The farnesoid X receptor -1G>T polymorphism influences the lipid response to rosuvastatin

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Abstract The bile acid-activated nuclear receptor farnesoid X receptor (FXR) plays an important role in lipid and glucose metabolism, and in addition, it regulates multiple drug transporters involved in statin disposition. We examined whether a functional single nucleotide polymorphism (SNP) in FXR (-1G>T) influenced the lipid-lowering effect of rosuvastatin. In 385 Chinese patients with hyperlipidemia who had been treated with rosuvastatin 10 mg daily for at least 4 weeks, the association between the FXR -1G>T SNP and lipid response to rosuvastatin was analyzed. The FXR -1G>T SNP was not associated with baseline lipids but was significantly associated with the LDL cholesterol (LDL-C) and total cholesterol response to rosuvastatin. Carriers of the T-variant allele (GT + TT = 68 + 3) had 4.4% (95% CI: 1.2, 7.5%, P = 0.006) and 2.6% (95% CI: 0.3, 5.0%; P < 0.05) greater reductions in LDL-C and total cholesterol, respectively, compared with those with homozygous wild-type alleles. The association between the FXR polymorphism and the LDL-C response to rosuvastatin remained significant after adjusting for other covariants. This association of the variant allele of the FXR -1G>T polymorphism with a greater LDL-C response to rosuvastatin may suggest that this polymorphism influences the expression of the hepatic efflux transporters involved in biliary excretion of rosuvastatin.—Hu, M., S. S. H. Lui, L-S. Tam, E. K. Li, and B. Tomlinson. The farnesoid X receptor -1G>T polymorphism influences the lipid response to rosuvastatin. J. Lipid Res. 2012. 53: 1384–1389.

Supplementary key words dyslipidemias • genetics • nuclear receptors/FXR • statins • transport

The farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily, which is activated by bile acids. Activation of FXR leads to altered expression of many genes responsible for bile acid and lipid and glucose metabolism and transport, resulting in decreased intracellular bile acid concentrations and reduced plasma glucose and triglyceride levels (1, 2). Current evidence suggests that FXR activation is beneficial in situations of energy excess, such as obesity and diabetes, and FXR agonists are being evaluated in preclinical studies for treating diabetes and metabolic disorders (2, 3). Although FXR functions as a bile acid receptor, studies have identified that FXR also regulates multiple drug metabolizing enzyme or drug transporter genes by binding to FXR response elements and promoting transcription of target genes, suggesting that FXR may play an important role in determining the pharmacokinetics and pharmacodynamics of numerous drugs (4).

Recent pharmacogenetic studies have demonstrated that drug transporters, in particular the solute carrier organic anion transporter family, member 1B1 (SLCO1B1) and ATP-binding cassette, subfamily G, member 2 (ABCG2), play an important role in determining the pharmacokinetics and pharmacodynamics of statins (5–7). It is known that the tissue protein expression of drug transporters is highly variable between individuals and that these interindividual variations in transporter expression may result in variabilities in lipid response to statins (4).

Loss of function single nucleotide polymorphisms (SNP) in the coding region of the SLCO1B1 and ABCG2 genes were associated with altered statin exposure and lipid-lowering effects (5–7), but these SNPs did not appear to affect overall protein expression (4, 8). Instead, the decreased transport activity of SLCO1B1 and ABCG2 associated with these SNPs is thought to result from membrane-trafficking defects (4, 9, 10).

FXR regulates several drug transporters involved in statin disposition, including SLCO1B1, SLCO1B3, sodium-taurocholate cotransporting polypeptide (NTCP), and

Abbreviations: BMI, body mass index; CAR, constitutive androgen receptor; CHD, coronary heart disease; FH, familial hypercholesterolemia; FXR, farnesoid X receptor; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NTCP, sodium-taurocholate cotransporting polypeptide; PXR, pregnane X receptor; SLC, solute organic anion transporter family, member 1B1; SNP, single nucleotide polymorphism.

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3The online version of this article (available at http://www.jlr.org) contains supplementary data in the form of two tables.

