Antimicrobial Activity of Telavancin Against *Enterococcus faecalis, E. faecium* and *E. avium*: Results From a European Surveillance Program (2007)

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ABSTRACT

Objectives. To evaluate the potency of telavancin against enterococcal isolates (*Enterococcus faecalis* [EF], *E. faecium* [EFM] and *E. avium* [EAV]) collected as part of a European surveillance protocol for 2007. Telavancin is an investigational, intravenous, semi-synthetic, bactericidal lipoglycopeptide that is broadly active against both aerobic and anaerobic Gram-positive bacteria. The agent has been evaluated in two Phase 3 complicated skin and skin structure infection clinical trials.

Methods. Non-duplicate clinical isolates (919 total; see **Table**) of EF (579), EFM (318) and EAV (12) were submitted from 26 medical centres in Europe participating in telavancin surveillance. Identifications were confirmed by the central monitor and all isolates were susceptibility tested using Clinical and Laboratory Standards Institute broth microdilution methods.

Results. The antimicrobial activity of telavancin against Year 2007 enterococcal isolates is shown in the **Table**. Among the comparators, telavancin was the most potent agent tested against *Enterococcus* spp. (EF and EFM; MIC_{50} values, 0.25 and 0.06 mg/L, respectively) compared with vancomycin (1 and 1 mg/L), daptomycin (1 and 2 mg/L), levofloxacin (1 and >4 mg/L) and linezolid (1 and 1 mg/L). Telavancin was 4-fold more active (MIC_{50}) than vancomycin against EF and 16-fold more active against EFM (only 15.4% of EFM had telavancin MIC values >1 mg/L compared with 29.6% having vancomycin MIC values >4 mg/L). Overall, 9.7% of tested enterococci were vancomycin-resistant, including 1.0% of EF and 25.8% of EFM; telavancin remained ≥16-fold more potent (MIC_{50}) than vancomycin against these resistant EFM strains. Among the comparators, only daptomycin and linezolid were uniformly active against all enterococci (>99% susceptible), followed by teicoplanin (92.4%) and vancomycin (88.9%). All but one strain of EAV were inhibited by ≤0.06 mg/L of telavancin.

Conclusions. Based on MIC_{50} potencies, telavancin was the most active agent tested against European (2007) *Enterococcus* spp. isolates. Telavancin inhibited 94.0% of strains at ≤1 mg/L, whereas only 88.9% were inhibited by ≤4 mg/L of vancomycin (current breakpoint). Continued monitoring for resistance emergence in enterococci and other Gram-positive pathogens will be critical in assessing the long-term efficacy of this promising agent.

Table. Antimicrobial activity of telavancin against Year 2007 enterococcal isolates

Organism (n tested)	MIC (mg/L)		Cumulative % inhibited at MIC (mg/L)					
	50%	90%	≤0.06	0.12	0.25	0.5	1	2
E. faecalis (579)	0.25	0.5	1	22	84	99	99	99
VAN-susceptible (573)	0.25	0.5	1	23	84	100	—	—
VAN-resistant (6)	>2	>2	0	0	0	0	0	0
E. faecium (318)	0.06	2	66	79	80	80	85	97
VAN-susceptible (224)	0.06	0.12	82	>99	100	—	—	—
VAN-resistant (82)	2	>2	18	21	21	22	40	88
E. avium (12)	0.06	0.06	92	92	92	92	100	—

