Clinical Pharmacology
in Drug Development
2021, 10(2) 144–152

DOI: 10.1002/cpdd.847

Effect of Hepatic Impairment on Cobimetinib Pharmacokinetics: The Complex Interplay Between Physiological Changes and Drug Characteristics

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Abstract

Cobimetinib is a kinase inhibitor indicated for use in combination with vemurafenib for treatment of unresectable/metastatic melanoma with specific BRAF mutations. Cobimetinib is extensively metabolized in liver; thus, patients with hepatic impairment (HI) might have increased cobimetinib exposure. In this study, we investigated the impact of HI on the pharmacokinetics (PK) and safety of cobimetinib. Subjects with normal hepatic function and mild to severe HI were enrolled. All subjects received a single oral dose of 10 mg cobimetinib, and serial blood samples were collected at specified times. Cobimetinib PK in subjects with mild and moderate HI was similar to that in those with normal liver function. However, subjects with severe HI, on average, showed ~30% lower total $AUC_{0\text{-}\infty}$ and ~2-fold higher unbound $AUC_{0\text{-}\infty}$ compared with those with normal hepatic function. These exposure differences can be explained by lower albumin levels observed in subjects with severe HI, the strong correlation between albumin level and the unbound fraction and the general PK variability of cobimetinib. In addition, previous studies with cobimetinib showed a lack of an exposure-response relationship for efficacy and safety. Therefore, collectively, our results suggest that the starting dose for patients with hepatic impairment can be the same as that for those with normal hepatic function.

Keywords

Child-Pugh classification, cobimetinib, hepatic impairment, pharmacokinetics, protein binding

Cobimetinib (also known as Cotellic, GDC-0973, XL518, or RO5514041; Figure 1) is a potent and selective oral inhibitor of MEK1/2, a kinase that activates ERK1/2 in the mitogen-activated protein kinase signaling cascade. This signaling pathway is highly conserved and plays an important role in cell proliferation, survival, migration, cell-cycle regulation, and angiogenesis.[1] Mutations in the *BRAF* gene have been implicated in several human cancers, with the highest incidence in melanoma.[2] Using a combination therapy of MEK and BRAF inhibitors, for example, a combination therapy of cobimetinib (an MEK inhibitor)

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Submitted for publication 15 January 2020; accepted 7 June 2020.

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[Correction added on 4 September 2020, after first online publication: "higher" is replaced by "lower" in the sentence "These exposure differences can be explained by higher albumin levels observed in subjects with severe HI, the strong correlation between albumin level and the unbound fraction and the general PK variability of cobimetinib."]

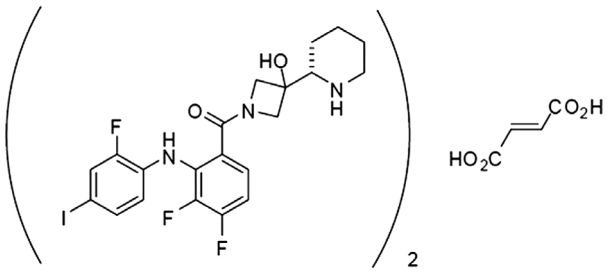

Figure 1. Chemical structure of cobimetinib ((S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl][3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate).

with vemurafenib (a BRAF inhibitor), has resulted in a greater suppression of the MAPK pathway.[3,4] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved cobimetinib, in combination with vemurafenib, for treating patients with unresectable or metastatic melanoma with a BRAF mutation. The recommended dose of cobimetinib is 60 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

Cobimetinib demonstrated linear pharmacokinetics (PK) in the dose range of 3.5 mg (initial dose of 0.05 mg/kg, assuming a 70-kg adult) to 100 mg. Following oral administration, cobimetinib is rapidly absorbed and reaches maximum plasma concentrations after approximately 1-3 hours.[5] Cobimetinib is 95% bound to human plasma proteins in vitro, independent of drug concentration.[6]

In healthy subjects, the absolute bioavailability of cobimetinib was determined to be 46%.[7] Results from a human mass balance study indicated that cobimetinib is extensively metabolized, followed by elimination in feces. Unchanged drug in feces and urine accounted for 6.6% and 1.6%, respectively, of the administered dose, indicating that cobimetinib is primarily metabolized with very little renal elimination. Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be major pathways of cobimetinib metabolism.[8] As hepatic impairment can affect the PK of drugs that are metabolized by the liver and may result in increased drug exposure, dose adjustments in patients with hepatic impairment may be needed depending on the degree of hepatic impairment, the extent of hepatic metabolism, and the clinical relevance of PK alteration.[9]

