Clinical Pharmacology in Drug Development
2019, 8(3) 346–354

DOI: 10.1002/cpdd.470

An Open-Label, Phase 1 Study to Assess the Effects of Hepatic Impairment on Pomalidomide Pharmacokinetics

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Abstract

Pomalidomide is an immunomodulatory drug and the dosage of 4 mg per day taken orally on days 1-21 of repeated 28-day cycles has been approved in the European Union and United States to treat patients with relapsed/refractory multiple myeloma. Because pomalidomide is extensively metabolized prior to excretion, a total of 32 subjects (8 healthy subjects in group 1; 8 subjects with severe hepatic impairment in group 2; 8 subjects with moderate hepatic impairment in group 3; and 8 subjects with mild hepatic impairment in group 4) were enrolled in a multicenter, open-label, single-dose study to assess the impact of hepatic impairment on pomalidomide exposure. Following administration of a single oral dose of 4-mg pomalidomide, the geometric mean ratios of pomalidomide total plasma exposures (AUC) were 171.5%, 157.5%, and 151.2% and the geometric mean ratios of pomalidomide plasma peak exposures (C_{max}) were 75.8%, 94.8%, and 94.2% for subjects with severe, moderate, or mild hepatic impairment, respectively, versus healthy subjects. Pomalidomide administered as a single oral 4-mg dose was safe and well tolerated by healthy subjects and subjects with severe, moderate, or mild hepatic impairment. Based on the pharmacokinetic results from this study, the pomalidomide prescribing information approved by the US Food and Drug Administration recommends for patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), a 3-mg starting daily dose (25% dose reduction) and for patients with severe hepatic impairment (Child-Pugh class C), a 2-mg starting daily dose (50% dose reduction).

Keywords

dose recommendation, hepatic impairment, pomalidomide, pharmacokinetics

Pomalidomide, an immunomodulatory drug analogue structurally similar to thalidomide,[1,2] is an immunomodulatory agent with antineoplastic activity.[3,4] In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells[5–9] and showed immunomodulatory activity.[10–12] Pomalidomide has been studied for treatment of various hematologic and non-neoplastic hematologic disorders,[1,13–15] and the dosage of 4 mg per day taken orally on days 1-21 of repeated 28-day cycles is approved (in combination with dexamethasone) in the European Union and United States for the treatment of patients with multiple myeloma who have received ≥2 prior therapies, including lenalidomide and bortezomib (in the European Union; a proteasome inhibitor in the United States), and who have progressed on or within 60 days of completion of the last therapy or have disease progression on the last therapy.[1,13,15] This combination (pomalidomide plus low-dose dexamethasone) increased progression-free survival and overall survival compared with high-dose dexamethasone.[1,13] Thrombocytopenia, neutropenia, and anemia were the most common grade 3/4 adverse events.[13]

The pharmacokinetics (PK) of pomalidomide after a single oral dose of 4 mg in plasma was characterized by rapid absorption (median time to peak plasma drug concentration [t_{max}] 2.50-3.25 hours post dose) and rapid elimination (mean terminal half-

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Submitted for publication 2 February 2018; accepted 20 March 2018.

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life [$t_{1/2}$] range of 8.90-11.21 hours). There was no clinically relevant impact of food intake on pomalidomide plasma exposure and pomalidomide can be taken without regard to food consumption. Human [^{14}C]pomalidomide absorption, metabolism, and excretion study showed that the recovery of total [^{14}C]-radioactivity was approximately 88% of the administered dose, with 72.8% and 15.5% recovered in urine and feces, respectively.[16] Pomalidomide and 8 metabolites were detected in human plasma. Based on exposure (area under the plasma drug concentration-time curve from time 0 to last time with detectable levels [$AUC_{0\text{-}t}$]), unchanged pomalidomide accounted for approximately 70% of circulating total radioactivity (TRA) exposure and no metabolite exposure exceeded 10% of the plasma TRA or pomalidomide. Unchanged pomalidomide was detected as a minor radio-component in the urine, accounting for 2.2% of the dose, while the 4 predominant metabolites (hydrolysis of glutarimide and glucuronide conjugates of hydroxylated pomalidomide) accounted for 52.8% of the dose excreted in the urine, suggesting extensive metabolism of pomalidomide prior to its excretion. Among the 15.5% of the administered dose recovered in feces, unchanged pomalidomide accounted for 7.7% of the dose in samples collected during the 96-hour post-dose period. In addition to pomalidomide, 4 metabolites were detected in fecal extracts. Consistently, several studies showed that the PK of pomalidomide was not remarkably affected in renally impaired patients,[17,18] and the liver plays the predominant role in eliminating pomalidomide in vivo.

