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Use of *In Vitro* Vancomycin Testing Results To Predict Susceptibility to Oritavancin, a New Long-Acting Lipoglycopeptide

Ronald N. Jones,[a] John D. Turnidge,[b] Greg Moeck,[c] Francis F. Arhin,[c] Rodrigo E. Mendes[a]

JMI Laboratories, North Liberty, Iowa, USA[a]; University of Adelaide, Adelaide, South Australia, Australia[b]; The Medicines Company, Ville Saint Laurent, Quebec, Canada[c]

Oritavancin is a recently approved lipoglycopeptide antimicrobial agent with activity against Gram-positive pathogens. Its extended serum elimination half-life and concentration-dependent killing enable single-dose treatment of acute bacterial skin and skin structure infections. At the time of regulatory approval, new agents, including oritavancin, are not offered in the most widely used susceptibility testing devices and therefore may require application of surrogate testing using a related antimicrobial to infer susceptibility. To evaluate vancomycin as a predictive susceptibility marker for oritavancin, 26,993 recent Gram-positive organisms from U.S. and European hospitals were tested using reference MIC methods. Organisms included *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), beta-hemolytic streptococci (BHS), viridans group streptococci (VGS), and enterococci (ENT). These five major pathogen groups were analyzed by comparing results with FDA-approved susceptible breakpoints for both drugs, as well as those suggested by epidemiological cutoff values and supported by pharmacokinetic/pharmacodynamic analyses. Vancomycin susceptibility was highly accurate (98.1 to 100.0%) as a surrogate for oritavancin susceptibility among the indicated pathogen species. Furthermore, direct MIC comparisons showed high oritavancin potencies, with vancomycin/oritavancin MIC_{90} results of 1/0.06, 2/0.06, 0.5/0.12,1/0.06, and >16/0.06 μg/ml for *S. aureus*, CoNS, BHS, VGS, and ENT, respectively. In conclusion, vancomycin demonstrated acceptable accuracy as a surrogate marker for predicting oritavancin susceptibility when tested against the indicated pathogens. In contrast, 93.3% of vancomycin-nonsusceptible enterococci had oritavancin MIC values of ≤0.12 μg/ml, indicating a poor predictive value of vancomycin for oritavancin resistance against these organisms. Until commercial oritavancin susceptibility testing devices are readily available, isolates that when tested show vancomycin susceptibility can be inferred to be susceptible to oritavancin by using FDA-approved breakpoints.

Newly approved (by the U.S. Food and Drug Administration [FDA] or European Medicines Agency [EMA]) antimicrobial agents rarely have validated commercial susceptibility testing products/systems available at the time of commercialization. In fact, the recent histories of such products demonstrate delays of years, even for those drugs possessing qualities that would favorably impact patient care. To support susceptibility assessments of these approved antimicrobial agents for treatment of indicated infections, clinical microbiology laboratories have resorted to "surrogate" susceptibility testing of a similar (class representative) currently tested agent to predict susceptibility of organisms to the new antimicrobial agent (1–6). This option has been successfully applied to several antimicrobial classes since the first standardization of susceptibility testing methods (7, 8).

Oritavancin, formerly LY333328 (9, 10), is a recently approved lipoglycopeptide with broad-spectrum activity against Gram-positive pathogens, including some strains nonsusceptible to vancomycin (11) (see Table 1, below). Initial global surveillance study results (11) across 12 countries demonstrated potent oritavancin activity *in vitro* against staphylococci (including methicillin-resistant *Staphylococcus aureus* strains [MRSA]), *Streptococcus pneumoniae*, and enterococci (including vancomycin-resistant enterococci [VRE]), a level of activity clarified by the subsequent understanding that a surfactant (polysorbate 80) was required in testing media for accurate MIC determinations in the plastic trays used for the broth microdilution MIC method (12, 13). Furthermore, the concentration-dependent bactericidal activity of oritavancin is based on the two sites of oritavancin action (the cell wall and membrane) and has led to pharmacokinetic/pharmacodynamic (PK/PD) investigations suggesting an optimal single 1,200-mg dosing regimen for acute bacterial skin and skin structure infections (ABSSSI) (14–17). This single dose of oritavancin was demonstrated to be noninferior to a vancomycin regimen administered twice daily for 7 to 10 days for treatment of adults with ABSSSI (18, 19).

As oritavancin emerges into clinical practice, the potential for immediate use of a surrogate agent (vancomycin) for susceptibility testing appears to be a prudent consideration. In our study, the results of reference MIC testing of oritavancin and vancomycin against a recent collection (from 2011 to 2013) of Gram-positive pathogens from the United States and Europe are presented. Analysis of a vancomycin surrogate susceptibility categorization to predict oritavancin susceptibility/activity at recently determined FDA MIC breakpoint levels (≤0.12 or ≤0.25 μg/ml) are presented along with corresponding accuracy rates previously reported (19).

