Genotyping of *ABCB1* (1199G>A, 1236C>T, 2677G>T, 2677G>A and 3435C>T), *POR*28* (rs1057868; C>T), PPARA (rs4253728; G>A) and *PPARA* (rs4823613; A>G) were performed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) methods, using DNA Engine Dyad® and Tetrad® 2 Thermal Cycler (Bio-Rad Laboratories, Inc.). Specific primers and enzymes were used for the different sequence variants. The different PCR products were digested with 1 Unit of the associated restriction

enzyme, and digested products were separated by electrophoresis on a 3% agarose gel, visualized under ultraviolet light after staining with GelRed™.

Calculations and data analyses

Peak concentration (C_{max}) and time to C_{max} (T_{max}) are the actual observed values. The area under the whole blood or plasma concentration versus time curve during a dose interval at steady state, from time zero to 12/24 hr post dose, was calculated in accordance with the log-trapezoidal rule. The terminal half-life ($T_{1/2}$) was calculated from the slope (k_{el}) of the semi-logarithmic plot of the linear phase (including at least the last three time points) according to the formula $T_{1/2} = \ln(2)/k_{el}$. Missing drug concentrations were generally not substituted with regards to AUC calculations, but in the case that the last concentration in a dose interval was unavailable it was substituted with the C_0 value of that individual.

The lipid lowering effect of rosuvastatin as well as the effect of rosuvastatin on everolimus PK was assessed using each patient as its own control (paired data analysis), comparing the levels at baseline (on steady state fluvastatin treatment) to after one month on rosuvastatin treatment. The safety of rosuvastatin in RTR was assessed by tabulating any adverse events and by comparing the steady state systemic exposure of rosuvastatin (AUC_{0-24}) with levels reported for non-transplant patients in the literature (26). In addition, the individual change in estimated glomerular filtration rate (eGFR) from before to after one month of rosuvastatin treatment was assessed using the Modification of Diet in Renal Disease (MDRD) formula (49, 50).

The influence of different genotypes on everolimus and rosuvastatin PK was tabulated for a descriptive analysis.

Statistics

A sample size of at least twelve patients was calculated to provide 80% power of detecting a 25% difference in AUC_{0-24} of everolimus.

Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY). Normality of data was assessed using the Shapiro-Wilk tests. Paired sample t-test and Wilcoxon signed rank test, for parametric and nonparametric data analyses, respectively, were used to compare means of variables before and after treatment with rosuvastatin. A p-value <0.05 was considered statistically significant. All individual AUC and C_{max} values were log-transformed and the European Medicines Agency guidelines for bioequivalence studies were used to assess the possible pharmacokinetic interaction (51).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALERT	Assessment of LEscol in Renal Transplantation
AUC	Area under the curve
BCRP	Breast cancer resistance protein
C_{max}	Peak concentration
CNI	Calcineurin inhibitor
MDRD	Modification of Diet in Renal Disease
mTOR	The mammalian target of rapamycin
LC-MS/MS	Liquid chromatography tandem mass spectrometry
PCR-RFLP	polymerase chain reaction restriction fragment length polymorphism
P-gp	P-glycoprotein

PK	Pharmacokinetic
OATP1B1	Organic anion transporting polypeptide 1B1
RTR	Renal transplant recipients
$T_{1/2}$	Terminal half-life
T_{max}	Time to C_{max}
TDM	Therapeutic Drug Monitoring

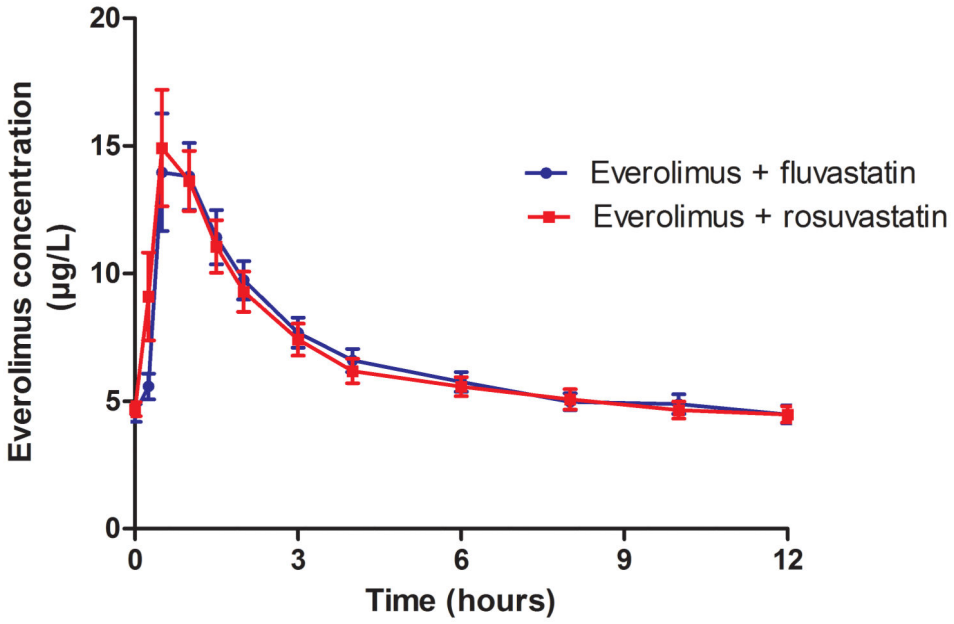

Figure 1. Mean (± SEM) everolimus whole-blood concentration-time profiles before and after concomitant treatment with rosuvastatin

