Eltrombopag increases plasma rosuvastatin exposure in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- OATP1B1 is important for hepatic uptake of rosuvastatin and BCRP is important for rosuvastatin absorption and elimination. Eltrombopag inhibits OATP1B1 and BCRP *in vitro* at clinically relevant concentrations. Inhibition of these transporters could change cholesterol-lowering efficacy and increase the risk of exposure-dependent toxicities. To determine if co-administration of eltrombopag with rosuvastatin alters plasma rosuvastatin exposure, an open-label study was conducted in 42 healthy adult subjects.

WHAT THIS STUDY ADDS

- Concomitant administration of eltrombopag with rosuvastatin was associated with increased rosuvastatin exposure via inhibition of drug transporters. The therapeutic index of HMG Co-A reductase inhibitors may be reduced by the concomitant use of eltrombopag. In subjects taking eltrombopag, a reduced dose of HMG Co-A reductase inhibitors may be needed.

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AIM

Eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist, inhibits the organic anion transporting polypeptide 1B1 (OATP1B1) and breast cancer resistance protein (BCRP) *in vitro*. OATP1B1 is important for hepatic uptake of rosuvastatin and inhibition of this transporter could reduce cholesterol-lowering efficacy and increase the risk of exposure-dependent toxicities. In contrast, BCRP is an efflux transporter and inhibition of this transporter could increase both hepatic and plasma rosuvastatin concentrations, resulting in increased efficacy and toxicity. To determine if co-administration of eltrombopag with rosuvastatin alters plasma rosuvastatin exposure, an open-label study was conducted in 42 healthy adult subjects.

METHODS

Subjects received rosuvastatin and eltrombopag orally: day 1, rosuvastatin 10 mg single dose; days 6 to 9, eltrombopag 75 mg once daily; day 10, eltrombopag 75 mg once daily and rosuvastatin 10 mg single dose. Adverse event assessments were performed daily and at the follow-up visit. Plasma samples for pharmacokinetic analysis were collected days 1 to 5 and days 10 to 14.

RESULTS

Co-administration of eltrombopag with rosuvastatin increased geometric mean (90% confidence interval) plasma rosuvastatin AUC(0,∞) by 55% (42%, 69%) and C_{max} by 103% (82%, 126%) in the overall study population, with a larger interaction in the non-Asian compared with Asian subjects.

CONCLUSIONS

Concomitant administration of eltrombopag with rosuvastatin was associated with increased rosuvastatin exposure. The therapeutic index of HMG Co-A reductase inhibitors may be reduced by the concomitant use of eltrombopag. In subjects taking eltrombopag, a reduced dose of HMG Co-A reductase inhibitors may be needed.

Introduction

Eltrombopag (GlaxoSmithKline) is an oral, nonpeptide thrombopoietin receptor agonist approved for the treatment of chronic immune thrombocytopenia (ITP). It is also being investigated for the treatment of thrombocytopenia due to other aetiologies including chronic liver disease and hepatitis C virus [1–3]. Eltrombopag binds to the transmembrane domain of the thrombopoietin receptor and increases platelet counts by stimulating proliferation and differentiation of megakaryocytes [4].

In preclinical studies, eltrombopag inhibited the organic anion transporting polypeptide 1B1 (OATP1B1) and breast cancer resistance protein (BCRP). Eltrombopag was also identified as a BCRP substrate *in vitro*. OATP1B1 is highly expressed in the liver and involved in the hepatic uptake of all HMG-CoA reductase inhibitors (statins) [5]. OATP1B1 is important for rosuvastatin disposition as demonstrated by genetic polymorphism, where subjects with the homozygous OATP1B1 (*SLCO1B1*) c.521CC genotype had 65% higher rosuvastatin mean area under the curve (AUC(0,48 h)) than those with the homozygous c.521TT (control) genotype [6]. The OATP1B1 (*SLCO1B1*) c.388GG genotype in combination with the c.521CC genotype (*SLCO1B1**15/*15) has also been associated with higher plasma rosuvastatin exposure [7]. BCRP is an efflux transporter that transports drugs from the liver into bile and also limits intestinal drug absorption. BCRP is important for rosuvastatin disposition as demonstrated by genetic polymorphism, where subjects with the heterozygous BCRP (*ABCG2*) c.421CA or homozygous c.421AA genotypes had approximately two-fold the rosuvastatin AUC(0,∞) compared with those with the homozygous c.421CC (control) genotype [8, 9]. The *ABCG2* c.421AA genotype was associated with greater reductions in low-density lipoprotein (LDL) cholesterol in subjects receiving rosuvastatin therapy [10].

