Activity of Telavancin and Comparator Agents Tested Against Gram-Positive Isolates Cultured From Skin and Skin-Structure Infections

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ABSTRACT

Background. Telavancin is a bactericidal lipoglycopeptide indicated in the US and Canada for treatment of adult patients with complicated skin and skin-structure infections (cSSSI) caused by susceptible Gram-positive bacteria. We assessed telavancin activity against Gram-positive isolates cultured for the treatment of SSSI during a global surveillance study.

Methods. Unique and clinically significant Gram-positive isolates (5062) were collected (94 hospitals, 27 countries) during 2007 and 2008, and sent to a central monitor. Identification was performed by standard algorithms and confirmed by Vitek 2. Isolates were tested for susceptibility by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods (M07-A8 and M100-S19).

Results. Isolates were collected from hospitalized patients in the USA (40%), Europe (30%), Asia-Pacific (20%), and Latin America (10%). Telavancin was very active against methicillin-susceptible and -resistant *S. aureus* (MSSA and MRSA; MIC_{90} for both, 0.25 µg/mL; 100.0% susceptible). Similar values were noted for methicillin-susceptible and -resistant coagulase-negative staphylococci (CoNS; MIC_{90}, 0.25 µg/mL). Only telavancin, vancomycin, daptomycin, and linezolid sustained activity against methicillin-resistant staphylococci. Telavancin (MIC_{90}, 1 µg/mL), daptomycin and linezolid (2 µg/mL; 99.8% susceptible) were the most active agents against enterococci (12.9% vancomycin-resistant [VRE]). Telavancin inhibited 99.4% and 68.5% of *E. faecalis* (2% VRE) and *E. faecium* (40.0% VRE) at ≤1 µg/mL, respectively. Telavancin was equally active against β-hemolytic streptococci and viridans group streptococci (MIC_{90}, 0.06 µg/mL; 100.0% susceptible). All streptococci were susceptible to vancomycin, linezolid, and levofloxacin (2.4% penicillin-resistant viridans group streptococci).

	MIC_{90} (µg/mL)/% susceptible					
Organism (no.)	**TLV**	**VAN**	**DAP**	**CLI**	**LZD**	**LEV**
S. aureus (3989)	0.25/100.0	1/>99.9	0.5/100.0	≤0.25/83.2	2/100.0	≤0.5/69.7
MSSA (2409)	0.25/100.0	1/100.0	0.5/100.0	≤0.25/94.4	2/100.0	≤0.5/94.6
MRSA (1580)	0.25/100.0	1/99.9	0.5/100.0	>2/66.1	2/100.0	>4/31.8
CoNS (177)	0.25/-[a]	2/100.0	0.5/99.4	>2/69.5	1/100.0	>4/56.5
MSCoNS (50)	0.25/-	2/100.0	0.5/100.0	0.5/90.0	1/100.0	≤0.5/94.0
MRCoNS (127)	0.25/-	2/100.0	0.5/99.2	>2/61.4	1/100.0	>4/41.7
Enterococci (495)	1/-	>16/86.3	2/99.8	>4/-	2/99.8	>4/55.2
E. faecalis (337)	0.5/99.4[b]	2/98.2	2/100.0	>4/-	2/99.7	>4/73.6
E. faecium (143)	>2/-	>16/58.0	4/99.3	>4/-	2/100.0	>4/8.4
VRE (68)	>2/-	>16/0.0	2/100.0	>4/-	2/100.0	>4/2.9
β-HS (339)	0.06/100.0	0.5/100.0	0.25/100.0	≤0.25/94.4	1/100.0	1/100.0
VGS (42)	0.06/100.0	1/100.0	0.5/100.0	>2/78.6	1/100.0	1/100.0

MIC, minimum inhibitory concentration; TLV, telavancin; VAN, vancomycin; DAP, daptomycin; CLI, clindamycin; LZD, linezolid; LEV, levofloxacin; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; MSCoNS, methicillin-susceptible CoNS; MRCoNS, methicillin-resistant CoNS; VRE, vancomycin-resistant enterococci; βHS, β-hemolytic streptococci; VGS, viridans group streptococci.

