Accuracy of Predicting Oritavancin Susceptibility Using Vancomycin Surrogate Susceptibility Testing of Gram-positive Isolates from Europe

R.N. Jones, M. Castanheira, D.J. Farrell, R.K. Flamm, H.S. Sader, R.E. Mendes

JMI Laboratories, North Liberty, IA, USA

Contact:
Ronald N. Jones
JMI Laboratories
345 Beaver Kreek Ctr, Ste A
North Liberty, Iowa, 52317, USA
ronald-jones@jmilabs.com

Introduction and Purpose

Oritavancin is a lipoglycopeptide antibacterial agent with broad-spectrum activity against Gram-positive pathogens including some strains with elevated vancomycin MIC values. Initial global surveillance study results across 12 nations demonstrated oritavancin activity against staphylococci (including methicillin-resistant *S. aureus* [MRSA]), *Streptococcus pneumoniae* and enterococci (including vancomycin-resistant [VRE strains]). The concentration-dependent bactericidal activity of oritavancin stems from its two sites of action (bacterial cell wall and membrane), and has led to pharmacokinetic/pharmacodynamic (PK/PD) investigations validating a single 1200 mg dose dosing regimen for acute bacterial skin and skin structure infections (ABSSSI). Analyses of oritavancin results from the Phase 3 SOLO I and SOLO II ABSSSI clinical trials have demonstrated the non-inferiority of this single 1200 mg oritavancin dose regimen compared to twice-daily vancomycin for 7-10 days, with comparable safety. Oritavancin was approved by the United States Food and Drug Administration (USA-FDA) in late 2014 for the treatment of ABSSSI. In January 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending the granting of a marketing authorisation for oritavancin for the treatment of ABSSSI in adults.

Newly approved antimicrobial agents, including oritavancin, rarely have validated commercial susceptibility testing products/systems available at the time of commercial introduction. In fact, the recent history of these products demonstrates delays numbered in years even for those drugs possessing qualities that could favourably impact patient care. To enable susceptibility testing in support of clinical decision-making on the treatment of indicated infections by these regulatory-approved compounds, clinical microbiology laboratories have resorted to "surrogate marker" strategy susceptibility testing of a similar, currently tested agent (class representative) to predict susceptibility of the new antimicrobial agent.

In this study, the results of reference MIC testing of oritavancin and vancomycin against a recent (2011-2013) European collection of Gram-positive pathogens are presented. Analysis of a vancomycin susceptibility categorization to predict oritavancin susceptibility/ activity at MIC breakpoint levels selected by regulatory organizations in the EU and USA, are presented with corresponding predictive accuracy rates.

Methods

Bacterial strains: All Gram-positive organisms tested in the SENTRY Antimicrobial Surveillance Program (Europe; 2011-2013) against oritavancin and vancomycin were used for cross-susceptibility analysis. This included 9,803 strains identified as follows: *Staphylococcus aureus* (7,410 strains, nearly 50% MRSA), β-haemolytic streptococci (βHS; 1,021 strains), viridans group streptococci (VGS; 587 strains), and 1,195 strains of *Enterococcus faecalis*, vancomycin-susceptible.

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 Thermo Fisher Scientific (Cleveland, Ohio, USA), and quality assurance was confirmed by using the following quality control organisms: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619.

Analysis followed the general intermethod comparison guidelines found in CLSI documents (M23-A3), calculations of ECOFF values (Turnidge et al), 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. Comparisons used published breakpoint criteria for oritavancin, (http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf). These oritavancin breakpoints for susceptibility at ≤0.12 mg/L for *S. aureus* and enterococci, with ≤0.25 mg/L used for the indicated streptococci were selected without assignment of an intermediate category for any species or genus analysis group.