The recommendations of the FDA and the EMA to study the effect of hepatic impairment on the PK of drugs under development are clearly aimed at generating, if possible, specific dosage recommendations for patients with hepatic dysfunction. For PK evaluations, overall severity of hepatic impairment is usually graded according to the Child-Pugh classification (grade A, mild hepatic impairment; grade B, moderate hepatic impairment; and grade C, severe hepatic impairment).[10]

We conducted a study in subjects with hepatic impairment to understand the impact of hepatic dysfunction on cobimetinib PK, thereby providing dosing recommendations for cobimetinib in this population. The objectives of our study were to investigate the PK, safety, and tolerability of cobimetinib following the administration of a single oral 10-mg dose to subjects with mild, moderate, or severe hepatic impairment, stratified according to the Child-Pugh classification (grades A, B, and C, respectively) and in age-, weight-, and sex-matched healthy control subjects. Although 60 mg is the approved dose in patients with cancer, a 20-mg single dose of cobimetinib was administered to healthy subjects in other clinical pharmacology studies based on the safety profile in patients with cancer and the lack of benefit in healthy subjects.[7] As there was a potential for increased exposure in subjects with hepatic dysfunction, a dose of 10 mg was chosen for this study such that the exposure would not exceed the exposure considered safe in previous healthy subject studies.

Methods

Study Design

This study was conducted in accordance with the applicable United States Code of Federal Regulations (CFR) governing the Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), institutional review boards (21 CFR 56), the Investigational New Drug Application (21 CFR 312), and FDA approval to market a new drug (21 CFR 314). As such, these sections of United States Title 21 CFR, along with the applicable International Conference on Harmonization Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

This was an open-label, multicenter, single-dose, parallel-group study to determine the PK, safety, and tolerability of cobimetinib administered as a single dose of 10 mg to fasted adult male and female subjects with varying degrees of hepatic function, as determined by the Child-Pugh classification of hepatic impairment, and matched healthy control subjects.

Subjects

This study included adult subjects with varying degrees of hepatic dysfunction: subjects were classified as grade A, mild hepatic impairment, total score of 5-6; grade B, moderate hepatic impairment, total score of 7-9); or grade C, severe hepatic impairment, total score of 10-15). For a total of 28 subjects, 18 with hepatic impairment (6 with mild impairment, 6 with moderate impairment, and 6 with severe impairment, per Child-Pugh classification), and 10 with normal hepatic function were enrolled. Subjects with normal

hepatic function were dosed as a healthy control group to match those with hepatic impairment (mild and/or moderate and/or severe) with respect to age (±5 years), body weight (±15%), and sex. Subjects were 18 to 74 years old with a body weight ≥ 45 kg and a body mass index of 17-41 kg/m^2. Subjects with hepatic impairment had chronic (>6 months) and stable (no acute episodes of illness within the previous 1 month before screening because of deterioration in hepatic function) hepatic insufficiency with features of cirrhosis from any etiology.

Subjects were excluded from the study if they met any of the following criteria: significant illness (including infections, or hospitalization within the 2 weeks before dosing, except for subjects with hepatic impairment, who, because of their liver disease, may have been affected by significant medical problems that required frequent hospitalizations); use of strong CYP3A inducers or inhibitors, alcohol, or drug abuse, significant cardiovascular disease, history of uncontrolled diabetes (glycosylated hemoglobin [Hb_{A1c}] ≥ 9.0), clinically significant deviations from normal ranges in creatine phosphokinase, and liver function tests. However, subjects with hepatic impairment who had values outside the normal ranges (consistent with their hepatic condition) were allowed in the study. Women who were pregnant, lactating, or not using adequate contraception were ineligible, as were subjects who had participated in another clinical trial in which receipt of an investigational study drug occurred within 5 half-lives or 30 days, whichever was longer, or those with exposure to any biological therapy or investigational biological agent within 90 days before study entry. Written informed consent was obtained from subjects who participated in the study.

Study Sites

The study was conducted at 3 clinical sites—Anaheim Clinical Trials, Anaheim, California, Orlando Clinical Research Center, Orlando, Florida, and Clinical Pharmacology of Miami, Miami, Florida. Schulman Associates (now Advarra, Columbia, Maryland) served as the institutional review board. The groups (mild, moderate, severe, and normal) were enrolled in a parallel manner and all sites contributed to each group.

