

Lack of a Clinically Significant Drug–Drug Interaction in Healthy Volunteers Between the Hepatitis C Virus Protease Inhibitor Boceprevir and the HIV Integrase Inhibitor Raltegravir

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Background. Patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are likely to use both HIV and HCV treatment. Drug–drug interactions have been demonstrated between boceprevir, an HCV protease inhibitor, and frequently prescribed antiretroviral drugs, such as efavirenz and boosted HIV protease inhibitors. Concomitant administration of boceprevir with these drugs should be avoided. This study was designed to investigate the absence of a drug–drug interaction between boceprevir and raltegravir, an HIV integrase inhibitor.

Methods. This was an open-label, randomized, 2-period, crossover phase 1 trial in 24 healthy volunteers. All subjects were randomly assigned to receive boceprevir 800 mg every 8 hours for 9 days plus a single dose of raltegravir 400 mg on day 10 followed by a washout period and a single dose of raltegravir 400 mg on day 38, or the same medication in reverse order. Blood samples for pharmacokinetics were collected and pharmacokinetic parameters were calculated.

Results. The geometric mean (GM) of raltegravir area under the concentration–time curve (AUC)_{0–12h} and maximum plasma concentration (C_{max}) for raltegravir + boceprevir vs raltegravir alone were 4.27 (95% confidence interval [CI], 3.22–5.66) vs 4.04 (95% CI, 3.09–5.28) mg * hour/L and 1.06 (95% CI, .76–1.49) vs 0.93 (95% CI, .70–1.23) mg/L, respectively. GM ratio estimates of raltegravir AUC_{0–12h} and C_{max} for raltegravir + boceprevir vs raltegravir alone were 1.04 (90% CI, .88–1.22) and 1.11 (90% CI, .91–1.36), respectively. The GM of boceprevir AUC_{0–8h}, C_{max}, and C_{8h} were 5.45 (95% CI, 5.11–5.81) mg * hour/L, 1.88 (95% CI, 1.72–2.06) mg/L, and 0.09 (95% CI, .07–.11) mg/L, respectively. These data are comparable to those from historical controls.

Conclusions. Due to the absence of a clinically significant drug interaction, raltegravir can be recommended for combined HIV/HCV treatment including boceprevir.

Clinical Trials Registration. NCT01288417.

Keywords. drug interactions; pharmacokinetics; hepatitis C; HIV.

The prevalence of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection ranges

from ±10% to 70% in Europe and North America [1]. Since the introduction of combination antiretroviral therapy (cART), the life expectancy of HIV-infected patients has improved dramatically. Since then, liver-related deaths have become the most frequent cause of non-AIDS-related deaths, to which HCV coinfection makes a substantial contribution [2].

The NS3 serine protease inhibitors boceprevir and telaprevir have been approved since 2011 for use in patients with chronic HCV genotype 1 infection. When added to the standard of care, sustained

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virological response (SVR) rates improve by 25%–31% shown in HCV monoinfected patients [3, 4]. In total SVR rates around 68–75% are seen.

According to US guidelines, first-line cART for HIV-infected patients should consist of the 2 nucleoside reverse transcriptase inhibitors (NRTIs) tenofovir and emtricitabine, in combination with the nonnucleoside reverse transcriptase inhibitor efavirenz, the ritonavir-boosted HIV protease inhibitors atazanavir or darunavir, or the integrase inhibitor raltegravir [5].

As HIV/HCV-coinfected patients are likely to use both HIV and HCV treatment, including the HCV protease inhibitors, simultaneously, it is important to know if drug–drug interactions occur. At this moment it is not recommended to coadminister boceprevir with darunavir/ritonavir, lopinavir/ritonavir, or efavirenz because decreased concentrations of boceprevir, as well as decreased concentrations of the boosted HIV protease inhibitors, have been found [6, 7]. Because the combination with atazanavir/ritonavir did not substantially influence boceprevir concentrations, although atazanavir levels were lower, coadministration of these drugs can be considered on a case-by-case basis [7]. The only remaining first-line antiretroviral agent that can be added to an NRTI backbone is raltegravir. Raltegravir is a substrate of UDP-glucuronosyltransferase (UGT) and does not influence cytochrome P450 (CYP) enzymes; boceprevir is a substrate of aldo-keto reductase and CYP3A and inhibits CYP3A. Hence, no significant interaction between boceprevir and raltegravir is expected, but pharmacokinetic drug–drug interaction studies are lacking.

