Population Pharmacokinetics of Pomalidomide

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Abstract
A population pharmacokinetic (PPK) model of pomalidomide was developed and the influence of demographic and disease-related covariates on PPK parameters was assessed based on data from 6 clinical trials of pomalidomide (dose range, 0.5–10 mg) in healthy participants (n = 96) and patients with multiple myeloma (MM; n = 144). PPK data described herein suggest that systemic clearance of pomalidomide is comparable between healthy study participants and patients with MM. However, apparent peripheral volume of distribution and apparent intercompartmental clearance between central and peripheral compartments were 8- and 3.7-fold higher in patients with MM vs. healthy subjects, suggesting drug exposure is higher in peripheral compartments of patients with MM vs. healthy subjects. Covariate analysis suggested pomalidomide clearance is not affected by demographic factors except for gender, and it is unlikely this factor is clinically relevant. In addition, renal function as measured by creatinine clearance or renal impairment (RI) does not significantly affect clearance of pomalidomide. In conclusion, pomalidomide has robust pharmacokinetic exposure, not affected by demographic factors or renal impairment. Pomalidomide is preferentially taken up by tumors over healthy tissues in patients with MM.

Keywords
pomalidomide, population pharmacokinetics, renal impairment, multiple myeloma

Pomalidomide (CC-4047) is a newer immunomodulatory agent with pleiotropic cytotoxic effects against multiple myeloma (MM) cells1,2 as well as antiproliferative,3,4 anti-angiogenic,5–7 and immunomodulatory activity.8,9 Pomalidomide has potent effects on cytokines, such as tumor necrosis factor-α, interferon-γ, and interleukin-10.10 Potential therapeutic benefits of pomalidomide have been demonstrated for treatment of various hematologic and nonneoplastic hematologic disorders.11–13 Pomalidomide is currently approved in the United States (Pomalyst) and European Union (Imnovid) in combination with dexamethasone for the treatment of patients who have received at least 2 prior therapies, including lenalidomide and bortezomib, and who have demonstrated disease progression on or within 60 days of completion of the last therapy.14,15 In combination with low-dose dexamethasone, pomalidomide significantly increased progression-free survival and overall survival when compared with high-dose dexamethasone.11 The most frequently reported grade 3/4 adverse events (AEs) with pomalidomide plus low-dose dexamethasone included neutropenia, anemia, and thrombocytopenia.11

Pharmacokinetics (PK) of pomalidomide have been determined previously in both healthy study participants and patients with relapsed and refractory MM (RRMM) in clinical studies.16,17 Pomalidomide is absorbed with maximum plasma concentration (Cmax) reached at a median time (Tmax) between 2 and 3 hours after a clinically relevant dose and >70% is absorbed following administration of a single oral dose.16,18 The systemic exposure to a single dose, as determined by the area under the plasma concentration-time curve (AUC), increased in an approximately dose-proportional manner, whereas Cmax generally increased in a less-than-dose-proportional manner, in the dose range of 0.5–20 mg (Celgene, data on file).14 Exposure was approximately dose proportional following multiple doses (at dose levels of 0.5, 1, and 2 mg), with steady state reached by day 3; accumulation appeared to be minimal after multiple doses. Mean (% CV) apparent volume of distribution (Vz/F) of pomalidomide ranged from 74 L (20%) to 138 L (30%) across a...
dose range of 1–10 mg (Celgene, data on file). The extent of plasma protein binding in human plasma ranged from 12% to 44%.14

Pomalidomide is extensively metabolized via multiple metabolic pathways, including CYP-mediated metabolism; <5% of the pomalidomide dose is excreted as an unchanged drug in the urine; however, pomalidomide metabolites are mainly excreted in urine as reflected in 72.83% of the total radioactivity recovered in urine in the mass balance study. CYP1A2, CYP3A4, and to a minor extent CYP2C19 and CYP2D6, have all been shown to contribute to pomalidomide metabolism.14,16 The mean half-life (t1/2) of pomalidomide is approximately 7.5 hours in patients with MM, and apparent clearance (CL/F) generally ranges from 6.5 to 10.8 L/h.14 Both CL/F and t1/2 in plasma appeared to be independent of dose and dosing duration (Celgene, data on file).

