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Activity of Oritavancin Against *S. aureus*, *S. epidermidis*, *Enterococcus* spp. and *S. pneumoniae* Isolated from Canadian Hospitals: Results of CANWARD 2007-2009

G.G. ZHANEL, K. NICHOL, P. LAGACÉ-WIENS, M. DeCORBY, R. VASHISHT, J.A. KARLOWSKY and D.J. HOBAN

University of Manitoba and Health Sciences Centre, Winnipeg, Manitoba, Canada

Dr. George Zhanel
Health Sciences Centre
MS673 - 820 Sherbrook St.
Winnipeg, MB, Canada R3A 1R9
Phone: (204) 787-4902
Email: ggzhanel@pcs.mb.ca

REVISED ABSTRACT

Background: Oritavancin (ORI) is a new lipoglycopeptide antimicrobial agent. We assessed the activity of ORI and comparators against Gram-positive pathogens causing infections in Canadian hospitals.

Methods: From January 2007 through November 2009, 15 sentinel Canadian hospitals (10 centres - 2008) submitted pathogens from hospitalized patients. A total of 6,433 Gram-positive pathogens were collected and 4,779 tested to date. Susceptibility testing used CLSI M7-A7 and M100-S18 broth microdilution which, for ORI, includes 0.002% polysorbate.

Results: MIC_{50} and MIC_{90} values for ORI, vancomycin (VAN) and linezolid (LZD) of isolates tested to date were:

Organism (# isolates)	ORI MIC_{50} / MIC_{90}	VAN MIC_{50} / MIC_{90}	LZD MIC_{50} / MIC_{90}
SPN-All (902)	≤0.002 / 0.004	≤0.25 / 0.25	1 / 1
- PenS (740)	≤0.002 / 0.004	≤0.25 / ≤0.25	0.5 / 1
- PenI (120)	≤0.002 / 0.008	≤0.25 / 0.5	0.5 / 1
- PenR (34)	0.004 / 0.008	≤0.25 / 0.5	0.5 / 1
MSSA (1979)	0.12 / 0.25	1 / 1	2 / 2
MRSA (631)	0.12 / 0.25	1 / 1	2 / 2
- CA-MRSA (173)	0.12 / 0.25	1 / 1	2 / 2
- HA-MRSA (433)	0.12 / 0.5	1 / 1	2 / 2
MSSE (202)	0.12 / 0.5	1 / 2	0.5 / 1
MRSE (34)	0.03 / 0.5	2 / 2	1 / 1
VS *E. faecalis* (308)	0.12 / 0.25	1 / 2	2 / 2
VS *E. faecium* (124)	0.03 / 0.12	0.5 / 4	2 / 2
Enterococcus spp. (371)	0.06 / 0.25	1 / 2	2 / 2
VRE (28)	0.12 / 0.5	>32 / >32	1 / 2
S. pyogenes (200)	0.06 / 0.25	0.5 / 0.5	1 / 1

SPN, *S. pneumoniae*; PenS, penicillin-susceptible; PenI, penicillin-intermediate; PenR, penicillin-resistant; HA, healthcare-associated; CA, community-associated; SA, *S. aureus*; MS, methicillin-susceptible; MR, methicillin-resistant; SE, *S. epidermidis*; VS, VAN-susceptible; VRE, VAN-resistant enterococci.

By MIC_{50}, oritavancin was more active than vancomycin and linezolid versus MSSA, MRSA (CA and HA), MSSE, MRSE, SPN and *Enterococcus* spp. including VRE. Methicillin susceptibility did not affect ORI activity against staphylococci. ORI activity was not adversely impacted by penicillin susceptibility in SPN or by vancomycin susceptibility in enterococci.

Conclusions: In the face of increasing incidence of antimicrobial resistance, ORI displays potential utility since its activity against gram-positive pathogens is unaltered by common resistance mechanisms. That CA- and HA-MRSA are equally susceptible to ORI may provide healthcare providers with another treatment option as the epidemiology of MRSA infection continues to evolve.

