Pharmacokinetics of Lenalidomide in Subjects With Various Degrees of Renal Impairment and in Subjects on Hemodialysis

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The present study investigated the effect of renal impairment and hemodialysis on the pharmacokinetics of lenalidomide following a single 25-mg oral dose in 30 subjects aged 39 to 76 years. A single 25-mg dose was well tolerated by renally impaired subjects. Renal impairment did not alter the oral absorption, protein binding, or non-renal elimination of lenalidomide. Mean urinary recovery of unchanged lenalidomide was 84% of the dose in subjects with normal renal function (creatinine clearance [\(\text{CL}^\text{cr}\] > 80 mL/min), and it declined to 69%, 38%, and 43% in subjects with mild (50 \(\leq\) \(\text{CL}^\text{cr}\) \(<\) 80 mL/min), moderate (30 \(\leq\) \(\text{CL}^\text{cr}\) \(<\) 50 mL/min), and severe (\(\text{CL}^\text{cr}\) < 30 mL/min) renal impairment, respectively. The differences in pharmacokinetic parameters between normal renal function and mild renal impairment were minor to modest (11%-32%). As renal impairment progressed to moderate, severe, or end-stage renal disease, total and renal lenalidomide clearance decreased drastically, area under the concentration-time curve increased by approximately 185% to 420%, and \(t_{1/2}\) was prolonged by approximately 6 to 12 hours. A 4-hour hemodialysis removed 31% of lenalidomide in the body. Therefore, lenalidomide dose adjustments should be considered for patients with \(\text{CL}^\text{cr}\) < 50 mL/min, and the recommendations are given for the starting doses.

Keywords: Lenalidomide; pharmacokinetics; renal impairment; hemodialysis


Lenalidomide is a novel oral immunomodulatory drug, with antiangiogenic and antineoplastic properties. It is structurally related to thalidomide but has an improved toxicity profile and more potent immunomodulatory activity. Lenalidomide is currently being used in the treatment of hematological malignancies, particularly multiple myeloma (MM) and a subset of myelodysplastic syndrome (MDS) harboring the deletion 5q chromosome abnormality. It has also shown promise in phase II studies for chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), amyloidosis, and myelofibrosis with myeloid metaplasia (MMM).

The pharmacokinetics of lenalidomide in healthy subjects are characterized by rapid oral absorption, with the maximal plasma concentration occurring at a median time of 0.6 to 1.5 hours postdose. Coadministration with food delays absorption, but it does not alter the extent of absorption. The pharmacokinetic disposition of lenalidomide is linear, with plasma exposure being dose proportional. Multiple dosing does not result in drug accumulation. Approximately two thirds of orally administered lenalidomide is eliminated as unchanged drug in urine, likely via both glomerular filtration and active tubular secretion. The exact mechanism for tubular secretion remains unknown. The half-life \((t_{1/2})\) of elimination is 3 to 4 hours. In elderly male and female MM patients with a baseline serum creatinine level \(\leq\) 1.6 mg/dL, a similar pharmacokinetic profile was observed, but the mean plasma exposure was 57% higher than that in healthy subjects. 15,16

Multiple myeloma and MDS generally occur later in life, at a time when renal function is diminishing.
PHARMACOKINETICS OF LENALIDOMIDE

Moreover, MM is a disease that damages kidneys, and renal impairment (RI) occurs frequently in patients with MM.17,18 In phase II and III studies that evaluated the efficacy and safety of lenalidomide, only patients with a baseline serum creatinine of 2.5 mg/dL or lower were recruited.5-8,16 Through these studies, the initial starting dose was established to be 25 mg/day for MM and 10 mg/day for MDS. Until now, there has been no information on the pharmacokinetics of lenalidomide in relation to various degrees of renal function. The present study investigated the effect of renal impairment and hemodialysis on the pharmacokinetics of lenalidomide. Results of this study are used to refine the starting dosing recommendations for patients with renal impairment.