Pomalidomide clearance pathways included cytochrome P450 (CYP)–mediated hydroxylation with subsequent glucuronidation (43% of the dose), glutarimide ring hydrolysis (25%), and excretion of unchanged drug (10%). 5-Hydroxy pomalidomide, the notable oxidative metabolite, was formed primarily via CYP1A2 and CYP3A4. A phase 1, two-part, open-label drug interaction trial[19] to evaluate the effect of multiple doses of a CYP3A/P-glycoprotein inhibitor (ketoconazole), a CYP1A2 inhibitor (fluvoxamine), and a CYP3A inducer (carbamazepine), on the PK of pomalidomide has been conducted. The results indicate that co-administration of a strong CYP3A inhibitor or inducer or a P-glycoprotein inhibitor with pomalidomide had no clinically relevant effect on exposure to pomalidomide, while co-administration of a strong CYP1A2 inhibitor with pomalidomide in the presence of a strong CYP3A inhibitor approximately doubled the exposure of pomalidomide.[19]

The intended patient population for pomalidomide is generally elderly, a population that has a higher prevalence of chronic liver disease compared with younger populations. As hepatic metabolism represents a relatively major clearance pathway for pomalidomide, hepatic impairment could potentially affect pomalidomide's PK by decreasing hepatic clearance. Therefore, a total of 32 subjects (8 healthy subjects in group 1; 8 subjects with severe hepatic impairment in group 2; 8 subjects with moderate hepatic impairment in group 3; and 8 subjects with mild hepatic impairment in group 4) were enrolled in a multicenter, open-label, single-dose study to assess the effect of hepatic impairment on pomalidomide exposure (CC-4047-CP-009). The primary objective of this study was to evaluate the effect of various degrees of hepatic impairment on the PK of a single oral dose of pomalidomide in male subjects; the secondary objective of this study was to evaluate the effect of hepatic impairment on the safety of a single oral dose of pomalidomide in male subjects.

Methods

All subjects provided written informed consent prior to screening. This study was conducted and monitored in accordance with Celgene procedures and the study protocol. These procedures comply with the ethical principles of the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice (GCP), as required by the major regulatory authorities. The conduct also complied with the Declaration of Helsinki, Title 21 of the US Code of Federal Regulations, Parts 50 and 56 concerning informed consent and institutional review board regulations, and applicable national, state, and local laws or regulations. This study was conducted in 2 clinical sites: DaVita Clinical Research (Minneapolis, Minnesota) and Division of Clinical Pharmacology, University of Miami (Miami, Florida) and was approved by the institutional review boards of Western Institutional Review Board (Puyallup, Washington) and University of Miami Human Subjects Research Office (Miami, Florida), respectively.

Study Design

This was a multicenter, open-label, single-dose study designed to assess the impact of severe (part 1, group 2) hepatic impairment on the PK of pomalidomide following oral administration of a single 4-mg dose of pomalidomide. Healthy subjects with normal hepatic function (part 1, group 1) were enrolled for PK comparison. Degrees of hepatic impairment were determined during screening by the subject's score according to the Pugh modification of the Child Classification of Severity of Liver Disease.[20,21] Because exposures in severely hepatically impaired subjects were substantially different from the healthy subjects, subjects with moderate and mild hepatic impairment (part 2, group 3 and group 4) were enrolled. Group 1 and

group 2 subjects were matched with respect to age (±10 years) and weight (±13.61 kg [±30 pounds]). Subjects in groups 3 and 4 were also similar to subjects in group 1 with respect to age and weight. Although light smokers (defined as smoking no more than 10 cigarettes, or consuming the equivalent in tobacco, per day) could participate in the study, smoking or the use of other tobacco products was not allowed for 7 days, from prior to baseline admission to the end of all study procedures.

