E-1681

Activity of Telavancin against 8,686 Gram-Positive Cocci Associated with Infections in Canadian Hospitals from 2007-2012

K.A. NICHOL[1], H.J. ADAM[1,2], N. LAING[2], B. WESHNOWESKI[1], R. VASHISHT[2], M.R. BAXTER[2], D.J. HOBAN[1,2] and G.G. ZHANEL[2]

Diagnostic Services of Manitoba[1] and University of Manitoba[2], Winnipeg, Manitoba, Canada

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

www.can-r.ca

ABSTRACT

Background: Telavancin is a bactericidal lipoglycopeptide with activity against methicillin-resistant *Staphylococcus aureus* and other Gram-positive pathogens. As part of the ongoing national CANWARD surveillance study, we assessed the activity of telavancin and comparators against Gram-positive cocci from Canadian hospitals.

Methods: Between 2007 and 2012, tertiary-care medical centres across Canada submitted isolates from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Annually, each centre was asked to submit pathogens (consecutive, one per patient per infection site) from blood, respiratory specimens, urine, and wound/intravenous infections. 29,932 isolates were collected in total, including 8,686 Gram-positive cocci. Susceptibility testing was performed by broth microdilution using CLSI methodology for comparator agents and FDA-approved dry-form panels for telavancin.

Results: Telavancin MIC ranges as well as MIC_{50} and MIC_{90} values for telavancin, vancomycin, daptomycin and linezolid versus 8,686 Gram-positive cocci are shown below:

Organism (n)	Telavancin MIC Range	Telavancin MIC_{50}/MIC_{90}	Vancomycin MIC_{50}/MIC_{90}	Daptomycin MIC_{50}/MIC_{90}	Linezolid MIC_{50}/MIC_{90}
MSSA (4734)	≤0.06 - 1	0.25 / 0.5	1 / 1	0.25 / 0.25	2 / 2
MRSA (1391)	≤0.06 - 1	0.25 / 0.5	1 / 1	0.25 / 0.25	2 / 2
- HA-MRSA (936)	0.12 - 1	0.25 / 0.5	1 / 1	0.12 / 0.25	2 / 4
- CA-MRSA (415)	≤0.06 - 1	0.25 / 0.5	1 / 1	0.25 / 0.25	2 / 2
MSSE (533)	≤0.06 - 1	0.25 / 0.5	1 / 2	0.12 / 0.25	0.5 / 1
MRSE (97)	≤0.06 - 1	0.25 / 0.25	1 / 2	0.12 / 0.25	1 / 1
S. pneumoniae - All (1931)	≤0.06 - 0.12	≤0.06 / ≤0.06	≤0.25 / 0.25	0.06 / 0.12	0.5 / 1
- PenS (1543)	≤0.06 - 0.12	≤0.06 / ≤0.06	≤0.25 / 0.25	0.06 / 0.12	0.5 / 1
- PenI (254)	≤0.06 - 0.06	≤0.06 / ≤0.06	≤0.25 / 0.5	0.06 / 0.12	1 / 1
- PenR (84)	≤0.06 - 0.06	≤0.06 / ≤0.06	≤0.25 / 0.5	0.06 / 0.12	0.5 / 1

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; HA-MRSA, healthcare-associated MRSA; CA-MRSA, community-associated MRSA; MSSE, methicillin-susceptible *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*.

Conclusions: Telavancin is more active in vitro than vancomycin and linezolid and has comparable activity to daptomycin against MSSA, MRSA (including CA-MRSA and HA-MRSA), MSSE, MRSE and *S. pneumoniae*.

BACKGROUND

Antibiotic resistance among Gram-positive pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Staphylococcus epidermidis* is a growing concern. The global escalation in both community- and healthcare-acquired antibiotic-resistant organisms is threatening our ability to effectively treat patients by significantly limiting the therapeutic options available to clinicians and increasing the risk of treatment failures. Management of infections caused by these difficult-to-treat pathogens is often complicated further by the fact that many of these strains are multidrug-resistant. These observations underscore the need for continued surveillance, more judicious antibiotic prescribing practices and new treatment alternatives.

