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Oritavancin *In Vitro* Activity Against a Collection of Gram-Positive Clinical Isolates Causing Bone and Joint Infections, Including Osteomyelitis, in United States and European Hospitals (2012–2016)

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Amended Abstract

Background: Bone and joint infections (BJI) are usually hard to treat and regularly involve prolonged and systemic use of antibiotics. Oritavancin has demonstrated *in vitro* activity against gram-positive isolates that are associated with infections, including BJI. This study evaluated the activity of oritavancin and comparators against a recent collection of pathogens causing BJI, including osteomyelitis.

Methods: This study included 992 organisms recovered from patients with BJI at 63 medical sites in the US and Europe during the 2012-2016 SENTRY Antimicrobial Surveillance Program. Isolates were identified by standard biochemical algorithms and MALDI-TOF. Susceptibility testing followed CLSI methods, and CLSI criteria were used to interpret MICs.

Results: *Staphylococcus aureus* (65.6%) was the most common gram-positive pathogen associated with BJI followed by coagulase-negative staphylococci (CoNS; 13.3%) and β-hemolytic streptococci (BHS; 10.9%). Enterococci and viridans group streptococci (VGS) were less frequently encountered. All *S. aureus* (32.4% MRSA) isolates were inhibited by oritavancin at the susceptible breakpoint (≤0.12 μg/mL). Oritavancin showed MIC results that were at least 4-fold lower than comparators against MRSA. All CoNS (64.4% methicillin-resistant) were inhibited by oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) at ≤0.12 μg/mL with MIC_{50} values at least 8-fold lower than vancomycin ($MIC_{50/90}$, 1/2 μg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), and ceftaroline ($MIC_{50/90}$, 0.25/1 μg/mL). Vancomycin ($MIC_{50/90}$, 1/2 μg/mL), daptomycin ($MIC_{50/90}$, 1/1 μg/mL), ampicillin ($MIC_{50/90}$, 1/1 μg/mL), and linezolid ($MIC_{50/90}$, 1/1 μg/mL) were similarly active against *Enterococcus faecalis*; oritavancin ($MIC_{50/90}$, 0.015/0.03 μg/mL) displayed MIC values up to 32-fold lower than these agents. *E. faecium* isolates (43.8% vancomycin-resistant) were resistant to most comparator drugs tested, exceptions being daptomycin ($MIC_{50/90}$, 2/2 μg/mL) and linezolid ($MIC_{50/90}$, 1/1 μg/mL); oritavancin ($MIC_{50/90}$, 0.004/0.06 μg/mL) inhibited all *E. faecium* at ≤0.06 μg/mL. Ceftaroline ($MIC_{50/90}$, ≤0.008/0.015 μg/mL), oritavancin ($MIC_{50/90}$, 0.03/0.012 μg/mL), and penicillin ($MIC_{50/90}$, ≤0.06/ ≤0.06 μg/mL) were the most potent agents tested against BHS. Oritavancin ($MIC_{50/90}$, 0.008/0.12 μg/mL) showed the lowest MIC values against VGS.

Conclusions: Oritavancin demonstrated potent activity against gram-positive isolates causing BJI, including osteomyelitis, in the US and Europe (2012–2016). These *in vitro* data warrant further consideration to develop oritavancin as a treatment for infections, such as BJI.

Introduction

- Bone and joint infections (BJIs) comprise a series of disorders that include septic arthritis, osteomyelitis, and prosthetic joint infections
  - BJIs may be life-threatening and generally require an aggressive and often complex management strategy in the acute phase that uses an antimicrobial treatment with a rapid and effective bactericidal effect
- BJIs may become chronic; therefore, the need is greater for antimicrobials that are effective in biofilm and adaptive to long-term treatment
- Common therapies include antimicrobial agents with gram-positive and gram-negative coverage
- Vancomycin is often considered for empiric treatment, because a high incidence of infections in the US are caused by community-associated methicillin-resistant *S. aureus* (MRSA)
- Oritavancin is a semisynthetic bactericidal lipoglycopeptide approved by the Food and Drug Administration (FDA; 2014) and by the European Medicines Agency (EMA; 2015) to treat adults with acute bacterial skin and skin structure infections (ABSSSIs)
- This study evaluated the activity of oritavancin against pathogens responsible for BJI, including osteomyelitis

