Clinical research

Personalized rosuvastatin therapy in problem patients with partial statin intolerance

Aleksandr B. Shek[1], Ravshanbek D. Kurbanov[1], Rano B. Alieva[1], Guzal J. Abdullaeva[1], Aleksandr V. Nagay[1], Alisher A. Abdullaev[2], Shavkat U. Hoshimov[1], Ulugbek I. Nizamov[1]

[1]Republican Specialized Center of Cardiology, Tashkent, Uzbekistan
[2]Institute of Genetics and Plant Experimental Biology, Uzbekistan Academy of Sciences, Tashkent, Uzbekistan

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Corresponding author:
Prof. Aleksandr B. Shek
Republican Specialized Center of Cardiology
4 Osyo
47/35 Mirobod St
100052 Tashkent, Uzbekistan
Phone: +99871 2525455
Fax: +99871 2341667
E-mail: shek-999@mail.ru

Abstract

Introduction: The aim was to study the pharmacogenetic determinants of switching simvastatin-intolerant ethnic Uzbek patients with coronary artery disease (CAD) to rosuvastatin treatment.
Material and methods: The study included 50 patients with CAD, who demonstrated statin-induced adverse liver symptoms, accompanied by an elevation in transaminase level (3-fold or more in 37 cases) or statin-induced adverse muscle symptoms, accompanied by elevations in serum (CK > 3 times above the upper limit of normal (ULN)) in simvastatin treatment with a dose of 10–20 mg/day. The control group consisted of 50 patients without side effects. Patients were genotyped for polymorphisms in the genes coding for the cytochrome P450 (CYP) metabolic enzymes CYP3A5(6986A>G), CYP2C9(430C>T), CYP2C9(1075A>C), and hepatic influx and efflux transporters SLCO1B1(521T>C) and BCRP(ABCG2, 421C>A) by means of the PCR-RFLP method.
Results: When the 50 patients of the case group were switched to the starting rosuvastatin dose of 5 mg, intolerance symptoms were not observed in 29 (58%) versus 21 with adverse symptoms. In this case-control study, the groups differed significantly only in the prevalence of the *3/*3 genotype CYP3A5 (OR = 5.25; 95% CI: 1.6–17.8; p = 0.014).
Conclusions: In a considerable proportion of ethnic Uzbek patients with CAD and simvastatin intolerance symptoms, serious side effects when switching to a starting dose of rosuvastatin were not observed, and it should be noted that in most cases (72.4%) this phenomenon was observed among the carriers of *3/*3 genotype of the CYP3A5 (6986A> G) gene.

Key words: statin intolerance, genetic determinants, personalized rosuvastatin therapy.

Introduction

The use of statins is a cornerstone of cardiovascular disease prevention and treatment, which is why their intolerance is a serious problem for clinicians [1, 2].

Recently, it has been shown that patients with acute coronary syndrome who are intolerant to statins are more likely to have recurrent MI or other subsequent coronary heart disease events, although it is not associated with an increased risk of all-cause mortality [3].

The European Atherosclerosis Society (EAS) in its Guidelines focuses on statin-associated muscle symptoms (SAMS) [4], which are indeed the most frequent side-effects [4, 5]. However, this can lead to underestimation of the real number of patients with statin intolerance [6]. Statin-induced adverse effects on the liver are rarely observed [6–8], but they can manifest as asymptomatic elevation of serum transaminase level (0.5–2% patients), hepatitis, cholestasis and very rarely acute liver failure [6, 9].

The Canadian working group [10] proposes to distinguish complete and partial statin intolerance depending on intolerance to any individual statin in its initial dose or some particular types of statins in a certain dose. The EAS Consensus Panel recommends in patients with statin adverse symptoms switching to a second statin (with different pharmacokinetics) after a 2–4-week washout [4]. Pharmacogenetic differences in statin metabolism may determine the selection of another statin, but they are not well defined. In our previous case-control study [11], we identified genetic determinants of simvastatin intolerance in ethnic Uzbek patients with coronary artery disease. However, further tactics according to the European guidelines after washout and the effectiveness of their transfer to another statin remained unexplored. This was the basis for the present study.

The aim of the study was to study the pharmacogenetic determinants of successful switching of simvastatin intolerant ethnic Uzbek patients with coronary artery disease (CAD) to rosuvastatin treatment.