Treatment

On the morning of the treatment day (day 1), a single 10-mg cobimetinib oral dose (as two 5-mg tablets) was administered after a fasting period of at least 8 hours. Administration of the study drug was followed by fasting from food for at least 4 hours postdose. Subjects were confined at the clinical site from the time of check-in (day 1) until clinic discharge on day 5. Subjects were required to attend outpatient visits on days 7, 10, 12, 15, 20, and 25 (study completion) for PK blood sampling and safety assessments.

Analytical Methods

Total cobimetinib concentrations were measured using an liquid chromatography-tandemo mass spectrometry (LC-MS/MS) method.[11] Free fraction of cobimetinib in a human plasma sample was obtained by a single-use rapid equilibrium dialysis device with dialysis membranes of molecular weight cutoff of approximately 8000 (Thermo Scientific, Rockford, Illinois). A 0.3-mL spiked human plasma volume would be dialyzed against a 0.5-mL blank phosphate buffer volume for the protein-binding determination. A time-to-equilibrium experiment for cobimetinib was conducted to determine that a 6-hour incubation time was necessary for unbound cobimetinib to reach equilibrium in the buffer and plasma compartments. Protein-binding samples in a mixed matrix of human plasma:buffer (1:1, v/v) were analyzed for cobimetinib concentrations using an LC-MS/MS method.[11] The unbound percentage of cobimetinib was determined at t_{max} and at the time of the lowest cobimetinib concentration that was above the expected lower limit of quantitation for the protein-binding assay. The unbound cobimetinib concentrations were determined based on the calculated unbound percentage and the total plasma concentration measured in human plasma samples.

Safety and Tolerability

Safety and tolerability were assessed for up to 25 days after administration of cobimetinib and at the final examination on day 25. Subjective tolerability was evaluated by questioning subjects about any adverse events (AEs) and by their spontaneous reporting of AEs. AEs were classified according to severity (mild, moderate, or severe) and importance (serious or nonserious), for which the AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used. Safety was assessed by summaries of AEs, laboratory test results, vital signs, and electrocardiogram parameters.

Pharmacokinetic Statistical Methodology

PK parameters for total cobimetinib, maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), half-life ($t_{1/2}$), and oral clearance (CL/F) were estimated using Phoenix WinNonlin (Pharsight Corporation, cersion 6.2.1). Unbound $AUC_{0-\infty}$ and C_{max} were determined for individual subjects by multiplying their individual fraction unbound (Fu) by total $AUC_{0-\infty}$ or C_{max}. The unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$)

Table 1. Summary of Characteristics and Degree of Hepatic Impairment of All Subjects Included in the Study (n = 28)

Demographic	Normal Hepatic Function (n = 10)	Mild (n = 6)	Moderate (n = 6)	Severe (n = 6)	All Hepatic Impairment (n = 18)	All Subjects (n = 28)
Age (years), mean ± SD (min, max)	56 ± 6.8 (43, 68)	59 ± 2.8 (56, 64)	61 ± 2.9 (58, 64)	53 ± 5.3 (46, 62)	58 ± 5.1 (46, 64)	57 ± 5.6 (43, 68)
Weight (kg), mean ± SD (min, max)	83.4 ± 16.5 (55.5,111.2)	76.8 ± 14.3 (55.0, 96.6)	89.5 ± 14.4 (70.4,111.0)	80.8 ± 23.2 (53.0, 112.0)	82.4 ± 17.6 (53.0, 112.0)	82.7 ± 16.9 (53.0, 112.0)
BMI (kg/m^2), mean ± SD (min, max)	28.3 ± 4.5 (21.0, 33.9)	27.2 ± 6.3 (17.6, 34.8)	30.3 ± 4.2 (23.9, 36.7)	27.4 ± 5.9 (19.4, 35.7)	28.3 ± 5.4 (17.6, 36.7)	28.3 ± 5.0 (17.6, 36.7)
Albumin (g/dL), mean ± SD (min, max)	4.3 ± 0.1 (4.1-4.6)	4.2 ± 0.2 (4.1-4.5)	4.0 ± 0.3 (3.8-4.6)	2.7 ± 0.4 (2.2-3.2)	3.7 ± 0.8 (2.2-4.6)	3.9 ± 0.7 (2.2-4.6)
Sex, n (%)						
Male	7 (70.0%)	3 (50.0%)	5 (83.3%)	4 (66.7%)	12 (66.7%)	19 (67.9%)
Female	3 (30.0%)	3 (50.0%)	1 (16.7%)	2 (33.3%)	6 (33.3%)	9 (32.1%)
Race, n (%)						
American Indian or Alaska Native	—	—	—	1 (16.7%)	1 (5.6%)	1 (3.6%)
Asian	—	1 (16.7%)	—	—	1 (5.6%)	1 (3.6%)
Other than Indian subcontinent	—	1 (16.7%)	—	—	1 (5.6%)	1 (3.6%)
Black or African American	1 (10.0%)	—	—	—	—	1 (3.6%)
White	8 (80.0%)	5 (83.3%)	6 (100%)	5 (83.3%)	16 (88.9%)	24 (85.7%)
Other race	1 (10.0%)	—	—	—	—	1 (3.6%)
Ethnicity, n (%)						
Hispanic or Latino	5 (50.0%)	3 (50.0%)	1 (16.7%)	4 (66.7%)	8 (44.4%)	13 (46.4%)
Not Hispanic or Latino	5 (50.0%)	3 (50.0%)	5 (83.3%)	2 (33.3%)	10 (55.6%)	15 (53.6%)

