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Telavancin Pharmacokinetics and Pharmacodynamics in Patients with Complicated Skin and Skin Structure Infections and Various Degrees of Renal Function

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This study characterized the pharmacokinetic/pharmacodynamic profiles of the Food and Drug Administration (FDA)-approved telavancin renal dose adjustment schemes. A previously published two-compartment open model with first-order elimination and a combined additive and proportional residual error model derived from 749 adult subjects in 11 clinical trials was used to simulate the individual concentration-time profiles for 10,260 subjects (NONMEM). The dosing regimens simulated were 10 mg/kg of body weight once daily for individuals with creatinine clearances (CL_{CR}s) of >50 ml/min, 7.5 mg/kg once daily for individuals with CL_{CR}s of 30 to 50 ml/min, and 10 mg/kg every 2 days for those with CL_{CR}s of <30 ml/min. The area under the concentration-time curve (AUC) under one dosing interval (AUC_{τ}) was computed as dose/CL. The probability of achieving an AUC_{τ}/MIC ratio of ≥219 was evaluated separately for each renal dosing scheme. Evaluation of the dosing regimens demonstrated similar AUC values across the different renal function groups. For all renal dosing strata, >90% of the simulated subjects achieved an AUC_{τ}/MIC ratio of ≥219 for MIC values as high as 2 mg/liter. For patients with CL_{CR}s of <30 ml/min, the probability of target attainment (PTA) exceeded 90% for both the AUC_{0-24} (AUC from 0 to 24 h) and AUC_{24-48} intervals for MICs of ≤1 mg/liter. At a MIC of 2 mg/liter, the PTAs were 89.3% and 23.6% for the AUC_{0-24} and AUC_{24-48} intervals, respectively. The comparable PTA profiles for the three dosing regimens across their respective dosing intervals indicate that the dose adjustments employed in phase III trials for complicated skin and skin structure infections were appropriate.

Telavancin is a lipoglycopeptide antibiotic recently approved in the United States and Canada for complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (3). Prior to the drug entering phase II/III cSSSI trials, pharmacokinetic/pharmacodynamic (PK/PD) system analyses were performed to generate estimates of the doses to be evaluated in these trials. Studies of multiple doses and schedules demonstrated that the ratio of area under the concentration-time curve for 24 h at steady state to MIC (AUC_{24}/MIC ratio) was the pharmacodynamic variable associated with effect in neutropenic murine-thigh infection model studies, and an AUC_{24}/MIC ratio of 219 was identified as the exposure target associated with a 1-log reduction in colony counts from baseline for MRSA (8, 11). Since dosing regimens with a high likelihood of achieving this exposure target have been associated with successful outcomes in cSSSI phase III trials (2), a Monte Carlo simulation (MCS) employing healthy volunteer PK data as a measure of interpatient exposure variability was performed to inform dose selection. Several regimens were evaluated in the MCS, and 10 mg of telavancin/kg of total body weight administered every 24 h (q24h) was identified as the optimal dosing scheme; this regimen demonstrated a >95% probability of achieving an AUC/MIC ratio of 219 for MIC values of ≤2 mg/liter (11).

While the pre-phase II and III PK/PD system analyses suggested that telavancin at 10 mg/kg intravenously (i.v.) every 24 h was the appropriate dosing scheme, several clinically important issues merited further investigation. As with most drugs, dose selection for the phase III cSSSI studies was based on the MCS using healthy volunteer PK data. Such simulations are often considered the most conservative probability-of-target-attainment (PTA) evaluation of a new drug because volunteers are young and healthy and thus likely to have the highest drug clearances and shortest half-life values for drugs. However, because the MCS explicitly creates a distribution, it is important to understand the measure of dispersion surrounding PK estimates. Due to the limited variation surrounding PK parameters from healthy volunteer studies, it is probable that they do not fully reflect the PTA among patients in clinical practice (9).

