Telavancin Activity against a Global Collection of *Staphylococcus aureus* Clinical Isolates (2013–2015)

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ABSTRACT

Background. Telavancin has shown broad activity against gram-positive organisms in international surveillance programs. This study evaluates the activity of telavancin against a challenge set of *Staphylococcus aureus* isolates from a worldwide network of medical centres (2013-2015).

Methods. 22,406 *S. aureus* isolates from 147 sites in the United States (14,019) and rest of world (ROW; 8,384 in Europe, Latin America, and Asia-Pacific) were included. Isolates were submitted to a central laboratory for bacterial identification and susceptibility testing. Methicillin-resistant *S. aureus* (MRSA) isolates displaying a resistance phenotype to at least 3 additional classes of drugs were considered multidrug-resistant (MDR).

Results. A total of 46.6% of US isolates were MRSA and 29.3% of those were MDR, while 31.5% of ROW isolates were MRSA with 40.0% of those being MDR. Telavancin had consistent $MIC_{50/90}$ values (0.03/0.06 mg/L,) against all methicillin-susceptible *S. aureus* (MSSA) and MRSA. Most *S. aureus* (58.7–60.0%) had vancomycin MICs at 1 mg/L, whereas 0.5% and 0.8% of US and ROW isolates, respectively, had elevated vancomycin MICs (i.e., 2 mg/L). Slightly higher telavancin MIC_{50} results ($MIC_{50/90}$, 0.06/0.06 mg/L) were noted against isolates displaying a vancomycin MIC of 2 mg/L compared to isolates with vancomycin MIC of ≤1 mg/L (MIC_{50}, 0.015–0.03 mg/L). When stratified by region, telavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) showed $MIC_{50/90}$ results 8- to 16-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and vancomycin ($MIC_{50/90}$, 1/1 mg/L) against the MRSA or MDR subsets.

Conclusions. Telavancin (100.0% susceptible) demonstrated potent *in vitro* activity against this global collection of *S. aureus* regardless of resistance phenotype, including isolates with vancomycin MIC of 2 mg/L. This *in vitro* activity was greater than comparators. Telavancin also showed consistent activity against these challenge sets.

INTRODUCTION

- Antimicrobial resistance is recognized as one of the most serious public health threats worldwide and failure to address it could compromise modern medical advances
- Among bacterial pathogens that cause healthcare-associated (HAI) and community-associated (CAI) infections, *Staphylococcus aureus* has proven to be a highly adaptable pathogen, fully capable of acquiring multiple resistance mechanisms as well as increased virulence
- The multidrug-resistant (MDR) capacity of *S. aureus*, especially healthcare-associated methicillin-resistant *S. aureus* (HA-MRSA), coupled with concerns regarding the adequacy of vancomycin in the treatment of complicated staphylococcal infections has challenged the management of *S. aureus* infections
- Telavancin is a parenteral, bactericidal, lipoglycopeptide agent that has been shown to be non-inferior to vancomycin in Phase 3 clinical trials of adult patients with complicated skin and skin structure infections (cSSSI) and with hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP), due to susceptible Gram-positive pathogens and *S. aureus*
- Telavancin is approved for clinical use by the Food and Drug Administration to treat (once daily) cSSSI and HABP/VABP when alternative agents are not suitable
- In Canada and Russia, TLV is approved for cSSSI and HABP/VABP, while in the European Union, TLV is approved for the treatment of nosocomial pneumonia, known or believed to be caused by MRSA when other alternative medicines are unsuitable
- This study evaluates the activity of telavancin against a challenge set of *S. aureus* isolates from a worldwide network of medical centres (2013–2015)

MATERIALS AND METHODS

Bacterial strain collection

- 22,406 unique (1 per patient) *S. aureus* isolates from 147 sites in the United States (14,019) and rest of world (ROW; 8,384 in Europe, Latin America, and Asia-Pacific) were included
- All isolates were deemed responsible for human infections per local guidelines
- Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa USA), as part of the SENTRY Antimicrobial Surveillance Program during 2013–2015
- Isolates were initially identified by the participating laboratory with identification confirmed by the reference monitoring laboratory by using standard algorithms and supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by broth microdilution (BMD), following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- The telavancin BMD MIC testing follows the CLSI-approved method supplemented with 0.002% polysorbate-80
- Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event
- MIC values were validated by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212)
- MIC breakpoint interpretation used current EUCAST criteria
- MRSA isolates displaying resistance phenotype to at least 3 classes of drugs other than ß-lactam agents were considered MDR

RESULTS

- A total of 46.6% of US and 31.5% of ROW isolates were MRSA **(Table 1)**
- MRSA rates were 39.0% in Latin America, followed by rates of 31.4% in Asia-Pacific, 30.1% in Europe, and 23.1% in Canada (data not shown)

Table 1. Antimicrobial activity and MIC distributions for telavancin when tested against 22,406 *S. aureus* isolates from the United States and rest of world (2013–2015)

