Activity of Telavancin Against Gram-positive Pathogens Isolated from Bone and Joint Infections in North American, Latin American, European and Asia-Pacific Nations

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AMENDED ABSTRACT

Background: Telavancin, a lipoglycopeptide, has broad *in vitro* activity against *S. aureus* (MIC_{90} 0.06 µg/ml), coagulase-negative staphylococci (CoNS; 0.06 µg/ml), β-hemolytic (BHS) and viridans group (VGS) streptococci (≤0.06 µg/ml) and vancomycin-susceptible enterococci (0.12 µg/ml). Telavancin, as a potential treatment option for osteomyelitis therapy, was tested against a worldwide collection of pathogens (967) isolated from bone and joint infections (BJI).

Methods: A SENTRY Program collection of BJI strains (2011-2014) was tested by reference broth microdilution susceptibility methods for telavancin and 13 other agents including vancomycin, oxacillin, daptomycin and teicoplanin. Data were analyzed by region (EU, LATAM, US, APAC), patient age (≤17 and ≥ 18 years) and resistant subgroups. Organism numbers tested were: *S. aureus* (642), CoNS (117), BHS (106), VGS (37) and enterococci (65).

Results: The most common pathogen was *S. aureus* (66.4%; range 48.9% [APAC] to 71.2% [LATAM]), having a 35.7% MRSA rate and telavancin $MIC_{50/90}$ of 0.03/0.06 µg/ml (100% susceptible by US-FDA/EUCAST breakpoint criteria). 64.1 and 13.7% of CoNS (12.1% of BJI) were methicillin- and teicoplanin-resistant, respectively, and these isolates had telavancin $MIC_{50/90}$ at 0.06/0.06 µg/ml. Streptococci were 100% susceptible to telavancin (MIC_{90}, 0.03-0.06 µg/ml). Most BJI isolates were from US (49.9%) followed by EU (26.4%), LATAM (14.4%) and APAC (9.3%). Only 12.5% of *S. aureus* were observed in patients ≤17 years and 31.2% were MRSA (36.6% in adults). Daptomycin-non-susceptible (0.2%) was noted in US, MRSA in adults and were all telavancin-susceptible (≤0.12µg/ml). Enterococci overall had telavancin $MIC_{50/90}$ at 0.12/0.25 µg/ml, but vancomycin-susceptible strains had telavancin MICs at ≤0.12 µg/ml. All VRE had VanA-phenotypes.

Conclusion: Telavancin demonstrated activity (MIC_{90}, 0.03-0.25 µg/ml; dominantly 16x more potent than vancomycin) against species isolated worldwide from BJI in 2011-2014. Only VRE were less susceptible to telavancin (MICs, 0.25-2 µg/ml). Telavancin may be a viable candidate for BJI/osteomyelitis treatment caused by Gram-positive cocci in adults and children.

INTRODUCTION

Telavancin, a once-daily dosed lipoglycopeptide, has been approved for use in the United States (US), Canada and Europe (EU) for designated infections caused by Gram-positive organisms. In the US, this intravenous agent is approved for complicated skin and skin structure infections (cSSSI) and hospital-acquired (HABP) and ventilator-associated bacterial pneumonia (VABP). Organisms susceptible to telavancin include *Staphylococcus aureus* (including methicillin-resistant [MRSA] isolates), β-hemolytic Streptococcus spp. (*S. agalactiae* and *S. pyogenes*), *Streptococcus anginosus* group and vancomycin-susceptible *Enterococcus faecalis*. Clinical studies are underway or completed to expand telavancin treatment experience in patients with bacteremia and the pediatric age group, as well as the Telavancin Observational Use Registry (TOUR™) that includes bone and joint infections (BJI) and other infection types (see clinical trials.gov 2016).

This investigation assesses the *in vitro* activity of telavancin using the recently modified broth microdilution method (0.002% polysorbate-80) when tested against a worldwide surveillance collection of Gram-positive pathogens cultured in 2011-2014. All isolates were determined to be the cause of patient BJI by the submitting facility and results reported to their physician on five continents (four geographic regions).

MATERIALS AND METHODS

Organisms: All strains tested were from BJI as identified in the SENTRY Antimicrobial Surveillance Program (2011-2014). The isolates were cultured in the US, EU, Latin America (LATAM), and the Asia-Pacific (APAC) regions to a total of 967 organisms. *S. aureus* (642) was the most common pathogen followed by coagulase-negative *Staphylococcus* spp. (CoNS; 117), β-haemolytic streptococci (βHS; 106), enterococci (65; including 44 *E. faecalis* and 19 *E. faecium*), and viridans group streptococci (VGS; 37 from 13 species groups). Isolates were further categorized by and within regions and additionally by patient age groups (≤17 years and ≥18 years).

