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

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Abstract

Telavancin had MIC_{50}, MIC_{90}, and MIC_{100} values of 0.03, 0.06, and 0.12 µg/mL, respectively, against methicillin-susceptible (MSSA), methicillin-resistant (MRSA), and MRSA multidrug-resistant (MDR) subsets of *Staphylococcus aureus*. Isolates with elevated vancomycin MIC values (2 µg/mL) resulted in a telavancin MIC_{50} (0.06 µg/mL) 2-fold higher than isolates with lower vancomycin MIC results (telavancin MIC_{50}, 0.03 µg/mL). However, telavancin had MIC_{90} and MIC_{100} results of 0.06 and 0.12 µg/mL (100% susceptible), respectively, regardless of methicillin-resistance phenotype.

Keywords: Telavancin activity; *Staphylococcus aureus*; Clinical isolates

Introduction

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 [1]. 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 treating complicated staphylococcal infections has prompted the development of several new agents with potent activity against MRSA, methicillin-susceptible *S. aureus* (MSSA), and MDR MRSA, including strains with elevated vancomycin MIC values [1-7].

S. aureus continues to be a leading cause of septicemia, osteoarticular infections, skin and skin structure infections (SSSI), pleuropulmonary infections, and device-related infections [1,8]. Whereas infection rates from MRSA appear to have stabilized or even decreased in industrialized countries, concerns regarding suboptimal responses to glycopeptides, the slow bactericidal activity of vancomycin, the emergence of isolates with reduced susceptibility to vancomycin and daptomycin on therapy, and possible MIC creep among susceptible isolates complicate managing *S. aureus* infections [1,3,4,6,7,9,10].

Telavancin is a parenteral, bactericidal, semisynthetic 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). Telavancin also was shown to be non-inferior to vancomycin in treating hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacteria pneumonia (VABP), due to susceptible gram-positive pathogens and *S. aureus,* respectively [5,11,12] Telavancin has been approved for clinical use by the United States (US) Food and Drug Administration (FDA) in the once-daily treatment of cSSSI and HABP/VABP. This agent has demonstrated comparable efficacy to vancomycin in a limited number of patients with either cSSSI or HABP/VABP and concurrent *S. aureus* bacteremia [13,14].

Previous studies demonstrated potent telavancin activity against *S. aureus* that included methicillin-resistant (MRSA) strains, heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and VISA isolates, and vancomycin-susceptible Enterococcus faecalis [5]. Not only does telavancin inhibit peptidoglycan synthesis, it also interacts with the bacterial cell membrane causing depolarization and increased membrane permeability [5]. This dual mechanism of action contributes to the bactericidal activity of telavancin and might also prevent emerging resistance when it is used clinically. In fact, only 1 report has been published about *in vivo* development of a nonsusceptible phenotype during telavancin therapy [5].

The sustained potency of telavancin versus *S. aureus* strains collected in Europe from 2007 to 2008 [15] and in the United States from 2011 to 2013 [16] has been documented. The objective of the present study was to expand on the studies of Mendes et al. [15,16] by including 22,406 *S. aureus* clinical isolates from 77 US medical centers; 2 Canadian medical centers; and the rest of the world (ROW) with 39 medical centers in 19 European countries/regions, 10 medical centers in 4 Latin American countries, and 19 Asian-Pacific medical

centers in 9 countries for the years 2013 to 2015. All testing was performed using the revised CLSI method with the new quality control (QC) MIC ranges and interpretive criteria [17,18].

