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In Vitro Activity of Telavancin against *Staphylococcus aureus* Causing Pneumonia or Skin and Skin Structure Infections with Concomitant Bloodstream Infections in United States Hospitals (2012-2016)

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ABSTRACT

Telavancin is approved for the treatment of complicated skin and skin-structure infections (cSSSI) and hospital-acquired and ventilator-associated bacterial pneumonia. This study evaluated telavancin activity against *Staphylococcus aureus* isolates causing pneumonia or SSSI, but recovered from blood in United States (US) hospitals.

A total of 674 *S. aureus* causing SSSI or pneumonia with concomitant bloodstream infections (BSI) were included. Isolates were recovered from 22 US sites, bacterial identification was confirmed, and isolates were susceptibility tested by CLSI methods. MIC interpretations used CLSI/EUCAST criteria. Methicillin-resistant *S. aureus* (MRSA) displaying a resistance phenotype to 3 or more drug classes were considered multidrug-resistant (MDR).

Telavancin inhibited all *S. aureus* at ≤0.12 µg/mL, the susceptibility breakpoint, with $MIC_{50/90}$ values of 0.03/0.06 µg/mL. Equivalent MICs ($MIC_{50/90}$, 0.03/0.06 µg/mL) were obtained for methicillin-susceptible (MSSA), MRSA, and MDR *S. aureus*. Overall, MSSA were susceptible to all agents tested (95.9–100.0% susceptible; CLSI), except for erythromycin and levofloxacin (69.2–88.3% susceptible). Telavancin was 8-fold more potent than daptomycin and 16- to 32-fold more potent than vancomycin against MRSA. Ceftaroline ($MIC_{50/90}$, 0.5/1 µg/mL; 92.5% susceptible), tetracycline ($MIC_{50/90}$, ≤0.5/1 µg/mL; 92.8–95.2% susceptible), and trimethoprim-sulfamethoxazole (TMP-SMX; $MIC_{50/90}$, ≤0.5/≤0.5 µg/mL; 95.8% susceptible) were also active against MRSA. Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL; 100.0% susceptible), daptomycin, and vancomycin were active against MDR MRSA with activities similar to those observed against MSSA; however, telavancin MICs were at least 8-fold lower than those of daptomycin and vancomycin. TMP-SMX ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL; 93.2% susceptible) and linezolid (100.0% susceptible) were also active against MDR MRSA, but other comparators had decreased coverage (0.0–89.3% susceptible).

Telavancin (100.0% susceptible) had potent activity against this US collection of *S. aureus* causing SSSI or pneumonia with concurrent BSI, including those caused by MDR isolates. These *in vitro* results indicate that telavancin may be a suitable alternative when treating indicated infections with associated BSI.

INTRODUCTION

- *Staphylococcus aureus* is a highly adaptable pathogen that causes serious health care-associated and community-associated infections
- *S. aureus* is a leading cause of bacteremia, which is associated with significant morbidity and mortality and requires careful management
- Skin and skin structure infections (SSSI) and pneumonia are among the most common causes of *S. aureus* bacteremia, but bacteremia itself can also lead to metastatic 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 cSSSI and with hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP), due to susceptible gram-positive pathogens, including *S. aureus* and methicillin-resistant isolates (MRSA)
- Telavancin is approved for clinical use by the Food and Drug Administration to treat (once daily) cSSSI and HABP/VABP when other alternatives are not suitable
- Telavancin is also approved in Canada to treat cSSSI caused by *S. aureus*, including methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates, and in Europe to treat adult patients with HABP/VABP caused by susceptible MRSA isolates
- This study evaluated the activity of telavancin against a set of *S. aureus* isolates from the US that caused SSSI or pneumonia with concomitant bloodstream infection (BSI) (2012–2016)

