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Results from Oritavancin Resistance Surveillance Programs (2011 to 2014): Clarification for Using Vancomycin as a Surrogate To Infer Oritavancin Susceptibility

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Measurement of vancomycin susceptibility has been shown to be highly predictive as a surrogate measure of oritavancin susceptibility among clinically indicated Gram-positive species. Results of studying over 30,000 pathogens (from 2011 to 2014) by cross-susceptibility analysis and determining the poor reproducibility of oritavancin-nonsusceptible results showed nearly perfect surrogate testing accuracy (99.86 to 99.94%). Any isolate of an indicated organism species with locally reproducible oritavancin-nonsusceptible results (extremely rare) should be referred to a reference laboratory for confirmation of the results and determination of the resistance mechanism.

Oritavancin, a novel lipoglycopeptide, was recently approved for single-dose treatment of acute bacterial skin and skin structure infections (ABSSSIs) in the United States and Europe (1, 2). The compound (formerly LY333328) has a long history of *in vitro* evaluations and drug development, dating from the late 1990s (3–5) and documenting a broad anti-Gram-positive organism spectrum comparable to those of vancomycin and teicoplanin. Initial worldwide surveillance (5) suggested that oritavancin had activity similar to that of existing glycopeptides; reference methods were subsequently modified to recognize the greater oritavancin activity (8- to 16-fold superior) against *Staphylococcus aureus* and various streptococcal species (1, 2, 6, 7).

The physicochemical characteristics of lipoglycopeptides (oritavancin, dalbavancin, and telavancin) are particularly challenging for the development of standardized *in vitro* susceptibility testing methods. Poor drug diffusion through agar-based media limits the application of the agar disk diffusion method, as published by several international standards organizations (8), and the binding of drug to various plastics compromises dilution MIC testing (7, 9). Reference broth microdilution methods (10, 11) for oritavancin require the surfactant polysorbate-80 (P-80) (0.002%) to recognize full antimicrobial potency, and adaption of commonly used commercial devices appears to be uncertain. Such delays in the use of commercial susceptibility testing systems to direct oritavancin chemotherapy may necessitate alternative testing strategies, such as the use of vancomycin susceptibility testing results as a surrogate predictive measure (12). In this investigation, (i) we update the analysis of 2011-2013 oritavancin surveillance results (12) for validation of the use of vancomycin MIC results to infer oritavancin susceptibility, following retesting of strains with previous nonsusceptible results, and (ii) we present 2014 oritavancin surveillance data to confirm the high predictive value of surrogate vancomycin testing for oritavancin susceptibility.

European and U.S. oritavancin resistance surveillance isolates from 2011 to 2013 (26,993 isolates; 22,606 indicated species) and 2014 (10,002 isolates; 7,688 indicated species) were tested by validated reference broth microdilution methods (10). For species and antimicrobial-resistant subset details, refer to Tables 1 and 2, as well as to reference 12. The interpretive breakpoint criteria used for oritavancin were those selected by the U.S. Food and Drug Administration (FDA) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the criteria for vancomycin were those published by the Clinical and Laboratory Standards Institute (CLSI) (11, 13–15). All quality control (QC) results were within published ranges (13), using the following QC organisms: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619.

An earlier publication (12) quantified the predictive accuracy of using vancomycin susceptibility to infer susceptibility to orita-

TABLE 1 Accuracy of vancomycin susceptibility test results (2011 to 2013) to infer susceptibility to oritavancin at U.S. FDA-approved breakpoints (14) for indicated Gram-positive pathogens (22,606 isolates)

Species[a]	No. of isolates tested	Surrogate accuracy (%)	
		Jones et al. (12)	Current reanalysis
S. aureus	17,717	98.8	>99.9
β-Hemolytic streptococci[b]	2,357	98.1	99.8
S. anginosus group[c]	368	100.0	100.0
E. faecalis, vancomycin susceptible	2,164	99.7	99.7
Overall	22,606	98.85	99.94

[a] Indicated species with interpretive criteria only (14).
[b] Includes *Streptococcus pyogenes*, *S. agalactiae*, and *S. dysgalactiae*.
[c] Includes *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*.

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TABLE 2 Accuracy of vancomycin susceptibility test results (2014) to infer susceptibility to oritavancin at U.S. FDA-approved breakpoints (14) for indicated Gram-positive species groups (10,002 isolates)

Species	No. of isolates tested	Surrogate accuracy (% [no. of nonsusceptible isolates])
S. aureus[a]	5,609	>99.9 (3)
CoNS[b]	641	100.0 (0)
β-Hemolytic streptococci[a]	1,049	99.2 (8)
S. anginosus group[a]	178	100.0 (0)
S. pneumoniae[b]	1,673	100.0 (0)
Enterococci[a]	852	100.0 (0)
Overall[a]	7,688	99.86 (11)

