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PHARMACOGENETICS

Effects of *ABCG2* and *SLCO1B1* gene variants on inflammation markers in patients with hypercholesterolemia and diabetes mellitus treated with rosuvastatin

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Abstract

Purpose Dysregulation of angiogenesis and inflammation play important roles in the development of atherosclerosis. Rosuvastatin (RST) was widely used in atherosclerosis therapy. Genetic variations of transporters may affect the rosuvastatin concentration in plasma and reflect different clinical treatment. The aim of this study was to explore the drug transport related single-nucleotide polymorphisms (SNPs) on RST pharmacokinetic and the further on pro-angiogenic and pro-inflammatory factors.

Methods A total of 269 Chinese patients with hypercholesterolemia and diabetes mellitus were enrolled. They were treated with RST to lower cholesterol. The plasma concentration of RST was determined using a validated UPLC-MS/MS method. Seven single-nucleotide polymorphisms (SNPs) in six genes were genotyped using the Sanger dideoxy DNA sequencing method. The serum concentrations of inflammation markers were determined using ELISA kits.

Results *ABCG2* 421C > A (rs2231142) and *SLCO1B1* 521 T > C (rs4149056) variations were highly associated with plasma concentrations of RST ($P < 0.01$, FDR < 0.05). The serum MCP-1, sVCAM-1, and TNF-α levels were significantly different between the *ABCG2* 421C > A and *SLCO1B1* 521 T > C genetic variation groups ($P < 0.01$). RST concentration was negatively correlated with sVCAM-1 concentration ($r = 0.150$, $P = 0.008$).

Conclusion *ABCG2* 421C > A (rs2231142) and *SLCO1B1* 521 T > C (rs4149056) genetic variants affect RST concentration significantly and potentially affect serum levels of pro-inflammatory and pro-angiogenic markers. The effects on anti-inflammation might not be related to high plasma exposure of RST.

Keywords Gene polymorphism · Rosuvastatin · Anti-inflammation · Plasma concentration · Hypercholesterolemia · Diabetes mellitus

Introduction

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are the most relevant drugs used to lower serum cholesterol levels [1]. They are highly effective in the prevention of cardiovascular events in atherosclerosis therapy [2]. Rosuvastatin (RST) is one of the most globally popular cholesterol-reducing drugs. It is used for atherosclerotic plaque stability, angiogenesis, and anti-inflammation [3, 4]. Genetic variant on transporters may influence the RST exposure in body and further on clinical results.

In previous studies, the anti-inflammatory effect of RST has been reported to reduce the activation of the mevalonate pathway by inhibiting HMG-CoA reductase [5]. Statins reduced the isoprenylated and geranylgeranylated protein levels, and in particular prenylated Ras level. The statin-induced Ras inhibition reduces the activity of the transcription factor nuclear factor kappa B (NF-kB) [6]. Some studies have indicated that statin therapy leads to suppression of NF-kB activity with further decrease in pro-inflammatory cytokines. Others have reported that statins decrease IL-6 and TNF-α

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production in monocytes of patients with hypercholesterolemia [7].

Atherosclerosis is responsible for several important adverse vascular events. Recent research has indicated that atherosclerosis might be associated with disregulation of neovascularization in diabetes [8, 9]. In patients with diabetes mellitus, atherosclerosis, which accounts for most cardiovascular morbidity and mortality, influences the disregulation of angiogenesis [10]. The serum levels of pro-angiogenic molecules such as MCP-1 and VCAM-1 are associated with neovascularization and inflammatory factor infiltration [11]. Rosuvastatin might exert anti-angiogenic and anti-inflammation effects by preventing atherosclerotic cardiovascular diseases.