[a] Data not applicable.

[b] Includes 6 vancomycin-resistant *E. faecalis*. All vancomycin-susceptible isolates were inhibited by telavancin at ≤1 µg/mL (100.0% susceptible).

Conclusions. Based on MIC_{90} potencies, telavancin was very active against this recent collection of Gram-positive isolates cultured from SSSI, with decreased activity observed only against VRE. Continued monitoring for resistance emergence in Gram-positive bacteria will be critical in assessing the sustained microbiologic efficacy of telavancin.

INTRODUCTION

- Skin and skin-structure infections (SSSI) are common and range in severity from mild superficial processes such as impetigo and simple cellulitis to deeper and more complex infections involving the tissue fascia and musculature.[1,2]
- Complicated SSSI (cSSSI) may require hospitalization and parenteral therapy.[2]
- SSSI rank as the third most common nosocomial infections, affecting approximately 14–16% of all hospitalized patients.[2] Surgical wound site infections (SWSI) represent a significant and costly source of SSSI.[3]

INTRODUCTION (cont.)

- Most SSSI are caused by Gram-positive bacteria, especially *Staphylococcus aureus*, enterococci, and β-hemolytic streptococci.[4]
  - The prevalence of multidrug resistance (MDR) continues to increase among Gram-positive isolates, particularly in *S. aureus*.[5]
  - The rates of methicillin (oxacillin) resistance among *S. aureus* (MRSA) exceed 50% in many institutions worldwide, and the emergence of community-acquired MRSA has become a significant health care concern.[4,5]
- Emerging concerns regarding the utility of vancomycin as the mainstay for treatment of MRSA and other MDR Gram-positive infections[2] underscore the need for new treatment options.[6]
- Telavancin is a novel, once-daily lipoglycopeptide antimicrobial agent that is indicated in the US and Canada for treatment of cSSSI in adults caused by *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *S. agalactiae*, *S. anginosus* group and *Enterococcus faecalis* (vancomycin-susceptible isolates only).[5,7,8]
- We present the results of a 2007 to 2008 international surveillance program comparing the activity of telavancin and comparator agents against Gram-positive clinical isolates obtained from patients with documented SSSI.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 5062 nonduplicate Gram-positive clinical isolates were submitted from 94 hospitals (27 countries) located in Europe (1859 isolates), United States (1618 isolates), the Asia-Pacific region (1326 isolates), and Latin America (259 isolates).
- Isolates from pyogenic wounds, abscesses, cellulitis aspirates, ulcers, and burns deemed to be clinically significant by the local site investigators were shipped to the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for subsequent identification, confirmation and antimicrobial susceptibility testing.
- The isolates were from a SSSI or SWSI and were either community-acquired or nosocomial. Identification was performed using an automated system (Vitek®; bioMérieux, Nazelwood, Missouri, USA) or conventional methods as required.

Antimicrobial susceptibility test methods

- The isolates were tested for susceptibility by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 2–5% lysed horse blood added for testing of streptococci) (M07-A8).[9]
- Telavancin and the comparator agents were obtained from the respective manufacturers or commercial sources (Sigma Chemical Co., St. Louis, Missouri, USA). Agents tested included: oxacillin, penicillin, ampicillin, vancomycin, teicoplanin, daptomycin, linezolid, quinupristin/dalfopristin, levofloxacin, erythromycin, clindamycin, gentamicin, streptomycin, tetracycline, and trimethoprim/sulfamethoxazole.
- Interpretation of minimum inhibitory concentration (MIC) results was in accordance with published CLSI (M100-S19) criteria.[10] Telavancin susceptible breakpoints for *S. aureus* (≤1 µg/mL), *E. faecalis* (≤1 µg/mL, for vancomycin-susceptible isolates only), viridans group streptococci, and β-hemolyticus streptococci (≤0.12 µg/mL) were those recently approved by the US Food and Drug Administration.[8]
- Quality control (QC) strains utilized were: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619; all MIC results were within CLSI listed QC ranges.[10]