Materials and Methods

Bacterial isolates

- A total of 651 *S. aureus*, 132 coagulase-negative staphylococci (CoNS), 108 β-hemolytic streptococci (BHS), 70 *Enterococcus* spp., and 31 viridans group streptococci (VGS) causing BJI were included (2012–2016)
- Isolates were collected from 29 medical sites in the US and 15 European countries (34 sites), including Russia (3 sites), Turkey (2 sites), Ukraine (1 site), and Israel (1 site)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- Participating laboratories initially identified isolates and JMI confirmed bacterial identifications by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07–A10 document
- Testing used reference 96-well panels manufactured by JMI Laboratories
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619)
- Breakpoint criteria for comparator agents were from CLSI (M100-S26)

Results

- *S. aureus* (65.6%) was the most common pathogen associated with BJI, followed by CoNS (13.3%) and BHS (10.9%) (Table 1)
- A total of 32.4% of *S. aureus* isolates were methicillin-resistant (41.4 % in the US and 20.6% in Europe), while 64.4% of CoNS (66.2% in the US and 62.5% in Europe) exhibited this phenotype (Tables 1 and 2)
- Most tested agents demonstrated *in vitro* activity against methicillin-susceptible *S. aureus* (MSSA) (≥93.0% susceptible)
  - Oritavancin (100.0% susceptible), daptomycin (99.5% susceptible), linezolid (100.0% susceptible), and vancomycin (100.0% susceptible) were the most active against MRSA (Table 2)
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) MIC results were at least 8-fold lower than those of daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), linezolid ($MIC_{50/90}$, 1/1 μg/mL), and vancomycin ($MIC_{50/90}$, 1/1 μg/mL) when tested against MRSA (Table 2)
- Only daptomycin, linezolid, and vancomycin (100.0% of isolates susceptible) showed *in vitro* activity against CoNS. Oritavancin had the lowest MIC_{50} and MIC_{90} results against CoNS (Table 2), with all isolates inhibited at ≤0.12 μg/mL
- All tested *E. faecalis* isolates were inhibited by oritavancin at ≤0.12 μg/mL (Table 1). High susceptibility rates for ampicillin (100.0% susceptible), daptomycin (100.0%), linezolid (100.0%), and vancomycin (98.1%) were observed against *E. faecalis* (Table 2)
- *E. faecium* isolates, all of which were inhibited by oritavancin at 0.06 μg/mL (Table 1), linezolid and daptomycin (100.0% susceptible) exhibited *in vitro* activity whereas the other tested agents had marginal coverage (43.8–100.0% resistant) (Table 2)
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL; 98.1% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL; 100.0% susceptible) were the most potent drugs against BHS (Table 2)
- Oritavancin ($MIC_{50/90}$, 0.008/0.12 μg/mL; 100.0% susceptible) was the most active agent against VGS
- Daptomycin, linezolid, and vancomycin were also active (100.0% susceptible) against VGS, whereas clindamycin (74.2% susceptible) had marginal activity (Table 2)

Table 1. Antimicrobial activity of oritavancin tested against the main organisms and organism groups of isolates included in this study

Organism / organism group (n)	Number of isolates at MIC (μg/mL; cumulative %)								
	MIC_{50}	MIC_{90}	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
S. aureus (651)	0.03	0.06	33 (5.1%)	273 (47.0%)	220 (80.8%)	98 (95.9%)	27 (100.0%)		
MSSA (440)	0.03	0.06	22 (5.0%)	188 (47.7%)	143 (80.2%)	71 (96.4%)	16 (100.0%)		
MRSA (211)	0.03	0.06	11 (5.2%)	85 (45.5%)	77 (82.0%)	27 (94.8%)	11 (100.0%)		
CoNS (132)	0.03	0.06	33 (25.0%)	18 (38.6%)	42 (70.5%)	31 (93.9%)	8 (100.0%)		
E. faecalis (54)	0.015	0.03	17 (31.5%)	25 (77.8%)	10 (96.3%)	0 (96.3%)	2 (100.0%)		
E. faecium (16)	0.004	0.06	9 (56.2%)	2 (68.8%)	2 (81.2%)	3 (100.0%)			
BHS (108)	0.03	0.12	9 (8.3%)	18 (25.0%)	33 (55.6%)	18 (72.2%)	21 (91.7%)	7 (98.1%)	2 (100.0%)
VGS (31)	0.008	0.12	17 (54.8%)	5 (71.0%)	4 (83.9%)	1 (87.1%)	3 (96.8%)	1 (100.0%)	

