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Activity of Telavancin Against *Staphylococcus* spp. Recovered From European Hospitals (2007–2008)

RE Mendes, HS Sader, RN Jones
JMI Laboratories, North Liberty, IA, USA

Contact information:
Ronald N. Jones, MD
JMI Laboratories
North Liberty, IA 52317
Phone: 319-665-3370
Fax: 319-665-3371
E-mail: ronald-jones@jmilabs.com

ABSTRACT

Background. Telavancin is an investigational Gram-positive antibiotic with dual mechanisms of action. It is under regulatory review in the United States (US) for the treatment of complicated skin and skin-structure infection (cSSSI) and nosocomial pneumonia (NP). Telavancin activity was evaluated against *S. aureus* and coagulase-negative *Staphylococcus* spp. (CoNS) collected from European sites in 2007–2008 as part of a global surveillance study.

Methods. A total of 3797 *S. aureus* and 950 CoNS were consecutively collected from 28 hospitals in 13 countries (2007–2008) and sent to a central monitor. Isolates were tested for susceptibility by CLSI methods. Identification was performed by standard algorithms and confirmed using a Vitek 2 automated system.

Results. Isolates were mainly from bacteremias (42.9%), skin and skin-structure infection (SSSI) (34.3%), and NP (10.7%). Telavancin showed the lowest MIC_{50} (0.25 µg/mL; **Table**) when tested against *S. aureus* and was 2-, 4-, and 8-fold more active than daptomycin or quinupristin/dalfopristin (MIC_{90}, 0.5 µg/mL), vancomycin (1 µg/mL), and linezolid (2 µg/mL), respectively. Against CoNS, telavancin was, respectively, 2-, 4-, and 8-fold more potent than daptomycin (MIC_{90}, 0.5 µg/mL), linezolid (1 µg/mL), and vancomycin (2 µg/mL). Telavancin inhibited all *S. aureus* (26.8% methicillin-resistant [MR]) and CoNS (78.9% MR) tested at ≤0.5 µg/mL and the methicillin-resistance phenotype had no adverse affect on telavancin activity. Telavancin potency did not vary against bacteremic, SSSI, or NP isolates/strains recovered from different years.

Conclusions. Telavancin was the most potent (MIC_{90}) agent tested against these staphylococcal isolates and maintained activity during the study period. These current data warrant continued longitudinal surveillance to monitor telavancin activity against staphylococci.

Table.

Organism	MIC (µg/mL)		Cumulative % inhibited at MIC (µg/mL)				
(no. tested)	MIC_{50}	MIC_{90}	≤0.03	0.06	0.12	0.25	0.5
S. aureus (3797)	0.12	0.25	0.3	6.1	70.6	99.4	100.0
MSSA (2780)	0.12	0.25	0.3	5.3	71.0	99.5	100.0
MRSA (1017)	0.12	0.25	0.1	8.1	69.5	99.3	100.0
CoNS (950)	0.12	0.25	1.5	10.4	63.7	96.9	100.0
MSCoNS (199)	0.12	0.25	3.5	15.6	68.3	98.5	100.0
MRCoNS (751)	0.12	0.25	0.9	9.0	62.4	96.5	100.0

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative *Staphylococcus* spp.; MSCoNS, methicillin-susceptible CoNS; MRCoNS, methicillin-resistant CoNS; MIC, minimum inhibitory concentration.