METHODS

Study Design and Subjects

This was an open-label, multicenter, single oral dose study in subjects with renal impairment due to nonmalignant conditions. The study was conducted at 3 centers in the United States: Orlando Clinical Research Center (Orlando, Florida), New Orleans Center for Clinical Research (Knoxville, Tennessee), and DaVita Clinical Research (Minneapolis, Minnesota). The study protocol and informed consent form were approved by the following investigational review boards prior to study initiation: Independent Investigational Review Board (Plantation, Florida), Crescent City Institutional Review Board (New Orleans, Louisiana), and Human Subjects Research Committee (Minneapolis, Minnesota).

Male and nonpregnant female subjects, >35 years old, were included. Subjects must have had adequate hematological and hepatic functions (absolute neutrophil counts ≥1000/µL, platelet counts ≥100,000/µL, hemoglobin ≥9 g/dL, total bilirubin ≤1.5 mg/dL, and alanine transaminase and aspartate transaminase ≤2-fold of the normal range upper limit). All subjects must have agreed to use a reliable method(s) of contraception during the study and for at least 28 days after the study. Inclusion of subjects with renal impairment required a documented history of stable renal impairment of 6 weeks or longer before screening and clinical laboratory results consistent with the underlying diseases for renal impairment. Subjects were excluded if they had active infection, preexisting neuropathy of grade ≥3, blood pressure higher than 170/100 mm Hg or lower than 90/50 mm Hg, heart rate higher than 90 or lower than 40 beats per minute, clinical significant findings in electrocardiogram (ECG), or a known hypersensitivity to lenalidomide or similar drugs.

Subjects were also excluded if they had positive results to the tests for drugs of abuse, alcohol, or cotinine or if they tested positive for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody.

A total of 30 subjects were recruited into this study. They were stratified into 5 groups based on their creatinine clearance (Clcr) values measured from a 24-hour urine collection or the need of hemodialysis therapy: normal renal function (Clcr > 80 mL/min), mild RI (50 ≤ Clcr ≤ 80 mL/min), moderate RI (30 ≤ Clcr < 50 mL/min), severe RI (Clcr < 30 mL/min), and end-stage renal disease (ESRD, requiring dialysis). Subjects among renal function groups were matched as closely as possible in terms of age, weight, and gender.

Subjects with normal renal function and subjects with mild, moderate, or severe RI received a single 25-mg oral dose of lenalidomide (given as 1 Revlimid capsule) under fasting conditions. Subjects with ESRD received 2 single 25-mg doses separated by at least 7 days: the first dose was administered on a nondialysis day, and the second dose was administered 3 hours before a 4-hour hemodialysis period.

Subjects with normal renal function were not allowed any concomitant medications other than acetaminophen prescribed by the investigator, whereas all treatments for the renally impaired subjects were continued during this study.

Safety Assessments

Physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), pregnancy test (women only), and 12-lead ECG were performed before and after the study. All subjects were monitored throughout the study for adverse events and vital signs and for the use of concomitant medications. Adverse events were evaluated by the investigator for intensity, seriousness, and relationship to the study drug.

Collection and Preparation of Pharmacokinetic Samples

Blood samples were collected into EDTA tubes before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 36, 48, and 72 hours after dosing. An additional sample at 3 hours postdose was collected for analysis of plasma protein binding. For subjects with ESRD during the hemodialysis period (3-7 hours after dosing), blood samples (at 3, 4, and 6 hours after dosing) were collected from both the pre- and postdialyzer lines. Within 1 hour of collection, blood samples were centrifuged at 4°C to
obtain plasma, which was stored at −70°C until analysis.

Total urine collections were made in subjects not requiring hemodialysis. Urine was pooled according to the following postdosing intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 72 hours. The total volume of urine collected over each interval was recorded. Subsequently, a 4-mL aliquot of urine was taken, acidified with an equal volume of Sorenson’s citrate buffer (pH 1.5), and stored at −70°C until analysis.

