Telavancin In Vitro Activity Against a Contemporary (2011–2012) Collection of Gram-positive Pathogens

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ABSTRACT (REVISED)

Background. Telavancin is a lipoglycopeptide antibiotic with bactericidal activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), resulting from a mechanism of action that combines inhibition of cell wall synthesis and disruption of membrane barrier function. This study assessed telavancin and comparator activities against Gram-positive pathogens responsible for documented infections in hospitalized patients.

Methods. 1032 Gram-positive isolates were collected from Europe and the Americas (72 sites/20 countries). Isolates were identified by biochemical algorithms and Vitek 2. Strains were susceptibility tested by broth microdilution methods (CLSI, M07-A9, 2012). FDA (telavancin), CLSI (M100-S23, 2013), and EUCAST (2013) criteria were applied.

Results. Telavancin and daptomycin were equally active against MRSA (**Tables**); both agents were 2- to 4-fold more potent than vancomycin and linezolid. Telavancin was active against coagulase-negative staphylococci, regardless of teicoplanin minimum inhibitory concentrations (MICs; ≤4 or >4 mg/L), as were daptomycin, vancomycin, and linezolid. All *Enterococcus faecalis* were inhibited by telavancin at the FDA breakpoint for susceptibility (≤1 mg/L), except for 4 VanA-type strains (telavancin MIC, >2 mg/L). Telavancin was active against vancomycin-susceptible *Enterococcus faecium*, while higher MICs were noted for VanA-type strains. Telavancin MIC_{50} values against *Streptococcus pneumoniae* (0.03 mg/L) were 16- to 32-fold lower than vancomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% susceptible), levofloxacin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible), and linezolid ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible), and 64-fold lower than penicillin ($MIC_{50/90}$, ≤0.03/2 mg/L; 91.2% susceptible [parenteral]). Telavancin and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L) were similarly active against ß-hemolytic streptococci, and telavancin was the most potent agent tested against viridans group streptococci.

Conclusions. Telavancin remains active against contemporary (2011–2012) Gram-positive pathogens, except for VanA-type enterococci. Clinically indicated pathogens were susceptible to telavancin (FDA breakpoints), supporting continued surveillance of telavancin activity.

INTRODUCTION

- Telavancin is a once-daily, intravenous, semi-synthetic lipoglycopeptide, with potent, concentration-dependent, bactericidal activity against Gram-positive clinical isolates, including methicillin-resistant *Staphylococcus aureus* (MRSA) and anaerobes.[1-3]
- Telavancin possesses a dual mechanism of action that combines a late-stage inhibition of peptidoglycan synthesis and cross-linking with the disruption of membrane potential and increased permeability.[4]
- Telavancin was approved by the US Food and Drug Administration (FDA) and Health Canada for the treatment of adults with complicated skin and skin structure infections (cSSSI) caused by susceptible organisms.[5]
- Telavancin is currently under review in the US for the treatment of nosocomial pneumonia (NP). Telavancin has marketing authorisation in Europe for NP due to MRSA when other alternatives are not suitable (at poster presentation, European marketing authorization is suspended until Theravance provides evidence of a new European Medicines Agency approved supplier).
- This investigation refers to a postmarketing surveillance study, in which telavancin potency and spectrum of activity were evaluated against contemporary (2011–2012) Gram-positive isolates collected from hospitalized patients.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 1032 Gram-positive clinical isolates were collected from medical sites in the USA (37 hospitals; 579 isolates), Europe (27 hospitals; 376 isolates), and Latin America (7 hospitals; 77 isolates).
- Consecutive, non-duplicated clinical isolates were included. These strains were collected in a prevalence-mode design from hospitalized patients with documented infections according to local guidelines. Strains were selected following pre-established surveillance protocols.
- Isolates were mostly recovered from bacteremia (65.5%), followed by SSSI (13.8%) and respiratory tract infections (9.1%), and submitted to a monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).
- Each primary medical center provided species identifications, which were confirmed when necessary by the monitoring laboratory using standard algorithms and the automated Vitek 2 system (bioMérieux, Hazelwood, Missouri, USA).
- The distribution of species included was as follows: *S. aureus* (315; 30.5%), coagulase-negative staphylococci (CoNS; 158; 15.3%), *Enterococcus faecalis* (103; 10.0%), *Enterococcus faecium* (105; 10.2%), *Streptococcus pneumoniae* (102; 9.9%), ß-hemolytic streptococci (BHS; 152; 14.7%), and viridans group streptococci (VGS; 97; 9.4%).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility using customized frozen-form broth microdilution panels manufactured according to the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012) recommendations.[6] Test media consisted of cation-adjusted Mueller–Hinton broth, which was supplemented with 2.5–5% lysed horse blood for testing of streptococci.
- Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S23, 2013)[7] quality control (QC) strains: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619.
- Interpretation of MIC results was in accordance with published CLSI (M100-S23) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria.[7,8] Telavancin-susceptible breakpoints for *S. aureus* (≤1 mg/L), vancomycin-susceptible *E. faecalis* (≤1 mg/L), BHS (≤0.12 mg/L), and VGS (≤0.12 mg/L) were those approved by the FDA.[5]
- Enterococcal isolates were clustered according to the glycopeptide-susceptible phenotype. The VanA phenotype was characterized by non-susceptibility to vancomycin (≥8 mg/L) and teicoplanin (≥16 mg/L), according to the CLSI interpretive criteria.[7]