BMI, body mass index; n, number of subjects for each category; max, maximum; min, minimum; N, number of subjects for each cohort/overall; % = n/N × 100.

was used to determine the unbound CL/F (CL/F_u; dose/$AUC_{0\text{-}\infty,u}$).

The primary PK parameters—C_{max} and $AUC_{0\text{-}\infty}$—were analyzed using a mixed-model analysis of variance to determine the 90% confidence interval (CI) of the ratio between each level of impaired hepatic function versus the control group. These analyses were performed on the log-transformed cobimetinib C_{max} and $AUC_{0\text{-}\infty}$. The least-squares (LS) means of the test and reference treatments obtained from the mixed model were back-transformed to give geometric LS means (a point estimate). The 90%CI for differences in LS means between the test and reference treatments obtained from the mixed model were also back-transformed to give 90%CIs for the ratio of the test treatment relative to the reference treatment. These calculations were performed using SAS version 9.3.

Results

Study Population

Overall, 28 subjects (19 men and 9 women) were enrolled in the study and were assigned to 1 of the 4 groups: healthy control, n = 10; mild hepatic impairment (Child-Pugh grade A, n = 6); moderate hepatic impairment (Child-Pugh grade B, n = 6); and severe impairment (Child-Pugh grade C, n = 6). The demographic characteristics were similar across the groups, with a mean age of 57 years and body mass index of 28.3 kg/m^2 (Table 1). Age, weight, BMI, and sex were similar among the 4 groups. None of the subjects with normal hepatic function had a history of hepatic disease or impairment.

Pharmacokinetics

Mean cobimetinib plasma concentration profiles in subjects with mild and moderate hepatic impairment were very similar to those in healthy subjects. However, exposure was lower in subjects with severe hepatic impairment. In all 4 groups of subjects, after reaching C_{max}, the plasma concentration of cobimetinib appeared to decline in a multiphasic manner, consistent with prior observations (Figure 2).

C_{max} and AUC were relatively unaffected in subjects with mild and moderate hepatic impairment compared with healthy subjects. The geometric mean ratios (GMRs) comparing C_{max} in subjects with mild and moderate hepatic impairment with those with normal hepatic function were 92.0% and 85.0%, respectively. Similarly, GMR comparing $AUC_{0\text{-}\infty}$ in subjects

