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Surrogate analysis of vancomycin to predict susceptible categorization of dalbavancin☆

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ABSTRACT

Dalbavancin (DAL) represents a recently approved addition for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Newly released antimicrobial agents are rarely found on commercial susceptibility testing devices, and surrogate testing may be an option for clinical microbiology laboratories. A total of 33,688 *Staphylococcus aureus*, 2800 viridans group streptococci (VGS), and 5722 β-hemolytic streptococci (BHS) were included in this cross-susceptibility (DAL versus vancomycin [VAN]) analysis as well as 4576 coagulase-negative staphylococci and 6515 enterococci (nonindicated species groups). Isolates were collected as part of the SENTRY Antimicrobial Surveillance Program for the United States (USA) and Europe (2011–2013). Susceptibility testing followed CLSI (M07-A9 and M100-S24) methods. USA Food and Drug Administration (DAL) and CLSI (VAN) breakpoint criteria were used for correlations between DAL and VAN susceptibility results. A categorical agreement (CA; susceptible) rate of 99.9% was observed between DAL and VAN when testing *S. aureus*. Only 48 (0.14%) very major (false-susceptible) errors were noted against VAN-susceptible isolates that displayed a DAL-nonsusceptible (MIC, 0.25 or 0.5 μg/mL) phenotype. When susceptible MIC correlations were analyzed against indicated BHS species (*Streptococcus agalactiae* and *Streptococcus pyogenes*), an overall CA rate of 97.7–100.0% was obtained. Complete (100.0%) CA was documented for *S. pyogenes*, as well as against all VGS isolates, including the indicated *Streptococcus anginosus* group (758 strains). In conclusion, 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 inferred to be inhibited by DAL (97.7–100.0%) at the regulatory agency–approved susceptible interpretive breakpoint of ≤0.12 μg/mL.

1. Introduction

Dalbavancin is a recently approved lipoglycopeptide agent for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in adults, known or suspected to be caused by designated susceptible strains of Gram-positive pathogens (Billeter et al., 2008; Boucher et al., 2014; Chambers, 2014; Dalvance™, 2014; Jones et al., 2005; Streit et al., 2004; Zhanel et al., 2010). Pharmacokinetic/pharmacodynamic characteristics of dalbavancin (terminal half-life of 2 weeks, 93% protein binding) allow for a 2 intravenous dose regimen of 1000 mg followed 1 week later by 500 mg (Andes and Craig, 2007; Chambers, 2014; Dorr et al., 2005). Two ABSSSI trials (DISCOVER 1 and DISCOVER 2) comparing dalbavancin to a control regimen of vancomycin/linezolid showed that dalbavancin was noninferior to the comparators leading to approval by the USA Food and Drug Administration (USA-FDA) (Boucher et al., 2014) and confirming conclusions from earlier clinical trials (Jauregui et al., 2005; Seltzer et al., 2003).

Lipoglycopeptides (dalbavancin, oritavancin, and telavancin) have physiochemical features that can challenge the development of in vitro methods for susceptibility testing (Rennie et al., 2007; Zhanel et al., 2010). Early studies, particularly with dalbavancin, demonstrated that reference MIC (agar dilution and 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 diffusion in agar due to the drug's high molecular size (Rennie et al., 2007). A reference broth microdilution method for all marketed lipoglycopeptides has been approved and published by the Clinical and Laboratory Standards Institute (CLSI) wherein 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 measuring drug potency (CLSI, 2012, 2014). Dalbavancin, among the clinically approved lipoglycopeptides, has been studied in resistance surveillance trials for over a decade (Biedenbach et al., 2009; Jones et al., 2005; Streit et al., 2004) and has a validated E-test (Fritsche et al., 2006) and a dry-form broth microdilution method (Jones et al., 2004), plus published quality control (QC) guidelines

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(Anderegg et al., 2003; CLSI, 2014) to assure precise measures of it's activity.

However, like other newer antimicrobial agents at the time of USA-FDA approval (Jones et al., 2013b), commercial diagnostic devices for dalbavancin may not be available. In the interim, 1 possible strategy for dalbavancin in vitro testing would be to apply the results of a commonly tested chemically similar agent such as vancomycin for a surrogate marker of susceptibility (CLSI, 2014; Jones and Pfaller, 2001; Jones et al., 2007). This type of analysis (cross-susceptibility) was initially reported for dalbavancin in 2006 (Jones et al., 2006) and showed diagnostic promise but did not use the recent regulatory-approved interpretive breakpoint criteria for this new agent (Dalvance™, 2014). 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.

2. Materials and methods

2.1. Organisms tested

Major Gram-positive pathogens collected by the SENTRY Antimicrobial Surveillance Program (64,815 strains) during 2011–2013 were used in this surrogate testing analysis. These organisms from USA and European medical centers included *Staphylococcus aureus* (33,688), coagulase-negative staphylococci (CoNS; 4576, including 5 major species with >200 isolates); enterococci (6515; mostly *Enterococcus faecalis* at 4126 isolates), β-hemolytic streptococci (5722, including 5 species or serogroups with >200 isolates); viridans group streptococci (2800, including 4 groups with >100 strains); and *Streptococcus pneumoniae* (11,514; data not shown). 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).

2.2. Susceptibility methods

Isolates were tested for susceptibility by the reference, validated broth microdilution method following the CLSI (2012, 2014) guidelines. Dalbavancin susceptibility was determined using specific testing method for lipoglycopeptides following the CLSI (M100-S24) and product package insert information (CLSI, 2014; Dalvance™, 2014). MIC values were quality assured by concurrent testing of CLSI-recommended QC strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (Anderegg et al., 2003). MIC interpretations for dalbavancin were based on USA-FDA–approved breakpoint criteria appropriate for indicated species (Dalvance™, 2014) and were as follows: susceptible only at ≤0.12 μg/mL for *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and the *Streptococcus anginosus* group (includes *S. anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*) of streptococci.