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certain efflux transporters (4, 8, 11–13). It has been reported that a common noncoding SNP resulting in a G-IT (*1B) substitution in the nucleotide adjacent to the translation initiation site of FXR was associated with significantly reduced function in vitro (14) and probably resulted from decreased translational efficiency (15). Gene expression analysis showed that livers carrying one copy of the variant allele had significantly decreased expression of hepatic FXR target genes, including small heterodimer partner (SHP), SLCO1B1, and SLCO1B3 (14). This polymorphism is relatively common among some populations, with a prevalence of 2.5% in Europeans, 3.2% in Africans, and 12.1% in Chinese. However, there is no study to report whether the FXR-1G>T polymorphism relates to interindividual or interethnic differences in the pharmacokinetics and pharmacodynamics of the substrate drugs of these transporters.

Rosuvastatin undergoes little metabolism, but it is a substrate of a number of drug transporters, including the uptake transporters SLCO1B1, SLCO1B3, SLCO2B1, SLCO1A2, and NTCP and the efflux transporters ABCG2 and ABCC2 (16–18). Early studies showed that loss-of-function SNPs in SLCO1B1 and ABCG2 were significantly associated with increased systemic drug exposure to rosuvastatin (6). Our previous study in Chinese patients with hypercholesterolemia also showed that the ABCG2 421C>A polymorphism was significantly associated with the lipid-lowering effect of rosuvastatin (19, 20). Given the importance of the FXR in lipid metabolism and in regulating the expression of the drug transporter genes that are involved in rosuvastatin disposition, we examined the association between the functional SNP FXR-1G>T and the lipid response to rosuvastatin in Chinese patients with hypercholesterolemia.

METHODS

Study population and design

Patients included in this analysis were Hong Kong Han Chinese patients with hypercholesterolemia, who had been involved in the pharmacogenetic analysis of the lipid response to rosuvastatin as described previously (19, 20). In brief, patients ages ≥18 years with baseline LDL cholesterol (LDL-C) ≥2.6 mmol/L were included if they were considered at increased risk of cardiovascular disease because of a history of coronary heart disease (CHD), other clinical evidence of atherosclerosis, diabetes mellitus, calculated 10-year CHD risk score >20% (21), or clinically diagnosed with familial hypercholesterolemia (FH) (22). A small group of patients with rheumatoid arthritis (n = 36) who had participated in a double-blind, placebo-controlled, randomized study to assess the effect of rosuvastatin 10 mg on carotid intima-media thickness and pulse wave velocity (ClinicalTrials.gov NCT00555230) were also included.

Individuals with poorly controlled hypo/hyperthyroidism, diabetes, hypertension, a history of statin intolerance, significant renal impairment, hepatic dysfunction, or unexplained high (>3 ULN) serum creatine kinase, or who had experienced a cardiovascular event within the three months before recruitment, or who were taking other drugs known to modify plasma lipids or to have an interaction with rosuvastatin (corticosteroids, cyclosporine, etc.) were excluded from this study.

All patients were treated with a single lipid-lowering therapy of rosuvastatin 10 mg per day for at least four weeks (median duration of treatment was six weeks), and drug compliance was assessed at study visit by tablet counting. Subjects with poor adherence (reported or calculated taking <80% of the prescribed number of tablets) were excluded from the analysis. The study was approved by the local Clinical Research Ethics Committee and was performed in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Laboratory tests

Fasting blood samples before and after at least four weeks of treatment with rosuvastatin 10 mg daily were collected for the measurement of lipid profiles and laboratory safety data, including serum alanine aminotransferase, creatine kinase, and creatinine. LDL-C concentrations were calculated according to the Friedewald formula or directly measured if the triglyceride level was greater than 4.5 mmol/L (23). All biochemistry tests were performed by standard methods in the Chemical Pathology Laboratory, Prince of Wales Hospital, which has international laboratory accreditation.

Genotyping

The FXR-1G>T polymorphism (rs56163822) was genotyped by using Taqman genotyping assay (C_25598386_10) on the ABI GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA) with reactions performed according to manufacturer’s instructions. The SNPs 421C>A in ABCG2 and 521T>C in SLCO1B1 were genotyped as described previously (19, 20).