Analytical Methods

Plasma and urine samples were analyzed for S- and R-lenalidomide concentrations by a validated chiral liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. In brief, samples, with 13C5-CC-5013 glutarimide as the internal standard (IS), were processed by a liquid-liquid extraction procedure followed by high-performance liquid chromatography (HPLC) using an Astec Chirobiotic V 5-μm column. Detection was performed by an AB/MDS Sciex API 4000 (for plasma samples) or a PE Sciex API 3000 (for urine samples) mass spectrometer configured with electrospray ionization in the positive ion mode. Data were acquired by multiple-reaction monitoring of mass transition pairs at m/z of 260.1/149.2 for R/S-lenalidomide and 265.1/190.2 for the IS. The R- and S-lenalidomide standard curves were linear from 5 to 200 ng/mL in plasma and from 100 to 20,000 ng/mL in urine. The lower limit of quantification of lenalidomide was 5 ng/mL in plasma and 100 ng/mL in urine. Between-day precision was within 6.1% in plasma assays and within 4.5% in urine assays. Assay accuracy was 97.3% to 99.7% for plasma samples and 92.7% to 103.7% for urine samples.

The ex vivo plasma protein binding of lenalidomide was determined by ultrafiltration technique. In brief, an aliquot of plasma was loaded into a Centrifree ultrafiltration device with a 30,000–molecular weight cutoff membrane (Millipore Co, Bedford, Massachusetts) and centrifuged at 37°C to obtain ultrafiltrates containing the unbound drug. Plasma and ultrafiltrate samples, with antipyrine as IS, were processed by protein precipitation followed by reversed-phase HPLC using a Gemini C18 5-μm column. Detection was performed by a SCIEX API 4000 triple quadrupole mass spectrometer configured with atmospheric pressure chemical ionization in the positive ion mode. Data were acquired by multiple-reaction monitoring of mass transition pairs at m/z of 259.99/149.2 for lenalidomide and 189.4/56.3 for the IS. The lenalidomide standard curve was linear from 0.3 to 300 ng/mL. The lower limit of quantification was 0.3 ng/mL. Intraday precision was within 5%, and assay accuracy was 87.4% to 94.5%. Percent binding of lenalidomide to plasma proteins was calculated as 100 × (1 − Cc/Ct), where Cc and Ct were the lenalidomide concentrations in ultrafiltrate and plasma, respectively.

Pharmacokinetic Analysis

Standard pharmacokinetic parameters were estimated from total (S- plus R-) lenalidomide concentration-time profiles by established noncompartmental methods using WinNonlin Professional Version 5.0 (Pharsight Corporation, Mountain View, California) or SAS Version 8.2 (SAS Institute, Cary, North Carolina). These parameters were as follows: maximum observed plasma concentration (Cmax), time to maximum plasma concentration (tmax), area under the plasma concentration-time curve from time 0 to the last measurable time point (AUCt), area under the plasma concentration-time curve from time 0 to infinity (AUC∞), apparent total body clearance when dosed orally (CL/F), apparent volume of distribution when dosed orally (V/F), terminal elimination half-life in plasma (t1/2), cumulative percentage of the dose recovered unchanged in urine (% dose), and renal clearance (CLr).

Dialysis clearance (CLHD) of lenalidomide was estimated based on plasma concentrations from the following equation:

\[
CL_{HD} = Q \times R \times (C_a - C_v)/C_a
\]

where C_a is the plasma concentration entering the dialyzer, C_v is the plasma concentration exiting the dialyzer, Q is the flow rate of blood through the dialyzer (350 mL/min), and R is the drug concentration ratio between blood and plasma (approximately 1, as determined in a mass balance study, data on file, Celgene, 2007).

Percentage of the drug in the body removed by dialysis (fHD) was calculated as the following:

\[
f_{HD} = 100\% \times [CL_{HD}/(CL/F + CL_{HD})] \times [1 - \exp(-k_{HD} \times t)]
\]

where k_{HD} is the elimination rate constant during dialysis, calculated as (CL/F + CL_{HD})/(V/F), and t is the dialysis period (4 hours).