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 (1-4). 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 (1-4).

PURPOSE

The purpose of this study was to assess the activity of telavancin and comparators against Gram-positive cocci obtained from Canadian hospitals between 2007 and 2012 as part of the ongoing national CANWARD surveillance study.

MATERIALS & METHODS

CANWARD Study Design

Between January 2007 and December 2012, 29,932 clinical isolates, including 8,686 Gram-positive 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 (12 in 2007, 10 in 2008, 15 in 2009, 14 in 2010, 15 in 2011, 12 in 2012) 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. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where they were subcultured onto appropriate media and stocked in skim milk at -80°C.

Antimicrobial Susceptibility Testing

Following two subcultures from frozen stock, the *in vitro* activities of telavancin and 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 Clinical and Laboratory Standards Institute (CLSI) guidelines (5). Antimicrobial minimum inhibitory concentrations (MICs) were determined using 96-well custom designed microtitre panels for comparator agents and Trek Sensititre dry-form panels for telavancin. Quality control was performed using the following ATCC organisms: *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 29213. MIC interpretive standards were defined according to CLSI breakpoints (6). The following interpretive breakpoints (FDA) were used with *S. aureus*: telavancin susceptible, ≤1 μg/ml; tigecycline susceptible, ≤0.5 μg/ml. With *S. pneumoniae*, an interpretive breakpoint (FDA) of ≤0.06 μg/ml was used for tigecycline susceptible. Tetracycline breakpoints were used to interpret *S. pneumoniae* doxycycline MIC values.

ACKNOWLEDGMENTS

Financial support for the CANWARD study was provided in part by Astellas Pharma Canada, Inc. and Theravance, Inc.

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

Dr. D. Roscoe – Vancouver Hospital, Vancouver
Dr. J. Fuller – University of Alberta Hospital, Edmonton
Dr. J. Blondeau – Royal University Hospital, Saskatoon
Drs. D. Hoban/G. Zhanel – Health Sciences Centre, Winnipeg
Dr. M. John – London Health Sciences Centre, London
Dr. S. Poutanen – UHN and Mount Sinai Hospital, Toronto
Dr. L. Matukas – St. Michael's Hospital, Toronto
Dr. C. Lee – St. Joseph's Hospital, Hamilton
Dr. F. Chan – Children's Hospital of Eastern Ontario, Ottawa
Dr. M. Desjardins – The Ottawa Hospital, Ottawa
Dr. M. Laverdière – Hôpital 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 telavancin and comparators against Gram-positive cocci from CANWARD 2007-2012