BACKGROUND

Infections caused by antibiotic resistant pathogens is a Canadian and global crisis. Antibiotic resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA, community associated-CA and healthcare associated-HA), vancomycin-resistant *Enterococcus* species (VRE) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are increasing in prevalence in Canada and around the world. Available therapeutic options for the treatment of these antibiotic resistant organisms are severely limited as these organisms frequently display a multidrug resistant (MDR) phenotype.

Oritavancin (ORI) is a new semisynthetic-lipoglycopeptide antimicrobial agent which is very active in vitro against a range of gram positive pathogens, including both susceptible and multidrug-resistant staphylococci and enterococci.[1] It was originally discovered and developed by scientists at Eli Lilly as a potential replacement for vancomycin.

PURPOSE

The purpose of this study was to compare the activity of oritavancin and several comparators against gram-positive pathogens causing infections in patients affiliated with Canadian hospitals.

MATERIALS & METHODS

Bacterial Isolates

From Jan 2007-Dec 2009, inclusive, sentinel hospitals in major population centres in 8 of the 10 provinces in Canada were recruited. These sites were geographically distributed in a population based fashion. Each study site was asked to collect and submit pathogens (consecutive isolates, one organism per specimen source per patient) from patients using the following the criteria: (a) 200 isolates from patients with respiratory tract infections (community or nosocomial); (b) 50 isolates from patients with skin/skin structure infections (wound/IV site infections); (c) 100 isolates from patients with urinary tract infections; (d) 20 blood stream infection isolates/site/month. All submitted isolates were deemed clinically significant by each site. All organisms were identified at each site using local site criteria and at the reference site, where indicated. At study sites, isolates were subcultured on appropriate solid media and incubated overnight. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), where isolates were subcultured on appropriate media and stocked in skim milk at - 80°C.

Antimicrobial Susceptibilities

A custom microtitre panel was designed with a variety of antimicrobials. Antimicrobials were obtained as laboratory-grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by the Clinical and Laboratory Standards Institute (2009 CLSI).[2] Following two subcultures from frozen stock, the MICs were determined by the CLSI-approved broth microdilution method.[2] Briefly, 96-well custom-designed microtitre plates containing doubling antibiotic dilutions in 100µL/well of cation adjusted Mueller-Hinton broth (eg. for Enterobacteriaceae) with or without lysed horse blood (2.5-5% V/V) (eg. for *S. pneumoniae*) were inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/mL and incubated in ambient air (35°C) for 20-24 hours prior to reading. Polysorbate-80 (0.002%) was added to both the stock solution of oritavancin and cation-adjusted broth used for panels. Quality control was performed periodically using a variety of ATCC QC organisms including: *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922 and *P. aeruginosa* 27853. For all antimicrobials tested, MIC interpretive standards were defined according to CLSI breakpoints.[3] The following interpretive breakpoints (FDA) were used for tigecycline susceptible (S), intermediate (I) and resistant (R) (µg/mL): *Staphylococcus aureus* (MSSA and MRSA) ≤ 0.5 (S); *Enterococcus* spp., ≤ 0.25 (S); Enterobacteriaceae, ≤ 2 (S), 4 (I), and ≥ 8 (R).

ACKNOWLEDGMENTS

This study was supported in part by the Medicines Company.

The authors would like to thank the investigators and laboratory site staff at each medical centre that participated in the Canadian Ward Surveillance Study (CANWARD) study:

Dr. D. Roscoe – Vancouver Hospital, Vancouver

Dr. R. Rennie – University of Alberta Hospital, Edmonton

Dr. J. Blondeau – Royal University Hospital, Saskatoon

Drs. D. Hoban/G. Zhanel – Health Sciences Centre, Winnipeg

Dr. Z. Hussain – London Health Sciences Centre, London

Dr. S. Poutanen – Mount Sinai Hospital, Toronto

Dr. L. Matukas – St. Michael's Hospital, Toronto

Dr. F. Chan – Children's Hospital of Eastern Ontario, Ottawa

Dr. M. Desjardins – The Ottawa Hospital, Ottawa

Dr. M. Laverdière – Hopital Maisonneuve-Rosemont, Montreal

Dr. V. Loo – Montreal General Hospital, Montreal

Dr. V. Loo – Royal Victoria Hospital, Montreal

Dr. M. Goyette – CHRTR Pavilion Ste. Marie, Trois-Rivières

Dr. M. Kuhn – South East Regional Health Authority, Moncton

Dr. R. Davidson – Queen Elizabeth II HSC, Halifax

RESULTS

Table 1. Activity of oritavancin and comparators against gram-positive cocci from CANWARD 2007-2009