An understanding of how the PK disposition changes as a function of creatinine clearance (CL_{CR}) is also essential when evaluating the PK/PD profile of a drug that is renally cleared (9, 12, 13). Telavancin is eliminated primarily by the kidneys, and dose adjustments are recommended for patients with CL_{CR}s of 10 to 50 ml/min (3). Current Food and Drug Administration (FDA)-approved dosing for cSSSI is 10 mg/kg i.v. every 24 h for patients with normal renal function, 7.5 mg/kg i.v. every 24 h for patients with CL_{CR}s of 30 to 50 ml/min, and 10 mg/kg i.v. every 48 h for patients with CL_{CR}s of 10 to 30 ml/min. There are no specific recommendations for dosing patients with CL_{CR}s of <10 ml/min. The effects of renal impairment and corresponding dosing adjustment schemes on PTAs of telavancin have not been described. Such knowledge is essential because renal impairment is likely to be

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TABLE 1 Demographic parameters in phase II and III cSSSI clinical trials of telavancin

Parameter	Phase II (references 15 and 17)	Phase III (reference 16)	Combined
n (males, females)	130 (72, 58)	383 (218, 165)	
Body wt (kg)[a]	78.34 (44.00–167.70)	78.00 (38.60–314.00)	
CL_{CR} (ml/min)[a]	100.26 (28.61–150.00)	105.61 (17.63–150.00)	
Age (yrs)[a]	44.15 (19.62–89.45)	44.00 (18.00–89.00)	
Height (cm)[a]	170.00 (142.00–193.04)	170.20 (139.70–200.70)	
Surgery (0, 1)[b]			322, 191
Eradication (0, 1, 2)[c]			53, 312, 122

[a] Shown as mean (range).
[b] 0, variable is not present; 1, variable is present.
[c] 0, not cured/eradicated; 1, cured/eradicated; 2, unknown.

prevalent among patients receiving telavancin, and their dosing regimens should be adjusted accordingly.

The 2-fold objectives of this analysis were (i) to characterize the PK/PD of telavancin among patients with cSSSI and various degrees of renal function and (ii) to assess the PK/PD profiles of the renal dose adjustment schemes used in clinical practice. To accomplish the study objectives, a previously described population PK model (10) was used to simulate telavancin plasma concentration-time profiles in cSSSI patients with various degrees of renal function and evaluate the ability of dosing regimens recommended for each CL_{CR} stratum to obtain an AUC/MIC ratio greater than the pharmacodynamic target of 219 for MIC values of 0.5, 1, and 2 mg/liter.

(This study was presented in part as a platform presentation [10] at the 20th European Congress of Clinical Microbiology and Infectious Diseases in Vienna, Austria, April 2010.)

MATERIALS AND METHODS

Telavancin population pharmacokinetic model. Telavancin exposure profiles were estimated from a previously published open 2-compartment population PK model with a combined additive and proportional residual error model (13a) derived from 749 adult subjects in seven phase I, two phase II, and two phase III clinical trials (5–7, 14–20). The structural model was parameterized on clearance (CL), volume of the central compartment (V_1), intercompartment clearance (Q), and volume of the peripheral compartment (V_2). The final clearance model included effects of CL_{CR}, weight, and gender and a flag for bacterial eradication. Body weight, CL_{CR}, and a flag for surgery were determined to be significant sources of interindividual variability in V_1; V_2 was influenced by body weight, and Q was influenced only by CL_{CR}.

Monte Carlo simulation. Individual concentration-time profiles were simulated for 10,260 subjects (NONMEM VI; Icon, Ellicott City, MD), using the aforementioned two-compartment full-population PK model with covariates (10). Data from the cohort of 513 patients enrolled in phase II and III clinical trials were used as the distribution of covariates in the MCS (Table 1). Based on this information, body weight and CL_{CR} values for 10,260 subjects were simulated in Matlab R2006a (Mathworks, Natick, MA). A normal distribution with a mean of 78 kg and a variance of 225 kg^2 was assumed for the body weight. Creatinine clearance was simulated according to a location-and-scale factor of the Weibull distribution. These simulations were based on the assumption of independence in the distributions of body weight and CL_{CR}, given that a scatter plot of the two parameters in the original data did not show any discernible trend (data not shown).