Results

- **Activity of oritavancin:** Among 7,410 *S. aureus*, vancomycin (MIC_{90}, 1 mg/L) inhibited all of strains at ≤2 mg/L; oritavancin was 16-fold more active with the MIC_{90} at 0.06 mg/L (Table 1). Oritavancin was also two-fold (βHS group) to >128-fold more active than vancomycin against other analysed Gram-positive species with greatest potency differences recorded against the enterococci (MIC_{90} values at 0.06 mg/L for oritavancin versus >8 mg/L for vancomycin when testing VRE; data not shown).
- **Surrogate testing of staphylococci:** Using the ≤2 mg/L vancomycin EUCAST susceptible criterion, the current oritavancin susceptibility predictive rate was 99.0% for *S. aureus* strains having MIC results at ≤0.12 mg/L (analysis of 7,410 strains; see Figure 1). This possible surrogate use of vancomycin susceptibility results to direct oritavancin categorical interpretation was considered acceptable (Table 2).
- **Surrogate testing of streptococci:** βHS (1,021 strains) and VGS (177 strains of *S. anginosus* group) had oritavancin MIC_{90} results at 0.12 and 0.015 mg/L, respectively. Among βHS, the lowest vancomycin surrogate prediction rate (98.5%; Figure 2) was noted for an oritavancin breakpoint of ≤0.25 mg/L, the ECOFF value. Use of the vancomycin surrogate marker among VGS (Figure 3) produced excellent predictive accuracy for oritavancin susceptibility of 100.0% at ≤0.12 (ECOFF) or ≤0.25 mg/L (Tables 1 and 2).
- **Surrogate testing of *E. faecalis*:** As shown in Figure 4, 18 (1.5%) of the enterococci had vancomycin non-susceptible (VAN-NS) MIC results. All of these VAN-NS organisms had oritavancin MIC values at ≤0.5 mg/L, and 83.3% of oritavancin MIC results were at ≤0.25 mg/L (ECOFF). In Figure 5 showing only vancomycin-susceptible *E. faecalis,* all but four strains had oritavancin MIC results at ≤0.12 mg/L yielding a 99.7% predictive value accuracy for vancomycin as a surrogate marker agent (Table 2).

Figure 1. Scattergram comparing 7,410 *S. aureus* isolates (2011-2013) tested against oritavancin and vancomycin. Breakpoint concentrations (EUCAST, 2015) for vancomycin (solid vertical line) are compared to the oritavancin susceptible breakpoint (≤0.12 mg/L) predicted by ECOFF and/or PK/PD analyses as well as regulatory approvals (see broken horizontal line).

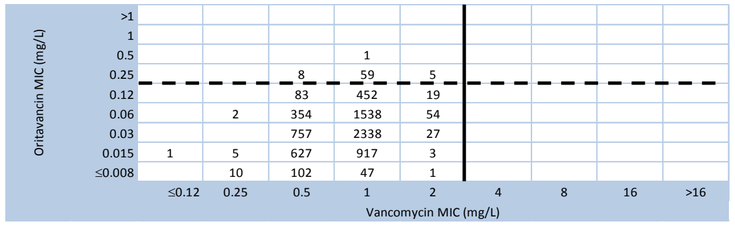


Figure 2. Scattergram comparing 1,021 β-haemolytic streptococci (2011-2013) tested against oritavancin and vancomycin. Breakpoint concentrations (EUCAST, 2015) for vancomycin (solid vertical line) are compared to the oritavancin susceptible breakpoint (≤0.25 mg/L) predicted by ECOFF and/or PK/PD analyses as well as regulatory approvals (see broken horizontal line).

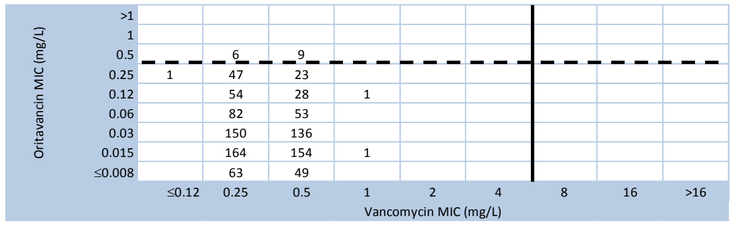


Figure 3. Scattergram comparing 177 *S. anginosus* group (2011-2013) tested against oritavancin and vancomycin. Breakpoint concentrations (EUCAST, 2015) for vancomycin (solid vertical line) are compared to the oritavancin susceptible breakpoint (≤0.25 mg/L) predicted by ECOFF and/or PK/PD analyses as well as regulatory approvals (see broken horizontal line).