The entire study consisted of a screening phase, one treatment period, and a follow-up telephone call. Parts 1 and 2 were conducted sequentially, with part 2 initiation dependent on the results from part 1. Within no more than 21 days (day –21) and no less than 2 days (day –2) prior to the start of the treatment, subjects underwent routine screening procedures, including complete physical examination (PE), 12-lead electrocardiogram (ECG), vital signs, clinical laboratory safety tests (chemistry, hematology, and urinalysis), serology screen, and drug/alcohol screen. Eligible subjects returned to the study center on day –1 of period 1 for baseline assessments. During the study period, subjects were confined at the study center from day –1 through the morning of day 3. Subjects were discharged from the study center on day 3 upon completion of study procedures. Upon completion of part 1, PK and safety data were reviewed by the investigator and Celgene and a decision was made to initiate part 2.

Results from separate clinical data assessing the impact of food on pomalidomide PK showed there was no clinically relevant effect of food intake on pomalidomide exposure, demonstrated by food only decreasing area under the plasma concentration time curve from time 0 extrapolated to infinity (AUC) by 8% (data on file). Although food does not affect pomalidomide PK and pomalidomide can be taken without regard to food consumption, as indicated on the product label, food restriction was still applied to all enrolled subjects in this protocol, ie, a single 4-mg pomalidomide tablet was administered to each subject at approximately 8 AM on the morning of day 1 with approximately 240 mL of noncarbonated, room temperature water. Water was allowed ad libitum except from 60 minutes prior to dosing until 2 hours post dose (excluding the water given with pomalidomide). After dosing, food and beverages (except water, as described above) were withheld from all subjects until at least 4 hours post dose.

In vitro data suggest that pomalidomide is a substrate of multiple CYP450 enzymes and its metabolism is mediated primarily by CYP1A2 and CYP3A4 isozymes; therefore, all subjects were required to refrain from consuming strong or moderate CYP1A2 and CYP3A inhibitors and inducers from 14 days prior to baseline admission to the end of all study procedures.

Blood Collection for Pharmacokinetic Analysis

Serial blood samples were collected pre dose and up to 48 hours post dose at the following time points: 0 (pre dose), 0.25, 1, 2, 2.5, 4, 6, 8, 12, 24, 30, 40, and 48 hours post dose) for determination of plasma pomalidomide concentrations.

Safety Assessment

Safety was monitored throughout the study. Safety evaluations included adverse event (AE) reporting, PEs, vital sign measurements, 12-lead ECGs, and clinical laboratory safety tests. All concomitant medications were assessed and recorded throughout the study, from the time the informed consent document was signed until study completion (follow-up safety telephone call). Adverse events and serious AEs (SAEs) were assessed and recorded from the time the subject signed the informed consent document until study completion (follow-up safety telephone call), and when made known to the investigator within 28 days after the last dose of pomalidomide (and SAEs that were suspected of being related to pomalidomide made known to the investigator at any time thereafter).

If repeated safety measurements were needed at discharge, subjects were instructed to return to the study center at appropriate times for further testing. Otherwise, the safety follow-up was conducted by telephone 7 days ± 1 day from the last dose.

Bioanalytical Methodology

To determine human plasma samples for pomalidomide concentrations, a validated liquid chromatography–tandem mass spectrometry assay was utilized[16]. As an internal standard, plasma samples were spiked with stable ^{13}C-labeled pomalidomide. Pomalidomide and ^{13}C-labeled pomalidomide were extracted from plasma (stabilized with citric acid) using liquid-liquid extraction with methyl tertiary butyl ether. After transfer to a new tube, the solvent was evaporated and the samples were reconstituted and injected for liquid chromatography–tandem mass spectrometry analysis using a Phenomenex analytical column (Luna C18 (2), 50 × 2.0 mm, 5 μm, Torrance, California). Positive ions were measured in the multiple reaction monitoring mode using a SciexAPI-4000 tandem mass spectrometer (Sciex, Framingham, Massachusetts) equipped with a Turbo Ion Spray source. For the quality control samples, the accuracy range was 91.0–106.9%. The lower limit of quantification was 0.25 ng/mL.