Rosuvastatin has known transporter-mediated drug interactions, such as its interaction with gemfibrozil and cyclosporin [11, 12]. The objective of this study was to evaluate the impact of eltrombopag on plasma rosuvastatin exposure.

Methods

Study design

An open-label, single sequence study was conducted at clinical research sites in Singapore and the United States in 42 healthy adult men and women. All subjects provided written, informed consent. Subjects received rosuvastatin and eltrombopag orally in the following sequence: day 1, rosuvastatin 10 mg single dose; day 6 through day 9, eltrombopag 75 mg once daily; day 10, eltrombopag 75 mg once daily and rosuvastatin 10 mg single dose. This study was designed and monitored in accordance with

Good Clinical Practice and the Declaration of Helsinki. The individual Institutional Review Boards at each study site approved the protocol before the study started.

To ensure treatment compliance and continuous safety monitoring, subjects received all doses of study drugs at the clinical research centre and remained in the clinical research unit from day –1 through day 5 and from days 10 through 14. Subjects returned for a follow-up visit approximately 7 to 14 days after the last dose of study medication. The duration of each individual's participation in the study from initial screening to follow-up was approximately 4 weeks.

Inclusion criteria required that participants be healthy. Male and non-pregnant female subjects 18 to 64 years weighing at least 50 kg for men and 45 kg for women were eligible for enrolment. Candidates were ineligible if they had any clinically relevant abnormality identified by prestudy screening history, physical examination, or laboratory testing, including electrocardiogram (ECG) abnormalities, cardiovascular or coagulation disorders, evidence of drug or alcohol abuse or tobacco use, a positive test for HIV, hepatitis B or hepatitis C virus, or use of prescription or non-prescription medications within 7 days (14 days for enzyme-inducing drugs) before receiving the first dose of study drug.

Adverse event (AE) assessments were performed daily for the duration of the study and at the follow-up visit. Standard meals were provided on study day –1 to day 5 and days 10 to 14. Participants fasted 8 h before and 4 h after administration of either study drug. Serial 3 ml blood samples for pharmacokinetic (PK) analysis were collected prior to and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84 and 96 h after single dose rosuvastatin administration on days 1 and 10. A blood sample was obtained on day –1 for the purpose of genotyping the OATP1B1 (*SLCO1B1*), BCRP (*ABCG2*) and NTCP [sodium taurocholate co-transporting polypeptide (*SLC10A1*)] transporters.

Analyses

Genotyping for polymorphisms in OATP1B1 (*SLCO1B1*) T521C and A388G and BCRP (*ABCG2*) C421A and NTCP (*SLC10A1*) exon 3 *3 and exon 4 *2, *4, and *5 was done. Regions spanning the single nucleotide polymorphisms (SNPs) of interest were first amplified from genomic DNA via polymerase chain reaction (PCR) using specific primers as presented in Table 1. PCR product sizes and purity were confirmed by agarose gel electrophoresis against a 100 base pair (bp) molecular weight marker.

For OATP1B1 (*SLCO1B1*) T521C and A388G, and NTCP (*SLC10A1*) exon 3 *3 and exon 4 *2, *4, and *5, the amplified fragments were subsequently analyzed by bidirectional sequencing using Bigdye V3.1 termination cycle sequencing kit (Applied Biosystems, Foster City, CA) on an ABI Avant 3100 genetic analyzer (Applied Biosystems). All polymorphisms were called using mutation analysis software

Table 1

Primer sequences

Primer name	Primer sequences (5'-3')	SNPs	Product size (bp)
OATP1B1 exon 5F	ggcgcaataaagggaata	A388G	386
OATP1B1 exon 5R	ttaatggcggaactgtga		
OATP1B1 exon 6F	ataagaatggactaatacacc	T521C	417
OATP1B1 exon 6R	tggtctaataaggtaaataataag		
NTCP exon 3F	ccaatttctacgtgtcttc	T668C (*3)	344
NTCP exon 3R	ctgcagtgcagctgagaatgtg		
NTCP exon 4F	cagcactgggacaaagttgc	C800T (*2)	320
NTCP exon 4R	ggctcaggtctaattggag	T836C (*4) A940G (*5)	
BCRP exon 5F	cagcactgggacaaagttgc	C421A	289
BCRP exon 5R	ggctcaggtctaattggag		

SNPs, single nucleotide polymorphisms.

