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Update of telavancin *in vitro* activity against a USA collection of Gram-positive clinical isolates (2014) causing skin and skin structure infections

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ABSTRACT

Background: Telavancin is a potent bactericidal lipoglycopeptide approved in the USA and Canada for the treatment of complicated skin and skin structure infections (cSSSI). This study provides a current *in vitro* activity analysis for telavancin and comparators against Gram-positive isolates causing SSSI in USA hospitals.

Methods: 1,591 isolates causing documented SSSI in 28 sites located in nine USA Census regions were included. Isolates were submitted to a central laboratory as part of the SENTRY Program for 2014. Identification was confirmed by MALDI-TOF and susceptibility testing was performed by CLSI (2015) methods. MIC interpretation used the USA FDA (telavancin), CLSI and EUCAST criteria.

Results: Telavancin (100.0% susceptible) showed MIC_{50}, MIC_{90} and MIC_{100} results of 0.03, 0.06 and 0.06 µg/ml, respectively, against all *S. aureus*, with equivalent results for methicillin-susceptible (MSSA) and -resistant (MRSA) isolates. The telavancin MIC values were eight-fold lower than daptomycin (100.0% susceptible) and 16-fold lower than vancomycin (100.0% susceptible) and linezolid (100.0% susceptible) against all *S. aureus*, with similar comparison results against the MSSA and MRSA subsets. All *E. faecalis* were inhibited by telavancin at the USA FDA breakpoint for susceptibility (i.e. ≤0.25 µg/ml), except for one isolate displaying a VanA-phenotype (telavancin MIC, 2 µg/ml). Ampicillin (100.0% susceptible), daptomycin (100.0% susceptible), vancomycin (98.9% susceptible) and linezolid (100.0% susceptible) were active against *E. faecalis*; however, these agents had MIC results eight- to 16-fold higher than telavancin. All indicated streptococcal isolates were susceptible to telavancin, which showed MIC_{90} values lower than tested comparator agents.

Conclusions: This study provides an updated *in vitro* activity analysis for telavancin and comparator agents. Telavancin continues to demonstrate potent *in vitro* activity against Gram-positive clinical isolates responsible for SSSI in USA hospitals.

INTRODUCTION

- Cellulitis, abscesses, and infected wounds are diseases included as part of the acute bacterial skin and skin structure infection (ABSSSI) spectrum. These are among the most common infections in health care and ABSSSIs account for 6.3 million physician office visits and over 850,000 hospital admissions annually in the United States. In Europe, it is estimated that ABSSSIs account for 1.5% to 3% of all attendances and, were second only to respiratory tract infections as the most common cause for inpatient antibiotic therapy. In addition, *Staphylococcus aureus* and *Streptococcus pyogenes* are the predominant causative pathogens, and incidences of methicillin-resistant *S. aureus* (MRSA) causing community-acquired ABSSSIs increased significantly.
- Several Gram-positive antimicrobial agents for treatment of ABSSSIs have become available in the last decade. Among those, telavancin is a once-daily parenteral semi-synthetic lipoglycopeptide agent approved in the United States and Canada for the treatment of adult patients with ABSSSIs caused by susceptible Gram-positive pathogens. This indication was based on randomized and controlled phase 3 clinical trials demonstrating non-inferiority of telavancin when compared with vancomycin. In this study, a current *in vitro* activity data analysis is provided for telavancin and comparator agents tested against Gram-positive isolates causing ABSSSIs in 28 USA medical sites during 2014.

MATERIALS AND METHODS

- **Bacterial strain collection.** A total of 1,591 isolates responsible for SSSI, per local guidelines, were included in the study. Isolates were collected from 28 sites located in nine USA Census regions, as part of the SENTRY Antimicrobial Surveillance Program for 2014. Selected isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA). Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring laboratory (JMI Laboratories) by 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, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). 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 interpretations for telavancin were based on breakpoints available in the product package insert, and are as follows: *S. aureus* at ≤0.12 µg/ml for susceptible (EUCAST breakpoint for MRSA only at ≤0.12 µg/ml for susceptible); *E. faecalis* (vancomycin-susceptible) at ≤0.25 µg/ml for susceptible; *S. pyogenes* and *Streptococcus agalactiae* at ≤0.12 µg/ml (used for ß-hemolytic streptococci [BHS]) and *Streptococcus anginosus* group at ≤0.06 µg/ml for susceptible (applied for viridans group streptococci [VGS]).