This pharmacokinetic study in healthy volunteers was performed to confirm that a clinically significant drug–drug interaction between raltegravir and boceprevir is absent.

MATERIALS AND METHODS

Study Design

This open-label, 2-period, randomized, crossover phase 1 trial was conducted from August to November 2011 at the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The study was designed to determine the effect of steady-state boceprevir on the pharmacokinetics of a single dose of raltegravir by intrasubject comparison. The secondary objective was to examine the effect of a single dose of raltegravir on the pharmacokinetics of steady state boceprevir (by comparison with historical controls) and to study the safety of a single-dose raltegravir coadministered with steady state boceprevir.

Healthy volunteers were equally randomized to 2 treatment groups. Group A received a single dose of 400 mg of raltegravir on day 10. After a washout period of 2 weeks, the participants took 800 mg of boceprevir every 8 hours with food for 9 days (days 29–37). On day 38 they received a single dose of 400 mg of raltegravir and 2 doses of 800 mg of boceprevir

(1 together with raltegravir and 1 dose 8 hours later). Group B received the same regimens but in reversed order. On days 10 and 38, a 12-hour pharmacokinetic curve was recorded.

Procedures

The trial was approved by the Investigational Review Board of the Radboud University Nijmegen Medical Centre. The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants signed informed consent prior to screening evaluations.

Study Population

Healthy male and female subjects aged 18–55 years and with a body mass index (BMI) of 18–30 kg/m² (extremes included) were eligible for enrollment. Included participants had to be in a good, age-appropriate health condition as established by physical examination, medical history, electrocardiography, and biochemical, hematologic, and urinalysis testing within 4 weeks prior to day 1. Main exclusion criteria were a history of sensitivity or idiosyncrasy to medicinal products or excipients; a positive HIV, hepatitis B or C test result; or the use of any medications (for 2 weeks preceding dosing) except for acetaminophen.

Study Drug and Dosing

The approved dose of boceprevir (Victrelis, Merck Sharp & Dohme) is 800 mg every 8 hours with food [6]. In this study, subjects took 4 capsules of 200 mg of boceprevir at approximately 08:00 hours, 16:00 hours, and 0:00 hours with a meal or a snack. A treatment duration of 10 days was chosen to reach steady state and to assess potential effects on metabolizing enzymes or drug transporters. Raltegravir (Isentress, Merck Sharp & Dohme) was administered as a single dose of 400 mg on day 10 and day 38 together with a standardized breakfast consisting of 2 slices of wheat bread (1 slice with cheese and 1 with sliced sausage) and 1 glass of milk.

Intake of medication at the clinical trial unit was supervised and recorded by the study personnel. Drug intake of boceprevir at home was monitored by use of microelectronic monitoring system (MEMS) caps (Aardex, Zug, Switzerland), which records the opening of the medication bottle. In addition, the weight of the bottles containing the boceprevir capsules was recorded on each visit day during boceprevir treatment to assess adherence. Subjects were asked to write down the exact times of medication intake in a booklet.

Pharmacokinetic Sampling and Safety Assessments

Blood samples for assessment of pharmacokinetic parameters of raltegravir were collected during a 12-hour period after intake of a single dose of 400 mg of raltegravir on days 10 and 38. Blood samples were collected into heparinized tubes and centrifuged for 10 minutes at 1900 g at 20°C. Plasma was

transferred to polypropylene tubes and stored at -40°C until further bioanalysis.

Blood samples for assessment of pharmacokinetic parameters of boceprevir were collected during an 8-hour period after intake of 800 mg of boceprevir on day 10 or 38. In addition, blood samples were taken predose on days 1, 3, 6, and 8 (group B) and on days 28, 31, 34, and 36 (group A). Blood samples for boceprevir were collected into prechilled potassium-ethylenediaminetetraacetic acid-containing tubes and centrifuged for 15 minutes at 1500 g at 4°C within 30 minutes after blood collection. Plasma (1.5 mL) was transferred to prechilled cryovials containing 75 μL of 85% phosphoric acid, mixed by a vortex mixer and stored at $\leq -20^{\circ}\text{C}$ within 1 hour of sample collection.

