Pharmacokinetics and bioequivalence evaluation of lenalidomide in Chinese patients with multiple myeloma

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To the Editor: Multiple myeloma (MM) is currently considered to be an incurable neoplasm and a systemic disease, and the first line of treatment plays a crucial role in MM patients, since the majority of patients do not survive beyond the first-line treatment.[1] Lenalidomide, a first-line drug in the treatment of MM, is sold as a capsule under the trade name Revlimid®, which is in great demand for an increasing incidence of MM. Additionally, there is little or no pharmacokinetic (PK) data pertaining to lenalidomide in Chinese MM patients, with most PK trials on lenalidomide being conducted on young healthy volunteers. This study was conducted to compare the PKs and bioequivalence of generic lenalidomide 10 mg capsule (batch No. 1308010) manufactured by Chongqing LUMMY Pharmaceutical Co., Ltd. (Chongqing, China) with Revlimid® 10 mg capsule (batch No. A0263BA), an original lenalidomide drug, manufactured by Celgene International Sarl (Boudry, Switzerland); the comparison was carried out in Chinese patients with MM, to provide an economical alternative to the branded lenalidomide for patients.

This was a multicenter, open-label, randomized, two-period, two-sequence, crossover study conducted in Chinese MM patients who were recruited all over the country by public announcement. The patients were randomly assigned into A (test-reference) and B (reference-test) groups. Each participant was treated with either the reference or test formulation first, after which each subject was switched to the other sequence after a 3-day washout period. The subjects were treated with a single dose of the drug with 200 mL water at 8 AM after fasting for at least 10 h. Water and standard meals were provided after 2 and 4 h, respectively. A 3-mL blood sample was taken as a no-treatment control 5 min before administration, and blood samples were collected at the following time points: 0.34, 0.67, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, and 24.00 h post-dosing. Adverse events (AEs) were monitored throughout the study. The study followed the International Conference on Harmonization — Good Clinical Practice guidelines and was conducted in accordance with the *Declaration of Helsinki*. The study protocol was reviewed by the Ethics Committees of West China Hospital (No.9, Clinical Trial [Western Medicine] Medical Ethics Review, West China Hospital, 2015) of Sichuan University and the First Affiliated Hospital of the Army Medical University. All participants provided written informed consent before initiation of study. The registration number was CTR20150620 (www.chinadrugtrials.org.cn).

A total of 50 MM patients who were newly diagnosed or at least seven drug half-lives later since last chemotherapy were involved in the screening. Males or postmenopausal females, aged 18 to 70 years with body mass index (BMI) between 18 and 26 kg/m^2 and Eastern Cooperative Oncology Group performance score $\leq$2, were eligible for inclusion. Participants enrolled also satisfied the following tests: creatinine clearance $\geq$60 mL/min; alanine aminotransferase and aspartate transaminase level of $\leq 2.5 \times$ upper limit of normal (ULN); a serum total bilirubin level of $\leq 1.5 \times$ ULN; a hemoglobin level of $\geq$80 g/L; an absolute neutrophil count of $\geq$1500 cells/mm^3 ($\geq 1.5 \times 10^9$/L); and a platelet count of $\geq$80,000/mm^3 ($\geq 80 \times 10^9$/L). Females in the trimester of pregnancy or suckling period were excluded due to the teratogenicity of the drugs. Other exclusion criteria were as follows: patients with significant active cardiac diseases; digestive tract diseases that seriously affect drug absorption; a history of deep vein thrombosis formation or pulmonary embolism in the past 12 months; urinary tract obstruction or dysuria; insufficient blood volume as reflected by the blood routine examination; a history of drug allergy, allergic diseases, or allergic constitution; peripheral neuropathy $\geq$2; a history of malignant tumors, except for MM, unless the patient has been cured for >3 years; and patients who participated in other drug tests and blood donation within 3 months. As

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a result, 39 subjects were enrolled in the study and involved in both PK and efficacy analysis with no withdrawn participant. The means ± standard deviation (ranges) for the age, height, weight, and BMI of the subjects were 53.40 ± 7.43 years, 160.00 ± 9.00 cm, 60.86 ± 8.78 kg, and 23.63 ± 1.95 kg/m^2, respectively.