The CLSI (2014) M100-S24 breakpoint criteria were applied for vancomycin. Data analysis generally followed the intermethod comparison error limit guidelines found in CLSI 2008 documents (M23-A3), and scattergrams and probability rates of cross-susceptibility (negative predictive value) were generated using only the vancomycin-susceptible organism population. Accuracy of the surrogate (vancomycin) to predict dalbavancin MIC at ≤0.12 μg/mL was considered acceptable if values approached 99.0–100.0% (CLSI, 2008, 2012, 2014)

3. Results and discussion

Table 1 presents the most recent published spectrum and activity of dalbavancin tested in a resistance surveillance study (SENTRY Program, 2011–2012) for a collection of 3144 isolates of Gram-positive pathogens (Jones et al., 2013a; Jones et al., 2013c). Dalbavancin exhibits high potencies (MIC_{90}, ≤0.06 μg/mL) for all tabulated species except *S. agalactiae* and the enterococci, and all MIC values were ≤0.25 μg/mL, except for 41.6% of *Enterococcus* spp. (vancomycin-resistant enterococci [VRE] phenotypes). These results were similar to those reported earlier and generally demonstrate a dalbavancin activity 8- to 32-fold greater than vancomycin (MIC_{90}, 1 μg/mL) (Biedenbach et al., 2009; Jones et al., 2005; Lin et al., 2005; Streit et al., 2004).

Surrogate use of vancomycin susceptibility to predict dalbavancin susceptibility (Table 2) concentrated on the probabilities when testing the 4 indicated species for ABSSSI (*S. aureus*, *S. pyogenes*, *S. agalactiae*, and *S. anginosus* group) at the USA-FDA susceptible breakpoint concentration of ≤0.12 μg/mL (Dalvance™, 2014). The calculated epidemiologic cutoff value was also ≤0.12 μg/mL for dalbavancin (Turnidge et al., 2006). When testing the 33,688 *S. aureus* strains, the surrogate had a 99.9% probability of concordant results (≤0.12 μg/mL); see Fig. 1 and Table 2. One vancomycin-intermediate *S. aureus* (VISA) strain (MIC 4 μg/mL) was observed to have a nonsusceptible dalbavancin MIC of 0.5 μg/mL, and a linear relationship was noted between the MIC values of these 2 agents (Fig. 1). Fig. 1 illustrates that the probability of a dalbavancin MIC at ≥0.25 μg/mL increases with the elevation of the vancomycin MIC: 0.1%, 2.9%, and 100.0% for strains with vancomycin MIC results at ≤1, 2, and 4 μg/mL, respectively. This illustrates the extremely low prevalence of dalbavancin MIC results at the upper limits of the wild-type population for contemporary *S. aureus*. Dalbavancin was also active against 4576 CoNS (MIC_{90}, 0.12 μg/mL; 97.6% of isolates inhibited at ≤0.12 μg/mL). False-susceptible surrogate errors were more likely to occur among CoNS when testing *Staphylococcus haemolyticus* strains (14.8% of isolates with MIC results of ≥0.25 μg/mL; data not shown), but only 6.9% of CoNS were

Table 1
Dalbavancin MIC results from year 2011–2012 surveillance strains in the United States (SENTRY Antimicrobial Surveillance Program; 3144 strains).[a]

Organism	No. (cumulative %) of strains at MIC in μg/mL: No. of isolates	≤0.03	0.06	0.12	0.25	0.5	1	2	≥4	MIC_{50}	MIC_{90}
Staphylococcus aureus[b]	2036	583 (28.6)	1327 (93.8)	123 (99.9)	3 (100.0)					0.06	0.06
MSSA	1014	301 (29.7)	654 (94.2)	57 (99.8)	2 (100.0)					0.06	0.06
MRSA	1022	282 (27.6)	673 (94.2)	66 (99.9)	1 (100.0)					0.06	0.06
β-Hemolytic streptococci	644	529 (82.1)	73 (93.5)	25 (97.4)	17 (100.0)					≤0.03	0.06
S. pyogenes[b]	306	288 (94.1)	16 (99.3)	2 (100.0)						≤0.03	≤0.03
S. agalactiae[b]	287	196 (68.3)	52 (86.4)	23 (94.4)	16 (100.0)					≤0.03	0.12
Viridans group streptococci[b]	111	93 (83.8)	16 (98.2)	2 (100.0)						≤0.03	0.06
Coagulase-negative staphylococci	237	136 (57.4)	80 (91.1)	19 (99.2)	2 (100.0)					≤0.03	0.06
Enterococcus spp.	116	18 (15.5)	35 (45.7)	12 (56.0)	3 (58.6)	0 (58.6)	2 (60.3)	0 (60.3)	46 (100.0)	0.12	≥4
Vancomycin susceptible	63	15 (23.8)	35 (79.4)	11 (96.8)	2 (100.0)					0.06	0.12
Vancomycin resistant	53	3 (5.7)	0 (5.7)	1 (7.5)	1 (9.4)	0 (9.4)	2 (13.2)	0 (13.2)	46 (100.0)	≥4	≥4
VanA	49	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (2.0)	2 (6.1)	0 (6.1)	46 (100.0)	≥4	≥4
VanB	4	3 (75.0)	0 (75.0)	1 (100.0)						≤0.03	0.06

[a] Dalbavancin surveillance data from Jones et al. (2013a, 2013c).
[b] USA-FDA–indicated species (Dalvance™, 2014). Only *S. anginosus* group among the viridans group streptococci.