Analysis of Vancomycin as a Surrogate Agent for Presumptive Susceptibility Categorization for Telavancin

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ABSTRACT

Background. The broth microdilution method and associated quality control ranges and interpretive criteria for telavancin were revised and recently approved by the U.S. Food and Drug Administration (FDA). Because commercial susceptibility testing devices for recently approved agents are not readily available, surrogate testing options can be considered. This study evaluated the use of vancomycin for predicting telavancin susceptibility results.

Methods. The following isolates were included: 15,304 *Staphylococcus aureus* (including 6 vancomycin-resistant [VRSA] and 6 vancomycin-intermediate [VISA] strains), 1,991 *Enterococcus faecalis* (44 vancomycin-resistant [VRE]), 1,155 viridans group streptococci (VGS), and 2,424 β-hemolytic streptococci (BHS). Isolates originated as part of the Telavancin International Surveillance Program (2011–2013), except for a challenge set of 6 VRSA and 5 VISA isolates from Network on Antimicrobial Resistance in *S. aureus* (NARSA). Susceptibility testing applied Clinical Laboratory Standards Institute (CLSI) methods (M07-A9 and M100-S24). FDA (telavancin) and CLSI (vancomycin) criteria were used for minimum inhibitory concentration interpretations. Correlations between telavancin and vancomycin susceptibility results were analyzed by regression statistics, scattergrams and error rates.

Results. Table 1 shows error and categorical agreement rates. A categorical agreement rate of 99.98% was noted for *S. aureus.* Minor errors occurred against 3 VISA isolates, which were susceptible to telavancin. A 99.65% categorical agreement rate was obtained for *E. faecalis*, with a single very major error (false-susceptibility; vancomycin-susceptible and telavancin-non-susceptible). Three VRE (teicoplanin-susceptible; VanB-phenotype) each were responsible for the major and minor errors observed for *E. faecalis*. When vancomycin-susceptible *E. faecalis* were analyzed, the categorical agreement rate was 99.95%. Absolute categorical agreement rates were obtained against BHS and VGS, where only susceptible isolates for both agents were available.

Conclusions. High categorical agreement rates were observed between telavancin and vancomycin. Errors were primarily observed for VISA and VanB-phenotype *E. faecalis* (not an indicated species in the prescribing information), due to greater activity of telavancin compared to vancomycin. VISA isolates should be tested for telavancin susceptibility.