The plasma concentrations of lenalidomide were measured using validated ultra-high-performance liquid chromatography-mass spectrometry (Xevo TQ-S, Waters Corporation, Milford, MA, USA) methods. Reference standard lenalidomide (Batch No. Len-130201D) was provided by Chongqing LUMMY Pharmaceutical Co., Ltd., with a chemical purity >99.70% and trimethoprim was used as an internal standard. Waters Ethylene Bridge Hybrid Technology C_{18} (50 × 2.1 mm, 1.7 μm) chromatographic column was used for material separation. Gradient elution was adopted, and in mobile phase A (water phase), a 0.10% formic acid aqueous solution was used, and we adopted the use of acetonitrile in mobile phase B (organic phase). The flow rate was 0.4 mL/min, and the column temperature was 40°C. Electrospray ion source, multi-reactive ion monitoring, and positive ion mode were adopted. Plasma samples were injected after protein precipitation. The retention times for lenalidomide and trimethoprim were 1.1 and 1.3 min, respectively [Supplementary Figure 1, http://links.lww.com/CM9/A724]. The linear range of lenalidomide in the standard curve was from 1.0 to 500 ng/mL, and the relative standard deviation within and between batches was <10%, with the recovery rate of this method being 90.7% to 107.20%.

The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were determined directly from the observed data. Other PK parameters including area under the plasma concentration-time curve (AUC) from time 0 to the last measurable concentration ($AUC_{(0-t)}$), AUC from time 0 to infinity ($AUC_{(0-\infty)}$), and half-life ($t_{1/2}$) were calculated using the method of statistical moment. Phoenix WinNonlin software version 6.1 (Pharsight Corporation, Mountain View, CA, USA) was used for the computation and the statistical analysis of the bioequivalence between the test and reference formulations through the use of log-transformation $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}. Means and the 90% confidence intervals (CIs) of each parameter were analyzed using analysis of variance. The test and reference drugs were considered to be PK equivalence if their log-transformations C_{max} and $AUC_{(0-\infty)}$ are within the 80% to 125% criteria at 90% CI.

Figure 1A depicts the mean plasma lenalidomide concentrations *vs.* time for the test and reference formulations. It was observed that the PK profile of lenalidomide is very similar in the two formulations. The PK parameters of lenalidomide in the test and reference formulations are as follows. Under fasting conditions, the C_{max} for the test and reference formulations reached 230.44 ± 59.72 and 235.70 ± 70.40 ng/mL, respectively, within 1 h. Also, both formulations had a short half-life of approximately 3 h. And their $AUC_{(0-t)}$ were 828.62 ± 201.79 and 856.58 ± 235.51 ng h/mL, respectively, and $AUC_{(0-\infty)}$ were 845.54 ± 200.08 and 873.09 ± 235.53 ng h/mL, respectively. Also, the subjects had an elimination constant (Ke) of 0.25 ± 0.06 and 0.24 ± 0.06 h, an apparent volume of distribution (V1/F) of 51.61 ± 11.47 and 52.85 ± 13.29 L, a apparent clearance (CL/F) of 12.47 ± 2.91 and 12.28 ± 3.34 L/h, and an mean residence time ($MRT_{(0-t)}$) of 3.75 ± 0.79 and 3.90 ± 0.88 h for the test and reference formulations, respectively. Moreover, the 90% CIs of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ for the test and reference formulations were 92.40% to 106.30%, 94.98% to 100.16%, and 95.20% to 100.17%, respectively, which satisfied the bioequivalence criteria. Consequently, bioequivalence was proven in the test and reference formulations.