Using cumulative data in healthy participants and patients with MM and the comorbid condition of various degrees of renal impairment (RI), the current analysis aimed to build a population PK (PPK) and covariate model that quantitatively describes the disposition of pomalidomide, associated variability, and that characterizes major sources of variability on pomalidomide PK exposure.

**Methods**

**Study Population and PK Sampling**

Data from 6 clinical studies (2 studies in healthy subjects and 4 studies in MM patients) with a total of 240 participants were employed in the PPK analysis. Pomalidomide was administered orally as a solid dosage form once daily or once every alternate day in the studies. All studies were reviewed and approved by institutional review boards (IRBs), and written informed consent was obtained from all study participants.

**Bioanalytical Methodology**

Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods with lower limits of quantification of ≤0.25 ng/mL were used to determine pomalidomide concentrations in human plasma samples. Plasma samples were spiked with stable label pomalidomide (as an internal standard), processed by liquid-liquid extraction, and analyzed using reversed phase HPLC with electrospray (ESI) MS/MS detection. Peak separation was achieved using high-performance liquid chromatography (LC) with a gradient of organic solvent and aqueous mobile phases.

**Population Pharmacokinetic Model Building**

Population PK analysis of the concentration-time data of pomalidomide was performed using the nonlinear mixed-effect modeling program (NONMEM version 7.2; ICONC Development Solution, Maryland), with first-order conditional estimation with the interaction option (FOCEI) throughout data analysis. Pomalidomide concentration data were logarithm-transformed. The S-Plus (version 8.2, TIBCO Software Inc., Somerville, Massachusetts) and R-based model building aid Perl-Speaks-NONMEM (PsN, version 3.5.3, by Kajsa Harling and Andrew Hooker) postprocessing software were used for graphic processing. NONMEM was installed on Windows XP with the Intel Visual FORTRAN Compiler (version 9.1). Comparison of structural models was based on the objective function value (OFV) and goodness-of-fit criteria. A value of $P < .001$, representing a decrease in OFV > 10.83, was considered statistically significant. Selection criteria during the model development process were based on goodness-of-fit plots, changes in OFV, residual distributions, parameter estimates, and their relative SE values.

Population PK model building started with a 1-compartment model and tested 2- and 3-compartment structure PK models. Based on visual inspection and data-fitting criteria, pomalidomide concentration-time data were best described by a 2-compartment structure PK model with the first-order absorption rate constant (KA), different absorption lag time (Alag1), apparent clearance (CL/F), apparent central compartment volume of distribution (V2/F), apparent intercompartmental clearance between central and peripheral compartments (Q/F), and peripheral volume of distribution (V3/F) for healthy participants and patients with MM.

Assuming a log-normal distribution for interindividual variability (IIV) in PK parameters, the IIV was modeled as follows:

$$P_i = P \cdot e^{\eta_i}$$

(1)

where $P$ is the typical value of the parameter in the population, $P_i$ is the value of the parameter for the $i$th individual, and $\eta_i$ is a random interindividual effect in the parameter for the $i$th participant with a mean of zero and variance $\omega^2$ (i.e., $\eta_i \sim N[0, \omega^2]$).

Intraindividual or residual variability (RV) was modeled as follows:

$$\ln(C_{ij}) = \ln(C_{mij}) + \epsilon_{ij}$$

(2)

where $C_{mij}$ is the model-predicted $j$th concentration in the $i$th participant, $C_{ij}$ is the observed $j$th concentration in the $i$th participant, and $\epsilon_{ij}$ is the random residual effect for the $j$th concentration in the $i$th participant with a mean of 0 and variance of $\sigma^2$. Given that the studies conducted in healthy participants are well controlled vs. patient studies, assumption of a constant RV for all individuals may result in biased parameter estimates. To reduce this possible bias, RV was modeled separately for healthy participants and patients with RRMM.

