C-824 In Vitro Activity of Oritavancin against Gram-Positive Pathogens Isolated in Canadian Hospitals from 2011 to 2013

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Revised Abstract

Background: Oritavancin (ORI) is a semisynthetic lipoglycopeptide that was approved by the United Stated Food and Drug Administration (FDA) in August 2014 for the single dose (1200mg) intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by, or suspected to be caused by, susceptible grampositive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). ORI's mechanism of action involves inhibition of two distinct steps in cell wall biosynthesis, as well as disruption of the cell membrane in gram-positive pathogens, and its spectrum of activity includes methicillin-susceptible and -resistant S. aureus (MSSA) and MRSA, methicillin-susceptible and -resistant coagulase-negative staphylococci (MSSE and MRSE), streptococci including penicillin-resistant Streptococcus pneumoniae, as well as vancomycin-susceptible and -resistant enterococci (Clinical Infectious Diseases 2012:54(S3):S203-13).

Methods: From January 2011 to October 2013, 15 sentinel Canadian hospital laboratories were asked to submit consecutive pathogens (1 per patient) from blood (n = 100), respiratory (n = 100), urine (n = 25), and wound (n = 25) infections. In total, 3245 gram-positive isolates were tested for antimicrobial susceptibilities using the CLSI broth microdilution method (M07-A9, 2012). MIC results for ORI were generated using frozen microdilution panels provided by The Medicines Company.

Results: Data for selected organisms and antimicrobial agents were:

 MIC_{50} (µg/mL)/ MIC_{90} (µg/mL)

Organism (n)	ORI	VAN	DAP	LZD	CIP	SXT
MSSA (1460)	0.03/0.06	1/1	0.25/0.25	2/2	0.5/8	≤0.12/≤0.12
MRSA (427)	0.03/0.06	1/1	0.25/0.5	2/2	>16/>16	≤0.12/≤0.12
MSSE (191)	0.06/0.12	1/2	0.25/0.25	0.5/1	0.5/>16	≤0.12/8
MRSE (30)	0.06/0.12	1/2	0.12/0.25	1/1	>16/>16	4/8
S. pyogenes (132)	0.03/0.25	0.5/0.5	0.06/0.12	1/1	0.5/1	≤0.12≤0.12
S. agalactiae (156)	0.03/0.25	0.5/0.5	0.25/0.25	1/2	1/2	≤0.12/≤0.12
PS S. pneumoniae (360)	0.002/0.008	≤0.25/0.25	0.06/0.12	0.5/1	1/2	≤0.12/0.5
PNS S. pneumoniae (64)	0.002/0.008	0.25/0.5	0.06/0.12	0.5/1	1/2	2/>8
VS E. faecium (87)	0.008/0.015	1/1	1/2	2/4	>16/>16	≤0.12/>8
VR E. faecium (22)	0.008/0.12	>32/>32	1/2	2/4	>16/>16	≤0.12/>8
VS E. faecalis (304)	0.03/0.06	1/2	0.5/1	2/2	1/>16	≤0.12/0.5

Abbreviations: VAN, vancomycin; DAP, daptomycin; LZD, linezolid; CIP, ciprofloxacin; SXT, trimethoprimsulfamethoxazole; PS, penicillin-susceptible; PNS, penicillin non-susceptible; VS, vancomycin-susceptible; VR, vancomycin-resistant.

Conclusions: Oritavancin demonstrated in vitro activity equivalent to, or more potent than, vancomycin, daptomycin, linezolid, and tigecycline against the isolates of methicillin-susceptible *S. aureus* (n = 1460; oritavancin MIC₉₀, 0.06 µg/ml; 99.7% oritavancin-susceptible), methicillin-resistant S. aureus (n = 427; oritavancin MIC₉₀, 0.06 μ g/ml; 99.5% oritavancin-susceptible), Streptococcus pyogenes (n = 132; oritavancin MIC₉₀, 0.25 µg/ml; 99.2% oritavancin-susceptible), Streptococcus agalactiae (n = 156; oritavancin MIC₉₀, 0.12 µg/ml; 100% oritavancin-susceptible), and Enterococcus faecalis (n = 304; oritavancin MIC₉₀, 0.06 µg/ml; 98.7% oritavancinsusceptible) tested from patients attending hospitals across Canada.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide that was approved by the United States Food and Drug Administration (FDA) in August 2014 for the single dose (1200 mg) intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by, or suspected to be caused by susceptible gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). The mechanism of action of oritavancin involves inhibition of two distinct steps in cell wall biosynthesis and disruption of cell membrane in gram-positive pathogens (1) and its spectrum of activity includes methicillin-susceptible and methicillin-resistant S. aureus (MSSA and MRSA), methicillin-susceptible and methicillin-resistant coagulase-negative staphylococci (MSSE and MRSE), streptococci including penicillin-resistant Streptococcus pneumoniae, as well as vancomycin-susceptible and vancomycinresistant enterococci (2, 3). The intent of the current study was to evaluate the in vitro activity of oritavancin and a collection of relevant comparator agents against a recent Canadian collection of common gram-positive bacterial pathogens.

