Surrogate Glycopeptide Testing Used to Predict Susceptibility to Dalbavancin: A Novel Glycolipopeptide

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ICID 2006

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ABSTRACT

Background: Dalbavancin is a new glycolipopeptide with an extended elimination half-life allowing once-weekly dosing for treatment of complicated skin and skin structure (SSTI). Dalbavancin activity and spectrum resembles available glycopeptides such as vancomycin and teicoplanin. Dalbavancin disk diffusion tests were suboptimal for clinical laboratory use and commercial MIC systems will not be immediately available for diagnostic use, thus a surrogate predictor of dalbavancin activity was sought.
Methods: International surveillance results (21,887 isolates) were available for comparison of dalbavancin MICs with those of glycopeptides. Isolates were tested by validated broth microdilution panels (TREK Diagnostics) with results observed within published CLSI ranges. MIC comparisons were analyzed among six groups: *S. aureus* (11,867), coagulase-negative staphylococci (CoNS; 3,450), ß-haemolytic (1,051) and viridians gr. (381) streptococci, *S. pneumoniae* (3,707) and enterococci (4,131). Categorical criteria for vancomycin and teicoplanin were those of CLSI and were compared with two candidate dalbavancin breakpoints (BKP) of ≤0.5 or ≤1 mg/L.
Results: Dalbavancin activity approximated that of vancomycin and teicoplanin with dalbavancin generally being 8- to 16-fold more active, see table.

Organism (no. tested)	Dalbavancin BKP	No. (%) by vancomycin category: Susceptible	Intermediate	Resistant
S. aureus (11,867)	≤0.5	11,866 (>99.9)	1 (<0.1)	-
	≤1	-	-	-
CoNS (3,450)	≤0.5	3,445 (99.9)	-	-
	≤1	3,450 (100.0)	-	-
Streptococci (5,139)	≤0.5	5,139 (100.0)	-	-
	≤1	-	-	-
Enterococci (4,131)	≤0.5	3,370 (81.6)	35 (0.8)	139 (3.4)
	≤1	-	-	29 (0.7)
	2	-	-	35 (0.8)
	≥4	-	-	523 (12.7)

Vancomycin used to predict *S. aureus*, CoNS, streptococci and enterococci dalbavancin susceptibility was (BKPs, ≤0.5/≤1 mg/L): >99/>99, 100/100 and 100/100% accurate, respectively, with only one minor test error (0.008%). Teicoplanin was similarly accurate (>99.9/>99.9, 96.5/99.6, 100/100%) with only minor or conservative false-resistant errors with CoNS. Versus enterococci, dalbavancin susceptibility was correctly assessed by vancomycin for 3,370/3,544 strains (4.9% false-resistance).
Conclusion: To accurately determine potential use of dalbavancin after US-FDA release, surrogate application of vancomycin or teicoplanin MIC results have acceptable performance (>95-100%; 2 candidate BKPs) with nearly all errors being minor (false-intermediate) or major (false-resistant) versus Gram-positive pathogens isolated from SSTI.

INTRODUCTION

A recurrent problem with modern antimicrobial susceptibility testing is the delay in the approval of commercial susceptibility testing products containing new drugs after their release for clinical use by the United States Food and Drug Administration (US-FDA). The appearance of new antimicrobials in commonly used automated systems (Vitek or Vitek 2; bioMerieux Hazelwood, MO, USA, and MicroScan WalkAway, MicroScan Dade Berhing, West Sacramento, CA, USA) can lag by 6 to 18 months, compromising utilization of these agents in clinical practice and their entry into hospital formularies where they may have significant favorable impact. In contrast, manual diffusion testing products (disks or Etest; AB BIODISK, Solna, Sweden) have more immediate utility along with published interpretive criteria that can be found in the reagent or antimicrobial product package inserts (US-FDA). To facilitate the more prompt use of newer antimicrobial agents, clinical microbiologists could select an agent available on a commercial system in the same or similar class to act as a "surrogate marker", e.g. the so called "class" disk or drug. Such practices have resulted in groupings of very similar agents in the standard documents (M2 or M7, Table 1) of the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) or via independent publications recommending the use of surrogates until the new antimicrobial becomes available in widely applied diagnostic products.