Isolates were initially identified by the participating laboratory as the cause of BJI, and organism identification confirmed by the monitoring laboratory using standard algorithms, supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods: Isolates were tested for susceptibility by the broth microdilution method following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was performed using reference panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, US). These panels provide telavancin results equivalent to the CLSI-approved broth microdilution 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. Confirmation of the MIC values was obtained by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212). MIC breakpoint interpretation used concurrent US-FDA, CLSI and EUCAST criteria (2016).

RESULTS

- A total of 967 BJI isolates were tested across 2011-2014 with 217 to 284 organisms processed per year from the US (483), EU (255), LATAM (139) and APAC (90) regions.
  - *S. aureus* was the most observed pathogen (66.4% overall; range 48.9% [APAC] to 71.2% [LATAM]
  - Rank order of other Gram-positive groups was CoNS (12.1%) > BHS (11.0%) > *Enterococcus* spp. (6.7%) > VGS (3.8%)
  - Eighty isolates (12.5%) of *S. aureus* came from patients ≤17 years of age
- *S. aureus* (35.7% MRSA) showed low MIC results to telavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml; 100.0% susceptible), as did the CoNS ($MIC_{50/90}$, 0.06/0.06 µg/ml, see **Table 1**) and streptococcal isolates with MIC_{90} results of 0.03-0.06 µg/ml. The seven vancomycin-resistant enterococci identified had telavancin MIC results ranging from 0.25-2 µg/ml (non-susceptible VanA phenotypes).
- **Table 2** shows the telavancin MIC values compared to 13 agents commonly used to treat serious Gram-positive pathogen infections. The broadest coverage of *S. aureus* (100.0% susceptible) was achieved by telavancin, vancomycin, linezolid and trimethoprim-sulfamethoxazole followed by ≥94.2% susceptibility rates for daptomycin, teicoplanin, gentamicin and the tetracyclines (**Table 2**).
- The potency of telavancin did not vary significantly across geographic regions or between the two analyzed patient age groups, regardless of pathogen group examined.
- BJI isolates of CoNS (117; 11 species) were also susceptible to vancomycin (100.0% susceptible) and daptomycin (100.0%) and linezolid (100.0%); while teicoplanin susceptibility varied (86.3-97.4%) according to breakpoint (**Tables 1-3**).
- BHS and VGS (143 isolates) were all telavancin-susceptible (US-FDA criteria) and the MIC results ranged from ≤0.015 to 0.12 µg/ml (MIC_{90}, 0.03 or 0.06 µg/ml). Macrolides (erythromycin 48.6-67.9% susceptible), clindamycin (81.1-84.8%) and the tetracyclines (45.7-67.6%) had the most compromised activity.
- **Table 3** exhibits the variations in some key resistance mechanisms across the examined geography including high MRSA rate (45.0% in US), teicoplanin-non-susceptibility in CoNS (40.0% in LATAM), VRE (18.2% in US), erythromycin-non-susceptible in BHS (36.5-36.7% in US and EU) and penicillin-non-susceptible in VGS (30.0% in EU).
- Finally, **Figure 1** illustrates the 16-fold potency advantage of telavancin versus vancomycin when tested against all Gram-positive isolates causing BJI in this worldwide sample. As noted in **Table 2** against *S. aureus*, telavancin was also at least eight–fold more active than daptomycin, oxacillin, erythromycin, levofloxacin and linezolid.

Table 1. Activity of telavancin tested against 967 Gram-positive pathogens causing bone and joint infections (BJI) during 2011-2014 worldwide.

BJI pathogen[a]/ Subset (no. tested)	No. isolates (cum. %) inhibited by telavancin at MIC (µg/ml): ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	MIC (µg/ml) 50%	90%
S. aureus (642)	34 (5.3)	366 (62.3)	242 (100.0)	--	--	--	--	--	0.03	0.06
MSSA (413)	25 (6.1)	240 (64.2)	148 (100.0)	--	--	--	--	--	0.03	0.06
MRSA (229)	9 (3.9)	126 (59.0)	94 (100.0)	--	--	--	--	--	0.03	0.06
CoNS (117)[b]	19 (16.2)	34 (45.3)	64 (100.0)	--	--	--	--	--	0.06	0.06
Enterococci (65)[c]	7 (10.8)	4 (16.9)	16 (41.5)	31 (89.2)	1 (90.8)	0 (90.8)	4 (96.9)	2 (100.0)	0.12	0.25
βHS (106)[d]	48 (45.3)	39 (82.1)	16 (97.2)	3 (100.0)	--	--	--	--	0.03	0.06
VGS (37)[e]	19 (51.4)	15 (91.9)	3 (100.0)	--	--	--	--	--	≤0.015	0.03