Pharmacokinetic Analyses

Noncompartmental PK parameters such as maximum plasma drug concentration (C_{max}), t_{max}, $AUC_{0\text{-}t}$, AUC, $t_{1/2}$, CL/F, and percentage of AUC due to extrapolation

from the time for the last quantifiable concentration to infinity (AUC%extrap) were calculated from the plasma concentration-time data with Phoenix WinNonlin Professional Version 6.3 (Pharsight, a Certara company, St. Louis, Missouri). Actual sampling times were used in the calculations. Descriptive statistics (sample size, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum) were provided for concentrations at each time point and for all PK parameters.

Statistical Analyses

No formal sample size calculation was performed. Up to 32 subjects (8 healthy subjects in group 1; 8 subjects in group 2; 6-8 subjects in group 3; and 6-8 subjects in group 4) were chosen as a suitable number to achieve the objective of this study, based on other similar studies from the literature. The goal was to have a sufficient number of evaluable plasma concentration time points to adequately characterize the PK of the study drug in each group.

For $AUC_{0\text{-}t}$, AUC, and C_{max}, an analysis of variance (ANOVA) model was performed to calculate the ratio of geometric means (GMR) and its 90% confidence interval between subjects with hepatic impairment and matched healthy subjects. The ANOVA model included group (severe, moderate, mild, and healthy) as fixed effect. The t_{max} was analyzed by nonparametric method.

All safety assessments, including AEs, vital sign measurements, clinical laboratory information, concomitant medications, PEs, and ECG interpretations, were tabulated and summarized as appropriate. Adverse events were recorded and classified using the Medical Dictionary for Drug Regulatory Activities classification system (Celgene-approved version). Treatment emergent AEs (TEAEs) were summarized by frequency, severity, and relatedness to study drug. The frequency (number of TEAEs and number of subjects experiencing a TEAE) of TEAEs were tabulated by system organ class and preferred term. In the per-subject analyses, a subject having the same event more than once was counted only once. Laboratory and vital sign data were summarized descriptively (sample size, mean, standard deviation, minimum, median, and maximum). There was no statistical comparison of safety parameters between treatments.

Results

Demographic and Other Baseline Characteristics

A total of 32 subjects were enrolled and 32 subjects (100%) completed the study. Demographic data are presented in Table 1. Overall, demographic characteristics were similar across the groups. All subjects were male and the majority were white (87.5%) and Hispanic or Latino (62.5%). Two subjects in the mild hepatic impairment group and one subject in the moderate hepatic impairment group had medical history findings that were considered clinically significant. None of the medical history findings prevented the subjects from enrolling into the study.

Five subjects (two subjects in the mild hepatic impairment group, two subjects in the moderate hepatic impairment group, and one subject in the severe hepatic impairment group) had a positive drug screen result at screening and/or day –1. The positive results were due to prescribed medications, which were allowed per protocol. A total of 14 subjects (6 subjects in the mild hepatic impairment group, 5 subjects in the moderate hepatic impairment group, and 3 subjects in the severe hepatic impairment group) had a positive result for hepatitis B virus surface antigen or hepatitis C virus antibody, or both. The positive results were allowed per protocol. None of the PE findings at screening

