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Antimicrobial Activity of Telavancin Against Contemporary Enterococci and Streptococci: Initial Results From a Global Surveillance Program (2007)

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ABSTRACT (Revised[a])

Background. Telavancin (TLV) is a novel lipoglycopeptide with multiple mechanisms of action against Gram-positive (GP) pathogens and has demonstrated efficacy in skin and skin structure infections. We tested potency of TLV against recent enterococci (ESP) and streptococci collected as part of a global surveillance protocol.
Methods. Non-duplicate clinical isolates (n = 2751; *E. faecalis* [EF], *E. faecium* [EFM], other ESP, *S. pneumoniae* [SPN], β-hemolytic [BHS], and viridans group *streptococci* [VGS]) were submitted from participating medical centers in North America, Europe, and Latin America. Identifications were confirmed by the central monitor and all isolates susceptibility (S) tested using CLSI methods.
Results. TLV was the most potent agent tested (Table) against ESP (EF, EFM; MIC_{50}, 0.25 µg/mL versus 1->4 µg/mL for vancomycin (VAN), daptomycin, levofloxacin, linezolid, and quinupristin/dalfopristin). Against SPN, BHS, and VGS, TLV potency was most similar to penicillin (0.03 vs. ≤0.015–0.06 µg/mL, respectively) and superior to other comparators. While 27.7% of ESP were VAN-R, only 4.4% had TLV MICs >2 µg/mL. TLV inhibited all SPN and VGS at ≤0.12 µg/mL, including penicillin non-susceptible strains and all BHS at ≤0.25 µg/mL.

	MIC (µg/mL)		Cum. % inhibited at MIC (µg/mL)				
Organism (N)	**50%**	**90%**	**≤0.12**	**0.25**	**0.5**	**1**	**2**
ESP (1314)	0.25	2	32	70	80	84	95
EF (825)	0.25	0.5	23	83	97	97	98
EFM (455)	1	>2	47	48	49	59	90
SPN (843)	0.03	0.03	100	–	–	–	–
BHS (464)	0.03	0.06	99	100	–	–	–
VGS (130)	0.03	0.06	100	–	–	–	–

Conclusions. TLV was the most potent agent tested against GP isolates originating from a 2007 global surveillance study. As clinical use of this agent grows, continued monitoring for R emergence to TLV and currently marketed agents will be necessary.

[a] Updated to include additional isolates.

INTRODUCTION

- Telavancin is an investigational, intravenous, semisynthetic lipoglycopeptide that is broadly active against both aerobic and anaerobic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and some vancomycin-resistant enterococci (VRE).[1-6]
  - Bactericidal activity of telavancin is mediated both by interference with cell wall synthesis (similar to the glycopeptides) and by disruption of cell membrane function.[3]
  - Recent success in Phase 2 and 3 complicated skin and skin structure clinical trials[7-9] have been followed by registration applications both in the European Union and in the United States.
- Emergence of bacterial resistance is especially significant in intensive care units, with MRSA rates being especially problematic in some locales.
- Furthermore, the dramatic spread of community-associated MRSA infections, including into the hospital environment, has created a public health emergency challenging the existing therapeutic armamentarium.[10]
- Increased usage of vancomycin in treating staphylococcal infections has further driven an increase in rates of VRE but also an increase in nonsusceptibility of *S. aureus* to vancomycin (vancomycin-intermediate *S. aureus* [VISA], but more commonly heterogeneous VISA).[11]
- The timely development and introduction of new effective agents are sorely needed.
- In this poster, we summarize the early 2007 results of an international surveillance testing program comparing the activity of telavancin and currently marketed glycopeptides with other antimicrobial agents against enterococcal and streptococcal clinical isolates submitted from medical centers located in the United States, Latin America, and Europe.
- In total, 2751 bacterial strains were tested by reference Clinical and Laboratory Standards Institute (CLSI) methods with susceptibilities to comparator agents interpreted by CLSI breakpoint criteria (M100-S17, 2007).

