Surrogate Analysis of Vancomycin to Predict Susceptible Categorization of Dalbavancin

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AMENDED ABSTRACT

Background: Dalbavancin (DAL) represents a recently approved addition for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Newly released antimicrobial agents are rarely found on commercial susceptibility testing devices, and surrogate testing may be an option for clinical microbiology laboratories. This study evaluated the use of vancomycin (VAN) results for predicting DAL susceptibility for 64,815 Gram-positive isolates.

Methods: A total of 33,688 *S. aureus*, 2,800 viridans group streptococci (VGS), and 5,722 β-hemolytic streptococci (BHS) were included in the cross-susceptibility analysis; as well as 4,576 CoNS, and 6,515 enterococci (non-indicated species groups). Isolates originated as part of the SENTRY Antimicrobial Surveillance Program for the USA and Europe (2011-2013). Susceptibility testing followed CLSI (M07-A9 and M100-S24) methods. FDA (DAL) and CLSI (VAN) criteria were used for correlations between DAL and VAN susceptibility results, which were analyzed by regression statistics, scattergrams and error rate methods. A susceptible categorical agreement (CA) rate of 95.0% was considered acceptable, with higher rates being preferred.

Results: A CA (susceptible) rate of 99.86% was observed between DAL and VAN when tested against *S. aureus*. Only 48 (0.14%) very major (false-susceptible) errors were obtained against VAN-susceptible isolates that displayed a DAL non-susceptible (MIC, 0.25 or 0.5 µg/ml) phenotype by the recently released FDA interpretive criteria (i.e. ≤0.12 µg/ml). A similar CA rate (99.75%) between agents was observed against MRSA. When MIC correlations were analyzed against indicated BHS species (*S. agalactiae, S. pyogenes*), an overall CA rate of 97.72-100.0% was obtained. All but two (serogroup G streptococcus) very major errors (1.03%) observed against the BHS group were obtained with *S. agalactiae*. Complete (100.00%) susceptibility correlations were noted for *S. pyogenes* and *S. dysgalactiae*, as well as against all VGS, including the indicated *S. anginosus* group (758 strains).

Conclusions: High susceptible CA rates between DAL and VAN were observed when testing a contemporary collection of indicated clinical isolates found in ABSSSI. VAN-susceptible isolates can be assumed to be inhibited by DAL (97.72– 100.00%) at the regulatory agency (USA-FDA) approved interpretive criteria of ≤0.12 µg/ml.

INTRODUCTION

Dalbavancin is a recently approved lipoglycopeptide agent for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive pathogens. The pharmacokinetic/pharmacodynamic characteristics of dalbavancin (terminal half-life of two weeks, 93% protein binding) allows for a two-dose regimen of 1000 mg followed one week later by 500 mg. Two ABSSSI trials (DISCOVER 1 and DISCOVER 2) comparing dalbavancin with a control regimen of vancomycin/linezolid showed that dalbavancin was non-inferior to the comparators, leading to regulatory approval by the USA-FDA.

Lipoglycopeptides (dalbavancin, oritavancin, and telavancin) have physiochemical features that can challenge the development of *in vitro* methods for susceptibility testing. Early studies, particularly with dalbavancin, demonstrated that reference MIC (agar dilution, broth microdilution) and agar diffusion (disk tests) methods were flawed by high binding affinities of these drugs for media components and plastics, as well as limited agar diffusion due to the drug's high molecular size. A reference broth microdilution method for all marketed lipoglycopeptides has been established and published by the Clinical and Laboratory Standards Institute (CLSI) where a surfactant (polysorbate-80 at 0.002%) supplement was added to the Mueller-Hinton broth to minimize binding to the plastic trays and thus accurately measure drug potency. Dalbavancin, among the clinically approved lipoglycopeptides, has been studied in resistance surveillance trials for over ten years, has a validated E-test and dry-form broth microdilution methods, plus published quality assurance guidelines to assure precise measures of activity.