INTRODUCTION

- *Staphylococcus* spp. isolates, mainly *S. aureus*, are frequently responsible for nosocomial and community-acquired infections, causing significant morbidity and mortality despite advances in medical care.[1,2]
  - *S. aureus* and coagulase-negative staphylococci (CoNS) are leading causes of bacteremia and skin and skin-structure infections (SSSI) in the United States and are among the top 3 pathogens responsible for SSSI in European hospitals.[2-4]
  - Deeper and more complex infections can occur, requiring hospitalization and parenteral therapy.[5]
  - Methicillin resistance among nosocomial *S. aureus* and CoNS isolates currently exceeds 50% and 75%, respectively, in many institutions worldwide.[1,4]
- Given the tendency for clonal dissemination and the spread of antimicrobial resistance, further options for the treatment of infections caused by these organisms are needed.[1]
- Telavancin is an investigational lipoglycopeptide agent with concentration-dependent bactericidal activity against Gram-positive bacteria.[6]
- The dual mode of action of telavancin includes inhibition of cell wall synthesis and disruption of membrane barrier function.[7,8]
- We report the results of an international resistance surveillance program comparing the activity of telavancin and selected antimicrobial agents tested against *S. aureus* and CoNS clinical isolates collected in European medical centers from January 2007 through December 2008. In addition, telavancin activity was evaluated against methicillin-resistant *S. aureus* (MRSA) displaying distinct multidrug-resistance (MDR) antibiogram patterns.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 4747 consecutive and nonduplicate *Staphylococcus* spp. clinical isolates (3797 *S. aureus* and 950 CoNS) were collected from 28 medical centers located in 13 countries in Europe as part of the international telavancin surveillance program (2007–2008).
- The isolates were recovered from blood (42.9%), skin and skin structures (34.3%), respiratory tract (10.7%), urinary tract (2.9%), catheter (1.2%), bone/joint (0.6%), and other less prevalent or undetermined clinical specimens (7.2%).
- Bacterial identification was confirmed by the central monitoring site (JMI Laboratories, North Liberty, Iowa, USA) using standard algorithms and an automated system, when needed (Vitek® 2; bioMérieux, Nazelwood, Missouri, USA).

Antimicrobial susceptibility test methods

- The isolates were tested for susceptibility by the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards [NCCLS]) broth microdilution method[9] using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth.
- Antimicrobial agents representing the most common therapeutic classes and examples of drugs used for empiric or directed treatment of staphylococcal infections were tested.
- Interpretation of minimum inhibitory concentration (MIC) results was in accordance with published CLSI (M100-S19)[10] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[11]
- Quality control (QC) strains utilized were: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619; all MIC results were within CLSI listed QC ranges.

RESULTS

- Telavancin was highly active against staphylococci, inhibiting all *S. aureus* (26.8% MRSA) and CoNS (78.9% methicillin-resistant) with MIC values at ≤0.5 µg/mL (**Table 1**).
- Against *S. aureus*, telavancin (MIC_{90}, 0.25 µg/mL; **Table 1**) was 2-, 4-, and 8-fold more active than daptomycin or quinupristin/dalfopristin (MIC_{90}, 0.5 µg/mL), vancomycin (MIC_{90},1 µg/mL), and linezolid (MIC_{90}, 2 µg/mL), respectively, although these comparators exhibited high susceptibility rates (≥99.6% by CLSI and EUCAST criteria).[10,11]
- The methicillin-resistance phenotype did not adversely affect the telavancin MIC values, a finding also noted for vancomycin, teicoplanin, daptomycin, linezolid, and trimethoprim/sulfamethoxazole (TMP/SMX) when comparing the MRSA MIC_{90} directly to methicillin-susceptible *S. aureus* (MSSA) MIC_{90} results (**Table 1**).
- Among the remaining comparators, only gentamicin and tetracycline (MIC_{90}, ≤1 µg/mL; ≥92.1% susceptible), and TMP/SMX (MIC_{90}, ≤0.5 µg/mL; 99.4% susceptible) demonstrated significant coverage against *S. aureus*.
- Levofloxacin (93.9% susceptible), clindamycin (≥97.1% susceptible), gentamicin (≥98.4% susceptible), and tetracycline (≥94.6% susceptible) were significantly active when tested against MSSA (**Table 1**).