(Mutation Surveyor V5.1) and qualified additionally by pre-determined sample controls.

The BCRP (*ABCG2*) C421A polymorphism was genotyped by *Taa* I PCR restriction fragment length polymorphism. Briefly, the amplified 289 bp PCR fragment encompassing the SNP of interest was subsequently incubated at 65°C with three units of a restriction enzyme (*Taa* I) for 3 h. The digested amplified products were loaded onto a 3% agarose gel to verify digested product sizes. A wt/wt (cc/cc) genotype would reveal a digested product size of 256 bp whereas a mt/mt (aa/aa) genotype would resist digestion by the enzyme to remain at 289 bp. Heterozygous genotypes exhibit both product sizes (289 bp and 256 bp).

Plasma PK samples collected on days 1 and 10 were assayed for rosuvastatin using a validated analytical method based on solid phase extraction, followed by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC/MS/MS) analysis. Using a 100 µl aliquot of plasma, the lower limit of quantification for the rosuvastatin assay was 0.2 ng ml⁻¹ and the higher limit of quantification was 30 ng ml⁻¹. Each batch of plasma samples was run against freshly prepared duplicate calibration standards (*n* = 8). Imprecision and inaccuracy between assays were <14%. Quality control (QC) samples at three concentrations (0.5, 5, and 25 ng ml⁻¹) were assayed along with study samples and the calculated QC sample concentrations deviated by <15% from the actual concentrations. Plasma PK samples collected on day 10 were assayed for eltrombopag using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. Using a 50 µl aliquot of plasma, the lower limit of quantification for the eltrombopag assay was 100 ng ml⁻¹ and the higher limit of quantification was 50 000 ng ml⁻¹. Each batch of plasma samples was run against freshly prepared duplicate calibration standards (*n* = 9). Imprecision and inaccuracy between assays were <14%. QC samples at three concentrations (400, 4000, and 40 000 ng ml⁻¹) were assayed along with study samples

and the calculated QC sample concentrations deviated by <15% from the actual concentrations.

The primary PK endpoints were maximum plasma concentration (C_{max}) and area under the plasma concentration vs. time curve starting from dosing and extrapolated to infinity ($AUC(0,\infty)$) of rosuvastatin when administered alone or co-administered with eltrombopag. C_{max} and the first time to reach C_{max} (t_{max}) were the actual observed values. The AUC was calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. The AUC from time zero to the last measurable concentration ($AUC(0,\tau)$) and $AUC(0,\infty)$ was determined. Values for $AUC(0,\infty)$ were estimated as the sum of $AUC(0,\tau)$ and C_t divided by the elimination rate constant (λ_z), where C_t was the last observed quantifiable concentration.

Steady-state plasma eltrombopag C_{max} and AUC over a dosing interval ($AUC(0,\tau)$) were estimated for the combination regimen only. In addition, plasma eltrombopag trough concentrations collected on day 10 prior to administration of rosuvastatin and 24 h after rosuvastatin co-administration were measured.

To assess the effects of eltrombopag on rosuvastatin PK, log transformed plasma rosuvastatin $AUC(0,\infty)$ and C_{max} were analyzed separately by analysis of variance (ANOVA) fitting terms for treatment and subject. Point estimates and associated 90% confidence intervals (CI) for the differences were constructed using the appropriate error term. The point and interval estimates on the log scale were then back-transformed to give point and interval estimates for the ratios. Plasma eltrombopag and rosuvastatin PK parameters were summarized by treatment and by race and gender within treatment. Plasma rosuvastatin concentration-time profiles were plotted by treatment, race and gender. Plasma rosuvastatin $AUC(0,\infty)$ was plotted by genotype combination (approach 2 as described in the following paragraph). Subgroup analyses were conducted as secondary analyses. Similar to the primary statistical analysis, plasma rosuvastatin PK values

were compared between treatments for subgroups based on race (Asian vs. non-Asian) and gender.