High plasma exposure to RST and genetic factors play crucial roles in cholesterol-reduction and anti-inflammation outcomes. Rosuvastatin is metabolized by isoenzyme CYP2C9, and transporters play an important role in the disposition of RST [12]. Several studies have revealed that *SLCO1B1*, which encodes the OATP1B1 importer contributed to RST passive membrane permeability and the genotype variation exist frequently in East Asians. The ABC cassette transporter gene family including *ABCG2* and *ABCB1* are widely expressed on important physiological barriers [13–16]. The variation in genotype is a potentially crucial heredity factor in the pharmacokinetic of RST. Gene polymorphisms might influence the body's exposure to RST and the concentrations of pro-inflammatory and pro-angiogenic cytokines.

The genotype variation influence on the exposure to RST in Chinese Han people is unclear and the correlation between plasma concentration of RST and serum level of pro-inflammatory and pro-angiogenic cytokines in the course of atherosclerosis and diabetes are still unknown. The present study was designed to evaluate the concentrations of pharmacokinetic-related SNPs and subsequently assessed the angiogenic factors and pro-inflammatory cytokines in patients with hypercholesterolemia and diabetes mellitus.

Materials and methods

Patients

A total of 269 patients with hypercholesterolemia and diabetes mellitus (DM) were recruited between January 2018 and April 2019 from the China-Japan Friendship Hospital. All the patients were treated with RST (AstraZeneca, 10 mg daily) for hypercholesterolemia for more than 4 weeks. Patients' baseline information, including demographics and biochemical measurements were obtained from the database of the hospital. All patients were with Chinese Han population genetic background. The study was approved by the Bioethical Committee of China-Japan Friendship Hospital and all the participants gave informed consent.

Hypercholesterolemia and diabetes mellitus were diagnosed according to the criteria of The American Diabetes Association (2014) and The European Society of Cardiology (ESC) (2013). The exclusion criteria were as follows: 1) RST combined with other statins for treatment or pretreated with other statins in 2 weeks; 2) age ≥ 80 years; 3) kidney and renal insufficiency (defined as serum CREA concentration is thrice greater than 345 μmol/L; serum alanine aminotransferase (ALT) concentration is thrice greater than 120 U/L; renal transplantation or cirrhosis diagnosis); and 4) inflammatory or malignant diseases.

Determination of RST concentration in plasma

Blood samples were collected from each eligible patient in the morning at 10–12 h after dosing RST and stained in EDTA-coated tubes. The plasma and blood cells were separated within 2 h. Centrifugated samples at 3000 rpm for 10 min at 4 °C and stored at −80 °C until further use.

A selective and sensitive ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was established and validated for the simultaneous quantification of RST in human plasma. Liquid–liquid extraction using 600 μL of acetonitrile was adopted to extract RST and the internal standard (IS; RST-d6) from 200 μL of human plasma. The analytes were chromatographically separated using an Acquity UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm) with 0.1% FA in acetonitrile and 1 mM ammonium formate in water. The mobile phase was produced with a gradient of 30%–70% 0.1% FA acetonitrile at a flow rate of 0.3 mL/min. The total run time was 5 min. The mass detection was performed using a Waters Xevo TQ-S triple-quadrupole mass spectrometer with the positive electrospray ionization mode. The mass transitions selected were m/z 481.9 → 258.1 and m/z 487.9 → 264.1 to quantify RST and IS, respectively.

Genotyping

Genomic DNA was mainly isolated from the peripheral blood samples using the TIANamp Blood DNA Kit (TianGen Biotech, Beijing, China). The quality control of DNA was based on the absorbance ratio at A_{260}/A_{280} (1.8–2.0) and the concentration of DNA was determined using Nano Drop 2000. For genotyping, we adopted the Sanger dideoxy DNA sequencing method using the ABI 3730xl-full automatic sequencing instrument (ABI Co; Majorbio Biotechnology Co., Ltd., Beijing, China). Seven genes were detected in our research. *ABCG2* 421A, *SLCO1B1* 521C, *ABCB1* 3435G, *ABCB1* 2677C, *SLCO1B3* 334A, *SLCO2B1* 1457 T and *CYP2C9* 1075C were detected as variant alleles for the respective genes.

Detection of cytokine levels in plasma

The serum concentrations of IL-1β, IL-6, TNF-α, MCP-1, IFN-γ, and sVCAM-1 were measured using the Human ELISA kits (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's instruction.

