Antimicrobial Activity of Telavancin Tested Against Contemporary Gram-Positive Pathogens: Results From an International Surveillance Program (2007)

TR Fritsche, 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

AMENDED ABSTRACT*

Background. Telavancin (TLV), an investigational lipoglycopeptide, has been studied in Phase 3 clinical trials of skin and skin structure infections and hospital-acquired pneumonia against Gram-positive (GP) pathogens, and is under regulatory review in the US, EU, and Canada. We evaluated TLV potency against GP isolates including staphylococci, enterococci (ESP), and streptococci collected in 2007 as part of a global surveillance protocol.

Methods. Nonduplicate clinical GP isolates (10,700 total; see **Table**) were submitted from medical centers in North America (45.2%), Europe (25.0%), the Asia-Pacific region (22.4%), and Latin America (7.4%) participating in TLV surveillance. Identifications were confirmed by the central monitor and susceptibility (S) tested using Clinical and Laboratory Standards Institute (CLSI) methods.

Results. TLV was highly potent against year 2007 isolates originating from 4 continents, inhibiting all *Staphylococcus aureus* (SA; 45.1% oxacillin-resistant [OX-R]) and coagulase-negative staphylococci (CoNS; 78.0% OX-R) at ≤0.5 µg/mL; all vancomycin (VAN)-S ESP at ≤1 µg/mL; and all *Streptococcus pneumoniae* (SPN), viridans group streptococci (VGS), and β-hemolytic streptococci at ≤0.25 µg/mL. While TLV minimal inhibitory concentration (MIC) values were elevated among VAN-R ESP (16.7% overall), 26.8% and 76.6% of VAN-R strains had TLV MIC values of ≤1 µg/mL and ≤2 µg/mL, respectively. OX-R among SA and penicillin nonsusceptibility among SPN and VGS had no adverse effect on TLV activity.

Organism (no. tested)	MIC (µg/mL)		Cum. % inhibited at MIC (µg/mL)				
	MIC_{50}	MIC_{90}	≤0.12	0.25	0.5	1	2
Staphylococcus aureus (5895)	0.12	0.25	84	>99	100	–	–
CoNS (1030)	0.12	0.25	85	>99	100	–	–
Enterococcus faecalis (1229)	0.25	0.5	21	83	98	98	98
Enterococcus faecium (680)	0.12	2	58	59	61	69	92
Streptococcus pneumoniae (984)	0.03	0.03	100	–	–	–	–
β-hemolytic strep (579)	0.06	0.06	>99	100	–	–	–
Viridans group strep (197)	0.03	0.06	100	–	–	–	–
Corynebacterium spp. (21)	0.03	0.03	100	–	–	–	–

CoNS, coagulase-negative staphylococcus; MIC, minimal inhibitory concentration.

Conclusions. TLV was the most potent (MIC_{90}) agent tested against GP isolates originating from a 2007 TLV global surveillance study. Pending regulatory agency approval and clinical introduction, continued monitoring for potential resistance emergence to TLV and other Gram-positive–targeted agents will be necessary.

*Updated to include additional isolates.