RESULTS

- Telavancin was very active against *S. aureus* (MIC_{90}, 0.25 µg/mL; 100.0% susceptible) and coagulase-negative staphylococci. (CoNS; MIC_{90}, 0.25 µg/mL), inhibiting all staphylococci at ≤0.5 µg/mL (**Table 1**).
- Methicillin-susceptible *S. aureus*, MRSA, and CoNS MIC_{90} values for telavancin were lower compared with vancomycin (by 2- to 4-fold), daptomycin (by 2-fold), linezolid (by 4- to 8-fold), and quinupristin/dalfopristin (by 2-fold; **Table 2**).
- Levofloxacin, erythromycin, clindamycin, and gentamicin had limited activity against MRSA and CoNS (**Table 2**). Antistaphylococcal activity was observed at suboptimal levels for tetracycline and trimethoprim/sulfamethoxazole (≥80.3 and ≥72.3% susceptible, respectively).
- Telavancin (MIC_{90}, 0.5 µg/mL) showed a susceptibility rate of 99.4% when tested against a collection of *E. faecalis*, which included 6 vancomycin-resistant isolates. All vancomycin-susceptible *E. faecalis* were inhibited by telavancin at ≤1 µg/mL (100.0% susceptible; **Tables 1** and **2**).
- Telavancin (MIC_{90}, 0.5 µg/mL) was 4-fold more potent than ampicillin (MIC_{90}, 2 µg/mL; 100.0% susceptible), vancomycin (MIC_{90}, 2 µg/mL; 98.2% susceptible), daptomycin (2 µg/mL; 100.0% susceptible), and linezolid (2 µg/mL; 99.7% susceptible) when tested against *E. faecalis* (**Table 2**).
- Whereas only 58.0% and 62.9% of *E. faecium* isolates were susceptible to vancomycin and teicoplanin, respectively, telavancin inhibited 68.5% of these isolates at ≤1 µg/mL (**Tables 1** and **2**). However, all vancomycin-susceptible *E. faecium* were inhibited by telavancin at ≤0.25 µg/mL (**Table 1**).
- Among β-hemolytic streptococci and viridans group streptococci, 10.9% and 21.4%, respectively, were refractory to macrolides and more than 30% of isolates in both groups were resistant to tetracycline (**Table 2**). Telavancin (MIC_{90}, 0.06–0.12 µg/mL) and penicillin (MIC_{90}, 0.06–0.12 µg/mL) were the most potent agents tested against streptococci.

Table 1. Antimicrobial activity of telavancin against organism species/groups and resistant subsets recovered from patients with skin and skin-structure infections (2007–2008)

	MIC (µg/mL)		Cumulative % inhibited at telavancin MIC (µg/mL) of:							
Organism (no. tested)	**50%**	**90%**	**≤0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**
S. aureus (3989)	0.12	0.25	0.1	0.3	5.1	67.3	98.1	100.0	–	–
MSSA (2409)	0.12	0.25	0.1	0.5	5.4	71.1	99.1	100.0	–	–
MRSA(1580)	0.12	0.25	0.1	0.1	4.7	61.5	97.3	100.0	–	–
CoNS (177)	0.12	0.25	1.7	4.0	15.3	73.5	97.7	100.0	–	–
MSCoNS (50)	0.12	0.25	0.0	8.0	24.0	82.0	98.0	100.0	–	–
MRCoNS (127)	0.12	0.25	2.4	2.4	11.8	70.1	97.6	100.0	–	–
E. faecalis (337)	0.25	0.5	0.3	0.3	0.3	15.1	65.6	99.1	99.4	99.4[a]
E. faecium (143)	0.12	>2	4.2	19.6	34.3	59.4	62.9	63.6	68.5	84.0
Vancomycin-susceptible *E. faecium* (83)	0.06	0.12	7.2	31.3	54.2	94.0	100.0	–	–	–
β-hemolytic streptococci[b] (339)	0.03	0.06	17.7	62.2	90.0	100.0	–	–	–	–
Viridans group streptococci[c] (42)	0.03	0.06	11.9	57.1	90.5	100.0	–	–	–	–