MATERIALS AND METHODS

Bacterial strain collection

- In total, 2751 nonduplicate consecutive Gram-positive clinical isolates were submitted from >60 medical centers located in North America, Latin America, and Europe as part of the international telavancin surveillance program for the first half of 2007.
- Isolates originated from patients with documented bloodstream, respiratory tract, or skin and soft tissue infections.
- The distribution of leading species includes *Enterococcus faecalis* (825 isolates), *Enterococcus faecium* (455), other *Enterococcus* spp. (34), *Streptococcus pneumoniae* (843), β-hemolytic streptococci (464), and viridans group streptococci (130).
- Identifications were confirmed by the central monitor (JMI Laboratories, North Liberty, Iowa).

Susceptibility test methods

- All strains were tested by the broth microdilution method using commercially validated and prepared panels (TREK Diagnostics, Cleveland, Ohio) in cation-adjusted Mueller-Hinton broth (with 2%–5% lysed horse blood added for testing of streptococci) 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 published CLSI criteria.[12,13]
- Quality control strains utilized included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619.

RESULTS

- Among comparators, telavancin was the most potent agent tested (**Tables 1–6**) against *Enterococcus* spp. (*E. faecalis* and *E. faecium*; MIC_{50}, 0.25 µg/mL vs 1–>4 µg/mL for vancomycin, daptomycin, levofloxacin, linezolid, and quinupristin/dalfopristin).
- Compared with vancomycin, telavancin was 4-fold more active (MIC_{50}) against *E. faecalis* and >16-fold more active against *E. faecium*; only 10% had telavancin MIC values of >2 µg/mL.
- Overall, 21.6% of tested enterococci were vancomycin-resistant, including 3.0% of *E. faecalis* and 56.3% of *E. faecium*; telavancin remained ≥8-fold more potent (MIC_{50}) than vancomycin against these resistant strains. Only daptomycin and linezolid were uniformly active against enterococci (>99% susceptible), followed by teicoplanin (80.2%) and vancomycin (77.6%).
- Against *S. pneumoniae*, β-hemolytic streptococci, and viridans group streptococci, telavancin activity was most similar to that demonstrated by penicillin (MIC_{50}, 0.03 µg/mL vs ≤0.015–0.06 µg/mL, respectively) and superior to that of other comparators (**Tables 7–9**).
- Telavancin inhibited all *S. pneumoniae* and viridans group streptococci at ≤0.12 µg/mL, including penicillin nonsusceptible strains (33.0% and 27.7%, respectively), and all β-hemolytic streptococci at ≤0.25 µg/mL. At current CLSI breakpoints, β-hemolytic and viridans group streptococci were all susceptible to vancomycin, linezolid, and daptomycin, and *S. pneumoniae* to vancomycin and linezolid.

Table 1. Antimicrobial activity of telavancin against 5 organism species/groups submitted as part of the 2007 international surveillance program

	MIC, µg/mL		Number (cumulative percentage) inhibited at each telavancin MIC, µg/mL							
Organism (no. tested)	**50%**	**90%**	**≤0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1.0**	**2.0**
Enterococcus spp. (1314)	0.25	2	3 (<1)	54 (4)	129 (14)	232 (32)	500 (70)	138 (80)	47 (84)	144 (95)
E. faecalis (825)	0.25	0.5	0	3 (<1)	6 (1)	182 (23)	490 (83)	120 (97)	0 (97)	3 (98)
E. faecium (455)	1	2	3 (<1)	47 (11)	115 (36)	47 (47)	4 (48)	7 (49)	46 (59)	140 (90)
S. pneumoniae (843)	0.03	0.03	207 (25)	567 (92)	69 (100)	–	–	–	–	–
β-hemolytic streptococci (125)	0.03	0.06	19 (4)	228 (53)	208 (98)	8 (>99)	1 (100)	–	–	–
Viridans group streptococci (130)	0.03	0.06	8 (6)	83 (70)	38 (>99)	1 (100)	–	–	–	–

MIC, minimum inhibitory concentration.