Table 1. Activity of telavancin and comparator antimicrobial agents tested against *Staphylococcus aureus* and coagulase-negative staphylococci (2007–2008)

Organism group (no. tested)/ Antimicrobial agents	MIC (µg/mL)		% by category[a] susceptible / resistant	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
***S. aureus* (3797)**				
Telavancin	0.12	0.25	– / –[b]	– / –
Oxacillin	0.5	>2	73.2 / 26.8	73.2 / 26.8
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	99.5[c] / 0.5
Daptomycin	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	1	2	100.0 / –	100.0 / 0.0
Quinupristin/dalfopristin	0.5	0.5	99.6 / 0.2	99.6 / 0.2
Levofloxacin	≤0.5	>4	71.9 / 27.7	71.9 / 27.7
Erythromycin	≤0.25	>4	70.1 / 28.9	70.8 / 28.9
Clindamycin	≤0.25	>2	89.4 / 10.5	88.9 / 10.6
Gentamicin	≤1	≤1	94.3 / 4.7	93.8 / 6.2
Tetracycline	≤1	≤1	92.3 / 7.4	92.1 / 7.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.4 / 0.6	99.4 / 0.6
MSSA (2780)				
Telavancin	0.12	0.25	–/–	– / –
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	99.9 / 0.1
Daptomycin	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	1	2	100.0 / –	100.0 / 0.0
Quinupristin/dalfopristin	≤0.25	0.5	99.9 / 0.0	99.9 / 0.1
Levofloxacin	≤0.5	≤0.5	93.9 / 5.8	93.9 / 6.8
Erythromycin	≤0.25	>4	84.5 / 14.6	85.1 / 14.6
Clindamycin	≤0.25	≤0.25	97.5 / 2.4	97.1 / 2.5
Gentamicin	≤1	≤1	98.5 / 1.3	98.4 / 1.6
Tetracycline	≤1	≤1	94.8 / 5.0	94.6 / 5.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.6 / 0.4	99.6 / 0.4
MRSA (1017)				
Telavancin	0.12	0.25	– / –	– / –
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	98.4 / 1.6
Daptomycin	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	1	2	100.0 / –	100.0 / 0.0
Quinupristin/dalfopristin	0.5	1	98.9 / 0.7	98.9 / 0.7
Levofloxacin	>4	>4	11.7 / 87.6	11.7 / 87.6
Erythromycin	>4	>4	30.5 / 68.1	31.7 / 68.1
Clindamycin	≤0.25	>2	67.2 / 32.5	66.3 / 32.8
Gentamicin	≤1	>8	82.2 / 14.3	80.8 / 19.2
Tetracycline	≤1	>8	85.3 / 14.1	85.2 / 14.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.9 / 1.1	98.9 / 1.1
MSCoNS (199)				
Telavancin	0.12	0.25	– / –	– / –
Vancomycin	1	2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	4	100.0 / 0.0	96.5 / 3.5
Daptomycin	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	1	1	100.0 / –	100.0 / 0.0
Quinupristin/dalfopristin	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	92.0 / 8.0	91.7 / 8.0
Erythromycin	≤0.25	>4	65.3 / 34.7	65.3 / 34.7
Clindamycin	≤0.25	≤0.25	94.0 / 4.5	94.0 / 6.0
Gentamicin	≤1	≤1	95.0 / 3.5	95.0 / 5.0
Tetracycline	≤1	4	90.5 / 9.5	89.9 / 10.1
Trimethoprim/sulfamethoxazole	≤0.5	2	90.8 / 9.2	90.8 / 9.2
MRCoNS (751)				
Telavancin	0.12	0.25	– / –	– / –
Vancomycin	2	2	100.0 / 0.0	98.8 / 1.2
Teicoplanin	≤2	8	97.2 / 0.5	89.6 / 10.4
Daptomycin	0.25	0.5	99.9 / –	99.9 / 0.1
Linezolid	1	1	99.6 / –	99.6 / 0.4
Quinupristin/dalfopristin	≤0.25	0.5	97.5 / 1.6	97.5 / 1.6
Levofloxacin	4	>4	29.2 / 66.7	29.2 / 66.7
Erythromycin	>4	>4	27.6 / 72.0	27.8 / 72.0
Clindamycin	≤0.25	>2	61.4 / 37.2	57.1 / 38.86
Gentamicin	8	>8	45.2 / 45.8	40.1 / 59.9
Tetracycline	≤1	>8	82.7 / 15.6	79.0 / 21.0
Trimethoprim/sulfamethoxazole	2	>2	51.5 / 48.5	51.5 / 49.5

MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute; EUCAST; European Committee on Antimicrobial Susceptibility Testing; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSCoNS, methicillin-susceptible coagulase-negative *Staphylococcus* spp.; MRCoNS, methicillin-resistant coagulase-negative *Staphylococcus* spp.