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. aureus							
MSSA (1979)							
Cefazolin	100.0		0.0	≤ 0.5	1	≤ 0.5	32
Clarithromycin	74.9	0.3	24.7	≤ 0.25	> 16	≤ 0.25	> 32
Clindamycin	91.8	0.6	7.7	≤ 0.25	≤ 0.25	≤ 0.12	> 8
Daptomycin	100.0			0.12	0.25	≤ 0.06	1
Levofloxacin	97.6	0.1	2.4	0.25	1	≤ 0.06	> 32
Linezolid	100.0			2	2	≤ 0.12	4
Meropenem	100.0			0.12	0.25	≤ 0.06	4
Oritavancin	No BP			0.12	0.25	≤ 0.008	1
Pip-Tazo	99.9		0.1	≤ 1	≤ 1	≤ 1	32
Tigecycline	99.8		0.2	0.25	0.25	≤ 0.03	1
TMP/SMX	99.3		0.7	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	≤ 0.25	2
MRSA (631)							
Cefazolin			100.0[a]	64	> 128	1	> 128
Clarithromycin	11.7	0.1	88.2	> 16	> 32	0.12	> 32
Clindamycin	44.0	0.1	55.9	> 8	> 8	≤ 0.12	> 8
Daptomycin	100.0			0.12	0.25	0.06	1
Levofloxacin	14.1		85.9	> 32	> 32	0.12	> 32
Linezolid	100.0			2	2	0.12	4
Meropenem			100.0[a]	8	32	0.12	> 64
Oritavancin	No BP			0.12	0.25	0.008	1
Pip-Tazo			100.0[a]	64	128	1	256
Tigecycline	99.3		0.7	0.25	0.5	≤ 0.06	1
TMP/SMX	90.3		9.7	≤ 0.12	1	≤ 0.12	> 8
Vancomycin	99.9	0.1		1	1	≤ 0.25	4
CA-MRSA (173)							
Cefazolin			100.0[a]	16	64	1	128
Clarithromycin	26.9	0.5	72.7	> 16	> 16	≤ 0.25	> 16
Clindamycin	86.1		13.9	≤ 0.25	> 16	≤ 0.25	> 8
Daptomycin	100.0			0.25	0.25	0.12	1
Levofloxacin	39.9		60.1	4	8	0.12	32
Linezolid	100.0			2	2	1	4
Meropenem			100.0[a]	2	4	0.12	16
Oritavancin	No BP			0.12	0.25	0.008	0.5
Pip-Tazo			100.0[a]	16	32	2	64
Tigecycline	99.6		0.5	0.25	0.25	0.06	1
TMP/SMX	100.0			≤ 0.12	≤ 0.12	≤ 0.12	2
Vancomycin	100.0			1	1	≤ 0.25	2
HA-MRSA (433)							
Cefazolin			100.0[a]	128	> 128	1	> 128
Clarithromycin	4.3		95.7	> 16	> 16	≤ 0.25	> 16
Clindamycin	27.3	0.2	72.0	> 8	> 8	≤ 0.25	> 8
Daptomycin	100.0			0.12	0.25	0.06	1
Levofloxacin	2.9		97.1	> 32	> 32	0.12	> 32
Linezolid	100.0			2	2	0.12	4
Meropenem			100.0[a]	16	> 32	0.25	> 32
Oritavancin	No BP			0.12	0.5	0.008	1
Pip-Tazo			100.0[a]	64	128	1	512
Tigecycline	99.2		0.8	0.25	0.5	0.12	1
TMP/SMX	86.5		13.5	≤ 0.12	8	≤ 0.12	> 8
Vancomycin	99.8	0.2		1	1	≤ 0.25	4

[a] Based on cefoxitin disk test.

