AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Oritavancin Activity Tested against Molecularly Characterized Staphylococci and Enterococci Displaying Elevated Linezolid MIC Results

Rodrigo E. Mendes, David J. Farrell, Helio S. Sader, Robert K. Flamm, Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

Oritavancin ($MIC_{50/90}$, 0.03/0.06 to 0.12 μg/ml) had potent activity against linezolid-resistant staphylococci, as well as *Enterococcus faecalis* and *Enterococcus faecium* (oritavancin $MIC_{50/90}$, 0.015/0.12 μg/ml against both species). All linezolid-resistant isolates were inhibited by oritavancin at ≤0.12 μg/ml. These results confirmed the absence of cross-resistance between linezolid and oritavancin in staphylococci and enterococci.

Staphylococcus aureus (including methicillin-resistant *S. aureus* [MRSA]), coagulase-negative staphylococci (CoNS), *Enterococcus faecium*, and multidrug-resistant (MDR) streptococci are frequently isolated pathogens responsible for various clinical infections (1). Several national and local studies have documented a decrease in the incidence of invasive MRSA infections in the United States (2–4). However, MRSA is still estimated to cause ~80,000 invasive infections and result in 11,000 deaths annually in the United States (5). Vancomycin-resistant enterococci (VRE) are estimated to cause 20,000 hospital-acquired infections and 1,300 deaths each year (5). Moreover, MRSA and *E. faecium* are among the defined ESKAPE organisms (*E. faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.), which cause the majority of U.S. nosocomial infections and are often refractory to many clinically available agents (6).

Linezolid is an anti-Gram-positive agent approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) (7), with potent activity against clinical pathogens causing infections worldwide according to large surveillance studies (8, 9). Although uncommon, linezolid resistance does occur, especially after prolonged administration (7, 10), and local investigations have reported occurrences of sporadic outbreaks (11–14) and dissemination of linezolid-dependent isolates (15, 16). Alterations in linezolid binding sites (23S rRNA and L3 and L4 ribosomal proteins) remain the most common mechanisms of oxazolidinone resistance (7). Additionally, transferrable resistance determinants, such as *cfr*, *cfr*(B), and *optrA*, represent newer mechanisms responsible for decreased susceptibility to linezolid (17–19). This study was conducted to evaluate the *in vitro* activity of oritavancin, a recently approved lipoglycopeptide for the treatment of ABSSSI (20), against a molecularly characterized collection of isolates displaying elevated linezolid MIC results.

A total of 25 *S. aureus* (linezolid MIC range, 4 to 32 μg/ml), 80 CoNS (linezolid MIC range, 4 to >128 μg/ml), and 45 enterococci (linezolid MIC range, 4 to 64 μg/ml) were included (see Table S1 in the supplemental material). These isolates were selected based on the presence of linezolid resistance mechanisms, although some staphylococcal isolates showed a linezolid MIC result (4 μg/ml) at the breakpoint for susceptibility (i.e., ≤4 μg/ml) (21). Isolates were recovered from a network of medical centers as part of the SENTRY Antimicrobial Surveillance Program and submitted

Received 3 February 2016 **Returned for modification** 22 February 2016
Accepted 10 March 2016

Accepted manuscript posted online 21 March 2016

Citation Mendes RE, Farrell DJ, Sader HS, Flamm RK, Jones RN. 2016. Oritavancin activity tested against molecularly characterized staphylococci and enterococci displaying elevated linezolid MIC results. Antimicrob Agents Chemother 60:3817–3820. doi:10.1128/AAC.00281-16.

Address correspondence to Rodrigo E. Mendes, rodrigo-mendes@jmilabs.com.

Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.00281-16.