Table 1. Demographic and Other Baseline Characteristics

	Group				
Demographics	1 Healthy Subjects (n = 8)	2 Severe Hepatic Impairment (n = 8)	3 Moderate Hepatic Impairment (n = 8)	4 Mild Hepatic Impairment (n = 8)	Total (N = 32)
Age (years)					
Mean (range)	55.8 (50–66)	53.1 (42–62)	59.3 (54–69)	56.4 (51–68)	56.1 (42–69)
Height (cm)					
Mean (range)	175.18 (167.0–182.3)	171.50 (152.0–182.0)	171.13 (160.0–181.0)	174.50 (165.0–187.0)	173.08 (152.0–187.0)
Weight (kg)					
Mean (range)	86.28 (70.0–101.2)	90.48 (69.0–114.0)	87.46 (71.5–100.3)	86.85 (71.7–103.0)	87.77 (69.0–114.0)
Body mass index (kg/m^2)					
Mean (range)	28.10 (24.3–31.9)	30.79 (23.9–36.6)	29.88 (24.9–35.2)	28.66 (23.1–34.4)	29.36 (23.1–36.6)
Race, n (%)					
White	7 (87.5)	7 (87.5)	8 (100)	6 (75.0)	28 (87.5)
Black or African American	1 (12.5)	1 (12.5)	0	2 (25.0)	4 (12.5)
Ethnicity, n (%)					
Hispanic or Latino	6 (75.0)	6 (75.0)	5 (62.5)	3 (37.5)	20 (62.5)
Not Hispanic or Latino	2 (25.0)	2 (25.0)	3 (37.5)	5 (62.5)	12 (37.5)

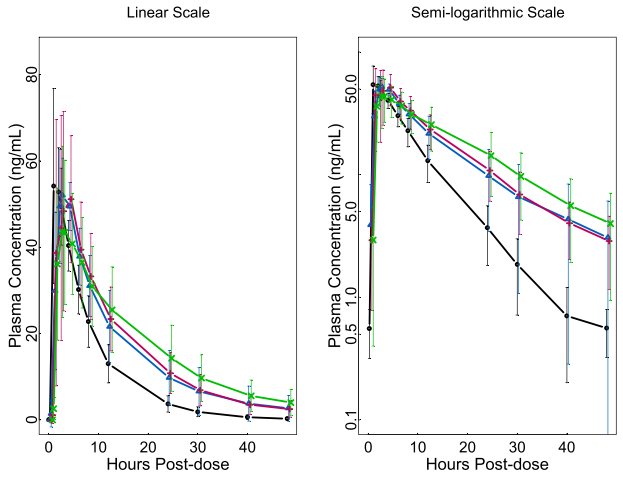

Figure 1. Arithmetic mean (± standard deviation) pomalidomide plasma concentrations-time profiles, by hepatic impairment group (black lines and symbols: subjects with normal hepatic function [n = 8]; blue lines and symbols: subjects with mildly impaired hepatic function [n = 8]; red lines and symbols: subjects with moderately impaired hepatic function [n = 8]; green lines and symbols: subjects with severely impaired hepatic function [n = 8]).

precluded subjects from entering the study. All subjects received a follow-up telephone call.

Plasma Pharmacokinetic Analyses of Pomalidomide

Mean plasma concentration profiles of pomalidomide from group 1 (subjects with normal hepatic function), group 2 (subjects with severe hepatic impairment), group 3 (subjects with moderate hepatic impairment), and group 4 (subjects with mild hepatic impairment) are presented in Figure 1. Mean plasma concentration-time profiles of pomalidomide were well characterized over the 48-hour postdose sampling interval, both in healthy subjects and in subjects with mild, moderate, or severe hepatic impairment. The AUC%extrap from all subjects was lower than 20% (range 0.4% 12.8%), suggesting adequate PK sampling schedule for subjects with various degrees of hepatic impairment.

The summary of the PK parameters of pomalidomide from group 1, group 2, group 3, and group 4 are presented by group in Table 2. Following administration of a single oral dose of 4-mg pomalidomide, pomalidomide was absorbed, with C_{max} of 60.7, 56.2, 58.0, and 49.1 μg/L and AUC of 497.8, 787.2, 810.0 and 908.3 μg·h/L from healthy subjects and subjects with mild, moderate, and severe hepatic impairment, respectively. In general, the PK parameters in the healthy group from this study were similar to those from the previous drug interaction study.[22]

For subjects with normal hepatic function, pomalidomide was rapidly absorbed, with a median t_{max} of 1.5 hours following administration of a single oral dose of pomalidomide. For subjects with impaired hepatic function, pomalidomide was absorbed with longer t_{max} (2.0 hours, 2.25 hours, and 2.5 hours for subjects with mild, moderate, and severe hepatic impairment, respectively).