Statistical analysis

All data analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Categorical data are presented as percentage and continuous variables are expressed as mean ± SD. The genotype frequencies were tested for Hardy–Weinberg equilibrium. Linear regression was used to assess the clinical baseline characteristic up on plasma exposure to RST. A logistic regression analysis was used to assess the effects of the baseline features and genotypes. The results with P values <0.05 were considered statistically significant. A univariate linear regression analysis was performed to assess the correlation of RST concentration with lipid profile and cytokines.

Results

Effects of genotypes on the plasma concentration of RST

In this study, the 269 patients were successfully genotyped. The genotype distribution of the seven SNPs is summarized in Table 1. The frequency distribution of all the SNPs was consistent with Hardy–Weinberg equilibrium. The RST concentration in the plasma of patients with the seven different SNPs ranged from 8.68 ± 4.69 to 16.74 ± 2.77 ng/mL.

The mean concentration of RST was significantly higher in the patients carrying *ABCG2* 421A than in non-carriers of this allele. The effects of this allele remained significant even after being adjusted by the baseline characteristics and FDR ($P = 5.75 \times 10^{-4}$, FDR = 0.0086). For *SLCO1B1*, patients with one or two copies of the variant allele had a significantly high plasma exposure to RST. The significance was found even after multiple testing ($P = 0.001$, FDR = 0.015). These results are listed in Table 1 and Fig. 1.

The gene-dose effect was not observed in the three genotypes of the two SNPs. In addition, plasma exposure to RST in patients with *ABCB1*, *SLCO1B3*, *SLCO2B1* and *CYP2C9* was not significantly different ($P > 0.01$, FDR > 0.05).

Effects of genotypes on plasma cytokine levels

On the basis of genetic variations, the 269 eligible patients were divided into different groups. The patients were divided into *ABCG2* 421A carriers and non-carriers; *SLCO1B1* 521C carriers and non-carriers. The clinical baseline characteristics and group information are summarized in Table 2. There were no significant differences detected in terms of age, sex, BMI, medical history, and drug combinations. The HbA1c, HDL-cholesterol, LDL-cholesterol, and triglyceride serum concentrations among the genetic variation groups were not statistically different.

The cytokine concentrations in the plasma are shown in Table 3. Among the six groups, the serum levels of factors, TNF-α, MCP-1, and sVCAM-1 showed a significant difference in patients carrying *ABCG2* 421A or *SLCO1B1* 521C (Fig. 1). As shown in Table 3, the serum TNF-α level was 7.98 ± 3.13 pg/mL in the *ABCG2* 421AA and *ABCG2* 421 AC groups and 15.11 ± 5.13 pg/mL in the *ABCG2* 421 CC group. The serum MCP-1 level was significantly lower in the *ABCG2* 421AA and AC group compared to *ABCG2* 421CC group (99.39 ± 37.16 vs. 126.44 ± 44.11 pg/mL). The serum sVCAM-1 level was also significantly lower in the *ABCG2* 421AA and AC group compared to *ABCG2* 421CC group (1043.43 ± 249.27 vs. 1194.36 ± 263.95 ng/mL). Patients carrying the *SLCO1B1* 521C allele produced significantly lower serum levels of TNF-α, MCP-1, and sVCAM-1. The serum level of the three factors was 7.27 ± 3.60 pg/mL, 79.92 ± 29.18 pg/mL, and 984.51 ± 183.98 ng/mL in the *SLCO1B1* 521 CC and *SLCO1B1* 521 TC groups and 12.08 ± 5.39 pg/mL, 124.24 ± 44.96 pg/mL, and 1187.08 ± 276.81 ng/mL in the *SLCO1B1* 521TT group, respectively.

The concentration of IL-1β, IL-6, and IFN-γ in the plasma is shown in Table 3. There were no significant differences between the genotype groups.