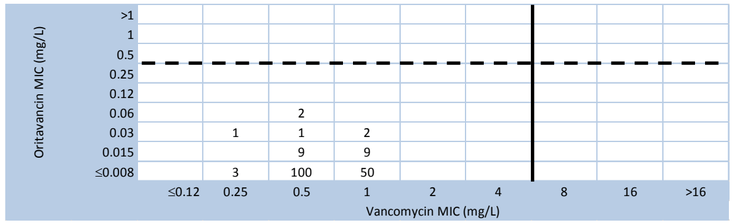


Table 1. Oritavancin antimicrobial activity when tested against 9,803 clinically indicated Gram-positive species (European medical centers; 2011-2013).

Indicated species (no. tested)	No. (cum. % inhibited) at oritavancin MIC (mg/L):							MIC (mg/L)	
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%	90%
S. aureus (7,410)	166(0.9)	1553(23.1)	3122(65.2)	1948(91.5)	554(99.0)[a]	72(>99.9)	1(100.0)	0.03	0.06
βHS (1,021)[b]	112(11.0)	319(42.2)	286(70.2)	135(83.4)	83(91.6)	71(98.5)	15(100.0)	0.03	0.12
S. anginosus grp (117)	153(86.4)	118(96.6)	4(98.9)	2(100.0)	0(100.0)	0(100.0)	-	≤0.008	0.015
E. faecalis (1,195)[c]	318(26.6)	489(67.5)	265(89.7)	95(97.7)	24(99.7)	4(100.0)	-	0.015	0.06

a. Underlined value is at USA-FDA and pending EUCAST/EMA breakpoint concentration.
b. βHS = β-haemolytic streptococci; includes: *S. pyogenes, S. agalactiae,* and *S. dysgalactiae.*
c. Vancomycin-susceptible only.

Table 2. Predictive ability of vancomycin susceptibility result to infer oritavancin susceptibility at published/proposed breakpoints (analyses of 9,803 clinically indicated species).

Indicated species (no. tested)	Surrogate test accuracy rate (%)	Indicated species (no. tested)	Surrogate test accuracy rate (%)
S. aureus (7,410)	99.0	VGS (587)	100.0
βHS (1,021)	98.5	*S. anginosus* group (177)	100.0
S. pyogenes (553)	98.4	*E. faecalis*, vancomycin-susc. (1,195)	99.7
S. agalactiae (379)	98.4	All strains (9,803)	99.1
S. dysgalactiae (89)	100.0		

Abbreviations: βHS = β-haemolytic streptococci and VGS = viridans group streptococci.

Figure 4. Scattergram comparing 1,213 *E. faecalis* (2011-2013) tested against oritavancin and vancomycin. Breakpoint concentrations (EUCAST, 2015) for vancomycin (solid vertical line) are compared to the oritavancin susceptible breakpoint (≤0.12 mg/L) predicted by ECOFF and/or PK/PD analyses as well as regulatory approvals (see broken horizontal line).

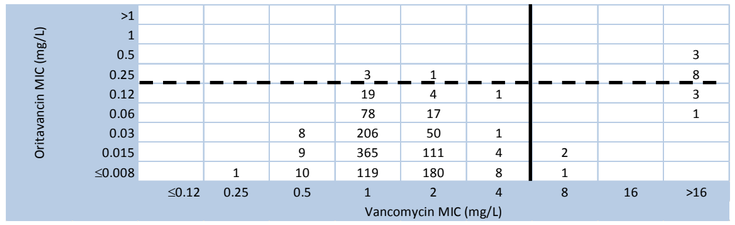
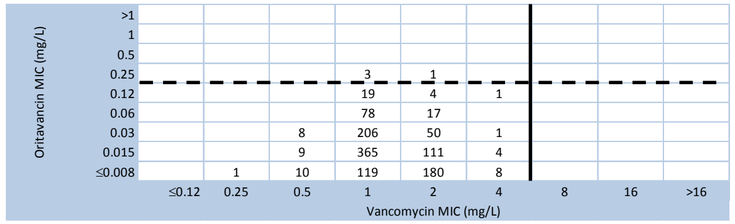


Figure 5. Scattergram comparing 1,195 vancomycin-susceptible *E. faecalis* (2011-2013) tested against oritavancin and vancomycin. Breakpoint concentrations (EUCAST, 2015) for vancomycin (solid vertical line) are compared to the oritavancin susceptible breakpoint (≤0.12 mg/L) predicted by ECOFF and/or PK/PD analyses as well as regulatory approvals (see broken horizontal line).