TABLE 1 Antimicrobial activity and MIC distribution for oritavancin against a challenge set of molecularly characterized Gram-positive clinical isolates displaying elevated linezolid MIC results

Organism[a] (no. of isolates tested)	MIC (μg/ml) at:		No. (cumulative %) inhibited at oritavancin MIC (μg/ml) of:				
	50%	90%	≤0.008	0.015	0.03	0.06	0.12
S. aureus (25)	0.03	0.06	0 (0.0)	3 (12.0)	15 (72.0)	6 (96.0)	1 (100.0)
cfr-carrying only (13)	0.03	0.06	0 (0.0)	3 (23.1)	6 (69.2)	3 (92.3)	1 (100.0)
CoNS (80)	0.03	0.12	7 (8.8)	6 (16.2)	33 (57.5)	25 (88.8)	9 (100.0)
E. faecalis (13)[b]	0.015	0.12	3 (23.1)	7 (76.9)	1 (84.6)	0 (84.6)	1 (92.3)
E. faecium (32)	0.015	0.12	14 (43.8)	4 (56.2)	6 (75.0)	2 (81.2)	6 (100.0)
VanA phenotype (24)	0.03	0.12	6 (25.0)	4 (41.7)	6 (66.7)	2 (75.0)	6 (100.0)

[a] All *S. aureus* isolates, except 1, were methicillin (oxacillin) resistant. VanA phenotype, vancomycin and teicoplanin MIC results of ≥8 and ≥16 μg/ml, respectively. CoNS, coagulase-negative staphylococci, including 2 *S. capitis*, 1 *S. cohnii*, 69 *S. epidermidis*, 5 *S. haemolyticus*, and 3 *S. hominis* isolates.
[b] One vancomycin-resistant *E. faecalis* isolate showed an oritavancin MIC value of 1 μg/ml.

TABLE 2 Antimicrobial activity of oritavancin and comparator against a challenge set of molecularly characterized Gram-positive clinical isolates displaying elevated linezolid MIC results

Organism[a] (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates with indicated status according to[b]:					
				CLSI			EUCAST		
	Range	50%	90%	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
S. aureus (25)									
Oritavancin	0.015 to 0.12	0.03	0.06	100.0			100.0		
Clindamycin	≤0.25 to >2	>2	>2	16.0	4.0	80.0	8.0	8.0	84.0
Daptomycin	0.25 to 0.5	0.25	0.5	100.0			100.0		0.0
Erythromycin	≤0.25 to >2	>2	>2	4.8	19.0	76.2	8.0	4.0	88.0
Levofloxacin	0.25 to >4	>4	>4	12.0	4.0	84.0	12.0	4.0	84.0
Linezolid	4 to 32	8	16	36.0		64.0	36.0		64.0
Tetracycline	≤2 to >8	≤2	>8	84.0	0.0	16.0	66.7	14.3	19.0
TMP-SMX[c]	≤0.5 to 4	≤0.5	≤0.5	96.0		4.0	96.0	4.0	0.0
Vancomycin	0.5 to 2	1	2	100.0	0.0	0.0	100.0		0.0
CoNS (80)									
Oritavancin	≤0.008 to 0.12	0.03	0.12						
Clindamycin	≤0.25 to >2	1	>2	32.5	30.0	37.5	20.0	12.5	67.5
Daptomycin	0.12to1	0.5	0.5	100.0			100.0		0.0
Erythromycin	≤0.25 to >2	>2	>2	20.0	41.4	38.6	23.8	16.2	60.0
Levofloxacin	≤0.5 to >4	>4	>4	3.8	3.8	92.5	3.8	3.8	92.5
Linezolid	4 to >128	32	128	7.5		92.5	7.5		92.5
Oxacillin	≤0.25 to >2	>2	>2	6.2		93.8	6.2		93.8
Teicoplanin	≤2 to >8	4	8	92.3	6.4	1.3	58.2		41.8
Tetracycline	≤2 to >8	≤2	≤2	92.5	0.0	7.5	76.5	14.7	8.8
TMP-SMX[c]	≤0.5 to >2	>2	>2	16.2		83.8	18.3	36.6	45.1
Vancomycin	1to2	2	2	100.0	0.0	0.0	100.0		0.0
E. faecalis (13)									
Oritavancin	≤0.008 to 1	0.015	0.12	92.3[d]					
Ampicillin	≤1 to 4	≤1	2	100.0		0.0	100.0	0.0	0.0
Daptomycin	0.5 to 2	1	2	100.0					
Levofloxacin[e]	1 to >4	>4	>4	15.4	0.0	84.6			
Linezolid	4 to 16	8	16	0.0	46.2	53.8	46.2		53.8
Teicoplanin	≤2 to >8	≤2	>8	91.7	0.0	8.3	84.6		15.4
Tetracycline	≤0.25 to >8	>8	>8	15.4	0.0	84.6			
Vancomycin	1 to >16	1	>16	84.6	0.0	15.4	84.6		15.4
E. faecium (32)									
Oritavancin	≤0.008 to 0.12	0.015	0.12						
Ampicillin	>8 to >8	>8	>8	0.0		100.0	0.0	0.0	100.0
Daptomycin	0.5 to 4	2	2	100.0					
Levofloxacin[e]	>4 to >4	>4	>4	0.0	0.0	100.0			
Linezolid	4 to 64	8	32	0.0	25.0	75.0	25.0		75.0
Teicoplanin	≤2 to >8	>8	>8	29.6	3.7	66.7	25.0		75.0
Tetracycline	≤2 to >8	≤2	>8	50.0	0.0	50.0			
Vancomycin	1 to >16	>16	>16	21.9	3.1	75.0	21.9		78.1