[a] MIC interpretive criteria as published by CLSI M100-S19 and EUCAST.[10,11]

[b] No breakpoints available.

[c] Teicoplanin breakpoints utilized for *S. aureus* were those recently revised (published on May 25, 2009) by EUCAST (≤2 µg/mL for susceptibility and >2 µg/mL for resistant).

RESULTS *(cont.)*

- Against methicillin-resistant CoNS, telavancin (MIC_{90}, 0.25 µg/mL) was 2-, 4-, 8-, and 16-fold more potent than daptomycin or quinupristin/dalfopristin (0.5 µg/mL), linezolid (1 µg/mL), vancomycin (2 µg/mL), and teicoplanin (8 µg/mL), respectively.
- A total of 41 antimicrobial resistance patterns were recognized among MRSA (**Table 2**). Three profiles predominated (19.0–28.5%) accounting for 68.7% of tested isolates. Macrolide, lincosamide (clindamycin), and fluoroquinolone resistance patterns prevailed.
- **Table 3** describes the MIC distribution for telavancin against MRSA isolates exhibiting different antimicrobial susceptibility profiles. Telavancin showed stable MIC_{50} values (0.25 µg/mL), regardless of MDR pattern, while the MIC_{90} varied slightly (0.12–0.25 µg/mL).
- Telavancin potency did not vary against bacteremic, SSSI, or nosocomial pneumonia isolates recovered from different years (data not shown).

Table 2. Occurrence of antimicrobial resistance patterns (41) among MRSA recovered from European hospitals

Antimicrobial resistance patterns[a]	Occurrences	
	No.	(%)
1 Antimicrobial		
OX (only)	43	4.2
2 Antimicrobials		
OX + LE	193	19.0
OX + TC	37	3.6
OX + ER	14	1.4
OX + GT	3	0.3
OX + CL	2	0.2
OX + TE	1	0.1
3 Antimicrobials		
OX + ER + LE	290	28.5
OX + LE + GT	16	1.6
OX + ER + CL	7	0.7
OX + LE + TC	6	0.6
OX + CL + LE	4	0.4
OX + ER + TC	4	0.4
OX + ER + GT	3	0.3
OX + LE + TE	2	0.2
OX + ER + TE	1	0.1
OX + GT + TE	1	0.1
OX + CL + TC	1	0.1
4 Antimicrobials		
OX + ER + CL + LE	216	21.2
OX + ER + LE + GT	26	2.6
OX + LE + GT + TC	10	1.0
OX + ER + LE + TC	4	0.4
OX + ER + LE + TE	1	0.1
OX + ER + LE + Q/D	1	0.1
OX + ER + CL + TC	1	0.1
5 Antimicrobials		
OX + ER + CL + LE + GT	33	3.2
OX + ER + LE + GT + TC	11	1.1
OX + ER + CL + LE + TC	8	0.8
OX + ER + CL + LE + Q/D	4	0.4
OX + LE + GT + TC + TE	2	0.2
OX + ER + LE + T/S + TC	1	0.1
OX + CL + LE + GT + TC	1	0.1
OX + ER + CL + LE + TE	1	0.1
6 Antimicrobials		
OX + ER + CL + LE + GT + TC	49	4.8
OX + ER + CL + LE + GT + Q/D	5	0.5
OX + ER + LE + GT + TC + TE	3	0.3
OX + ER + CL + GT + TC + TE	1	0.1
OX + ER + LE + GT + T/S + TC	1	0.1
OX + ER + CL + LE + TC + Q/D	1	0.1
7 Antimicrobials		
OX + ER + CL + LE + GT + T/S + TC	6	0.6
OX + ER + CL + LE + GT + TC + TE	3	0.3
Total	**1017**	**100.0**

MRSA, methicillin-resistant *Staphylococcus aureus*; OX, oxacillin; LE, levofloxacin; TC, tetracycline; ER, erythromycin; GT, gentamicin; CL, clindamycin; TE, teicoplanin; Q/D, quinupristin/dalfopristin; T/S, trimethoprim/sulfamethoxazole.