Conclusions

- The accuracy of using a vancomycin susceptibility test result to infer susceptibility to oritavancin at published oritavancin breakpoints (≤0.12 or ≤0.25 mg/L) by these cross-susceptibility analyses was as follows: for *S. aureus*, 99.0%; for βHS, 98.5%; for VGS, 100.0%; and for enterococci, 99.7% (Table 2). These surrogate test rates are considered acceptable for any of the susceptible breakpoints that have been qualified via ECOFF or PK/PD analyses and clinical trial outcomes through the recent regulatory processes (USA-FDA, EUCAST/EMA).
- Oritavancin's *in vitro* potency and Gram-positive spectrum, combined with a novel dosing regimen (single intravenous dose), offers a therapeutic option not previously available for ABSSSI. Isolates of designated Gram-positive organisms can be considered to be susceptible to oritavancin when the tested strain is susceptible to vancomycin as assessed by the currently utilized laboratory method. Isolates that test as non-susceptible to vancomycin should be tested for susceptibility to oritavancin directly, using the broth microdilution reference method.

Disclosures

RNJ, MC, DJF, RKF, REM and HSS are employees of JMI Laboratories that coordinates an oritavancin international surveillance programme for The Medicines Company. JMI Laboratories receives grant funding from various other pharmaceutical/diagnostics industry sources for *in vitro* evaluations/surveillance of glycopeptide-like agents that could be impacted by these analyses. RNJ is the guarantor for the data. Co-authors also acknowledge the following JMI Laboratories employees for support via analysis and poster preparation: K. Hass, A. Fuhrmeister and J. Streit.

References

1. Arhin FF, Sarmiento I, Belley A, McKay GA, Draghi DC, Grover P, Sahm DF, Parr TR, Jr., Moeck G (2008). Effect of polysorbate 80 on oritavancin binding to plastic surfaces: Implications for susceptibility testing. *Antimicrob Agents Chemother* 52: 1597-1603.
2. Arias CA, Mendes RE, Stilwell MG, Jones RN, Murray BE (2012). Unmet needs and prospects for oritavancin in the management of vancomycin-resistant enterococcal infections. *Clin Infect Dis* 54 Suppl 3: S233-S238.
3. Belley A, Arhin FF, Sarmiento I, Deng H, Rose W, Moeck G (2013). Pharmacodynamics of a simulated single 1,200-milligram dose of oritavancin in an in vitro pharmacokinetic/pharmacodynamic model of methicillin-resistant *staphylococcus aureus* infection. *Antimicrob Agents Chemother* 57: 205-211.
4. Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard- tenth edition.* Wayne, PA: CLSI.
5. Clinical and Laboratory Standards Institute (2015). *M100-S25. Performance standards for antimicrobial susceptibility testing: 25th informational supplement.* Wayne, PA: CLSI.
6. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
7. Jones RN, Flamm RK, Sader HS, Stilwell MG (2013). Interim susceptibility testing for ceftaroline, a new MRSA-active cephalosporin: selecting potent surrogate β-lactam markers to predict ceftaroline activity against clinically-indicated species. *Diagn Microbiol Infect Dis* 75: 89-93.
8. Mendes RE, Farrell DJ, Sader HS, Jones RN (2012). Oritavancin microbiologic features and activity results from the surveillance program in the United States. *Clin Infect Dis* 54 Suppl 3: S203-S213.
9. Turnidge J, Kahlmeter G, Kronvall G (2006). Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values. *Clin Microbiol Infect* 12: 418-425.
10. Zeckel ML, Preston DA, Allen BS (2000). In vitro activities of LY333328 and comparative agents against nosocomial gram-positive pathogens collected in a 1997 global surveillance study. *Antimicrob Agents Chemother* 44: 1370-1374.
11. Zhanel GG, Schweizer F, Karlowsky JA (2012). Oritavancin: Mechanism of action. *Clin Infect Dis* 54 Suppl 3: S214-S219.

Presented at ECCMID 2015 (25th European Congress of Clinical Microbiology and Infectious Diseases) 25-28 April 2015, Copenhagen, Denmark

Poster # EV0765