Model evaluation was performed using visual predictive check (VPC), which provided an evaluation of model...
assumption and population parameter estimates by comparing model predictions with observations. The ability of the final PPK model to describe observed concentration data was evaluated by simulating 1,000 data sets with the same doses, dosing schedules, and sampling times as in the original data set and by performing VPCs.

Stability of the final PK parameter estimates and 90% CIs were evaluated using the nonparametric bootstrap approach. The final model was fit to each of the 500 bootstrap data sets, and all the model parameters were estimated for each data set; 96% of the 500 bootstrap runs were successful. Median and nonparametric 90% CIs (5th–95th percentiles) for each of the 500 estimates were calculated for each parameter.

Covariate Analysis

Covariates that were tested for their correlation with all PK parameters of the 2-compartment model mentioned above included demographic factors (age, body weight, body surface area, sex, and race), hepatic function markers (total bilirubin, albumin, aspartate aminotransferase, or other markers as appropriate), renal function markers (creatinine clearance [CLcr] estimated by Cockcroft-Gault formula19), and status of health (healthy participants vs. patients). Covariates were initially selected by graphic inspection and biological plausibility. Further testing of potential covariates was performed by a 3-stage approach for the selection of covariates.

First, covariates identified by graphic analysis were introduced into the structural model individually for univariate analysis. In the second step (forward selection), the covariate with the highest significance by univariate analysis was included first, and other significant covariates from univariate analysis were included in rank order of their significance. In the third step (backward elimination), covariates were removed from the full model obtained from forward selection, in sequence, until there were no further insignificant covariates remaining.

The stepwise covariate model (SCM) building tool of PsN was used for development of the pomalidomide covariate model, which implemented forward selection and backward elimination of covariates for the pomalidomide PPK model. There is a fixed set of PK parameter-covariate relations defined in the SCM; predefined shapes for the parameter-covariate relations for continuous covariates for pomalidomide covariate model development include the following:

Linear equation: \( P = \theta \cdot (1 + \theta_{\text{cov}} \cdot (\text{COV}_i - \text{COV}_m)) \) \( (3) \)

and power equation \( P = \theta \cdot \left( \frac{\text{COV}_i}{\text{COV}_m} \right)^{\theta_{\text{cov}}} \) \( (4) \)

where \( P \) is the typical value of a PK parameter in the population after adjusting for values of covariates of individual participants, \( \theta \) is the typical value of the PK parameter, \( \theta_{\text{cov}} \) is the coefficient for the effect of the covariate, \( \text{COV}_i \) is the covariate value for individual participants, and \( \text{COV}_m \) is the median value of covariates in the study population.

Categorical covariates were included in the pomalidomide covariate model development as follows:

\[
P = \theta \cdot (1 + \theta_{\text{cov}} \cdot Z_{\text{ind},k})
\]

where \( Z_{\text{ind},k} \) is an indicator variable representing 1 or 0 from a binary covariate and \( \theta_{\text{cov}} \) is the coefficient for the effect of the covariate.

Results

Populations Included in the Analyses and Demographics

A total of 240 participants with 3,909 evaluable pomalidomide concentration records were included in the final population PPK analysis data set. The design of studies involved in the population PPK analysis, eg, dose, schedule, N of subjects, PK collection time information is summarized in Supplementary Table 1. Baseline characteristics are summarized in Table 1. Participants were primarily white (78%), not Hispanic or Latino (65.7%),