VAN, vancomycin

INTRODUCTION

- The dramatic spread of methicillin-resistant *Staphylococcus aureus* (MRSA) infections into the hospital environment, including strains characteristically found in the community (community-acquired), has significantly changed antimicrobial prescribing practices in recent years.
- Increased use of vancomycin for treating staphylococcal infections has driven rates of vancomycin-resistant enterococci (VRE) to high levels in some regions, and has produced an increase in *S. aureus* that are nonsusceptible to vancomycin (most commonly heterogeneous vancomycin-intermediate *S. aureus* [hVISA], but also VISA and rare vancomycin-resistant [VRSA] strains).
- The timely development and introduction of new agents with potency and pharmacokinetic/pharmacodynamic properties that can prevent further resistance emergence among enterococci and staphylococci are sorely needed.
- Telavancin is an investigational, parenteral, semi-synthetic lipoglycopeptide that is broadly active against aerobic and anaerobic Gram-positive bacteria, including *S. aureus* and coagulase-negative staphylococci (methicillin-susceptible and -resistant strains), streptococci and enterococci (including some VRE strains).[1–5]
- Telavancin is bactericidal by means of inhibition of bacterial cell wall synthesis and disruption of bacterial membrane function.
- Efficacy and safety of telavancin have been demonstrated in Phase 2 and 3 complicated skin and skin structure clinical trials.[6–8] Phase 3 trials for nosocomial pneumonia have been completed.
- This poster summarises the 2007 results of an international surveillance testing programme comparing the activity of telavancin and currently marketed glycopeptides with other antimicrobial agents against enterococcal clinical isolates submitted from medical centres located in Europe.
- Submitted strains were tested by reference broth microdilution methodology of the Clinical and Laboratory Standards Institute (CLSI) with susceptibilities to comparator agents interpreted by CLSI breakpoint criteria (M100-S18 [2008][9]).

MATERIALS AND METHODS

Bacterial strain collection

- 919 non-duplicate, consecutive enterococcal clinical isolates were submitted from 26 medical centres located in Europe as part of an international resistance surveillance programme for 2007.
- Isolates originated predominantly from patients with documented bloodstream, respiratory tract or skin and soft tissue infections.
- The distribution of leading species included *E. faecalis* (579 isolates), *E. faecium* (318) and *E. avium* (12).
- Identifications were confirmed by the central monitor (JMI Laboratories, Iowa, USA).

Table 1. Antimicrobial activity of telavancin against European *Enterococcus* spp. submitted as part of the 2007 international surveillance programme

Organism (n tested)	MIC (mg/L)		Number (cumulative %) inhibited at each telavancin MIC (mg/L)							
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2
Enterococcus spp. (919)	0.25	0.5	3 (<1)	76 (9)	152 (25)	163 (43)	358 (82)	95 (92)	17 (94)	39 (98)
E. faecalis (579)	0.25	0.5	0 (0)	1 (<1)	6 (1)	122 (22)	355 (84)	89 (99)	0 (99)	0 (99)
Vancomycin-susceptible (573)	0.25	0.5	0 (0)	1 (<1)	6 (1)	122 (23)	355 (84)	89 (100)	–	–
Vancomycin-resistant (6)	>2	–	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E. faecium (318)	0.06	2	3 (<1)	70 (23)	138 (66)	40 (79)	2 (80)	1 (80)	15 (85)	39 (97)
Vancomycin-susceptible (224)	0.06	0.12	3 (<1)	64 (30)	117 (82)	38 (>99)	2 (100)	–	–	–
Vancomycin-resistant (82)	2	>2	0 (0)	3 (4)	12 (18)	2 (21)	0 (21)	1 (22)	15 (40)	39 (88)
E. avium (12)	0.06	0.06	0 (0)	3 (25)	8 (92)	0 (92)	0 (92)	0 (92)	1 (100)	–

Susceptibility test methods

- 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 enterococcal pathogens. Testing was by the broth microdilution method (M7-A7 [2006][10]) using commercially prepared and validated panels (TREK Diagnostics, Ohio, USA) in cation-adjusted Mueller-Hinton broth.
- Interpretation of MIC results was in accordance with published CLSI criteria.
- Quality control strains utilised included *E. faecalis* ATCC 29212.

RESULTS

- Among tested agents, telavancin was one of the most active against *E. faecalis*, *E. faecium* and *E. avium* (MIC_{50} values, 0.25, 0.06 and 0.06 mg/L, respectively; **Tables 1** and **2**) compared with vancomycin (1, 1 and 0.5 mg/L), daptomycin (1, 2 and 0.5 mg/L), levofloxacin (1, >4 and 2 mg/L) and linezolid (1, 1 and 1 mg/L; **Table 2**).
- Telavancin was 4-fold more active (MIC_{50}) than vancomycin against *E. faecalis* and 16-fold more active against *E. faecium* (only 15.4% of *E. faecium* had telavancin MIC values >1 mg/L compared with 29.6% having vancomycin MIC values >4 mg/L [nonsusceptible]).
- Overall, 9.7% of tested enterococci were vancomycin-resistant (3.5% VanB phenotype), including 1.0% of *E. faecalis* and 25.8% of *E. faecium*; telavancin remained ≥16-fold more potent (MIC_{50} results) than vancomycin against these VanB *E. faecium* strains. Telavancin exhibited limited activity (MIC_{50}, >2 mg/L) against the six vancomycin-resistant *E. faecalis* isolates.
- Among comparators, only daptomycin and linezolid were uniformly active against all enterococci (>99% susceptible), followed by teicoplanin (92.4%) and vancomycin (88.9%).
- While vancomycin resistance (8.3%) was present among tested *E. avium* isolates, all strains were susceptible to linezolid and daptomycin and were inhibited by ≤1 mg/L of telavancin.