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. aureus							
MSSA (4734)							
Telavancin[a]	100			0.25	0.5	≤ 0.06	1
Vancomycin	100			1	1	≤ 0.25	2
Cefazolin	100			≤ 0.5	1	≤ 0.5	32
Clarithromycin	74.9	0.2	24.9	0.25	> 16	≤ 0.25	> 16
Clindamycin	92.8	0.3	6.9	≤ 0.25	≤ 0.25	≤ 0.25	> 8
Daptomycin	100			0.25	0.25	≤ 0.06	1
Levofloxacin	90.1	0.3	9.6	0.25	1	≤ 0.06	> 32
Linezolid	100			2	2	≤ 0.12	4
Meropenem	100			0.12	0.25	≤ 0.12	4
Moxifloxacin	90.1	0.6	9.3	≤ 0.06	0.5	≤ 0.06	> 16
Pip-Tazo	99.9		0.1	≤ 1	≤ 1	≤ 1	32
Tigecycline[a]	99.9		0.1	0.12	0.25	≤ 0.03	1
TMP/SMX	99.4		0.6	≤ 0.12	≤ 0.12	≤ 0.12	> 8
MRSA (1391)							
Telavancin[a]	100			0.25	0.5	≤ 0.06	1
Vancomycin	99.9	0.1		1	1	≤ 0.25	4
Cefazolin			100[b]	64	> 128	1	> 128
Clarithromycin	13.0	0.1	86.9	> 16	> 16	≤ 0.25	> 16
Clindamycin	50.0	0.1	49.9	0.5	> 8	≤ 0.25	> 8
Daptomycin	100			0.25	0.25	0.06	1
Levofloxacin	14.1		85.9	> 32	> 32	0.12	> 32
Linezolid	100			2	2	≤ 0.12	4
Meropenem			100[b]	8	32	0.12	> 32
Moxifloxacin	15.5	2.2	82.3	8	> 16	≤ 0.06	> 16
Pip-Tazo			100[b]	32	128	≤ 1	512
Tigecycline[a]	99.6		0.4	0.25	0.5	0.06	2
TMP/SMX	92.5		7.5	≤ 0.12	≤ 0.12	≤ 0.12	> 8
CA-MRSA (415)							
Telavancin[a]	100			0.25	0.5	0.12	1
Vancomycin	100			1	1	0.5	2
Cefazolin			100[b]	16	64	1	> 128
Clarithromycin	26.0	0.2	73.8	> 16	> 16	≤ 0.25	> 16
Clindamycin	86.9		13.1	≤ 0.25	> 8	≤ 0.25	> 8
Daptomycin	100			0.25	0.25	0.12	1
Levofloxacin	40.0		60.0	4	8	0.12	32
Linezolid	100			2	2	1	4
Meropenem			100[b]	2	4	0.12	32
Moxifloxacin	35.8	6.7	57.5	2	2	≤ 0.06	16
Pip-Tazo			100[b]	16	32	2	128
Tigecycline[a]	100			0.25	0.25	0.06	0.5
TMP/SMX	100			≤ 0.12	≤ 0.12	≤ 0.12	2
HA-MRSA (936)							
Telavancin[a]	100			0.25	0.5	≤ 0.06	1
Vancomycin	99.9	0.1		1	1	≤ 0.25	4
Cefazolin			100[b]	128	> 128	1	> 128
Clarithromycin	4.9		95.1	> 16	> 16	≤ 0.25	> 16
Clindamycin	32.1	0.1	67.8	> 8	> 8	≤ 0.25	> 8
Daptomycin	100			0.25	0.25	0.06	1
Levofloxacin	2.9		97.1	> 32	> 32	0.12	> 32
Linezolid	100			2	4	≤ 0.12	4
Meropenem			100[b]	8	> 32	0.25	> 32
Moxifloxacin	3.5	0.2	96.3	8	> 16	≤ 0.06	> 16
Pip-Tazo			100[b]	64	128	≤ 1	512
Tigecycline[a]	99.4		0.6	0.25	0.5	0.06	2
TMP/SMX	88.9		11.1	≤ 0.12	8	≤ 0.12	> 8

[a] Interpretive breakpoints defined by FDA.
[b] Based on oxacillin susceptibility.
S, susceptible; I, intermediate; R, resistant.

CA-MRSA, community-associated methicillin-resistant *S. aureus*.
HA-MRSA, healthcare-associated methicillin-resistant *S. aureus*.