Correlation analysis

The univariate regression analysis results between RST concentration and lipid profile such as HDL-cholesterol, LDL-cholesterol, and triglyceride serum concentrations and pro-angiogenic and pro-inflammatory factors such as TNF-α, MCP-1, and sVCAM-1 are shown in Fig. 2. No significant correlations were observed between RST concentration and triglyceride, CK, and HbAlc levels. The results show a positive correlation between RST concentration and HDL-cholesterol levels and a negative correlation between RST concentration and LDL-cholesterol levels. A negative correlation between RST concentration and sVCAM-1 level was found between the *ABCG2* and *SLCO1B1* genotype groups ($r = -0.150$, $p = 0.008$ for AC and AA group; $r = -0.171$, $p = 0.003$ for CC group and $r = -0.170$, $p = 0.003$ for TC and CC group; $r = -201$, $p = 0.007$ for TT group, respectively).

Table 1 Genotypes and their effects on the plasma exposure of RST

Gene	SNP	Genotype	n(%)	Plasma RST concentratin		
				(ng/ml per 10 mg)		
				Concentration	P value	FDR
ABCG2	rs2231142	CC	75(27.88)	8.68 ± 4.69	5.75 × 10–4	0.0086
		AC	164(60.67)	12.97 ± 3.66		
		AA	30(11.45)	19.42 ± 4.68		
ABCB1	rs1045642	AA	27(10.04)	13.09 ± 3.16	0.336	0.502
		AG	152(56.51)	9.51 ± 4.68		
		GG	90(33.45)	12.32 ± 5.18		
	rs2032582	AA	77(28.62)	13.21 ± 3.77	0.227	0.382
		AC	152(56.51)	14.88 ± 2.64		
		CC	40(14.87)	10.52 ± 4.10		
SLCO1B1	rs4149056	TT	208(77.32)	8.83 ± 3.49	0.001	0.015
		CT	46(17.10)	15.40 ± 4.18		
		CC	15(5.58)	16.74 ± 2.77		
SLCO1B3	rs4149117	GG	30(11.15)	14.89 ± 4.57	0.25	0.629
		AG	86(31.97)	11.17 ± 4.13		
		AA	153(56.88)	9.73 ± 3.56		
SLCO2B1	rs2306168	CC	167(62.08)	11.44 ± 4.62	0.483	0.626
		CT	82(30.48)	10.34 ± 3.42		
		TT	20(7.44)	9.63 ± 3.73		
CYP2C9	rs1057910	AA	253(94.05)	10.79 ± 4.94	0.437	0.696
		CA + CC	16(5.95)	13.94 ± 3.92		

Discussion

Our study revealed that genotype variation in *ABCG2* 421C > A and *SLCO1B1* 521 T > C were associated with the high systemic exposure to RST. Low dose of RST can reduce serum levels of pro-inflammatory cytokines and a significant difference was among genotype variations. To the best of our knowledge, we identified for the first time the relationship