MIC, minimum inhibitory concentration; MSSA, methicillin (oxacillin)-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; MSCoNS, methicillin-susceptible coagulase-negative staphylococci; MRCoNS, methicillin-resistant coagulase-negative staphylococci.

[a] Includes 6 vancomycin-resistant *E. faecalis*. All vancomycin-susceptible isolates were inhibited by telavancin at ≤1 µg/mL (100.0% susceptible).

[b] Includes: *S. dysgalactiae* (11 strains), *S. equi* (2 strains), Group A streptococci (189 strains), Group B streptococci (83 strains), Group C streptococci (9 strains), Group F streptococci (1 strain), Group G streptococci (42 strains), and unspecified β-hemolytic streptococci (2 strains).

[c] Includes: *S. anginosus* (21 strains), *S. constellatus* (7 strains), *S. intermedius* (2 strains), *S. milleri* (3 strains), *S. oralis* (1 strain), *S. salivarius* (1 strain), *S. uberis* (1 strain), *S. vestibularis* (1 strain), unspecified *Streptococcus* spp. (1 strain), and unspecified viridans group streptococci (4 strains).

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against 5062 Gram-positive isolates responsible for skin and skin-structure infections (2007–2008)

	MIC (µg/mL)[a]			% by category[b]	
Organism (no. tested)/Antimicrobial agent	**Range**	**50%**	**90%**	**Susceptible**	**Resistant**
S. aureus (3989)					
Telavancin	≤0.015 – 0.5	0.12	0.25	100.0	–
Oxacillin	≤0.25 – >2	0.5	>2	60.4	39.6
Vancomycin	0.25 – 4	1	1	>99.9	0.0
Teicoplanin	≤2 – >16	≤2	≤2	>99.9	<0.1
Daptomycin	≤0.06 – 1	0.25	0.5	100.0	–
Linezolid	0.25 – 2	2	2	100.0	–
Quinupristin/dalfopristin	≤0.25 – >2	≤0.25	0.5	99.8	0.1
Levofloxacin	≤0.5 – >4	≤0.5	>4	69.7	30.0
Erythromycin	≤0.25 – >4	0.5	>4	53.6	45.8
Clindamycin	≤0.25 – >2	≤0.25	>2	83.2	16.7
Gentamicin	≤2 – >8	≤2	>8	89.5	10.1
Tetracycline	≤2 – >8	≤2	>8	88.6	11.1
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	≤0.5	94.9	5.1
MSSA (2409)					
Telavancin	≤0.015 – 0.5	0.12	0.25	100.0	–
Vancomycin	0.25 – 2	1	1	100.0	0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0	0.0
Daptomycin	≤0.06 – 1	0.25	0.5	100.0	–
Linezolid	0.5 – 2	2	2	100.0	–
Quinupristin/dalfopristin	≤0.25 – 2	≤0.25	0.5	>99.9	0.0
Levofloxacin	≤0.5 – >4	≤0.5	≤0.5	94.6	5.2
Erythromycin	≤0.25 – >4	≤0.25	>4	77.0	22.3
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	94.4	5.6
