Comment on: Acute renal insufficiency during telavancin therapy in clinical practice

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Sir,

The recent article by Marcos et al.1 raises serious concerns about the current dosing recommendations for telavancin. The retrospective nature of their study (as the authors acknowledge) prevents direct attribution of the observed acute kidney injury (AKI) events to the use of telavancin.1 However, their findings regarding a link between high body mass index (BMI) and AKI are not entirely unexpected based on the population pharmacokinetics of telavancin.2 The currently recommended intravenous dose of telavancin is 10 mg/kg every 24 h in patients with a creatinine clearance (ClCR) >50 mL/min, and a reduction in dosage to 7.5 mg/kg every 24 h (30–50 mL/min) or 10 mg/kg every 48 h (10 to <30 mL/min).3 The dosage of telavancin is based on total body weight (TBW), but the ClCR value used to adjust its dose is estimated using the Cockcroft–Gault equation with ideal body weight (IBW).4 Marcos et al.1 indicated that the telavancin dose was based on the estimated ClCR using the Cockcroft–Gault equation and TBW, which is inconsistent with the telavancin product label.5 This is an important distinction because TBW overestimates kidney function, while IBW underestimates kidney function in patients with a high BMI.6

As a specific example, overestimation of ClCR using TBW might have contributed to the use of a higher dosing tier of telavancin in Patient 5 (ClCR of 55 mL/min), as shown in Tables 1 and 2 of Marcos et al.1 A lower dose might have been selected if IBW had been used to estimate ClCR, as recommended in the product label.7 Unfortunately, this potential dosing error reflects the disharmonious approach to estimation of kidney function during drug development.8 This disharmony is evident with daptomycin, the dosage of which, like that of telavancin, is based on TBW but is adjusted for ClCR using the Cockcroft–Gault equation and TBW (not IBW).9 Similarly, automatic laboratory-reported glomerular filtration values should be used cautiously when defining telavancin doses until they have been validated. Beyond estimation of kidney function as a source of dosing error, a larger issue at hand is whether TBW is the right dosing scalar for telavancin in patients with a high BMI. Dosing on TBW implies that this scalar reduces inter-individual pharmacokinetic variability and leads to bioequivalent systemic exposures across the weight continuum. The population pharmacokinetic model that is the basis for telavancin dose justification actually suggests that this is not the case.2

The final population pharmacokinetic model for telavancin clearance (Cl)=[0.286+0.00456×(ClCR×0.0039×(TBW))×sex+0.0847×ERAD, where ClCR is based on the Cockcroft–Gault equation and IBW, sex=1 for males and 0.907 for females, and ERAD is a flag for eradication (no eradication=0 and eradication=1).2 Population pharmacokinetic modellers will appreciate that TBW would likely not exist as an independent covariate of Cl in this final model if ClCR estimated using the Cockcroft–Gault equation had actually used TBW instead of IBW. This is because IBW is often considered to be a weight dimension when in reality it is a height dimension transformed erroneously to weight.6 Despite these potential model development errors, the existing model for telavancin CL can still be used to simulate the AUC from 0 to 24 h (AUC0–24) of telavancin across the clinical weight spectrum based on the equation AUC=dose/Cl.

Figure 1 illustrates the projected AUC0–24 values based on a dose of 10 mg/kg every 24 h and assumes fixed ClCR estimates of 51, 100 or 150 mL/min, using the above telavancin CL model. This projection is based on a random mean (coefficient of variation) normal weight distribution of 81 (27%) kg, with a random distribution for sex and eradication for 10,000 subjects using StataSE version 11 (StataCorp, College Station, TX, USA). As shown (Figure 1), dosing on BW leads to a steady rise in AUC0–24 as a function of BW, implying non-bioequivalence across TBW. A mean (minimum, maximum) fractional change in telavancin AUC0–24 values of 3.47 (1.45, 5.91) is expected in patients with ClCR of 100 mL/min across the simulated weight range of 30–173 kg with current TBW-based dosing. Given that drug-induced AKI is likely to be related to systemic exposure, higher telavancin AUC0–24 values in larger patients should contribute to a higher risk of AKI. Post hoc analyses of two Phase 3 trials revealed the incidence of renal events to be 6.4% in patients with BMI ≥35 kg/m² and 2.3% in those with BMI <35 kg/m² treated with telavancin.6 This 2.8-fold difference in the incidence of renal events for telavancin between BMI groups was not observed with the use of vancomycin. As a result, the clinical documentation of high rates of AKI by Marcos et al.1 in obese individuals is consistent with the expected high telavancin exposure with weight-based dosing. Hence, a reappraisal of telavancin dosing in obese patients should be considered to reduce the risk of AKI without compromising its efficacy. Studies evaluating therapeutic drug monitoring of telavancin to define exposure–response (safety and efficacy) relationships in the clinical setting will aid with this reappraisal.
Transparency declarations

None to declare.

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Acute renal insufficiency during telavancin therapy in clinical practice—authors’ response

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Sir,

We appreciate the thoughtful comments by Pai,1 who makes an excellent point about weight and telavancin dosing and raises a concern about the dosing of telavancin in our study.2 We should clarify that this was a retrospective cohort and clinicians caring for the patients at the time based their telavancin dosing on total body weight (TBW) in those with normal renal function. The calculated CLCR was taken from the hospital physician order entry system. To clarify, this system uses ideal body weight (IBW) and the Cockroft–Gault equation. Thus, all patients were dosed with telavancin for a calculated CLCR according to the IBW–Cockroft–Gault-based equation, as recommended in the telavancin label.1 Thus, Patient 5, as well as the rest of the patients in this cohort, received the adjusted dose of telavancin according to CLCR calculated using IBW, not TBW; and none was overdosed with telavancin for their degree of renal function. Thus, we are able to confirm the accuracy of our telavancin dosing based on package label recommendations.

In terms of the clinical results described, we feel it important to highlight that our primary endpoint of acute kidney injury, as defined as ≥50% increase in serum creatinine from baseline to ≥1.5 mg/dL (132.6 mmol/L), was irrespective of body weight. Therefore, our determinations of the occurrence of acute renal insufficiency, as defined above, are accurate as reported. We did also assess the magnitude of the glomerular filtration rate (GFR) reduction utilizing the Cockroft–Gault equation based on TBW4 as originally described in 1976.5 It is true that had we used IBW instead of TBW for Cockroft–Gault-derived GFR reduction determinations, the actual GFR results prior to and after therapy (Table 1 in Marcos et al.), as well as the absolute magnitude of GFR decline, would have been numerically lower than the values presented in the paper. However, the percentage of GFR reductions in the event that IBW had been used instead of TBW in Cockroft–Gault-determined GFR reduction determinations would have been mathematically unchanged.

Transparency declarations

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