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. pneumoniae							
All (1931)							
Telavancin	No BP			≤ 0.06	≤ 0.06	≤ 0.06	0.12
Vancomycin	100			≤ 0.25	0.25	≤ 0.25	1
Ceftriaxone	99.3	0.5	0.2	≤ 0.12	≤ 0.12	≤ 0.12	4
Clarithromycin	80.0	3.5	16.5	≤ 0.03	4	≤ 0.03	> 32
Clindamycin	93.0	0.5	6.5	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Doxycycline[c]	93.2	3.0	3.8	≤ 0.25	1	≤ 0.25	> 16
Levofloxacin	99.0	0.2	0.8	1	1	≤ 0.06	32
Linezolid	100			0.5	1	≤ 0.12	2
Meropenem	95.5	2.8	1.7	≤ 0.06	≤ 0.06	≤ 0.06	2
Penicillin	82.0	13.5	4.5	≤ 0.03	0.25	≤ 0.03	> 8
Tigecycline[a]	99.7		0.3	0.03	0.06	≤ 0.03	0.25
TMP/SMX	85.1	6.4	8.5	≤ 0.12	2	≤ 0.12	> 8
PSSP (1543)							
Telavancin	No BP			≤ 0.06	≤ 0.06	≤ 0.06	0.12
Vancomycin	100			≤ 0.25	0.25	≤ 0.25	1
Ceftriaxone	100			≤ 0.12	≤ 0.12	≤ 0.12	0.25
Clarithromycin	87.8	2.7	9.5	≤ 0.03	0.5	≤ 0.03	> 32
Clindamycin	97.6	0.4	2.0	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Doxycycline[c]	96.9	1.5	1.6	≤ 0.25	≤ 0.25	≤ 0.25	> 16
Levofloxacin	99.3	0.2	0.5	1	1	≤ 0.06	32
Linezolid	100			0.5	1	≤ 0.12	2
Meropenem	99.9	0.1		≤ 0.06	≤ 0.06	≤ 0.06	0.5
Penicillin	100.0			≤ 0.03	0.06	≤ 0.03	0.06
Tigecycline[a]	99.9		0.1	0.03	0.06	≤ 0.03	0.25
TMP/SMX	91.9	5.4	2.7	≤ 0.12	0.5	≤ 0.12	> 8
PISP (254)							
Telavancin	No BP			≤ 0.06	≤ 0.06	≤ 0.06	0.06
Vancomycin	100			≤ 0.25	0.5	≤ 0.25	1
Ceftriaxone	98.8	0.8	0.4	≤ 0.12	0.5	≤ 0.12	4
Clarithromycin	49.0	9.5	41.5	0.5	> 32	≤ 0.03	> 32
Clindamycin	79.5	1.1	19.4	≤ 0.12	> 8	≤ 0.12	> 8
Doxycycline[c]	75.9	6.3	17.8	≤ 0.25	16	≤ 0.25	> 16
Levofloxacin	98.0		2.0	1	1	0.25	16
Linezolid	100			1	1	≤ 0.12	2
Meropenem	91.7	7.5	0.8	≤ 0.06	0.25	≤ 0.06	1
Penicillin		100		0.25	1	0.12	1
Tigecycline[a]	99.2		0.8	0.03	0.06	≤ 0.03	0.12
TMP/SMX	66.1	12.6	21.3	0.25	8	≤ 0.12	> 8
PRSP (84)							
Telavancin	No BP			≤ 0.06	≤ 0.06	≤ 0.06	0.06
Vancomycin	100			≤ 0.25	0.5	≤ 0.25	1
Ceftriaxone	88.1	8.3	3.6	0.5	2	≤ 0.12	4
Clarithromycin	31.0	2.3	66.7	16	> 32	≤ 0.03	> 32
Clindamycin	48.8	2.4	48.8	0.5	> 8	≤ 0.12	> 8
Doxycycline[c]	75.0	21.4	3.6	1	4	≤ 0.25	> 16
Levofloxacin	97.6		2.4	1	1	0.25	16
Linezolid	100			0.5	1	0.25	2
Meropenem	26.2	38.1	35.7	0.5	1	≤ 0.06	2
Penicillin			100	2	4	2	> 8
Tigecycline[a]	98.8		1.2	0.03	0.06	≤ 0.03	0.12
TMP/SMX	15.5	5.9	78.6	8	> 8	≤ 0.12	> 8

[a] Interpretive breakpoints defined by FDA.
[c] Tetracycline breakpoints used to interpret MIC values.
PSSP, penicillin-susceptible *S. pneumoniae*.
PISP, penicillin-intermediate *S. pneumoniae*.
PRSP, penicillin-resistant *S. pneumoniae* (MIC ≥2 μg/ml).
S, susceptible; I, intermediate; R, resistant.
No BP, no breakpoints defined.