RESULTS

- Telavancin (100.0% susceptible) showed MIC_{50}, MIC_{90} and MIC_{100} results of 0.03, 0.06 and 0.06 µg/ml, respectively, against all *S. aureus*, with equivalent results for methicillin-susceptible (MSSA) and MRSA isolates (**Table 1**).
- Overall, telavancin had MIC_{50} and MIC_{90} values of 0.03 and 0.06 µg/ml against the entire population of coagulase-negative staphylococci (CoNS), respectively (**Tables 1 and 2**).
- Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) was eight-fold more potent than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml), and 16- to 32-fold more active than vancomycin ($MIC_{50/90}$, 1/1 µg/ml) and linezolid ($MIC_{50/90}$, 1/1 µg/ml) against MRSA (**Table 2**).
- Among antimicrobial agents presented in **Table 2**, only telavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml), vancomycin ($MIC_{50/90}$, 1/2 µg/ml), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml) and linezolid ($MIC_{50/90}$, 0.5/0.5 µg/ml) had optimum antimicrobial coverage (>90% susceptible) against CoNS.
- All *E. faecalis* were inhibited by telavancin at ≤0.12 µg/ml (USA FDA breakpoint for susceptibility, ≤0.25 µg/ml), except for one non-indicated isolate displaying a VanA-phenotype (telavancin MIC, 2 µg/ml; **Table 1**).
- Ampicillin ($MIC_{50/90}$, 1/2 µg/ml), daptomycin ($MIC_{50/90}$, 1/2 µg/ml), vancomycin ($MIC_{50/90}$, 1/2 µg/ml) and linezolid ($MIC_{50/90}$, 1/1 µg/ml) were active against *E. faecalis*; however, these agents had MIC results eight- to 16-fold higher than telavancin ($MIC_{50/90}$, 0.12/0.12 µg/ml; **Table 2**).
- VGS and BHS exhibited very low MIC results for telavancin ($MIC_{50/90}$, ≤0.015-0.03/0.03 µg/ml), which inhibited all isolates at ≤0.06 µg/ml (**Table 1**).
- Telavancin ($MIC_{50/90}$, 0.03/0.03 µg/ml) and penicillin ($MIC_{50/90}$, ≤0.06/0.25 µg/ml) were the most active compounds tested against VGS, followed by vancomycin ($MIC_{50/90}$, 0.5/0.5 µg/ml), daptomycin ($MIC_{50/90}$, 0.25/1 µg/ml), linezolid ($MIC_{50/90}$, 0.5/1 µg/ml) and levofloxacin ($MIC_{50/90}$, 0.5/1 µg/ml; **Table 2**).
- Telavancin ($MIC_{50/90}$, ≤0.015/0.03 µg/ml), penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) and daptomycin ($MIC_{50/90}$, ≤0.06/0.25 µg/ml) were the most active agents tested against BHS (**Table 2**; all 100.0% susceptible). Linezolid ($MIC_{50/90}$, 0.5/1 µg/ml) and levofloxacin ($MIC_{50/90}$, 0.5/1 µg/ml) also demonstrated antimicrobial activity.

Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against contemporary (2014) clinical isolates from USA medical centers causing SSSIs.