The mean $t_{1/2}$ was similar in subjects with impaired hepatic function (10.3, 10.1, and 12.7 hours for subjects with mild, moderate, and severe hepatic impairment, respectively) and greater than that in subjects with healthy hepatic function (6.2 hours).

Effect of Hepatic Impairment on the PK of Pomalidomide

For $AUC_{0\text{-}t}$, AUC, and C_{max}, ANOVA was performed to compare PK parameters of pomalidomide between the groups of subjects with hepatic impairment and the healthy subjects. The results are presented in Table 3 and Table 4.

Following administration of a single oral dose of 4-mg pomalidomide, the GMR (%) of pomalidomide AUC was 171.5%, 157.5%, and 151.2% for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus

Table 2. Summary of Pomalidomide Plasma Pharmacokinetic Parameters, by Group

Pomalidomide PK Parameters	Group 1 (Healthy Subjects) n = 8	Group 2 (Severe Hepatic Impairment) n = 8	Group 3 (Moderate Hepatic Impairment) n = 8	Group 4 (Mild Hepatic Impairment) n = 8
$AUC_{0\text{-}t}$ (μg·h/L)	493.3 (122.4)	821.9 (289.2)	764.5 (239.6)	728.4 (243.8)
AUC (μg·h/L)	497.8 (124.6)	908.3 (358.9)	810.0 (261.1)	787.2 (317.5)
C_{max} (μg/L)	60.7 (14.1)	49.1 (18.5)	58.0 (15.1)	56.2 (7.3)
t_{max} (h)[a]	1.5 (1.0, 2.5)	2.5 (1.0, 6.0)	2.25 (1.0, 4.0)	2.0 (2.0, 4.0)
$t_{1/2}$ (h)	6.2 (1.0)	12.7 (3.9)	10.1 (3.5)	10.3 (4.9)
CL/F (L/h)	8.4 (1.9)	5.4 (3.3)	5.6 (2.6)	5.8 (2.2)

$AUC_{0\text{-}t}$, area under the plasma concentration time curve from time 0 to last time with detectable levels; AUC, area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F, apparent total plasma clearance when dosed orally; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; t_{max}, time to maximum plasma concentration; $t_{½}$, half-life in terminal phase.
Arithmetic mean (standard deviation) data are presented.
[a]Median (min, max).

Table 3. Statistical Comparison of Pomalidomide Plasma Pharmacokinetic Parameters ($AUC_{0\text{-}t}$, AUC, and C_{max})

Pharmacokinetic Parameter (Unit)	Group	N	Geometric Mean	Comparison	Ratio (%) of Geometric Mean (Impaired vs Healthy)	90%CI of Ratio of Geometric Mean
$AUC_{0\text{-}t}$ (μg·h/L)	Severe hepatic impairment	8	762.1	Severe vs healthy	158.4	(116.6–215.0)
	Moderate hepatic impairment	8	725.0	Moderate vs healthy	150.6	(110.9–204.5)
	Mild hepatic impairment	8	692.8	Mild vs healthy	143.9	(106.0–195.4)
	Healthy	8	481.3			
AUC (μg·h/L)	Severe hepatic impairment	8	832.8	Severe vs healthy	171.5	(123.5–238.4)
	Moderate hepatic impairment	8	764.4	Moderate vs healthy	157.5	(113.3–218.8)
	Mild hepatic impairment	8	733.9	Mild vs healthy	151.2	(108.8–210.1)
	Healthy	8	485.5			
C_{max} (μg/L)	Severe hepatic impairment	8	44.9	Severe vs Healthy	75.8	(57.7–99.7)
	Moderate hepatic impairment	8	56.2	Moderate vs Healthy	94.8	(72.1–124.6)
	Mild hepatic impairment	8	55.8	Mild vs Healthy	94.2	(71.6–123.8)
	Healthy	8	59.2			

$AUC_{0\text{-}t}$, area under the plasma concentration time curve from time 0 to last time with detectable levels; AUC, area under the plasma concentration time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic.