Multivariate analyses of the relationship between day 1 plasma rosuvastatin AUC(0,∞) and C_{max} and potential covariates was completed. The analysis included race (Asian vs. non-Asian), gender, body weight, and OATP1B1 (*SLCO1B1*) A388G and T521C and BCRP (*ABCG2*) C421A genotypes. Genotypes were included three ways. Approach 1: each gene variant was included separately. Approach 2: *SLCO1B1* haplotype and *ABCG2* genotype combinations were categorized, Category 1 included *SLCO1B1* haplotypes *1a/*1a, *1a/*1b, and *1b/*1b, Category 2 included *SLCO1B1* haplotypes *1a/*15 and *1b/*15, Category 3 included the *ABCG2* c.421CA genotype in combination with *SLCO1B1* haplotypes *1a/*1a, *1a/*1b, or *1b/*1b and Category 4 included the *ABCG2* c.421CA genotype in combination with *SLCO1B1* haplotypes *1b/*15 or *15/*15 and the *ABCG2* c.421AA genotype in combination with *SLCO1B1* haplotype *1b/*1b. Approach 3: combinations of gene variants c.388AA, c.388AG, c.521TT, c.521TC and c.421CC were assigned zero, c.388GG, c.521CC and c.421CA were assigned 1 and c.421AA was assigned 2, and the scores were summed across the three gene variants (possible score of 0 to 4).

Results

Demographics and genotypes

Similar numbers of Asian and non-Asian subjects were enrolled in the study (Table 2). Of the genotypes evaluated in the current study, only the OATP1B1 (*SLCO1B1*) A388G genotypes were relatively evenly distributed overall and within Asian and non-Asian groups (Table 3). The majority of subjects had homozygous wild-type OATP1B1 (*SLCO1B1*) c.521TT and BCRP (*ABCG2*) c.421CC genotypes, with 20 to 40% having the heterozygous genotype (Table 3). There was a broad range of OATP1B1 (*SLCO1B1*) haplotype and BCRP (*ABCG2*) genotype combinations (Table 3).

Pharmacokinetics

Race ($P < 0.001$) and gender ($P < 0.05$) were retained as significant predictors of plasma rosuvastatin AUC(0,∞) and C_{max} in the final multivariate models where genotype by approach 1 and approach 2 were tested. Race ($P < 0.001$), gender ($P < 0.05$) and genotype ($P < 0.05$) were retained in the final model as significant predictors of plasma rosuvastatin AUC(0,∞) and C_{max} where genotype by approach 3 was tested. Body weight was not a significant covariate in any of the analyses. Only one of 21 Asian subjects was female, so the gender effect was driven by data within the non-Asian group (seven of 18 non-Asian subjects were female). Asian participants had a 109% higher rosuvastatin AUC(0,∞) and a 139% higher C_{max} compared with non-Asian subjects when rosuvastatin was administered alone

Table 2

Subject disposition and demographics

Disposition	Total
Subjects enrolled, <i>n</i>	42
Subjects included in safety analysis, <i>n</i> (%)	42 (100)
Subjects included in PK analysis, <i>n</i> (%)	39 (93)*
Subjects withdrawn from study, <i>n</i> (%)	2 (5)
Withdrawn for AE	1 (2)
Subject decision	1 (2)
Demographics	
Mean age (SD) (years)	33.6 (7.8)
Mean weight (min, max) (kg)	76 (54, 98)
Gender, <i>n</i> (%)	
Men	33 (79)
Women	9 (21)
Race, <i>n</i> (%)	
African American/African heritage	12 (29)
American Indian/Alaska native	4 (10)
Asian	22 (52)
East Asian	19 (45)
Central/South Asian	2 (5)
Southeast Asian	1 (2)
White/Caucasian/European heritage	4 (10)

AE, adverse event; PK, pharmacokinetic; SD, standard deviation. *Two subjects who completed the study were excluded from the PK analysis because the rosuvastatin terminal elimination phase half-life could not be estimated.

(Table 4). Within the non-Asian population, female participants had 50% higher rosuvastatin AUC(0,∞) and 84% higher C_{max} compared with male subjects when rosuvastatin was administered alone.