However, like other newer antimicrobial agents at the time of regulatory approval, commercial diagnostic devices will not be available at the time of launch. In the interim, one possible strategy for dalbavancin *in vitro* testing would be to apply the results of a chemically similar, commonly tested agent (vancomycin) as a surrogate marker. This type of analysis (cross-susceptibility) was initially reported for dalbavancin in 2006 and showed promise, but did not use the recent regulatory-approved interpretive breakpoint criteria for this new agent. We present here, an updated analysis of year 2011-2013 clinical strains of Gram-positive pathogens to establish vancomycin susceptibility results as a possible surrogate predictor of dalbavancin activity.

MATERIALS AND METHODS

Organisms tested: Major Gram-positive pathogens collected by the SENTRY Antimicrobial Surveillance Program (64,815 strains) during 2011-2013 were used in this analysis. These organisms from USA and European medical centers included: *Staphylococcus aureus* (33,688); coagulase-negative staphylococci (CoNS; 4,576, including five major species with >200 isolates); enterococci (6,515; mostly *Enterococcus faecalis* at 4,126 isolates); β-haemolytic streptococci (5,722; including five species or serogroups with >200 isolates; viridans group streptococci (2,800; including four groups with >100 strains); and *Streptococcus pneumoniae* (11,514). The latter species are shown for complete dalbavancin spectrum analysis only. All strains were identified by the participating surveillance laboratories and confirmed by reference/molecular methods by the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA).

Susceptibility methods: Isolates were tested for susceptibility by the reference, validated broth microdilution following the CLSI guidelines (M07-A9). Dalbavancin susceptibility was determined using specific testing method for lipoglycopeptides following the CLSI (M100-S24) and product package insert information. MIC values were quality assured by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619). All QC results were within published acceptable ranges. MIC interpretations for dalbavancin were based on recently USA-FDA approved breakpoint criteria appropriate for indicated species and are as follows: Susceptible only at ≤0.12 µg/ml for *S. aureus* (including MRSA), *S. pyogenes, S. agalactiae,* and *S. anginosus* group (includes *S. anginosus, S. constellatus,* and *S. intermedius*).

The CLSI M100-S24 (2014) breakpoint criteria were applied for vancomycin. Data analysis generally followed the intermethod comparison guidelines found in CLSI documents (M23-A3), and scattergrams and accuracy rates were generated using only the vancomycin-susceptible organism population (cross-susceptibility only). Accuracy of the surrogate (vancomycin) to predict dalbavancin MIC at ≤0.12 µg/ml was considered acceptable at ≥95.0%, with ≥98.0% being preferred.