Material and methods

The study was performed with the protocol approved by the Local Ethics Committee of the Republican Specialized Center of Cardiology, Tashkent. It included 50 patients who in the previous case-control study demonstrated simvastatin-induced adverse effects on the liver (transaminase level increased 3-fold or more in 37 cases) or SAMS with statin-induced elevations in serum CK (of > 3 × UNL in 13 cases) for treatment with a simvastatin dose of 10–20 mg/day for 3 months of treatment.

Blood lipids spectrum parameters: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), atherogenic index (AI), biochemical indicators (ALT, AST, CK) Daytona (Randox, Ireland) were studied.

Determination of genotypic frequencies

PCR-restriction fragment length polymorphism (PCR-RFLP) analysis was used to determine the genotypic frequencies of five polymorphisms. The primers and restriction endonucleases used for PCR-RFLP analysis are summarized in Table I [12–16].

Statistical analysis

The Statistica 6.0 advanced statistical analysis package was used for the statistical analysis of obtained data. The obtained data were presented as mean and standard deviation (mean ± standard deviation), where the statistical significance of the obtained measurements for compared mean values was determined by Student's *t*-test (*t*) with calculated error probability (*P*) to check normality of the distribution. If the distribution of studied variables differed from the normal distribution, a non-parametric analysis test, the Mann-Whitney *U*-test for two samples, was used. In order to evaluate the difference between qualitative statistical measures, the χ^2 method was used together with Fisher's exact test for small samples.

The empirical genotype frequency distribution conformance to the theoretically expected Hardy-Weinberg equilibrium was checked by the χ^2 test.

In order to compare favorable and unfavorable outcome frequencies in independent groups of events the odds ratios (OR) were calculated by determining the 95% confidence interval (CI). Differences in the studied binary characteristics were considered to be statistically significant if the CI for the OR did not include 1. The confidence level of $p < 0.05$ was accepted as statistically significant.

Table I. Primers used in the study

Gene	Primer set	Position	Detection	Annealing [°C]	*Refs.
CYP3A5*3	Forward: 5-CCTGCCTTCAATTTTCACT-3 Reverse: 5-GGTCCAAACAGGGAAGAGGT-3	(6986A>G)	RFLP RsaI	61	[12]
CYP2C9*2	Forward: 5'-ATCCACATGGCTGCCCAGTGTCA-3 Reverse: 5-CACATGAGCTAACAACCAGACTCA-3	(430C>T)	RFLP Bme18I	56	[13]
CYP2C9*3	Forward: 5-TGCACGAGGTCCAGAGGTAC -3 Reverse: 5'-ACAAACTTACCTTGGGAATGAGA3	(1075A>C)	RFLP KpnI	56	[14]
SLCO1B1	Forward: 5-TTG TCA AAG AAG TTT GCA AAG TG-3 Reverse: 5-GAA GCA TAT TAC CCA TGA GC -3.	(521T>C)	RFLP AspLE I	56	[15]
BCRP (ABCG2)	Forward: 5-TGTTGTGATGGGCACTCTGATG-3 Reverse: 5-ATCAGAGTCATTTTATCCACAC -3	(421C>A)	RFLP Bst4CI	56	[16]

Results

In the previous study, we noted that the most frequent homozygous genotypes with the variant genotypes (Table II) were in the case group. The CYP3A5 gene *3/*3 genotype (p = 0.0001) and the variant genotype CA BCRP gene (p = 0.024) were found to be predominant. At the same time, when 37 patients with simvastatin-induced liver effects were compared with the control group, the *3/*3 genotype of the CYP3A5 gene (p = 0.0001) and variant genotype of the CA BCRP gene (p = 0.0001) were also observed more frequently (Table II B). However, when the 13 patients who had SAMS were compared with the control group (n = 50), it was found that in the case group the genotype 3*/3* of the CYP3A5 gene (p = 0.003) and C allele SLCO1B1 gene polymorphism carriers (p = 0.017) were predominant (Table II C).

When the 50 patients of the case group were switched to the starting rosuvastatin dose of 5 mg, intolerance symptoms were not observed in 29 (58%) vs. 21 with adverse symptoms. In this case-control study the two compared groups did not differ in the main baseline characteristics (Table III), and they differed significantly

Table II. A – Distribution of polymorphic gene markers of studied genotypes in case and control groups (1 : 1)*, **B** – Distribution of polymorphic gene markers of studied genotypes in patients with hepatic side-effects in case and control groups (1 : 1.35)*, **C** – Distribution of polymorphic gene markers of studied genotypes in patients with muscular side-effects in case and control groups (1 : 3.85)*

