C-565



lealth Sciences Centre

Activity of Telavancin against Gram-Positive Cocci from Canadian Hospitals using Revised CLSI Guidelines: CANWARD 2013 and 2014

IAGNOSTIC SERVICES SERVICES DIAGNOSTIC **JANITOBA** MANITOBA

ABSTRACT

Background: Telavancin (TLV) is a bactericidal lipoglycopeptide with activity against methicillin-resistant Staphylococcus aureus and other Gram-positive pathogens. In 2014, CLSI published revised guidelines for broth microdilution (BMD) susceptibility testing of TLV which recommend the use of DMSO as solvent/diluent for stock solution preparation/dilution and the addition of 0.002% polysorbate-80 (P-80) to the BMD test medium. Using this revised methodology, we assessed the in vitro activity of TLV against Gram-positive cocci associated with infections in Canadian hospitals

Methods: From 2013-2014, more than 2,500 Gram-positive cocci were collected from tertiary-care medical centres across Canada as part of the ongoing national CANWARD surveillance study. Vancomycinintermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA) isolates from the Network on Antimicrobial Resistance in S. aureus (NARSA) repository were also included in this comparison. TLV activity was evaluated using the revised BMD method and MICs were interpreted using updated FDAapproved breakpoint criteria. Susceptibility testing of comparator agents was performed by BMD following CLSI guidelines

Results: The activity of TLV and select comparators (vancomycin [VAN], daptomycin [DAP], linezolid [LZD]) against Gram-positive cocci is summarized below:

Ormaniam (n)		Comparator MIC ₅₀ /MIC ₉₀ (μg/mL)								
Organism (n)	ILV MIC ₅₀ /MIC ₉₀ /Range (μg/mL)	VAN	DAP	LZD						
MSSA (1250)	0.03/0.06/0.008-0.12	0.5/1	0.25/0.5	2/2						
MRSA (293)	0.06/0.06/0.03-0.12	0.5/1	0.25/0.5	2/2						
- HA-MRSA (179)	0.06/0.06/0.03-0.12	1/1	0.25/0.5	2/2						
- CA-MRSA (114)	0.03/0.06/0.03-0.12	0.5/1	0.25/0.5	2/2						
hVISA (8)	0.06/0.12/0.03-0.12	2/2	0.25/0.5	1/2						
VISA (11)	0.12/0.25/0.06-0.25	4/8	0.5/1	1/2						
VRSA (7)	0.5/1/0.5-1	32/>32	0.25/0.25	2/2						
S. epidermidis (130)	0.06/0.12/0.03-0.25	1/2	0.25/0.25	0.5/1						
S. pneumoniae (334)	0.008/0.015/≤0.002-0.03	0.25/0.25	0.12/0.12	1/2						
S. pyogenes (87)	0.03/0.06/0.015-0.06	0.25/0.5	0.12/0.12	1/2						
S. agalactiae (124)	0.03/0.06/0.03-0.06	0.5/0.5	0.25/0.25	1/2						
E. faecalis (112)	0.12/0.12/0.015-0.25	1/2	1/2	2/2						
E. faecium (45)	0.03/>2/0.015->2	0.5/>32	2/2	2/2						
- VanS (34)	0.03/0.06/0.015-0.12	0.5/1	2/2	2/2						
- VanR (11)	2/>2/0.25->2	>32/>32	1/2	2/4						
MSSA methicillin augopatible S. aurougi MDSA methicillin registerat S. aurougi HA MDSA bashbaara apagaistad MDSA CA										

MSSA, methicillin-susceptible S. aureus; MRSA, methicillin-resistant S. aureus; HA-MRSA, healthcare-associated MRSA; CA-MRSA, community-associated MRSA; hVISA, heterogeneous vancomycin-intermediate S. aureus.

Conclusions: TLV was more active in vitro than VAN, DAP and LZD against MSSA and MRSA, including CA-MRSA and HA-MRSA genotypes. TLV was also the most active agent tested against hVISA and VISA. Although VRSA had TLV MICs above the susceptible breakpoint, TLV remained more active than VAN and LZD against these isolates. Against S. epidermidis, S. pneumoniae and b-hemolytic streptococci, TLV demonstrated activity comparable to or greater than DAP and superior than VAN and LZD.