a. MSSA – methicillin-susceptible *S. aureus*; MRSA - methicillin-resistant *S. aureus*. CoNS – coagulase-negative staphylococci, βHS – beta-hemolytic streptococci and VGS – viridans group streptococci
b. Organisms include: unspeciated CoNS (3), *Staphylococcus capitis* (9), *S. cohnii* (1), *S. caprae* (2), *S. epidermidis* (72), *S. haemolyticus* (5), *S. hominis* (5), *S. lugdunensis* (12), *S. pettenkoferi* (1), *S. pseudointermedius* (1), *S. simulans* (2) and *S. warneri* (8)
c. Organisms include: *Enterococcus avium* (1), *E. faecalis* (44), *E. faecium* (19) and *E. gallinarum* (1)
d. Organisms include: *Streptococcus pyogenes* (27), *S. agalactiae* (49), Group C *Streptococcus* (3), Group G *Streptococcus* (10) and *S. dysgalactiae* (17)
e. Organisms include: *Streptococcus constellatus* (2), *S. cristatus* (1), *S. gordonii* (3), *S. anginosus* group (1), *S. mitis* group (5), *S. mitis/oralis* (4), *S. parasanguinis* (2), *S. salivarius* (2), *S. anginosus* (2) and unspeciated VGS (1)

Table 2. Comparative activity of telavancin and 13 other agents tested against staphylococci, streptococci and enterococci causing BJI worldwide (2011-2014)

Pathogen (no. tested); Antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% Susceptible[a]: EUCAST	CLSI
S. aureus (642)					
Telavancin	0.03	0.06	≤0.015 - 0.06	100.0[b]	100.0
Vancomycin	1	1	≤0.12 – 2	100.0	100.0
Teicoplanin	≤2	≤2	≤2 – 8	99.8	100.0
Daptomycin	0.25	0.5	≤0.06 – 2	99.8	99.8
Oxacillin	0.5	≥2	≤0.25 - >2	64.3	64.3
Clindamycin	≤0.25	>2	≤0.25 - >2	87.9	88.2
Erythromycin	0.25	>16	≤0.12 - >16	57.9	57.6
Gentamicin	≤1	≤1	≤1 - >8	94.5	95.3
Levofloxacin	0.25	>4	≤0.12 - >4	70.7	70.7
Linezolid	1	2	≤0.12 – 2	100.0	100.0
Tetracycline	≤0.5	≤0.5	≤0.5 - >8	94.2	95.2
TMP-SMX[c]	1	1	≤0.12 – 2	100.0	100.0
CoNS (117)[d]					
Telavancin	0.06	0.06	≤0.015 - 0.06	--	--
Vancomycin	1	2	0.5 - 2	100.0	100.0
Teicoplanin	≤2	8	≤2 - 16	86.3	97.4
Daptomycin	0.25	0.5	≤0.06 - 1	100.0	100.0
Oxacillin	2	>2	≤0.25 - >2	35.9	35.9
Clindamycin	≤0.25	>2	≤0.25 - >2	70.9	70.9
Erythromycin	16	>16	≤0.12 - >16	45.3	45.3
Gentamicin	≤1	>8	≤1 - >8	67.5	70.1
Levofloxacin	0.25	>4	≤0.12 - >4	62.4	62.4
Linezolid	0.5	1	≤0.25 – 2	100.0	100.0
Tetracycline	≤0.5	>8	≤0.5 - >8	81.2	85.5
TMP-SMX[c]	≤0.5	>4	≤0.5 - >4	76.1	76.1
Enterococci (65)[d]					
Telavancin	0.12	0.25	≤0.015 – 2	--	100.0
Vancomycin	1	>16	0.5 - >16	89.2	89.2
Teicoplanin	≤2	16	≤2 - >16	89.2	89.2
Daptomycin	1	2	0.12 – 2	--	100.0
Ampicillin	1	>8	0.5 - >8	72.3	73.8
Levofloxacin	2	>4	0.5 - >4	55.4	53.8
Linezolid	1	2	0.25 - 2	100.0	100.0
Tetracycline	>8	>8	≤0.5 - >8	--	35.4
βHS (106)[d]					
Telavancin	0.03	0.06	≤0.015 – 0.12	--	100.0
Vancomycin	0.5	0.5	0.25 – 0.5	100.0	100.0
Teicoplanin	≤2	≤2	≤2	100.0	--
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0	100.0
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100.0	100.0
Clindamycin	≤0.25	>2	≤0.25 - >2	84.8	82.8
Erythromycin	≤0.12	>16	≤0.12 - >16	67.9	67.9
Levofloxacin	0.5	1	0.25 – >4	97.2	99.1
Linezolid	1	1	0.25 – 1	100.0	100.0
Tetracycline	4	>8	≤0.5 - >8	45.7	46.7
VGS (37)[d]					
Telavancin	≤0.015	0.03	≤0.015 – 0.06	--	100.0
Vancomycin	0.5	1	0.25 – 1	100.0	100.0
Teicoplanin	≤2	≤2	≤2	100.0	--
Daptomycin	0.5	1	≤0.06 – 1	--	100.0
Penicillin	≤0.06	1	≤0.06 – 8	86.5	83.8
Clindamycin	≤0.25	>2	≤0.25 - >2	81.1	81.1
Erythromycin	1	>16	≤0.12 - >16	--	48.6
Levofloxacin	1	2	0.25 - >4	--	91.9
Linezolid	0.5	1	0.25 – 2	--	100.0
Tetracycline	≤0.5	>8	≤0.5 - >8	--	67.6