Statistical Analysis

Pharmacokinetic parameters (AUC, Cmax, t1/2, CL/F, V/F, and CLr) were compared by use of analysis of
variance (ANOVA) on the log-transformed data, with renal function group as a fixed effect, followed by pairwise comparisons between the normal renal function group and each of the RI groups. Statistical comparisons of $t_{\text{max}}$ between renal function groups were performed using the nonparametric Wilcoxon rank sum test. Subsequently, the data from subjects with normal renal function or mild RI were combined to form a reference point. The geometric mean ratio for drug exposure ($C_{\text{max}}$ and $\text{AUC}_\infty$), along with 90% confidence intervals (CIs) for the ratio, was calculated between moderate RI, severe RI, or ESRD and the combined group (Normal + Mild RI, $CL_{\text{Cr}} \geq 50 \text{ mL/min}$).

Comparisons of pharmacokinetic parameters for ESRD subjects on a nondialysis day with those on a dialysis day were performed using the paired $t$ test ($\text{AUC}, C_{\text{max}}, t_{1/2}$) or the Wilcoxon signed rank test ($t_{\text{max}}$). The relationship between $CL_{\text{Cr}}$ and each of the parameters ($C_{\text{max}}, \text{AUC}_\infty, \text{AUC}_\infty, t_{1/2}, CL/F, V/F, CLr, \% \text{dose}$) was assessed by linear regression analyses.

In standard clinical practice, $CL_{\text{Cr}}$ are usually estimated by the Cockcroft-Gault formula: $CL_{\text{Cr}} = ([140 - \text{age}) \times \text{body weight})/(72 \times \text{serum creatinine level}) \times (0.85 \text{ for women}).^{21}$ Thus, in addition to the $CL_{\text{Cr}}$ measured from a 24-hour urine collection, the $CL_{\text{Cr}}$ estimated by the Cockcroft-Gault formula was also used to classify renal function for calculating the geometric mean ratio and used as an independent variable for linear regression analyses.

**Simulation**

Based on the dose proportionality of lenalidomide observed in healthy subjects$^{15}$ and MM patients,$^{16}$ the single-dose plasma concentration-time data obtained from each renal function group were normalized to the concentrations at the recommended dose using the following equation: normalized concentration = actual concentration at 25 mg/25 $\times$ recommended dose (mg). The steady-state plasma concentration-time profiles at the recommended dosing regimen were simulated from the normalized single-dose data using the nonparametric superposition principle (WinNonlin).

**RESULTS**

**Demographics**

All of the enrolled subjects completed the study. The major demographic characteristics are summarized for each renal function group in Table I. The cause of renal impairment in most of the subjects was the result of either cardiovascular and/or endocrine disorders. The mean age of each renal function group was in the age range for MM and MDS patient population.$^{3-8}$

**Safety**

There were no serious adverse events. No subjects were discontinued from the study due to adverse events. A total of 25 adverse events were reported by 11 subjects, with 3 subjects each in the normal renal function and ESRD groups, 2 subjects each in the moderate and severe RI groups, and 1 subject in the mild RI group. Of the 25 adverse events, 18 were considered mild in severity, and 7 were moderate. The investigator suspected 16 of the adverse events to be related to the study drug, and all adverse events were resolved during the study. The most common adverse event with a suspected relationship to lenalidomide was pruritus (3 subjects: 1 with severe RI and 2 with ESRD). Most of the laboratory abnormalities were thought to be reflective of the subjects’ underlying diseases, and the investigator considered all of the abnormal changes in laboratory parameters to be clinically insignificant. There was no indication of further decreased renal function. No treatment-related trends were observed in vital signs and ECGs.
Ex Vivo Binding of Lenalidomide to Plasma Proteins

The binding of lenalidomide to proteins in plasma was low in all subjects. The mean protein binding was 35.4% ± 4.1% for mild RI, 37.2% ± 6.3% for moderate RI, 39.8% ± 6.3% for severe RI, and 44.3% ± 3.9% for ESRD (off dialysis). These results were not meaningfully different from that determined for the normal renal function group (40.2% ± 4.5%).