Co-administration of eltrombopag with rosuvastatin increased plasma rosuvastatin AUC(0,∞) by 55% and C_{max} by 103% in the overall study population compared with administration of rosuvastatin alone (Table 4). The impact of eltrombopag on plasma rosuvastatin exposure differed by race. Plasma rosuvastatin AUC(0,∞) increased by 88% and C_{max} increased 165% in non-Asian subjects, whereas AUC(0,∞) increased by 32% and C_{max} increased 61% in Asian subjects (Table 4). Median plasma rosuvastatin concentration–time profiles are displayed for the overall population and by race for each treatment in Figure 1. The impact of eltrombopag on plasma rosuvastatin exposure appeared to differ by gender within the non-Asian population (Table 4).

Subjects with combined genotype scores (approach 3) of 2–3 had higher plasma rosuvastatin exposures than subjects with scores of 0–1, and there was also a trend for higher plasma rosuvastatin exposures for subjects in category 4 (approach 2). However, given the small sample size, it is difficult to draw firm conclusions regarding the relationship between genotype and plasma rosuvastatin exposure. Plasma rosuvastatin AUC(0,∞) vs. genotype combination (approach 2) are displayed in Figure 2, along with race and gender details.

Table 3

Summary of genotype frequency

Gene variant	Genotype	Asian <i>n</i> = 21 (%)	Non-Asian <i>n</i> = 18 (%)	Overall <i>n</i> = 39 (%)
<i>SLCO1B1</i> A388G	AA	3 (14)	5 (28)	8 (21)
	AG	8 (38)	5 (28)	13 (33)
	GG	10 (48)	8 (44)	18 (46)
<i>SLCO1B1</i> T521C	TT	17 (81)	13 (72)	30 (77)
	TC	4 (19)	4 (22)	8 (21)
	CC	0	1 (6)	1 (3)
<i>ABCG2</i> C421A	CC	11 (52)	13 (72)	24 (62)
	CA	9 (43)	5 (28)	14 (36)
	AA	1 (5)	0	1 (3)
<i>SLCO1B1</i> haplotype and <i>ABCG2</i> C421A genotype		Asian <i>n</i> = 21 (%)	Non-Asian <i>n</i> = 18 (%)	Overall <i>n</i> = 39 (%)
*1a/*1a		2 (10)	3 (17)	5 (13)
*1a/*1b		4 (19)	2 (11)	6 (15)
*1b/*1b		3 (14)	5 (28)	8 (21)
*1a/*15		0	2 (11)	2 (5)
*1b/*15		2 (10)	1 (6)	3 (8)
*1a/*1a + c.421CA		1 (5)	2 (11)	3 (8)
*1a/*1b + c.421CA		4 (19)	1 (6)	5 (13)
*1b/*1b + c.421CA		2 (10)	0	2 (5)
*1b/*15 + c.421CA		2 (10)	1 (6)	3 (8)
*15/*15 + c.421CA		0	1 (6)	1 (3)
*1b/*1b + c.421AA		1 (5)	0	1 (3)

93% to 100% of subjects had the homozygous wild-type genotype for NTCP. Two subjects were not included in the PK analysis; one was non-Asian with AG/TT/CC genotypes (*1a/*1b haplotype) and one was Asian with GG/TT/CC genotypes (*1b/*1b haplotype).

Table 4

Summary of plasma rosuvastatin pharmacokinetics and treatment comparisons

Plasma rosuvastatin PK parameter*	Rosuvastatin	Rosuvastatin + eltrombopag	Rosuvastatin + eltrombopag vs. rosuvastatin†
All subjects (<i>n</i> = 39)			
AUC(0,∞) (ng ml ⁻¹ h)	61.9 (72)	96.0 (50)	1.55 (1.42, 1.69)
C _{max} (ng ml ⁻¹)	5.97 (81)	12.1 (53)	2.03 (1.82, 2.26)
Asian subjects (<i>n</i> = 21)‡			
AUC(0,∞) (ng ml ⁻¹ h)	87.0 (58)	114 (47)	1.32 (1.19, 1.46)
C _{max} (ng ml ⁻¹)	8.93 (63)	14.4 (51)	1.61 (1.44, 1.80)
Non-Asian subjects (<i>n</i> = 18)			
AUC(0,∞) (ng ml ⁻¹ h)	41.6 (58)	78.2 (45)	1.88 (1.68, 2.10)
C _{max} (ng ml ⁻¹)	3.74 (59)	9.91 (47)	2.65 (2.35, 3.00)
Non-Asian female subjects (<i>n</i> = 7)			
AUC(0,∞) (ng ml ⁻¹ h)	53.3 (38)	95.4 (38)	1.79 (1.59, 2.02)
C _{max} (ng ml ⁻¹)	5.43 (46)	11.9 (41)	2.19 (1.91, 2.51)
Non-Asian male subjects (<i>n</i> = 11)			
AUC(0,∞) (ng ml ⁻¹ h)	35.6 (64)	68.9 (45)	1.93 (1.62, 2.31)
C _{max} (ng ml ⁻¹)	2.95 (52)	8.82 (48)	3.00 (2.53, 3.55)