RESULTS

- Overall, telavancin ($MIC_{50/90}$, 0.25/0.5 mg/L) exhibited equivalent potencies when tested against *S. aureus* and CoNS, and inhibited all staphylococci at ≤1 mg/L, regardless of oxacillin resistance patterns (**Table 1**).
- When tested against MRSA, telavancin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100% susceptible) and daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.4% susceptible) were equally potent, and 2- to 4-fold more potent than vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible; **Table 2**).
- Telavancin ($MIC_{50/90}$, 0.25/0.5 mg/L) was 2-fold more potent than daptomycin ($MIC_{50/90}$, 0.5/1 mg/L) and linezolid ($MIC_{50/90}$, 0.5/1 mg/L), and 4-fold more potent than vancomycin ($MIC_{50/90}$, 1/2 mg/L), when tested against a collection of CoNS (**Table 2**).
- When tested against *E. faecalis*, telavancin ($MIC_{50/90}$, 0.5/1 mg/L) inhibited all clinical isolates at ≤1 mg/L. The only exceptions were noted for 4 VanA-type strains that exhibited telavancin MIC values >2 mg/L; however, telavancin is not indicated for the treatment of infections caused by vancomycin-resistant *E. faecalis* (**Tables 1 and 2**).
- Except for levofloxacin, all agents tested against *E. faecalis* showed acceptable in vitro coverage (susceptible rates, >90.0%). Against these strains, telavancin ($MIC_{50/90}$, 0.5/1 mg/L) demonstrated MIC_{50} and MIC_{90} values 2-fold lower than ampicillin ($MIC_{50/90}$, 1/2 mg/L), vancomycin ($MIC_{50/90}$, 1/2 mg/L), daptomycin ($MIC_{50/90}$, 1/2 mg/L), and linezolid ($MIC_{50/90}$, 1/2 mg/L; **Table 2**).
- When telavancin was tested against vancomycin-susceptible *E. faecium* ($MIC_{50/90}$, 0.12/0.25 mg/L), the $MIC_{50/90}$ results obtained were 4-fold lower than those observed against vancomycin-susceptible *E. faecalis* ($MIC_{50/90}$, 0.5/1 mg/L; data not shown).
- Vancomycin-susceptible *E. faecium* displayed MIC values for telavancin ($MIC_{50/90}$, 0.12/0.25 mg/L) 4- to 8-fold lower than vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L), and 16-fold lower than daptomycin ($MIC_{50/90}$, 2/4 mg/L; **Table 2**). Vancomycin-resistant (VanA-type) *E. faecium* isolates had high telavancin MIC results ($MIC_{50/90}$, >2/>2 mg/L).
- Telavancin exhibited MIC_{50} and MIC_{90} values of 0.03/0.03 and 0.06/0.06 mg/L when tested against *S. pneumoniae* and VGS clinical isolates, respectively (**Table 2**); whereas telavancin ($MIC_{50/90}$, 0.06/0.12 mg/L) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L) were the most potent agents tested against BHS.