INTRODUCTION

- Acquisition or emergence of bacterial resistance among Gram-positive and Gram-negative species is of great concern in most hospitals and especially in critical care units.
  - The widespread use of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) has contributed significantly to rising rates of vancomycin-resistance among staphylococci[1] and enterococci,[2] creating a public health emergency challenging traditional infection control practices.
  - Nonsusceptibility to penicillin among *Streptococcus pneumoniae*[3] and viridans group streptococci (VGS)[4] is driving the use of fluoroquinolones, with concomitant increases in resistance mutations.[5]
- These developments have created an urgent need for the development and introduction of new agents active against Gram-positive species expressing resistant phenotypes.
- Telavancin is an investigational, parenteral, semisynthetic lipoglycopeptide[6] that is active against both aerobic and anaerobic Gram-positive bacteria, including MRSA, vancomycin-intermediate (VISA), heterogeneous VISA (hVISA), vancomycin-resistant (VRSA) *S. aureus*, streptococci, and some vancomycin-resistant enterococci (VRE).[7-10]
  - The agent is bactericidal by means of interference with cell wall synthesis and disruption of the bacterial cell membrane function through depolarization and increased permeability.[11,12]
  - Positive results from Phase 2 and 3 trials for complicated skin and skin structure infections[13] and Phase 3 trials for hospital-acquired pneumonia[14] have been followed by registration applications in the United States, Canada, and the European Union.
  - This report summarizes results of an international resistance surveillance testing program for the year 2007 comparing the activity of telavancin and currently marketed glycopeptides with other antimicrobial agents against staphylococcal, enterococcal, and streptococcal clinical isolates.

MATERIALS AND METHODS

Bacterial strain collection

- As part of the international telavancin surveillance program for 2007, a total of 10,700 nonduplicate, consecutive, Gram-positive isolates were submitted for processing by a central laboratory monitor (JMI Laboratories, North Liberty, Iowa) from 105 medical centers located in North America (45.2%), Europe (25.0%), the Asia-Pacific region (22.4%), and Latin America (7.4%).
- Isolates originated from patients with documented bloodstream infections (35.8%), skin and soft tissue infections (30.0%), infections of the respiratory tract (21.4%), and other infections (12.7%).
- The most prevalent bacterial species in the collection were *S. aureus* (5895 isolates; 45.1% oxacillin-resistant), coagulase-negative staphylococci (CoNS; 1030 isolates; 78.0% oxacillin-resistant), enterococci (1949 isolates), *S. pneumoniae* (984 isolates), β-hemolytic streptococci (579 isolates), and VGS (197 isolates).
- Identifications were confirmed by the central laboratory monitor.

Antimicrobial susceptibility test methods

- In vitro antimicrobial susceptibility was assayed by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method[15,16] using commercially prepared and validated dry-form panels (TREK Diagnostics, Cleveland, Ohio) in cation-adjusted Mueller-Hinton broth (with the addition of 2–5% lysed horse blood for testing of fastidious streptococci).
- All strains were tested against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen.
- Interpretation of minimum inhibitory concentration (MIC) results was in accordance with CLSI criteria.[15,16]
- *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 were utilized as quality control strains.

RESULTS

- Telavancin was highly active against year 2007 isolates inhibiting all *S. aureus* strains (45.1% oxacillin-resistant) and CoNS strains (78.0% oxacillin-resistant) at MIC values ≤0.5 µg/mL (**Tables 1** and **2**). Telavancin potencies were not affected by the oxacillin-resistance status of these staphylococci.
- Telavancin inhibited 98% of the *E. faecalis* strains (2.4% vancomycin-resistant) and 61% of the *Enterococcus faecium* strains (43.4% vancomycin-resistant) at MIC values ≤0.5 µg/mL (**Tables 1** and **2**).
- Among VRE, 26.8% and 76.6% of the tested strains had telavancin MIC values at ≤1 µg/mL and ≤2 µg/mL, respectively (data not shown).
- All *S. pneumoniae*, VGS, and β-hemolytic streptococci were inhibited by ≤0.25 µg/mL of telavancin (**Tables 1** and **3**). Penicillin nonsusceptibility among *S. pneumoniae* and VGS strains had no adverse influence on telavancin activity.
- Telavancin was the most potent agent tested against *Corynebacterium* spp., inhibiting all strains at MIC values ≤0.06 µg/mL compared with ≤0.5 and ≤4 µg/mL for vancomycin and teicoplanin, respectively (**Table 1**; comparator data not shown).