CONCLUSIONS

- Based on MIC_{50} values, telavancin was the most active agent tested against contemporary (2007) European *Enterococcus* spp. isolates. Telavancin inhibited 94.0% of strains at ≤1 mg/L, whereas only 88.9% were inhibited by ≤4 mg/L of vancomycin (current CLSI breakpoint).
- Overall, 9.7% of tested enterococci were vancomycin-resistant, including 1.0% of *E. faecalis*, 25.8% of *E. faecium* and 8.3% of *E. avium*; telavancin remained ≥16-fold more active (MIC_{50}) than vancomycin against the commonly occurring resistant *E. faecium* strains in Europe.
- Continued monitoring for resistance emergence in problematic pathogens, especially enterococci and staphylococci, will be critical in assessing the long-term efficacy of this promising agent.

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Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against European *Enterococcus* spp. (919 isolates)

Organism (n tested)/ antimicrobial agent	MIC (mg/L)			% Susceptible/ resistant, by category*
	50%	90%	Range	
Enterococcus spp. (919)				
Telavancin	0.25	0.5	≤0.015–>2	– / –
Vancomycin	1	16	0.25–>16	88.9 / 9.7
Teicoplanin	≤2	≤2	≤2–>16	92.4 / 7.3
Daptomycin	1	2	≤0.06–4	100.0 / –
Linezolid	1	2	0.5–4	99.7 / 0.0
Quinupristin-dalfopristin	>2	>2	≤0.25–>2	24.5 / 68.0
Levofloxacin	>4	>4	≤0.5–>4	45.2 / 53.9
Tetracycline	>8	>8	≤2–>8	44.6 / 55.1
Ampicillin	2	>16	≤1–>16	67.6 / 32.4
Gentamicin (HL)	≤500	>1000	≤500–>1000	60.6 / 39.4
Streptomycin (HL)	≤1000	>2000	≤1000–>2000	60.0 / 40.0
E. faecalis (579)				
Telavancin	0.25	0.5	0.03–>2	– / –
Vancomycin	1	2	0.25–>16	99.0 / 1.0
Teicoplanin	≤2	≤2	≤2–>16	99.0 / 1.0
Daptomycin	1	1	≤0.06–2	100.0 / –
Linezolid	1	2	0.5–2	100.0 / 0.0
Quinupristin-dalfopristin	>2	>2	≤0.25–>2	0.5 / 95.5
Levofloxacin	1	>4	≤0.5–>4	61.1 / 38.9
Tetracycline	>8	>8	≤2–>8	25.6 / 73.9
Ampicillin	≤1	2	≤1–16	99.7 / 0.3
Gentamicin (HL)	≤500	>1000	≤500–>1000	62.9 / 37.1
Streptomycin (HL)	≤1000	>2000	≤1000–>2000	63.6 / 36.4
E. faecalis vancomycin-susceptible (573)				
Telavancin	0.25	0.5	0.03–0.5	– / –
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Daptomycin	1	1	≤0.06–2	100.0 / –
Linezolid	1	2	0.5–2	100.0 / 0.0
Quinupristin-dalfopristin	>2	>2	≤0.25–>2	0.5 / 95.6
Levofloxacin	1	>4	≤0.5–>4	61.8 / 38.2
Tetracycline	>8	>8	≤2–>8	25.3 / 74.2
Ampicillin	≤1	2	≤1–16	99.7 / 0.3
Gentamicin (HL)	≤500	>1000	≤500–>1000	63.2 / 36.8