A

Genotypes		I (case) *N* = 50	II (control) *N* = 50	OR, *p*-value
CYP3A5	*3/*3	28	6	OR = 9.33 95% CI: 3.37–25.9 χ^2 = 19.7; p < 0.001
	*1 carriers: *1/*3 and *1/*1	22	44	
CYP2C9*2	*1/*1	40	39	OR = 1.13 95% CI: 0.43–2.96 χ^2 = 0.00; p = 1.00
	Variants *2 carriers: *1/*2 and *2/*2	10	11	
CYP2C9*3	*1/*1	40	42	OR = 0.76 95% CI: 0.27–2.13 χ^2 = 0.07; p = 0.80
	*3 carriers: *1/*3 (no *3/*3)	10	8	
BCRP	C carriers: CA (no CC)	19	8	OR = 3.22 95% CI: 1.25–8.30 χ^2 = 5.07; p = 0.024
	AA	31	42	
SLCO1B1	TT	35	36	OR = 0.91 95% CI: 0.38–2.15 χ^2 = 0.000; p = 1.00
	C carriers TC, CC	15^	14^^	

B

Genotypes		I (case) *N* = 37	II (control) *N* = 50	OR, *p*-value
CYP3A5	*3/*3	21	6	OR = 9.63 95% CI: 3.29–28.1 χ^2 = 17.9; p < 0.001
	*1 carriers: *1/*3 and *1/*1	16	44	
CYP2C9*2	*1/*1	31	39	OR = 1.46 95% CI: 0.49–4.38 χ^2 = 0.16; p = 0.69
	Variants *2 carriers: *1/*2 and *2/*2	6	11	
CYP2C9*3	*1/*1	30	42	OR = 0.82 95% CI: 0.27–2.50 χ^2 = 0.005; p = 0.95
	*3 carriers: *1/*3 (no *3/*3)	7	8	
BCRP	C carriers: CA (no CC)	22	8	OR = 7.7 95% CI: 2.83–20.9 χ^2 = 15.9; p < 0.001
	AA	15	42	
SLCO1B1	TT	30	36	OR = 1.67 95% CI: 0.60–4.66 χ^2 = 0.53; p = 0.47
	C carriers TC, CC	7^	14^^	

Table II. Cont. **C** – Distribution of polymorphic gene markers of studied genotypes in patients with muscular side-effects in case and control groups (1 : 3.85)*

C

Genotypes		I (case) *N* = 13	II (control) *N* = 50	OR, *p*-value
CYP3A5	*3/*3	7	6	OR = 8.56 95% CI: 2.14–34.1 χ^2 = 8.63; *p* = 0.003
	*1 carriers: *1/*3 and *1/*1	6	44	
CYP2C9*2	*1/*1	9	39	OR = 0.64 95% CI: 0.16–2.46 χ^2 = 0.88; *p* = 0.77
	Variants *2 carriers: *1/*2 and *2/*2	4	11	
CYP2C9*3	*1/*1	10	42	OR = 0.64 95% CI: 0.14–2.83 χ^2 = 0.036; *p* = 0.85
	*3 carriers: *1/*3 (no *3/*3)	3	8	
BCRP	C carriers: CA (no CC)	4	8	OR = 2.33 95% CI: 0.58–9.46 χ^2 = 0.66; *p* = 0.42
	AA	9	42	
SLCO1B1	C carriers TC, CC	8^	14^^	OR = 4.11 95% CI: 1.15–14.8 χ^2 = 3.74; *p* = 0.05
	TT	5	36	
SLCO1B1 alleles	C alleles	10	15	OR = 3.54 95% CI: 1.35–9.27 χ^2 = 5.7; *p* = 0.017
	T alleles	16	85	

**A –^2 with CC genotype, ^^1 with CC genotype; *B – ^none with CC genotype, ^^1 with CC genotype; *C –^2 with CC genotype, ^^1 with CC genotype.*

(Table IV) only in the prevalence of the *3/*3 genotype CYP3A5 (OR = 5.25; 95% CI: 1.6–17.8; *p* = 0.014): *3/*3 genotype CYP3A5 was observed in 21 of 29 (72.4%) patients in the first group, and only in 7 of 21 (33.4%) in the second group. Moreover, 8 (61.5%) of 13 patients with muscle and 21 (56.8%) of 37 patients with liver adverse effects of simvastatin tolerated a 5 mg dose of rosuvastatin.