(These results were presented in part at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy in Denver, CO, 10 to 13 September 2013 [20].)

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Address correspondence to Ronald N. Jones, ronald-jones@jmilabs.com.

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TABLE 1 Comparative *in vitro* potencies of oritavancin and vancomycin against 26,993 Gram-positive pathogens isolated in the United States and Europe, 2011 to 2013

Pathogen (no. tested) and antimicrobial	Cumulative % inhibited at MIC (μg/ml) of:									
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (17,717)										
Oritavancin	23.7	64.8	91.3[a]	98.8	>99.9	100.0				
Vancomycin	0.0	0.0	0.0	0.0	0.1	20.7	98.5	100.0		
CoNS (2,073)										
Oritavancin	36.2	66.0	95.0	99.8	100.0					
Vancomycin	0.0	0.0	0.0	0.1	0.4	11.6	52.3	99.7	100.0	
BHS (2,357)										
Oritavancin	44.7	72.8	84.8	92.7	98.1	>99.9	100.0			
Vancomycin	0.0	0.0	0.0	0.1	45.5	99.8	100.0			
VGS (1,248)										
Oritavancin	75.5	86.0	94.6	99.3	100.0					
Vancomycin	0.0	0.0	0.0	0.7	10.4	86.4	100.0			
Enterococci (3,598)[b]										
Oritavancin	66.4	85.3	94.6	98.4	99.7	100.0				
Vancomycin	0.0	0.0	0.0	0.0	0.1	5.8	59.6	77.9	78.9	79.3

[a] Underlined values are MIC_{90}s. The MIC_{90} for vancomycin among the tested enterococci was >16 μg/ml.
[b] Includes *E. faecalis* (n = 2,217) and *E. faecium* (n = 1,381) isolates. MIC_{50}s were 0.015 and 1 μg/ml for oritavancin and vancomycin, respectively, for 746 VRE isolates (MIC, >16 μg/ml), including 696 *E. faecium* isolates and 50 *E. faecalis* isolates.

MATERIALS AND METHODS

Bacterial strains. All Gram-positive organisms tested in the SENTRY Antimicrobial Surveillance Program (i.e., U.S. and Europe isolates) against oritavancin and vancomycin in 2011 to 2013 were used for cross-susceptibility analysis. This included 26,993 strains: *Staphylococcus aureus* (17,717 strains, nearly 50% MRSA), coagulase-negative staphylococci (CoNS; 2,073 strains), beta-hemolytic streptococci (BHS; 2,357 strains), viridans group streptococci (VGS; 1,248 strains), and enterococci (*Enterococcus faecalis* and *Enterococcus faecium*; 3,598 strains; 746 were VRE). Results reported by Vidaillac et al. (21) were also included for oritavancin and vancomycin when testing vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA).

Susceptibility testing and analysis. All organisms were tested by the reference broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) (7, 8) with appropriate medium supplementation with 2.5 to 5.0% lysed horse blood for testing fastidious streptococci. These tests were performed in validated broth microdilution panels produced by Thermo Fisher Scientific (Cleveland, Ohio, USA), and quality

TABLE 2 Direct comparisons of oritavancin and vancomycin reference MICs for 19 Gram-positive pathogens in ABSSSI, 2011 to 2013

Pathogen (no. tested)[a]	Vancomycin MIC (μg/ml) (susceptibility category)[b]	Oritavancin MIC (μg/ml)					Surrogate accuracy (%)
		≤0.06	0.12[c]	0.25[d]	0.5	1	
S. aureus (17,717)	4 (I)	0	0	0	0	0	98.8
	2 (S)	195	55	10	0	0	
	1 (S)	12,474	1,130	189	1	0	
	≤0.5 (S)	3,501	147	15	0	0	
BHS (2,357)[e]	1 (S)	1	3	0	1	0	98.1
	0.5 (S)	1,080	69	46	21	1	
	≤0.25 (S)	920	113	80	22	0	
S. anginosus group (368)[f]	1 (S)	128	0	0	0	0	100.0
	0.5 (S)	226	0	0	0	0	
	≤0.25 (S)	14	0	0	0	0	
E. faecalis (2,164), vancomycin susceptible	4 (S)	26	1	0	0	0	99.7
	2 (S)	620	9	1	0	0	
	≤1 (S)	1,454	47	6	0	0	

[a] Only the indicated species were tabulated (19).
[b] Susceptibility categories: I, intermediate; S, susceptible.
[c] The susceptibility breakpoint for staphylococci (*S. aureus*) and enterococci (*E. faecalis*) (19).
[d] The susceptibility breakpoint for beta-hemolytic streptococci (*S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae*) and the *S. anginosus* group (19).
[e] Beta-hemolytic streptococci included only *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae*.
[f] Includes *S. anginosus*, *S. constellatus*, and *S. intermedius*.