BACKGROUND

Telavancin is a semisynthetic lipoglycopeptide with a dual mechanism of action against a broad spectrum of clinically relevant Gram-positive bacteria, including both susceptible and multidrug-resistant staphylococci and streptococci as well as enterococci. The rapid bactericidal activity of telavancin is derived from its ability to inhibit synthesis of the bacterial cell wall as well as to disrupt bacterial membrane integrity and increase cell membrane permeability.

In January 2014, the Clinical and Laboratory Standards Institute (CLSI) published revised guidelines for broth microdilution susceptibility testing of telavancin. This method utilizes DMSO as both solvent and diluent for stock solution preparation/dilution to increase drug solubility and incorporates 0.002% polysorbate-80 (P-80) in the broth microdilution test medium to minimize binding of the drug to plastic panels (M100-S24, CLSI 2014).

The purpose of this study was to assess the activity of telavancin against Gram-positive cocci associated with infections in Canadian hospitals using the revised CLSI broth microdilution method.

MATERIALS & METHODS

CANWARD Study Design

Between January 2013 and December 2014, 6,685 clinical isolates, including more than 2,500 Grampositive cocci, were collected as part of the ongoing CANWARD study assessing pathogen prevalence and antibiotic resistance in Canadian hospitals. Isolates were received from tertiary-care medical centres (15 in 2013, 13 in 2014) that were geographically distributed in a population-based fashion in eight of the ten Canadian provinces. Annually, each study site was asked to submit clinical isolates (consecutive, one per patient per infection site) from inpatients and outpatients with respiratory, urine, wound and bloodstream infections. Isolates were collected from patients attending hospital clinics, emergency rooms, medical/surgical wards and intensive care units. All organisms were identified by the submitting centre and were deemed clinically significant using local site criteria.

Additional Test Isolates

Eight heterogeneous vancomycin-intermediate S. aureus (hVISA) identified as part of the CANWARD study, as well as 11 vancomycin-intermediate S. aureus (VISA) and 7 vancomycin-resistant S. aureus (VRSA) isolates from the Network on Antimicrobial Resistance in S. aureus (NARSA) repository were also included in this comparison.

Antimicrobial Susceptibility Testing

The in vitro activities of comparator agents, including cefazolin, ceftriaxone, clarithromycin, clindamycin, ciprofloxacin, daptomycin, doxycycline, ertapenem, levofloxacin, linezolid, meropenem, moxifloxacin, penicillin, piperacillin-tazobactam, tigecycline, trimethoprim-sulfamethoxazole and vancomycin, were determined by broth microdilution in accordance with CLSI guidelines (M7-A7, CLSI 2012). Telavancin susceptibility testing was performed by the revised broth microdilution method, which utilizes DMSO as both solvent and diluent for stock solution preparation/dilution and incorporates 0.002% P-80 in the test medium. MIC interpretive standards were defined according to CLSI breakpoints for comparator agents (M100-S24, CLSI 2014). The following interpretive breakpoints (FDA) were used for telavancin susceptible: S. aureus, ≤0.12 µg/ml; *S. pyogenes*, ≤0.12 µg/ml; *S. agalactiae*, ≤0.12 µg/ml; and *E. faecalis* (vancomycin-susceptible) ≤0.25 µg/ml

Telavancin was more active than the comparator agents vancomycin, daptomycin and linezolid against MSSA and MRSA, including both community- and healthcare-associated strains.

Telavancin remained active against hVISA (100% susceptible), but exhibited reduced activity against VISA strains (81.8% susceptible). All VRSA were telavancin non-susceptible.

Telavancin had greater activity than vancomycin, daptomycin and linezolid against hVISA and VISA strains and was more active than vancomycin and linezolid against VRSA.

Televancin was more active than vancomycin, daptomycin and linezolid against *S. epidermidis*.

Telavancin demonstrated comparable activity to penicillin and superior activity to vancomycin and linezolid against S. pyogenes and S. agalactiae, and was the most potent agent tested against S. pneumoniae.

Financial support for the CANWARD study was provided in part by Pendopharm, a division of Pharmascience Inc. and drug by Theravance Biopharma Antibiotics, Inc.

The authors would like to thank the participating centres, investigators and laboratory site staff for their continued support.