CONCLUSIONS

- Against *S. aureus* and CoNS, telavancin displayed higher activity than the tested comparators (MIC_{50} and MIC_{90} values for both, 0.12 and 0.25 µg/mL) and inhibited all isolates at MIC values ≤0.5 µg/mL, regardless of oxacillin susceptibility.
- Against *S. pneumoniae*, VGS, and β-hemolytic streptococci, telavancin MIC values were ≤0.06, ≤0.12, and ≤0.25 µg/mL, respectively.
- Overall, 16.7% of tested enterococci were vancomycin-resistant (including 2.4% of *E. faecalis* and 43.4% of *E. faecium*). Telavancin remained ≥16-fold more active (MIC_{50} at 2 µg/mL vs >16 µg/mL) than either vancomycin or teicoplanin against these isolates.

Table 1. Antimicrobial activity of telavancin against 8 organism species/groups and resistant subsets submitted as part of the 2007 international surveillance program

Organism (no. tested)	MIC, µg/mL		Cumulative percentage inhibited at each telavancin MIC							
	MIC_{50}	MIC_{90}	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2
Staphylococcus aureus (5895)	0.12	0.25	0	<1	9	84	>99	100	–	–
Oxacillin-susceptible (3237)	0.12	0.25	0	<1	10	87	>99	100	–	–
Oxacillin-resistant (2658)	0.12	0.25	0	<1	7	80	>99	100	–	–
Coagulase-negative staphylococci (1030)	0.12	0.25	<1	1	16	85	>99	100	–	–
Oxacillin-susceptible (227)	0.12	0.25	<1	4	26	89	>99	100	–	–
Oxacillin-resistant (803)	0.12	0.25	<1	<1	13	84	>99	100	–	–
Enterococcus spp. (1949)	0.25	2	<1	4	17	35	74	85	88	96
Vancomycin-susceptible (1609)	0.25	0.5	<1	5	19	41	88	>99	100	–
Vancomycin-resistant (325)	2	>2	0	<1	4	6	7	10	27	77
Enterococcus faecalis (1229)	0.25	0.5	0	<1	<1	21	83	98	98	98
Enterococcus faecium (680)	0.12	2	<1	10	45	58	59	61	69	92
Streptococcus pneumoniae (984)	0.03	0.03	29	93	100	–	–	–	–	–
Penicillin-susceptible (616)	0.03	0.03	23	91	100	–	–	–	–	–
Penicillin-nonsusceptible (368)	0.03	0.03	39	95	100	–	–	–	–	–
Viridans group streptococci (197)	0.03	0.06	6	62	97	100	–	–	–	–
Penicillin-susceptible (141)	0.03	0.06	6	64	98	100	–	–	–	–
Penicillin-nonsusceptible (56)	0.03	0.06	4	57	96	100	–	–	–	–
β-hemolytic streptococci (579)	0.06	0.06	4	48	92	>99	100	–	–	–
Corynebacterium spp. (21)	0.03	0.03	43	90	100	–	–	–	–	–

MIC, minimum inhibitory concentration.

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *S. aureus*, coagulase-negative staphylococci, *E. faecalis*, and *E. faecium*