Effect of Renal Impairment on Lenalidomide Pharmacokinetics

Because the ratio of S- to R-lenalidomide in plasma and urine was not significantly altered by renal impairment, only the results based on the total lenalidomide (sum of S- and R-lenalidomide) are presented.

Mean plasma lenalidomide concentrations are shown in Figure 1. Lenalidomide was absorbed rapidly after oral administration, with median t_max values ranging between 1 and 1.5 hours in all groups. After reaching the C_max, the plasma lenalidomide concentration declined in a monoexponential manner in all groups (Figure 1, inset). Mean plasma concentrations were similar between normal renal function and mild RI groups, with lenalidomide concentrations being undetectable within 24 hours. In contrast, mean plasma lenalidomide concentrations were significantly higher during the elimination phase in subjects with moderate RI, severe RI, or ESRD (Figure 1).

Cumulative urinary excretion of unchanged lenalidomide is shown in Figure 2 (subjects with ESRD were not included in this analysis as they were anuric). Urinary excretion of unchanged total lenalidomide was mostly completed by 24 hours postdose in all subjects. Thus, the urine collection period was adequate in subjects with renal impairment. Mean urinary recovery of unchanged lenalidomide was 84% of the dose in subjects with normal renal function, and it declined to 38% to 43% in subjects with moderate or severe RI (Figure 2).

Mean pharmacokinetic parameters for lenalidomide are summarized in Table II. Overall, with diminishing renal function, total (CL/F) and renal (CL_r) clearance of lenalidomide decreased, whereas total drug exposure (AUC_t and AUC_∞) and the terminal half-life (t_1/2) increased. The CL/F of 38 mL/min in subjects with ESRD (off dialysis) reflected the nonrenal clearance of lenalidomide in these subjects. This value was similar to the nonrenal clearance in subjects with normal renal function (40 mL/min, calculated as CL/F – CL_r = 199-159 mL/min).

Statistical analysis by ANOVA revealed that, except for C_max, t_max, and V/F, a group effect was observed for all other pharmacokinetic parameters (P < .001). However, the differences in CL/F, CL_r, AUC, and t_1/2 between normal renal function and mild RI groups were minor to modest (11%-32%) and fell within the range of intersubject variability for the drug. In addition, they did not reach statistical significance by pairwise comparisons. As renal impairment progressed to moderate or worse, mean
PHARMACOKINETICS OF LENALIDOMIDE

Table II  Pharmacokinetic Parameters Following a Single Oral 25-mg Dose of Lenalidomide