Methods

From January 2011 to October 2013, 15 sentinel Canadian hospital laboratories were asked to submit consecutive bacterial pathogens (1 per patient) from blood (100), respiratory (100), urine (25), and wound (25) infections. During this time period, 2108 staphylococci, 424 S. pneumoniae, 413 enterococci, and 288 β-hemolytic streptococci were collected.

Results

Table 1. In vitro activities of oritavancin and comparative agents against Staphylococcus spp.

Organism (no. tested)/ antimicrobial agent	50%	90%	Range	% Susceptible	% Intermediate	% Resistan
Methicillin-Susceptible Staphylococcus aureus (1460)						
Oritavancin ¹	0.03	0.06	≤0.004-0.25	99.7	_3	-
Vancomycin	0.5	1	≤0.12-2	100	0	0
Daptomycin	0.25	0.25	≤0.03-1	100	-	-
Linezolid	2	4	≤0.12-4	100	-	0
Tigecycline ²	0.12	0.25	0.06-1	99.8	-	-
Doxycycline	≤0.12	0.25	≤0.12-16	98.7	0.9	0.4
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	99.5	-	0.5
Clindamycin	≤0.12	≤0.12	≤0.12->8	95.5	0.1	4.4
Clarithromycin	0.25	>32	≤0.03->32	76.9	0.7	22.4
Moxifloxacin	≤0.06	0.25	≤0.06->16	91.1	0.9	8.0
lethicillin-Resistant						
Staphylococcus aureus (427)						
Oritavancin	0.03	0.06	≤0.004-0.25	99.5	-	-
Vancomycin	1	1	0.5-2	100	0	0
Daptomycin	0.25	0.5	0.12-2	99.8	-	-
Linezolid	2	4	0.5-4	100	-	0
Tigecycline	0.12	0.25	0.06-2	98.4	-	-
Doxycycline	≤0.12	1	≤0.12-16	98.1	0.7	1.2
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	97.2	-	2.8
Clindamycin	≤0.12	>8	≤0.12->8	66.0	0	34.0
	>32	>32	≤0.03->32	20.0	0.9	79.1
Moxifloxacin	4	>16	≤0.06->16	21.1	5.1	73.8
Staphylococcus epidermidis (191)						
Oritavancin	0.06	0.12	0.008-0.5	NA ⁴	NA	NA
Vancomycin	1	2	≤0.12-2	100	0	0
Daptomycin	0.25	0.25	≤0.03-0.5	100	-	-
Linezolid	0.5	1	≤0.12-4	100	-	0
Tigecycline	0.12	0.25	≤0.03-1	NA	NA	NA
Doxycycline	0.25	1	≤0.12-32	94.8	3.7	1.5
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12->8	62.3	-	37.7
Clindamycin	≤0.12	>8	≤0.12->8	61.8	1.6	36.6
Clarithromycin	>32	>32	≤0.03->32	34.0	0.5	65.5
Moxifloxacin	0.5	16	≤0.06->16	52.3	8.4	39.3
Aethicillin-Resistant Staphylococcus epidermidis (30)						
Oritavancin	0.06	0.12	0.03-0.25	NA	NA	NA
Vancomycin	1	2	1-2	100	0	0
Daptomycin	0.25	0.25	0.12-0.5	100	-	-
	1	1	0.25-2	100	-	0
	0.12	0.25	0.06-0.25	NA	NA	NA
Doxycycline	0.5	1	≤0.12-4	100	0	0
I rimethoprim-sulfamethoxazole	4	8	≤0.12->8	20.0	-	80.0
	>8	>8	≤0.12->8	20.0	0	80.0
Clindamycin		>32	≤0.03->32	23.3	0	76.7
Clindamycin Clarithromycin	>32		0 40	^	^	4.0.0

Antimicrobial susceptibility testing was performed using in-house prepared, 96-well broth microdilution panels according to CLSI guidelines (M07-A9, 2012; M100-S24, 2014) for all agents except oritavancin. MIC results for oritavancin were generated using frozen broth microdilution panels provided by The Medicines Company (Parsippany, NJ). FDA MIC interpretative breakpoints were used for oritavancin: S. aureus, $\leq 0.12 \, \mu \text{g/ml}$ (susceptible);

Table 2. In vitro activities of oritavancin and comparative agents against Streptococcus spp.