Statistical analysis

Differences in baseline characteristics and lipid responses to rosuvastatin between the FXR-1G>T genotype groups were assessed using Student t-test for normally distributed variables or Mann-Whitney test for skewed variables. The degree of skewness of the variables was assessed by the Kolmogorov-Smirnov normality test and the Normal Q-Q plot. χ² tests were used to test Hardy-Weinberg equilibrium and comparisons for categorical variables. ANCOVA was performed to determine the effect of the FXR-1G>T polymorphism on the lipid responses to rosuvastatin after adjusting for confounding factors. The effects of the FXR and ABCG2 genotypes on LDL-C response to rosuvastatin were analyzed by ANOVA, followed by the posthoc Fisher’s least significant difference test. P < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

In 386 patients with good adherence to rosuvastatin, genotyping of FXR-1G>T SNP was successful in 385 subjects. Of these patients, 314 had GG genotype, 68 were heterozygous, and 3 were homozygous for the T-variant alleles. The frequency of the T-variant allele was 9.9%, and the genotype distribution was in Hardy-Weinberg equilibrium (P > 0.05). The data of the GT and TT genotype groups were combined due to the small number of the homozygous TT subjects for comparison with those who were homozygous for the G wild-type allele.

The baseline characteristics of the study subjects stratified by the FXR-1G>T genotype groups are shown in Table 1. There were no significant differences in the baseline characteristics, except for body mass index (BMI,
Subjects with one or two copies of the T-variant allele (n = 71) had 4.4% (95% CI: 1.2, 7.5%) and 2.6% (95% CI: 0.3, 5.0%) greater reductions in LDL-C and total cholesterol, respectively, compared with those with homozygous wild-type alleles. The three subjects who were homozygous for the wild-type alleles (n = 43) had 5.0% (95% CI: 1.2, 7.5%) versus 57.8% (P = 0.023) between the two genotype groups (Table 1). Subjects with one or two copies of the T-variant allele had a higher BMI than those with GG genotype, but the differences in waist circumference and body fat were not statistically significant between the two groups. Further subgroup analysis showed that the significant association between the FXR-1G>T genotype and BMI was found only in females and not in males (supplementary Table 1).

There were significant differences in the percentage reductions in LDL-C (P = 0.006) and total cholesterol (P = 0.026) between the FXR-1G>T genotype groups (Table 2). Subjects with one or two copies of the T-variant allele (n = 71) had 4.4% (95% CI: 1.2, 7.5%) and 2.6% (95% CI: 0.3, 5.0%) greater reductions in LDL-C and total cholesterol, respectively, compared with those with homozygous wild-type alleles. The three subjects who were homozygous for TT appeared to have the greatest LDL-C response to rosuvastatin, whereas the heterozygotes had intermediate responses, which were significantly different from those in homozygotes for the wild-type alleles (Fig. 1). The differences in LDL-C response to rosuvastatin between the genotype groups remained significant after adjustment for age, gender, BMI, having FH, and the SLCO1B1 521T>C and ABCG2 421C>A polymorphisms, which may potentially confound the results [GG versus GT+TT = -51.3% (-52.6, -49.9%) versus -55.0% (-57.8, -52.2%), P = 0.021].

As the ABCG2 421C>A polymorphism had a significant effect on the LDL-C response to rosuvastatin in this group of patients as shown previously (19, 20), further analyses were carried out to adjust for its effect. There were significant differences (P < 2 × 10^{-6}) in LDL-C response among the four groups stratified according to the FXR-1G>T and the ABCG2 421C>A polymorphisms (Fig. 2). Subjects homozygous for the wild-type alleles of the FXR-1G>T and the ABCG2 421C>A polymorphisms (FXR-1GG / ABCG2 421CC) had the smallest reduction in LDL-C, those with variant alleles of these two SNPs had the greatest LDL-C reduction, and those with mutations in one of the two SNPs had intermediate values. The difference in LDL-C response to rosuvastatin between subjects with FXR-1GG versus -1GT/TT was significant in subjects with the ABCG2 421CC genotype but not for those with one or two copies of the ABCG2 421A variant allele (Fig. 2).