Table 1. Antimicrobial activity of telavancin tested against a collection of Gram-positive clinical isolates (2011–2012)

Organism (number tested) / Resistant subsets	MIC (mg/L) 50%	MIC (mg/L) 90%	Number (cumulative %) of isolates inhibited at each telavancin MIC (mg/L) of:[a] ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2
Staphylococcus aureus (315)	0.25	0.5	0 (0.0)	0 (0.0)	0 (0.0)	63 (20.0)	**214 (87.9)**	33 (98.4)	5 (100.0)	–	–
Oxacillin-susceptible (191)	0.25	0.25	0 (0.0)	0 (0.0)	0 (0.0)	40 (20.9)	**132 (90.1)**	19 (100.0)	–	–	–
Oxacillin-resistant (124)	0.25	0.5	0 (0.0)	0 (0.0)	0 (0.0)	23 (18.6)	**82 (84.7)**	14 (96.0)	5 (100.0)	–	–
Coagulase-negative staphylococci (158)	0.25	0.5	0 (0.0)	0 (0.0)	2 (1.3)	26 (17.7)	**95 (77.9)**	31 (97.5)	4 (100.0)	–	–
Enterococcus faecalis (103)	0.5	1	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	14 (15.4)	**41 (54.8)**	**42 (95.2)**	0 (95.2)	4 (100.0)[b]
Enterococcus faecium (105)	2	2	0 (0.0)	0 (0.0)	1 (0.9)	**28 (27.6)**	18 (44.8)	3 (47.6)	2 (49.5)	6 (55.2)	47 (100.0)
Vancomycin-susceptible (48)	0.12	0.25	0 (0.0)	0 (0.0)	1 (2.1)	**26 (56.3)**	17 (91.7)	3 (97.9)	1 (100.0)	–	–
VanA-type *E. faecium* (54)	>2	>2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (1.9)	1 (3.7)	6 (14.8)	**46 (100.0)**
Streptococcus pneumoniae (102)	0.03	0.03	28 (27.5)	**70 (96.1)**	4 (100.0)	–	–	–	–	–	–
ß-hemolytic streptococci (152)	0.06	0.12	0 (0.0)	12 (7.9)	**124 (89.5)**	16 (100.0)	–	–	–	–	–
Viridans group streptococci (97)	0.06	0.06	3 (3.1)	28 (32.0)	**61 (94.9)**	5 (100.0)	–	–	–	–	–

MIC, minimum inhibitory concentration.
[a] Modal MIC values are in bold; [b] VanA-type *E. faecalis* strains.

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against a collection of Gram-positive clinical isolates (2011–2012)