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci; BHS, β-hemolytic streptococci; VGS, viridans group streptococci

Table 2. Antimicrobial activity of oritavancin and comparator agents against contemporary gram-positive isolates causing BJIs in the US and Europe

Organism/ group[a] (no.) Antimicrobial agent[b]	MIC_{50}	MIC_{90}	Range	CLSI[c] %S	%I	%R
MSSA (440)						
Oritavancin	0.03	0.06	≤0.002 — 0.12	100	-	-
Ceftaroline	0.25	0.25	0.12 — 0.5	100	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	97.3	0.0	2.7
Daptomycin	0.25	0.5	≤0.12 — 1	100	-	-
Erythromycin	0.25	>8	≤0.12 — >8	73.2	6.4	20.5
Levofloxacin	≤0.12	0.25	≤0.12 — >4	93.6	0.0	6.4
Linezolid	1	1	≤0.12 — 2	100	-	0.0
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	96.6	0.2	3.2
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	99.5	-	0.5
Vancomycin	1	1	≤0.12 — 2	100	0.0	0.0
MRSA (211)						
Oritavancin	0.03	0.06	0.004 — 0.12	100	-	-
Ceftaroline	0.5	1	0.25 — 2	96.8	3.2	0.0
Clindamycin	≤0.25	>2	≤0.25 — >2	74.9	0.0	25.1
Daptomycin	0.25	0.5	≤0.12 — 2	99.5	-	-
Erythromycin	>8	>8	≤0.12 — >8	25.6	0.5	73.9
Levofloxacin	4	>4	≤0.12 — >4	29.9	1.9	68.2
Linezolid	1	1	0.25 — 2	100	-	0.0
Tetracycline	≤0.5	8	≤0.5 — >8	89.5	1.4	9
TMP-SMX	≤0.5	≤0.5	≤0.5 — >4	97.6	-	2.4
Vancomycin	1	1	≤0.12 — 2	100	0.0	0.0
CoNS (132)[d]						
Oritavancin	0.03	0.06	≤0.002 — 0.12	-	-	-
Ceftaroline	0.25	1	≤0.06 — 2	-	-	-
Clindamycin	≤0.25	>2	≤0.25 — >2	66.7	0.8	32.6
Daptomycin	0.25	0.5	≤0.12 — 1	100	-	-
Erythromycin	>8	>8	≤0.12 — >8	40.9	0.8	58.3
Levofloxacin	0.25	>4	≤0.12 — >4	59.1	4.5	36.4
Linezolid	0.5	1	0.25 — 2	100	-	0
Oxacillin	2	>2	≤0.25 — >2	35.6	-	64.4
Tetracycline	≤0.5	>8	≤0.5 — >8	84.1	1.5	14.4
TMP-SMX	≤0.5	>4	≤0.5 — >4	74.2	-	25.8
Vancomycin	1	2	≤0.12 — 2	100	0.0	0.0
***E. faecalis* (54)**						
Oritavancin	0.015	0.03	0.004 — 0.12	100	-	- [e]
Ampicillin	1	1	≤0.5 — 4	100	-	0.0
Daptomycin	1	1	≤0.25 — 2	100	-	-
Erythromycin	16	>16	≤0.12 — >16	13.9	33.3	52.8
Levofloxacin	1	>4	≤0.5 — >4	77.8	0.0	22.2[f]
Linezolid	1	1	≤0.25 — 2	100	0.0	0.0
Tetracycline	>8	>8	≤1 — >8	20.4	0.0	79.6
Vancomycin	1	2	≤0.5 — >16	98.1	0.0	1.9