TABLE 3 Vancomycin test result accuracy for prediction of oritavancin susceptibility[a]

Pathogen or species group (no. tested)	Surrogate accuracy for breakpoint (μg/ml) of: ≤0.12	≤0.25
S. aureus (17,717)	98.8[b]	>99.9
CoNS (2,073)	99.8	100.0
S. epidermidis (1,177)	100.0	100.0
S. haemolyticus (182)	98.4	100.0
S. lugdunensis (138)	100.0	100.0
Enterococci (2,840)[c]	99.7	100.0
E. faecalis (2,164)[a]	99.7	100.0
E. faecium (676)	100.0	100.0
Beta-hemolytic streptococci (2,357)	NA[d]	98.1
S. pyogenes (1,209)	NA	97.8
S. agalactiae (1,016)	96.4	98.5
S. dysgalactiae (132)	NA	97.7
Viridans group streptococci (1,248)	99.3	100.0
S. anginosus group (368)	100.0	100.0
S. mitis group (406)	99.8	100.0

[a] Based on two breakpoint concentrations (≤0.12 and ≤0.25 μg/ml) when tested against 26,993 Gram-positive pathogens isolated during 2011 to 2013.
[b] Underlined results indicate the accuracy at the FDA breakpoint for the indicated species (19). For BHS, data were tabulated only the three indicated species.
[c] Data were tabulated only for vancomycin-susceptible strains.
[d] NA, not acceptable; accuracy was <95.0%.

assurance was confirmed by using the following quality control (QC) organisms: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 (8). All QC results were within specified ranges.

Analysis followed the general intermethod comparison guidelines provided in CLSI documents (7, 22) and previously applied to other agents active against Gram-positive pathogens and in the same antimicrobial class (2, 4). Interpretations for oritavancin focused on the use of a single surrogate agent (vancomycin) to predict concurrent susceptibility while minimizing false-positive (susceptibility) errors. Comparisons used published breakpoint criteria (8) or recently approved oritavancin breakpoints (19) for susceptibility at either ≤0.12 or ≤0.25 μg/ml, consistent with PK/PD data and clinical outcomes, but without assignment of an intermediate category (see Table 2, below). No other surrogate was considered, in an attempt to include in the analysis only an agent chemically similar and having a comparable, wide Gram-positive spectrum of activity; however, note that oritavancin would still remain active *in vitro* against many strains of VRE, as summarized in recent publications (23, 24), but not against VISA or VRSA strains (21).

RESULTS AND DISCUSSION

Comparative *in vitro* activities of oritavancin and vancomycin. Table 1 presents the cumulative percentages of isolates from five pathogen groups inhibited by increasing concentrations of oritavancin and vancomycin. Among 17,717 *S. aureus* isolates, vancomycin (MIC_{90}, 1 μg/ml) inhibited all strains at ≤2 μg/ml. Oritavancin was 16-fold more active than vancomycin, with a MIC_{90} of 0.06 μg/ml against *S. aureus*. Oritavancin was also 4-fold (BHS group) to >128-fold more active than vancomycin against other analyzed Gram-positive species, with the greatest potency difference recorded against the enterococci (MIC_{90} values of 0.06 μg/ml for oritavancin versus >8 μg/ml for vancomycin). All 26,993 tested surveillance strains had oritavancin MIC values of ≤1 μg/ml, and >99.9% of staphylococci had oritavancin MICs of ≤0.25 μg/ml (Table 1). These findings confirm and update data described in several previous publications (14, 23–26).

Surrogate testing of staphylococci. Table 2 summarizes the ability of FDA-published oritavancin susceptibility breakpoints to be predicted by the vancomycin MIC for testing the indicated species (19). Using the ≤2-μg/ml vancomycin susceptibility breakpoint for *S. aureus*, the predicted oritavancin susceptibility rate was 98.8% for strains having oritavancin MICs of ≤0.12 μg/ml (FDA breakpoint for *S. aureus*) (19). The epidemiological cutoff value (ECOFF) for oritavancin was calculated at ≤0.12 μg/ml (27). Among the 2,073 CoNS strains tested (Table 3), vancomycin susceptibility results (≤4 μg/ml) predicted oritavancin susceptibility at ≤0.12 and ≤0.25 μg/ml with 99.8 and 100.0% accuracy, respectively. Whereas this high level of accuracy suggests that vancomycin susceptibility is predictive of oritavancin activity against these organisms, there is no FDA-established breakpoint for oritavancin against CoNS.