INTRODUCTION

- Telavancin was approved in the United States and Canada for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive pathogens.[6]
- Telavancin was also approved in the United States and Europe for the treatment of adult patients with hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia due to susceptible isolates of *Staphylococcus aureus* (methicillin-resistant strains *S. aureus* [MRSA] only in Europe), when alternative treatments are not suitable.
- Earlier this year (2014), a revised broth microdilution susceptibility testing method for telavancin was published by the Clinical and Laboratory Standards Institute (CLSI; M100-S24), followed by the U.S. Food and Drug Administration (FDA) approval.[3,6]
  - This revised method follows the current CLSI guidelines for water-insoluble agents and includes the addition of polysorbate-80 (P-80; 0.002%) to the test medium.
  - The revised broth microdilution method for telavancin provides more accurate and reproducible results by minimizing drug loss during panel preparation (increased solubility) and minimum inhibitory concentrations (MIC) testing (decreasing binding on plastic trays).[4]
- Validated commercial susceptibility testing products/systems that would provide results equivalent to the revised broth microdilution testing method for telavancin are not yet available for clinical microbiology laboratories.
- The use of results obtained from an antimicrobial agent, potentially a class representative that is commonly tested by the microbiology laboratories, can be an option for determining the susceptibility results of the new antimicrobial. Thus, this study evaluated the use of vancomycin for predicting telavancin susceptibility results.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 15,304 *S. aureus* (including 6 vancomycin-resistant [VRSA] and 6 vancomycin-intermediate [VISA] strains), 1991 *Enterococcus faecalis* (44 vancomycin-resistant [VRE]), 1155 viridans group streptococci (VGS) and 2,424 β-hemolytic streptococci (BHS) were included in this study.
- The isolates originated from the Telavancin International Surveillance Program, which is part of the SENTRY Antimicrobial Surveillance Program. The challenge set of 6 VRSA and 5 VISA isolates was provided by the Network on Antimicrobial Resistance in *S. aureus* (NARSA).
- The isolates included in the Telavancin International Surveillance Program were collected from medical centers located in the United States and Europe (2011–2013). These isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA).
- Identification was initially performed by the participating laboratory and confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by broth microdilution following the CLSI guidelines (M07-A9).[2] Telavancin susceptibility was determined using the revised testing method following the CLSI (M100-S24) and product package insert information.[3,6]
- MIC values were quality assured by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* American Type Culture Collection [ATCC] 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619).[3,5] All QC results were within published acceptable CLSI ranges. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event.
- MIC interpretations for telavancin were based on recently approved breakpoint criteria appropriate for the revised broth microdilution testing method, as specified in the updated product package insert (2014),[6] and are as follows:
  - *S. aureus* at ≤0.12 μg/mL for susceptible; *E. faecalis* (vancomycin-susceptible) at ≤0.25 μg/mL for susceptible; *Streptococcus pyogenes* and *Streptococcus agalactiae* at ≤0.12 μg/mL for susceptible; and *Streptococcus anginosus* group at ≤0.06 μg/mL for susceptible
  - The CLSI M100-S24 (2014) breakpoint criteria were applied for vancomycin.[3]
- Data analysis generally followed the intermethod comparison guidelines found in CLSI documents (M23-A3), and scattergrams and error rates were generated.[1]
  - A categorical agreement rate of ≥90.0%, and very major, major and minor error rates of ≤1.5, ≤3.0 and ≤5.0% were considered acceptable, respectively.
  - Very major (vancomycin-susceptible and telavancin-non-susceptible); major (vancomycin-resistant and telavancin-susceptible); and minor (vancomycin-intermediate and telavancin-susceptible) error rates were calculated using total number of isolates as the denominator.

RESULTS

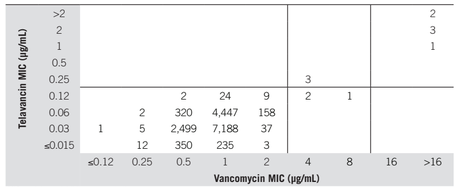
- **Table 1** shows a summary of categorical agreement results and error rates obtained when performing an intermethod comparison analysis between telavancin and vancomycin tested against a recent collection of Gram-positive isolates.
- Telavancin was active against all 15,292 vancomycin-susceptible *S. aureus* (99.94% of all *S. aureus*). Telavancin MIC results of 0.12–0.25 and ≥1 μg/mL were obtained against VISA and VRSA isolates, respectively (**Figure 1**).
- These MIC results provided an overall categorical agreement rate of 99.98% for *S. aureus*. Minor errors (0.02%) occurred against 3 VISA isolates, which were susceptible to telavancin (**Table 1** and **Figure 1**).
- When tested against *E. faecalis*, categorical agreement rates of 99.65% and 99.95% were obtained against all isolates and the vancomycin-susceptible set, respectively (**Table 1**). A single (0.05%) very major error was observed (a false-susceptibility result; vancomycin-susceptible and telavancin-non-susceptible).
- Other major and minor errors (0.3%) were noted for 6 VRE isolates displaying a VanB-phenotype. These isolates were susceptible to telavancin (when applying the breakpoint for vancomycin-susceptible *E. faecalis*) and intermediate or resistant to vancomycin (**Table 1** and **Figure 2**).
- All streptococcal isolates included in this investigation were telavancin- and vancomycin-susceptible, and these comparison analyses resulted in absolute categorical agreement rates (**Table 1** and **Figures 3** and **4**).