Gentamicin	≤2 – >8	≤2	≤2	97.5	2.4
Tetracycline	≤2 – >8	≤2	≤2	94.0	5.7
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	≤0.5	98.2	1.8
MRSA (1580)					
Telavancin	≤0.015 – 0.5	0.12	0.25	100.0	–
Vancomycin	0.25 – 4	1	1	99.9	0.0
Teicoplanin	≤2 – >16	≤2	≤2	99.9	0.1
Daptomycin	≤0.06 – 1	0.25	0.5	100.0	–
Linezolid	0.25 – 2	1	2	100.0	–
Quinupristin/dalfopristin	≤0.25 – >2	0.5	0.5	99.7	0.1
Levofloxacin	≤0.5 – >4	4	>4	31.8	67.8
Erythromycin	≤0.25 – >4	>4	>4	17.9	81.6
Clindamycin	≤0.25 – >2	≤0.25	>2	66.1	33.7
Gentamicin	≤2 – >8	≤2	>8	76.8	22.3
Tetracycline	≤2 – >8	≤2	>8	80.3	19.4
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	>2	89.8	10.2
E. faecalis (337)					
Telavancin	≤0.015 – >2	0.25	0.5	99.4[c]	–
Ampicillin	≤1 – 8	≤1	2	100.0	0.0
Vancomycin	0.5 – >16	1	2	98.2	1.8
Teicoplanin	≤2 – >16	≤2	≤2	99.4	0.6
Daptomycin	0.12 – 4	1	2	100.0	–
Linezolid	0.5 – 4	1	2	99.7	0.0
Quinupristin/dalfopristin	0.5 – >2	>2	>2	0.3	96.7
Levofloxacin	≤0.5 – >4	1	>4	73.6	25.8
Gentamicin (HL)	≤500 – >1000	≤500	>1000	64.7	35.3
Streptomycin (HL)	≤1000 – >2000	≤1000	>2000	62.9	37.1
Tetracycline	≤2 – >8	>8	>8	21.4	78.6
E. faecium (143)					
Telavancin	≤0.015 – >2	0.12	>2	–	–
Ampicillin	≤1 – >16	>16	>16	9.8	90.2
Vancomycin	0.5 – >16	1	>16	58.0	39.9
Teicoplanin	≤2 – >16	≤2	>16	62.9	34.3
Daptomycin	0.12 – 8	2	4	99.3	–
Linezolid	1 – 2	2	2	100.0	0.0
Quinupristin/dalfopristin	≤0.25 – >2	1	>2	71.3	15.4
Levofloxacin	≤0.5 – >4	>4	>4	8.4	88.1
Gentamicin (HL)	≤500 – >1000	≤500	>1000	59.4	40.6
Streptomycin (HL)	≤1000 – >2000	≤1000	>2000	53.1	46.9
Tetracycline	≤2 – >8	≤2	>8	66.4	32.9
β-hemolytic streptococci (339)					
Telavancin	≤0.015 – 0.12	0.03	0.12	100.0	–
Penicillin	≤0.015 – 0.12	≤0.015	0.06	100.0	–
Vancomycin	0.012 – 1	0.5	0.5	100.0	–
Teicoplanin	≤2 – 4	≤2	≤2	–	–
Daptomycin	≤0.06 – 1	≤0.06	0.25	100.0	–
Linezolid	0.5 – 2	1	1	100.0	–
Quinupristin/dalfopristin	≤0.25 – 1	≤0.25	0.5	100.0	0.0
Levofloxacin	≤0.5 – 2	≤0.5	1	100.0	0.0
Erythromycin	≤0.25 – >2	≤0.25	2	87.3	10.9
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	94.4	5.6
Tetracycline	≤2 – >8	≤2	>8	63.4	34.5

Table 2 (cont.). Antimicrobial activity of telavancin and comparator antimicrobial agents against 5062 Gram-positive isolates responsible for skin and skin-structure infections (2007–2008)