Materials and Methods

Isolates included in this study were part of the 2013–2015 US and ROW SENTRY Antimicrobial Surveillance Program, which monitors antimicrobial resistance and prevalence of pathogens causing bloodstream infections (BSI), community-acquired pneumonia, pneumonia in hospitalized patients, SSSI, intra-abdominal infections (IAI), and urinary tract infections (UTI). Participating sites follow instructions specific for each protocol to select and include consecutive and unique (1 per patient) isolates that were deemed clinically relevant based on local criteria until they reached a target number of 250–500 pathogens per site (depending on hospital size). Isolates that met the selection criteria for each of the 6 specific protocols were initially identified by the participant laboratory using local practices and were submitted to the coordinating monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA). Isolate bacterial identifications were confirmed by standard methods per Murray et al. [19]. Isolates showing questionable phenotypic and/or biochemical results had their identification confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Isolates included in the study were recovered from BSI (4,080; 18.2%), SSSI (11,122; 49.6%), pneumonia in hospitalized patients (5,163; 23.0%), IAI (486; 2.2%), UTI (333; 1.5%), and other less prevalent or undetermined infection sources (1,222; 5.5%). Isolates were tested for susceptibility by broth microdilution following CLSI guidelines [17]. Telavancin was tested by the revised method according to CLSI [18,20] and product package insert [14] using panels manufactured at JMI Laboratories (2015) or purchased from Thermo Fisher Scientific (2013–2014) (Cleveland, Ohio, USA). Quality control for MIC values were quality assured by concurrently testing *S. aureus* (ATCC 29213) and *E. faecalis* (ATCC 29212). Telavancin MIC interpretation for *S. aureus* applied the recently approved breakpoint criterion (≤ 0.12 µg/mL for susceptible) appropriate for the revised testing method [18,21]. CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria were applied for comparator agents [18,21]. Isolates were categorized according to their vancomycin (≤ 1 versus 2 µg/mL) MIC results. In addition, *S. aureus* isolates showing a resistant phenotype to oxacillin and a nonsusceptible phenotype to at least 3 additional classes of antimicrobial agents were defined as multidrug-resistant (MDR). The drugs used to categorize isolates as MDR [18] were: clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin.

Results and Discussion

Overall, telavancin demonstrated MIC_{50} and MIC_{90} values of 0.03 and 0.06 µg/mL, respectively, against *S. aureus* (100.0% susceptible), and equivalent values were observed against the MSSA, MRSA, and MDR MRSA subsets from the United States and ROW **(Table 1)**. When tested against the isolate subset displaying vancomycin 2 µg/mL MIC results, the telavancin MIC_{50} value (0.06 µg/mL) was 2-fold higher than that (MIC_{50}, 0.03 µg/mL) obtained from isolates with lower MIC values for vancomycin (≤ 1 µg/mL). Similarly, when tested against *S. aureus* with a vancomycin MIC of 2 µg/mL, daptomycin ($MIC_{50/90}$, 0.5/1 µg/mL) demonstrated MIC_{50} values 2-fold higher than those observed for isolates with vancomycin MIC values of ≤ 1 µg/mL (daptomycin $MIC_{50/90}$, 0.25/0.5 µg/mL) (data not shown). *In vitro* activity comparison analysis resulted in telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) showing MIC values 8-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) and 16 to 32-fold lower than vancomycin ($MIC_{50/90}$, 1/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/1 µg/mL) against MSSA, the overall MRSA group, and the MDR subset **(Table 2)**. Gentamicin, tetracycline, and trimethoprim-sulfamethoxazole also had good antimicrobial coverage (>90.0% susceptible; CLSI) when tested against MRSA, and these agents plus levofloxacin and clindamycin were active against MSSA.

Table 1 Antimicrobial activity and MIC distribution for telavancin against a contemporary (2013–2015) global collection of *S. aureus* clinical isolates. [a]MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR MRSA, multidrug-resistant defined as MRSA (methicillin [oxacillin]-resistant) nonsusceptible to 3 or more drug classes; ROW, rest of the world.