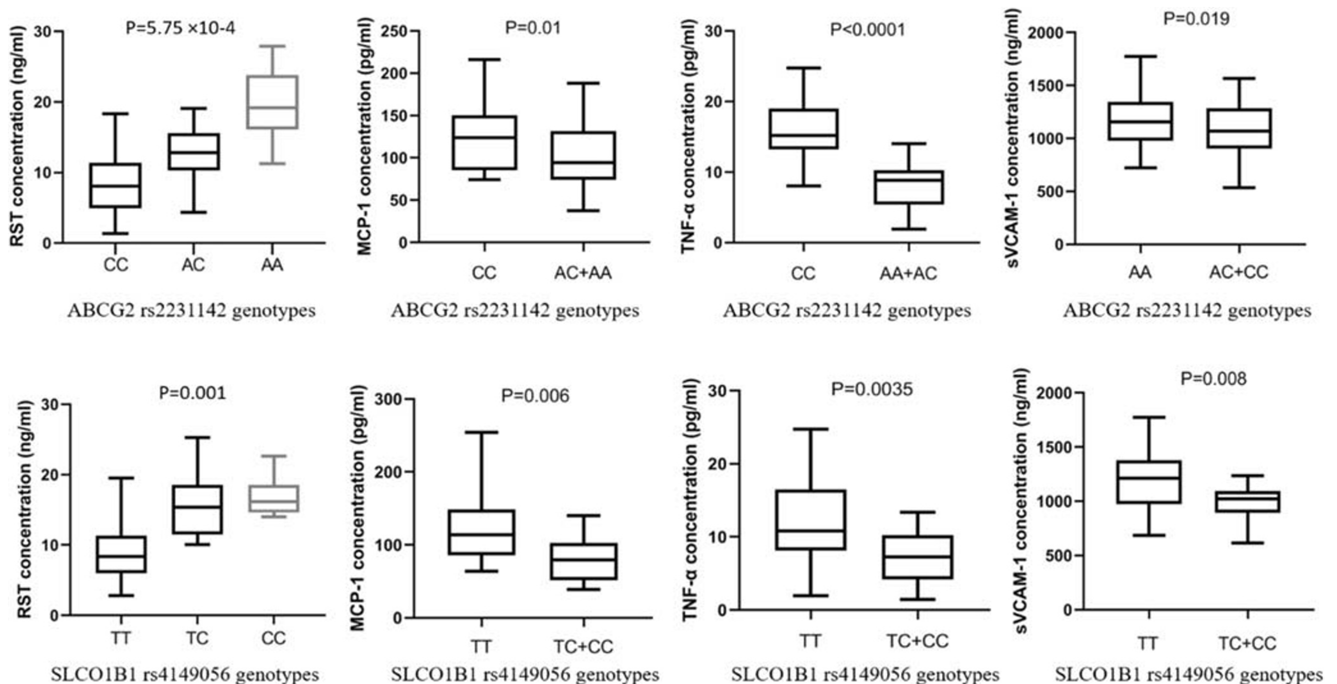

Fig. 1 Genotypes and their effects on the concentration of RST and inflammation markers

