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Analysis of Telavancin *in vitro* Activity Tested Against a USA Collection of *Staphylococcus aureus* Clinical Isolates Causing Hospital-Acquired Pneumonia (2013-2014)

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ABSTRACT

Background: Telavancin is approved in the USA and Europe (methicillin-resistant [MRSA] only) for the treatment of hospital-acquired (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by *S. aureus* when alternative treatments are not suitable. This study provides a current *in vitro* activity analysis for telavancin and comparators against *S. aureus* causing HABP in USA hospitals during 2013 – 2014.

Methods: 1,353 *S. aureus* collected from 29 USA sites located in the nine USA Census regions were included. Susceptibility testing was performed based on CLSI guidelines (M07-A10 and M100-S25). MIC interpretation was guided by FDA (2014), CLSI (2015) and/or EUCAST (2015) criteria. MRSA resistant to three or more drug classes were defined as multidrug-resistant (MDR).

Results: Telavancin had MIC_{50}, MIC_{90} and MIC_{100} of 0.03, 0.06 and 0.06 µg/mL, respectively, against methicillin-susceptible, MRSA, non-MDR and MDR subsets. All isolates were inhibited by telavancin at the susceptible breakpoint (i.e. ≤0.12 µg/mL). Telavancin MIC values were at least 16-fold lower than vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL) MIC results against MRSA isolates (all 100.0% susceptible to vancomycin and linezolid). Telavancin, vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL) showed activity against the MDR subset, while other agents had limited coverage. *S. aureus* with vancomycin MIC=2 µg/mL had telavancin MIC_{50} (0.06 µg/mL) two-fold higher than those with vancomycin MIC at ≤1 µg/mL. However, telavancin had MIC_{100} results of 0.06 µg/mL, regardless of subset.

Conclusions: Telavancin had potent *in vitro* activity against *S. aureus* causing HABP, including less susceptible and MDR subsets, inhibiting all *S. aureus* at ≤0.06 µg/mL. These results confirm the potent *in vitro* activity of telavancin against *S. aureus* causing HABP in USA hospitals.

INTRODUCTION

- Hospital-acquired bacterial pneumonia (HABP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide-range of preventive measures. HAP is the second most common nosocomial infection in the United States and is a leading cause of mortality among hospital-acquired infection (HAI). The rate of HABP is thought to be between 5 and 10 cases per 1,000 admissions in the United States, with the incidence of VAP being much higher.
- Telavancin is a lipoglycopeptide antibacterial agent with a dual mechanism of action that combines inhibition of cell wall synthesis and disruption of bacterial cell membrane function. Telavancin is approved in the United States for HABP and VAP due to *Staphylococcus aureus* (methicillin-susceptible [MSSA] and -resistant *S. aureus* [MRSA]) when other alternatives are unsuitable, and in Europe for treatment of MRSA nosocomial pneumonia when other alternatives are unsuitable. This study provides a current *in vitro* activity analysis for telavancin and comparators against *S. aureus* causing HABP in USA hospitals during 2013 – 2014.

MATERIALS AND METHODS

- **Bacterial strain collection.** A total of 1,353 *S. aureus* isolates collected from 29 sites located in nine USA Census regions were included. These isolates were part of the Telavancin Surveillance Program for Resistance (2013 - 2014), which is part of the SENTRY Antimicrobial Surveillance Program. Isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) by the participating laboratory. Bacterial identification was confirmed by the reference monitoring laboratory (JMI Laboratories) using standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).
- **Antimicrobial susceptibility test methods.** Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These validated panels provide MIC results equivalent to the CLSI-approved broth microdilution method which includes 0.002% polysorbate-80 in the testing media. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Quality of the MIC values was assured by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212). All QC results were within published acceptable ranges (M100-S25).
- MIC interpretations for comparator agents were based on the CLSI M100-S25 (2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) criteria, as available. MIC interpretation for telavancin tested against *S. aureus* was based on the breakpoints available in the product package insert and EUCAST (for MRSA only), which are ≤0.12 µg/mL for susceptible for both international agencies. MRSA isolates were categorized as multidrug-resistant (MDR) when a resistance phenotype to three or more drug classes of drugs in addition to ß-lactam agents was observed.