Organism (n), Antibiotic	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. epidermidis							
MSSE (533)							
Telavancin	No BP			0.25	0.5	≤ 0.06	1
Vancomycin	100			1	2	≤ 0.25	4
Cefazolin	100			1	4	≤ 0.5	8
Clarithromycin	34.2	1.3	64.5	> 16	> 16	≤ 0.25	> 16
Clindamycin	62.2	0.9	36.9	≤ 0.25	> 8	≤ 0.25	> 8
Daptomycin	100			0.12	0.25	≤ 0.06	1
Levofloxacin	51.9	1.1	47.0	0.25	> 32	0.12	> 32
Linezolid	100			0.5	1	≤ 0.12	4
Meropenem	80.3	11.4	8.3	1	8	≤ 0.12	32
Moxifloxacin	53.5	7.5	39.0	0.12	16	≤ 0.06	> 16
Pip-Tazo	98.5		1.5	≤ 1	4	≤ 1	64
Tigecycline	No BP			0.12	0.5	≤ 0.03	1
TMP/SMX	65.8		34.2	≤ 0.12	8	≤ 0.12	> 8
MRSE (97)							
Telavancin	No BP			0.25	0.5	≤ 0.06	1
Vancomycin	100			1	2	≤ 0.25	2
Cefazolin			100	128	> 128	32	> 128
Clarithromycin	14.4		85.6	> 16	> 16	≤ 0.25	> 16
Clindamycin	16.5		83.5	> 8	> 8	≤ 0.25	> 8
Daptomycin	100			0.12	0.25	≤ 0.06	0.5
Levofloxacin	2.2	2.2	95.6	> 32	> 32	1	> 32
Linezolid	100			1	1	≤ 0.12	1
Meropenem	1.0	2.1	96.9	32	32	4	> 32
Moxifloxacin	3.1	2	94.9	> 16	> 16	≤ 0.06	> 16
Pip-Tazo	7.3		92.7	32	64	≤ 1	128
Tigecycline	No BP			0.12	0.25	0.06	0.5
TMP/SMX	19.6		80.4	4	8	≤ 0.12	> 8

No BP, no breakpoints defined.
S, susceptible; I, intermediate; R, resistant.

MSSE, methicillin-susceptible *S. epidermidis*.
MRSE, methicillin-resistant *S. epidermidis*.

Table 2. MIC distribution of telavancin against Gram-positive cocci from CANWARD 2007-2012

Organism (no. tested)	Number (cumulative percentage) at each MIC ≤ 0.06	0.12	0.25	0.5	1
Methicillin-susceptible *S. aureus* (3729)	21 (0.6)	1255 (34.2)	1563 (76.1)	789 (97.3)	101 (100)
Methicillin-resistant *S. aureus* (1087)	1 (0.1)	308 (28.4)	440 (68.9)	301 (96.6)	37 (100)
Community-associated MRSA (349)		101 (28.9)	143 (69.9)	95 (97.1)	10 (100)
Healthcare-associated MRSA (703)	1 (0.1)	196 (28.0)	284 (68.4)	196 (96.3)	26 (100)
Methicillin-susceptible *S. epidermidis* (424)	36 (8.5)	157 (45.5)	160 (83.3)	64 (98.3)	7 (100)
Methicillin-resistant *S. epidermidis* (79)	3 (3.8)	33 (45.6)	34 (88.6)	6 (96.2)	3 (100)
S. pneumoniae (1862)	1858 (99.8)	4 (100)			
Penicillin-susceptible *S. pneumoniae* (1507)	1503 (99.7)	4 (100)			
Penicillin-intermediate *S. pneumoniae* (251)	251 (100)				
Penicillin-resistant *S. pneumoniae* (84)	84 (100)				

MIC, minimum inhibitory concentration (μg/ml).

CONCLUSIONS

Against methicillin-susceptible and methicillin-resistant *S. aureus* (including both community- and healthcare-associated strains), telavancin had comparable activity to daptomycin and superior activity to vancomycin and linezolid as measured by the MIC.

Telavancin was more active than vancomycin and linezolid against methicillin-susceptible and methicillin-resistant *S. epidermidis* and was comparable to daptomycin.

Against *S. pneumoniae*, telavancin was more active than vancomycin, linezolid and penicillin. Telavancin was the most potent agent tested against penicillin-resistant *S. pneumoniae*.

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53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, September 10-13, 2013