<table>
<thead>
<tr>
<th>Renal Function Groups</th>
<th>Normal n = 7</th>
<th>Mild RI n = 5</th>
<th>Moderate RI n = 6</th>
<th>Severe RI n = 6</th>
<th>ESRD (off HD) n = 6</th>
<th>ESRD (on HD) n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C_{max}, ng/mL</strong></td>
<td>568 (39)</td>
<td>684 (16)</td>
<td>568 (33)</td>
<td>761 (11)</td>
<td>538 (25)</td>
<td>370 (32)</td>
</tr>
<tr>
<td><strong>t_{max}, h</strong></td>
<td>1.00 (0.5-2.0)</td>
<td>1.00 (1.0-1.0)</td>
<td>1.00 (0.5-1.5)</td>
<td>1.50 (0.5-2.0)</td>
<td>1.25 (1.0-2.0)</td>
<td>2.00 (0.5-6.0)</td>
</tr>
<tr>
<td><strong>AUC_c, ng\cdot h/mL</strong></td>
<td>1977 (32)</td>
<td>2514 (37)</td>
<td>5668 (14)*</td>
<td>7766 (19)*</td>
<td>10 346 (19)*</td>
<td>6238 (17)</td>
</tr>
<tr>
<td><strong>AUC_c, ng\cdot h/mL</strong></td>
<td>2091 (32)</td>
<td>2627 (36)</td>
<td>5964 (16)*</td>
<td>8088 (18)*</td>
<td>10 958 (19)*</td>
<td>6778 (14)</td>
</tr>
<tr>
<td><strong>CL/F, mL/min</strong></td>
<td>199 (32)</td>
<td>159 (36)</td>
<td>70 (16)*</td>
<td>52 (18)*</td>
<td>38 (19)*</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vz/F, L</strong></td>
<td>56 (30)</td>
<td>50 (25)</td>
<td>60 (30)</td>
<td>40 (20)</td>
<td>51 (17)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>t_{1/2}, h</strong></td>
<td>3.26 (23)</td>
<td>3.61 (20)</td>
<td>9.97 (44)*</td>
<td>8.93 (29)*</td>
<td>15.5 (7)*</td>
<td>16.0 (11)</td>
</tr>
<tr>
<td><strong>Urine excretion, % dose</strong></td>
<td>84 (10)</td>
<td>69 (12)</td>
<td>38 (48)*</td>
<td>43 (28)*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>CLr, mL/min</strong></td>
<td>159 (36)</td>
<td>109 (36)</td>
<td>27 (63)*</td>
<td>22 (44)*</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Geometric means (geometric coefficient of variation [CV%]) are presented. RI, renal impairment; ESRD, end-stage renal disease; HD, hemodialysis; NA, not applicable.

α. Median (Min-Max).

β. P < .05 versus Normal group (analysis of variance [ANOVA] followed by pairwise comparisons); data from ESRD subjects during hemodialysis were not included in the ANOVA.

Table III  Pharmacokinetic Parameters: Normal + Mild RI Group Versus MM Patients With a Baseline Serum Creatinine ≤ 1.6 mg/dL

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Normal + Mild RI Group (Current Study) Mean Age: 62 Years (n = 12)</th>
<th>MM Patients (CC-5013-MM-001)* Mean Age: 58 Years (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C_{max}, ng/mL</strong></td>
<td>613 (32)</td>
<td>481 (21)b</td>
</tr>
<tr>
<td><strong>t_{max}, h</strong></td>
<td>1.00 (0.50-2.00)</td>
<td>1.00 (0.42-4.00)</td>
</tr>
<tr>
<td><strong>AUC_c, ng\cdot h/mL</strong></td>
<td>2300 (34)</td>
<td>2154 (28)b</td>
</tr>
<tr>
<td><strong>CL/F, mL/min</strong></td>
<td>181 (34)</td>
<td>193 (28)</td>
</tr>
<tr>
<td><strong>Vz/F, L</strong></td>
<td>53 (27)</td>
<td>56 (25)</td>
</tr>
<tr>
<td><strong>t_{1/2}, h</strong></td>
<td>3.4 (22)</td>
<td>3.3 (20)</td>
</tr>
</tbody>
</table>

Geometric means (geometric coefficient of variation [CV%]) are presented. RI, renal impairment; MM, multiple myeloma.

α. See Richardson et al16 for study design.

β. Dose-normalized value: normalized value = observed value at X mg/X mg × 25 mg.

γ. Median (Min-Max).

CL/F and CLr decreased drastically, mean AUC increased by approximately 185% to 420%, and mean terminal t_{1/2} was prolonged by approximately 6 to 12 hours (Table II).

The data from subjects with normal renal function or mild RI were therefore combined and used as a reference point (Normal + Mild RI, CL_{Ccr} ≥ 50 mL/min). The pharmacokinetic parameters for this combined group were comparable to those for the patients with relapsed or refractory MM in an early clinical study (Table III). Geometric mean ratios for AUC\_c and C_{max} between moderate RI, severe RI, or ESRD (off dialysis) and the combined group are shown in Table IV. The results were similar when either the measured CL_{Ccr} (from 24-hour urine collection) or the estimated CL_{Ccr} (from the Cockcroft-Gault formula) was used to classify the renal function. Mean AUC\_c increased by approximately 140% to 160% in moderate RI, 250% to 270% in severe RI, and 370% to 380% in ESRD, as compared with that in the combined group. Changes in C_{max} in the moderate RI, severe RI, or ESRD (off dialysis) group versus the combined group ranged from −13% to 24% (Table IV).