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *Enterococcus* spp. (n=1314)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.25	2	≤0.015 – >2	– / –
Vancomycin	1	>16	0.12 – >16	77.6 / 21.6
Teicoplanin	≤2	>16	≤2 – >16	80.2 / 17.7
Daptomycin	1	2	≤0.06 – 4	100.0 / –
Linezolid	1	2	0.25 – >8	99.5 / 0.5
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	28.7 / 65.5
Levofloxacin	>4	>4	≤0.5 – >4	44.4 / 54.9
Gentamicin (HL)	>1000	>1000	1000 – >1000	0 / 30.7
Streptomycin (HL)	>2000	>2000	2000 – >2000	0 / 32.3
Tetracycline	>8	>8	≤2 – >8	43.5 / 56.5
Ampicillin	≤1	>16	≤1 – >16	67.8 / 32.2

HL, high-level resistance; MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 3. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 vancomycin-susceptible *Enterococcus* spp. (n=1020)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.25	0.5	≤0.015 – 0.5	– / –
Vancomycin	1	2	≤0.12 – 4	100.0 / 0
Teicoplanin	≤2	≤2	≤2 – >16	99.8 / 0.2
Daptomycin	1	2	≤0.06 – 4	100.0 / –
Linezolid	1	2	0.25 – >8	99.9 / 0.1
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	13.2 / 80.9
Levofloxacin	2	>4	≤0.5 – >4	56.8 / 42.3
Gentamicin (HL)	>1000	>1000	1000 – >1000	0 / 29.7
Streptomycin (HL)	>2000	>2000	2000 – >2000	0 / 31.4
Tetracycline	>8	>8	≤2 – >8	37.5 / 62.5
Ampicillin	≤1	>16	≤1 – >16	84.6 / 15.4

HL, high-level resistance; MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 4. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 vancomycin-resistant *Enterococcus* spp. (n=284)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	2	>2	0.03 – >2	– / –
Vancomycin	>16	>16	>16	0 / 100.0
Teicoplanin	>16	>16	≤2 – >16	9.2 / 81.0
Daptomycin	1	2	0.25 – 4	100.0 / –
Linezolid	1	2	0.5 – >8	98.2 / 1.8
Quinupristin/dalfopristin	0.5	>2	≤0.25 – >2	83.1 / 11.6
Levofloxacin	>4	>4	2 – >4	0.4 / 99.6
Gentamicin (HL)	>1000	>1000	1000 – >1000	0 / 34.5
Streptomycin (HL)	>2000	>2000	2000 – >2000	0 / 36.3
Tetracycline	≤2	>8	≤2 – >8	63.7 / 36.3
Ampicillin	>16	>16	≤1 – >16	8.8 / 91.2

HL, high-level resistance; MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 5. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *E. faecalis* (n=825)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.25	0.5	0.03 – >2	– / –
Vancomycin	1	2	≤0.12 – >16	96.8 / 3.0
Teicoplanin	≤2	≤2	≤2 – >16	97.1 / 2.9
Daptomycin	1	1	≤0.06 – 2	100.0 / –
Linezolid	1	2	0.5 – 2	100.0 / 0
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	0.8 / 96.0
Levofloxacin	1	>4	≤0.5 – >4	62.9 / 36.8
Gentamicin (HL)	>1000	>1000	1000 – >1000	0 / 30.9
Streptomycin (HL)	>2000	>2000	2000 – >2000	0 / 29.3
Tetracycline	>8	>8	≤2 – >8	29.0 / 71.0
Ampicillin	≤1	2	≤1 – 8	99.8 / 0.2

HL, high-level resistance; MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 6. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *E. faecium* (n=455)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	1	>2	≤0.015 – >2	– / –
Vancomycin	>16	>16	0.5 – >16	42.2 / 56.3
Teicoplanin	16	>16	≤2 – >16	48.6 / 45.3
Daptomycin	2	2	0.12 – 4	100.0 / –
Linezolid	1	2	0.5 – >8	98.5 / 1.3
Quinupristin/dalfopristin	0.5	>2	≤0.25 – >2	80.2 / 11.6
Levofloxacin	>4	>4	≤0.5 – >4	9.0 / 89.5
Gentamicin (HL)	1000	>1000	1000 – >1000	0 / 30.8
Streptomycin (HL)	>2000	>2000	2000 – >2000	0 / 38.9
Tetracycline	≤2	>8	≤2 – >8	70.3 / 29.7
Ampicillin	>16	>16	≤1 – >16	8.1 / 91.9