**DISCUSSION**

It has been proposed that variants in regulatory protein coding genes, such as FXR, may contribute to the overall variation of drug transporter expression in tissues and thereby influence drug disposition and responses (4, 24). This study is the first to report that the common polymorphism (-1G>T) in FXR resulting in significantly reduced function of the gene was associated with a greater LDL-C response to rosuvastatin in Chinese patients with hypercholesterolemia and that this association remained significant after adjusting for the potential confounding factors.

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**TABLE 1.** Baseline characteristics of the study subjects stratified by the FXR-1G>T genotype

| Characteristic | GG (n = 314) | GT/TT (n = 68/3) | P      |
|---------------|-------------|-----------------|--------|
| Age, years    | 55.5 ± 11.5 | 56.7 ± 11.2     | 0.412  |
| Male, n (%)   | 143 (45.5)  | 30 (42.3)       | 0.615  |
| Body weight, kg| 64.4 ± 13.5 | 65.8 ± 13.2     | 0.429  |
| Body mass index, kg/m² | 25.0 ± 4.1 | 26.2 ± 4.3     | 0.023  |
| Waist circumference, cm | 86.3 ± 11.3 | 88.0 ± 12.2 | 0.273  |
| Body fat, %   | 29.6 ± 8.2  | 31.2 ± 9.8      | 0.271  |
| FH, n (%)     | 138 (43.9)  | 28 (39.4)       | 0.488  |
| Hypertension, n| 150 (47.8)  | 41 (57.7)       | 0.129  |
| Type 2 diabetes, n | 90 (28.7)  | 19 (26.8)    | 0.748  |
| History of CVD, n | 45 (14.3)  | 10 (14.1)      | 0.957  |
| Total cholesterol, mmol/l | 7.49 ± 1.75 | 7.56 ± 1.94 | 0.744  |
| LDL-C, mmol/l  | 5.13 ± 1.66 | 5.21 ± 1.87     | 0.718  |
| Triglycerides, mmol/l | 1.99 ± 1.08 | 2.05 ± 2.09 | 0.300  |
| HDL-C, mmol/l  | 1.51 ± 0.39 | 1.52 ± 0.44     | 0.905  |
| ABCG2 421C>A   |            |                 |        |
| CC             | 159         | 35              |        |
| CA             | 112         | 24              | 0.781  |
| AA             | 43          | 12              |        |
| SLCO1B1 521T>C |            |                 |        |
| TT             | 230         | 57              |        |
| TC             | 70          | 13              | 0.086  |
| CC             | 10          | 0               |        |

Data is given as mean (95% CI).

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**TABLE 2.** Lipid response to rosuvastatin 10 mg stratified by the FXR-1G>T genotype

|                | GG (n = 314) | GT/TT (n = 68/3) | Difference in Change | P      |
|----------------|-------------|-----------------|----------------------|--------|
| % Change in total cholesterol | -37.2 (-38.2, -36.2) | -39.9 (-41.8, -37.9) | -2.6 (-0.3, -5.0) | 0.026  |
| % Change in LDL-C     | -51.0 (-52.4, -49.6) | -55.4 (-57.8, -53.0) | -4.4 (-1.2, -7.5) | 0.006  |
| % Change in triglycerides | -19.8 (-23.6, -16.0) | -17.4 (-24.5, -10.4) | -2.4 (-6.3, 11.1) | 0.214  |
| % Change in HDL-C     | 1.46 (0.04, 2.89) | 2.29 (-1.37, 5.78) | 0.74 (-2.69, 4.18) | 0.672  |
It has been shown that the T-variant allele of the FXR -1G>T was associated with reduced mRNA expression of \( SLCO1B1 \) (14), but the result of the present study suggests that the association of the FXR polymorphism and statin response is mediated by transporters other than SLCO1B1, as reduced expression of \( SLCO1B1 \) is expected to be associated with a reduced LDL-C response to statins as shown previously (25). The functional SNP 521T>C in \( SLCO1B1 \) is associated with decreased transport activity of SLCO1B1 and is consequently associated with increased systemic exposure to rosuvastatin (26), but it did not influence the lipid response to rosuvastatin significantly in our study subjects (supplementary Table II) (19). It has been proposed that the \( SLCO1B1 \) polymorphism may affect the systemic exposure to substrate drugs but may only have a minor influence on liver exposure, as observed with rifampin (27, 28). This probably explains the lack of association between the \( SLCO1B1 \) polymorphism and the lipid response to rosuvastatin, as liver exposure would determine the lipid-lowering effect of statins.