Organism (number tested) / Antimicrobial agent	Range	MIC (mg/L) 50%	MIC (mg/L) 90%	% Susceptible / Resistant[a] CLSI	% Susceptible / Resistant[a] EUCAST
MSSA (191)					
Telavancin	0.12–0.5	0.25	0.25	100.0 / –[b]	– / –
Vancomycin	0.5–2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.12–1	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	0.5–2	1	2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.12–>4	≤0.12	0.25	93.7 / 5.8	93.7 / 5.8
Erythromycin	≤0.12–>16	0.25	>16	75.9 / 19.9	76.4 / 22.5
Clindamycin	≤0.25–>2	≤0.25	≤0.25	96.9 / 3.1	96.3 / 3.1
Gentamicin	≤1–>8	≤1	≤1	97.4 / 2.1	96.3 / 3.7
Tetracycline	≤0.25–>32	≤0.25	≤0.25	96.8 / 3.2	95.8 / 4.2
Trimethoprim/sulfamethoxazole	≤0.5–>4	≤0.5	≤0.5	99.5 / 0.5	99.5 / 0.5
MRSA (124)					
Telavancin	0.12–1	0.25	0.5	100.0 / –	– / –
Vancomycin	0.5–2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2–4	≤2	≤2	100.0 / 0.0	99.2 / 0.8
Daptomycin	0.12–2	0.25	0.5	98.4 / –	98.4 / 1.6
Linezolid	0.5–2	1	1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.12–>4	>4	>4	29.0 / 71.0	29.0 / 71.0
Erythromycin	≤0.12–>16	>16	>16	17.7 / 82.3	17.7 / 82.3
Clindamycin	≤0.25–>2	≤0.25	>2	66.9 / 33.1	66.9 / 33.1
Gentamicin	≤1–>8	≤1	≤1	91.9 / 8.1	91.9 / 8.1
Tetracycline	≤0.25–>8	≤0.25	0.5	95.2 / 4.0	93.5 / 4.8
Trimethoprim/sulfamethoxazole	≤0.5–>4	≤0.5	≤0.5	99.2 / 0.8	99.2 / 0.8
CoNS (158)					
Telavancin	0.06–1	0.25	0.5	– / –	– / –
Oxacillin	≤0.25–>2	2	>2	33.1 / 66.9	33.1 / 66.9
Vancomycin	0.25–4	1	2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2–16	≤2	8	93.7 / 0.0	82.3 / 17.7
Daptomycin	≤0.06–2	0.5	1	96.2 / –	96.2 / 3.8
Linezolid	0.25–>8	0.5	1	98.7 / 1.3	98.7 / 1.3
Levofloxacin	≤0.12–>4	1	>4	51.3 / 46.8	51.3 / 46.8
Erythromycin	≤0.12–>16	>16	>16	35.4 / 63.9	35.4 / 64.6
Clindamycin	≤0.25–>2	≤0.25	>2	75.9 / 22.8	73.4 / 24.1
Gentamicin	≤1–>8	≤1	>8	72.6 / 21.7	68.2 / 31.8
Tetracycline	≤0.25–>8	0.5	>8	83.5 / 14.6	73.4 / 19.0
Trimethoprim/sulfamethoxazole	≤0.5–>4	≤0.5	>4	63.7 / 36.3	63.7 / 19.1
E. faecalis (103)[c]					
Telavancin	0.12–>2	0.5	1	100.0[d] / –	– / –
Ampicillin	≤0.25–>8	1	2	98.1 / 1.9	98.1 / 1.9
Vancomycin	0.5–>16	1	2	95.1 / 4.9	95.1 / 4.9
Teicoplanin	≤2–>16	≤2	≤2	94.2 / 4.9	94.2 / 5.8
Daptomycin	0.12–4	1	2	100.0 / –	– / –
Linezolid	0.5–4	1	2	99.0 / 0.0	100.0 / 0.0
Levofloxacin	0.25–>4	1	>4	64.1 / 35.9	– / –
E. faecium					
Vancomycin-susceptible (48)					
Telavancin	0.06–1	0.12	0.25	– / –	– / –
Ampicillin	≤0.25–>8	>8	>8	27.1 / 72.9	27.1 / 72.9
Vancomycin	0.5–2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5–>8	2	4	97.9 / –	– / –
Linezolid	0.25–2	1	2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	1–>4	>4	>4	27.1 / 64.6	– / –
VanA-type *E. faecium* (54)					
Telavancin	0.25–>2	>2	>2	– / –	– / –
Ampicillin	8–>8	>8	>8	1.9 / 98.1	0.0 / 98.1
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	16–>16	>16	>16	0.0 / 87.0	0.0 / 100.0
Daptomycin	0.5–4	2	2	100.0 / –	– / –
Linezolid	0.5–8	1	2	96.3 / 1.9	98.1 / 1.9
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / –
S. pneumoniae (102)					
Telavancin	0.008–0.06	0.03	0.03	– / –	– / –
Penicillin (parenteral)[e]	≤0.06–8	≤0.06	2	91.2 / 1.0	– / –
Penicillin (oral)	≤0.06–8	≤0.06	2	65.7 / 16.7	65.7 / 8.8
Vancomycin	0.25–1	0.25	0.5	100.0 / –	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	– / –	100.0 / 0.0
Daptomycin	≤0.06–>8	0.12	0.25	– / –	– / –
Linezolid	0.25–2	1	1	100.0 / –	100.0 / 0.0
Levofloxacin	≤0.12–2	1	1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.12–>16	≤0.12	>16	72.5 / 26.5	72.5 / 26.5
Clindamycin	≤0.25–>2	≤0.25	>2	86.3 / 13.7	86.3 / 13.7
Tetracycline	≤0.25–>8	0.5	>8	79.4 / 20.6	79.4 / 20.6
Viridans group streptococci (97)					
Telavancin	0.008–0.12	0.06	0.06	100.0 / –	– / –
Penicillin	≤0.06–>8	≤0.06	2	69.1 / 6.2	79.4 / 6.2
Vancomycin	0.25–1	0.5	1	100.0 / –	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	– / –	100.0 / 0.0
Daptomycin	≤0.06–2	0.25	1	96.9 / –	– / –
Linezolid	≤0.12–2	1	1	100.0 / –	– / –
Levofloxacin	0.25–>4	1	2	95.9 / 4.1	– / –
Erythromycin	≤0.12–>16	1	>16	48.5 / 50.5	– / –
Clindamycin	≤0.25–>2	≤0.25	>2	83.5 / 16.5	83.5 / 16.5
ß-hemolytic streptococci (152)					
Telavancin	0.03–0.12	0.06	0.12	100.0 / –	– / –
Penicillin	≤0.06–0.12	≤0.06	≤0.06	100.0 / –	100.0 / 0.0
Vancomycin	≤0.12–0.5	0.5	0.5	100.0 / –	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	– / –	100.0 / 0.0
Daptomycin	≤0.06–0.5	0.12	0.25	100.0 / –	100.0 / 0.0
Linezolid	0.5–1	1	1	100.0 / –	100.0 / 0.0
Levofloxacin	≤0.12–>4	0.5	1	99.3 / 0.7	94.7 / 0.7
Erythromycin	≤0.12–>16	≤0.12	>16	69.7 / 30.3	69.7 / 30.3
Clindamycin	≤0.25–>2	≤0.25	>2	80.9 / 19.1	80.9 / 19.1

CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.
[a] Criteria for susceptibility as published by the Clinical and Laboratory Standards Institute (M100-S23, 2013) and European Committee on Antimicrobial Susceptibility Testing (2013). For telavancin, the FDA-approved susceptible breakpoints for *S. aureus* (≤1 mg/L), vancomycin-susceptible *E. faecalis* (≤1 mg/L), viridans group streptococci (≤0.12 mg/L), and ß-hemolytic streptococci (≤0.12 mg/L) were applied. [b] – indicates no breakpoint available. [c] Includes 4 VanA-type strains. All vancomycin-susceptible isolates were inhibited by telavancin at ≤1 mg/L. [d] % susceptible / resistant based on the CLSI breakpoints for treating non-meningeal pneumococcal infections.

CONCLUSIONS

- All *S. aureus* and CoNS were inhibited by telavancin ($MIC_{50/90}$, 0.25/0.5 mg/L) at the FDA breakpoint for susceptibility (≤1 mg/L), as were all vancomycin-susceptible *E. faecalis*. VanA-type enterococci exhibited higher MIC values (≥2 mg/L), as previously documented.
- Telavancin demonstrated highly potent activity against *S. pneumoniae*, VGS (100% susceptible) and BHS (100% susceptible) with MIC_{90} results of 0.03, 0.06, and 0.12 mg/L, respectively.
- In summary, telavancin continues to exhibit overall in vitro potency similar to or greater than that of comparator agents against indicated staphylococci, streptococci, and vancomycin-susceptible *E. faecalis* pathogens. Further monitoring for emergence of resistance is warranted.

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