[a] All *S. aureus* isolates, except 1, were methicillin (oxacillin) resistant. CoNS, coagulase-negative staphylococci, including 2 *S. capitis*, 1 *S. cohnii*, 69 *S. epidermidis*, 5 *S. haemolyticus*, and 3 *S. hominis* isolates.

[b] Breakpoint criteria were those from CLSI (22) and EUCAST (23), as available.

[c] TMP-SMX, trimethoprim-sulfamethoxazole.

[d] Breakpoint available for vancomycin-susceptible *E. faecalis* only. A total of 92.3% of all *E. faecalis* and 100.0% of vancomycin-susceptible *E. faecalis* isolates were susceptible to oritavancin. One *E. faecalis* isolate displaying a VanA phenotype (i.e., vancomycin and teicoplanin MIC values of ≥8 and ≥16 μg/ml, respectively) had an oritavancin MIC result of 1 μg/ml.

[e] For uncomplicated urinary tract infection only.

to a central monitoring laboratory (JMI Laboratories, North Liberty, IA). Bacterial identification was confirmed by the central laboratory using Vitek identification systems (bioMérieux, Hazelwood, MO) and/or matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA). Isolates received through the SENTRY Antimicrobial Surveillance Program that exhibited elevated MIC results for linezolid (i.e., MIC, ≥4 μg/ml) were molecularly characterized at the central laboratory. Characterization consisted of screening for *cfr* and *cfr*(B) (17) and *optrA* (18) and mutations in the 23S rRNA and ribosomal proteins (L3 and L4) (8, 9, 17) as previously described. Isolates were tested for susceptibility by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) document M 07-A10 guidelines (21). Testing was

performed centrally, and validation of the MIC values occurred by concurrent testing of reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212) (22). MIC interpretations were based on CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria (22, 23).

Totals of 48.0% (12/25), 16.0% (4/25), and 12.0% (3/25) of *S. aureus* isolates had *cfr*, 23S rRNA mutations, or L3/L4 alterations alone, respectively. Other *S. aureus* isolates (6/25 [24.0%]) showed a combination of linezolid resistance mechanisms (see Table S1 in the supplemental material). Oritavancin had modal MIC, MIC_{50}, and MIC_{90} results of 0.03, 0.03, and 0.06 μg/ml, respectively, against *S. aureus*, displaying elevated MIC values for linezolid (Table 1). Similar results were observed for oritavancin against Cfr-producing *S. aureus*. The MIC_{50} result for oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/ml) was 8- and 32-fold lower than those for daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/ml) and vancomycin ($MIC_{50/90}$, 1/2 μg/ml), respectively, against all *S. aureus* isolates, including those carrying *cfr* (Table 2).