| Variable                              | Value      |
|---------------------------------------|------------|
| **Demographics**                      |            |
| Sex, n (%)                            |            |
| Male                                  | 175 (74.2) |
| Female                                | 61 (25.8)  |
| Race, n (%)                           |            |
| Asian                                 | 2 (0.8)    |
| Black or African American             | 47 (19.9)  |
| Native Hawaiian or other Pacific Islander | 1 (0.4) |
| Other                                 | 2 (0.8)    |
| White                                 | 184 (78.0) |
| Ethnicity, n (%)                      |            |
| Hispanic or Latino                    | 53 (22.5)  |
| Not Hispanic or Latino                | 155 (65.7) |
| Unknown                               | 28 (11.9)  |
| **Patient characteristics, median (range)** |     |
| Age, year                             | 53.0 (19.0, 83.0) |
| Body weight (kg)                      | 78.1 (44.4, 127.0) |
| Height (cm)                           | 171.5 (142.0, 191.3) |
| Body mass index (kg/m²)               | 26.5 (16.4, 48.3) |
| Hepatic function, median (range)      |            |
| Albumin (g/dL)                        | 4.00 (1.70, 5.20) |
| Total bilirubin (µM)                  | 9.2 (1.9, 52.3) |
| Total protein (g/L)                   | 75.0 (56.0, 148.0) |
| Asparate aminotransferase (U/L)       | 22.0 (9.0, 73.0) |
| Alkaline phosphatase (U/L)            | 60.6 (25.0, 255.0) |
| Renal function, median (range)        |            |
| Serum creatinine (µmol/L)             | 85.7 (47.7, 332.0) |
| Creatinine clearance (mL/min)         | 100.4 (20.8, 188.2) |
and male (74.2%). They had a median age of 53.0 years (range, 19.0–83.0 years) and median body weight of 78.1 kg (range, 44.4–127 kg). Median total bilirubin was 9.2 μM, with 29 participants (12%) having a value above the upper limit of normal (ULN) of 17 μM and 6 participants (3%) with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤5 ULN). Median CLcr, a marker associated with renal function, was 100.4 mL/min (range, 20.8–188.2 mL/min). Forty participants (17%) had RI (CLcr 30–60 mL/min), and 3 participants (1.3%) had severe RI (CLcr <30 mL/min).

Structural PK Model Characterization
Concentration-time data of pomalidomide were best described by a 2-compartment model, which was preferred over a 1-compartment model (ΔOFV = −482, P < .0001). Introducing an absorption lag time significantly improved the model fit according to goodness-of-fit and statistical criteria (ΔOFV = −624, P < .0001). Considering the inherently better quality of PK data collected from well-controlled studies in healthy participants compared with those from studies in patients, a different residual error model (OFV = −4,528) was tested and preferred over the model with same residual error (OFV = −3,160).

Visual examination of dose-normalized concentration vs time profiles (Figure 1) demonstrated a longer terminal phase in patients with MM vs. healthy normal participants, potentially indicating deeper tissue/organ distribution of pomalidomide in patients with MM. Therefore, a 2-compartment model containing different Q/F, CL/F, V2/F, and V3/F values between patients with MM and healthy participants was tested and preferred over the 2-compartment model with the same values between patients with MM and healthy participants.

Thus, according to goodness-of-fit and statistical criteria, a 2-compartment model with a first-order absorption rate constant incorporating different lag time, CL/F, Q/F, V3/F, V2/F, and error model between patients with MM and healthy participants was found to adequately describe pomalidomide PK. This model described pomalidomide PK in both healthy participants and patients with MM and was selected as the final structural PPK model. Final population variable estimates are outlined in Table 2. The PPK analysis revealed that healthy participants and patients with MM have comparable CL/F and V2/F; however, V3/F in patients with MM was found to be 71.5 L, approximately 8-fold higher than was observed in healthy participants (8.45 L), and Q/F in patients with MM was 3.75 L/h, approximately 3.7-fold higher than observed in healthy participants (1.0 L/h). The NONMEM analysis results of attributing observed longer lingering terminal phase in patients with MM to a deeper tissue/organ distribution (larger V3/F and Q/F) instead of a slower elimination were also confirmed from a separate dedicated DDI study in which the elimination of pomalidomide (metabolism) was decreased by CYP3A4 and CYP1A2 inhibitors that reflected in the initial concentration decline (α phase) not the terminal decline (β phase) supporting the terminal phase in patients with MM or healthy subjects reflects slower tissue distribution and redistribution of pomalidomide from tissue to circulation rather than elimination.