Region/phenotypea	MIC (µg/mL)			Number (cumulative %) inhibited at telavancin MIC (µg/mL) of:			
(no. tested)	50%	90%		≤ 0.015	0.03	0.06	0.12
US (14,019)							
MSSA (7,488)	0.03	0.06		545 (7.3%)	5,721 (83.7%)	1,220 (>99.9%)	2 (100.0%)
MRSA (6,531)	0.03	0.06		282 (4.3%)	5,180 (83.6%)	1,059 (99.8%)	10 (100.0%)
MDR (1,926)	0.03	0.06		79 (4.1%)	1,409 (77.3%)	435 (99.8%)	3 (100.0%)
Vancomycin MIC=2 µg/mL (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%)	3,961 (74.7%)	1,450 (99.9%)	5 (100.0%)
MRSA (2,639)	0.03	0.06		122 (4.6%)	1,644 (66.9%)	860 (99.5%)	13 (100.0%)
MDR (1,081)	0.03	0.06		45 (4.2%)	564 (56.3%)	465 (99.4%)	7 (100.0%)
Vancomycin MIC=2 µg/mL (71)	0.06	0.06			11 (15.5%)	55 (93.0%)	5 (100.0%)

Daptomycin MIC results ($MIC_{50/90}$, 0.5/1 µg/mL) obtained against *S. aureus* isolates with elevated vancomycin MIC values (2 µg/mL) were 2-fold higher than those obtained against isolates with vancomycin MIC data points at ≤ 1 µg/mL ($MIC_{50/90}$, 0.25/0.5 µg/mL; data not shown). Daptomycin (97.3/97.3% susceptible [CLSI/EUCAST]) and linezolid ($MIC_{50/90}$, 1/1 µg/mL; 99.3/99.3% susceptible, [CLSI/ and EUCAST]) were active against *S. aureus* isolates with vancomycin MIC values of 2 µg/mL; however, telavancin had MIC results 8 to 16-fold lower than these comparators. There were 10 isolates for which the daptomycin MIC values were >1 µg/mL (resistant by EUCAST criteria) and all showed telavancin MIC values of 0.06 µg/mL (susceptible by CLSI criteria). Gentamicin, tetracycline, and trimethoprim-sulfamethoxazole also remained active *in vitro* against the *S. aureus* subset and showed vancomycin MIC values of 2 µg/mL (susceptibility range, 81.8–94.6%). The same 3 agents also remained active *in vitro* against the MDR MRSA subset (susceptibility range, 76.5–92.8%; **Table 2**).

Table 2 Antimicrobial activity of telavancin and comparator agents when tested against a contemporary (2013–2015) global collection of clinical isolates using the CLSI broth microdilution susceptibility testing method. [a]MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant. [b]Telavancin breakpoint criteria for *S. aureus* according to CLSI (2017) and EUCAST (2017; MRSA only) at ≤ 0.12 µg/mL for susceptible. [c]Breakpoint not available.

Organisma (no. tested)	**MIC (µg/mL)**			**% Susceptible/% Intermediate/% Resistantb**		
Antimicrobial agent	**50%**	**90%**			**CLSI**	**EUCAST**
MSSA (13,236)						
Telavancin	0.03	0.06			100.0/-c/-	-/-/-
Vancomycin	1	1			100.0/0.0/0.0	100.0/-/0.0
Daptomycin	0.25	0.5			>99.9/-/-	>99.9/0.0/<0.1
Linezolid	1	1			100.0/-/0.0	100.0/-/0.0
Levofloxacin	0.25	0.5			91.6/0.4/8.0	91.6/-/8.4
Erythromycin	0.25	>8			73.5/4.8/21.8	73.9/1.7/24.4
Clindamycin	≤ 0.25	≤ 0.25			96.0/0.1/3.9	95.7/0.3/4.0
Gentamicin	≤ 1	≤ 1			98.2/0.2/1.7	97.9/-/2.1
Tetracycline	≤ 0.5	≤ 0.5			95.1/0.6/4.3	94.1/0.2/5.7
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5			99.6/-/0.4	99.6/0.1/0.4
MRSA (9,170)						
Telavancin	0.03	0.06			100.0/-/-	100.0/-/0.0
Vancomycin	1	1			100.0/0.0/0.0	100.0/-/0.0
Daptomycin	0.25	0.5			99.9/-/-	99.9/-/0.1
Linezolid	1	1			99.9/-/0.1	99.9/-/0.1
Levofloxacin	4	>4			28.6/1.2/70.2	28.6/-/71.4
Erythromycin	>8	>8			17.1/3.8/79.1	17.5/1.0/81.6
Clindamycin	≤ 0.25	>2			69.7/0.3/30.1	69.4/0.2/30.3
Gentamicin	≤ 1	≤ 1			91.3/0.3/8.4	90.9/-/9.1
Tetracycline	≤ 0.5	2			91.4/0.8/7.8	89.8/1.1/9.1
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5			97.3/-/2.7	97.3/0.4/2.3