CoNS (linezolid $MIC_{50/90}$, 32/128 μg/ml) showed a diverse array of linezolid resistance mechanisms and the highest linezolid MIC results observed among pathogens included in this study (Table 1; see also Table S1 in the supplemental material). Although often considered contaminants, CoNS isolates are also recognized as increasingly important causes of bloodstream and medical device-related infections in hospitalized patients (24). The majority of nosocomial CoNS isolates belong to clonal complex 2 (25–27), and some isolates associated with this lineage have demonstrated linezolid dependence (15, 16). Moreover, the linezolid resistance mechanisms observed among CoNS isolates have evolved considerably over time and become more complex (7). In this study, oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/ml) inhibited all CoNS isolates at ≤0.12 μg/ml and had MIC values that were 4- to 16-fold lower than those of daptomycin ($MIC_{50/90}$, 0.5/0.5 μg/ml) and 16- to 128-fold lower than those of vancomycin ($MIC_{50/90}$, 2/2 μg/ml) or teicoplanin ($MIC_{50/90}$, 4/8 μg/ml) (Table 2).

The majority of linezolid-nonsusceptible enterococci showed the G2576T alteration in 23S rRNA, and three isolates (6.7%) had a concomitant presence of *cfr*. Two *E. faecium* and seven *E. faecalis* isolates had the recently described *cfr*(B) variant and *optrA* ABC transporter, respectively (see Table S1 in the supplemental material). A total of 15.4% and 75.0% of linezolid-nonsusceptible *E. faecalis* and *E. faecium*, respectively, were vancomycin resistant (all VanA phenotype) (Tables 1 and 2). Oritavancin ($MIC_{50/90}$, 0.015/0.12 μg/ml) inhibited all enterococcal isolates at ≤0.12 μg/ml, except for one isolate of *E. faecalis* (MIC, 1 μg/ml) (Tables 1 and 2). Oritavancin ($MIC_{50/90}$, 0.015/0.12 μg/ml), ampicillin ($MIC_{50/90}$, ≤1/2 μg/ml), and daptomycin ($MIC_{50/90}$, 1/2 μg/ml) were active against *E. faecalis*, and oritavancin ($MIC_{50/90}$, 0.015/0.12 μg/ml) and daptomycin ($MIC_{50/90}$, 2/2 μg/ml) were also active against *E. faecium* (Table 2).

Oritavancin became clinically available in the United States and Europe as a single-dose treatment for ABSSSIs (20). The results obtained herein document potent *in vitro* activity of oritavancin against a collection of Gram-positive pathogens with elevated linezolid MICs, regardless of the linezolid resistance mechanism. Overall, oritavancin inhibited all tested isolates at ≤0.12 μg/ml (except for one isolate of vancomycin-resistant *E. faecalis*; MIC, 1 μg/ml), including isolates expressing newly characterized and transferable (plasmid-encoded) linezolid resistance mechanisms. The absence of *in vitro* cross-resistance between linezolid and oritavancin as documented in this study is likely to be based on the distinct mechanisms of action of these two agents (29, 30).

ACKNOWLEDGMENTS

We thank L. Duncan, M. Huband, M. Janechek, J. Oberholser, P. Rhomberg, J. Ross, J. Schuchert, J. Streit, and L. Woosley of JMI Laboratories (North Liberty, IA, USA) for technical support and/or assistance with manuscript preparation.

JMI Laboratories, Inc., has received research and educational grants in 2014–2015 from Achaogen, Actavis, Actelion, Allergan, American Proficiency Institute (API), AmpliPhi, Anacor, Astellas, AstraZeneca, Basilea, Bayer, BD, Cardeas, Cellceutix, CEM-102 Pharmaceuticals, Cempra, Cerexa, Cidara, CorMedix, Cubist, Debiopharm, Dipexium, Dong Wha, Durata, Enteris, Exela, Forest Research Institute, Furiex, Genentech, GSK, Helperby, ICPD, Janssen, Lannett, Longitude, Medpace, Meiji Seika Kasha, Melinta, Merck, Motif, Nabriva, Novartis, Paratek, Pfizer, Pocared, PTC Therapeutics, Rempex, Roche, Salvat, Scynexis, Seachaid, Shionogi, Tetraphase, Theravance, ThermoFisher, VenatoRX, Vertex, Wockhardt, and Zavante. Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance.

FUNDING INFORMATION

This surveillance study was sponsored by an educational/research grant from The Medicines Company (Parsippany, NJ, USA) via the SENTRY Antimicrobial Surveillance Program. JMI Laboratories also received compensation fees from The Medicines Company for services with regard to manuscript preparation. The Medicines Company had no involvement in the collection, analysis, or interpretation of data.

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