C-560 Oritavancin *In Vitro* Activity Against a Collection of Molecularly-characterized Staphylococci and Enterococci Displaying Elevated Linezolid MIC Values

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Abstract

Background: Oritavancin was approved by the US-FDA (2014) for the treatment of acute bacterial skin and skin structure infections caused by gram-positive organisms.

Methods: 105 staphylococci (linezolid MIC, 4 - >128 μg/mL) and 45 enterococci (linezolid MIC, 4 – 64 μg/mL) were included. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MICs used FDA (oritavancin), CLSI (2015) and/or EUCAST (2015) criteria. Mutations in 23S rRNA, L3 and L4, and the presence of *cfr* were investigated.

Results: 16.0% (4/25), 12.0% (3/25) and 48.0% (12/25) of *S. aureus* had 23S rRNA mutations, L3/L4 alterations and *cfr*, respectively. Other *S. aureus* showed a combination of linezolid resistance mechanisms. Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) had MIC_{50} results 8- and 32-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and vancomycin ($MIC_{50/90}$, 1/1-2 μg/mL), respectively, against all *S. aureus* or those carrying *cfr* only. The majority of enterococci showed the G2576T alteration and three isolates (6.7%) had a concomitant presence of *cfr.* Oritavancin ($MIC_{50/90}$, 0.015/0.12 μg/mL) showed potent activity against *E. faecalis* (linezolid $MIC_{50/90}$, 8/16 μg/mL) and *E. faecium* (linezolid $MIC_{50/90}$, 8/32 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 daptomycin ($MIC_{50/90}$, 2/2 μg/mL) was also active against *E. faecium.* 75.0% (24/32) of the *E. faecium* were vancomycin-resistant (VanA-phenotype) and oritavancin had a MIC_{100} of 0.12 μg/mL against this subset. Coagulase-negative staphylococci (linezolid $MIC_{50/90}$, 32/128 μg/mL) showed a diverse array of linezolid resistance mechanisms and highest linezolid MICs. Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) had MICs 4- to 16-fold lower than daptomycin ($MIC_{50/90}$, 0.5/0.5 μg/mL) and 16- to 128-fold lower than vancomycin ($MIC_{50/90}$, 2/2 μg/mL) or teicoplanin ($MIC_{50/90}$, 4/8 μg/mL) against coagulase-negative staphylococci.

Conclusions: Oritavancin had potent *in vitro* activity against this collection of gram-positive isolates exhibiting elevated linezolid MICs. These results confirm the absence of cross-resistance between linezolid and oritavancin.

Background

Staphylococcus aureus, particularly methicillin-resistant *S. aureus* (MRSA), coagulase-negative staphylococci (CoNS), *Enterococcus faecium* and multidrug-resistant (MDR) streptococci are frequently isolated pathogens responsible for a variety of clinical infections. MRSA and *E. faecium* are among the so-called ESKAPE organisms (*E. faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.), which cause the majority of USA nosocomial infections and are refractory to most clinically available agents.

Linezolid was the first oxazolidinone approved for complicated skin and skin structure infections (cSSSIs) and one of the few drugs approved for the treatment of vancomycin-resistant *E. faecium* (VRE) infections. Its oral formulation makes linezolid an attractive alternative. However, although rare, resistance occurs, especially after prolonged use, and new resistance genes encoding for methyltransferases (i.e. *cfr* and *cfr*(B)) and ABC transporters (i.e. *optrA*) have been described. This study was conducted to evaluate the *in vitro* activity of oritavancin against a molecularly-characterized set of isolates displaying elevated linezolid MIC results.

Methods

Bacterial strain collection. A total of 105 staphylococci (linezolid MIC range, 4 - >128 μg/mL) and 45 enterococci (linezolid MIC range, 4 – 64 μg/mL) were included (Table 1). Isolates were recovered from a network of medical centers as part of the SENTRY Antimicrobial Surveillance Program and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, USA). Bacterial identification was confirmed by the central laboratory using Vitek Identification Systems (bioMerieux, Hazelwood, Missouri, USA), matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, Massachusetts, USA), and/or 16S rRNA sequencing.

Detection of linezolid resistance mechanisms. Isolates received as part of the SENTRY Antimicrobial Surveillance Program that showed elevated MIC results for linezolid (i.e. MIC, ≥4 μg/mL) were selected for further molecular characterization at the central laboratory. Presence of *cfr*, and mutations in the 23S rRNA and ribosomal proteins (L3 and L4) were investigated by PCR and sequencing of amplicons on both strands. 23S rRNA and ribosomal protein sequences obtained were compared to those from the respective wildtype species using the Lasergene® software package (DNASTAR; Madison, Wisconsin).

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was centrally performed using panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These panels provide oritavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event.

Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212). All QC results were within published acceptable ranges (M100-S25). MIC interpretations for oritavancin were based on the Food and Drug Administration (FDA) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) breakpoint criteria. Interpretive criteria from CLSI and EUCAST were applied for comparator agents, as available.