Organism (no. tested)/ Antimicrobial agent	MIC, µg/mL		Percent susceptible/resistant[a]
	MIC_{50}	MIC_{90}	
Staphylococcus aureus (5895)			
Oxacillin-susceptible (3237)			
Telavancin	0.12	0.25	– / –
Vancomycin	1	1	100.0 / 0
Teicoplanin	≤2	≤2	100.0 / 0
Daptomycin	0.25	0.5	100.0 / –
Linezolid	1	2	100.0 / –
Quinupristin/dalfopristin	≤0.25	0.5	>99.9 / 0
Levofloxacin	≤0.5	≤0.5	92.6 / 7.3
Erythromycin	≤0.25	>2	76.2 / 23.5
Clindamycin	≤0.25	≤0.25	95.1 / 4.8
Tetracycline	≤2	≤2	94.5 / 5.2
Oxacillin-resistant (2658)			
Telavancin	0.12	0.25	– / –
Vancomycin	1	1	>99.9 / 0
Teicoplanin	≤2	≤2	100.0 / 0
Daptomycin	0.25	0.5	>99.9 / –
Linezolid	1	2	99.9 / –
Quinupristin/dalfopristin	0.5	0.5	99.7 / 0.2
Levofloxacin	>4	>4	21.7 / 77.8
Erythromycin	>2	>2	11.4 / 88.3
Clindamycin	≤0.25	>2	56.4 / 43.4
Tetracycline	≤2	>8	81.7 / 18.1
Coagulase-negative staphylococci (1030)			
Oxacillin-susceptible (227)			
Telavancin	0.12	0.25	– / –
Vancomycin	1	2	100.0 / 0
Teicoplanin	≤2	4	100.0 / 0
Daptomycin	0.25	0.5	100.0 / –
Linezolid	1	1	99.6 / –
Quinupristin/dalfopristin	≤0.25	≤0.25	100.0 / 0
Levofloxacin	≤0.5	4	87.7 / 12.3
Erythromycin	≤0.25	>2	60.4 / 39.6
Clindamycin	≤0.25	≤0.25	93.0 / 5.3
Tetracycline	≤2	>8	87.2 / 11.5
Oxacillin-resistant (803)			
Telavancin	0.12	0.25	– / –
Vancomycin	2	2	99.9 / 0
Teicoplanin	≤2	4	98.9 / 0.2
Daptomycin	0.25	0.5	99.8 / –
Linezolid	0.5	1	99.1 / –
Quinupristin/dalfopristin	≤0.25	0.5	99.3 / 0.4
Levofloxacin	4	>4	29.8 / 65.8
Erythromycin	>2	>2	25.2 / 74.5
Clindamycin	≤0.25	>2	59.0 / 39.5
Tetracycline	≤2	>8	82.9 / 16.2

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *S. aureus*, coagulase-negative staphylococci, *E. faecalis*, and *E. faecium* *(continued)*

Organism (no. tested)/ Antimicrobial agent	MIC, µg/mL		Percent susceptible/resistant[a]
	MIC_{50}	MIC_{90}	
Enterococcus faecalis (1229)			
Vancomycin-susceptible (1197)			
Telavancin	0.25	0.5	– / –
Teicoplanin	≤2	≤2	100.0 / 0
Daptomycin	1	2	99.9 / –
Linezolid	1	2	99.7 / 0.1
Quinupristin/dalfopristin	>2	>2	0.3 / 96.7
Levofloxacin	1	>4	66.8 / 32.7
Gentamicin (HL)	≤500	>1000	65.7 / 34.3
Streptomycin (HL)	≤1000	>2000	69.4 / 30.6
Tetracycline	>8	>8	26.0 / 73.9
Ampicillin	≤1	2	99.9 / 0.1
Vancomycin-resistant (30)			
Telavancin	>2	>2	– / –
Teicoplanin	>16	>16	16.7 / 83.3
Daptomycin	0.5	1	100.0 / –
Linezolid	1	2	100.0 / 0
Quinupristin/dalfopristin	>2	>2	0 / 96.7
Levofloxacin	>4	>4	0 / 100.0
Gentamicin (HL)	>1000	>1000	20.0 / 80.0
Streptomycin (HL)	≤1000	>2000	66.7 / 33.3
Tetracycline	>8	>8	26.7 / 73.3
Ampicillin	≤1	2	100.0 / 0
Enterococcus faecium (680)			
Vancomycin-susceptible (377)			
Telavancin	0.06	0.12	– / –
Teicoplanin	≤2	≤2	99.7 / 0.3
Daptomycin	2	4	100.0 / –
Linezolid	2	2	99.5 / 0.3
Quinupristin/dalfopristin	1	>2	63.1 / 17.2
Levofloxacin	>4	>4	13.0 / 83.0
Gentamicin (HL)	1000	>1000	47.5 / 52.5
Streptomycin (HL)	≤1000	>2000	53.6 / 46.4
Tetracycline	≤2	>8	69.0 / 30.2
Ampicillin	>16	>16	11.7 / 88.3
Vancomycin-resistant (295)			
Telavancin	2	>2	– / –
Teicoplanin	>16	>16	8.5 / 80.0
Daptomycin	2	2	100.0 / –
Linezolid	1	2	98.0 / 2.0
Quinupristin/dalfopristin	0.5	1	92.2 / 2.7
Levofloxacin	>4	>4	0.3 / 99.7
Gentamicin (HL)	≤500	>1000	65.1 / 34.9
Streptomycin (HL)	≤1000	>2000	64.4 / 35.6
Tetracycline	≤2	>8	69.8 / 30.2
Ampicillin	>16	>16	0 / 100.0