Table 2 Patients' characteristics of different groups

Variables		ABCG2 rs2231142 n (%) or mean ± SD		Univariate logistic regression		SLCO1B1 rs4149056 n (%) or mean ± SD		Univariate logistic regression	
				Adjusted OR (95% CI)	P			Adjusted OR (95% CI)	P
Demographic data		AC + AA	CC			TC + CC	TT		
Total no.		194	75			61	208		
Age (year)		63.15 ± 10.31	62.31 ± 11.90	1.033(0.981–1.051)	0.114	64.38 ± 12.01	61.19 ± 10.76	1.021(0.973–1.071)	0.126
Male	Yes	76(39.2)	30(40.0)	0.877(0.172–2.811)	0.215	21(41.2)	85(38.9)	0.893(0.293–2.725)	0.071
BMI (kg/m2)		25.11 ± 5.24	26.42 ± 4.73	0.207(0.185–3.715)	0.317	28.51 ± 5.35	27.92 ± 4.90	0.251(0.155–3.911)	0.288
Medical history									
Hear failure	Yes	100(51.5)	39(52.0)	1.704(0.445–6.928)	0.752	22(43.1)	114(52.3)	1.560(0.233–7.902)	0.611
Hypertension	Yes	53(27.3)	19(25.3)	1.142(0.251–3.111)	0.422	13(25.4)	59(27.1)	1.390(0.205–4.311)	0.505
Arrhythmia	Yes	13(6.7)	7(9.3)	0.582(0.145–2.732)	0.616	3(5.8)	17(7.3)	0.570(0.194–2.021)	0.781
Biochemical measurements									
CRP		4.26 ± 3.98	5.02 ± 3.45	0.948(0.826–1.088)	0.163	2.99 ± 2.17	5.06 ± 4.02	0.781(0.592–1.030)	0.657
HbA1c (%)		6.54 ± 1.16	6.78 ± 1.94	0.900(0.651–1.245)	0.358	6.30 ± 1.06	6.73 ± 1.62	0.986(0.953–1.011)	0.35
GLU		6.78 ± 2.97	6.99 ± 3.69	0.981(0.843–1.140)	0.418	6.04 ± 1.48	7.09 ± 3.58	0.852(0.729–1.053)	0.3
HDL (mmol/L)		1.09 ± 0.31	1.00 ± 0.27	3.027(0.513–7.862)	0.402	1.03 ± 0.19	1.06 ± 0.32	3.744(0.795–8.804)	0.384
LDL (mmol/L)		2.37 ± 1.02	2.19 ± 0.89	1.213(0.715–2.057)	0.882	1.89 ± 0.60	2.40 ± 1.02	1.304(0.730–2.101)	0.845
CHO (mmol/L)		3.99 ± 1.41	3.65 ± 1.10	1.242(0.826–1.867)	0.558	3.46 ± 1.05	3.95 ± 1.34	1.503(0.404–1.922)	0.494
TG (mmol/L)		1.77 ± 1.71	1.55 ± 0.66	1.155(0.733–1.919)	0.813	2.08 ± 2.69	1.56 ± 0.68	1.205(0.839–1.863)	0.844
CK (U/L)		83.18 ± 37.79	84.89 ± 41.97	0.999(0.986–1.012)	0.466	74.21 ± 22.66	86.55 ± 42.51	0.991(0.974–1.008)	0.231
Medication									
Aspirin	Yes	144(74.2)	56(74.6)	1.004(0.345–2.928)	0.493	33(64.7)	167(76.6)	0.611(0.188–1.981)	0.315
Clopidogrel	Yes	104(53.6)	40(53.3)	1.032(0.396–2.686)	0.325	15(29.4)	129(59.2)	0.282(0.087–0.920)	0.522
Metformin	Yes	134(69.1)	38(50.6)	2.225(0.832–5.953)	0.411	28(54.9)	144(66.1)	0.703(0.233–2.121)	0.428
Acarbose	Yes	35(18.0)	29(38.6)	0.667(0.205–2.166)	0.5	9(17.6)	55(25.2)	0.799(0.194–3.283)	0.531

BMI body mass index, *CRP* c-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CHO* cholesterol, *TG* triglyceride, *CK* creatine kinase

between RST concentration and pro-inflammatory cytokines in patients with hypercholesterolemia and diabetes mellitus.

The human *ABCG2* gene belonging to the *ABC* gene family encoded BCRP/ABCG2 protein. BCRP/ABCG2 protein is a key transporter driving the efflux of diverse drugs, leading the drug resistance in target cells and mediating the drug pharmacokinetic and toxicokinetic profiles [14]. ABCG2 plays important physiological roles in limiting drug's absorption, distribution, elimination and excretion. *SLCO1B1* encoded OATP1B1 protein. OATP1B1 is almost exclusively expressed in human hepatocytes. It accepts widely therapeutic drugs, as its substrates, suggesting that OATP1B1 plays a

Table 3 Plasma concentrations of inflammation markers

Inflammation markers	ABCG2 rs2231142			SLCO1B1 rs4149056		
	CC	AA+AC	p value	TT	TC + CC	p value
TNF-a	15.11 ± 5.13	7.98 ± 3.13	4.23 × 10–4	12.08 ± 5.39	7.27 ± 3.60	3.53 × 10–3
MCP-1	126.44 ± 44.11	99.39 ± 37.16	0.01	124.24 ± 44.96	79.92 ± 29.18	0.006
sVCAM-1	1194.36 ± 263.95	1043.43 ± 249.27	0.019	1187.08 ± 276.81	984.51 ± 183.98	0.008
IL-6	4.92 ± 1.54	4.27 ± 1.64	0.087	5.11 ± 1.60	4.98 ± 2.01	0.105
IL-1b	0.58 ± 0.33	0.61 ± 0.27	0.577	0.61 ± 0.37	0.55 ± 0.34	0.611
IFN-γ	19.33 ± 4.19	17.64 ± 5.10	0.433	19.01 ± 4.79	18.81 ± 5.68	0.527