Figure 1. Individual dose-normalized pomalidomide concentration vs. time profiles: healthy normal participants vs. patients with relapsed and refractory multiple myeloma (RRMM).
Table 2. Population Pharmacokinetic (PPK) Parameters for the Final PPK Model of Pomalidomide

| PK Parameter                        | Estimate     | Bootstrap Estimate (95%CI) | Shrinkage (%) |
|-------------------------------------|--------------|---------------------------|---------------|
| $ka$, h<sup>-1</sup>               | 1.25         | 1.25 (1.07–1.47)          | 14.8          |
| $V_2/F$, L                           | 58.3         | 58.25 (55.79–60.88)       | 19.9          |
| $V_3/F$, L                           | 8.45         | 8.48 (7.47–9.40)          |               |
| $Q/F$, L/h                           | 1.01         | 1.00 (0.75–1.28)          |               |
| $CL/F$, L/h                          | 8.52         | 8.51 (8.04–8.99)          | 7.89          |
| $\text{Alag}_1$, h                  | 0.385        | 0.38 (0.37–0.40)          |               |
| $\text{CL/F}_{\text{MM patient/HNP}}$ | 0.913        | 0.911 (0.798–1.056)       |               |
| $\text{Alag}_1\text{MM patient}$, h | 0.206        | 0.207 (0.177–0.231)       |               |
| $V_2/F_{\text{MM patient/HNP}}$     | 8.46         | 8.38 (5.92–11.80)         |               |
| $Q/F_{\text{MM patient/HNP}}$       | 3.71         | 3.68 (2.50–5.35)          |               |
| $V_2/F_{\text{MM patient/HNP}}$     | 1.20         | 1.19 (1.07–1.37)          |               |
| Effect of TPT on $V_2/F$             | 0.00609      | 0.00602 (0.0024–0.0103)   |               |
| Effect of weight on $V_2/F$          | 0.686        | 0.685 (0.497–0.862)       |               |
| Effect of sex on $CL/F$              | −0.234       | −0.232 (−0.369 to −0.077) |               |

Interindividual variability

| $\omega_{\text{ka}}^2$              | 0.976        | 0.961 (0.652–1.388)       |               |
| $\omega_{V_2/F}^2$                   | 0.0352       | 0.0349 (0.0240–0.050)     |               |
| $\omega_{V_2/F,\text{CL/F}}$         | 0.0599       | 0.0589 (0.0395–0.0841)    |               |
| $\omega_{CL/F}^2$                    | 0.168        | 0.164 (0.127–0.213)       |               |

Residual variability

| $\sigma_{\text{res}}^2_{\text{MM patient}}$ | 0.04         | 0.04 (0.033–0.047)        | 5.09          |
| $\sigma_{\text{res}}^2_{\text{HNP}}$        | 0.240        | 0.235 (0.192–0.295)       | 7.65          |

Alag<sub>1</sub>, absorption lag time; Alag<sub>1</sub><sub>MM patient</sub>, absorption lag time in patients with MM; CL/F, apparent clearance; CL/F<sub>MM patient/HNP</sub>, ratio of CL/F between patients with MM and healthy participants; HNP, healthy normal study participant; $ka$, first-order absorption rate constant; MM, multiple myeloma; $Q/F$, apparent intercompartmental clearance between central and peripheral compartments; $Q/F_{\text{MM patient/HNP}}$, ratio of $Q/F$ between patients with MM and healthy participants; TPT, total protein; $V_2/F$, apparent central compartment volume of distribution; $V_2/F_{\text{MM patient/HNP}}$, ratio of $V_2/F$ between patients with MM and healthy participants; $V_3/F$, apparent peripheral compartment volume of distribution; $V_2/F_{\text{MM patient/HNP}}$, ratio of $V_2/F$ in patients with MM and healthy participants.

