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Interim Use of Vancomycin Susceptibility Testing Results to Predict Activity of Oritavancin, a New Long-Acting Lipoglycopeptide

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Amended Abstract

Background: Oritavancin (ORI) is an investigational lipoglycopeptide with activity against Gram-positive (GP) pathogens. Its prolonged serum half-life enables single-dose treatment of serious GP infections. At approval by regulatory agencies (USA-FDA, EMA), new agents are uncommonly found on the most used susceptibility (S) testing devices therefore requiring potential use of surrogate testing with a closely related agent.

Methods: To evaluate vancomycin (VAN) as a possible surrogate marker, GP organisms from hospitals worldwide were reference MIC tested (CLSI, 2012). These strains included *S. aureus* (21,349, nearly 50% MRSA), coagulase-negative staphylococci (CoNS; 3,084), β-haemolytic streptococci (βHS; 3,018), viridans group streptococci (VGS; 1,799) and 4,179 strains of *E. faecalis* (EF) and *E. faecium* (EFM) (collectively, ENT) including 880 VAN-resistant ENT (VRE).

Results: Five major GP pathogen groups were analyzed by comparing VAN-S results (CLSI, 2013) to three possible susceptible breakpoints for ORI (≤0.12, ≤0.25, ≤0.5 μg/mL), as suggested by ECOFF values and supported by PK/PD analyses. The Table illustrates high accuracy of VAN used as a surrogate marker of ORI activity (96.85-99.96% at proposed breakpoints). There were no errors at ≤1 μg/mL breakpoint (data not shown). Furthermore, direct MIC comparison showed VAN/ORI MIC_{90} results of 1/0.12, 2/0.12, 0.5/0.25,1/0.06 and >16/0.06 μg/mL for SA, CoNS, βHS, VGS and ENT, respectively. ORI was slightly more active against EFM ($MIC_{50/90}$, ≤0.008/0.06 μg/mL) than EF ($MIC_{50/90}$, 0.015/0.06 μg/mL) with all ENT inhibited at ≤0.5 μg/mL.

Conclusions: VAN demonstrated very high accuracy as a candidate surrogate for predicting ORI activity and S against targeted GP pathogens. ORI was generally two- to >64-fold more potent than VAN and inhibited all tested VRE and SA at ≤0.5 μg/mL. Until ORI commercial S devices/systems are available, VAN-S GP isolates can be assumed to be inhibited by ORI (96.9-100.0% at ≤0.25 μg/mL, varying by species).

Abstract Table

	Accuracy (%) at proposed ORI breakpoint of:		
Pathogen (no. tested)	≤0.5 μg/mL	≤0.25 μg/mL	≤0.12 μg/mL
SA (21,349)	100.00%	99.96%[a]	98.42%
CoNS (3,084)	100.00%	100.00%	99.64%[a]
βHS (3,018)	99.97%	96.85%[a]	89.82%
VGS (1,799)	100.00%	99.72%	99.17%[a]
ENT (4,179)	100.00%	100.0%[a]	99.45%

a. Underlined value is calculated ECOFF MIC breakpoint.

Introduction

Newly approved (United States Food and Drug Administration [USA-FDA] or European Medicines Agency [EMA]) antimicrobial agents rarely have validated commercial susceptibility testing products/systems available at the time of commercial launch. In fact, the recent history of these products demonstrates delays numbered in years even for those drugs possessing qualities that could favorably impact patient care. To avoid adverse effects on the treatment of indicated infections by these agency-approved compounds, clinical microbiology laboratories have resorted to "surrogate marker" susceptibility testing of a similar, currently tested agent (class representative) to predict susceptibility of the new antimicrobial.

Oritavancin, formerly LY333328, is an investigational lipoglycopeptide having a broad-spectrum activity against Gram-positive pathogens including strains with elevated vancomycin MIC values, see Table 1. Initial "global surveillance study" results reported in 2000, across 12 countries demonstrated oritavancin activity against staphylococci (including methicillin-resistant strains [MRSA]), *Streptococcus pneumoniae* and enterococci (including vancomycin-resistant [VRE] strains), a level of potency found to be enhanced by the subsequent understanding that a surfactant was required for accurate MIC determinations in the plastic trays for broth microdilution MIC method. Furthermore, the concentration-dependent bactericidal activity was determined to follow from two sites of oritavancin action (cell wall and membrane), and has led to pharmacokinetic/pharmacodynamic (PK/PD) investigations validating a single 1,200 mg dosing regimen for acute bacterial skin and skin structure infections (ABSSSI). Analyses of oritavancin results from the recent SOLO-II ABSSSI clinical trials have been quite positive when directly compared with vancomycin multi-dose therapy.

In this study, the results of reference MIC testing of oritavancin and vancomycin against a recent (2011-2012) Europe and USA collection of Gram-positive pathogens are presented. Analysis of a vancomycin susceptibility categorization to predict oritavancin susceptibility/activity at three MIC breakpoint levels (≤0.12, ≤0.25, ≤0.5 μg/mL) are presented with corresponding accuracy rates.