[a] Includes the indicated species (*Staphylococcus aureus*, *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus*, *S. constellatus*, *S. intermedius*, and vancomycin-susceptible *E. faecalis* among all enterococci).
[b] *S. aureus* interpretive criteria (susceptible, [0.12 μg/ml) were applied to coagulase-negative staphylococci (CoNS) and pneumococci for the vancomycin surrogate test comparison only; no errors were observed.

vancin (Table 1). Across all U.S. FDA-indicated species for oritavancin treatment (22,606 isolates) (14), the surrogate accuracy was 98.85%, ranging from 98.7% (β-hemolytic streptococci) to 100.0% (*Streptococcus anginosus* group). Subsequent to that publication, organisms with oritavancin-nonsusceptible MIC values (10) were retested to determine MIC reproducibility. Among 215 retested isolates of *S. aureus*, only 1.4% (3 isolates) had reproducible oritavancin MIC results of ≥0.25 μg/ml. Similarly, repeated β-hemolytic streptococcal reproducibility ranged from nil (*Streptococcus pyogenes*) to 6.7% (*Streptococcus agalactiae*). The most frequently reproducible oritavancin-nonsusceptible results were recorded for *Streptococcus dysgalactiae* (MIC of 0.5 μg/ml, 1 doubling dilution above the breakpoint).

Figure 1 (modified from reference 12) provides updated vancomycin surrogate accuracy data for 17,717 *S. aureus* isolates following oritavancin MIC retesting. The vancomycin surrogate accuracy rate improved to >99.9%, and the overall acceptable cross-susceptibility rate for all indicated species increased to 99.94% (formerly 98.85%) (Table 1).

In the vancomycin surrogate cross-susceptibility validations using the most recent 2014 oritavancin surveillance isolates from the United States and Europe (Table 2), all oritavancin-nonsusceptible isolates were routinely retested. A similar pattern of very high cross-susceptibility (accuracy) between vancomycin and oritavancin was encountered, compared to the 2011-2013 statistics (Table 1). For the 7,688 Gram-positive isolates from the indicated species, the predictive accuracy of the surrogate vancomycin susceptibility values ranged from 99.32% (β-hemolytic streptococci) to 100.0% (*S. anginosus* group and vancomycin-susceptible *E. faecalis*); the overall accuracy was 99.86%. It should be noted that, among all enterococci tested (1,086 isolates), seven vancomycin-intermediate isolates had oritavancin MIC values of 0.004 to 0.015 μg/ml. Although oritavancin is not approved for the treatment of infections caused by vancomycin-resistant enterococci (VRE) (*E. faecalis* or *Enterococcus faecium*), 200 VRE isolates tested in this study had oritavancin MIC results ranging from 0.002 to 1 μg/ml and an MIC_{90} of only 0.12 μg/ml (data not shown). Figure 2 illustrates the high cross-susceptibility rate (>99.9%) among the 5,609 *S. aureus* isolates in 2014.

Also found in Table 2 for the 2014 surveillance isolates are the cross-susceptibility statistics for coagulase-negative staphylococci (CoNS) (641 isolates) and *S. pneumoniae* (1,673 isolates); oritavancin is not indicated for either species (14). All of the isolates for these two pathogen groups were vancomycin susceptible (MICs of ≤1 or ≤2 μg/ml, respectively), except for one isolate of vancomycin-intermediate CoNS. Oritavancin was also very active, with all MIC results being ≤0.06 and ≤0.12 μg/ml for the pneumococci and CoNS, respectively.

Oritavancin has a remarkable combination of high antimicrobial activity against prevalent Gram-positive pathogens (1, 2) and a pharmacokinetic (PK)/pharmacodynamic (PD) profile that justifies single-dose intravenous therapy for ABSSSIs (14, 16, 17). Favorable results from the phase III SOLO I and SOLO II trials demonstrated comparable (noninferior) outcomes, compared to vancomycin-containing regimens (18, 19). Additional *in vitro* investigations support potential future studies regarding use against VRE infections (20), methicillin-resistant *S. aureus* (MRSA) infections with the novel *mecC* gene mechanism or infections emerging in the community setting (21, 22), some *S. aureus* strains with elevated vancomycin MIC values or heteroresistant variations (23, 24), and uncommonly isolated Gram-positive species (25). Furthermore, favorable *in vitro* drug combination (synergy) results have been reported for oritavancin testing against staphylococci (26).