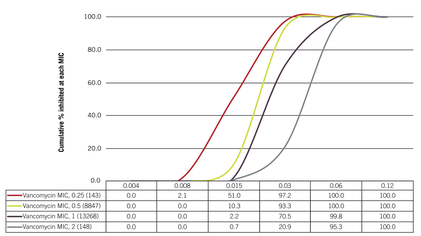
Region / phenotype[a] (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at telavancin MIC (mg/L) of:			
	50%	90%	≤0.015	0.03	0.06	0.12
US (14,019)						
MSSA (7,488)	0.03	0.06	545 (7.3%)	5721 (83.7%)	1220 (>99.9%)	2 (100.0%)
MRSA (6,531)	0.03	0.06	282 (4.3%)	5180 (83.6%)	1059 (99.8%)	10 (100.0%)
MDR (1,916)	0.03	0.06	79 (4.1%)	1402 (77.3%)	432 (99.8%)	3 (100.0%)
Vancomycin MIC=2 mg/L (77)	0.06	0.06	1 (1.3%)	19 (26.0%)	55 (97.4%)	2 (100.0%)
ROW (8,387)						
MSSA (5,748)	0.03	0.06	332 (5.8%)	3961 (74.7%)	1450 (99.9%)	5 (100.0%)
MRSA (2,639)	0.03	0.06	122 (4.6%)	1644 (66.9%)	860 (99.5%)	13 (100.0%)
MDR (1,055)	0.03	0.06	43 (4.1%)	550 (56.2%)	456 (99.4%)	6 (100.0%)
Vancomycin MIC=2 mg/L (71)	0.06	0.06		11 (15.5%)	55 (93.0%)	5 (100.0%)

[a]MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant defined as MRSA (methicillin (oxacillin)-resistant) resistant to 3 or more drug classes and to ß-lactam agents; ROW, rest of the world

RESULTS (CONTINUED)

- Among the MRSA collection, 29.3% of US isolates were MDR, while 40.0% of isolates from ROW were designated MDR **(Table 1)**
- Telavancin had consistent $MIC_{50/90}$ values (0.03/0.06 mg/L,) against all MSSA, MRSA, and MDR subsets regardless of geographic region **(Table 1)**
- Telavancin, daptomycin, linezolid, teicoplanin, vancomycin, and trimethoprim-sulfamethoxazole were *in vitro* active (97.2–100.0% susceptible) against MRSA from the US and ROW, while ceftaroline, gentamicin, and tetracycline were active (92.2–96.4% susceptible) against US isolates **(Table 2)**
- Telavancin, daptomycin, linezolid, teicoplanin, vancomycin, and trimethoprim-sulfamethoxazole were also *in vitro* active (92.2–100.0% susceptible) against MDR MRSA from the US and ROW **(Table 2)**
- Telavancin ($MIC_{50/90}$, 0.06/0.06 mg/L) was at least 8-fold more potent than active comparators tested against MRSA or MDR isolates from the US or ROW **(Table 2)**
- Most *S. aureus* (58.7–60.0%) had vancomycin MICs at 1 mg/L, whereas 0.5% of US and 0.8% of ROW isolates had elevated vancomycin MICs (2 mg/L) **(Table 1)**
- Telavancin MIC results obtained against *S. aureus* increased as the vancomycin MIC values increased **(Table 1 and Figure 1)**
- Telavancin inhibited all isolates (100.0% susceptible) at the susceptibility breakpoint (≤0.12 mg/L)
- Similarly, when tested against *S. aureus* with vancomycin MIC of 2 mg/L, daptomycin demonstrated MIC_{50} values 2-fold higher than that observed for isolates with vancomycin MIC values of ≤1 mg/L **(Table 2)**, which was noted against isolates from the US and ROW (data not shown)

Figure 1. Cumulative MIC distribution of telavancin against *S. aureus* displaying vancomycin MIC results of 0.25, 0.5, 1 and 2 mg/L



	0.004	0.008	0.015	0.03	0.06	0.12
Vancomycin MIC, 0.25 (143)	0.0	2.1	51.0	97.2	100.0	100.0
Vancomycin MIC, 0.5 (8847)	0.0	0.0	10.3	93.3	100.0	100.0
Vancomycin MIC, 1 (13268)	0.0	0.0	2.2	70.5	99.8	100.0
Vancomycin MIC, 2 (148)	0.0	0.0	0.7	20.9	95.3	100.0

Table 2. Antimicrobial activity of telavancin and comparator agents tested against 22,406 *S. aureus* isolates from the United States (US) and rest of the world (ROW) (2013–2015)

