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Oritavancin Activity against Gram-Positive Pathogens causing Bone and Joint Infections in European Medical Centres (2015–2019)

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Introduction

- Oritavancin is a long-acting lipoglycopeptide with prolonged tissue exposure at the site of infection approved by the European Medicines Agency and US-FDA for treating acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive (GP) pathogens.
- Due to these characteristics, oritavancin has been considered as an alternative agent to short-acting antibiotics for difficult-to-treat infections, such as bone and joint infections (BJI).
- This study assessed the *in vitro* activity of oritavancin and comparators against a contemporary collection of Gram-positive isolates causing BJI in Europe.

Materials and Methods

Bacterial isolates

- A total of 451 Gram-positive cocci were collected from patients with BJI between 2015 and 2019. Only isolates (1 per patient per infection episode) determined to be clinically significant by local criteria as the probable cause of infection were included.
- The isolates were recovered from 30 medical centres in Western (W-EU; 9 countries; 414 isolates) and Eastern (E-EU; 5 countries; 37 isolates) Europe.
- Gram-positive pathogens included 313 *Staphylococcus aureus*, 57 beta-haemolytic streptococci (BHS), 42 coagulase-negative staphylococci (CoNS), 19 *Enterococcus faecalis*, and 13 viridans group streptococci (VGS). Pathogen distribution is shown in Figure 1.
- Bacteria were identified by standard microbiology methods and/or MALDI-TOF.

Susceptibility testing

- The broth microdilution method was conducted according to CLSI guidelines (M07, 2018). Frozen-form panels were manufactured by JMI Laboratories (North Liberty, Iowa, USA) and contained cation-adjusted Mueller-Hinton broth, with 2.5–5% lysed horse blood added for streptococci.
- Oritavancin minimal inhibitory concentrations (MICs) were determined in the presence of polysorbate-80 (0.002%).
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619).
- Susceptibility determinations were based on EUCAST (2020) breakpoint criteria. For comparison, the oritavancin CLSI breakpoint for vancomycin-susceptible *E. faecalis* was applied to all *E. faecalis* isolates.

Results

- Oritavancin was active against *S. aureus* isolates ($MIC_{50/90}$, 0.03/0.03 mg/L) regardless of the European region (W-EU, $MIC_{50/90}$, 0.015/0.03 mg/L; E-EU, $MIC_{50/90}$, 0.03/0.03 mg/L).
- Oritavancin retained potent *in vitro* activity against methicillin-resistant *S. aureus* (MRSA; $MIC_{50/90}$, 0.015/0.03 mg/L; Table 1).
  - Oritavancin inhibited all MRSA and MSSA isolates at ≤0.06 and ≤0.12 mg/L, respectively (Figure 2)
- Oritavancin, vancomycin, linezolid, teicoplanin, and daptomycin inhibited all *S. aureus* isolates at their respective susceptible breakpoints.
- MRSA rates varied among European regions (W-EU, 16.2%; E-EU, 48.3%); however, based on MIC_{90}, oritavancin showed consistent potency (MIC_{90}, 0.03 mg/L) regardless of region (Table 1).
- Oritavancin inhibited all CoNS isolates at ≤0.12 mg/L, which is the EUCAST susceptible breakpoint for *S. aureus* (Table 2).
  - All CoNS isolates were susceptible to daptomycin and vancomycin.
- Oritavancin ($MIC_{50/90}$, 0.015/0.03 mg/L), vancomycin ($MIC_{50/90}$, 1/2 mg/L), ampicillin ($MIC_{50/90}$, 1/2 mg/L), and linezolid ($MIC_{50/90}$, 1/2 mg/L) were also active against *E. faecalis* isolates (100% susceptible; Table 2).
- Oritavancin showed activity against BHS ($MIC_{50/90}$, 0.06/0.25 mg/L; 96.5% susceptible), as did vancomycin, penicillin, linezolid, and daptomycin (100% susceptible; Table 2).
  - Only 2 (3.5%) BHS isolates among the entire collection (both from France), 1 *S. pyogenes* and 1 *S. dysgalactiae*. were non-susceptible to oritavancin (MIC of ≥0.5 mg/L).
- Oritavancin and vancomycin inhibited all VGS isolates at their respective susceptible breakpoints (Table 2).
  - Penicillin (92.3% susceptible), teicoplanin (100% susceptible), and vancomycin (100% susceptible) were also active against VGS isolates (Table 2).
- No difference in oritavancin activity against Gram-positive pathogens causing BJI were observed between Eastern and Western Europe.