K.A. NICHOL¹, H.J. ADAM^{1,2}, N. LAING², B. WESHNOWESKI¹, R. VASHISHT², M.R. BAXTER², J.A. KARLOWSKY^{1,2}, D.J. HOBAN^{1,2}, G.G. ZHANEL², and the CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA) Diagnostic Services Manitoba¹ and University of Manitoba², Winnipeg, Manitoba, Canada

CONCLUSIONS

ACKNOWLEDGEMENTS

Table 1 Activity of televancin and comparators against Gram-positive coc

% of Isolates per Category		MIC (µg/mL)				% of Iso	% of Isolates per Category			MIC (µa/mL)		Γ		% of Isolates per Category				MIC (ug/mL)			
Organism (n), Antibiotic	<u> </u>	 	R	50%	<u>90%</u>	Range	Organism (n), Antibiotic	S	I	R	50%	<u>90%</u>	Range	C	Organism (n), Antibiotic	<u> </u>	I	R	50%	<u>90%</u>	Range
S. aureus							S. aureus	-					J								
MSSA (1250)							CANWARD hVISA (8)								S. pneumoniae (334)						
Telavancin ^a	100			0.03	0.06	0.008 - 0.12	Telavancin ^a	100			0.06	0.12	0.03 - 0.12		Telavancin	No BP			0.008	0.015	≤0.002 - 0.03
Vancomycin	100			0.5	1	≤0.12 - 2	Vancomycin	100			2*	2	2		Vancomycin	100			0.25	0.25	≤0.12 - 0.5
Cefazolin	No BP			≤0.5	≤0.5	≤0.5 - 8	Cefazolin			100 ^b	>128*	>128	1 - >128		Ceftriaxone	99.4	0.6		≤0.12	0.25	≤0.12 - 2
Clarithromycin	76.7	1.0	22.3	0.12	>32	≤0.03 - >32	Clarithromycin			100	>32*	>32	>32		Clarithromycin	75.2	3.6	21.2	≤0.03	2	≤0.03 - >32
Clindamycin	94.1	0.4	5.5	≤0.12	≤0.12	≤0.12 - >8	Clindamycin	25.0		75.0	>8*	>8	≤0.12 - >8		Clindamycin	92.7	0.6	6.7	≤0.12	≤0.12	≤0.12 - >64
Daptomycin	100			0.25	0.5	0.06 - 1	Daptomycin	100			0.25*	0.25	0.12 - 0.5		Doxycycline	84.8	0.9	14.2	≤0.25	4	≤0.25 - 16
Linezolid	99.9		0.1	2	2	≤0.12 - 8	Linezolid	100			1*	2	0.5 - 2		Levofloxacin	98.5		1.5	1	1	≤0.06 - 16
Meropenem	No BP			0.12	0.25	≤0.03 - 2	Meropenem			100 ^b	>32*	>32	0.5 - >32		Linezolid	100			1	2	≤0.12 - 2
Moxifloxacin	90.8	1.1	8.1	≤0.06	0.25	≤0.06 - >16	Moxifloxacin	12.5		87.5	>16*	>16	≤0.06 - >16		Meropenem	93.0	4.2	2.7	≤0.06	≤0.06	≤0.06 - 1
Pip-Tazo	No BP			≤1	≤1	≤1 - 16	Pip-Tazo			100 ^b	256*	512	8 - 512		Penicillin	85.8	9.7	4.5	≤0.03	0.25	≤0.03 - 4
Tigecycline ^a	99.7			0.25	0.25	≤0.03 - 1	Tigecycline ^a	100			0.12*	0.25	0.06 - 0.25		Tigecycline ^a	100			≤0.015	0.03	≤0.015 - 0.06
TMP/SMX	99.5		0.5	≤0.12	≤0.12	≤0.12 - >8	TMP/SMX	100			≤0.12*	≤0.12	≤0.12		TMP/SMX	83.2	5.8	11	≤0.12	4	≤0.12 - >8
MRSA (293)							NARSA VISA (11)								S. pyogenes (87)						
Telavancin ^a	100			0.06	0.06	0.03 - 0.12	Telavancin ^a	81.8			0.12*	0.25	0.06 - 0.25		Telavancin	100			0.03	0.06	0.015 - 0.06
Vancomycin	100		h	0.5	1	≤0.12 - 2	Vancomycin		100	h	4*	8	4 - 8		Vancomycin	100			0.25	0.5	0.25 - 0.5
Cefazolin			100 ^{<i>b</i>}	32	>128	1 - >128	Cefazolin			100 ^{<i>b</i>}	>64*	>128	4 - >128		Ceftriaxone	98.9			≤0.12	≤0.12	≤0.12 - 1
Clarithromycin	20.3	1.9	77.8	>32	> 32	≤0.03 - >32	Clarithromycin	9.1		90.9	>32*	>32	0.12 - >32		Clarithromycin	94.3		5.7	≤0.03	≤0.03	≤0.03 - 4
Clindamycin	64.8		35.2	≤0.12	> 8	≤0.12 - >8	Clindamycin	9.1		90.9	>8*	>8	≤0.12 - >8		Clindamycin	98.9		1.1	≤0.12	≤0.12	≤0.12 - >64
Daptomycin	100			0.25	0.25	0.12 - 0.5	Daptomycin	100			0.5*	1	0.25 - 1		Doxycycline	No BP			≤0.25	0.5	≤0.25 - 16
Linezolid	100		h	2	2	1 - 4	Linezolid	100		h	1^	2	1 - 2		Levofloxacin	100			0.5	1	0.25 - 2
Meropenem	04.0	7.0	100 ⁵	4	32	0.12 - >32	Meropenem			100°	8^ 4*	16	1 - >32		Linezolid	97.7		2.3	1	2	0.25 - 4
	21.6	7.6	70.8	4	>16	≤0.06 - >16				100	4"	8	2-8		Meropenem	100			≤0.06	≤0.06 <0.02	≤0.06 - 0.12