AUC, area under the curve; C_{max}, maximum plasma concentration. *Geometric mean and coefficient of variation between subjects (CV%) for PK summary. †Geometric least squares (GLS) mean (90% CI) for treatment comparisons. ‡20 of 21 Asian subjects were male.

For the overall population, the geometric mean of plasma eltrombopag C_{max} was 8.00 µg ml⁻¹ and AUC(0,τ) was 102 µg ml⁻¹ h, and plasma eltrombopag exposures were similar between Asian and non-Asian subjects and between the BCRP (*ABCG2*) c.421CC and c.421CA genotypes (Table 5). The one subject (Asian male) with the

c.421AA genotype had the highest plasma eltrombopag AUC(0,τ) (247 µg ml⁻¹ h), but the exposure was similar to the highest AUC(0,τ) (227 µg ml⁻¹ h) observed for an Asian male subject with the c.421CC genotype. When races were combined, plasma eltrombopag exposure was similar between males and females (Table 5), but within the non-

Figure 1

Median plasma rosuvastatin concentration–time profiles. rosuvastatin alone (no symbol = rosuvastatin + eltrombopag) (▲); overall population (—); Asian (---); non-Asian (.....)

Figure 2

Plasma rosuvastatin AUC(0,∞) by OATP1B1 (*SLCO1B1*) haplotype and BCRP (*ABCG2*) C421A genotype. non-Asian male (□); Asian male (○); non-Asian female (■); Asian female (●)

Asian group, women had approximately 46% higher plasma eltrombopag AUC(0,τ) (126 vs. 86 $\mu\text{g ml}^{-1} \text{h}$) and 37% higher C_{max} (9.48 vs. 6.94 $\mu\text{g ml}^{-1}$). Median (range) eltrombopag trough concentrations of 2.98 $\mu\text{g ml}^{-1}$ (1.14–6.97 $\mu\text{g ml}^{-1}$) collected on day 10 prior to co-administration of rosuvastatin were similar to trough concentrations of 3.22 $\mu\text{g ml}^{-1}$ (1.22–6.94 $\mu\text{g ml}^{-1}$) collected 24 h after co-administration of a single dose of rosuvastatin.

Safety

AEs were reported by 10% to 21% of subjects per treatment. AEs reported by more than one subject on a given treatment included gastroenteritis, headache and upper respiratory infection. No serious AEs were reported by study participants. Subjects experienced no clinically significant changes in vital signs, ECG abnormalities or QT_c prolongation. Increased platelet counts were observed in

Table 5

Summary of plasma eltrombopag pharmacokinetics

	Overall <i>n</i> = 39	Rosuvastatin + eltrombopag*						
		By race Asian <i>n</i> = 21	Non-Asian <i>n</i> = 18	By gender Male <i>n</i> = 31	Female <i>n</i> = 8	By BCRP (<i>ABCG2</i>) CC <i>n</i> = 24	C421A genotype CA <i>n</i> = 14	AA <i>n</i> = 1
AUC(0,∞) (μg ml ⁻¹ h)	102 (44)	105 (48)	100 (39)	98.5 (48)	119 (20)	105 (35)	91.6 (52)	247
C _{max} (μg ml ⁻¹)	8.00 (39)	8.14 (43)	7.83 (35)	7.74 (42)	9.10 (21)	8.21 (34)	7.25 (44)	16.5

AUC, area under the curve; C_{max}, maximum plasma concentration. Geometric mean (CV%). *Eltrombopag exposures were only collected when co-administered with rosuvastatin.

several subjects following administration of eltrombopag. At the follow-up visit, 16 subjects (38%) had platelet counts >400 Gi l⁻¹ (range 415–684 Gi l⁻¹), the upper limit of normal. Changes from baseline in these individuals ranged from 32% to 113%. In these subjects, platelet counts decreased to normal no later than day 117. Because lens changes have been observed in preclinical animal studies and in clinical studies, ophthalmic assessments were conducted in this study. No changes in ocular status due to cataracts were observed during the study.