Table III. Baseline characteristics of the compared groups of patients within the case group (1 – tolerance to rosuvastatin, 2 – intolerance)

Indicators	1 (*n* = 29)	2 (*n* = 21)
Male	10 (34.5%)	11 (52.4%)
Female	19 (65.5%)	10 (47.6%)
Age	60.8 ±8.2	57.0 ±10.9
Arterial hypertension	17 (49%)	9 (43%)
Myocardial infarction in medical history	5 (17%)	16 (32%)
Diabetes mellitus type 2	5 (17.3%)	6 (28.6%)
Rosuvastatin dose, mg/day	5	5
Total cholesterol (TC) [mg/dl]	216.9 ±42.3	204.4 ±61.0
TG [mg/dl]	156.4 ±60.9	168.2 ±93.8
LDL-C [mg/dl]	140.3 ±38.0	126.8 ±51.9
HDL-C [mg/dl]	43.4 ±11.6	43.1 ±8.3
VLDL-C [mg/dl]	31.3 ±12.1	33.6 ±18.6
AI [relative units]	4.2 ±1.5	4.0 ±1.5

Discussion

It is well known that the cost of pharmacogenetic tests hinders their clinical use to prevent SAMS in the era of low-cost generic drugs. Despite controversy, "major health systems across the globe are obtaining and making use of genome sequence data in patients they care for, hoping this approach will prove beneficial" [17]. As has been shown in recent studies, provision of genetic testing results and supporting information directly to patients was associated with significantly higher adherence to statin therapy [18]. A relationship of a number of genetic polymorphisms with lipid phenotypes has also been established, which may have an effect on events related to dyslipidemia [19]. High adherence and longer durations of persistence with statins are associated with a reduction of the risk of cardiovascular events. Cost-effective genetic tests assess common variations in drug metabolic and transport genes and allow patient treatment noncompliance to be reduced.

In our study the genotypes *3*3 CYP3A5 and CA BCRP were observed with a high level of confidence in patients with simvastatin intolerance. It

Table IV. Results of switching simvastatin intolerant patients with coronary artery disease to rosuvastatin treatment (group 1 – tolerance to rosuvastatin, group 2 – intolerance)

Genes	Compared genotypes	1 (*n* = 29)	2 (*n* = 21)	CI, P
CYP3A5	*3*3 /*1*3 + *1*1	21/8 (72.4%)	7/14 (33.3%)	OR = 5.25; 95% CI: 1.6–17.8; χ^2 = 6.05; *p* = 0.014
CYP2C9*2	*1*2 + *2*2 /*1*1	4/25 (13.8%)	6/15 (28.6%)	OR = 0.40; 95% CI: 0.1–1.7; χ^2 = 0.87; *p* = 0.35
CYP2C9*3	*1*3 /*1*1^	6/23 (21.0%)	4/17 (19.1%)	OR = 1.11; 95% CI: 0.3–4.6; χ^2 = 0.05; *p* = 0.83
BCRP (ABCG2)	CA /AA^^	12/17 (41.4%)	7/14 (33.3%)	OR = 1.41; 95% CI: 0.4–4.6; χ^2 = 0.08; *p* = 0.78
SLCO1B1	CC+TC /TT	9/20 (31.0%)	6/15 (28.6%)	OR = 1.13; 95% CI: 0.3–3.9; χ^2 = 0.02; *p* = 0.90

*^no genotype *3*3, ^^no genotype CC. This may indicate the presence of other metabolic pathways of the hydrophilic rosuvastatin in the liver, unlike the lipophilic simvastatin.*

is well documented that simvastatin is extensively metabolized by both CYP3A4 and CYP3A5 [20].

Since *3 allele expression is accompanied by decreased CYP3A5 activity, this can contribute to the statin-associated concentration increase in blood plasma. In the Kim *et al.* [21] study, the group of healthy Korean volunteers carriers of the CYP3A5 *3*3 genotype demonstrated much higher (3.3 times higher) 12-hour simvastatin exposure in the blood, which was also supported by another study concerning African-Americans [17], although it was not observed in Caucasians. Also, in a number of studies there was found a correlation between carriage of the CYP3A5*3*3 genotype and much higher lipid-lowering efficacy of simvastatin treatment in Caucasian and Chinese patients [22–24].

At the same time, Fiegenbaum *et al.* did not discover any simvastatin-associated efficacy or intolerance in CYP3A5*3 carriers [25]. In other studies, the relation between the cholesterol level lowering effect and carriage of the CYP3A4*22 allele was demonstrated mainly for Caucasian ancestry patients [26], which was supported by the experimental data [27, 28].