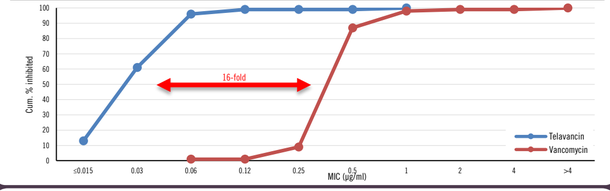
a. Interpretive criteria of the EUCAST and CLSI
b. For MRSA only
c. TMP-SMX = trimethoprim-sulfamethoxazole
d. See footnotes by species group in Table 1

Table 3. Regional[a] and patient age group variations in the activity of telavancin and key comparison agents tested against 967 BJI pathogens

Pathogen (no. tested)/ (resistant subgroup %)[b]	All strains	Telavancin $MIC_{50/90}$ (µg/ml): Patients (years) ≤17	≥18	Region US	EU	LATAM	APAC
S. aureus (642)	0.03 / 0.06	0.03 / 0.06	0.03 / 0.06	0.03 / 0.06	0.03 / 0.06	0.06 / 0.06	0.06 / 0.06
(MRSA %)[b]	(35.7)	(31.2)	(36.6)	(45.0)	(18.5)	(40.4)	(13.6)
CoNS (117)	0.06 / 0.06	--	--	0.03 / 0.06	0.06 / 0.06	0.06 / 0.06	0.06 / 0.06
(Teicoplanin-NS %)[b]	(13.7)			(2.7)	(17.1)	(40.0)	(0.0)
Enterococci (65)	0.12 / 0.25	--	--	0.12 / 1	0.06 / 0.12	0.12 / 0.12	≤0.15 [c] / -
(VRE %)[b]	(10.8)			(18.2)	(5.9)	(0.0)	(0.0)
βHS (106)	0.03 / 0.06	--	--	0.03 / 0.06	≤0.015 / 0.03	≤0.015 / -	0.03 / 0.06
(Erythromycin-NS %)[b]	(32.1)			(36.5)	(36.7)	(25.0)	(15.0)
VGS (37)	≤0.015 / 0.03	--	--	≤0.015 / 0.03	≤0.015 / 0.03	0.03 / -	0.03 / -
(Penicillin-NS %)[b]	(13.5)			(10.5)	(30.0)	(0.0)	(0.0)

a. US = United States; EU = Europe; LATAM = Latin America; and APAC = Asia-Pacific
b. NS = non-susceptible subsets (EUCAST criteria) for methicillin (MRSA), teicoplanin, vancomycin (VRE), erythromycin and penicillin.
c. - = small subset and represents MIC value of a single isolate.

Figure 1. Telavancin and vancomycin MIC distributions for all BJI pathogens combined (967 isolates, five species groups) demonstrating the greater potency of telavancin. Data presented as the cumulative percentage of strains inhibited at each MIC (µg/ml)



CONCLUSIONS

- Based on *in vitro* susceptibility, telavancin demonstrates a clear potency advantage when directly compared to other Gram-positive-active agents versus major pathogen groups isolated from BJI in the SENTRY Program.
- Telavancin was equally active and more potent against all five pathogen groups when judged against other valuable and currently used treatments for BJI. Telavancin may represent a potential treatment option for osteomyelitis therapy.

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