Figure 1 shows a scattergram of oritavancin and vancomycin MIC values among the 17,717 *S. aureus* surveillance isolates and also the results of testing 60 VISA and 10 VRSA isolates (21). *S. aureus* strains that were vancomycin nonsusceptible (NS; MIC, ≥4 μg/ml) had oritavancin MIC values ranging from 0.12 to 4 μg/ml, with 98.6% of isolates NS at ≥0.25 μg/ml (MIC_{50}/MIC_{90}, 0.5/2 μg/ml). As noted above, 98.8% of vancomycin-susceptible strains were also inhibited by oritavancin at ≤0.12 μg/ml (FDA breakpoint for susceptibility) (19)

Surrogate testing of streptococci. BHS and VGS had oritavan-

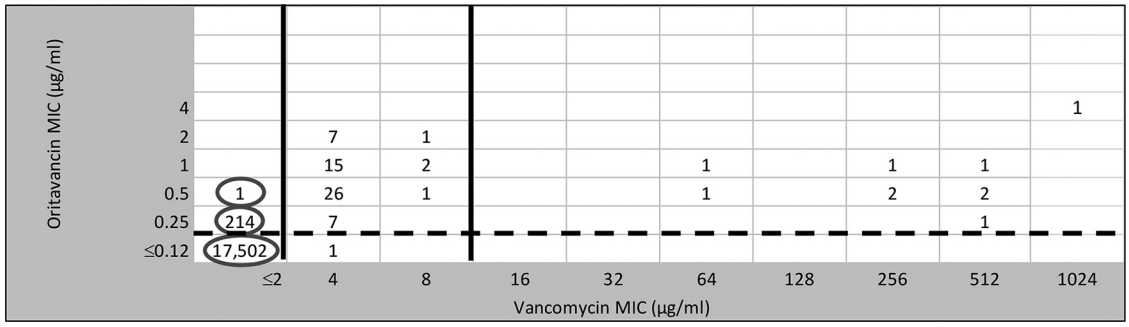

FIG 1 Scattergram comparing 17,717 *S. aureus* surveillance isolates (obtained between 2011 and 2013) tested against oritavancin and vancomycin (note the circled results). Also, data for 60 VISA (vancomycin MICs of 4 or 8 μg/ml) and 10 VRSA (MICs of 64 to 1,024 μg/ml) isolates are shown (originally reported in reference 21). Solid vertical lines, CLSI breakpoints; broken horizontal lines, FDA breakpoints (for vancomycin and oritavancin, respectively) (8, 19).

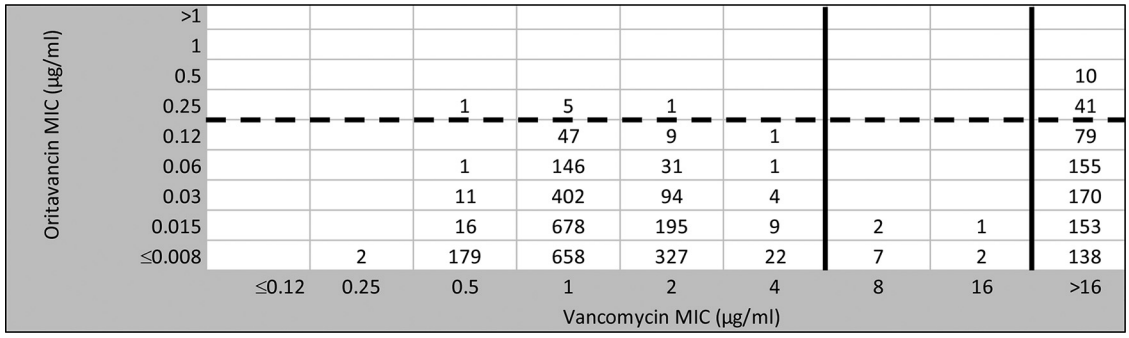

FIG 2 Scattergram comparing 3,598 *Enterococcus* spp. surveillance isolates (obtained from 2011 to 2013) tested against oritavancin and vancomycin. Breakpoint concentrations for vancomycin (solid vertical lines) were compared to the oritavancin breakpoint (≤0.12 μg/ml for vancomycin-susceptible *E. faecalis*; broken horizontal line) assigned by the FDA and/or proposed elsewhere based on ECOFF and PK/PD analyses (8, 15–17, 19, 27). A total of 12 and 746 isolates had intermediate susceptibility or resistance to vancomycin, and of those isolates, 93.3% were inhibited by 0.12 μg/ml oritavancin, e.g., they were oritavancin susceptible.