		MIC (µg/	/mL)			
Organism (no. tested)/ antimicrobial agent	50%	90%	Range	% Susceptible	% Intermediate	% Resistant
Streptococcus pyogenes (132)						
Oritavancin ¹	0.03	0.25	≤0.0005-0.5	99.2	_3	-
Vancomycin	0.5	0.5	0.25-1	100	-	-
Daptomycin	0.06	0.12	≤0.03-0.12	100	-	-
Linezolid	1	2	0.25-4	98.5	-	-
Tigecycline ²	≤0.015	0.06	≤0.015-0.25	100	-	-
Clindamycin	≤0.12	≤0.12	≤0.12->64	99.2	0	0.8
Clarithromycin	≤0.03	≤0.03	≤0.03->32	94.7	0	5.3
Streptococcus agalactiae (156)						
Oritavancin	0.03	0.12	0.001-0.25	100	-	-
Vancomycin	0.5	0.5	0.25-1	100	-	-
Daptomycin	0.25	0.25	≤0.03-0.5	100	-	-
Linezolid	1	2	0.25-2	100	-	-
Tigecycline	0.03	0.06	≤0.015-1	99.4	-	-
Clindamycin	≤0.12	>64	≤0.12->64	83.3	0.7	16.0
Clarithromycin	≤0.03	32	≤0.03->32	69.9	4.5	25.6
Penicillin-Susceptible Streptococcus pneumoniae (360)						
Oritavancin	0.002	0.008	≤0.0005-0.06	NA ⁴	NA	NA
Vancomycin	0.25	0.25	≤0.12-1	100	-	-
Daptomycin	0.12	0.12	≤0.03-0.5	NA	NA	NA
Linezolid	1	2	≤0.12-2	100	-	-
Tigecycline	≤0.015	0.03	≤0.015-0.06	100	-	-
Doxycycline	≤0.25	≤0.25	≤0.25-16	92.5	1.4	6.1
Trimethoprim-sulfamethoxazole	0.25	0.5	≤0.12->8	91.9	4.8	3.3
Clindamycin	≤0.12	≤0.12	≤0.12->64	96.1	0.8	3.1
Clarithromycin	≤0.03	2	≤0.03->32	82.8	0.8	16.4
Moxifloxacin	0.12	0.25	≤0.06-4	98.9	0.8	0.3
Penicillin Non-Susceptible Streptococcus pneumoniae (64)						
Oritavancin	0.002	0.008	≤0.0005-0.015	NA	NA	NA
Vancomycin	0.25	0.25	≤0.12-0.5	100	-	-
Daptomycin	0.12	0.25	0.06-0.5	NA	NA	NA
Linezolid	0.5	1	0.25-2	100	-	-
Tigecycline	0.03	0.03	≤0.015-0.03	100	-	-
Doxycycline	2	16	≤0.25-16	37.5	0	62.5
Trimethoprim-sulfamethoxazole	1	8	≤0.12->8	48.5	10.9	40.6
Clindamycin	≤0.12	>64	≤0.12->64	57.8	0	42.2
Clarithromycin	1	>32	≤0.03->32	37.5	7.8	54.7
Moxifloxacin	0.12	0.25	≤0.06-4	96.9	1.5	1.6

¹ Oritavancin United States FDA breakpoint: Streptococcus spp. other than S. pneumoniae, ≤0.25 µg/ml (susceptible). ² Tigecycline United States FDA breakpoint: Streptococcus spp. other than S. pneumoniae, $\leq 0.25 \,\mu$ g/ml (susceptible). ³ -, no MIC breakpoint available. MIC breakpoints for intermediate and resistant categories have not been not defined by CLSI (2014) or United States FDA. An isolate with an MIC exceeding the susceptible breakpoint is defined as non-

susceptible.

⁴ NA, not applicable.

Streptococcus spp. other than S. pneumoniae, $\leq 0.25 \ \mu g/ml$ (susceptible); and E. faecalis (vancomycin-susceptible), ≤0.12 µg/ml (susceptible). MICs for comparator agents were interpreted using CLSI M100-S24 (2014) for all agents except tigecycline (FDA breakpoints used). Colony counts were performed periodically to confirm inocula. Quality control was performed using CLSI-recommended (M100-S24) ATCC organisms.