[a] Antibiogram using 9 agents tested against MRSA isolates with intermediate and resistant results grouped as resistant. Criteria for susceptibility were from the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[11] In addition, teicoplanin breakpoints (≤2 µg/mL for susceptibility and >2 µg/mL for resistant) were recently revised (published on May 25, 2009) by EUCAST. Nonsusceptibility results for vancomycin, daptomycin, or linezolid were not observed.

Table 3. Activity of telavancin against *Staphylococcus aureus* and CoNS, resistant subsets and the 12 most frequently occurring resistance patterns among MRSA isolates submitted as part of the 2007–2008 international surveillance program

Organism/Resistance pattern[a] (no. tested / %)	MIC (µg/mL)		Cumulative % inhibited at each telavancin MIC (µg/mL)					
	MIC_{50}	MIC_{90}	≤0.015	0.03	0.06	0.12	0.25	0.5
***Staphylococcus aureus* (3797)**	0.12	0.25	–	0.3	6.0	70.6	99.4	100.0
Methicillin-susceptible (2780)	0.12	0.25	–	0.1	8.0	69.5	99.3	100.0
Methicillin-resistant (1017)	0.12	0.25	–	0.3	5.3	71.0	99.5	100.0
OX, ER, LE (290 / 28.5)	0.12	0.25	–	–	12.1	81.0	99.7	100.0
OX, ER, LE, CL (216 / 21.2)	0.12	0.25	–	–	6.9	71.8	99.1	100.0
OX, LE (193 / 19.0)	0.12	0.25	–	–	9.8	66.8	100.0	–
OX, ER, LE, CL, GT, TC (49 / 4.8)	0.12	0.25	–	–	–	57.1	100.0	–
OX (43 / 4.2)	0.12	0.25	–	–	11.6	67.4	100.0	–
OX, TC (37 / 3.6)	0.12	0.25	–	–	–	83.8	97.3	100.0
OX, ER, LE, CL, GT (33 / 3.2)	0.25	0.25	–	–	–	24.2	97.0	100.0
OX, ER, LE, GT (26 / 2.6)	0.12	0.25	–	–	11.5	69.2	100.0	–
OX, LE, GT (16 / 1.6)	0.12	0.25	–	–	6.3	75.0	100.0	–
OX, ER (14 / 1.4)	0.12	0.25	–	–	14.3	85.7	100.0	–
OX, ER, LE, GT, TC (11 / 1.1)	0.25	0.25	–	–	–	45.5	90.9	100.0
OX, LE, GT, TC (10 / 1.0)	0.25	0.25	–	–	–	20.0	100.0	–
CoNS (950)	0.12	0.25	0.6	1.5	10.4	63.7	96.9	100.0
Methicillin-susceptible (199)	0.12	0.25	1.0	3.5	15.6	68.3	98.5	100.0
Methicillin-resistant (751)	0.12	0.25	0.5	0.9	9.0	62.4	96.5	100.0

CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration; OX, oxacillin; ER, erythromycin; LE, levofloxacin; CL, clindamycin; GT, gentamicin; TC, tetracycline.

[a] Antibiogram using 9 agents tested against methicillin-resistant *Staphylococcus aureus* isolates with intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[11] Nonsusceptibility results for vancomycin, daptomycin, or linezolid were not observed.

CONCLUSIONS

- Telavancin was the most potent drug against the tested *S. aureus* and CoNS clinical isolates and inhibited all isolates at ≤0.5 µg/mL.
- Methicillin resistance among the tested staphylococci had no effect on telavancin $MIC_{90/90}$ results. Among MRSA displaying distinct antimicrobial resistance patterns, telavancin demonstrated stable potencies (MIC_{90}, 0.12 µg/mL).
- The in vitro data presented here suggest a potential role for telavancin for treating infections due to *Staphylococcus* spp., especially MRSA.
- These current data warrant continued longitudinal surveillance to monitor telavancin activity against staphylococci.

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