Table 4. Statistical Comparison of Pomalidomide Plasma Pharmacokinetic Parameters (t_{max})

Pharmacokinetic Parameter (Unit)	Group	N	Geometric Mean	Comparison	Median Difference (Impaired–Healthy)	90%CI of Median Difference
t_{max} (h)	Severe hepatic impairment	8	2.5	Severe vs Healthy	0.75	(0.00–2.50)
	Moderate hepatic impairment	8	2.38	Moderate vs Healthy	1.0	(0.00–1.50)
	Mild hepatic impairment	8	2.25	Mild vs Healthy	1.0	(0.00–1.50)
	Healthy	8	1.5			

PK, pharmacokinetic; t_{max}, time to maximum plasma concentration.

healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

Following administration of a single oral dose of 4-mg pomalidomide, the GMR (%) of pomalidomide C_{max} was 75.8%, 94.8%, and 94.2% for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

The difference in pomalidomide median t_{max} was 0.75, 1.0, and 1.0 for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

Safety

Overall, 6 of 32 (18.8%) subjects reported a total of 8 TEAEs. The majority of TEAEs were reported by subjects in the mild hepatic impairment group (4 subjects, 50.0%); 1 subject each in the severe and moderate hepatic impairment groups reported TEAEs (12.5%). No TEAEs were reported by the healthy subjects in this study. A total of 3 subjects (9.4%) reported at least

1 TEAE related to pomalidomide; 2 subjects (25.0%) in the mild hepatic impairment group and 1 subject (12.5%) in the severe hepatic impairment group. No deaths, SAEs, or TEAEs leading to discontinuation were reported.

All TEAEs were mild in severity except for 1 subject with the moderate TEAE of bronchitis. No severe TEAEs were reported during the study. Overall, 1 subject (9.4%) had TEAEs of diarrhea, nausea, headache, and flushing that were suspected of being related to pomalidomide.

No deaths or other SAEs were reported and no subjects were discontinued during this study.

Discussion

Assessing the effect of hepatic impairment on drug exposures is required for all investigational drugs if hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of a parent drug or active metabolite.[20,21] In the human [^{14}C]pomalidomide absorption, metabolism, and excretion study,[16] even though 72.8% of total [^{14}C]-radioactivity was recovered in urine, unchanged pomalidomide was detected as a minor radio-component in the urine, accounting for only 2.2% of the dose, while the 4 predominant metabolites (hydrolysis of glutarimide and glucuronide conjugates of hydroxylated pomalidomide) accounted for 52.8% of the dose excreted in the urine, suggesting extensive metabolism of pomalidomide prior to its excretion. In addition, a meta-analysis pooling data from patients with relapsed and refractory multiple myeloma with normal renal function, moderately impaired renal function, and severely impaired renal function showed there was no remarkable difference in pomalidomide exposure among different renal function groups, suggesting pomalidomide is cleared predominately via nonrenal routes, accounting for approximately 70% of pomalidomide total body clearance.[18] Both studies suggest that the liver plays the predominant role in eliminating pomalidomide in vivo.

Impaired hepatic clearance could result in increased pomalidomide exposure and, in turn, potentially manifest as increased adverse reactions (thrombocytopenia, neutropenia, and anemia) in patients with impaired hepatic function. The target patient population for pomalidomide tends to be elderly and may have some degree of hepatic impairment; therefore, it is clinically relevant to assess the impact of hepatic impairment on pomalidomide exposure.

This was a multicenter, open-label, single-dose study designed to assess the effect of hepatic impairment on the PK of pomalidomide following oral administration of a single 4-mg dose of pomalidomide. The dose of 4 mg was chosen because it is the intended clinical starting dose for multiple myeloma patients. Subjects with normal or impaired hepatic function were enrolled for PK comparison.