HL, high-level resistance; MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 7. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 *S. pneumoniae* (n=843)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.03	0.03	≤0.015 – 0.06	– / –
Vancomycin	≤1	≤1	≤1	100.0 / –
Teicoplanin	≤2	≤2	≤2	– / –
Daptomycin	0.12	0.12	≤0.06 – 0.25	– / –
Linezolid	1	1	≤0.12 – 2	100.0 / –
Quinupristin/dalfopristin	0.5	0.5	≤0.25 – 1	100.0 / 0
Levofloxacin	1	1	≤0.5 – >4	99.3 / 0.6
Erythromycin	≤0.25	>2	≤0.25 – >2	66.3 / 33.3
Clindamycin	≤0.25	>2	≤0.25 – >2	83.3 / 16.5
Tetracycline	≤2	>8	≤2 – >8	78.2 / 21.4
Penicillin	≤0.03	2	≤0.03 – 8	67.0 / 17.7

MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 8. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 β-hemolytic streptococci (n=464)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.03	0.06	≤0.015 – 0.25	– / –
Vancomycin	0.5	0.5	0.25 – 1	100.0 / –
Teicoplanin	≤2	≤2	≤2 – 4	– / –
Daptomycin	≤0.06	0.25	≤0.06 – 0.25	100.0 / –
Linezolid	1	1	0.25 – 2	100.0 / –
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25 – 1	100.0 / 0
Levofloxacin	≤0.5	1	≤0.5 – >4	100.0 / 0
Erythromycin	≤0.25	>2	≤0.25 – >2	81.6 / 17.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.0 / 8.0
Tetracycline	≤2	>8	≤2 – >8	57.6 / 39.2
Penicillin	≤0.015	0.06	≤0.015 – 0.12	100.0 / –

MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

Table 9. Antimicrobial activity of telavancin and comparator antimicrobial agents when tested against year 2007 viridans group streptococci (n=130)

Antimicrobial agent	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Range	Percent susceptible / resistant[a]
Telavancin	0.03	0.06	≤0.015 – 0.12	– / –
Vancomycin	0.5	1	≤0.12 – 1	100.0 / –
Teicoplanin	≤2	≤2	≤2	– / –
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / –
Linezolid	0.5	1	0.12 – 2	100.0 / –
Quinupristin/dalfopristin	0.5	1	≤0.25 – 2	99.2 / 0
Levofloxacin	1	2	≤0.5 – >4	96.9 / 2.3
Erythromycin	0.55	>2	≤0.25 – >2	47.7 / 50.0
Clindamycin	≤0.25	0.5	≤0.25 – >2	89.2 / 9.2
Tetracycline	≤2	>8	≤2 – >8	68.5 / 28.5
Penicillin	0.06	2	≤0.015 – 32	72.3 / 6.9

MIC, minimum inhibitory concentration.
[a] Criteria as published by the CLSI (2007).[13]

CONCLUSIONS

- Based on MIC_{50} values, telavancin was the most potent agent tested against contemporary (2007) *Enterococcus* spp. isolates, and telavancin was most similar to that of penicillin in "by weight" activity against *S. pneumoniae*, β-hemolytic streptococci, and viridans group streptococci (all MICs, ≤0.25 µg/mL).
- Almost 95% of enterococci were inhibited by ≤2 µg/mL of telavancin, whereas only 77.6% were inhibited by ≤4 µg/mL of vancomycin (current breakpoint).
- Following the recent completion of Phase 3 clinical trials, continued monitoring for resistance emergence to telavancin, especially in enterococci and staphylococci, will be critical in assessing long-term efficacy of this promising agent.

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