	00.0		100~	32	128	≤1 - 256 0.00 - 0		100		100~	128"	128	32 - 256			100			≤0.03	<u>≤</u> 0.03	≤0.03 - 0.06
	96.8		7 5	0.25	0.5	0.06 - 2		100		27.2	0.25	0.5	0.12 - 0.5		TMD/CMX	100 No DD			≤0.015 <0.12	0.06	≤0.015 - 0.06
	92.5		7.5	≤0.12	<u>≤</u> 0.12	≤0.12 - 20		12.1		27.5	0.25	>0	<u>≤</u> 0.12 - 20	-	11VIP/31VIA S agalactico (124)	NU DP			≤0.1Z	0.25	≤0.12 - 20
Televencin ^a	100			0.03	0.06	0.03 - 0.12	Televencin ^a	0.0			0.5*	1	05-1		Jelavancin ^a	100			0.03	0.06	0.03 - 0.06
Vancomycin	100			0.05	0.00	0.03-0.12	Vancomycin	0.0		100	32*	- 32	16 - \32		Vancomycin	100			0.03	0.00	0.03 - 0.00
Cefazolin	100		100 ^b	8	64	1 - >128	Cefazolin			100 ^b	<u>∖128*</u>	>128	<0.5 - >128		Ceftriaxone	100			<0.0	<0.5	<0.12
Clarithromycin	27.2	18	71 1	32	>32	0 12 - >32	Clarithromycin			100	>32*	>32	>32		Clarithromycin	70.2	32	26.6	<0.12	32	<0.03 - >32
Clindamycin	88.6		11.4	≤0 12	>8	≤0.12 - >8	Clindamycin			100	>8*	>8	>8		Clindamycin	83.9	0.8	15.3	=0.00 ≤0.12	>64	≤0.12 - >64
Daptomycin	100			0.25	0.5	0.25 - 0.5	Daptomycin	100		100	0.25*	0.25	0.12 - 0.25		Doxycycline	No BP	0.0	10.0	8	16	≤0.25 - >16
Linezolid	100			2	2	1 - 4	Linezolid	100			2*	2	1 - 2		Levofloxacin	96.8		3.2	0.5	1	0.25 - >32
Meropenem			100 ^b	2	4	0.12 - 32	Meropenem			100 ^b	16*	>32	0.12 - >32		Linezolid	100			1	2	1 - 2
Moxifloxacin	26.3	19.3	54.4	2	2	≤0.06 - 16	Moxifloxacin			100	4*	>16	4 - >16		Meropenem	100			≤0.06	≤0.06	≤0.06 - 0.12
Pip-Tazo			100 ^b	16	32	2 - 256	Pip-Tazo			100 ^b	64*	128	≤1 - 128		Penicillin	100			≤0.03	0.06	≤0.03 - 0.12
Tigecycline ^a	100			0.25	0.25	≤0.03 - 0.5	Tigecycline ^a	100			0.12*	0.5	0.12 - 0.5		Tigecycline ^a	99.2			0.06	0.12	≤0.015 - 1
TMP/SMX	100			≤0.12	≤0.12	≤0.12 - 1	TMP/SMX	100			≤0.12*	2	≤0.12 - 2		TMP/SMX	No BP			≤0.12	0.25	≤0.12 - 1
HA-MRSA (179)							S. epidermidis (130)							_	a lateraretive has also sint defin			stils la suitauia			
Telavancin ^a	100			0.06	0.06	0.03 - 0.12	Telavancin	No BP			0.06	0.12	0.03 - 0.25		^a Interpretive breakpoint defin ^b Based on oxacillin susceptib	ied by the FDA; vility	, only susce	ptible criteria	a assigned		
Vancomycin	100			1	1	≤0.12 - 2	Vancomycin	100			1	2	≤0.25 - 2		* Median MIC value	Jinty					
Cefazolin			100 ^b	128	>128	1 - >128	Cefazolin	No BP			1	16	≤0.5 - >128								
Clarithromycin	12.3	2.2	85.5	>32	>32	≤0.03 - >32	Clarithromycin	41.1	1.6	57.4	32	>32	≤0.0.03 - >32		Abbreviations:	d					
Clindamycin	46.9		53.1	>8	>8	≤0.12 - >8	Clindamycin	55.8	3.9	40.3	≤0.12	>8	≤0.12 - >8		S susceptible: L intermediate	a R resistant					
Daptomycin	100			0.25	0.5	0.12 - 0.5	Daptomycin	100			0.25	0.25	≤0.06 - 0.5		MSSA, methicillin-susceptible	S. aureus					
Linezolid	100		L	2	2	1 - 4	Linezolid	100			0.5	1	0.25 - 2		MRSA, methicillin-resistant S.	. aureus					
Meropenem			100 ^b	16	>32	0.25 - >32	Meropenem	No BP			1	32	≤0.0.03 - >32		CA-MRSA, community-associ	ated methicillin	-resistant S	. aureus			
Moxifloxacin	3.5	0.2	96.3	8	>16	≤0.06 - >16	Moxifloxacin	54.3	8.5	37.2	0.5	>16	≤0.06 - >16		hVISA, heterogeneous vanco	mycin-intermed	tiate S. aure	aureus aus			
Pip-Tazo			100°	64	128	≤1 - 256	Pip-Tazo	No BP			≤1	8	≤1 - 64		VISA, vancomycin-intermedia	ate S. aureus					
Tigecycline	94.4		5.6	0.25	0.5	0.06 - 1	Tigecycline	No BP			0.12	0.25	≤0.03 - 1		VRSA, vancomycin-resistant	S. aureus					
IMP/SMX	93.9		6.1	≤0.12	≤0.12	≤0.12 - >8	IMP/SMX	65.1		34.9	0.5	8	≤0.12 - >8								