Covariate Analysis

The majority of the participants in the PPK data set were white (78%); therefore all nonwhite patients were grouped as one population for the covariate analysis of race. The PPK data set also contained a minority of Hispanic or Latino study participants (22.5%) and participants with unknown ethnicity (11.9%), and so all Hispanic or Latino participants and those with unknown ethnicity were grouped as one for covariate analysis. It was demonstrated in graphic analysis that female study participants appeared to have significantly lower CL/F compared with male participants, and CL/F was also significantly different between Hispanic or Latino and non-Hispanic participants. There was no apparent relationship between $V_2/F$ and sex, race, or ethnicity.

All proposed covariates were included in covariate model development using the SCM building tool of PsN. The output of SCM-building log file indicated that inclusion of body weight and TPT into $V_2/F$ and inclusion of sex into CL/F in the forward selection step significantly improved the model fit. Both linear and power equations were tested for the $V_2/F$ vs. body weight and TPT relationships. A linear equation between $V_2/F$ and TPT values and a power equation between $V_2/F$ and body weight significantly improved the model fit by decreasing OFV from −4,872 to −4,944.

Although body weight, albumin, and CLcr appeared to be positively correlated with CL/F, age appeared to be negatively correlated with CL/F. By graphic analysis, age appeared to be positively correlated, and albumin and bilirubin levels negatively correlated, with $V_2/F$; these correlations were not of statistical significance in the forward selection step. The final model was identified through a backward elimination process. No covariates identified from the forward selection step were removed from the full model.

The final covariate model at the population level was described as follows:

$$ (\text{CL/F})_\text{TV} = \frac{8.45 \text{ (male study participants)}}{8.45 \cdot (1 - 0.234) \text{ (female study participants)}} $$

and

$$ (V_2/F)_\text{TV} = 58.3 \cdot \left( \frac{\text{WT}}{78.3} \right)^{0.686} \cdot (1 + 0.00609 \cdot (\text{TPT} - 73.0)) $$

Typical reference values of pomalidomide CL/F and $V_2/F$ for male participants with a median body weight of 78.3 kg and median TPT of 73 g/L were 8.45 L/h and 58.3 L, respectively. The final PPK model suggested that female participants had 23.4% lower CL/F vs. male
participants, and $V_2/F$ increases with increasing body weight or TPT levels. Despite the statistical significance of the effect of sex on CL/F, and the effect of body weight and TPT on $V_2/F$, the contribution of sex to the IIV of CL/F and the contribution of body weight and TPT levels to IIV of $V_2/F$ were marginal, reducing the IIV from 44.1% in the base model to 42.77% in the final model and from 22.3% in the base model to 18.9% in the final model for CL/F and $V_2/F$, respectively. Therefore, none of these covariates (sex on CL/F and body weight and TPT on $V_2/F$) appeared to be clinically relevant for pomalidomide PK.

**Model Evaluation**

The final PPK model was subjected to a bootstrap resampling stability test to assess its robustness. Bootstrap analyses (N = 500) were performed using the final PPK model, with 483 (96.6%) successfully minimized. As shown in Table 1, median values of the parameters obtained from bootstrap replications were similar to the original NONMEM estimates. The relative difference between the final model estimate and the bootstrap median was $\leq 15\%$ for the fixed-effect parameters and $\leq 4\%$ for the random-effect parameters, suggesting that the final model is robust and stable.

The results of the goodness-of-fit plots and the VPC evaluation (Supplementary Figure 1–5) suggested that there was good agreement in the time course and central tendency between distributions of observed and simulated data, with no obvious bias. Overall, the estimated IIV adequately described observed variability in pomalidomide PK.