Methods

Bacterial strains: All Gram-positive organisms tested in the SENTRY Antimicrobial Surveillance Program (USA and Europe) against oritavancin and vancomycin were used for cross-susceptibility analysis. This included 33,429 strains identified as follows: *Staphylococcus aureus* (21,349 strains, nearly 50% MRSA), coagulase-negative staphylococci (CoNS; 3,084 strains), β-haemolytic streptococci (βHS; 3,018 strains), viridans group streptococci (VGS; 1,799 strains), and 4,179 strains of *Enterococcus faecalis* and *E. faecium* (880 were VRE).

Susceptibility testing and analysis: All organisms were tested by the reference broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) with appropriate supplementation of 2.5-5.0% lysed horse blood for testing streptococci. These tests were performed in validated broth microdilution panels produced by ThermoFisher Scientific (Cleveland, Ohio, USA), and quality assurance was confirmed by using the following quality control organisms: *S. aureus* ATCC 25923 and 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619.

Analysis followed the general intermethod comparison guidelines found in CLSI documents (M23-A3) and previously applied to other Gram-positive-active agents. Interpretations for oritavancin focused on the use of a single surrogate agent (vancomycin) to predict concurrent susceptibility while minimizing false-susceptibility errors to ≤1.5% and false-intermediate rates to ≤5%, if applicable. Comparisons used published breakpoint criteria or potential oritavancin agency/product package insert content at drug approval. Those three potential oritavancin breakpoints for susceptibility (≤0.12, ≤0.25, ≤0.5 μg/mL) were considered without assignment of an intermediate category for any species or genus analysis group (Table 2).

Results-1

- **Comparative activity of oritavancin and vancomycin**. Among 21,349 *S. aureus*, vancomycin (MIC_{90}, 1 μg/mL) inhibited >99.9% of strains at ≤2 μg/mL; oritavancin was eight-fold more active with a MIC_{90} at 0.12 μg/mL (Table 1). Oritavancin was also two-fold (βHS group) to >128-fold more active than vancomycin against other analyzed Gram-positive species with greatest potency advantages recorded against the enterococci (MIC_{90} values at 0.06 μg/mL versus >8 μg/mL).
- **Surrogate testing of staphylococci**. Using the ≤2 μg/mL vancomycin susceptible criteria, the current oritavancin susceptibility rates were 98.42, 99.96 and 100.00% for *S. aureus* strains having MIC results at ≤0.12, ≤0.25 and ≤0.5 μg/mL (analysis of 21,349 strains) see Figure 1 and Table 2. Among the 3,084 CoNS tested, vancomycin susceptibility results (≤4 μg/mL) predicted oritavancin susceptibility at ≤0.12 and ≤0.25 μg/mL (ECOFF) with 99.64 and 100.00% accuracy. All of these possible surrogate uses of vancomycin staphylococcus results to direct oritavancin use are considered very acceptable.
- **Surrogate testing of streptococci**. βHS (3,018 strains) and VGS (1,799 strains) had oritavancin MIC_{90} results at 0.25 and 0.06 μg/mL, respectively. For βHS the lowest vancomycin surrogate accuracy rate (89.82%) was noted for an oritavancin breakpoint of ≤0.12 μg/mL, but the ECOFF was at ≤0.25 μg/mL where the surrogate accuracy improved to 96.85% and then elevated to 99.97% at ≤0.5 μg/mL. Use of the vancomycin surrogate marker among VGS produced excellent predictive accuracy for oritavancin susceptibility ranging from 99.17% at ≤0.12 μg/mL (ECOFF) to 100.00% at ≤0.5 μg/mL (Tables 1 and 2).
- **Surrogate testing of *E. faecalis* and *E. faecium***. As shown in Tables 1 and 2, 880 (21.1%) enterococci had vancomycin non-susceptible (V-NS) MIC results. All of these V-NS organisms had oritavancin MIC results at ≤0.5 μg/mL, and 99.6% of results were at ≤0.25 μg/mL (ECOFF). In Figure 2 showing only *E. faecium*, all of the vancomycin-susceptible strains had oritavancin MIC results at ≤0.03 μg/mL yielding 100.00% accuracy for vancomycin as a surrogate marker agent. For all enterococci, the vancomycin surrogate utility ranged from 99.45% at an oritavancin breakpoint at ≤0.12 μg/mL to 100.00% accuracy at either ≤0.25 (ECOFF) or ≤0.5 μg/mL.

Table 1. Comparative potencies of oritavancin and vancomycin when tested against 33,429 Gram-positive pathogens isolated in the USA and Europe (2011-2012).

