Successful Target Attainment of Telavancin at Elevated MICs: Fact or Fiction?

Lodise et al. aimed to characterize the pharmacokinetics and pharmacodynamics of telavancin among patients with complicated skin and skin structure infections (cSSSIs) and various degrees of renal function (6). During evaluation, an area under the concentration-time curve (AUC)/MIC ratio of 219 or more was selected as the pharmacodynamic target. The authors concluded that all proposed dosing regimens would achieve a 93% or higher coverage in the population when the MIC is equal to 2 mg/liter (6).

First, Lodise et al. referenced the target AUC/MIC ratio of 219 or more as the exposure target associated with a 1-log-unit decrease in colony count from the baseline for methicillin-resistant *Staphylococcus aureus* (MRSA) (6). In multiple publications, there is evidence of significant variability between strains for the magnitude of the pharmacokinetic/pharmacodynamic (PK/PD) index needed to achieve the same pharmacodynamic endpoint (5, 8). As a matter of fact, 2 of the 4 MRSA strains achieved the target 1-log-unit kill with approximately 60% less drug than the single strain MRSA 33591. On the basis of the linear ($R^2 = 0.99$) relationship between the dose of telavancin and the resulting AUC, one can easily conclude that the same killing effect for some strains in this study was achieved by an AUC/MIC ratio severalfold smaller than the target chosen by the authors (5).

Second, the target used by Lodise et al. was established in an earlier publication on the basis of the results from the single strain MRSA 33591 (7). In the original study, the telavancin MIC for this strain was 1 mg/liter, as presented by Hegde et al. in Table 1 of reference 5. In contrast, and in the same publication, Hegde et al. reference a value of 0.4 mg/liter for telavancin MIC for the same strain (5). Further review of the literature also yielded several other publications in which the telavancin MIC for MRSA 33591 was consistent with the value of 0.5 mg/liter or lower (2, 4, 9–11).

Considering a more likely value of 0.5 mg/liter for an MIC for this particular strain, the target of 219 or more should be 438 or more. This alternative target would also better support the currently approved U.S. FDA telavancin susceptibility breakpoint for *Staphylococcus aureus* (1). Considering recently documented activity of telavancin against *Staphylococcus aureus*, all FDA-approved dosing regimens would provide greater than 95% cumulative fraction of response at this target, which in turn would support the high likelihood of successful outcomes in cSSSI drug trials (3).

In summary, the data presented by Lodise et al. should be interpreted very conservatively. While currently available literature does support adequate probabilities of target attainment of telavancin up to an MIC of 1 mg/liter, at MICs higher than that, the data are much less clear (3, 6). Further research focusing on multistrain experiments may shed light and help us better understand the true magnitude of the PK/PD index needed to achieve with telavancin that results in positive outcomes.

REFERENCES


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