RESULTS

- Approximately 50% of the *S. aureus* included in the study displayed a methicillin-resistant phenotype; and among these 42.0% had a MDR phenotype **(Table 1)**.
- Telavancin had MIC_{50}, MIC_{90} and MIC_{100} of 0.03, 0.06 and 0.06 µg/mL, respectively, against the overall collection, MRSA, non-MDR and MDR subsets. All isolates were inhibited by telavancin at the susceptible breakpoint (i.e. ≤0.12 µg/mL; **Table 1**).
- *S. aureus* with vancomycin MIC values of 2 µg/mL had telavancin MIC_{50} results (0.06 µg/mL) two-fold higher than those with vancomycin MIC values at ≤1 µg/mL. However, telavancin had MIC_{100} results of 0.06 µg/mL (i.e. below the breakpoint for susceptibility), regardless of the vancomycin phenotype (**Table 1**).
- Telavancin MIC values were 16-fold lower than vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL) against methicillin-susceptible (MSSA), MRSA and both MRSA subsets (all 100.0% susceptible; **Table 2**).
- Among other comparator agents, clindamycin, gentamicin, tetracycline and trimethoprim-sulfamethoxazole (94.1 - 99.7% susceptible) had *in vitro* antimicrobial coverage against MSSA, and the MRSA non-MDR groups (**Table 2**).
- While gentamicin, tetracycline and trimethoprim-sulfamethoxazole (91.0 - 97.5% susceptible) were active against the overall MRSA population, only trimethoprim-sulfamethoxazole (99.2% susceptible) had high susceptible rates against the MRSA MDR subset (**Table 2**).

Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against contemporary (2013-2014) *S. aureus* clinical isolates from USA medical centers causing HABP.

S. aureus (no. tested)	MIC (µg/mL)		Number of isolates (cumulative %) inhibited at MIC (µg/mL)					
	50%	90%	≤0.015		0.03		0.06	
All (1,353)	0.03	0.06	63	(4.7)	**1002**	(78.7)	288	(100.0)
Methicillin-susceptible (677)	0.03	0.03	35	(5.2)	**504**	(79.6)	138	(100.0)
Methicillin-resistant (676)	0.03	0.06	28	(4.1)	**498**	(77.8)	150	(100.0)
MDR (284)	0.03	0.06	7	(2.5)	**203**	(73.9)	74	(100.0)
Non-MDR (392)	0.03	0.06	21	(5.4)	**295**	(80.6)	76	(100.0)
Vancomycin MIC, ≤1 µg/mL (1,341)	0.03	0.06	63	(4.7)	**999**	(79.2)	279	(100.0)
Vancomycin MIC = 2 µg/mL (12)	0.06	0.06	0	(0.0)	3	(25.0)	**9**	(100.0)

MDR = multidrug-resistant, defined as MRSA (methicillin [oxacillin]-resistant) resistant to three or more drug classes in addition to ß-lactam agents. Modal MIC results are in bold.

CONCLUSIONS

- Telavancin had potent *in vitro* activity against *S. aureus* causing HABP among hospitalized patients in USA institutions, including isolates less susceptible to vancomycin and MDR subsets.
- All *S. aureus* were inhibited by telavancin at ≤0.06 µg/mL and telavancin was consistently more potent than comparator agents. These *in vitro* results support the use of telavancin for the treatment of HABP caused by *S. aureus* in USA hospitals.

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Table 2. Antimicrobial activity of telavancin and comparator agents tested against contemporary (2013-2014) *S. aureus* clinical isolates from USA medical centers causing HABP.