cin MIC_{90}s of 0.12 and 0.06 μg/ml, respectively (Table 1). For BHS, vancomycin surrogate accuracy was 98.1% (Tables 2 and 3) for the FDA-approved oritavancin breakpoint of ≤0.25 μg/ml. Use of the vancomycin susceptibility surrogate among VGS similarly produced excellent predictive accuracy for oritavancin susceptibility, ranging from 99.3% at ≤0.12 μg/ml (ECOFF) to 100.0% at ≤0.25 μg/ml (19) (Table 3).

Surrogate testing of *E. faecalis* and *E. faecium*. Due to the greater *in vitro* potency and spectrum of activity for oritavancin compared to vancomycin against VRE, the vancomycin surrogate use accuracy calculations can only be applied to vancomycin-susceptible strains (Table 2). As illustrated in Table 1 and Fig. 2, a total of 21.1% of enterococci were nonsusceptible to vancomycin (MIC, ≥8 μg/ml) (8). All vancomycin-nonsusceptible organisms were inhibited by oritavancin at ≤0.5 μg/ml, and 98.4% of all enterococci (Table 1) were inhibited at ≤0.12 μg/ml, the FDA oritavancin breakpoint for vancomycin-susceptible isolates of *E. faecalis* (19). Nearly all (99.7%) vancomycin-susceptible *E. faecalis* strains were inhibited by oritavancin at ≤0.12 μg/ml, emphasizing a high degree of accuracy for vancomycin's use as a surrogate susceptibility marker agent (Tables 2 and 3). Among the 2,840 vancomycin-susceptible enterococci (Table 3 and Fig. 1), the vancomycin surrogate utility ranged from 99.7% at an oritavancin breakpoint of ≤0.12 μg/ml (for *E. faecalis* alone) to 100.0% for *E. faecium*. Notably, 707 of 758 (93.3%) vancomycin-nonsusceptible enterococci had an oritavancin MIC of ≤0.12 μg/ml, e.g., oritavancin susceptible (Fig. 2).

These cross-susceptibility analyses validate the surrogate use of vancomycin results to predict oritavancin activity and should allow the immediate, directed clinical use of this novel lipoglycopeptide agent (14). This antimicrobial susceptibility testing strategy, used effectively for decades with other organism/agent combinations, enables newly approved agents to be represented by other compounds within a class (shared resistance mechanisms) without any compromise to patient care (1–10). The vancomycin surrogate susceptibility testing predictive probabilities based on recently published oritavancin breakpoints (19) for the organism groups studied here (Tables 2 and 3) were as follows: for *S. aureus*, 98.8% at ≤0.12 μg/ml; for BHS, 98.1% at ≤0.25 μg/ml; for VGS, 100.0% at ≤0.25 μg/ml; for enterococci, 99.7% at ≤0.12 μg/ml. These high rates are considered very acceptable for any of these applied conservative breakpoints that have been qualified via ECOFF data (27) and PK/PD analyses (16) through regulatory (FDA and EUCAST/EMA) processes (19).

The *in vitro* potency and activity spectrum characteristics of oritavancin (14, 23–26), combined with a novel single-dosing strategy (15–17), may represent a potential therapeutic option not previously available for the treatment of ABSSSI (18). The present lack of *in vitro* susceptibility testing devices for oritavancin, owing to suboptimal disk/agar diffusion tests, is compounded by projected delays in availability of automated antimicrobial susceptibility testing devices containing oritavancin. These limitations can be initially overcome by the application of a validated surrogate susceptibility marker testing strategy (7, 8, 12, 13), as demonstrated here with vancomycin. To this end, oritavancin susceptibility could be inferred with a high degree of confidence when the tested strain is vancomycin susceptible based on the currently utilized laboratory susceptibility testing method and when both peptides are influenced by common resistance mechanisms. One limitation of this approach is that oritavancin maintains *in vitro* activity against many strains of VRE (Fig. 1) (14, 23, 24); however, it should be noted that among enterococci, only vancomycin-susceptible isolates of *E. faecalis* are indicated pathogens (Table 2) in the oritavancin FDA prescribing information (19). Furthermore, *S. aureus* NS to vancomycin usually have oritavancin MIC results of ≥0.25 μg/ml (21). Overall, the surrogate testing approach for oritavancin may be opportune, but we strongly urge further studies to develop accurate commercial susceptibility tests for direct assessment of oritavancin activity in the clinical microbiology laboratory.

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