To further assess the relationship between renal function and lenalidomide pharmacokinetics, linear regression analyses were performed by plotting individual values of a pharmacokinetic parameter as a function of CL_{Ccr} for all subjects. Highly significant linear relationships were observed between CL/F, CLr, AUC\_c, AUC\_r, or t\_{1/2} and the measured CL_{Ccr} (R^2 > 0.7, P < .001). Graphic presentations of CL/F, CLr, and AUC\_c versus the measured CL_{Ccr} demonstrated that CL/F and CLr decreased and AUC\_c increased with decreasing renal function (Figure 3). Noticeably, linear regression of CL/F and CLr against the measured CL_{Ccr} produced similar slopes (1.9). There were no relationships between C_{max} and the measured CL_{Ccr} (Figure 3). Similar results were obtained when using the CL_{Ccr} estimated by the Cockcroft-Gault formula as the independent variable for regression analyses (data not shown).
Effect of Hemodialysis on Lenalidomide Pharmacokinetics

During hemodialysis, the mean plasma lenalidomide concentration exiting from the dialyzer was significantly lower than that entering the dialyzer (Figure 4). Based on the plasma data, the dialysis clearance was estimated to be 146 ± 18 mL/min. Thus, 31% ± 3.86% of the amount of lenalidomide in circulation at the start of dialysis is expected to be removed during a 4-hour hemodialysis session (fHD).

In the current study, where lenalidomide was administered to ESRD patients 3 hours prior to initiation of hemodialysis, Cmax, AUCt, and AUC∞ were approximately 31%, 40%, and 38%, respectively, lower as compared to a nondialysis day (Table II). However, only the difference in AUC was statistically significant (P < .01, paired t test). The terminal t1/2 was similar between both days.

Predicted Steady-State Lenalidomide Concentrations

Steady-state plasma lenalidomide concentrations were simulated from single-dose data to aid in the selection of doses and dosing schedules for renally impaired patients. The results are illustrated in Figure 5. Reduction of the dose to 10 mg once daily in subjects with moderate RI would result in a similar AUC value (104%) but a lower Cmax value (45%) as compared with a daily 25-mg dose in the combined group (Normal + Mild RI, CLCr ≥ 50 mL/min).
A dosing regimen of 15 mg every 48 hours for subjects with severe RI would also produce a similar mean daily AUC value (105%) but a lower C\text{max} value (77%) in comparison with the full dose in the combined group. In subjects with ESRD, at 15 mg 3 times a week, the average daily AUC value over a 1-week period would be slightly higher (120%), but the C\text{max} value would remain lower (63%) than the values at 25 mg in the combined group. In all adjusted dosing regimens, steady-state trough concentrations in subjects with moderate RI, severe RI, or ESRD are predicted to be less than or close to 10% of the C\text{max} level in the combined group.

DISCUSSION

The results of this study provide pharmacokinetic data for lenalidomide in subjects with varying degrees of renal impairment. The pharmacokinetic parameters were expressed in terms of the total drug (free plus bound) concentration, as binding of lenalidomide to plasma proteins was low and not significantly altered by renal impairment.

The present study again demonstrated that lenalidomide is eliminated predominantly via urinary excretion of the unchanged drug. In elderly male and female subjects with normal renal function, approximately 84% of the dose was recovered unchanged from urine, with renal clearance accounting for approximately 80% of the total drug clearance. In anuric subjects (ESRD), mean CL/F on a nondialysis day was 38 mL/min, reflecting the nonrenal clearance of lenalidomide in these subjects. This value was similar to the nonrenal clearance in subjects with normal renal function (40 mL/min). Thus, renal impairment did not alter the nonrenal elimination pathways for lenalidomide.