MATERIALS AND METHODS

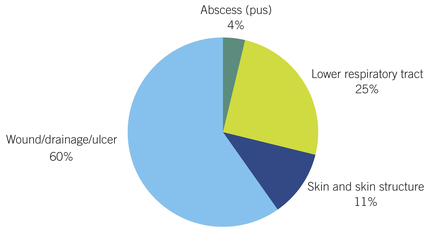
Bacterial Strain Collection

- 674 unique (1 per patient) *S. aureus* isolates from 22 sites in the US were included
- All isolates were deemed responsible for human infections per local guidelines
- The isolates were all derived from SSSI or pneumonia with concomitant BSI (Figure 1)
- Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa USA) as part of the SENTRY Antimicrobial Surveillance Program during 2012–2016
- Isolates were initially identified by the participating laboratory with identification confirmed by the central monitoring laboratory using standard algorithms 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 followed CLSI-approved methodology, which included supplementation 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 CLSI and EUCAST criteria
- MRSA isolates displaying a resistance phenotype (CLSI criteria) to at least 3 classes of drugs in addition to oxacillin were considered MDR

Figure 1. Original infection source of tested *S. aureus* BSI isolates



RESULTS

- A total of 49.4% of US isolates were MRSA (Table 1)
- Among the MRSA collection, 30.9% of isolates were MDR (Table 1)
- Telavancin inhibited all isolates (100.0% susceptible) at the susceptibility breakpoint (≤0.12 µg/mL; Table 1)
- Telavancin had identical $MIC_{50/90}$ values (0.03/0.06 µg/mL) against all MSSA, MRSA, and MRSA MDR subsets (Table 1) and infection sources (data not shown)
- Telavancin MIC_{50} values (0.03 µg/mL) were identical for *S. aureus* isolate subsets stratified by year (2012 through 2016; data not shown)
- All tested agents except clindamycin, erythromycin, and levofloxacin were *in vitro* active (92.5–100.0% susceptible) against the MRSA subset (Table 2)
- In contrast, only telavancin, daptomycin, linezolid, teicoplanin, trimethoprim-sulfamethoxazole, and vancomycin were *in vitro* active (93.2–100.0% susceptible) against the MDR MRSA subset (Table 2)
- Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) was at least 8-fold more potent than active comparators tested against MRSA and MRSA MDR isolates (Table 2)
- Telavancin retained activity (MIC range 0.06-0.12 µg/mL) against 5 isolates with elevated vancomycin MIC values (2 µg/mL) (Table 1)

Table 1. Antimicrobial activity of telavancin tested against *S. aureus* isolates from the US causing SSSI or pneumonia with concomitant BSI

Organism / organism group (no. of isolates)	No. of isolates at MIC in µg/mL (cumulative %)				MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12		
***Staphylococcus aureus* (674)**	50 (7.4)	526 (85.5)	97 (99.9)	1 (100.0)	0.03	0.06
Methicillin-susceptible (341)	31 (9.1)	263 (86.2)	46 (99.7)	1 (100.0)	0.03	0.06
Vancomycin MIC, 2 µg/mL (3)			2 (66.7)	1 (100.0)	0.06	–[a]
Vancomycin MIC, <2 µg/mL (338)	31 (9.2)	263 (87.0)	44 (100.0)		0.03	0.06
Methicillin-resistant (333)	19 (5.7)	263 (84.7)	51 (100.0)		0.03	0.06
MDR[b] (103)	4 (3.9)	78 (79.6)	21 (100.0)		0.03	0.06
Vancomycin MIC, 2 µg/mL (2)			2 (100.0)		0.06	–[a]
Vancomycin MIC, <2 µg/mL (331)	19 (5.7)	263 (85.2)	49 (100.0)		0.03	0.06

[a] Result not available when number of isolates <10
[b] MDR, multidrug-resistant defined as MRSA (methicillin [oxacillin]-resistant) resistant to 3 or more other drug classes

Table 2. Antimicrobial activity of telavancin and comparator agents tested against *S. aureus* isolates from the US causing SSSI or pneumonia with concomitant BSI