Organism[a] (no. tested)	MIC (µg/ml)		Number (cumulative %) inhibited at telavancin MIC (µg/ml)[b]							
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	>1
S. aureus (1,051)	0.03	0.06	59 (5.6)	792 (81.0)	200 (100.0)					
MSSA (527)	0.03	0.06	41 (7.8)	386 (81.0)	100 (100.0)					
MRSA (524)	0.03	0.06	18 (3.4)	406 (80.9)	100 (100.0)					
CoNS (88)	0.03	0.06	32 (36.4)	16 (54.5)	38 (97.7)	2 (100.0)				
E. faecalis (87)	0.12	0.12	0 (0.0)	4 (4.6)	35 (44.8)	47 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)[b]
VGS (63)	0.03	0.03	30 (47.6)	32 (98.4)	1 (100.0)					
S. anginosus group (39)	≤0.015	0.03	21 (53.8)	18 (100.0)						
BHS (302)	≤0.015	0.03	201 (66.6)	95 (98.0)	6 (100.0)					
S. pyogenes (156)	≤0.015	0.03	139 (89.1)	14 (98.1)	3 (100.0)					
S. agalactiae (104)	0.03	0.03	24 (23.1)	78 (98.1)	2 (100.0)					

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; BHS = ß-hemolytic streptococci.
b. All vancomycin-susceptible *E. faecalis* were susceptible to telavancin (i.e. all inhibited below breakpoint; i.e. ≤0.25 µg/ml). One *E. faecalis* displaying a VanA-phenotype (i.e. vancomycin and teicoplanin MIC values of >4 and >8 µg/ml, respectively) had a telavancin MIC result of 2 µg/ml.

CONCLUSIONS

- This study provides an updated *in vitro* activity analysis for telavancin and comparator agents evaluated against the primary species of staphylococci, enterococci and streptococci causing SSSIs in USA medical centers in 2014.
- Telavancin inhibited all indicated pathogens at or below the respective breakpoints for susceptibility established by the USA FDA. In addition, telavancin demonstrated *in vitro* potency greater than comparator antimicrobial agents with similar indications.

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Table 2. Antimicrobial activity of telavancin and comparator agents tested against contemporary (2014) clinical isolates from USA medical centers causing SSSIs.