The dosing regimens used in the Monte Carlo simulation were (i) 10 mg/kg once daily for individuals with CL_{CR}s of >50 ml/min, (ii) 7.5 mg/kg for individuals with CL_{CR}s between 30 and 50 ml/min, and (iii) 10 mg/kg every 2 days for those with CL_{CR}s of <30 ml/min. The maximum steady-state plasma concentrations (C_{max}) for each regimen were the simulated concentrations at the end of drug infusion (1 h), while the minimum steady-state plasma concentrations were the simulated predose concentrations. The AUC under one dosing interval (AUC_τ) associated with each regimen was computed as dose/CL. Note that the FDA-approved dosing interval was 24 h in subjects with CL_{CR}s of >30 ml/min and 48 h among those with CL_{CR}s of <30 ml/min. The numbers of subjects achieving an AUC_τ/MIC ratio of 219 or greater for MIC values of 0.5, 1, and 2 mg/liter were calculated for each dosing scheme (11).

Since the AUC/MIC target of 219 was derived from q24h dosing in the neutropenic mouse-thigh MRSA infection model, additional PTA analyses were conducted for subjects with severe renal impairment using a daily partitioned AUC interval of AUC_{0-24} and AUC_{24-48}. In these daily partitioned PTA analyses, AUC_{0-24} and AUC_{24-48} were assumed to be 65% and 35% of the AUC_τ, respectively. Unfortunately, the AUC/MIC target based on a 48-h dosing interval is unknown at this time. In the absence of an AUC/MIC target for a 48-h dosing interval, we believed that it was prudent to assess the probability of achieving the AUC/MIC target of 219 for each 24-h interval within the 48-h dosing schedule. Since it is unclear whether cumulative or noncumulative (daily partitioned) PD exposures have a greater impact on clinical outcome in these patients, we assessed both PD exposures in patients with a CL_{CR} of <30 ml/min.

RESULTS

The simulations of the distributions of body weight and CL_{CR} using normal and scale-location Weibull probability density functions were qualitatively similar to the distribution of the original data in phase II and III clinical trials of telavancin (Fig. 1). Since the distributions were comparable, the Monte Carlo simulation of 10,260 individual concentration-time profiles was based on the simulated distributions of body weight and CL_{CR}, which were incorporated as covariates in the population model.

Summary statistics of the simulated AUC_τ values of individuals with various degrees of renal function are included in Table 2. Using the three dosing regimens, AUC values were relatively similar across the different renal function groups. Although the mean AUC_τ was ~30% higher in individuals with CL_{CR}s of <30 ml/min, the AUC values presented in Table 2 are the AUC for one dosing interval. The dosing interval is 48 h in individuals with CL_{CR}s of <30 ml/min. In contrast, the dosing interval is 24 h for individuals with CL_{CR}s of ≥30 ml/min. If one considers the cumulative AUC for a 48-h interval, the total AUC is slightly higher for individuals with CL_{CR}s of ≥30 ml/min than for those with a CL_{CR} of <30 ml/min. However, the AUC distributions overlap considerably.

Results of the PTA analyses are provided in Tables 2 and 3. More than 99% of the simulated subjects achieved an AUC_τ/MIC ratio of 219 or greater, assuming a MIC of 0.5 or 1 mg/liter, and at least 93% of the simulated population had AUC_τ/