Table 2. MIC distribution for telavancin against Gram-positive cocci

Organism (no. tested)	Number (cumulative percentage) inhibited at telavancin MIC (µg/mL)											
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1			
Methicillin-susceptible S. aureus (1250)		2 (0.2)	6 (0.6)	641 (51.9)	571 (97.6)	30 (100)						
Methicillin-resistant S. aureus (293)				144 (49.1)	140(96.9)	9 (100)						
Community-associated MRSA (114)				58 (50.9)	54 (98.2)	2 (100)						
Healthcare-associated MRSA (179)				86 (48.0)	86 (96.1)	7 (100)						
CANWARD hVISA (8)				1 (12.5)	6 (87.5)	1 (100)						
NARSA VISA (11)					2 (18.2)	7 (81.8)	2 (100)					
NARSA VRSA (7)								4 (57.1)	3 (100)			
S. epidermidis (130)				27 (20.8)	73 (76.9)	27 (97.7)	3 (100)					
S. pneumoniae (334)	23 (6.9)	183 (61.7)	127 (99.7)	1 (100)								
S. pyogenes (87)			4 (4.6)	71 (86.2)	12 (100)							
S. agalactiae (124)				81 (65.3)	43 (100)							

ICAAC/ICC 2015, San Diego, CA, September 17-21, 2015

CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE





Kim Nichol Health Sciences Centre MS673 - 820 Sherbrook St. Winnipeg, MB, Canada R3A 1R9 Phone: (204) 787-4902 Email: knichol@dsmanitoba.ca

RESULTS