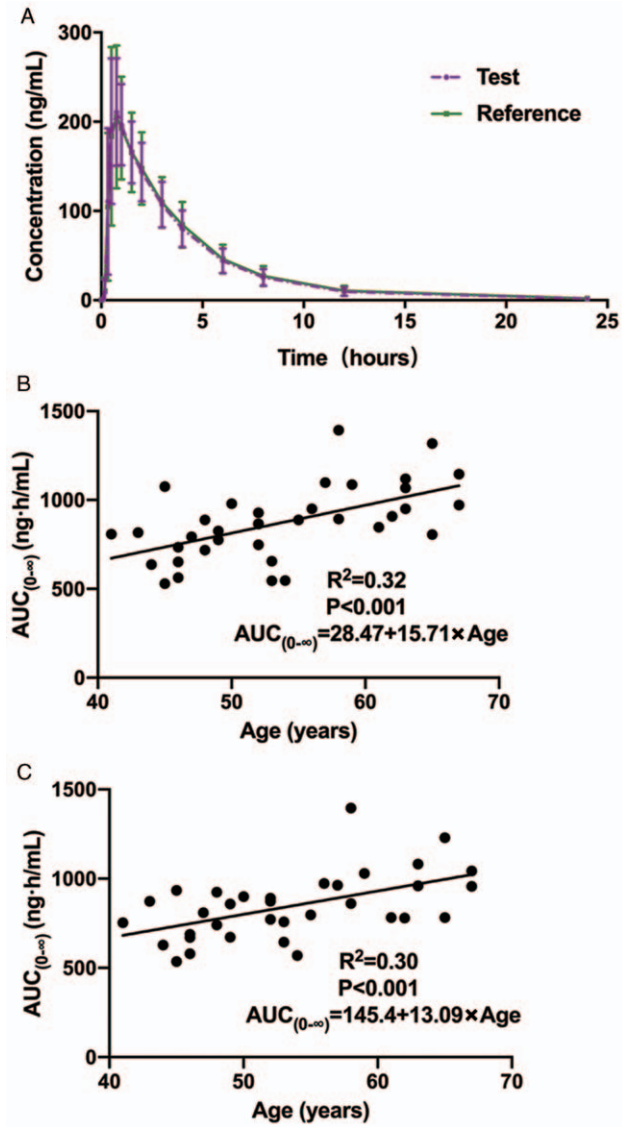

Figure 1: (A) Plasma concentration-time profiles of the test and reference formulations indicated that PK profiles of lenalidomide were very similar in the two formulations. The relationship between age and $AUC_{(0-\infty)}$ showed that total plasma exposure of the reference formulation (B) and test formulation (C) increased in proportion to age. $P < 0.001$: significant difference; R^2 = SSR/SST. AUC: Area under the plasma concentration-time curve; $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from time 0 to infinity; PK: Pharmacokinetic; SSR: Sum of squares for regression; SST: Sum of squares for total.

However, compared with the data in Japanese patients with relapsed/refractory MM,[2] significant differences were observed in the PK data between Chinese and Japanese patients. The C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ of

Japanese patients in that report were 315 ng/mL, 962, and 1037 $ng \cdot h^{-1} \cdot mL^{-1}$, respectively, which were higher than that of Chinese patients in the present study. However, it is worth noting that the average age of the Japanese patients was 64 (54–68) years, which was significantly higher than the average age of 53 (41–67) years in the present study.

It is important to examine the reasons for the differences in the PK data within the two populations. Low sensitivity to ethnic factors regarding PKs of lenalidomide was reported by multiple reports. While a previous report suggested that plasma exposure of participants after treatment with lenalidomide might vary with age.[3] Therefore, we explored the correlation between age and AUC statistically. A linear regression model was fitted by plotting the individual values of $AUC_{(0-\infty)}$ as a function of the 36 subjects (three out of 39 were excluded due to interference linearity) after the oral administration of the reference and test formulations. Significant linear relationships were observed between $AUC_{(0-\infty)}$ and age in both the reference formulation ($R^2 = 0.32$, $P < 0.001$) and the test formulation ($R^2 = 0.30$, $P < 0.001$). As shown in Figure 1B and 1C, $AUC_{(0-\infty)}$ has a significant positive correlation with patients in the age range of 41 to 67 years, which indicated that aging contributed to higher plasma exposure. And it was consistent with the phenomenon that the plasma exposure in Japanese patients was higher than that of Chinese patients with a lower average age in this study.

Furthermore, older adults are more susceptible to MM. A real-world retrospective study on MM patients age 65 years or older revealed that lower dose lenalidomide had comparable efficacy to higher dose lenalidomide.[4] Another study (lenalidomide-bortezomib-dexamethasone [RVD]-lite) certified that reduced-dose RVD was effective with low levels of toxicity and it provided support to using reduced-dosing RVD in elderly patients.[5] These phenomena might be due to the high exposure of lenalidomide in elderly patients, which reminded clinicians to reduce the dosage of lenalidomide for the elderly.

When it comes to safety, nine (23.07%) MM patients experienced 11 AEs after treatment with lenalidomide. Among them, eight subjects (20.51%) experienced at least one of the eight possible AEs: four incidences of D-dimer increase, two incidences of leucopenia, two incidences of neutropenia, and one fever incidence. The above AEs were manageable by supportive care. In the study, one possibly irrelevant blood glucose elevation occurred in one patient (2.56%). Also, one possibly irrelevant serious AE, fever, was reported in a patient and the patient was diagnosed with normal leukocyte and neutrophil levels, which was due to the development of MM or the patient being at the last stage of the disease. The patient was treated with lenalidomide-dexamethasone chemotherapy and blood replacement and died 2 months after positive treatment. The AEs observed in this study were in accordance with previously reported common AEs. One observed AE (fever) was unrelated to the study as judged by a hematologist. Both the test and reference formulations were well tolerated.

Conclusively, lenalidomide 10 mg capsule (test formulation) and Revlimid® 10 mg capsule (reference formulation) showed similar PK profiles in this study, suggesting bioequivalence between the two formulations of lenalidomide. Also, the plasma exposure of lenalidomide in MM patients increases in proportion to age, thus suggesting that appropriately reduced dosage can be administered in elderly patients.

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Conflicts of interest

None.

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