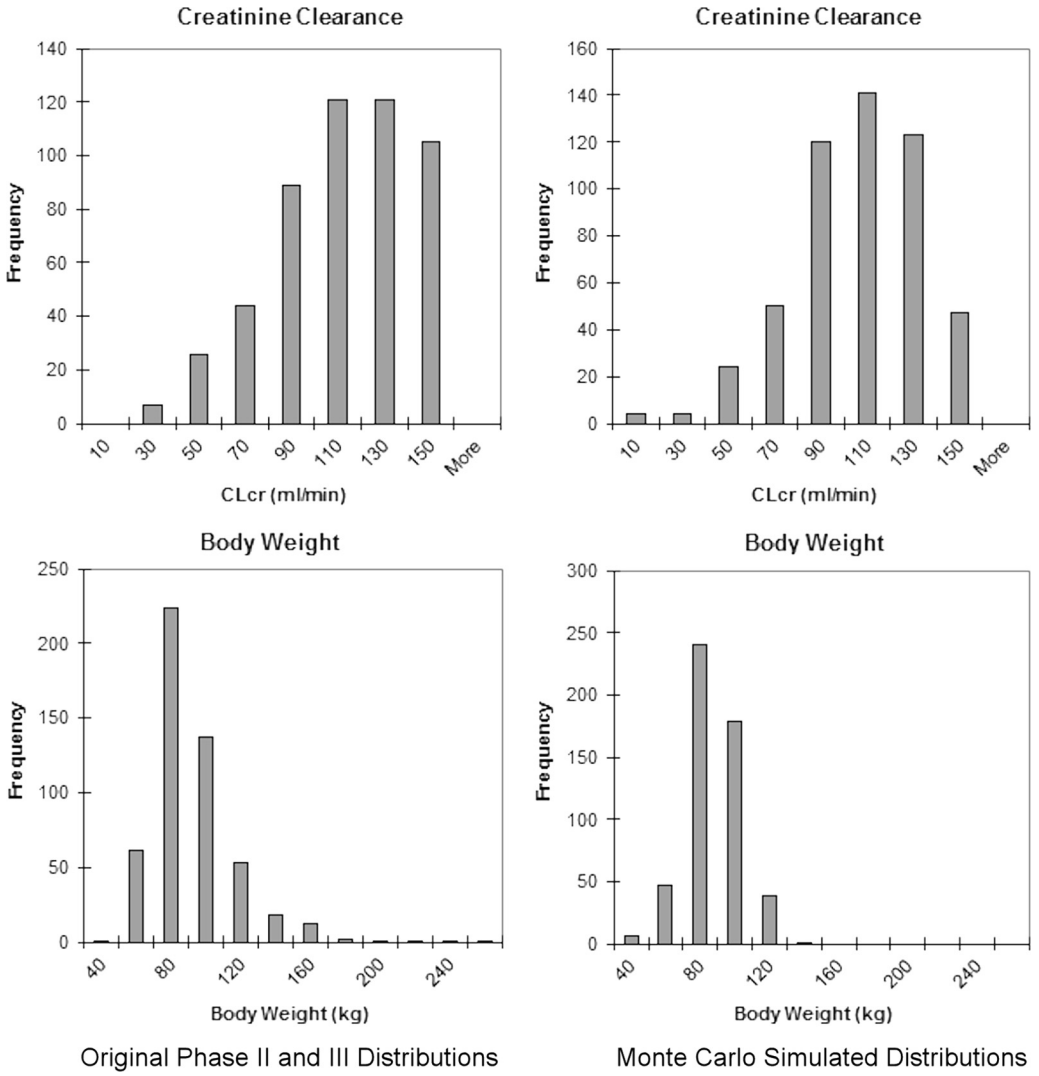

FIG 1 Body weight and creatinine clearance histograms of the original and simulated populations.

MIC ratios of 219 or greater for a MIC value of 2 mg/liter (Table 2). The percentages of subjects with severe renal impairment achieving AUC_{0-24}/MIC or AUC_{24-48}/MIC ratios of 219 are presented in Table 3. The probability of achieving an AUC/MIC ratio of 219 exceeded 90% for both the AUC_{0-24} and AUC_{24-48} intervals at a MIC of 1 mg/liter. At a MIC of 2 mg/liter, the PTAs were 89.3% and 23.6% for the AUC_{0-24} and AUC_{24-48} intervals, respectively.