Organisma (number tested) Antimicrobial agent	Range	MIC (µg/mL)		% Susceptible/%Intermediate/%Resistant[b]					
		50%	90%	CLSI			EUCAST		
MSSA (677)									
Telavancin	≤0.015 — 0.06	0.03	0.06	100.0	-	-	-	-	-
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
Linezolid	0.25 — 2	1	1	100.0	-	0.0	100.0	-	0.0
Levofloxacin	≤0.12 — >4	0.25	4	87.1	0.6	12.3	87.1	0.6	12.3
Erythromycin	≤0.12 — >16	0.25	>16	64.0	6.6	29.4	64.3	2.2	33.5
Clindamycin	≤0.25 — >2	≤0.25	≤0.25	94.2	0.1	5.6	94.1	0.1	5.8
Gentamicin	≤1 — >8	≤1	≤1	98.8	0.0	1.2	98.5	-	1.5
Tetracycline	≤0.5 — >8	≤0.5	≤0.5	95.6	0.4	4.0	94.4	0.4	5.2
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	99.3	-	0.7	99.3	0.0	0.7
MRSA (676)									
Telavancin	≤0.015 — 0.06	0.03	0.06	100.0	-	-	100.0	-	0.0
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
Linezolid	0.25 — >8	1	1	99.9	-	0.1	99.9	-	0.1
Levofloxacin	≤0.12 — >4	>4	>4	18.8	0.6	80.6	18.8	0.6	80.6
Erythromycin	≤0.12 — >16	>16	>16	8.3	5.0	86.7	8.6	0.9	90.5
Clindamycin	≤0.25 — >2	≤0.25	>2	58.3	0.4	41.3	58.0	0.3	41.7
Gentamicin	≤1 — >8	≤1	≤1	95.4	0.1	4.4	95.3	-	4.7
Tetracycline	≤0.5 — >8	≤0.5	1	93.5	0.1	6.4	91.0	2.4	6.7
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	97.5	-	2.5	97.5	0.0	2.5
MRSA Non-MDR (392)									
Telavancin	≤0.015 — 0.06	0.03	0.06	100.0	-	-	100.0	-	0.0
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
Linezolid	0.25 — 2	1	1	100.0	-	0.0	100.0	-	0.0
Levofloxacin	≤0.12 — >4	4	>4	32.3	1.0	66.7	32.3	1.0	66.7
Erythromycin	≤0.12 — >16	>16	>16	14.0	8.2	77.8	14.5	1.3	84.2
Clindamycin	≤0.25 — >2	≤0.25	≤0.25	96.9	0.8	2.3	96.7	0.3	3.1
Gentamicin	≤1 — >8	≤1	≤1	99.7	0.0	0.3	99.7	-	0.3
Tetracycline	≤0.5 — >8	≤0.5	≤0.5	97.4	0.0	2.6	97.4	0.0	2.6
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	99.2	-	0.8	99.2	0.0	0.8
MRSA MDR (284)									
Telavancin	≤0.015 — 0.06	0.03	0.06	100.0	-	-	100.0	-	0.0
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
Linezolid	0.25 — >8	1	1	99.6	-	0.4	99.6	-	0.4
Levofloxacin	0.5 — >4	>4	>4	0.4	0.0	99.6	0.4	0.0	99.6
Erythromycin	0.25 — >16	>16	>16	0.4	0.7	98.9	0.4	0.4	99.3
Clindamycin	≤0.25 — >2	>2	>2	4.9	0.0	95.1	4.6	0.4	95.1
Gentamicin	≤1 — >8	≤1	>8	89.4	0.4	10.2	89.1	-	10.9
Tetracycline	≤0.5 — >8	≤0.5	>8	88.0	0.4	11.6	82.0	5.6	12.3
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	95.1	-	4.9	95.1	0.0	4.9

MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant, defined as MRSA (methicillin [oxacillin]-resistant) resistant to three or more drug classes in addition to ß-lactam agents; TMP-SMX = trimethoprim-sulfamethoxazole.
Breakpoint for telavancin according to the labeling supplement for the product VIBATIV® (i.e. ≤0.12 µg/mL for susceptible, under the CLSI column; EUCAST breakpoint for telavancin against MRSA only (i.e. ≤0.12 µg/mL for susceptible); breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and EUCAST (2015); "-" = breakpoint not available.

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