Table 1. Summary of categorical agreement results and error rates between telavancin and vancomycin when tested against Gram-positive isolates

		% Error rate[b]		
Pathogen[a] (no. tested)	Very major	Major	Minor	% CA[c]
S. aureus (15,304)	0.00	0.00	0.02	99.98
MRSA (5,975)	0.00	0.00	0.05	99.95
E. faecalis[d] (1,991)	0.05	0.15	0.15	99.65
Vancomycin-susceptible (1,947)	0.05	NA	NA	99.95
BHS (2,424)	0.00	NA	NA	100.00
VGS (1,155)	0.00	NA	NA	100.00

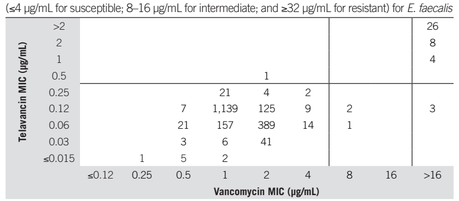
a. BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. Very major = vancomycin-susceptible and telavancin-non-susceptible; Major = vancomycin-resistant and telavancin-susceptible; Minor = vancomycin-intermediate and telavancin-susceptible. All error rates were calculated using total number of isolates as the denominator. NA = not applicable due to absence non-susceptible isolates.
c. CA = Categorical agreement rate across all three categories.
d. A single (0.05%) very major error (false-susceptibility) and a 99.95% agreement rate if only vancomycin-susceptible isolates were analyzed.

Figure 1. Scattergram comparing the telavancin and vancomycin MIC results tested against 15,304 *S. aureus* isolates. The horizontal line represents FDA-approved susceptible breakpoint for telavancin (≤0.12 μg/mL), while vertical lines represent the vancomycin breakpoints (≤2 μg/mL for susceptible; 4–8 μg/mL for intermediate; and ≥16 μg/mL for resistant) for *S. aureus*



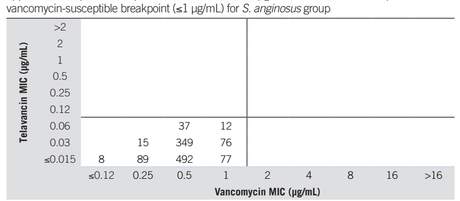
MIC = minimum inhibitory concentration.

Figure 2. Scattergram comparing the telavancin and vancomycin MIC results tested against 1,991 *E. faecalis* isolates. The horizontal line represents FDA-approved susceptible breakpoint for telavancin (≤0.25 μg/mL), while vertical lines represent the vancomycin breakpoints (≤4 μg/mL for susceptible; 8–16 μg/mL for intermediate; and ≥32 μg/mL for resistant) for *E. faecalis*



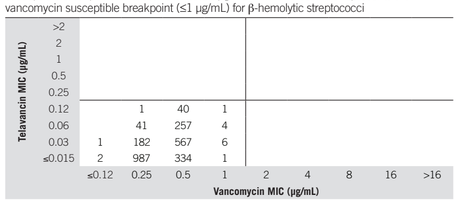
MIC = minimum inhibitory concentration.

Figure 3. Scattergram comparing the telavancin and vancomycin MIC results tested against 1,155 viridans group streptococcal clinical isolates. The horizontal line represents FDA-approved susceptible breakpoint for telavancin (≤0.06 μg/mL), while vertical line represents the vancomycin-susceptible breakpoint (≤1 μg/mL) for *S. anginosus* group



MIC = minimum inhibitory concentration.

Figure 4. Scattergram comparing the telavancin and vancomycin MIC results tested against 2,424 β-hemolytic streptococci (includes1,052 *S. pyogenes*, 963 *S. agalactiae*, 141 *S. dysgalactiae* and 268 other species). The horizontal line represents FDA-approved susceptible breakpoint for telavancin (≤0.12 μg/mL), while vertical line represents the vancomycin susceptible breakpoint (≤1 μg/mL) for β-hemolytic streptococci



MIC = minimum inhibitory concentration.

CONCLUSIONS

- High categorical agreement rates were observed between telavancin and vancomycin when tested against a contemporary (2011–2013) collection of Gram-positive isolates from medical centers in the United States and Europe.
- Susceptibility error results were primarily (telavancin-susceptible and vancomycin-non-susceptible) observed for VISA and VanB-phenotype *E. faecalis* (not an indicated species in the prescribing information), due to greater activity of telavancin compared with vancomycin.
- Based on these *in vitro* broth microdilution results and intermethod comparison analysis, vancomycin can be utilized as a surrogate marker testing strategy for determining telavancin susceptibility with an accuracy of >99.99%. VISA isolates require susceptibility testing specifically for telavancin.

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