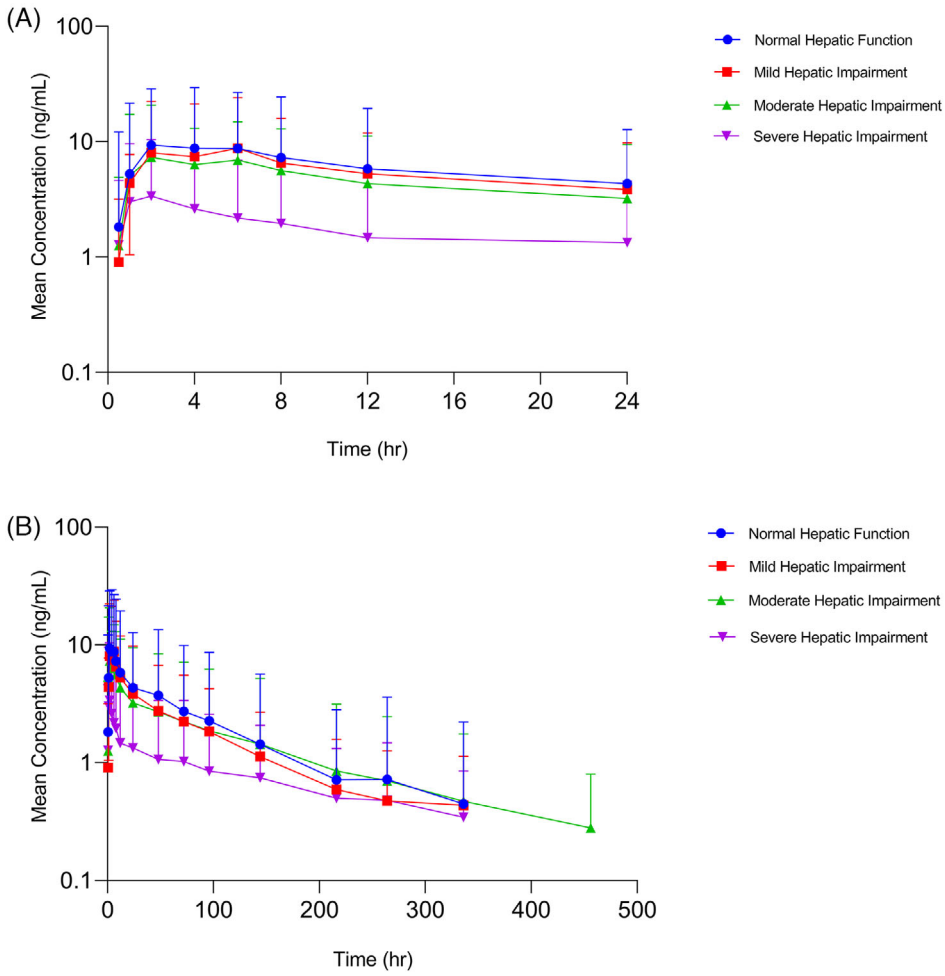

Figure 2. Cobimetinib mean + SE plasma pharmacokinetic profiles (A) 0-24 hours and (B) 0-t_{last} in healthy subjects (n = 10) and subjects with mild hepatic impairment (n = 6) or moderate hepatic impairment (n = 6) or severe hepatic impairment (n = 6) after administration of a single 10-mg dose of cobimetinib.

with mild and moderate hepatic impairment with those with normal hepatic function were 98.0% and 103.0%, respectively. In contrast, comparison of subjects with severe hepatic impairment and subjects with normal hepatic function resulted in GMRs of 39.0% for C_{max} and 68.5% for $AUC_{0-\infty}$ (Table 2).

Other PK parameters of cobimetinib are shown in Table 2. The terminal elimination half-life ($t_{1/2}$) in subjects with mild and moderate hepatic impairment was within approximately 1.1- and 1.3-fold, respectively, relative to those with normal hepatic function. However, mean $t_{1/2}$ was longer in subjects with severe hepatic impairment compared with those with normal hepatic function (~1.8-fold).

Unbound C_{max} of cobimetinib in subjects with mild, moderate, or severe hepatic impairment was comparable to that in healthy subjects (Figure 3A). However, there was a trend of higher unbound $AUC_{0-\infty}$ in patients with hepatic impairment compared with those with normal liver function (Figure 3B). PK parameters for unbound cobimetinib are summarized in Table 3. The GMRs comparing unbound exposure (C_{max}, $AUC_{0-\infty}$) in subjects with mild and moderate hepatic impairment with those with normal hepatic function were generally near 100.0% (range, 113%-137%), and every 90%CI was inclusive of 100.0% (Table 3). A similar trend was observed for C_{max} in subjects with severe hepatic impairment; however, the GMR for $AUC_{0-\infty}$ was 196.0 (90%CI, 131-292) in these subjects.

Mean ± SD albumin levels in subjects with normal function and subjects with mild, moderate, and severe hepatic impairment were 4.42 ± 0.27, 4.34 ± 0.32, 4.02 ± 0.19, and 2.73 ± 0.40 g/dL, respectively. A strong correlation was observed between albumin level and unbound fraction of cobimetinib in this study (Figure 4).