Organism/ group[a] (no.) Antimicrobial agent[b]	MIC_{50}	MIC_{90}	Range	CLSI[c] %S	%I	%R
***E. faecium* (16)**						
Oritavancin	0.004	0.06	0.002 — 0.06	-	-	-
Ampicillin	>8	>8	>8	0.0	-	100
Daptomycin	2	2	0.5 — 2	100	-	-
Erythromycin	>16	>16	4 — >16	0.0	6.7	93.3
Levofloxacin	>4	>4	>4	0.0	0.0	100[f]
Linezolid	1	1	0.5 — 2	100	0.0	0.0
Tetracycline	>8	>8	≤0.5 — >8	25	6.2	68.8
Vancomycin	1	>16	0.5 — >16	56.2	0.0	43.8
BHS (108)[g]						
Oritavancin	0.03	0.12	0.008 — 0.5	98.1	-	-
Daptomycin	0.12	0.25	≤0.06 — 1	100	-	-
Ceftaroline	≤0.008	0.015	≤0.008 — 0.03	100.0	-	-
Clindamycin	≤0.25	>2	≤0.25 — >2	77.6	0.9	21.5
Erythromycin	≤0.12	>4	≤0.12 — >4	62	0.0	38
Levofloxacin	0.5	1	0.12 — >4	99.1	0.0	0.9
Linezolid	1	1	0.5 — 2	100	-	-
Penicillin	≤0.06	≤0.06	≤0.06	100	-	-
Tetracycline	>8	>8	≤0.5 — >8	45.8	3.7	50.5
TMP-SMX	≤0.5	≤0.5	≤0.5 — 1	-	-	-
Vancomycin	0.25	0.5	0.12 — 0.5	100	-	-
VGS (31)[h]						
Oritavancin	0.008	0.12	0.001 — 0.25	100	-	-
Daptomycin	0.5	1	0.12 — 1	100	-	-
Ceftaroline	0.015	0.015	0.015	-	-	-
Clindamycin	≤0.25	>2	≤0.25 — >2	74.2	0.0	25.8
Erythromycin	1	>4	≤0.12 — >4	41.9	0.0	58.1
Levofloxacin	1	2	0.25 — >4	90.3	0.0	9.7
Linezolid	0.5	1	0.25 — 1	100	-	-
Penicillin	≤0.06	1	≤0.06 — 8	80.6	12.9	6.5
Tetracycline	4	>8	≤0.5 — >8	45.2	6.5	48.4
TMP-SMX	≤0.5	2	≤0.5 — >4	-	-	-
Vancomycin	0.5	1	0.25 — 1	100	-	-

[a] MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci; BHS, β-hemolytic streptococci; VGS, viridans group streptococci

[b] TMP-SMX, trimethoprim-sulfamethoxazole

[c] Breakpoint criteria for oritavancin and comparator agents were those from CLSI (2016), as available."-" breakpoint not available. Breakpoint for *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* applied to all beta-hemolytic streptococci. *S. anginosus* group applied to all viridans group streptococci

[d] Includes: *Staphylococcus capitis* (10), *S. caprae* (6), *S. cohnii* (1), *S. epidermidis* (76), *S. haemolyticus* (7), *S. hominis* (7), *S. lugdunensis* (16), *S. pettenkoferi* (1), *S. pseudintermedius* (1), *S. simulans* (3), *S. warneri* (4)

[e] Breakpoint for vancomycin-susceptible *E. faecalis* applied for all isolates.

[f] Uncomplicated UTI only

[g] Includes: *Streptococcus agalactiae* (54), *S. dysgalactiae* (25), *S. pyogenes* (29)

[h] Includes: *Streptococcus anginosus* (7), *S. constellatus* (3), *S. gordonii* (2), *S. mitis* (1), *S. mitis* group (3), *S. mitis/oralis* (4), *S. oralis* (6), *S. parasanguinis* (2), *S. salivarius* (2), *S. sanguinis* (1)

Conclusions

- Staphylococcal isolates were the most frequent pathogens responsible for BJI in this study population
- A total of 32.4% of staphylococcal isolates were methicillin-resistant, which may complicate empiric treatment or limit treatment options
- Oritavancin demonstrated potent *in vitro* activity against common gram-positive isolates that caused BJI in the US and Europe (2012–2016), making oritavancin a promising candidate for treating BJI, including osteomyelitis caused by gram-positive cocci

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