Discussion

This study was conducted because *in vitro* data identified eltrombopag as an inhibitor of both OATP1B1 and BCRP with IC₅₀s of 2.7 μM (1.19 μg ml⁻¹). Eltrombopag concentrations achieved clinically are higher than this IC₅₀ value (Table 5), and OATP1B1 and BCRP are important for rosuvastatin disposition. Statins are widely used cholesterol-lowering agents [13] and are generally used as chronic therapy, but they are associated with significant toxicities, such as rhabdomyolysis and increases in liver transaminases, the incidence of which can increase in the presence of elevated plasma drug concentrations. In addition, the efficacy of statins can be reduced if their uptake into the liver is impaired. Thus, drug interactions involving statins can be clinically important for both safety and efficacy. The central finding of the study was that co-administration of eltrombopag 75 mg once daily with a single dose of rosuvastatin 10 mg increased plasma rosuvastatin C_{max} by 103% and AUC(0,∞) by 55% in the overall study population compared with rosuvastatin alone (Table 4).

Because it was known that Asian subjects have higher rosuvastatin exposures than non-Asian subjects [7], this study enrolled subjects at one site in Singapore and one site in the United States. Consistent with previous data, Asian race was associated with higher plasma rosuvastatin exposure, with Asian subjects having approximately twice the exposure as non-Asian subjects enrolled in the current study when rosuvastatin was given alone. Interestingly, the non-Asian group studied by Lee *et al.* [7] was composed of White subjects, whereas the non-Asian group in the

current study included a high percentage of African American subjects. The observed interindividual variability in plasma rosuvastatin exposure could be due to different genetic polymorphisms that encode drug-metabolizing transporters [14]. It was anticipated that inhibition of OATP1B1 by eltrombopag would have a lesser effect on plasma rosuvastatin exposure in Asian subjects compared with non-Asian subjects, whose transporter activity is more functional, and this was confirmed when the drug interaction results were summarized by race (Table 4).

OATP1B1 (*SLCO1B1*) T521C polymorphisms independently and in combination with the c.388GG polymorphisms (*SLCO1B1**15/*15) have not been associated with racial differences in rosuvastatin PK, but have been associated with rosuvastatin PK variability in White subjects [7]. BCRP C421A polymorphisms have been associated with rosuvastatin PK variability as well [8]. The study was not designed to stratify enrolment by *SLCO1B1* A388G, *SLCO1B1* T521A or *ABCG2* C421T genotypes or by *SLCO1B1* haplotype and *ABCG2* C421A genotype combinations. Of the gene variants evaluated in the current study, only *SLCO1B1* A388G genotypes, which have not been independently associated with plasma rosuvastatin exposure, were relatively evenly distributed across the enrolled population. In a multivariate analysis where each gene variant was included separately, genotype was not significantly associated with plasma rosuvastatin exposure when race, gender and body weight were included in the model. In multivariate analyses including *SLCO1B1* haplotype and *ABCG2* genotype combinations, there was some association between haplotype and genotype combinations and plasma rosuvastatin exposure when race, gender and body weight were included in the model, but given the small sample size within each combination, it is difficult to draw conclusions (Figure 2).

The finding of statistically significant higher plasma rosuvastatin exposures in female subjects has not been reported in the literature to our knowledge. However, there was a trend for higher exposures reported for Chinese female healthy volunteers [15].

Because the *in vitro* inhibition potency of eltrombopag is similar for OATP1B1 and BCRP and because genetic polymorphisms in both transporters are known to be

associated with rosuvastatin exposure, it is probable that the increased rosuvastatin exposure observed with eltrombopag co-administration is due to inhibition of both transporters. Inhibition of OATP1B1 increases plasma rosuvastatin exposure by reducing the hepatic uptake; in this scenario, rosuvastatin efficacy may be reduced and toxicity may be increased. In contrast, inhibition of BCRP increases plasma rosuvastatin exposure by enhancing rosuvastatin absorption and/or by inhibiting rosuvastatin elimination in the bile; in this scenario rosuvastatin efficacy and toxicity may both be increased. *In vitro* evidence also suggests that rosuvastatin is a substrate for other hepatic uptake transporters including OATP1B3, OATP2B1, OATP1A2, as well as a substrate for the bile acid uptake transporter NTCP [13]. It is not known if eltrombopag has an impact on these other transporters.