Results

- Table 1 describes the challenge set of organisms utilized in this study. A total of 16.0% (4/25), 12.0% (3/25) and 48.0% (12/25) of *S. aureus* had 23S rRNA mutations, L3/L4 alterations and *cfr*, respectively. Other *S. aureus* showed a combination of linezolid resistance mechanisms.
- Oritavancin had modal MIC, MIC_{50} and MIC_{90} results of 0.03, 0.03 and 0.06 μg/mL, respectively, when tested against all *S. aureus* displaying elevated MIC values for linezolid (Table 2). Similar results were observed for oritavancin against Cfr-producing *S. aureus*.
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) had an MIC_{50} result that was 8- and 32-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and vancomycin ($MIC_{50/90}$, 1/2 μg/mL), respectively, against all *S. aureus*, including those carrying *cfr* (Table 3).
- Coagulase-negative staphylococci (linezolid $MIC_{50/90}$, 32/128 μg/mL) showed a diverse array of linezolid resistance mechanisms and highest linezolid MIC results among pathogens included in the study (Tables 1 and 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) had MIC values 4- to 16-fold lower than daptomycin ($MIC_{50/90}$, 0.5/0.5 μg/mL) and 16- to 128-fold lower than vancomycin ($MIC_{50/90}$, 2/2 μg/mL) or teicoplanin ($MIC_{50/90}$, 4/8 μg/mL) against coagulase-negative staphylococci (Table 3).
- The majority of 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 newly described *cfr*(B) variant and *optrA* ABC transporter (Table 1).
- A total of 15.4% and 75.0% of linezolid-non-susceptible *E. faecalis* and *E. faecium* were vancomycin-resistant (all VanA-phenotype), respectively (Table 3). Oritavancin ($MIC_{50/90}$, 0.015/0.12 μg/mL) inhibited all isolates at ≤0.12 μg/mL, except for one isolate (MIC, 1 μg/mL; Tables 2 and 3).
- 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 active against *E. faecium* (Table 3).

Table 1. Summary of gram-positive isolates exhibiting elevated linezolid MIC results with characterized resistance mechanisms utilized in this study.

Organism/ No. tested	MIC (μg/mL)		Linezolid resistance mechanism[a]			
	Linezolid	Oritavancin	23S rRNA	L3	L4	*cfr*/*optrA*[b]
S. aureus						
12	4 - 16	0.015 - 0.12	WT	WT	WT	*cfr*
4	8 - 16	0.03 - 0.06	G2576T	WT	WT	-
1	8	0.03	G2576T	WT	WT	*cfr*
2	4 - 8	0.03	WT	ΔS145	WT	-
1	4	0.03	WT	WT	A118V	*cfr*
1	8	0.03	WT	ΔS145, G155D	WT	-
1	32	0.03	G2576T	ΔS145	WT	-
1	16	0.06	G2576T	ΔH146, P151L	WT	*cfr*
1	16	0.03	G2576T	G152D, D159E	WT	*cfr*
1	32	0.03	G2576T	D159E, G152D	WT	*cfr*
E. faecalis						
5	4 - 16	0.008 - 1	G2576T	WT	WT	-
1	16	0.015	WT	WT	WT	*cfr*
7	4 - 8	0.008 - 0.03	WT	WT	WT	*optrA*
E. faecium						
3	4 - 8	0.015 - 0.12	G2576T	WT	WT	*cfr*
29	4 - 64	0.008 - 0.12	G2576T	WT	WT	-
S. epidermidis						
1	>128	0.12	C2534T, T2504A	G152D, D159Y	WT	-
2	32 - 128	0.008 - 0.03	G2576T	G137S, H146P, F147Y, M156T	71G72 insertion	-
3	64 - 128	0.03 - 0.06	G2576T	G137S, H146P, M156T	71G72 insertion	-
1	>128	0.06	G2576T	G137S, H146P, F147Y, M156T	71G72 insertion	*cfr*
1	64	0.06	G2576T	G137S, H146P, M156T	WT	-
2	16 - 32	0.06 - 0.12	G2576T	M156	WT	-
1	16	0.03	G2576T	F147L	WT	-
1	64	0.03	WT	F147L	WT	*cfr*
1	32	0.03	G2576T	H146P, M156T	WT	-
1	64	0.12	G2576T	H146R, M156T	71G72 insertion	-
1	32	0.03	G2576T	H146R, V154L, M156T	71G72 insertion	-
1	128	0.03	G2576T	G137S, H146P, M156R	G69R, 71G72 insertion	-
1	128	0.12	G2576T	H146R, M156R	71G72 insertion	-
1	32	0.03	G2576T	H146P, M156T	WT	-
1	64	0.03	G2576T	H146R, M156T	71G72 insertion	-
1	32	0.015	G2576T	V154L, M156T	WT	-
1	128	0.06	G2576T	H146R, V154L, M156T	71G72 insertion	-
1	64	0.03	G2576T	H146R, V154L, M156T	WT	-
2	64 - 128	0.03 - 0.06	G2576T	G137D, H146R, V154L, M156T	71G72 insertion	-
15	8 - 128	0.03 - 0.12	G2576T	WT	WT	-
2	64 - >128	0.015 - 0.03	G2576T	WT	WT	*cfr*
1	128	0.06	T2504A	G152D, D159E, A160P	WT	-
6	4 -32	0.015 - 0.06	WT	WT	WT	*cfr*
1	>128	0.06	T2504A	G152D, D159E, A160P	WT	-
1	>128	0.06	T2504A, C2534T	G152D, D159Y	WT	-
1	4	0.06	WT	A157R	WT	-
1	16	0.03	WT	A157R	WT	*cfr*
1	16	0.03	WT	V154L, A157R	WT	-
1	128	0.12	WT	G137S, H146Q, V154L, A157R	71G72 insertion	*cfr*
2	16	0.03 - 0.06	WT	H146Q	WT	-
1	4	0.12	WT	S158Y, D159Y	WT	-
1	16	0.06	WT	V154L, A157R	71G72 insertion	-
1	128	0.06	WT	V154L, A157R	WT	*cfr*
1	8	0.03	WT	V154L, A157R	P171S	-
5	16	0.03 - 0.06	WT	H146Q, V154L, A157R	71G72 insertion	-
4	128 - >128	0.008 - 0.06	WT	H146Q, V154L, A157R	71G72 insertion	*cfr*
S. capitis						
1	16	0.008	G2576T	T83A	WT	-
1	8 - 32	0.008	WT	WT	WT	*cfr*
S. conii						
1	32	0.008	WT	WT	WT	*cfr*
S. haemolitycus						
3	8 - 16	0.015 - 0.03	G2576T	WT	WT	-
1	32	0.03	G2576T	M156T	WT	-
1	4	0.06	WT	M156T	WT	*cfr*
S. hominis						
1	32	0.008	G2576T	M156T	WT	-
1	32	0.008	G2576T	M156T, F147I	S77Y	-
1	4	0.015	WT	M169L	WT	*cfr*