In this report, the results from simultaneous reference MIC testing of dalbavancin, vancomycin and teicoplanin were analyzed to validate a potential "surrogate marker" agent for dalbavancin activity against indicated species producing skin and soft tissue infections. Dalbavancin is a novel injectable, bactericidal glycolipopeptide with enhanced activity against Gram-positive cocci; most similar to that demonstrated by teicoplanin and vancomycin. These MIC results from an international study platform (2001-2004) allowed the direct comparisons of reference MIC values from 16,749 strains, both quantitatively and by interpretive category.

MATERIALS AND METHODS

A total of 16,749 gram-positive cocci were entered into the final analysis (Table 1), each from a documented clinical infection within international surveillance trials monitoring organisms from Europe, North and Latin America. These organisms were distributed as follows for direct comparison of dalbavancin and vancomycin MICs or dalbavancin and teicoplanin MICs: *Staphylococcus aureus* (11,867/11,867 strains), coagulase-negative staphylococci (CoNS; 3,450/3,450 strains), ß-haemolytic streptococci (1,051/1,050 strains), and viridans group streptococci (381/380 strains; Table 1). *Streptococcus pneumoniae* (3,707/727 strains), and *Enterococcus* spp. (4,131/4,128 strains) were also tested, but their results were not included among indicated skin and soft tissue pathogen data presented here.

Three agents active against Gram-positive cocci were tested: dalbavancin, teicoplanin and vancomycin. Validated broth microdilution reference test panels were utilized produced by TREK Diagnostics (Cleveland, OH, USA) conforming to CLSI methods. All quality control MIC determinations for CLSI recommended strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212) were within published ranges, originally derived from studies that used 0.002% polysorbate-80 containing Mueller-Hinton broth for dalbavancin testing.

Categorical interpretations for vancomycin and teicoplanin found in M100-S16 (2006) were used for comparisons to dalbavancin quantitative test results (Table 1). Potential breakpoint concentrations for dalbavancin were based on published pharmacokinetic (PK) and pharmacodynamic (PD) studies, as well as results from additional pharmacodynamic target (AUC/MIC and T>MIC) attainment studies with Monte Carlo simulations that suggested conservative susceptible breakpoints ranging from ≤0.5 to ≤1 mg/L (Pfizer Inc., data on file). Error rates (as percentages) were calculated using all organisms as the denominator, but further analyses were limited by the variety of contemporary Gram-positive isolates observed to be non-susceptible to these agents (exceptions: teicoplanin versus CoNS, all agents versus enterococci). Generally, serious interpretative errors (very major or major) should be minimized (≤1.5 and ≤3%, respectively), while achieving an absolute categorical agreement between drugs at ≥90%; however, >95% agreement would be preferred.

RESULTS

- Table 1 lists the comparative MIC results for 11,867 *S. aureus* strains; only one and two strains had non-susceptible vancomycin (MIC, >2 mg/L) and teicoplanin (MIC, >8 mg/L) results, respectively. The potency of dalbavancin (MIC_{90}, 0.06 mg/L) was 16-fold greater than vancomycin (MIC_{90}, 1 mg/L), and only one minor, false-intermediate error (0.008%) was detected for a VISA strain using the recently changed CLSI breakpoint (Figure 1). Teicoplanin was equally accurate in predicting dalbavancin susceptibility (99.8%) at either potential breakpoint concentration.