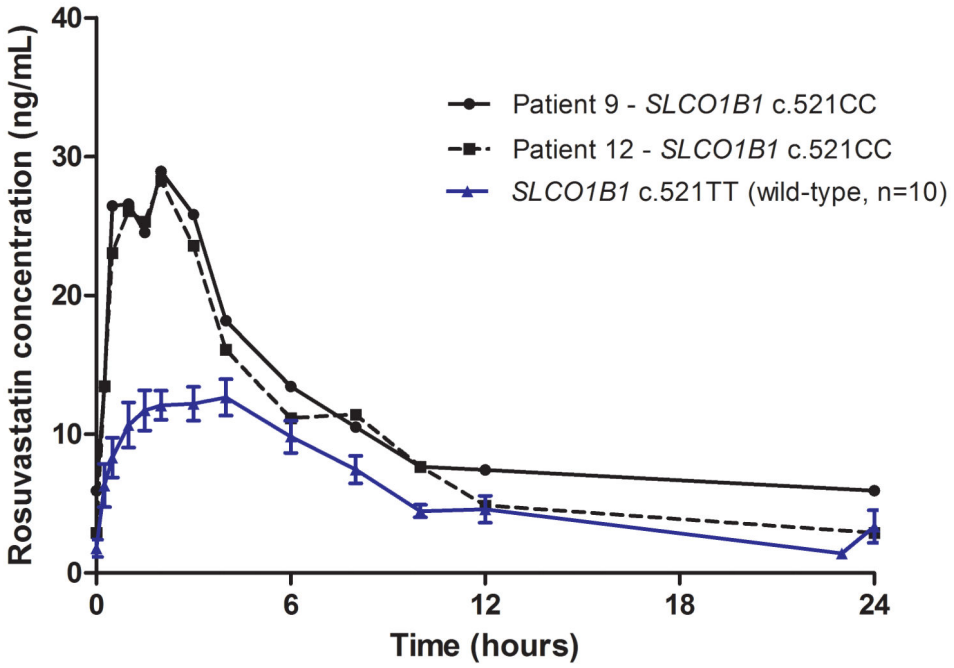

Figure 2.

Mean (± SEM) rosuvastatin plasma concentration-time profiles in patients with the *SLCO1B1* c.521TT variant (wild-type) (n=10) and individual rosuvastatin plasma concentration-time profiles in two patients with the *SLCO1B1* c.521CC genotype.

Table 1

Patients' characteristics at baseline

Characteristics	n=12
Age (years, mean ± SD)	61 ± 10
Gender (male/female, n)	5/7
Weight (kg, mean ± SD)	84 ± 28
Height (m, mean ± SD)	1.72 ± 0.10
BMI (kg/m^2 , mean ± SD)	27.8 ± 6.4
HLA-AB mismatch (mean ± SD)	2.1 ± 1.4
HLA-DR mismatch (mean ± SD)	0.9 ± 0.5
Time after transplantation (years, median range)	3 (1-38)
LD/DD (n)	8/4
Everolimus dose (mg/day, mean ± SD)	2.5 ± 1.0
Treated with MPA (n)	11/12
Prednisolone dose (mg/day, mean ± SD)	4.6 ± 1.0
Fluvastatin dose (mg/day, mean ± SD)	80 ± 0.0
P-creatinine (μmol/L, mean ± SD)	104 ± 36

BMI, body mass index; LD, living donor; DD, deceased donor; HLA, human leucocyte antigen; MPA, mycophenolate acid.

Table 2

Mean (SD) lipid levels on steady state fluvastatin and rosuvastatin treatment, and percent change from steady state fluvastatin treatment to one month of treatment with 20 mg rosuvastatin per day in renal transplant recipients.

Lipid parameter	On fluvastatin treatment	On rosuvastatin treatment	% Change	*P*-value
LDL-cholesterol				
mmol/L	3.54 (0.93)	2.45 (0.72)	-30.2 (12.2)	< 0.01
mg/dL	137 (36.0)	94.6 (27.6)		
Total cholesterol				
mmol/L	5.98 (1.05)	4.82 (0.81)	-18.2 (9.59)	< 0.01
mg/dL	231 (40.7)	187 (31.3)		
HDL-cholesterol				
mmol/L	1.63 (0.42)	1.71 (0.48)	5.38 (10.4)	0.14
mg/dL	62.7 (16.4)	65.9 (18.5)		
Triglycerides				
mmol/L	2.38 (1.04)	1.85 (0.71)	-18.2 (17.7)	0.01
mg/dL	210 (91.9)	164 (63.0)		

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3

Everolimus pharmacokinetic variables during concomitant treatment with either 80 mg fluvastatin or 20 mg rosuvastatin daily. All variables except T_{max} were ln-transformed before statistical analysis with paired Student's t-test. T_{max} was analyzed with Wilcoxon signed rank test. Data are presented as mean (SD).

	Everolimus + fluvastatin	Everolimus + rosuvastatin	Ratio	*P*-value
AUC_{0-12} (μg*h/L)	80.3 (21.3)	78.5 (21.9)	0.98	0.61
C_{max} (μg/L)	15.6 (7.48)	16.2 (7.37)	1.05	0.39
CL/F (L/h)	16.5 (8.52)	17.4 (7.53)	1.08	0.25
$T_{1/2}$ (h)	20.4 (9.63)	19.9 (7.47)	1.02	0.42
T_{max} (h)	0.79 (0.26)	0.69 (0.28)	0.96	0.37
C_0 (μg/L)	4.54 (1.19)	4.69 (0.96)	1.05	0.35

AUC_{0-12}, area under the plasma concentration versus time curve from zero to 12 hours; C_{max}, maximum plasma concentrations; $T_{1/2}$, half-life; T_{max}, time to C_{max}; C_0, concentrations before the dose.