Table 2. Pharmacokinetic Parameters of Cobimetinib After the Administration of a Single Oral 10-mg Dose to Healthy Subjects and Subjects With Mild, Moderate, or Severe Hepatic Impairment

Pharmacokinetic Parameters	Descriptive Statistics	Normal Hepatic Function (n = 10)	Mild Hepatic Impairment (n = 6)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment (n = 6)
Cmax, ng/mL	Geo mean (%CV)	9.07 (62.3)	8.36 (42.9)	7.70 (33.2)	3.54 (63.5)
	Mean (SD)	10.7 (7.41)	9.00 (4.09)	8.03 (2.49)	3.97 (1.77)
$AUC_{0-\infty}$, ng·h/mL	Geo mean (%CV)	499 (73.4)	487 (51.3)	515 (58.1)	342 (46.8)
	Mean (SD)	637 (606)	530 (206)	579 (301)	370 (163)
C_{max}, GMR (90%CI)	NA	NA	92.2 (61.9, 137.3)	84.9 (57.0, 126.5)	48.2 (31.6, 73.6)
$AUC_{0-\infty}$, GMR (90%CI)	NA	NA	97.6 (59.3, 160.6)	103 (62.6, 169.6)	68.5 (40.4, 116.2)
tmax (h)	Median (min, max)	2.00 (1.00, 6.00)	6.00 (2.00, 6.00)	4.00 (2.00, 6.00)	2.00 (1.00, 4.00)
t1/2 (h)	Geo mean (%CV)	76.3 (29.0)	87.3 (45.8)	101 (25.3)	139 (25.8)
	(min, max)	(51.1, 113)	(54.7, 187)	(73.9, 130)	(116, 212)
	Mean (SD)	79.1 (22.7)	95.2 (48.2)	104 (24.4)	143 (40.4)
CL/F (L/h)	Geo mean (%CV)	20.0 (73.4)	20.5 (51.3)	19.4 (58.1)	29.2 (46.8)
	Mean (SD)	23.4 (11.6)	22.9 (13.2)	21.9 (11.7)	31.7 (14.5)

Geo mean, geometric mean; %CV, coefficient of variation; mean, arithmetic mean; SD, standard deviation; min, minimum; max, maximum; n, number of subjects; GMR, geometric mean ratio (test/reference); CI, confidence interval; CL/F, oral clearance; C_{max}, maximum plasma concentration; AUC0-∞, area under the plasma concentration-time curve from time 0 to infinity.

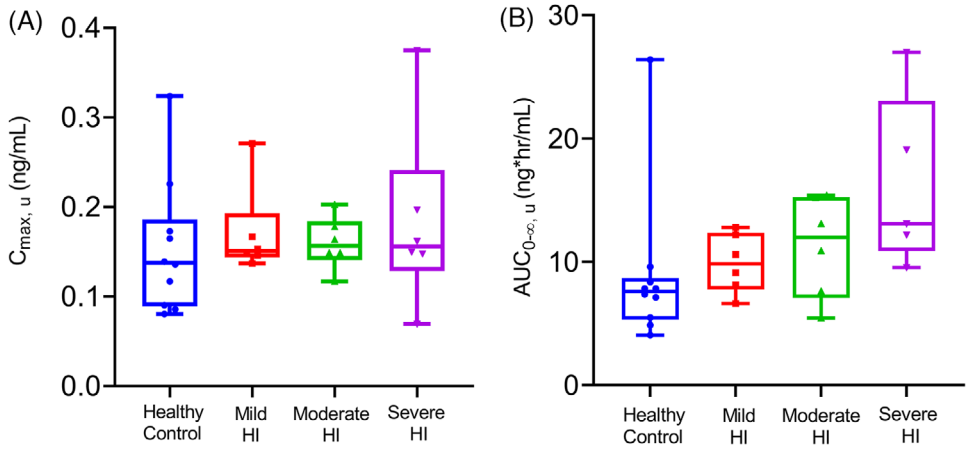

Figure 3. Unbound cobimetinib C_{max} (A) and $AUC_{0-\infty}$ (B) in healthy subjects (n = 10) and subjects with mild hepatic impairment (n = 6), moderate hepatic impairment (n = 6), or severe hepatic impairment (n = 6) after administration of a single 10-mg dose of cobimetinib.

Safety and Tolerability

Single oral doses of 10 mg cobimetinib were well tolerated in subjects with mild, moderate, or severe hepatic impairment and subjects with normal hepatic function. The type and incidence of treatment-emergent AEs (TEAEs) were generally similar across all groups. The TEAEs were dyspepsia, dizziness, gastroesophageal reflux disease, and headache. No deaths, serious AEs, or grade ≥ 3 TEAEs were reported, and no subjects discontinued the study because of a TEAE. Except for 1 subject in the normal hepatic function cohort, who had one grade 2 TEAE (moderate; an episode of gout during the study that was judged by the investigator to be unrelated to cobimetinib). All TEAEs were grade 1 (mild).