Bioanalytic Methods

Concentrations of raltegravir in plasma were analyzed by use of a validated reversed-phase high-pressure liquid chromatography (HPLC) method with fluorescence detection [8]. The linear calibration ranges in plasma were from 0.014 mg/L to 10.0 mg/L. The raltegravir assay was performed at the laboratory of the Pharmacy of the Radboud University Nijmegen Medical Centre and was externally validated through the International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma [9] as well as by the Proficiency Testing Program of the ACTG/IMPAACT group [10].

Boceprevir (SCH503034) is an approximately equal mixture of 2 diastereomers; SCH534128, the active diastereomer and SCH534129, which is inactive. The predominant metabolic pathway produces inactive stereoisomers, together called SCH629144 [11]. Concentrations of boceprevir were determined as the sum of concentrations of the 2 diastereomers SCH534128 and SCH534129. Concentrations of SCH629144 were obtained as the sum of concentrations of 4 analytes, namely, SCH783004, SCH783005, SCH783006, and SCH783007. The overall lower limit of quantification (LLOQ) was 0.0048 mg/L for boceprevir and 0.0025 mg/L for SCH629144. The calibration range for SCH534128 and SCH534129 and for the 4 metabolites were from the LLOQ to 5.20 mg/L, 4.80 mg/L, and 2.50 mg/L, respectively. Concentrations of both diastereomers and its metabolites in collected plasma samples were determined using HPLC-tandem mass spectrometry at PPD Global Central Labs (Middleton, Wisconsin).

Pharmacokinetic Analysis

Based on the individual plasma concentration-time data, the following pharmacokinetic parameters of raltegravir were determined: the area under the concentration-time curve from 0 to 12 hours after intake ($\text{AUC}_{0-12\text{h}}$), maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), the bioavailability adjusted volume of distribution (V/F), apparent oral clearance

(CL/F), and the apparent elimination half-life ($T_{1/2}$). For boceprevir (both diastereomers and metabolites) the same parameters were determined plus the concentration at 8 hours after intake ($C_{8\text{h}}$); AUC was determined from 0 to 8 hours after intake ($\text{AUC}_{0-8\text{h}}$). All pharmacokinetic parameters were calculated by noncompartmental methods using the linear log trapezoidal rule.

Statistical Analysis

The data obtained in this study were analyzed according to an equivalence approach that is recommended for pharmacokinetic interaction studies [12, 13]. The main pharmacokinetic parameter to be evaluated in this respect was the exposure to raltegravir, as expressed in the $\text{AUC}_{0-12\text{h}}$. The required sample size was calculated (power of 80%) assuming no difference in $\text{AUC}_{0-12\text{h}}$ of raltegravir with or without boceprevir and an intrasubject coefficient of variation of 22.5% of raltegravir AUCs. The required number of participants was 20. Taking dropouts into account, in total 24 subjects were included in the study.

The geometric mean ratio estimates of all determined pharmacokinetic parameters of raltegravir with boceprevir vs raltegravir alone, except for T_{max} , were calculated using the mixed model analysis, with the Kenward-Roger approach for the evaluation of the fixed effects. In addition, the nonparametric Wilcoxon signed-rank test was done for T_{max} values between the 2 regimens. Geometric mean ratio estimates with 90% confidence interval (CI) entirely within the range of 0.80–1.25 were considered to indicate no significant interaction.

Pharmacokinetic parameters of boceprevir (diastereomers and metabolites) were compared with historical data from healthy volunteers.

Statistical analyses were carried out using SPSS software version 16.0 or higher (SPSS, Chicago, Illinois) and SAS 9.2. Descriptive statistics were calculated using Excel 2007 software (Microsoft Corporation) or WinNonlin version 5.3 (Pharsight Corporation).

RESULTS

Baseline Characteristics

Twenty-four healthy volunteers (12 males) were included in the study. Subjects were of white ($n = 22$), black ($n = 1$), or mixed Asian/white ($n = 1$) ethnicity. The mean age and BMI were 38 years (range, 20–55 years) and 23 kg/m^2 (18–27 kg/m^2).