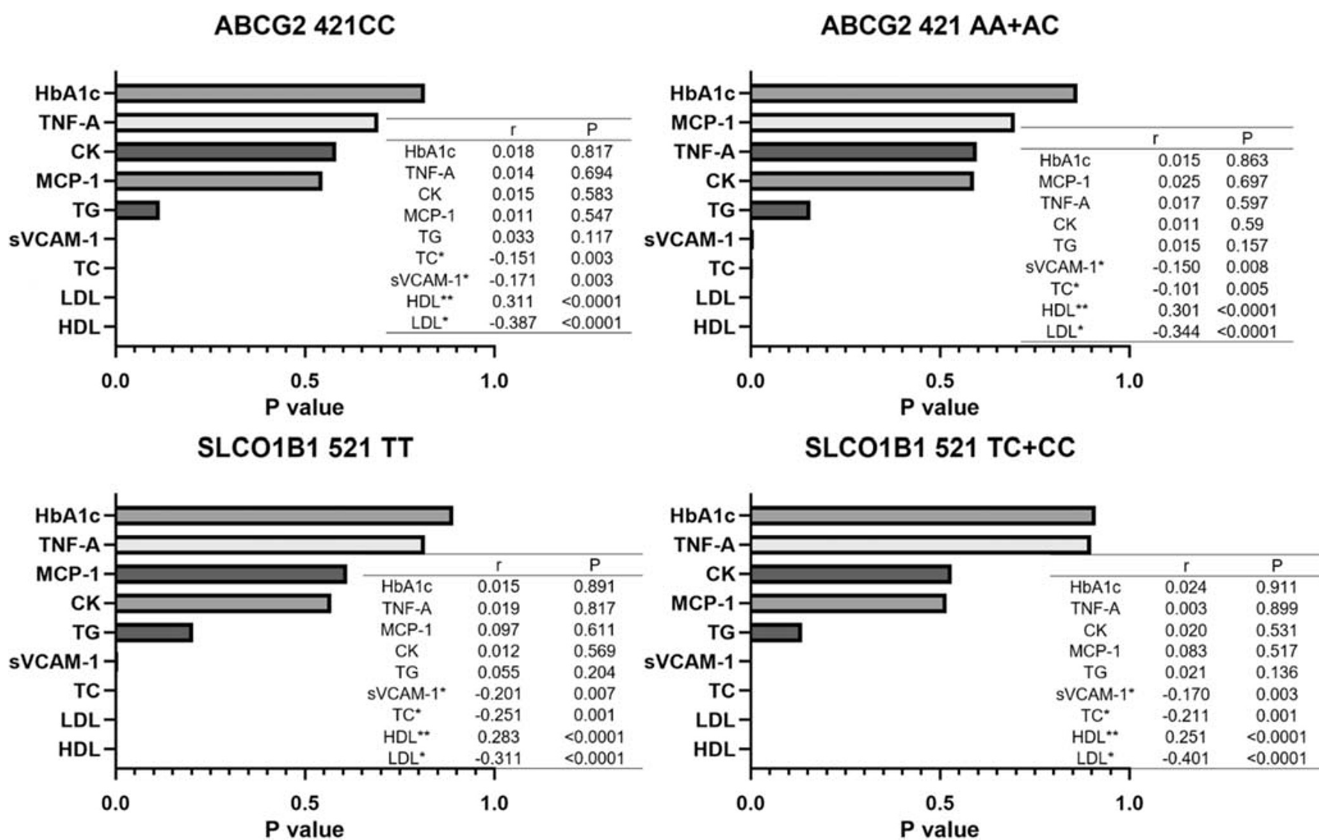

Fig. 2 Correlation between RST concentration and lipid profile and inflammation markers. (**positive correlation; *negative correlation)

crucial role in the hepatic uptake and clearance of these therapeutic drugs [17].