Discussion

This study was conducted to assess the potential impact of hepatic dysfunction on the PK of cobimetinib following a single oral dose of 10 mg. Given that cobimetinib is extensively metabolized in the liver, the goal of this study was to develop a recommendation for dose adjustment should it be found that subjects with hepatic dysfunction would be at risk of increased drug levels because of reduced clearance of cobimetinib.

Analysis of the PK data from this study indicated no effect of mild and moderate hepatic impairment on the total cobimetinib exposure (C_{max} and AUC) compared with subjects with normal hepatic function. In addition,

Table 3. Pharmacokinetic Parameters of Unbound Cobimetinib After the Administration of a Single Oral 10-mg Dose to Healthy Subjects and Subjects With Mild, Moderate, or Severe Hepatic Impairment

Pharmacokinetic Parameters	Descriptive Statistics	Normal Hepatic Function (n = 10)	Mild Hepatic Impairment (n = 6)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment (n = 6)
Unbound (%)	Geo mean (%CV)	1.54 (26.2)	1.97 (26.2)	2.05 (33.2)	4.43 (24.0)
	Mean (SD)	1.59 (0.389)	2.04 (0.584)	2.16 (0.785)	4.54 (1.08)
Cmax, u (ng/mL)	Geo mean (%CV)	0.140 (46.7)	0.166 (25.3)	0.158 (18.9)	0.163 (58.5)
	Mean (SD)	0.154 (0.0750)	0.171 (0.0500)	0.160 (0.0293)	0.184 (0.103)
AUC0-∞, u (ng·h/mL)	Geo mean (%CV)	7.71 (54.2)	9.66 (25.6)	10.6 (43.4)	15.1 (42.6)
	Mean (SD)	8.90 (6.38)	9.91 (2.39)	11.3 (4.07)	16.2 (6.97)
Unbound CL/F (L/h)	Geo mean (%CV)	1300 (54.2)	1040 (25.6)	947 (43.4)	662 (42.6)
	Mean (SD)	1430 (575)	1060 (276)	1020 (466)	705 (264)
$C_{max,u}$, GMR (90%CI)	NA	NA	118 (83-168)	113 (80-160)	116 (82-165)
AUC0-∞, u GMR (90%CI)	NA	NA	125 (86-183)	137 (94-200)	196 (131-292)

Geo mean, geometric mean; %CV, coefficient of variation; mean, arithmetic mean; SD, standard deviation; n, number of subjects; GMR, geometric mean ratio (test/reference); CI, confidence interval; $C_{max,u}$, maximum plasma concentration of unbound cobimetinib; AUC0-∞,u, area under the unbound plasma concentration-time curve from time 0 to infinity; unbound CL/F, oral clearance of unbound cobimetinib.

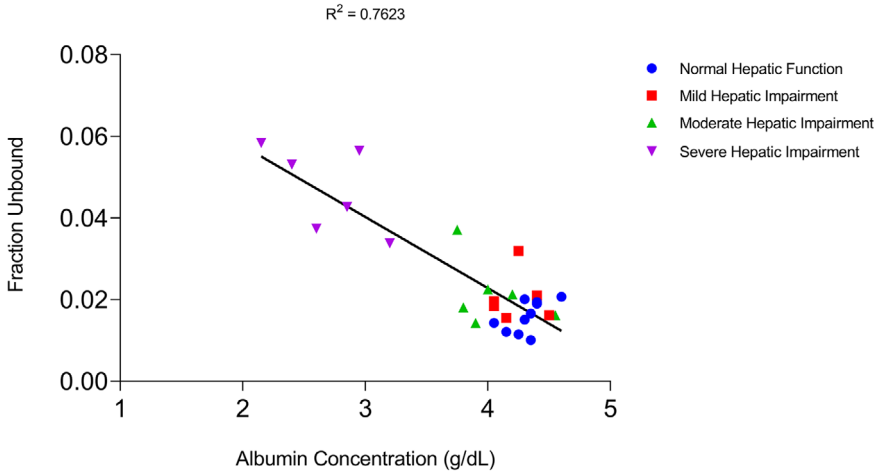

Figure 4. Individual fraction unbound versus albumin concentrations in patients with normal or impaired hepatic function.

the single 10-mg oral dose was safe and well tolerated in these groups of patients. Therefore, it was concluded that dose adjustment of cobimetinib would not be required for patients with mild and moderate hepatic impairment.