Twenty-two subjects (10 males) completed the trial. One subject had to discontinue due to nonadherence to the study protocol and another subject because of elevated alanine aminotransferase. Both dropouts completed the raltegravir alone treatment and remained included in the demographics, safety, and pharmacokinetic analyses.

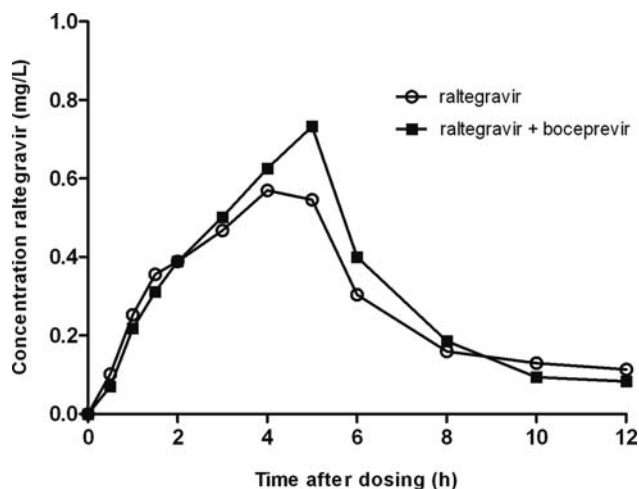


Figure 1. Geometric mean plasma concentrations of raltegravir following a single dose of 400 mg raltegravir in the presence and absence of steady-state boceprevir.

Compliance

The compliance to boceprevir treatment was good. All but 1 subject (21/22) took all doses of boceprevir and raltegravir according to pill count, diary, and MEMS caps recordings. Only 1 subject missed 1 dose of boceprevir. Seven subjects (1–3 times per subject) took the dose of boceprevir outside a 2-hour time frame (07:00–09:00 hours/15:00–17:00 hours/23:00–01:00 hours).

Pharmacokinetics

Pharmacokinetic parameters were calculated on all available data from the 24 subjects included in the trial. The plasma

concentration vs time curves of raltegravir alone and of raltegravir with boceprevir are shown in Figure 1. The pharmacokinetic parameters of raltegravir with and without boceprevir are shown in Table 1. For raltegravir coadministered with boceprevir relative to raltegravir alone, the geometric mean ratio estimates of AUC_{0-12h} and C_{max} were 1.04 (90% CI, .88–1.22) and 1.11 (90% CI, .91–1.36). The geometric mean ratio estimates with 90% CI of the main pharmacokinetic parameter raltegravir AUC_{0-12h} fell entirely within the range of 0.80 to 1.25, which indicates no significant interaction with boceprevir. It is suggested that boceprevir does not influence the other pharmacokinetic parameters of raltegravir.

The plasma concentrations vs time curves of boceprevir, the active diastereomer SCH534128, and the inactive diastereomer SCH534129 after multiple doses of boceprevir are shown in Figure 2. The pharmacokinetic parameters of boceprevir, the diastereomers, and the metabolites together as SCH629144 are given in Table 2. The AUC_{0-8h} of boceprevir in this study was 5.45 mg * hour/L and in historical controls the AUC_{0-8h} of boceprevir was 5.41 mg * hour/L [6]. No differences in exposure to boceprevir or the individual diastereomers were observed compared with historical controls.

Adverse Events and Safety Assessments

No serious adverse events were reported. In total, 90 adverse events were reported by 22 subjects after intake of study medication. The most frequently reported adverse experiences that were possibly, probably, or definitely drug-related are shown in Table 3. Two adverse events (creatinine kinase elevation and myalgia) were reported as grade 4 of intensity. All other adverse events were grade 1 or 2 of intensity. No additional side effects were seen when raltegravir was added to steady state boceprevir.