	MIC (µg/mL)[a]			% by category[b]	
Organism (no. tested)/Antimicrobial agent	**Range**	**50%**	**90%**	**Susceptible**	**Resistant**
CoNS (177)					
Telavancin	≤0.015 – 0.5	0.12	0.25	–	–
Oxacillin	≤0.25 – >2	2	>2	28.2	71.8
Vancomycin	0.25 – 4	1	2	100.0	0.0
Teicoplanin	≤2 – >16	≤2	8	97.2	0.6
Daptomycin	≤0.06 – 2	0.25	0.5	99.4	–
Linezolid	0.12 – 2	1	1	100.0	–
Quinupristin/dalfopristin	≤0.25 – >2	≤0.25	0.5	98.9	0.6
Levofloxacin	≤0.5 – >4	≤0.5	>4	56.5	39.5
Erythromycin	≤0.25 – >4	>4	>4	45.8	53.7
Clindamycin	≤025 – >2	≤0.25	>2	69.5	28.2
Gentamicin	≤2 – >8	≤2	>8	72.3	23.5
Tetracycline	≤2 – >8	≤2	>8	86.4	12.4
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	>2	72.3	27.7
Viridans group streptococci (42)					
Telavancin	≤0.015 – 0.12	0.03	0.06	100.0	–
Penicillin	≤0.015 – 16	0.06	0.12	95.2	2.4
Vancomycin	0.25 – 1	0.5	1	100.0	–
Teicoplanin	≤2	≤2	≤2	–	–
Daptomycin	≤0.06 – 1	0.25	0.5	100.0	–
Linezolid	0.012 – 2	1	1	100.0	–
Quinupristin/dalfopristin	≤0.25 – 2	0.5	1	97.6	0.0
Levofloxacin	≤0.5 – 2	≤0.5	1	100.0	0.0
Erythromycin	≤0.25 – >2	≤0.25	>2	71.4	21.4
Clindamycin	≤0.25 – >2	≤0.25	>2	78.6	19.0
Tetracycline	≤2 – >8	≤2	>8	69.0	31.0

MIC, minimum inhibitory concentration; MSSA, methicillin (oxacillin)-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; HL, high-level aminoglycoside resistance; CoNS, coagulase-negative staphylococci.

[a] 50% and 90% MIC encompassing 50% and 90% of isolates tested, respectively.

[b] Criteria for susceptible and resistant as published by the Clinical and Laboratory Standards Institute (M100-S19, 2009). Telavancin susceptible breakpoints for *S. aureus* (≤1 µg/mL), *E. faecalis* (≤1 µg/mL), viridans group streptococci, and β-hemolyticus streptococci (≤0.12 µg/mL) were those recently approved by the US Food and Drug Administration. Dashes (-) indicate lack of interpretive criteria.

[c] Includes 6 vancomycin-resistant *E. faecalis*. All vancomycin-susceptible isolates were inhibited by telavancin at ≤1 µg/mL (100.0% susceptible).

CONCLUSIONS

- Overall, telavancin demonstrated potent activity against *S. aureus* (100.0% susceptible) and CoNS (MIC_{90} values for both, 0.25 µg/mL), regardless of resistance to other antimicrobial classes. In addition, telavancin exhibited 2- to 8-fold greater potency (MIC_{90}) than the comparators (vancomycin, daptomycin, linezolid, and quinupristin/dalfopristin) when tested against MRSA.
- Telavancin was very active against vancomycin-susceptible *E. faecalis* (100.0% susceptible) and exhibited the lowest MIC_{90} result (0.5 µg/mL) when compared with the other agents tested.
- Telavancin MICs were elevated against *E. faecium* likely due to the high rate of vancomycin resistance phenotype within this species (39.9%).
- Telavancin inhibited all β-hemolytic streptococci at ≤0.12 µg/mL (100.0% susceptible). Equivalent potent activity was only observed for penicillin (MIC_{90}, 0.06 µg/mL; 100.0% susceptible).
- The in vitro data presented here document the activity of telavancin against Gram-positive isolates from SSSI cultures, including MRSA. Continued longitudinal surveillance to monitor telavancin activity is warranted.

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