- For the CoNS (3,450 strains), dalbavancin MIC values ranged up to 1 mg/L (only 5 occurrences) and vancomycin MICs to 4 mg/L (the CLSI susceptible breakpoint). Using a dalbavancin breakpoint of ≤1 mg/L achieved complete categorical agreement for vancomycin as a predictor of dalbavancin susceptibility, whereas the superior activity of dalbavancin and vancomycin against these CoNS species produced more numerous, but acceptable levels of conservative, major (0.7%; false-resistant) and minor (2.8%) errors compared to teicoplanin results.

- In Table 1 are the comparisons of MIC results for the three glycopeptides tested against 1,432 streptococci. For ß-haemolytic streptococci (including *S. pyogenes*), as well as α-haemolytic species, all strains had dalbavancin MIC_{90} values at ≤0.03 mg/L compared to 0.5 or 1 mg/L for vancomycin (Figure 2). When using vancomycin MIC values to predict dalbavancin susceptibility, all isolates of ß-haemolytic streptococci (Table 1 and Figure 2) were susceptible to vancomycin (MIC, ≤1 mg/L) and had dalbavancin MIC values at ≤0.25 mg/L.

- Dalbavancin spectrum of activity against enterococci most resembles that of teicoplanin, generally being inactive against *vanA* type vancomycin-resistant enterococci (VRE), but harboring some residual potency versus *vanB* VRE strains. Absolute categorical agreement between vancomycin and dalbavancin (≤1 mg/L as susceptible, ≥4 mg/L as resistant) was 94.3% with no false-susceptible error. Teicoplanin as the surrogate marker for dalbavancin, showed 95.9% absolute categorical agreement (data not shown).

Table 1. Comparison of dalbavancin MIC results to those of vancomycin and teicoplanin tested by CLSI methods versus four gram-positive organism groups (16,749 strains)

Organism (no. tested)	Dalbavancin MIC (mg/L)	Occurrences (%) by surrogate glycopeptide: Vancomycin MIC (mg/L) ≤1	2	4	8	16	≥32	Teicoplanin MIC (mg/L) ≤8	16	≥32
S. aureus (11,867/11,867)	≤0.5[a]	11,472 (96.7)	394 (3.3)[b]	1 (<0.1)	-	-	-	11,865 (>99.9)[b]	2 (<0.1)	-
	1[a]	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-
	≥4	-	-	-	-	-	-	-	-	-
CoNS (3,450/3,450)	≤0.5[a]	2,040 (59.1)	1,388 (40.2)	17 (0.5)[b]	-	-	-	3,329 (96.4)[b]	96 (2.8)	20 (0.6)
	1[a]	-	3 (<0.1)	2 (<0.1)[b]	-	-	-	4 (0.1)[b]	-	1 (<0.1)
	2	-	-	-	-	-	-	-	-	-
	≥4	-	-	-	-	-	-	-	-	-
ßHS (1,051/1,050)	≤0.5[a]	1,051 (100.0)[b]	-	-	-	-	-	1,050 (100.0)	-	-
	1[a]	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-
	≥4	-	-	-	-	-	-	-	-	-
VGS (381/380)	≤0.5[a]	381 (100.0)[b]	-	-	-	-	-	380 (100.0)	-	-
	1[a]	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-
	≥4	-	-	-	-	-	-	-	-	-

CoNS = Coagulase-negative staphylococci, ßHS = ß-haemolytic streptococci, VGS = viridans group streptococci.
a. Category determined by CLSI criteria (2006) and using two possible breakpoints for dalbavancin (≤0.5 and ≤1 mg/L; data on file Pfizer, Inc.).
b. CLSI susceptible breakpoints for vancomycin and teicoplanin. No interpretive criteria for teicoplanin when testing streptococcal isolates has been published by the CLSI. Also, intermediate and resistant categories have not been defined for vancomycin when tested against streptococci.

Figure 1. Scattergram plot comparing the dalbavancin and vancomycin MIC results for 11,867 *S. aureus* isolates tested by the broth microdilution method (CLSI M7-A7, 2006). Vertical solid lines indicate vancomycin CLSI (2006) interpretive criteria for susceptible (≤2 mg/L) and resistant (≥16 mg/L). Solid and broken horizontal lines show potential dalbavancin MIC breakpoints for ≤1 and ≤0.5 mg/L, respectively.