a. WT = wildtype sequence, which was defined to be identical to those from the respective linezolid-susceptible control species. Alterations in the 23S rRNA were determined based on the *Escherichia coli* nucleotide numbering, while L3 and L4 mutations are described in terms of amino acid alteration and position.
b. Cfr and OtrpA are plasmid-encoded methyltransferase and ABC transporter, respectively. Cfr-producing *E. faecium* includes two isolates carrying the newly described *cfr*(B) variant.

Table 2. Antimicrobial activity and MIC distribution for oritavancin when tested against a challenge set of molecularly-characterized gram-positive clinical isolates displaying elevated linezolid MIC results.

Isolates[a] (No. tested)	MIC (μg/mL)		Number (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)	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* were methicillin-resistant, except for one isolate. VanA-phenotype = vancomycin and teicoplanin MIC results of ≥8 and ≥16 μg/mL, respectively. CoNS = coagulase-negative staphylococci and includes: two *S. capitis*, one *S. cohnii*, 69 *S. epidermidis*, five *S. haemolyticus* and three *S. hominis*. One vancomycin-resistant *E. faecalis* showed an oritavancin MIC value of 1 μg/mL.

Table 3. Antimicrobial activity of oritavancin and comparator agents tested against a challenge set of molecularly-characterized gram-positive clinical isolates displaying elevated linezolid MIC results.

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

a. All *S. aureus* were methicillin-resistant, except for one isolate. CoNS = coagulase-negative staphylococci (includes: two *S. capitis*, one *S. cohnii*, 69 *S. epidermidis*, five *S. haemolyticus* and three *S. hominis*).
b. Breakpoint criteria for oritavancin according to the FDA package insert (CLSI column) and EUCAST, as available. *S. aureus* at ≤0.12 μg/mL for susceptible; *E. faecalis* at ≤0.12 μg/mL for susceptible (FDA breakpoint for vancomycin-susceptible only). Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and EUCAST (2015), as available.
c. 92.3% of all *E. faecalis* and 100.0% of vancomycin-susceptible *E. faecalis* were susceptible to oritavancin. One *E. faecalis* displaying a VanA-phenotype (i.e. vancomycin and teicoplanin MIC values of >4 and >8 μg/mL, respectively) had an oritavancin MIC result of 1 μg/mL.

Conclusions

- Oritavancin had potent *in vitro* activity against this collection of Gram-positive isolates exhibiting elevated linezolid MIC results, including isolates with newly characterized and transferable (plasmid-encoded) linezolid resistance mechanisms.
- All Gram-positive isolates exhibiting elevated linezolid MIC results included in this study were inhibited by oritavancin at ≤0.12 μg/mL, except for one vancomycin-resistant (VanA-phenotype) *E. faecalis* (MIC, 1 μg/mL).
- The results presented here confirm the absence of *in vitro* cross-resistance between linezolid and oritavancin. Moreover, these data suggest that oritavancin could be an option for treating ABSSSIs, including those caused by isolates displaying decreased susceptibility to linezolid.

Disclosures

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