![Figure 2. Time course comparison of pomalidomide exposure in the central compartment (A) and peripheral compartment (B) after a single dose of 4 mg in healthy participants and in patients with relapsed and refractory multiple myeloma (RRMM).](image-url)
concentrations. As such, pomalidomide concentrations in the logarithmic range of 0.006–5.19 (ie, 1.0–179 ng/mL) were well characterized by the final PPK model.

Discussion

This is the first reported population pharmacokinetics analysis for pomalidomide quantitatively describing pomalidomide PK and associated IIV and RV in both healthy study participants and patients with RRMM and assessing the effect of covariates of interest on pomalidomide PK. Pomalidomide exhibits linear, time-independent PK. Following oral administration, pomalidomide undergoes biphasic disposition. Healthy participants and patients with MM had comparable plasma CL/F (8.52 and 7.78 L/h, respectively) and V2/F (58.3 and 69.9 L, respectively), suggesting comparable plasma exposure. Interestingly, visual examination of dose-normalized concentration vs. time profiles from healthy participants and patients with MM showed longer lingering of plasma concentrations at the terminal phase in patients with MM than in healthy participants, indicating possibly deeper tissue/organ distribution of pomalidomide in patients with MM. Therefore, a 2-compartment model with different Q/F and V3/F between patients with MM and healthy participants was tested and preferred over the 2-compartment model with same Q/F and V3/F between patients with MM and healthy participants. The analysis results indicated that pomalidomide PPK parameters of tissue distributions for healthy participants and patients with MM are markedly different. Q/F from patients with MM was found to be 3.7-fold higher than that from healthy participants, suggesting faster distribution of drug into tissues in patients with MM. V3/F was 8-fold higher in patients with MM (71.5 L) vs. healthy participants (8.5 L), suggesting deeper penetration of the drug into tissues.

Pomalidomide exposure in plasma (central compartment) and peripheral tissues/organs (peripheral compartment) was compared between healthy participants and patients with MM using simulations. At the clinically relevant dose of 4 mg, differences in overall plasma concentration profiles were relatively small between healthy participants and patients with MM except for the slower concentration decline at the terminal phase (Figure 2A); however, the model predicted that considerably more drug was delivered into tissues/organs of patients with MM (Figure 2B). These data indicate an effect of disease on the disposition of pomalidomide that is consistent with the drug’s action on malignant plasma cells. The effect of disease on the disposition of pomalidomide was further examined by assessing the correlation between the drug exposure in tissues/organs and the disease stage. The stage of MM at screening was used to categorize the patients into 3 groups (stage I: early disease with some symptoms; stage II: multiple symptoms and more advanced disease; and stage III: multiple areas with MM cells and more serious symptoms). Patients with stage III MM showed the highest peripheral drug exposure followed by patients with stage II MM, and patients with stage I MM showed the least peripheral drug exposure (Figure 3). For a drug such as pomalidomide,
which has a target that is primarily outside the plasma, the plasma concentration of systemic AUC would not be expected to be a good surrogate of its pharmacologic effect. Rather, the distribution of drug into tissues would be better associated with the drug effect as a drug’s antitumor activity is decided by the amount and extent of its distribution into the target tissues. Thus, the distribution difference observed between healthy participants and patients with MM is expected to result in a better clinical efficacy/safety profile in patients with MM.

The present analysis indicated that the systemic clearance of the drug was significantly correlated only with sex, according to the criteria defined for covariate analysis. There are many potential reasons for sex differences in pomalidomide PK, such as differences in gastric pH (higher in females), lower hepatic blood flow, and, consequently, lower hepatic metabolic capacity, which could partly explain the findings. The resulting differences in drug exposure between female and male participants were small (<30%) relative to the observed overall variability in pomalidomide PK. Therefore, this finding was not considered to be clinically relevant, and no dosage adjustment is required.