S, susceptible; I, intermediate; R, resistant.
No BP, no breakpoints available.
CA-MRSA, community-associated methicillin-resistant *S. aureus*.
HA-MRSA, healthcare-associated methicillin-resistant *S. aureus*.
Pip-Tazo, piperacillin-tazobactam.
TMP/SMX, trimethoprim-sulfamethoxazole.

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. epidermidis							
MSSE (202)							
Cefazolin			100.0	64	128	32	128
Clarithromycin	11.1		88.9	> 16	> 16	0.12	> 32
Clindamycin	13.3		86.7	> 8	> 8	≤ 0.12	> 8
Daptomycin	100.0			0.12	0.25	≤ 0.06	0.5
Levofloxacin	2.2	2.2	95.6	> 32	> 32	1	> 32
Linezolid	100.0			1	1	0.25	1
Meropenem			100.0	32	32	8	64
Oritavancin	No BP			0.03	0.5	0.008	0.5
Pip-Tazo			100.0	32	64	8	128
Tigecycline	No BP			0.25	0.25	0.06	0.5
TMP/SMX	24.4		75.6	4	8	≤ 0.12	> 8
Vancomycin	100.0			2	2	1	2
***S. pneumoniae* (902)**							
Ceftriaxone	99.4	0.4	0.2	≤ 0.06	0.12	≤ 0.06	4
Clarithromycin	81.3	4.3	14.5	≤ 0.03	2	≤ 0.03	> 32
Clindamycin	93.5	0.6	5.9	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Doxycycline	93.2	2.8	4.0	≤ 0.25	1	≤ 0.06	> 16
Levofloxacin	99.1	0.2	0.8	1	1	≤ 0.06	32
Linezolid	100.0			0.5	1	≤ 0.12	2
Meropenem	96.4	2.5	1.1	≤ 0.06	≤ 0.06	≤ 0.06	2
Oritavancin	No BP			≤ 0.004	0.004	≤ 0.002	0.12
Penicillin	81.1	14.5	4.4	≤ 0.03	0.25	≤ 0.03	> 8
Tigecycline	98.6		1.5	≤ 0.03	≤ 0.03	≤ 0.03	0.5
TMP/SMX	85.6	6.3	8.1	≤ 0.12	1	≤ 0.12	> 8
Vancomycin	100.0			≤ 0.25	≤ 0.25	≤ 0.25	1
Penicillin-resistant (34)							
Ceftriaxone	93.9	3.0	3.0	0.5	1	0.25	4
Clarithromycin	60.6	3.0	36.4	≤ 0.03	32	≤ 0.03	> 32
Clindamycin	75.8		24.2	≤ 0.12	8	≤ 0.12	> 8
Doxycycline	81.8	12.1	6.1	≤ 0.25	2	≤ 0.25	> 16
Levofloxacin	100.0			0.5	1	0.25	2
Linezolid	100.0			0.5	1	0.25	2
Meropenem	45.5	48.5	6.1	0.5	1	≤ 0.06	2
Oritavancin	No BP			0.004	0.008	≤ 0.002	0.06
Penicillin			100.0	2	8	2	> 8
Tigecycline	No BP			≤ 0.03	0.12	≤ 0.03	0.12
TMP/SMX	30.3	6.1	63.6	4	8	≤ 0.12	> 8
Vancomycin	100.0			0.25	0.5	≤ 0.25	0.5