Table 1. Comparison of Single-Dose Pharmacokinetic Parameters of Raltegravir With or Without Coadministration of Multiple Doses of Boceprevir in Healthy Volunteers

| | No. | RAL + BOC, Geometric Mean (95% CI) | | No. | RAL, Geometric Mean (95% CI) | | No. ^a | Geometric Mean Ratio Estimate (90% CI) | |
|----------------------------|-----|------------------------------------|---------------|-----|------------------------------|---------------|------------------|--|------------|
| AUC_{0-12h} (mg * h/L) | 22 | 4.27 | (3.22–5.66) | 24 | 4.04 | (3.09–5.28) | 22 | 1.04 | (.88–1.22) |
| C_{max} (mg/L) | 22 | 1.06 | (.76–1.49) | 24 | 0.93 | (.70–1.23) | 22 | 1.11 | (.91–1.36) |
| T_{max} (h) ^b | 22 | 5.00 | (1.00–12.00) | 24 | 4.00 | (1.00–12.03) | 22 | | |
| V/F (L) | 19 | 261.2 | (176.6–386.2) | 19 | 335.3 | (234.8–478.9) | 17 | 0.75 | (.58–.98) |
| CL/F (L/h) | 19 | 82.5 | (58.0–117.3) | 19 | 81.4 | (54.8–120.9) | 17 | 0.99 | (.73–1.35) |
| $T_{1/2}$ (h) | 15 | 1.83 | (1.42–2.34) | 13 | 1.80 | (1.31–2.47) | 10 | 0.98 | (.74–1.30) |

Data are geometric mean (95% CI) values, unless otherwise indicated.

Abbreviations: AUC_{0-12h} , area under the plasma concentration-time curve 0–12 hours after intake; BOC, boceprevir; CI, confidence interval; CL/F, apparent oral clearance; C_{max} , maximum plasma concentration; RAL, raltegravir; $T_{1/2}$, elimination half-life; T_{max} , time to reach C_{max} ; V/F, volume of distribution.

^a The number of paired samples per parameter is given.

^b For T_{max} , median + range is reported; the result of the Wilcoxon signed-rank test was $P = .312$.

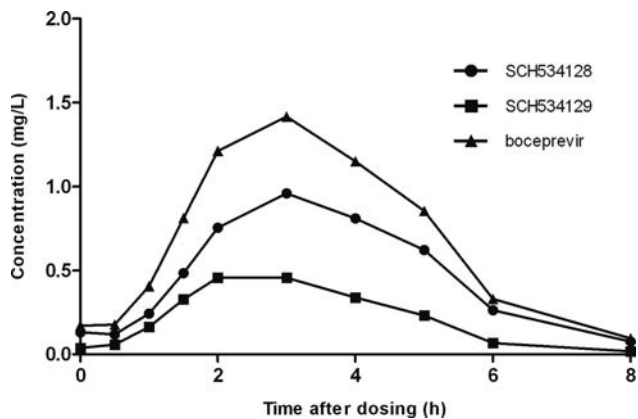


Figure 2. Geometric mean plasma concentrations of boceprevir, SCH534128, and SCH534129 after multiple doses of boceprevir 800 mg and a single dose of raltegravir 400 mg.

DISCUSSION

No significant difference was observed for the most important pharmacokinetic parameter of raltegravir, AUC_{0-12h} , between raltegravir alone and raltegravir in combination with boceprevir. Exposure to boceprevir in the presence of raltegravir was comparable to historical controls. Because boceprevir interacts with many other first-line antiretroviral drugs, it is relevant to know that boceprevir combined with raltegravir is a good treatment option for HIV/HCV-coinfected patients because of the absence of a clinically significant drug–drug interaction.

Boceprevir and telaprevir have shown some extensive drug–drug interactions with various drugs and drug classes. Several drug combinations with boceprevir or telaprevir should be avoided or should be used with great caution. These HCV

protease inhibitors can be the perpetrator or victim of such interactions. Since there is an association between boceprevir and telaprevir exposure and HCV decline [14–16], a reduction in plasma concentrations might lead to a decreased efficacy of treatment or even to resistance.

An explanation for the large number of drug–drug interactions with boceprevir and telaprevir, is that both HCV protease inhibitors are substrates and inhibitors of the CYP3A enzyme [6, 7, 17, 18], which is responsible for the metabolism of numerous drugs. Besides that, they are also substrates and inhibitors of P-glycoprotein (P-gp) [6, 7, 17, 18], an efflux transporter that plays a significant role in the absorption and elimination of many drugs.