If hepatic dysfunction had affected the clearance of cobimetinib, the total drug exposure would be expected to be higher in subjects with hepatic impairment compared with normal hepatic function. Conversely, the total cobimetinib exposure in subjects with severe hepatic impairment in this study was lower than that in subjects in other cohorts. C_{max} was about 60% lower and AUC was 30% lower in these subjects relative to those of subjects with normal hepatic function.

Cobimetinib, like ceftriaxone and clarithromycin, is a low extraction drug (extraction ratio of 0.13) with high protein binding (95%).[9,12] Its hepatic clearance is sensitive to both intrinsic clearance and, more importantly, changes in the protein binding.[12,13]

Liver dysfunction not only reduces drug hepatic metabolism, it can also affect plasma protein binding, which in turn could influence distribution and elimination processes.[14,15] The albumin levels in patients with severe hepatic impairment in this study were lower by approximately 50% compared with those in other cohorts. In addition, a strong correlation between albumin concentration and unbound fraction of cobimetinib was observed, suggesting that the unbound fraction increased with a reduction in albumin level because of hepatic dysfunction. Drug clearance generally increases when there is more unbound drug available in plasma that passes through hepatic membranes to reach hepatocytes, where it is metabolized.[16] The observed decrease in total drug exposure in subjects with

severe hepatic impairment in this study is consistent with this hypothesis.

On the other hand, changes in the unbound fraction would not affect the unbound exposure of a drug like cobimetinib, which has a low extraction ratio cleared by liver and administered orally.[17,18] In this study, unbound C_{max} was comparable in the hepatic impairment groups and the healthy control group. Although average unbound AUC_{inf} ($AUC_{inf,u}$) for cobimetinib was ~2-fold higher in the severe hepatic impairment group relative to the healthy control group, the range of individual $AUC_{inf,u}$ between the 2 groups overlapped, suggesting that the change in unbound exposure is likely within the general PK variability of cobimetinib.

Among various cobimetinib studies conducted in cancer patients, including a pivotal phase 3 study, high variability in the total cobimetinib exposure (60%CV for apparent clearance) was observed. However, the unbound concentrations of cobimetinib were not measured in these studies, and the relationship between unbound concentration and patient safety was not assessed. An exposure-response analysis was conducted with Phase 3 study data using total (free and bound) cobimetinib exposure and showed a lack of an exposure-response relationship for both efficacy and safety (adverse events). The 2-fold increase in the unbound cobimetinib exposure observed in the present hepatic impairment study would likely be within the exposure range of unbound concentrations in cancer patients. Cancer patients with hepatic impairment receiving multiple doses of cobimetinib would be expected to have similar changes as seen after a single dose in this study because cobimetinib has linear PK (with dose and time). The results from this study, along with the lack of an exposure-safety relationship, suggest that the marketed dose (60 mg) would be tolerated in patients with severe hepatic impairment. Therefore, the starting dose for these patients with severe hepatic impairment would be the same as that for patients with normal hepatic function, and dose adjustment would only be warranted if clinically indicated based on patient tolerability.

When cobimetinib was first approved, the recommendation that no dose adjustment is needed for patients with mild hepatic impairment was based on a population PK analysis, which showed similar steady-state AUC in subjects with mild hepatic impairment and those with normal hepatic function.[19] Because of the limited number of patients with moderate and severe hepatic impairment included in that analysis, no definitive recommendation could be provided for these patients with moderate and severe hepatic impairment regarding dose of cobimetinib. This dedicated hepatic impairment study provides further support for the recommendation in patients with mild hepatic impairment and expands the understanding of the impact of moderate and severe hepatic dysfunction on cobimetinib PK. Based on the results presented in this study, no dose adjustment was recommended for cobimetinib in patients with moderate and severe hepatic impairment. Lastly, this study also highlights the complex interplay between the disease state and drug characteristics, leading to changes in the PK parameters of cobimetinib that were not easily predictable.

Acknowledgments

The authors acknowledge Silver Alkhafaji for her contributions to this article. Editorial assistance was provided by Anshin BioSolutions Corp.

Conflicts of Interest

The authors are either employees of Genentech Inc. and/or stockholders of the Roche Group.

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