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
***E. faecalis* (308)**							
Ciprofloxacin	45.5	19.2	35.4	2	> 16	0.25	> 16
Clarithromycin	No BP			> 16	> 32	0.06	> 32
Clindamycin	No BP			> 8	> 8	≤ 0.12	> 8
Daptomycin	100.0			0.5	1	≤ 0.06	4
Ertapenem	No BP			8	16	0.25	> 32
Levofloxacin	65.6	1.1	33.3	2	> 32	0.25	> 32
Linezolid	99.5	0.5		2	2	0.5	4
Meropenem	No BP			4	8	≤ 0.06	> 32
Oritavancin	No BP			0.12	0.25	0.015	0.25
Pip-Tazo	No BP			4	8	≤ 1	512
Tigecycline	97.9		2.1	0.12	0.25	0.015	1
Vancomycin	100.0			1	2	0.5	4
***E. faecium* (124)**							
Ciprofloxacin	6.0	4.0	90.0	> 16	> 16	0.5	> 16
Clarithromycin	No BP			> 32	> 32	0.12	> 32
Clindamycin	No BP			> 8	> 8	≤ 0.12	> 8
Daptomycin	100.0			1	2	0.12	4
Ertapenem	No BP			> 32	> 32	4	> 32
Levofloxacin	10.0	1.3	88.7	> 32	> 32	1	> 32
Linezolid	96.0	4.0		2	2	0.5	4
Meropenem	No BP			> 32	> 64	2	> 64
Oritavancin	No BP			0.03	0.12	0.008	0.5
Pip-Tazo	No BP			512	> 512	2	> 512
Tigecycline	No BP			0.12	0.12	0.06	2
Vancomycin	100.0			8	8	≤ 0.25	4
VRE (28)							
Ciprofloxacin		100.0		> 16	> 16	> 16	> 16
Clarithromycin	No BP			> 32	> 32	1	> 16
Clindamycin	No BP			> 8	> 8	0.25	> 8
Daptomycin	100.0			1	2	0.03	2
Ertapenem	No BP			> 32	> 32	> 32	> 32
Linezolid		100.0		2	> 32	> 32	> 32
Meropenem	No BP			> 32	> 32	> 32	> 32
Oritavancin	No BP			0.12	0.5	0.008	0.5
Pip-Tazo	No BP			> 512	> 512	64	128
Tigecycline	No BP			0.25	0.12	0.06	0.25
Vancomycin		100.0		32	> 32	> 32	> 32

Table 2. MIC distribution of oritavancin against gram-positive cocci from CANWARD 2007-2009

Organism (no. tested)	Number (cumulative percentage) at each MIC <=0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
Methicillin-susceptible *S. aureus* (1979)		107(5.4)	427(27.0)	339(44.1)	36(45.9)	427(67.5)	472(91.4)	162(99.5)	9(100)
Methicillin-resistant *S. aureus* (631)		43(6.8)	114(24.9)	76(36.9)	14(39.1)	152(63.2)	176(91.1)	52(99.4)	4(100)
Community-associated MRSA (173)		13(7.5)	34(27.2)	27(42.8)	2(43.9)	45(69.9)	43(94.8)	9(100)	
Healthcare-associated MRSA (433)		30(6.9)	78(24.9)	45(35.3)	12(38.1)	100(61.2)	122(89.4)	42(99.1)	4(100)
Methicillin-susceptible *S. epidermidis* (202)		5(2.5)	20(12.4)	37(30.7)	26(43.6)	39(62.9)	49(87.1)	22(98.0)	4(100)
Methicillin-resistant *S. epidermidis* (34)		5(14.7)	7(35.3)	5(50.0)	0(50.0)	5(64.7)	6(82.4)	6(100)	
S. pneumoniae (902)	837(92.8)	49(98.2)	14(99.8)	0(99.8)	1(99.9)	1(100)			
Penicillin-resistant *S. pneumoniae* (34)	29(85.3)	3(94.1)	1(97.1)	0(97.1)	1(100)				
E. faecalis (308)			3(1.0)	23(8.4)	97(39.9)	124(80.2)	52(97.1)	8(99.7)	1(100)
E. faecium (124)		9(7.0)	29(29.5)	55(72.1)	17(85.3)	10(93.0)	5(96.9)	4(100)	

MIC, minimum inhibitory concentration (µg/mL)

CONCLUSIONS

Oritavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. aureus*, including community-associated and hospital-associated strains.

Oritavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. epidermidis*.

Oritavancin is more active than comparators against *S. pneumoniae*, including penicillin-resistant strains.

Oritavancin is more active than comparators against *E. faecalis and E. faecium*, including vancomycin-resistant strains.

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