Pathogen (no. tested)[a] /Antimicrobial	Cumulative % inhibited at MIC in μg/mL:								
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8
***S. aureus* (21,349)**									
Oritavancin	61.3	89.7	98.4[b]	>99.9[c]	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.0	0.0	15.4	98.3[b]	>99.9	100.0	-
CoNS (3,084)									
Oritavancin	61.3	89.7	98.4	>99.9[c]	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.1	0.6	11.1	49.8	99.6	100.0	-
βHS (3,018)									
Oritavancin	65.3	79.2	89.8	96.9[c]	>99.9	100.0	-	-	-
Vancomycin	0.0	0.0	0.2	34.8	99.4	100.0	-	-	-
VGS (1,799)									
Oritavancin	86.3	94.6	99.2[c]	99.7	100.0	-	-	-	-
Vancomycin	0.0	0.0	0.9	10.5	83.9	100.0	-	-	-
Enterococci (4,179)									
Oritavancin[d]	81.6	93.2	97.8	99.6[c]	100.0	-	-	-	-
Vancomycin[d]	0.0	0.0	0.0	0.1	4.3	59.3	77.3	78.6	78.8

a. CoNS=coagulase-negative staphylococci; βHS=β-haemolytic streptococci; VGS=viridans group streptococci.
b. Underlined value is MIC_{90}. MIC_{90} for vancomycin among the tested enterococci was >16 μg/mL.
c. ECOFF value.
d. MIC_{50} comparison was 0.015 and 1 μg/mL for oritavancin and vancomycin, respectively; 880 VRE (MIC at >16 μg/mL, 800 *E. faecium* and 80 *E. faecalis*).

Results-2

Table 2. Direct comparisons of oritavancin and vancomycin reference MIC results when tested against 33,429 Gram-positive pathogens.

Pathogen (no. tested)	Vancomycin MIC in μg/mL (category)	Oritavancin MIC (μg/mL)			
		1	0.5	0.25	≤0.12
***S. aureus* (21,349)**	4 (I)	0	1	0	0
	2 (S)	0	0	10	354
	1 (S)	0	9	298	17,385
	≤0.5 (S)	0	0	21	3,271
CoNS (3,084)	4 (S)	0	1	0	12
	2 (S)	0	0	5	1,529
	1 (S)	0	0	5	1,191
	≤0.5 (S)	0	0	0	341
βHS (3,018)	1 (S)	1	5	1	12
	0.5 (S)	0	68	150	1,725
	≤0.25 (S)	0	21	62	973
VGS (1,799)	1 (S)	0	0	1	289
	0.5 (S)	0	5	6	1,309
	≤0.25 (S)	0	0	3	186
Enterococci (4,179)	>16 (R)	0	15	58	807
	16 (I)	0	0	0	4
	8 (I)	0	0	0	9
	4 (S)	0	0	0	56
	2 (S)	0	0	3	747
	≤1 (S)	0	0	15	2,465

Figure 1. Scattergram comparing 21,349 S. aureus isolates (2011-2012) tested against oritavancin and vancomycin. Breakpoint concentrations (CLSI, 2013) for vancomycin (solid vertical line) are compared to possible oritavancin breakpoint crriteria (≤0.25 and ≤0.5 μg/mL) predicted by ECOFF and/or PK/PD analyses (see broken horizontal lines).

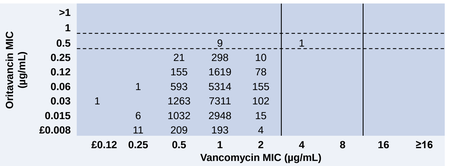
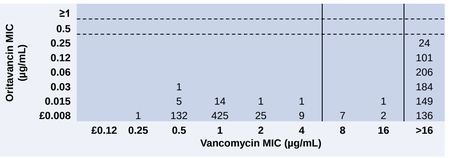


Figure 2. Scattergram comparing 1,424 E. faecium isolates (2011-2012) tested against oritavancin and vancomycin. Breakpoint concentrations (CLSI, 2013) for vancomycin (solid vertical lines) are compared to possible oritavancin breakpoint criteria (≤0.25 and ≤0.5 μg/mL) predicted by ECOFF and/or PK/PD analyses (see broken horizontal lines).



Conclusions

- The vancomycin surrogate accuracy at projected oritavancin breakpoints (≤0.12/≤0.25/≤0.5 μg/mL) for these organism groups studied here were as follows: for *S. aureus* (98.42/99.96/100.00%); for CoNS (99.64/100.00/100.00%); for βHS (89.82/96.85/99.97%), for VGS (99.17/99.72/100.00%) and for enterococci (99.45/100.00/100.00%). These accuracy rates are considered acceptable for any of the potential breakpoints that would be qualified via ECOFF or PK/PD analyses and clinical trial outcomes through the regulatory process.
- The oritavancin potency and spectrum characteristics, combined with a novel dosing regimen, clearly offers a therapeutic option not previously available for ABSSSI. Oritavancin could be used with confidence when the tested strain is vancomycin-susceptible by the currently utilized laboratory method, realizing that among the *E. faecalis* and *E. faecium* VRE strains, oritavancin will also be active if tested by the reference MIC method.

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