S. aureus with vancomycin MIC 2 µg/mL (148)						
Telavancin	0.06	0.06			100.0/-/-	-/-/-
Vancomycin	2	2			100.0/0.0/0.0	100.0/-/0.0
Daptomycin	0.5	1			97.3/-/-	97.3/-/2.7
Linezolid	1	1			99.3/-/0.7	99.3/-/0.7
Levofloxacin	4	>4			47.3/0.0/52.7	47.3/-/52.7
Erythromycin	>8	>8			42.6/3.4/54.1	42.6/1.4/56.1
Clindamycin	≤ 0.25	>2			60.8/0.0/39.2	59.5/1.4/39.2
Gentamicin	≤ 1	>8			82.4/0.7/16.9	81.8/-/18.2
Tetracycline	≤ 0.5	4			90.5/0.0/9.5	85.1/4.7/10.1
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5			94.6/-/5.4	94.6/0.7/4.7
MDR MRSA (3,007)						
Telavancin	0.03	0.06			100.0/-/-	100.0/-/ 0.0
Vancomycin	1	1			100.0/0.0/0.0	100.0/-/ 0.0
Daptomycin	0.25	0.5			99.7/-/-	99.7/-/ 0.3
Linezolid	1	1			99.8/-/ 0.2	99.8/-/ 0.2
Levofloxacin	>4	>4			1.7/0.7/97.7	1.7/-/ 98.3
Erythromycin	>8	>8			0.8/2.5/96.8	0.9/0.6/98.4
Clindamycin	>2	>2			11.7/0.6/87.7	11.5/0.2/88.3
Gentamicin	≤ 1	>8			77.1/0.6/22.3	76.5/-/23.5
Tetracycline	≤ 0.5	>8			80.2/1.4/18.4	76.7/3.1/20.2
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5			92.8/-/ 7.2	92.8/1.2/6.0

Conclusions

In this *in vitro* study, telavancin maintained potent activity against *S. aureus*, including isolates with decreased susceptibility to comparator agents, and maintained MIC_{90} and MIC, results of 0.06 and 0.12 µg/mL, respectively, against all examined resistant isolate subsets that included MRSA (100.0% susceptible). In addition, the telavancin potency observed was at least 8-fold greater than tested comparators. These results confirm telavancin had more potent activity when compared to earlier studies [22-24] that underestimated the potency of the drug due to solubility and drug binding to plastic trays during susceptibility testing [20].

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Transparency statement

JMI Laboratories contracted to perform services in 2016 for Achaogen, Actelion, Allecra Therapeutics, Allergan, AmpliPhi Biosciences, API, Astellas Pharma, AstraZeneca, Basilea Pharmaceutica, Bayer AG, BD, Biomodels, Cardeas Pharma Corp., CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Debiopharm Group, Dipexium Pharmaceuticals, Inc., Duke, Entasis Therapeutics, Inc., Fortress Biotech, Fox Chase Chemical Diversity Center, Inc., Geom Therapeutics, Inc., GSK, Laboratory Specialists, Inc., Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., Micromyx, MicuRx Pharmaceuticals,

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