Body weight was a significant factor influencing pomalidomide V2/F. A large volume of distribution of pomalidomide suggests that pomalidomide may be distributed by diffusion into the extracellular fluids, the volume of which increases with body weight; thus,

Figure 4. Correlation between renal function (creatinine clearance) and the clearance of pomalidomide (CL/F): (A) creatinine clearance was categorized into 4 renal function groups and (B) creatinine clearance was treated as a continuous variable.
the estimated increases in the V2/F of pomalidomide with increased body weight are consistent with the physiological effects of weight.

TPT (ranging from 56 to 148 g/L) was another significant factor influencing pomalidomide V2/F. MM is associated with an elevated TPT, and higher disease stage is also correlated with higher serum protein levels. A higher TPT level may correlate with higher-stage disease, for which more drugs may enter the peripheral compartment, resulting in large central volume of distribution.

Although renal function (as assessed by CLcr) appeared to be positively correlated with CL/F in the graphic analysis (correlation coefficient = 0.2042), it did not reach the predefined statistical significance in the univariate covariate analysis. The relationship between CLcr and pomalidomide CL/F was further examined using individual Bayesian estimates of CL/F from the final PPK model. CLcr values at baseline were used to categorize the patient into different renal function groups according to US Food and Drug Administration (FDA) guidance on renal impairment study.22 The geometric mean CL/F appeared comparable among patients with normal, mild, and moderate RI (Figure 4A), suggesting that the kidneys may not contribute significantly to pomalidomide elimination in vivo, which is consistent with findings from a pomalidomide absorption, distribution, metabolism, and excretion study, in which <5% of the pomalidomide dose was excreted as unchanged drug in the urine. In addition, according to the FDA’s guidance on the data analysis from the renal impairment study, a linear regression approach between CLcr and CL/F has been conducted as follows:

\[
\text{CL/F} = \alpha + \beta \times \text{CLcr}
\]

where the intercept \(\alpha\) represents the nonrenal clearance and the slope \(\beta\) represents the sensitivity of CL/F to CLcr. It was shown that there is a weak correlation between renal function (CLcr) and pomalidomide clearance (Figure 4B). The intercept from the linear regression is approximately 5.93 (90%CI: 4.45–7.41) L/h, suggesting that nonrenal clearance contributes to \(\geq 77\%\) of whole-body clearance, and the slope from the linear regression is approximately 0.019 (90%CI: 0.0016, 0.036), suggesting that elimination of pomalidomide is not sensitive to renal function. In the above regression analysis data set, 40 patients with MM had normal renal function (CLcr > 90 mL/min), 54 had mildly impaired renal function (CLcr \(\geq 60\) to \(<90\) mL/min), 40 had moderately impaired renal function (CLcr \(\geq 30\) to \(<60\) mL/min), and 3 had severe RI (CLcr < 30 mL/min); therefore, the nonclinically significant association between CLcr and CL/F in patients with MM was applicable for a wide range of observed CLcr levels (20.8–188.2 mL/min). Preliminary data from an ongoing dedicated RI study in patients with MM showed that drug exposure in patients with MM with severely impaired renal function is comparable with that in patients with MM and “normal” renal function at the clinically relevant dose of 4 mg.23

In conclusion, the PPK analysis described in this study suggests pomalidomide CL/F is not affected by demographic factors except for sex, and the influence of sex on CL/F is minimal and unlikely to be clinically relevant. Elimination of pomalidomide is not sensitive to renal function or renal impairment. Pomalidomide is preferentially taken up by tumors with a disease-mediated drug disposition of more rapid and deeper tissue/organ distribution of pomalidomide in MM patients.

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Declaration of Conflicting Interests

Yan Li, Yejun Xu, Liangang Liu, Xiaomin Wang, Maria Palmisano, and Simon Zhou are employees of and hold equity ownership in Celgene Corporation.

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