Among all SNPs in our study, the polymorphisms of *ABCG2* 421C > A played important roles in the systemic exposure of RST ($P < 0.01$, FDR < 0.05). The mutation frequency of *ABCG2* 421C > A was obviously higher in East Asians than in Caucasians [18]. The variation in *ABCG2* was proved to be the primary genetic determinant of the pharmacokinetic difference in RST exposure in Chinese population. *SLCO1B1* 521 T > C was significantly correlated with RST-induced myopathy in previous studies [19]. This might be due to the transporters such as OATP1B1 encoded by *SLCO1B1*. In our study, subjects carrying *SLCO1B1* 521C showed significantly higher serum concentrations than those of non-carriers ($P < 0.01$, FDR < 0.05). The transporters were involved in the disposition of RST, and gene polymorphisms played important roles in the pharmacokinetics of RST.

According to the *ABCG2* and *SLCO1B1* genotypes, the patients were divided into different groups in our study. The results proved that the effect of RST on the potent pro-angiogenic factors MCP-1 and sVCAM-1 is different. MCP-1 and sVCAM-1 levels in the serum were significantly lower in patients with hypercholesterolemia and diabetes mellitus carrying the *ABCG2* 421A or *SLCO1B1* 521C alleles than in the non-carriers. Furthermore, in the correlation analysis, positive results were observed between RST concentration and sVCAM-1 level. Previous studies have showed anti-angiogenic effect of statins in patients suffering from inflammation-dependent pathologies, diabetes type 2, and atherosclerosis without current ischemic episodes without hypoxia [20–22]. The pro- and anti-angiogenic effect of statins might be related to the systemic exposure and affected by gene polymorphism.

Atherosclerosis is a chronic inflammatory arterial disease. Statin therapy leads to the suppression of NF-KB activity with a further decrease in pro-inflammatory cytokines [23]. In our study, the TNF-α concentration in the plasma was significantly lower in the *ABCG2* 421A and *SLCO1B1* 521C groups ($P < 0.001$). There were no differences among the genetic variation groups in the IL-6, IL-1b, and IFN-γ concentrations. Statins were found to have an inhibitory effect on the NF-KB signaling pathway. They effectively suppress NF-KB activity and inflammatory pathways to decrease inflammation in the vascular and non-vascular systems [6]. According to our results, significant differences were observed in the TNF-α concentration among the genotype variants, while the correlation between RST concentration and pro-inflammatory factor serum levels was not detected. These results indicated that the gene polymorphisms of *ABCG2* 421C > A and *SLCO1B1* 521 T > C influence on serum cytokine levels may be not relate to RST concentration singly. Genetic variants and other baseline characteristics (such as physician disease and

inflammation response) may affect the anti-inflammation of RST multiplicate.

There is overwhelming evidence that inflammation and angiogenic markers such as MCP-1, sVCAM-1, IL-1b, TNF-, IL-6, and IFN-γ play a critical role in the development of atherosclerosis. In patients with type 2 diabetes, they are produced at high levels with acute coronary syndrome. It could be associated with increased risk of atherosclerosis development in patients with diabetes [24, 25]. Gene polymorphisms affect the pharmacokinetic and metabolism profiles of RST. The correlation between RST concentration and inflammation markers was only observed for sVCAM-1. The effect of gene polymorphism on RST anti-inflammation should be validated by future studies in a large sample.

Conclusions

Gene polymorphisms of *ABCG2* 421C > A (rs2231142) and *SLCO1B1* 521 T > C (rs4149056) affect RST concentration significantly and potentially affect the serum levels of pro-inflammatory and pro-angiogenic markers in patients with hypercholesterolemia and diabetes mellitus treated with RST. The genotype effects on anti-inflammation were not related to the high plasma exposure of RST. These findings offer further insight into the anti-inflammatory mechanism of RST.

Author contributions DZ: analyzed data and wrote the manuscript. YMD, XXW, WYX, WWD and WQC: contributed to the development, interpretation of results. XLZ and PML revision of the manuscript.

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Compliance with ethical standards The protocol for study was approved by the Bioethical Committee of China-Japan Friendship Hospital and all the participants gave informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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