Relationships between renal function and pharmacokinetic parameters were analyzed by treating renal function as both categorical and continuous variables. Both analyses suggest that the total (CL/F) and renal (CL\text{r}) clearance of lenalidomide are directly proportional to renal function (CL\text{Cr}). Decreases in lenalidomide clearance led to increases in the total systemic exposure (AUC) and the plasma t\text{1/2}. No relationship between renal function and C\text{max} or t\text{max} was observed, suggesting that lenalidomide absorption is not affected by renal impairment.

In the present study, subjects with varying renal function were found to be best described by 2 distinct populations: those with CL\text{Cr} < 50 mL/min and CL\text{Cr} ≥ 50 mL/min. Subjects with CL\text{Cr} < 50 mL/min (moderate RI, severe RI, or ESRD) experienced substantially reduced lenalidomide clearance, greatly increased total drug exposure, and prolonged t\text{1/2}, suggesting that dosing adjustments are necessary for these subjects. In contrast, subjects with CL\text{Cr} ≥ 50 mL/min (ie, Normal + Mild RI) displayed a pharmacokinetic profile comparable to that in the MM patients who were included in an early clinical study (Table III). Those MM patients had a baseline serum creatinine level less than or equal to 1.6 mg/dL. They belong to the population with normal renal function or mild renal impairment and to the MM patient population currently treated with a starting dose of 25 mg.
Clinical data suggested that an initial exposure level associated with 25 mg lenalidomide was generally tolerated by those MM patients. Therefore, dose adjustment is not needed for subjects with mild renal impairment. In addition, the average exposure level in subjects with CL\textsubscript{Cr} ≥ 50 mL/min can be used as a reference point for estimating the dose adjustment factor in subjects with CL\textsubscript{Cr} < 50 mL/min, which was obtained by calculating the geometric mean ratio for drug exposure between moderate RI, severe RI, or ESRD group and the combined group (Table IV).

Recommendations for the initial starting doses in MM and MDS patients with moderate RI, severe RI, or ESRD are outlined in Table V. As the relationship between the plasma lenalidomide exposure and CL\textsubscript{cr} was similar when CL\textsubscript{cr} was calculated from a 24-hour urine collection (measured CL\textsubscript{cr}) or the Cockcroft-Gault formula (estimated CL\textsubscript{cr}), these dose adjustments are applicable to renal function classified by both methods. Selection of doses and dosing intervals aimed at approximating similar average daily AUC levels and maintaining low trough concentrations at the steady state to limit occurrences of drug-related toxicities. Simulations of the steady-state lenalidomide concentrations predicted that the recommended dosing regimens would achieve similar average daily AUC across all renal function groups, with an approximate 23% to 55% reduction in C\textsubscript{max} and a limited increase in trough concentrations in patients with CL\textsubscript{Cr} < 50 mL/min.

A 4-hour hemodialysis removed 31% of lenalidomide in the body in ESRD patients. Accordingly, when hemodialysis is completed prior to dosing, it is expected to lower the trough concentration by a similar fraction, without a significant impact on AUC and C\textsubscript{max}. Thus, no supplemental dose would be required for ESRD patients on a dialysis day if the recommended dose is given immediately following completion of each dialysis.

It should be noted that the current dose recommendations are based on the single-dose pharmacokinetic study in subjects with renal impairment due to nonmalignant conditions. The safety, efficacy, and steady-state pharmacokinetics of lenalidomide using these recommended dosing regimens remain to be evaluated in renally impaired MM and MDS patients.

In conclusion, a single 25-mg dose of lenalidomide was well tolerated in subjects with renal impairment. On the basis of the pharmacokinetic results of this study, dose adjustments are necessary for patients with CL\textsubscript{cr} < 50 mL/min. For this population, the starting dose is recommended to be reduced by 40% to 60% compared with that given to patients with CL\textsubscript{cr} ≥ 50 mL/min. Furthermore, for patients with CL\textsubscript{cr} < 30 mL/min, the reduced dose is recommended to be administered at extended dosing intervals.

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REFERENCES