Table 4 shows the maximum and minimum simulated steady-state concentrations of telavancin stratified by CL_{CR}. There were no marked differences in the simulated C_{max} or C_{min} among patients with renal impairment from those of normal patients, based on the CL_{CR} adjusted dose regimens. Although the C_{max} and C_{min} distributions were overlapping, there were differences in the mean

TABLE 2 Simulated AUC_τ and the probability of achieving an AUC_τ/MIC ratio of ≥219 in subjects with various degrees of renal function

Parameter	CL_{CR} (ml/min)		
	<30[a]	30–50[b]	>50[c]
AUC_τ (mean ± SD, mg · h/liter)	1,058 ± 316	762 ± 238	776 ± 264
AUC_τ range (minimum, maximum; mg · h/liter)	466, 2,071	318, 1,974	203, 2,820
Probability (%) of achieving AUC_τ/MIC ratio ≥ 219 at MIC			
0.5 mg/liter	100	100	100
1 mg/liter	100	100	100
2 mg/liter	98.6	95.0	93.8

[a] Based on 140 simulated profiles.
[b] Based on 480 simulated profiles.
[c] Based on 9,640 simulated profiles.

TABLE 3 Simulated probability of achieving AUC_{0-24}/MIC and AUC_{24-48}/MIC ratios of ≥219 in subjects with severe renal impairment

MIC (mg/liter)	Probability (%) of achieving AUC_τ/MIC ratio ≥ 219	
	AUC_{0-24}/MIC ratio	AUC_{24-48}/MIC ratio
0.5	100	100
1	100	92.4
2	89.3	23.6

TABLE 4 Summary statistics of simulated telavancin C_{max} and C_{min} at steady state

Pharmacokinetic parameter	CL_{CR} (ml/min)[d]			
	≥80 (n = 7,710)	50–79 (n = 2,040)	30–49 (n = 420)	<30 (n = 140)
C_{max} (μg/ml)[a]				
Mean ± SD (μg/ml)	101 ± 21.8	101 ± 26.2	76.4 ± 18.6	82.3 ± 23.8
Interquartile range[b]	85.1, 98.9, 114	82.3, 97.5, 117	63.5, 74.7, 88.4	65.9, 79.6, 97.0
C_{min} (μg/ml)[c]				
Mean ± SD (μg/ml)	10.7 ± 7.90	16.8 ± 10.6	15.9 ± 8.39	6.97 ± 4.99
Interquartile range[b]	4.74, 8.93, 14.6	9.07, 14.5, 22.4	9.85, 14.7, 51.8	3.57, 5.55, 9.95

[a] C_{max} = simulated value at the end of the 1-h infusion.
[b] Interquartile range is listed as first quartile, median, and third quartile.
[c] C_{min} = predose value (telavancin was administered q24h in subjects with CL_{CR}s of ≥30 ml/min and q48h in subjects with CL_{CR}s of <30 ml/min).
[d] n is number of simulated subjects.

estimates of C_{max} and C_{min} between CL_{CR} strata. A higher mean C_{max} was observed in individuals with a CL_{CR} of ≥50 ml/min than in those with a CL_{CR} of <50 ml/min. In contrast, a lower C_{min} was observed for CL_{CR}s of <30 ml/min than for the other strata. The C_{min} for CL_{CR}s of <30 ml/min reflects the predose concentration 48 h after the last dose at steady state. If one were to consider the concentration at hour 24 in the stratum of CL_{CR}s of <30 ml/min, the point estimates of the means would be similar across all CL_{CR} groups.

DISCUSSION

This study distinguishes itself by using a population model-based approach to characterize the PK/PD profiles of current telavancin renal dosing schemes used in clinical practice. While valuable information for dose selection can be obtained by an MCS employing phase I data, it is imperative to validate initial dose selection as more data become available among the target population (1, 2). This is especially true for antibiotics that are renally cleared and dose adjusted for patients with renal impairment. Often, the process of selecting antimicrobial renal dosing schemes is arbitrary and based on prespecified dose adjustments (i.e., 50 to 75% dose reduction) at prespecified CL_{CR} thresholds (i.e., <50 ml/min). In most cases, renal dose adjustment schemes are put into practice without consideration of the PK/PD profile (9, 12, 13).