Thus, the simvastatin metabolism is combined with effects caused by the CYP3A4 and functional CYP3A5 activities; the existence of such a dual combination partially impairs the clinical effects of the CYP3A5 genetic polymorphism, but in the case of its insufficiency a higher total activity of CYP3A, particularly a more significant role of CYP3A4, is required in subjects [29]. By combining CYP3A4*22 with CYP3A5 alleles *1, *3 and *7 one can obtain a promising biomarker allowing prediction of overall CYP3A activity.

On one hand, the simvastatin-induced adverse muscular side effects observed in this study in the genotype CYP3A5*3*3 carrier ethnic Uzbeks can be explained by the increased exposure of its lactone form in blood plasma [21]. On the other hand, it is known that the solute protein-transporter gene SLCO1B1 (c.521T>C) single nucleotide polymorphism reduces transport activity of OATP1B1, which reduces hepatic uptake of the acid form of simvastatin, which is accompanied by elevation of its concentration in blood plasma and increases myopathy risk at high doses of simvastatin [30, 31].

However, in our study, in the case group along with 13 SAMS cases, the reason for therapy discontinuation in 37 examined patients was simvastatin-induced effects on liver. This may be because an increased content of the lactone of simvastatin in the liver (CYP3A5 *3/*3), as well as increased discharge of lipophilic simvastatin lactone in bile (BCRP CA), may cause cholehepatic shunting and promote lipophilic hepatic drug accumulation [32, 33].

It is well known in cardiology that ursodeoxycholic acid and some new agents [34] contribute to elimination of cholehepatic shunting and decrease of statin-induced side effects.

It should be noted that an analysis of the Swedish Adverse Drug Reaction Advisory Committee found a rate of drug-induced liver injury (DILI) of 1.2 per 100,000 patients on statin treatment [35]. In addition, 30 of 73 patients with DILI were taking atorvastatin (41.1%), 28 (38.4%) simvastatin and 2 (2.7%) rosuvastatin, but atorvastatin and simvastatin were more frequently prescribed than rosuvastatin.

As mentioned above, the EAS Consensus Panel recommends in patients with statin adverse symptoms switching to the second statin after a 2–4-week washout. Additional approaches include the use of intermittent (i.e., non-daily) dosing of a highly efficacious statin or the use of other lipid-lowering medications, including ezetimibe and PCSK9 inhibitors [36–38].

However, unfortunately, the criteria to select the new statin are not well defined. In 2015, the International Lipid Expert Panel stated that 'the risk of myopathy is suggested to be lowest with pravastatin and fluvastatin, possibly because they are more hydrophilic and as a result have

less muscle penetration' [7]. Another possibility could be to change from a P450-dependent to a non-P450-dependent statin [39]. *In vivo* and *in vitro* studies both indicate that metabolism is of little importance in the disposition of rosuvastatin; it has low extrahepatic tissue penetration, low potential for CYP3A interactions and may therefore have some advantages in patients with simvastatin adverse symptoms [40]. Several clinical trials also suggest that alternate-day dosing of rosuvastatin may achieve similar levels of low-density lipoprotein cholesterol (LDL-C) reduction compared to daily dosing and may improve tolerance [36, 41]. The data of our study showed that the positive results of the transfer of patients with simvastatin adverse symptoms to rosuvastatin were mainly observed among the carriers of *3/*3 genotype of the CYP3A5 (6986A>G) gene.

This may indicate the presence of other (non-CYP3A-family) metabolic pathways (CYP2C9, CYP2C19) of the hydrophilic rosuvastatin [42] in the liver unlike the lipophilic simvastatin.

The major limitation of this study is the small number of studied subjects. Further research is needed, which should be carried out on a large number of observations.

Also an obvious limitation of this study, with hindsight, is the method for gathering data, based on the selection of a case group of patients with simvastatin intolerance, whereas this phenomenon is not uniform. Future studies should be planned concentrating on one of the intolerance phenomena-simvastatin-associated muscle (SAMS) or liver symptoms – which will allow more careful analysis of the results to be carried out. However, as it seems to us, the study allowed us to establish the main advantage of rosuvastatin use in simvastatin-intolerant patients: the presence of different (non-CYP3A-family) metabolic pathways.

In conclusion, in a considerable proportion of ethnic Uzbek patients with CAD and simvastatin intolerance symptoms, serious side effects upon switching to a starting dose of rosuvastatin were not observed, and it should be noted that in most cases this phenomenon was observed among carriers of the *3/*3 genotype of the CYP3A5 (6986A> G) gene.

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Conflict of interest

The authors declare no conflict of interest.

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