MIC, minimum inhibitory concentration; HL, high-level resistance.
[a] Criteria as published by the CLSI.[16] When testing staphylococci, β-lactam susceptibility should be directed by the oxacillin test results.

Table 3. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *S. pneumoniae*, β-hemolytic streptococci, and viridans group streptococci

Organism (no. tested)/ Antimicrobial agent	MIC, µg/mL		Percent susceptible/resistant[a]
	MIC_{50}	MIC_{90}	
Streptococcus pneumoniae (984)			
Penicillin-susceptible (616)			
Telavancin	0.03	0.03	– / –
Vancomycin	≤1	≤1	100.0 / –
Teicoplanin	≤2	≤2	– / –
Daptomycin	0.12	0.25	– / –
Linezolid	1	1	100.0 / –
Quinupristin/dalfopristin	0.5	0.5	100.0 / 0
Levofloxacin	1	1	99.2 / 0.8
Erythromycin	≤0.25	>2	82.0 / 17.5
Clindamycin	≤0.25	≤0.25	93.8 / 6.2
Tetracycline	≤2	>8	88.8 / 10.7
Penicillin-nonsusceptible (368)			
Telavancin	0.03	0.03	– / –
Vancomycin	≤1	≤1	100.0 / –
Teicoplanin	≤2	≤2	– / –
Daptomycin	0.12	0.25	– / –
Linezolid	1	1	100.0 / –
Quinupristin/dalfopristin	0.5	1	98.6 / 0
Levofloxacin	1	1	99.5 / 0.3
Erythromycin	>2	>2	24.7 / 75.0
Clindamycin	≤0.25	>2	53.3 / 46.2
Tetracycline	>8	>8	41.8 / 57.9
β-hemolytic streptococci (579)			
Telavancin	0.06	0.06	– / –
Vancomycin	0.5	0.5	100.0 / –
Teicoplanin	≤2	≤2	– / –
Daptomycin	≤0.06	0.25	100.0 / –
Linezolid	1	1	100.0 / –
Quinupristin/dalfopristin	≤0.25	0.5	100.0 / 0
Levofloxacin	≤0.5	1	98.1 / 1.7
Erythromycin	≤0.25	>2	81.2 / 18.3
Clindamycin	≤0.25	>2	89.8 / 10.0
Tetracycline	≤2	>8	50.9 / 47.7
Penicillin	≤0.015	0.06	100.0 / –
Viridans group streptococci (197)			
Telavancin	0.03	0.06	– / –
Vancomycin	0.5	1	100.0 / –
Teicoplanin	≤2	≤2	– / –
Daptomycin	0.25	0.5	99.5 / –
Linezolid	1	1	100.0 / –
Quinupristin/dalfopristin	0.5	1	97.5 / 0.5
Levofloxacin	1	2	95.4 / 3.0
Erythromycin	≤0.25	>2	52.8 / 44.7
Clindamycin	≤0.25	>2	87.3 / 11.2
Tetracycline	≤2	>8	62.9 / 34.0
Penicillin	0.06	1	71.6 / 6.1

MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI.[16]

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