Group[a] (no. tested; US/ROW) / agent[b]	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	%S[c]	%I	%R	%S	%I	%R
	US		ROW		US			ROW		
MRSA (6,531/2,639)										
Telavancin	0.03	0.06	0.03	0.06	100.0	-	0.0 [b]	100.0	-	0.0 [b]
Ceftaroline	0.5	1	1	2	96.4	-	3.6	86.2	-	13.8
Clindamycin	≤0.25	>2	≤0.25	>2	71.7	0.3	28.1	63.9	0.2	35.9
Daptomycin	0.25	0.5	0.25	0.5	99.9	-	0.1	99.9	-	0.1
Erythromycin	>8	>8	>8	>8	11.8	0.8	87.4	31.6	1.3	67.1
Gentamicin	≤1	≤1	≤1	>8	96.0	-	4.0	78.1	-	21.9
Levofloxacin	4	>4	>4	>4	31.1	1.5	67.5	22.6	0.5	76.9
Linezolid	1	1	1	1	99.9	-	0.1	>99.9	-	<0.1
Teicoplanin	≤2	≤2	≤2	≤2	99.9	-	0.1	99.0	-	1.0
Tetracycline	≤0.5	1	≤0.5	>8	92.2	1.4	6.4	83.8	0.3	16.0
TMP-SMX	≤0.5	≤0.5	≤0.5	≤0.5	97.2	0.4	2.4	97.5	0.4	2.1
Vancomycin	1	1	1	1	100.0	-	0.0	100.0	-	0.0
MDR (1,916/1,055)										
Telavancin	0.03	0.06	0.03	0.06	100.0	-	0.0 [b]	100.0	-	0.0 [b]
Ceftaroline	1	2	1	2	88.3	-	11.7	69.5	-	30.5
Clindamycin	>2	>2	>2	>2	9.7	0.5	89.8	11.7	0.3	88.1
Daptomycin	0.25	0.5	0.25	0.5	99.7	-	0.3	99.7	-	0.3
Erythromycin	>8	>8	>8	>8	0.3	0.2	99.5	0.2	1.2	98.6
Gentamicin	≤1	≤1	≤1	>8	90.0	-	10.0	60.1	-	39.9
Levofloxacin	>4	>4	>4	>4	1.6	0.7	97.7	1.0	0.6	98.4
Linezolid	1	1	1	1	99.7	-	0.3	99.9	-	0.1
Teicoplanin	≤2	≤2	≤2	≤2	99.7	-	0.3	97.8	-	2.2
Tetracycline	≤0.5	>8	≤0.5	>8	78.7	4.8	16.5	73.2	0.7	26.2
TMP-SMX	≤0.5	≤0.5	≤0.5	≤0.5	92.2	1.4	6.4	93.7	0.9	5.3
Vancomycin	1	1	1	1	100.0	-	0.0	100.0	-	0.0
Vancomycin MIC=2 mg/L (77/71)										
Telavancin	0.06	0.06	0.06	0.06	-	-	-	-	-	-
Ceftaroline	0.5	1	0.25	1	90.0	-	10.0	90.0	-	10.0
Clindamycin	≤0.25	>2	≤0.25	>2	57.1	0.0	42.9	62.0	2.8	35.2
Daptomycin	0.5	1	0.5	0.5	97.4	-	2.6	97.2	-	2.8
Erythromycin	>8	>8	0.25	>8	29.9	1.3	68.8	56.3	1.4	42.3
Gentamicin	≤1	≤1	≤1	>8	90.9	-	9.1	71.8	-	28.2
Levofloxacin	4	>4	0.25	>4	42.9	0.0	57.1	52.1	0.0	47.9
Linezolid	1	1	1	1	98.7	-	1.3	100.0	-	0.0
Oxacillin	>2	>2	1	>2	45.5	-	54.5	52.1	-	47.9
Teicoplanin	≤2	≤2	≤2	4	93.5	-	6.5	87.3	-	12.7
Tetracycline	≤0.5	2	≤0.5	>8	84.4	9.1	6.5	85.9	0.0	14.1
TMP-SMX	≤0.5	≤0.5	≤0.5	2	97.4	1.3	1.3	91.5	0.0	8.5
Vancomycin	2	2	2	2	100.0	-	0.0	100.0	-	0.0

[a]MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole; MDR, multidrug resistance (defined as MRSA-resistant to 3 or more drug classes in addition to ß-lactam agents)
[b]TMP-SMX, trimethoprim-sulfamethoxazole
[c]Breakpoint criteria for telavancin according to EUCAST (2016): breakpoint criteria for telavancin comparator agents, as available; -, breakpoint not available

CONCLUSIONS

- Telavancin (100.0% susceptible) demonstrated potent *in vitro* activity against this global collection of *S. aureus* regardless of resistance phenotype, including isolates with decreased susceptibility to vancomycin (MIC, 2 mg/L) or geographic region
- Moreover, the telavancin *in vitro* activity was consistently more potent than comparators, including against the MDR challenge sets
- Data indicate that telavancin may be an option for treating infections caused by these organisms

ACKNOWLEDGEMENTS

- The research and publication process was supported by Theravance Biopharma R&D, Inc. Poster production support was coordinated by AlphaBioCom, funded by Theravance Biopharma R&D, Inc.

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The research and publication process was supported by Theravance Biopharma R&D, Inc.