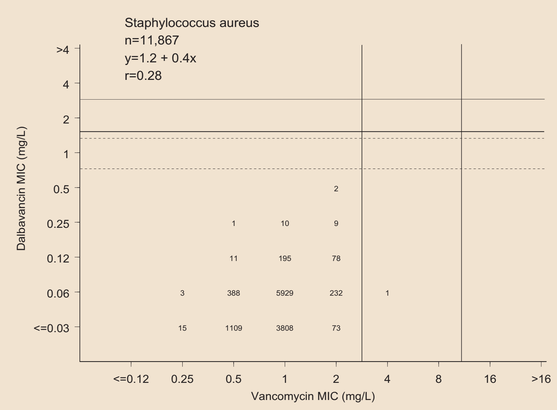
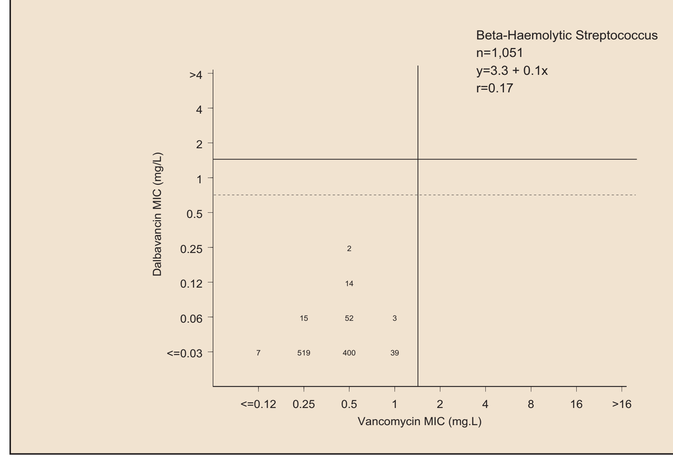


Figure 2. Scattergram plot comparing the dalbavancin and vancomycin MIC results for 1,051 ß-haemolytic streptococci isolates tested by the broth microdilution method (CLSI M7-A7, 2006). The single vertical line shows the susceptible only breakpoint for vancomycin (≤1 mg/L). Solid and broken horizontal lines show potential dalbavancin breakpoints of ≤1 and ≤0.5 mg/L, respectively.



CONCLUSIONS

- Dalbavancin, a potent glycolipopeptide active against many antimicrobial-resistant Gram-positive cocci, has demonstrated clinical efficacy against organisms associated with skin and soft tissue infections.

- Extensive PK and PD studies characterizing dalbavancin and Monte Carlo simulations suggest potential susceptible breakpoint concentrations ranging from ≤0.5 mg/L (staphylococci) to ≤4 mg/L (streptococci). Candidate dalbavancin interpretative criteria for MIC values of ≤0.5 or ≤1 mg/L were used in this analysis to determine if currently tested glycopeptides within commercial systems (validated against this reference test) could predict dalbavancin susceptibility with acceptable accuracy.

- Surrogate marker agents (vancomycin or teicoplanin) were observed to be highly predictive and produced only a single minor error (false-intermediate for a VISA strain among staphylococci and ß-haemolytic streptococci) when using the 2006 CLSI vancomycin breakpoint.

- The dalbavancin disk diffusion test has been observed to be suboptimal due to poor drug diffusion in agar and will not be available as an immediate, simple diagnostic procedure, but another agar diffusion method (Etest) has been successfully evaluated for accuracy (Pfizer, Inc., manuscript in press 2006).

ACKNOWLEDGEMENTS

The co-authors would like to thank the following persons for contributions to statistical analysis or assistance with manuscript preparation: N. O'Mara, M.G. Stilwell, P. Strabala, and J. Ross. This study was supported by an educational/research grant from Pfizer, Inc.

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