Table 1. Antimicrobial activity of oritavancin and comparator agents tested against *S. aureus* isolates causing BJI in European hospitals.

Organisms / Antimicrobial agent	All isolates			Western Europe			Eastern Europe		
	MIC (mg/L)		EUCAST[a]	MIC (mg/L)		EUCAST[a]	MIC (mg/L)		EUCAST[a]
	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S
MSSA (*n*=253)				**MSSA (*n*=238)**			**MSSA (*n*=15)**		
Oritavancin	0.03	0.06	100.0	0.03	0.06	100.0	0.03	0.03	100.0
Ceftaroline	0.25	0.25	100.0 [b]	0.25	0.25	100.0 [b]	0.25	0.25	100.0 [b]
Clindamycin	≤0.25	≤0.25	100.0	≤0.25	≤0.25	100.0	≤0.25	≤0.25	100.0
Daptomycin	0.25	0.5	100.0	0.25	0.5	100.0	0.25	0.5	100.0
Erythromycin	0.25	>8	78.7	0.25	>8	77.7	0.25	0.25	93.3
Linezolid	1	2	100.0	1	2	100.0	1	2	100.0
Teicoplanin	≤0.5	≤0.5	100.0	≤0.5	≤0.5	100.0	≤0.5	1	100.0
Tetracycline	≤0.5	≤0.5	98.0	≤0.5	≤0.5	98.7	≤0.5	>8	86.7
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0
MRSA (*n*=60)				**MRSA (*n*=46)**			**MRSA (*n*=14)**		
Oritavancin	0.015	0.03	100.0	0.015	0.03	100.0	0.015	0.03	100.0
Ceftaroline	1	2	88.6 [b]	1	1	90.6 [b]	1	2	83.3 [b]
Clindamycin	≤0.25	>2	78.3	≤0.25	>2	80.4	≤0.25	>2	71.4
Daptomycin	0.25	0.5	100.0	0.25	0.5	100.0	0.25	0.5	100.0
Erythromycin	8	>8	46.7	8	>8	43.5	0.25	>8	57.1
Linezolid	1	2	100.0	1	2	100.0	1	1	100.0
Teicoplanin	≤0.5	≤0.5	100.0	≤0.5	≤0.5	100.0	≤0.5	1	100.0
Tetracycline	≤0.5	>8	80.0	≤0.5	>8	80.4	≤0.5	>8	78.6
Vancomycin	0.5	1	100.0	0.5	1	100.0	1	1	100.0

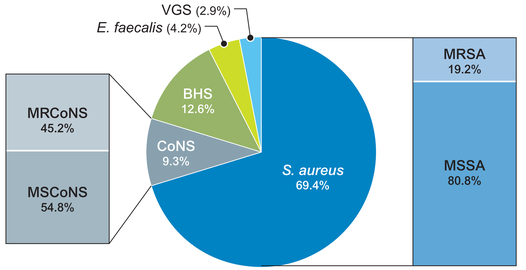
Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.
[a] Criteria as published by EUCAST (2020).
[b] Using a breakpoint for infections other than pneumonia.