The population pharmacokinetic model used in this analysis (10) was derived from 749 adult subjects in seven phase I, two phase II, and two phase III clinical trials. Overall, the model fit the data extremely well, and the PK parameters were physiologic in nature (10). While informative in understanding the behavior of telavancin in patients with various degrees of renal function, the major strength of this population PK model is its use in verifying the optimal dosing for telavancin in patients with impaired renal function. In particular, this model was embedded into a Monte Carlo simulation program and used to estimate exposure profiles for dosing regimens at fixed CL_{CR} ranges (12). After reviewing the pharmacodynamic exposure distribution for current renal dosage regimens, our results verify that current renal dosing schemes used in clinical practice are appropriate. The exposure profiles, as measured by C_{max}, C_{min}, and AUC_{τ}, were relatively comparable between regimens across the different renal strata. In addition, these regimens provided acceptable PTAs for the range of *Staphylococcus aureus* MIC values classified as susceptible by the FDA and Clinical and Laboratory Standards Institute (CLSI) (MIC values ≤ 1 mg/liter) (4). All proposed dosing regimens of telavancin are expected to provide an AUC_{τ}/MIC ratio of 219 or greater in at least 99% of the population, for a MIC of 1 mg/liter or less. When the MIC was assumed to be equal to 2 mg/liter, the PTA was at least 93%. However, given that patients with severe renal impairment (CL_{CR} of <30 ml/min) require every-other-day administration of telavancin, it was also important to consider the daily partitioned AUC values (AUC_{0-24}, AUC_{24-48}) given that the AUC/MIC target of 219 was derived using once-daily dosing regimens. Our analysis demonstrated that for the daily partitioned AUC values, the PTA was sufficient (>90%) for current Clinical and Laboratory Standards Institute (CLSI)- and FDA-approved breakpoints for *Staphylococcus aureus* (MIC ≤ 1 mg/liter) (3, 4). At a MIC of 2 mg/liter, however, the PTAs were 89.3% and 23.6% for the AUC_{0-24} and AUC_{24-48} intervals, respectively.

Several things should be noted when interpreting the results of this study. First, the PK/PD target (AUC_{24}/MIC ratio of 219) used in this study was identified as the exposure target associated with a 1-log reduction in colony counts from baseline in the neutropenic mouse-thigh MRSA infection model. While achievement of this exposure target has been shown to have important implications for patients with cSSSI (2), data are lacking on the PK/PD target associated with optimal response using clinical data. Future studies are sorely needed to quantify the exposure targets for both efficacy and toxicity in humans. If these data become available, the utility of the FDA-approved renal dosing scheme should be revisited. Second, the AUC/MIC target of 219 was based on q24h dosing. It is currently unknown what the PK/PD target is for a 48-h dosing interval. Cognizant of this, we evaluated the AUC/MIC target for each 24-h interval within the 48-h dosing schedule for patients with a CL_{CR} of <30 ml/min. Since patients who require q48h dosing have lower exposures during the 24- to 48-h interval than during the 0- to 24-h interval, it is imperative that further analyses assess whether cumulative or noncumulative (daily partitioned) PD exposures have a greater impact on clinical outcome. Third, given that there were subtle differences in C_{max} and C_{min} values across CL_{CR} strata, future PK/PD system analyses should evaluate the clinical relevance of these findings as more data become available.

In conclusion, a robust PK/PD analysis was performed using PK data from 11 studies involving 749 patients (5–7, 14–20). The dose adjustments for renal impairment utilized in phase III protocols (7.5 mg/kg q24h for moderate renal impairment and 10 mg/kg q48h for severe renal impairment) appear appropriate

based on the observed reductions in telavancin clearance among subjects with moderate and severe renal impairment (3). The concentration-time and PTA profiles were similar for the three dosing regimens across their respective dosing intervals for the different renal function groups, indicating that dose adjustments employed in phase III cSSSI trials were appropriate. All proposed telavancin dosing regimens are expected to provide an AUC_{τ}/MIC ratio of 219 or greater in at least 90% of the population, for organisms with a MIC within current CLSI- and FDA-approved breakpoints for *Staphylococcus aureus* (4). Since PK/PD system analysis is an iterative process, the utility of the FDA-approved renal dosing scheme should be revisited as more clinically derived PK/PD data become available.

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