RESULTS

- Dalbavancin had potent activity against *S. aureus* (MIC_{90}, 0.06 µg/ml), β-haemolytic streptococci (MIC_{90}, 0.06 µg/ml), viridans group streptococci (MIC_{90}, 0.06 µg/ml), CoNS (MIC_{90}, 0.12 µg/ml) and enterococci (MIC_{90}, 0.06 µg/ml). Vancomycin-resistant enterococci (VRE) have elevated dalbavancin MIC values (MIC_{50}, >4 µg/ml); but dalbavancin was generally 16-fold more active than vancomycin (**Table 1**). Dalbavancin was also very active against *S. pneumoniae* (MIC_{90}, ≤0.03 µg/ml).
- Cross-susceptibility analyses were applied to assess the possible use of vancomycin MIC results to predict dalbavancin susceptibly (surrogate testing strategy), when using reference MIC methods and USA-FDA clinical breakpoints. For the clinically indicated species (ABSSSI), the predictive accuracy was (**Table 2**):
  - *S. aureus* (including MRSA) at 99.86%, see **Figure 1**;
  - *S. pyogenes* at 100.0%, see **Figure 2**;
  - *S. agalactiae* at 97.72%, see **Figure 3**; and
  - *S. anginosus* group among viridans group streptococci at 100.0%, see **Figure 4**.
- Similar analysis for the broader species groupings of Gram-positive pathogens often listed in breakpoint documents (CLSI) also demonstrated high surrogate accuracy as follows (**Table 2**):
  - β-haemolytic streptococci at 98.97% (≤0.12 µg/ml);
  - Viridans group streptococci at 100.0% (≤0.12 µg/ml);
  - CoNS at 97.55% (≤0.12 µg/ml, the *S. aureus* breakpoint) and
  - All enterococci at 98.43% (≤0.12 µg/ml).
- Among the 33,688 tested isolates of *S. aureus*, one VISA strain was observed that had a non-susceptible dalbavancin MIC of 0.5 µg/ml (**Figure 1**).
- VRE (VanA phenotype) generally had dalbavancin MIC results at ≥0.25 µg/ml (data not shown); see **Table 1**.
- False-susceptible surrogate errors among β-haemolytic streptococci (1.03%) were generally *S. agalactiae* (**Table 2** and **Figure 3**).
- While surrogate accuracy of CoNS overall was 97.55% at ≤0.12 µg/ml, the *S. aureus* breakpoint, false-susceptible surrogate errors were more likely to occur when testing the subgroup of *S. haemolyticus* strains (14.8% of isolates with MIC results of ≥0.25 µg/ml; data not shown).

Table 2. Summary of vancomycin test result accuracy for predicting dalbavancin susceptibility using two breakpoint concentrations (≤0.12 and ≤0.25 µg/ml) when tested against eight Gram-positive pathogen/groups in 2011-2013.

Pathogen or species group (no. tested)	Surrogate accuracy for breakpoint at:	
	≤0.12	≤0.25
S. aureus (33,688)	99.86[a]	99.99
β-haemolytic streptococci (5,722)	98.97	100.00
S. pyogenes (2,297)	100.00[a]	100.00
S. agalactiae (2,495)	97.72[a]	100.00
Viridans group streptococci (2,800)	100.00	100.00
S. anginosus group (758)	100.00[a]	100.00
CoNS (4,576)	97.55	99.87
Enterococci (6,515)	98.43	99.94

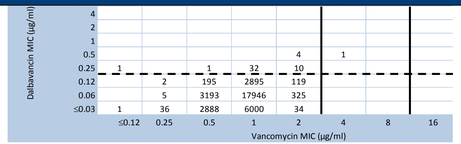
a. Underlined percentage shows USA-FDA approved breakpoint for clinical use versus indicated species/groups.

Table 1. Dalbavancin MIC results from year 2011-2013 surveillance strains in the USA and Europe (SENTRY Antimicrobial Surveillance Program; 64,815 strains).

Organism	No. of Isolates	No. (cum.%) strains at MIC in µg/ml:								MIC_{50}	MIC_{90}
		≤0.03	0.06	0.12	0.25	0.5	1	2	≥4		
S. aureus[a]	33688	8959 (26.6)	21469 (90.3)	3211 (99.9)	44 (100.0)	5 (100.0)	--	--	--	0.06	0.06
βHS	5722	5029 (87.9)	484 (96.3)	150 (99.0)	59 (100.0)	--	--	--	--	≤0.03	0.06
S. pyogenes[a]	2297	2153 (93.7)	129 (99.3)	15 (100.0)	--	--	--	--	--	≤0.03	≤0.03
S. agalactiae[a]	2495	2052 (82.2)	266 (92.9)	120 (97.7)	57 (100.0)	--	--	--	--	≤0.03	0.06
VGS	2800	2485 (88.8)	292 (99.2)	23 (100.0)	--	--	--	--	--	≤0.03	0.06
S. anginosus grp[a]	758	746 (98.4)	11 (99.9)	1 (100.0)	--	--	--	--	--	≤0.03	≤0.03
CoNS	4576	1948 (42.6)	1916 (84.4)	600 (97.6)	106 (99.9)	5 (100.0)	1 (100.0)	--	--	0.06	0.12
Enterococcus spp.	6515	1161 (17.8)	3070 (64.9)	1024 (80.7)	131 (82.7)	31 (83.1)	63 (84.1)	72 (85.2)	963 (100.0)	0.06	> 4
S. pneumoniae	11514	11164 (97.0)	346 (100.0)	4 (100.0)	--	--	--	--	--	≤0.03	≤0.03