At this moment, there are a number of studies performed on potential drug–drug interactions with the HCV protease inhibitors and antiretroviral drugs. Boceprevir did not influence the AUC of the NRTI tenofovir [19]. The nonnucleoside reverse transcriptase inhibitor efavirenz is known to induce CYP3A enzymes and P-gp transporters and boceprevir AUC and trough concentrations were reduced by 19% and 44%, respectively, in combination with efavirenz [19]; this combination should be avoided. When the HIV protease inhibitors boosted with ritonavir are coadministered with telaprevir or boceprevir, higher concentrations of the HCV protease inhibitors were theoretically expected (due to CYP3A inhibition by ritonavir), but controversially, concentrations were found to be lower. Trough concentrations of boceprevir were 18%, 35%, and 57% lower in combination with boosted atazanavir, darunavir, and lopinavir, respectively [20]. In addition, decreased concentrations of the HIV protease inhibitors were found when taken with boceprevir.

Until now, the effect of boceprevir on raltegravir or vice versa was not known, but a drug–drug interaction was not

Table 2. Pharmacokinetic Parameters of Multiple Doses of Boceprevir in Healthy Volunteers

| | No. ^a | Boceprevir | | SCH534128 (active) | | SCH534128 (inactive) | | SCH629144 (metabolites) | |
|----------------------------|------------------|------------|---------------|--------------------|---------------|----------------------|---------------|-------------------------|---------------|
| | | GM | (95% CI) | GM | (95% CI) | GM | (95% CI) | GM | (95% CI) |
| AUC_{0-8h} (mg * h/L) | 22 | 5.45 | (5.11–5.81) | 3.74 | (3.50–4.01) | 1.69 | (1.56–1.82) | 22.69 | (19.94–25.83) |
| C_{max} (mg/L) | 22 | 1.88 | (1.72–2.06) | 1.23 | (1.13–1.35) | 0.65 | (.59–.73) | 5.19 | (4.53–5.95) |
| T_{max} (h) ^b | 22 | 3.00 | (1.50–5.00) | 3.00 | (1.50–5.00) | 2.00 | (1.50–5.00) | 4.00 | (2.00–5.00) |
| C_{8h} (mg/L) | 22 | 0.09 | (.07–.11) | 0.07 | (.06–.08) | 0.02 | (.01–.02) | 1.30 | (1.04–1.62) |
| V/F (L) | 22 | 224.5 | (201.6–250.0) | 334.2 | (298.7–373.9) | 671.6 | (587.7–767.4) | 73.9 | (64.1–85.2) |
| CL/F (L/h) | 22 | 143.0 | (133.9–152.7) | 207.0 | (193.1–221.9) | 467.1 | (431.9–505.2) | 30.7 | (26.7–35.1) |
| $T_{1/2}$ (h) | 20 | 1.10 | (1.04–1.17) | 1.14 | (1.07–1.21) | 1.01 | (.94–1.08) | 1.65 | (1.49–1.84) |

Abbreviations: AUC_{0-8h} , area under the plasma concentration–time curve 0–8 hours after intake; C_{8h} , concentration at 8 hours after intake; CI, confidence interval; CL/F, apparent oral clearance; C_{max} , maximum plasma concentration; GM, geometric mean; $T_{1/2}$, elimination half-life; T_{max} , time to reach C_{max} ; V/F, volume of distribution.

^a $n = 13$ for the SCH629144 $T_{1/2}$.

^b For T_{max} , median (range) has been reported.

Table 3. Most Frequently Reported Treatment Drug-Related Adverse Events in Number of Subjects Reporting This Adverse Event

| Adverse Effect | Raltegravir (n = 24) (%) | Washout Raltegravir (n = 12) (%) | Boceprevir (n = 22) (%) | Boceprevir + Raltegravir (n = 22) (%) | Washout Boceprevir + Raltegravir (n = 10) (%) | Total (n = 24) (%) |
|----------------------|-----------------------------|--|----------------------------|---|---|--------------------|
| Dysgeusia | | | 17 (77) | | | 17 (77) |
| Headache | | 2 (17) | 4 (18) | 3 (14) | | 8 (33) |
| Atypical lymphocytes | | | 3 (14) | | | 3 (14) |
| Nausea | | | 3 (14) | | | 3 (13) |
| Xerostomia | | | 3 (14) | | | 3 (13) |
| Elevated ALT | | | 2 (9) | | 1 (10) | 3 (13) |
| Myalgia | | 1 (8) | 2 (9) | | | 2 (8) |
| Sore throat | | | 2 (9) | | | 2 (8) |
| Dyspepsia | | | 2 (9) | | | 2 (8) |
| Elevated AST | | | 1 (5) | | 1 (10) | 2 (8) |
| Diarrhea | | | 1 (5) | 1 (5) | | 2 (8) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