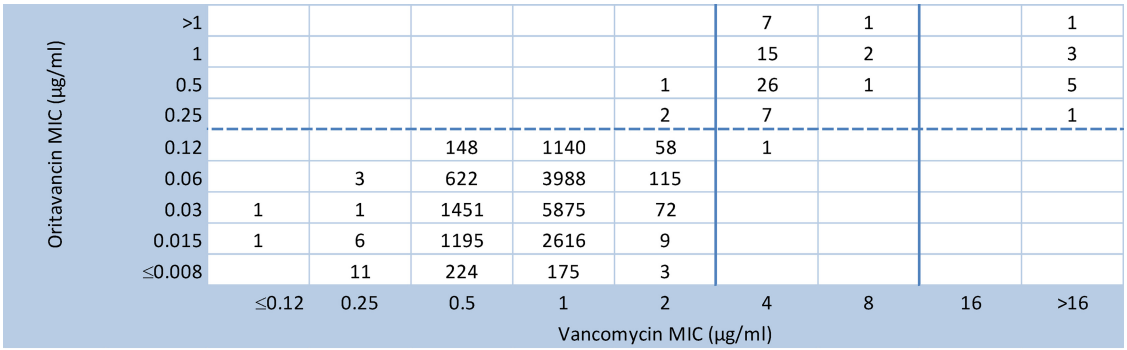

FIG 1 Chart comparing vancomycin and oritavancin MIC results for 17,717 *S. aureus* isolates obtained between 2011 and 2013. Data for 60 vancomycin-intermediate *S. aureus* isolates (vancomycin MICs of 4 or 8 μg/ml) and 10 vancomycin-resistant *S. aureus* isolates (MICs of 64 to 1,024 μg/ml) are also shown (originally reported in reference 24). CLSI breakpoints (solid vertical line) and U.S. FDA breakpoints (dashed horizontal line) for vancomycin and oritavancin, respectively (13, 14), as modified from the report by Jones et al. (12), are shown.

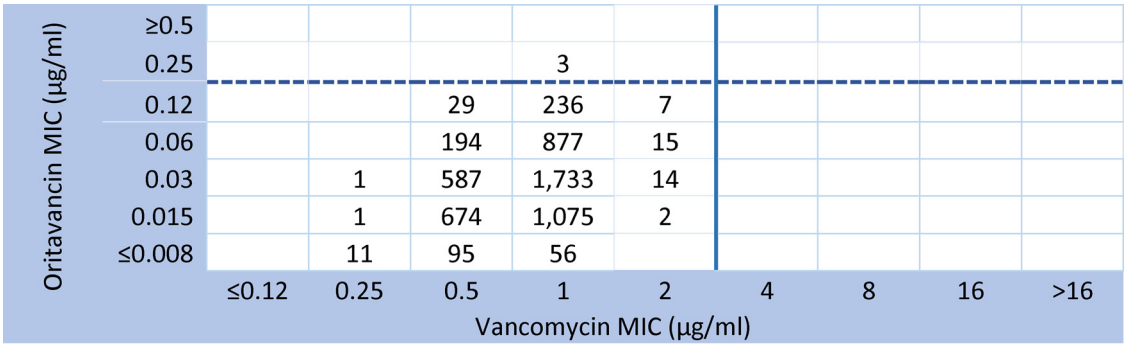

FIG 2 Chart comparing vancomycin and oritavancin MIC results for 5,609 *S. aureus* surveillance program isolates obtained in the United States and Europe in 2014. Organisms with reproducible oritavancin-nonsusceptible results (MICs of 0.25 μg/ml) are shown (only 3 isolates [0.05%]).

With this favorable microbiological, PK/PD, and clinical trial background, oritavancin provides a valuable addition to our antimicrobial armamentarium to treat infections caused by resistant Gram-positive cocci. Unfortunately, direct measurements of oritavancin susceptibility in hospital clinical microbiology laboratories will be compromised by the technical difficulties of *in vitro* testing for this antimicrobial class (lipoglycopeptides) (7, 9). A highly accurate and simple solution would be to utilize the test results for another drug in the same class (vancomycin, a glycopeptide of lesser potency) to predict oritavancin susceptibility. The results of a 4-year cross-susceptibility analysis of surveillance isolates from the United States and Europe reported here (Tables 1 and 2) confirm the nearly perfect accuracy (99.86 to 99.94%) of this testing option across all species listed by regulators for oritavancin therapy (11, 14). The occurrences of nonsusceptibility to oritavancin among contemporary Gram-positive clinical isolates is exceedingly rare. When oritavancin *in vitro* tests become available and such oritavancin-nonsusceptible values are observed (a very low probability), the test should be repeated to ensure reproducibility.

Finally, the background data presented here in part have led to the following statements in the oritavancin U.S. FDA product labeling: "The current absence of resistant isolates precludes defining any results other than 'Susceptible.' Isolates yielding test results other than 'Susceptible' should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing" (14). The recommendation that susceptibility to dalbavancin, oritavancin, and telavancin can be inferred from the vancomycin susceptibility results is also found in the USCAST breakpoint tables (27). Furthermore, the EUCAST has published the following three relevant guidelines regarding oritavancin tests and breakpoints (15). (i) Nonsusceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test results for any such isolate must be confirmed and the isolate sent to a reference laboratory. (ii) MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated). The manufacturers' instructions should be followed for commercial systems. (iii) *S. aureus* isolates susceptible to vancomycin can be reported as susceptible to (dalbavancin and) oritavancin. These recommendations have achieved great harmonization internationally regarding susceptibility testing for the lipoglycopeptides, especially oritavancin (11, 14, 15, 27).

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