Organism (number tested) Antimicrobial agent[a]	Range	MIC (µg/ml)		% Susceptible/%Intermediate/%Resistant[b]					
		50%	90%	CLSI			EUCAST		
MRSA (524)									
Telavancin	≤0.015 — 0.06	0.03	0.06	100.0	-[c]	-	100.0	-	0.0
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100. 0	-	0.0
Daptomycin	0.12 — 2	0.25	0.5	99.8	-	-	99.8	-	0.2
Linezolid	0.25 — 2	1	1	100.0	-	0.0	100.0	-	0.0
Levofloxacin	≤0.12 — >4	4	>4	39.3	0.6	60.1	39.3	0.6	60.1
Erythromycin	≤0.12 — >16	>16	>16	11.5	1.1	87.4	11.6	0.2	88.2
Clindamycin	≤0.25 — >2	≤0.25	>2	80.9	0.2	18.9	80.9	0.0	19.1
Gentamicin	≤1 — >8	≤1	≤1	97.3	0.4	2.3	96.8	-	3.2
Tetracycline	≤0.5 — >8	≤0.5	2	92.3	0.8	6.9	89.5	1.3	9.2
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	97.7	-	2.3	97.7	0.6	1.7
CoNS (88)									
Telavancin	≤0.015 — 0.12	0.03	0.06	-	-	-	-	-	-
Oxacillin	≤0.25 — >2	1	>2	55.7	-	44.3	55.7	-	44.3
Vancomycin	0.5 — 2	1	2	100.0	0.0	0.0	100.0	-	0.0
Daptomycin	≤0.06 — 1	0.25	0.5	100.0	-	-	100.0	-	0.0
Linezolid	0.25 — 1	0.5	0.5	100.0	-	0.0	100.0	-	0.0
Levofloxacin	≤0.12 — >4	0.25	>4	75.0	1.1	23.9	75.0	1.1	23.9
Erythromycin	≤0.12 — >16	0.25	>16	56.8	1.1	42.0	56.8	0.0	43.2
Clindamycin	≤0.25 — >2	≤0.25	>2	77.3	1.1	21.6	72.7	4.5	22.7
Gentamicin	≤1 — >8	≤1	>8	87.5	1.1	11.4	86.4	-	13.6
Tetracycline	≤0.5 — >8	≤0.5	>8	87.4	1.1	11.5	80.5	2.3	17.2
TMP-SMX	≤0.5 — >4	≤0.5	4	89.8	-	10.2	89.8	8.0	2.3
***E. faecalis* (87)**									
Telavancin	0.03 — 2	0.12	0.12	98.9[d]	-	-	-	-	-
Ampicillin	0.5 — 2	1	2	100.0	-	0.0	100.0	0.0	0.0
Vancomycin	0.25 — >16	1	2	98.9	0.0	1.1	98.9	-	1.1
Daptomycin	≤0.06 — 2	1	2	100.0	-	-	-	-	-
Linezolid	≤0.12 — 1	1	1	100.0	0.0	0.0	-	-	-
Levofloxacin	0.25 — >4	1	>4	70.1	0.0	29.9	-	-	-
Tetracycline	≤0.5 — >8	>8	>8	26.4	1.1	72.4	-	-	-
VGS (63)									
Telavancin	≤0.015 — 0.06	0.03	0.03	100.0	-	-	-	-	-
Penicillin	≤0.06 — >8	≤0.06	0.25	88.9	7.9	3.2	93.7	3.2	3.2
Vancomycin	≤0.12 — 1	0.5	0.5	100.0	-	-	100.0	-	0.0
Daptomycin	≤0.06 — 1	0.25	1	100.0	-	-	-	-	-
Linezolid	≤0.12 — 1	0.5	1	100.0	-	-	-	-	-
Levofloxacin	≤0.12 — >4	0.5	1	98.4	0.0	1.6	-	-	-
Erythromycin	≤0.12 — >16	0.25	>16	50.8	4.8	44.4	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	79.4	0.0	20.6	79.4	-	20.6
Tetracycline	≤0.5 — >8	4	>8	47.6	9.5	42.9	-	-	-
BHS (302)									
Telavancin	≤0.015 — 0.06	≤0.015	0.03	100.0	-	-[b]	-	-	-
Penicillin	≤0.06 — 0.12	≤0.06	≤0.06	100.0	-	-	100.0	-	0.0
Vancomycin	0.25 — 0.5	0.25	0.5	100.0	-	-	100.0	-	0.0
Daptomycin	≤0.06 — 0.5	≤0.06	0.25	100.0	-	-	100.0	-	0.0
Linezolid	0.5 — 1	0.5	1	100.0	-	-	100.0	0.0	0.0
Levofloxacin	0.25 — >4	0.5	1	99.3	0.0	0.7	98.3	1.0	0.7
Erythromycin	≤0.12 — >16	≤0.12	>16	70.8	1.3	27.9	70.8	1.3	27.9
Clindamycin	≤0.25 — >2	≤0.25	>2	84.4	0.7	15.0	85.0	-	15.0
Tetracycline	≤0.5 — >8	≤0.5	>8	56.6	2.3	41.1	56.0	0.7	43.4

a. MRSA = methicillin-resistant *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; BHS = ß-hemolytic streptococci.
b. Breakpoint criteria for telavancin according to the labeling supplement for the product VIBATIV®, as available. *S. aureus* at ≤0.12 µg/ml for susceptible; EUCAST breakpoint for telavancin against MRSA only at ≤0.12 µg/ml for susceptible; *E. faecalis* (vancomycin-susceptible) at ≤0.25 µg/ml for susceptible; breakpoint for VGS was that from S. anginosus group (≤0.06 µg/ml for susceptible); while the interpretive criterion for *S. pyogenes* and *S. agalactiae* (≤0.12 µg/ml for susceptible) was applied for BHS. Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and EUCAST (2015), as available.
c. Breakpoint not available.
d. 98.9% of all *E. faecalis* or 100.0% of vancomycin-susceptible *E. faecalis* were susceptible to telavancin. One *E. faecalis* displaying a VanA-phenotype (i.e. vancomycin and teicoplanin MIC values of >4 and >8 µg/ml, respectively) had a telavancin MIC result of 2 µg/ml.

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