OATP1B1 is highly expressed on the basolateral (sinusoidal) membrane of hepatocytes and involved in the hepatic uptake of all HMG-CoA reductase inhibitors (statins) [5, 13]. However, the importance of OATP1B1 on the HMG-CoA reductase inhibitors' disposition varies among the drugs of this class. For example, subjects with the homozygous OATP1B1 (*SLCO1B1*) 521CC genotype had 1.65- to 3.21-fold higher exposures of rosuvastatin, pravastatin, simvastatin, lovastatin and atorvastatin than those with the homozygous 521TT (control) genotypes [6, 16, 17]. In contrast, fluvastatin exposure was not different among the T521C genotypes, further suggesting that OATP1B1 may not be important for fluvastatin disposition. BCRP is highly expressed on the apical membrane of enterocytes of the small intestine and the bile canalicular membrane of the hepatocyte and involved in the efflux of some statins out of the intestine and into the bile. BCRP polymorphisms have been associated with rosuvastatin, atorvastatin, fluvastatin and simvastatin lactone (but not acid), but not pravastatin or pitavastatin [8, 9, 18, 19].

Given that exposures to several HMG-CoA reductase inhibitors are associated with OATP1B1 (*SLCO1B1*) and/or BCRP (*ABCG2*) polymorphisms, the results of the eltrombopag-rosuvastatin interaction study may be extended to other statins. In subjects who were co-administered eltrombopag and rosuvastatin, increased rosuvastatin C_{max} (mean 103% increase) and AUC(0,∞) (mean 55% increase) were observed. This suggests that clinicians should consider reducing a subject's dose of statin when co-administered with eltrombopag. Monitoring side effects, clinical chemistry, and lipid concentrations is warranted in subjects receiving both eltrombopag and a statin. As noted by other investigators, most clinically significant drug-drug interactions involving lipid-lowering drugs can be avoided by appropriate drug selection and dosing [5].

The impact of rosuvastatin on plasma eltrombopag PK was not formally assessed. However, eltrombopag trough concentrations collected prior to co-administration of rosuvastatin were similar to trough concentrations col-

lected 24 h after co-administration of a single dose of rosuvastatin. In addition, plasma eltrombopag exposure for the 75 mg once daily regimen (in combination with a single dose of rosuvastatin) was generally as expected based on plasma eltrombopag exposures observed in other eltrombopag studies [20–22]. Therefore, there does not appear to be a significant impact of rosuvastatin on plasma eltrombopag PK.

Plasma eltrombopag exposures collected in the presence of rosuvastatin were similar between Asian and non-Asian subjects. This is inconsistent with previous studies that have shown approximately two-fold higher plasma eltrombopag exposures in Asian vs. non-Asian subjects [21, 22]. In these prior studies, the non-Asian populations were predominantly White/Caucasian, whereas, in the current study, the non-Asian population included a high percentage of African Americans. Within the non-Asian population, female subjects had higher plasma eltrombopag exposure, which is consistent with previous reports [22]. Eltrombopag is a BCRP substrate and plasma eltrombopag exposure was similar between c.421CC and c.421CA genotypes. Although the one subject (Asian male) with the c.421AA genotype had the highest plasma eltrombopag AUC(0,τ) (247 μg ml⁻¹ h), the exposure was similar to the highest AUC(0,τ) (227 μg ml⁻¹ h) observed for an Asian male subject with the c.421CC genotype. Given the limited data for the c.421AA genotype, no conclusions can be drawn as to whether this genotype is associated with plasma eltrombopag exposure.

In conclusion, concomitant administration of eltrombopag with rosuvastatin was associated with increased rosuvastatin exposure. The therapeutic index of HMG Co-A reductase inhibitors may be reduced by the concomitant use of eltrombopag. In subjects taking eltrombopag, a reduced dose of HMG Co-A reductase inhibitors may be needed.

Competing Interests

Alicia Allred, Carolyn Bowen and Mary Beth Wire are employees of GlaxoSmithKline (GSK), and are stock holders. Bin Peng and Jung Wook Park were employees of GSK during the time that the study was conducted, and are stock holders. Daphne Williams was an employee of GSK during the time that the study was conducted. Edmund Lee does not have conflicts of interest to disclose.

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