Group[a] (no. tested) / agent	MIC_{50}	MIC_{90}	CLSI[b] %S	CLSI %I	CLSI %R	EUCAST[b] %S	EUCAST %I	EUCAST %R
All isolates (674)								
Telavancin	0.03	0.06	100.0			100.0		0.0[c]
Ceftaroline	0.5	1	95.9	4.1	0.0	95.9		4.1
Clindamycin	≤0.25	>2	82.9	0.1	16.9	82.5	0.4	17.1
Daptomycin	0.25	0.5	100.0			100.0		0.0
Erythromycin	>8	>8	40.4	4.2	55.5	40.8	1.3	57.9
Gentamicin	≤1	≤1	97.8	0.0	2.2	96.9		3.1
Levofloxacin	0.25	>4	59.2	1.5	39.3	59.2		40.8
Linezolid	1	1	100.0		0.0	100.0		0.0
Oxacillin	2	>2	50.6		49.4	50.6		49.4
Teicoplanin	≤2	≤2	100.0	0.0	0.0	99.9		0.1
Tetracycline	≤0.5	≤0.5	96.4	0.7	2.8	93.8	1.2	5.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.5		2.5	97.5	0.3	2.2
Vancomycin	1	1	100.0	0.0	0.0	100.0		0.0
MSSA (341)								
Telavancin	0.03	0.06	100.0			100.0		0.0[c]
Ceftaroline	0.25	0.25	100.0	0.0	0.0	100.0		0.0
Clindamycin	≤0.25	≤0.25	95.9	0.0	4.1	95.3	0.6	4.1
Daptomycin	0.25	0.5	100.0			100.0		0.0
Erythromycin	0.25	>8	69.2	5.3	25.5	69.8	2.1	28.2
Gentamicin	≤1	≤1	99.4	0.0	0.6	98.5		1.5
Levofloxacin	0.25	4	88.3	0.9	10.9	88.3		11.7
Linezolid	1	1	100.0		0.0	100.0		0.0
Teicoplanin	≤2	≤2	100.0	0.0	0.0	99.7		0.3
Tetracycline	≤0.5	≤0.5	97.7	0.3	2.1	94.7	0.3	5.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	99.1		0.9	99.1	0.0	0.9
Vancomycin	0.5	1	100.0	0.0	0.0	100.0		0.0
MRSA (333)								
Telavancin	0.03	0.06	100.0			100.0		0.0
Ceftaroline	0.5	1	92.5	7.5	0.0	92.5		7.5
Clindamycin	≤0.25	>2	69.7	0.3	30.0	69.4	0.3	30.3
Daptomycin	0.25	0.5	100.0			100.0		0.0
Erythromycin	>8	>8	10.8	3.0	86.2	11.1	0.6	88.3
Gentamicin	≤1	≤1	96.1	0.0	3.9	95.2		4.8
Levofloxacin	4	>4	29.4	2.1	68.5	29.4		70.6
Linezolid	1	1	100.0		0.0	100.0		0.0
Teicoplanin	≤2	≤2	100.0	0.0	0.0	100.0		0.0
Tetracycline	≤0.5	1	95.2	1.2	3.6	92.8	2.1	5.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	95.8		4.2	95.8	0.6	3.6
Vancomycin	1	1	100.0	0.0	0.0	100.0		0.0
MDR MRSA (103)								
Telavancin	0.03	0.06	100.0			100.0		0.0
Ceftaroline	1	2	77.6	22.4	0.0	77.6		22.4
Clindamycin	>2	>2	9.7	0.0	90.3	9.7	0.0	90.3
Daptomycin	0.25	0.5	100.0			100.0		0.0
Erythromycin	>8	>8	0.0	0.0	100.0	0.0	0.0	100.0
Gentamicin	≤1	>8	89.3	0.0	10.7	88.3		11.7
Levofloxacin	>4	>4	5.8	0.0	94.2	5.8		94.2
Linezolid	1	1	100.0		0.0	100.0		0.0
Teicoplanin	≤2	≤2	100.0	0.0	0.0	100.0		0.0
Tetracycline	≤0.5	8	88.3	1.9	9.7	83.5	3.9	12.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	93.2		6.8	93.2	1.0	5.8
Vancomycin	1	1	100.0	0.0	0.0	100.0		0.0

[a] MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MDR, multidrug-resistant (defined as MRSA resistant to 3 or more additional drug classes)
[b] Criteria as published by CLSI [2017] and EUCAST [2017]
[c] Breakpoint applied to all *S. aureus*, but approved for MRSA isolates only

CONCLUSIONS

- Telavancin demonstrated potent *in vitro* activity against this US collection of *S. aureus* isolates (100.0% susceptible) regardless of methicillin and MDR-resistance phenotype or infection source
- The telavancin *in vitro* activity was consistently more potent than all tested comparators against each isolate subset, including MDR MRSA
- These data indicate that telavancin may be an attractive option for treating SSSI and pneumonia with concomitant BSI that are caused by *S. aureus*, regardless of resistance phenotype

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