Rosuvastatin is excreted mostly unchanged into the bile; therefore, interactions with hepatic apical efflux transporters may influence its lipid-lowering efficacy in the liver. There is convincing evidence showing that human ABCG2 is the major determinant of the pharmacokinetics and lipid-lowering effect of rosuvastatin (5). In addition, it has been suggested that another efflux transporter, ABCC2, is involved in the biliary excretion of rosuvastatin in humans (18), whereas animal studies in rats identified a possible role of bile acid export pump (Bsep) in the biliary clearance of rosuvastatin (29). It is known that \( ABCC2 \) (11) and \( BSEP \) (30) are both regulated by FXR. The mutation -1G>T in FXR may result in reduced function of these efflux transporters and thus reduced biliary clearance of rosuvastatin, which is in line with the greater LDL-C response in subjects with the variant allele of -1G>T in this study.

To our knowledge, there is no study reporting whether the gene for ABCG2, the major efflux transporter of rosuvastatin, is a target of FXR, but indirect evidence suggests that hepatic ABCG2 expression is regulated by some nuclear receptors, such as constitutive androstane receptor (CAR) and pregnane X receptor (PXR) (31), and the latter is a target of FXR (32). Therefore, it is possible that the reduced FXR activity due to the -1G>T mutation may reduce the ABCG2 expression via effects on PXR. Given the strong association between the \( ABCC2 \) 421C>A polymorphism and the LDL-C response to rosuvastatin, we further evaluated the effect of the \( FXR \)-1G>T polymorphism in subgroups of patients stratified by the \( ABCC2 \) 421C>A genotype. It appears that the association between the \( FXR \)-1G>T polymorphism and the LDL-C response to rosuvastatin is more evident in subjects homozygous for the wild-type alleles than in those with one or two copies of the variant allele of the \( ABCC2 \) 421C>A polymorphism. This result may suggest that the effect of the \( FXR \) polymorphism...
on the lipid-lowering effect of rosuvastatin is mediated through a regulatory effect on ABCG2 expression, but this idea needs to be further investigated.

FXR plays an important role in maintaining bile acid, lipid, and glucose homeostasis, and it is a key regulator of whole-body energy metabolism (1, 2). Deficiency of FXR in mice results in increases in systemic and hepatic HDL cholesterol (HDL-C) and triglyceride concentrations (33), whereas activation of FXR by synthetic FXR agonists reduces plasma triglyceride and HDL-C levels (34–36). In this study, the FXR -1G>T polymorphism was not associated with baseline lipid levels, but a potential influence of this polymorphism on the lipid metabolism pathways, which may influence statin pharmacodynamics and thereby the lipid-lowering effect of rosuvastatin, cannot be excluded. In this study, female but not male subjects with the FXR -1T-variant allele had higher BMI than those homozygous for the wild-type alleles. The association between the FXR -1G>T polymorphism and obesity in females is probably related to the reduced energy metabolism induced by the reduced function of FXR in subjects with the variant allele (2).

It is also noteworthy that a recent in vitro study suggested that statins could activate some nuclear receptors, including PXR, CAR and FXR, in a dose-dependent and concentration-dependent manner (28). It is also important to note that statins could activate some nuclear receptors, including PXR, CAR and FXR, in a dose-dependent and concentration-dependent manner (28). In this study, female but not male subjects with the FXR -1T-variant allele had higher BMI than those homozygous for the wild-type alleles. The association between the FXR -1G>T polymorphism and obesity in females is probably related to the reduced energy metabolism induced by the reduced function of FXR in subjects with the variant allele (2).

In conclusion, this study showed that the variant allele of the common FXR -1G>T polymorphism was significantly associated with a greater LDL-C response to rosuvastatin in Chinese patients with hypercholesterolemia. The association is probably through the influence of the FXR -1G>T polymorphism on the expression of the efflux transporters that determine the hepatic exposure to rosuvastatin, but a potential effect of this polymorphism on lipid metabolism/pharmacodynamic pathways of rosuvastatin cannot be excluded.

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