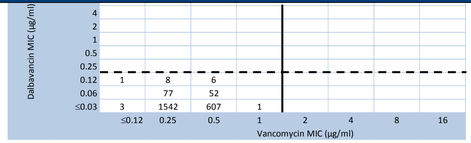
Abbreviations: βHS – β-hemolytic streptococci; VGS – Viridans group streptococci.
a. Indicated species per USA-FDA approval (May 2014).

Figure 1. *S. aureus* (33,688 strains) isolated from the USA and Europe in 2011-2013[a].



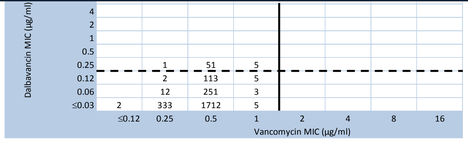
a. Broken horizontal line shows USA-FDA breakpoint (≤0.12 µg/ml) having acceptable predictive values (≥95.0%); and the solid vertical lines are the vancomycin breakpoints.

Figure 2. *S. pyogenes* (2,297 strains) isolated from USA and Europe in 2011-2013[a].



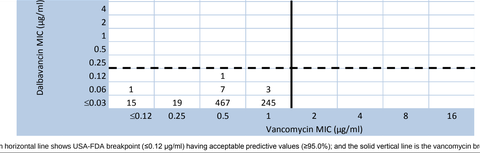
a. Broken horizontal line shows USA-FDA breakpoint (≤0.12 µg/ml) having acceptable predictive values (≥95.0%); and the solid vertical line is the vancomycin breakpoint.

Figure 3. *S. agalactiae* (2,495 strains) isolated from USA and Europe in 2011-2013[a].



a. Broken horizontal line shows USA-FDA breakpoint (≤0.12 µg/ml) having acceptable predictive values (≥95.0%); and the solid vertical line is the vancomycin breakpoint.

Figure 4. *S. anginosus* group (758 strains) isolated from USA and Europe in 2011-2013[a].



a. Broken horizontal line shows USA-FDA breakpoint (≤0.12 µg/ml) having acceptable predictive values (≥95.0%); and the solid vertical line is the vancomycin breakpoint.

CONCLUSIONS

- Dalbavancin, in recent (2011-2013) surveillance studies from the USA and Europe, demonstrated potent activity with MIC_{90} results ranging from ≤0.03 to 0.12 µg/ml for staphylococci and streptococci. Due to VRE strains, dalbavancin MIC_{90} values for enterococci were at >4 µg/ml, but MIC_{50} results ranged from only 0.06 to 0.25 µg/ml (highest for *E. faecium*).
- Vancomycin susceptibility test results can be used as a surrogate marker with high confidence/accuracy to predict dalbavancin activity at ≤0.12 µg/ml (97.72 to 100.0% accuracy for indicated species).
- These surrogate uses of vancomycin to predict dalbavancin activity (susceptibility at ≤0.12 µg/ml per USA-FDA) generally confirm a similar analysis of 16,749 Gram-positive isolates published in 2006 (Jones et al.). This cited publication found only 22 errors among 11,867 analyzed *S. aureus* strains (99.81% surrogate accuracy; 99.86% in this report), applying the recently established clinical breakpoint of ≤0.12 µg/ml. These data demonstrate the sustained dalbavancin potency against indicated species without evidence of MIC creep across nearly a decade of resistance surveillance studies.

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