Pomalidomide was teratogenic in preclinical species when administered during the period of organogenesis. To minimize risk of exposure of females of childbearing potential to pomalidomide, only male subjects were enrolled in this study. However, previous pomalidomide population PK showed there was no clinically relevant impact of sex or other demographic factors (age, body weight, body surface area, and race) on pomalidomide PK, which supports the applicability of the data collected from male subjects in this study to female subjects.[23] Healthy male subjects and male subjects with severe hepatic impairment were matched with respect to age (±10 years) and weight (±13.61 kg [±30 pounds]). To the extent possible, subjects in the moderate and mild hepatic impairment groups were similar to the healthy subjects with respect to age and weight.

Results from a separate clinical study assessing the impact of CYP1A2 induction by smoking on pomalidomide PK showed that pomalidomide PK was not remarkably affected in heavy smokers (approximately 25 cigarettes per day); in heavy smokers, AUC was 30% lower and C_{max} was 14.4% higher than in nonsmokers (data on file). Therefore, light smokers (defined as smoking no more than 10 cigarettes, or consuming the equivalent in tobacco, per day) could participate in the study. However, smoking or the use of other tobacco products was not allowed from 7 days prior to baseline admission to the end of all study procedures. In fact, only 1 enrolled subject with mild hepatic impairment in this study was a light smoker. A sensitivity analysis was conducted and demonstrated that including or excluding the PK data from this subject did not alter the PK findings and conclusions.

This study showed that pomalidomide PK were adequately characterized in subjects with various degrees of hepatic impairment. Severe hepatic impairment decreased pomalidomide clearance and increased its exposure by approximately 70%; mild and moderate hepatic impairment had similar effects on pomalidomide clearance and increased its exposure by approximately 50% and approximately 60%, respectively. These findings suggest hepatic metabolism is reduced moderately (30%-50%) by hepatic impairment and is relatively sensitive to degree of hepatic impairment. In addition to slower metabolism and elimination, hepatic impairment appeared to cause slower and/or incomplete pomalidomide absorption, as reflected in the longer t_{max} and lower C_{max} values. Taken together, hepatic impairment moderately reduced pomalidomide metabolism and elimination; these effects were countered by slower and/or reduced pomalidomide oral absorption, with the

net effect being a moderate increase (50%-70%) in pomalidomide exposure.

Regarding safety, pomalidomide administered as a single oral 4-mg dose was safe and well tolerated by healthy male subjects and male subjects with severe, moderate, or mild hepatic impairment. Overall, 6 of 32 subjects (18.8%) reported a total of 8 TEAEs. Three subjects (9.4%) reported at least one TEAE related to study drug; two subjects (25.0%) in the mild hepatic impairment group and one subject (12.5%) in the severe hepatic impairment group. No TEAEs were reported by the healthy subjects. All TEAEs were mild in severity except for 1 subject in the moderate hepatic impairment group with the moderate TEAE of bronchitis. Overall, 3 subjects (9.4%) had TEAEs of diarrhea, nausea, headache, and flushing that were suspected of being related to investigational product. All TEAEs resolved by the end of the study. There were no deaths and no subject discontinued due to a TEAE. Mean alanine aminotransferase, aspartate aminotransferase, bilirubin, and glucose values were elevated in subjects with hepatic impairment but were not considered clinically significant. No subject had a clinical laboratory, vital sign, or ECG result that was considered clinically significant or reported as a TEAE. There were no apparent group-related trends in clinical laboratory results, vital sign measurements, or 12-lead ECG results.

In conclusion, a single dose of 4-mg pomalidomide was safe and well tolerated by healthy male subjects and male subjects with severe, moderate, or mild hepatic impairment. Following administration of a single oral dose of 4-mg pomalidomide, the GMRs of pomalidomide AUC were 171.5%, 157.5%, and 151.2% for subjects with severe, moderate, or mild hepatic impairment, respectively, versus healthy subjects. Based on the PK results from this study, in the pomalidomide prescription labeling approved by US Food and Drug Administration, for patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction) and for patients with severe hepatic impairment (Child-Pugh class C), the recommended starting dose is 2 mg (50% dose reduction).

Disclosures

Yan Li, Xiaomin Wang, Liangang Liu, Chengyue Zhang, Josephine Reyes, Maria Palmisano, and Simon Zhou are employees of and hold equity ownership in Celgene Corporation.

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