expected based on the pharmacokinetic characteristics of both drugs. Boceprevir is metabolized by 2 distinctive pathways, mainly through ketone reduction by aldo-keto reductase (AKR1C2 and AKR1C3) and to a lesser extent by CYP3A4 and CYP3A5 [6, 7]. Because the biotransformation and clearance of boceprevir involves 2 different enzymatic pathways, it is less likely to be subject to significant drug–drug interactions with concomitant medication affecting only 1 of these pathways. Boceprevir is a strong inhibitor of CYP3A4 and CYP3A5 [6, 7]. Raltegravir is not a substrate of CYP and does not influence CYP-mediated metabolism of other agents [21, 22]. It is a P-gp substrate [23], and is metabolized by UGT but does not itself influence UGT-mediated metabolism of other agents [21, 22].

Because raltegravir is not a CYP3A substrate and thus will not be affected by the strong inhibition of CYP3A by boceprevir, and because raltegravir is metabolized by UGT but boceprevir is not known to influence UGT, a major drug–drug interaction is unlikely with this combination. A minor interaction may occur through inhibition of P-gp mediated transport of raltegravir by boceprevir.

However, even when no drug interaction is expected theoretically, it may be recommended to collect sufficient clinical evidence to support this hypothesis because unexpected interactions with antiretroviral agents have been observed in the past. This is also true for raltegravir; for instance, there is a 17% decrease in atazanavir AUC_{0-12h} when combined with raltegravir [24], and combined use of tenofovir and raltegravir leads to 49% increase in raltegravir AUC [25].

Since raltegravir has been demonstrated to be a drug with a low interaction profile and in general is the victim and not the perpetrator of drug–drug interactions, the primary objective of this study was to determine the effect of multiple doses of

boceprevir on the pharmacokinetics of a single dose of raltegravir. Because influence of raltegravir on boceprevir was considered unlikely, and to reduce exposure of the drugs to healthy volunteers, we chose to perform a 1-way interaction study and therefore compared the pharmacokinetic data on boceprevir found in our study with data from historical controls. In light of other unexpected findings from drug–drug interaction studies with boceprevir [20] that are known at this moment, a 2-way interaction study would be preferred in order to compare the boceprevir pharmacokinetics with and without raltegravir intraindividually. Our study was conducted in healthy volunteers, limiting our interpretation in HIV/HCV-coinfected patients. There are few data on the pharmacokinetics of a single dose of 400 mg raltegravir in the target population. The pharmacokinetics of boceprevir are not different in HCV-positive or -negative patients [6, 7], but in patients with cirrhosis higher plasma concentrations of boceprevir are found [6]. It is, however, not likely that higher concentrations of boceprevir and/or raltegravir will affect the possibility of an interaction between these drugs.

Phase 2 clinical trials with boceprevir in HIV-coinfected patients is ongoing and interim results seem to be promising [26]. Twelve weeks after therapy with boceprevir added to pegylated interferon-alfa and ribavirin, 60.7% of patients had an undetectable HCV load vs 26.5% of patients on standard of care only. In the study with boceprevir, patients were not allowed to use efavirenz and the number of patients on ritonavir-boosted HIV protease inhibitors or raltegravir was small. Unfortunately, drug concentration data have not yet been presented and, therefore, up till now, it remains unknown if reduced drug concentrations have contributed to HIV or HCV breakthroughs.

In conclusion, coadministration of multiple-dose boceprevir with raltegravir did not meaningfully affect single-dose raltegravir exposure. Steady-state boceprevir exposure after coadministration with a single dose of raltegravir was comparable to the exposure of boceprevir administered alone as reported for historical controls. Due to the absence of a clinically significant drug-drug interaction, raltegravir can be recommended for combined HIV/HCV treatment including boceprevir. In the groups of healthy volunteers participating in this study, coadministration of single-dose raltegravir to steady-state boceprevir was safe and well tolerated.

Notes

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Potential conflicts of interest. D. M. B. has served as a speaker, a consultant, or an advisory board member for Merck Sharp & Dohme. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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