Table 3. In vitro activities of oritavancin and comparative agents against *Enterococcus* spp.

		MIC (µg	/mL)			
Drganism (no. tested)/ ntimicrobial agent	50%	90%	Range	% Susceptible	% Intermediate	% Resistant
ancomycin-Susceptible Interococcus faecalis (304)						
Oritavancin ¹	0.03	0.06	≤0.004-0.5	98.7	_3	-
Vancomycin	1	2	0.25-4	100	0	0
Daptomycin	1	2	≤0.03-4	100	-	-
Linezolid	2	4	0.5-4	89.4	10.6	0
Tigecycline ²	0.12	0.12	≤0.03-0.5	99.3	-	-
Doxycycline	8	16	≤0.12-32	38.5	42.1	19.4
Ciprofloxacin	1	>16	0.25->16	67.4	4.0	28.6
ancomycin-Susceptible nterococcus faecium (87)						
Oritavancin	0.008	0.015	≤0.004-0.03	NA ⁴	NA	NA
Vancomycin	0.5	1	0.25-2	100	0	0
Daptomycin	1	2	≤0.03-4	100	-	-
Linezolid	2	4	1-4	83.9	16.1	0
Tigecycline	0.12	0.12	≤0.03-0.25	NA	NA	NA
Doxycycline	≤0.12	8	≤0.12-16	86.2	5.8	8.0
Ciprofloxacin	>16	>16	0.25->16	11.8	0	88.2
ncomycin-Resistant nterococcus faecium (22)						
Oritavancin	0.008	0.12	≤0.004-0.5	NA	NA	NA
Vancomycin	>32	>32	32->32	0	0	100
Daptomycin	1	2	0.25-2	100	-	-
Linezolid	2	4	1-4	81.8	18.2	0
Tigecycline	0.12	0.25	0.06-0.5	NA	NA	NA
Doxycycline	2	8	≤0.12-16	77.3	13.6	9.1
Ciprofloxacin	>16	>16	>16	0	0	100

¹ Oritavancin United States FDA breakpoint: *E. faecalis* (vancomycin-susceptible), ≤0.12 µg/ml (susceptible).

² Tigecvcline United States FDA breakpoint: *E. faecalis* (vancomycin-susceptible), ≤0.25 µg/ml (susceptible). ³ -, no MIC breakpoint available. MIC breakpoints for intermediate and resistant categories have not been not defined by CLSI (2014) or United States FDA. An isolate with an MIC exceeding the susceptible breakpoint is defined as nonsusceptible.

⁴ NA, not applicable.



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Conclusions

- Based upon MIC_{an}, oritavancin demonstrated in vitro activity that was equivalent to or more potent than vancomycin, daptomycin, linezolid or tigecycline against a recent collection of clinical isolates of S. aureus, both MRSA and MSSA.
- 99.7% (1881/1887) of isolates were susceptible to oritavancin (MIC $\leq 0.12 \ \mu g/ml$); all isolates of S. aureus tested had oritavancin MICs of ≤0.25 µg/ml.
- Based upon MIC_{90} , oritavancin demonstrated in vitro activity that was equivalent to or more potent than vancomycin, daptomycin, linezolid or tigecycline against a recent collection of clinical isolates of S. pyogenes, S. agalactiae and S. pneumoniae (both penicillin-susceptible and penicillin non-susceptible isolates).
- All isolates of S. agalactiae tested were susceptible to oritavancin (MICs ≤0.25 µg/ml); 99.2% (131/132) of S. pyogenes were susceptible to oritavancin; all isolates of S. pyogenes had MICs ≤0.5 µg/ml.
- All isolates of S. pneumoniae tested had MICs ≤0.06 µg/ml.
- Based upon MIC₉₀, oritavancin demonstrated in vitro activity that was more potent than vancomycin, daptomycin, linezolid or tigecycline against a recent collection of clinical isolates of enterococci (both vancomycin-susceptible and vancomycinresistant isolates).
- All isolates of *E. faecalis* tested were susceptible to vancomycin; 98.7% (300/304) of isolates were susceptible to oritavancin (MIC ≤0.12 µg/ml); all isolates of *E. faecalis* had oritavancin MICs ≤0.5 µg/ml. All isolates of vancomycinsusceptible E. faecium tested had oritavancin MICs ≤0.03 µg/ml; the highest oritavancin MIC detected among vancomycin-resistant *E. faecium* was 0.5 µg/ml.

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