Streptomycin (HL)	≤1000	>2000	≤1000–>2000	63.3 / 36.7
E. faecalis vancomycin-resistant (6)				
Telavancin	>2	–	>2	– / –
Teicoplanin	>16	–	>16	0.0 / 100.0
Daptomycin	1	–	0.25–1	100.0 / –
Linezolid	1	–	1–2	100.0 / 0.0
Quinupristin-dalfopristin	>2	–	2–>2	0.0 / 83.3
Levofloxacin	>4	–	>4	0.0 / 100.0
Tetracycline	≤2	–	≤2–>8	50.0 / 50.0
Ampicillin	≤1	–	≤1–4	100.0 / 0.0
Gentamicin (HL)	1000	–	≤500–1000	33.3 / 66.7
Streptomycin (HL)	≤1000	–	≤1000–2000	83.3 / 16.7
E. faecium (318)				
Telavancin	0.06	2	≤0.015–>2	– / –
Vancomycin	1	>16	0.25–>16	70.4 / 25.8
Teicoplanin	≤2	>16	≤2–>16	80.2 / 19.2
Daptomycin	2	2	0.12–4	100.0 / –
Linezolid	1	2	0.5–4	99.1 / 0.0
Quinupristin-dalfopristin	1	>2	≤0.25–>2	68.6 / 20.4
Levofloxacin	>4	>4	≤0.5–>4	12.9 / 84.3
Tetracycline	≤2	>8	≤2–>8	79.6 / 20.4
Ampicillin	>16	>16	≤1–>16	7.2 / 92.8
Gentamicin (HL)	≤500	>1000	≤500–>1000	55.0 / 45.0
Streptomycin (HL)	≤1000	>2000	≤1000–>2000	50.9 / 49.1
E. faecium vancomycin-susceptible (224)				
Telavancin	0.06	0.12	≤0.015–0.25	– / –
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Daptomycin	2	2	0.12–4	100.0 / –
Linezolid	1	2	0.5–4	99.6 / 0.0
Quinupristin-dalfopristin	1	>2	≤0.25–>2	66.5 / 23.7
Levofloxacin	>4	>4	≤0.5–>4	14.7 / 81.7
Tetracycline	≤2	>8	≤2–>8	76.8 / 23.2
Ampicillin	>16	>16	≤1–>16	10.3 / 89.7
Gentamicin (HL)	≤500	>1000	≤500–>1000	58.0 / 42.0
Streptomycin (HL)	2000	>2000	≤1000–>2000	45.5 / 54.5
E. faecium vancomycin-resistant (82)				
Telavancin	2	>2	0.03–>2	– / –
Teicoplanin	>16	>16	≤2–>16	23.2 / 74.4
Daptomycin	2	2	0.25–4	100.0 / –
Linezolid	1	2	1–4	98.8 / 0.0
Quinupristin-dalfopristin	1	>2	≤0.25–>2	70.7 / 13.4
Levofloxacin	>4	>4	1–>4	9.8 / 89.0
Tetracycline	≤2	>8	≤2–>8	84.1 / 15.9
Ampicillin	>16	>16	>16	0.0 / 100.0
Gentamicin (HL)	1000	>1000	≤500–>1000	47.6 / 52.4
Streptomycin (HL)	≤1000	>2000	≤1000–>2000	63.4 / 36.6
E. avium (12)				
Telavancin	0.06	0.06	0.03–1	– / –
Vancomycin	0.5	1	0.5–>16	91.7 / 8.3
Teicoplanin	≤2	≤2	≤2–16	91.7 / 0.0
Daptomycin	0.5	1	0.25–2	100.0 / –
Linezolid	1	1	0.5–2	100.0 / 0.0
Quinupristin-dalfopristin	2	2	0.5–>2	16.7 / 8.3
Levofloxacin	2	>4	1–>4	83.3 / 16.7
Tetracycline	>8	>8	≤2–>8	25.0 / 75.0
Ampicillin	≤1	4	≤1–>16	91.7 / 8.3
Gentamicin (HL)	≤500	>1000	≤500–>1000	75.0 / 25.0
Streptomycin (HL)	≤1000	≤1000	≤1000–>2000	91.7 / 8.3

*Criteria as published by the CLSI (2008)

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