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against other Gram-positive pathogens causing BJI from European hospitals

Organisms / Antimicrobial agent	MIC (mg/L)		EUCAST[a]	
	MIC_{50}	MIC_{90}	%S	%R
BHS (57)				
Oritavancin	0.06	0.25	96.5 [b]	3.5
Ceftaroline	≤0.008	0.015	100.0	0.0
Clindamycin	≤0.25	>2	84.2	15.8
Daptomycin	≤0.06	0.25	100.0	0.0
Erythromycin	≤0.03	>4	71.9	28.1
Linezolid	1	2	100.0	0.0
Penicillin	≤0.03	0.06	100.0	0.0
Teicoplanin	0.12	0.25	100.0	0.0
Tetracycline	0.5	>4	54.4	45.6
Vancomycin	0.25	0.5	100.0	0.0
VGS (13)				
Oritavancin	0.008	0.12	100.0 [c]	0.0
Clindamycin	≤0.25	>2	69.2	30.8
Daptomycin	0.25	0.5	—	—
Erythromycin	≤0.03	>4	—	—
Linezolid	1	1	—	—
Penicillin	≤0.03	0.25	92.3	0.0
Teicoplanin	≤0.06	—	100.0	0.0
Tetracycline	1	>4	—	—
Vancomycin	0.5	1	100.0	0.0
CoNS (42)				
Oritavancin	0.03	0.12	—	—
Clindamycin	≤0.25	>2	78.6	21.4
Daptomycin	0.25	0.5	100.0	0.0
Erythromycin	0.12	>8	52.4	45.2
Linezolid	0.5	1	97.6	2.4
Oxacillin	1	>2	45.2	54.8
Teicoplanin	1	4	90.5	9.5
Tetracycline	≤0.5	1	92.9	7.1
Vancomycin	1	2	100.0	0.0
***E. faecalis* (19)**				
Oritavancin	0.015	0.03	—	—
Ampicillin	1	2	100.0	0.0
Daptomycin	1	1	—	—
Erythromycin	0.5	—	—	—
Linezolid	1	2	100.0	0.0
Teicoplanin	≤2	≤2	100.0	0.0
Tetracycline	>8	>8	—	—
Vancomycin	1	2	100.0	0.0

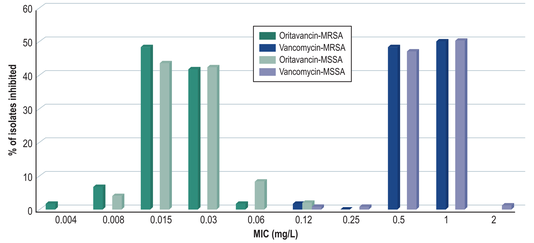
Abbreviations: BHS, β-hemolytic streptococci; VGS, viridans group streptococci; CoNS, coagulase-negative *Staphylococcus* spp.
[a] Criteria as published by EUCAST (2020).
[b] Breakpoints for streptococci groups A, B, C, and G have been applied to all beta-hemolytic streptococci.
[c] The breakpoint for the *S. anginosus* group was applied to all viridans group streptococci.

Figure 1. Gram-positive pathogens causing BJI in European medical centres (2015–2019)



Abbreviations: BHS, β-hemolytic streptococci; VGS, viridans group streptococci; CoNS, coagulase-negative *Staphylococcus* spp.; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MRCoNS, methicillin-resistant coagulase-negative *Staphylococcus* spp.; MSCoNS, methicillin-susceptible coagulase-negative *Staphylococcus* spp.

Figure 2. MIC distributions of oritavancin and vancomycin against MRSA and MSSA isolates causing BJI in Europe (2015–2019)



Conclusions

- Oritavancin demonstrated potent *in vitro* activity against Gram-positive pathogens causing BJI in Europe.
- Where breakpoints are available, high susceptibility rates were observed for oritavancin and comparator agents against the most frequent organisms and organism groups causing BJI, including MRSA.
- Within the BHS collection, only 2 isolates were non-susceptible to oritavancin (1 *S. pyogenes* and 1 *S. dysgalactiae*).
- Oritavancin appears to be a viable candidate for the treatment of BJI caused by Gram-positive pathogens.
- Clinical studies to further evaluate the role of oritavancin in treating BJI, are warranted.

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