Activity of Telavancin Tested Against Viridans Group and Beta-Haemolytic Streptococci and Multidrug-Resistant *Streptococcus pneumoniae*

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ABSTRACT

Objectives. To evaluate the activity of telavancin tested against viridans group streptococci (VGS, five species), beta-haemolytic streptococci and *Streptococcus pneumoniae*, including multidrug-resistant strains. Telavancin is an investigational, bactericidal lipoglycopeptide active against Gram-positive pathogens, including resistant subsets, and has been evaluated in complicated skin and skin structure infection clinical trials.

Methods. The activity of telavancin was compared with those of other antimicrobial classes using reference broth microdilution (Clinical and Laboratory Standards Institute, M7-A7; Mueller-Hinton broth supplemented with 2–5% lysed horse blood) methods tested against 1005 streptococci (100 each of five VGS species; 100 each of Lancefield Groups B, C and G beta-haemolytic streptococci; and 205 *S. pneumoniae*, including multidrug-resistant patterns [>3 classes]) recovered from global surveillance programmes.

Results. Among tested VGS, 99.8% had telavancin MICs of ≤0.06 mg/L. All MIC_{50} and MIC_{90} values for *S. anginosus*, *S. constellatus*, *S. mitis* and *S. oralis* were 0.03 mg/L; *S. intermedius* showed an elevated MIC_{90} (0.06 mg/L) and the highest telavancin MIC (0.25 mg/L). Serogroups B, C and G beta-haemolytic streptococci had the same modal telavancin MIC (0.03 mg/L), but MIC_{90} results varied from 0.03 mg/L for Group C beta-haemolytic streptococci to 0.06 mg/L for Groups B and G beta-haemolytic streptococci. All beta-haemolytic streptococci were inhibited by ≤0.12 mg/L. Against *S. pneumoniae*, telavancin had a pronounced modal MIC at 0.015 mg/L (also MIC_{50} and MIC_{90}) and 99.5% of results were either 0.008 or 0.015 mg/L (highest MIC). No difference in the telavancin MIC_{90} (0.015 mg/L) was observed, but the MIC_{50} was slightly lower (0.008 mg/L) for two resistance phenotypes (penicillin-nonsusceptible [30 strains] and erythromycin-resistant [10 strains]). Telavancin MIC results did not correlate with mechanisms of resistance found for beta-lactams, macrolides, tetracyclines, fluoroquinolones or trimethoprim/sulfamethoxazole. Overall, >99% of telavancin MIC results occurred within three dilution steps (0.015–0.06 mg/L) for the tested streptococci.

Conclusions. Telavancin was found to be highly potent against prevalent VGS, beta-haemolytic streptococci and *S. pneumoniae*. All isolates were inhibited by ≤0.06 mg/L telavancin, with two exceptions (0.2%): one Group G beta-haemolytic streptococcal isolate at 0.12 mg/L and one *S. intermedius* at 0.25 mg/L. These results demonstrate that telavancin may be an excellent therapeutic candidate for serious infections caused by these pathogenic organisms.

INTRODUCTION

- Empiric therapy for serious complicated skin and skin structure infections (cSSSIs) and other infections where Gram-positive pathogens are suspected should include coverage of streptococci.
- Penicillin nonsusceptibility among strains of *Streptococcus pneumoniae* and viridans group streptococci (VGS) is driving the use of other antistreptococcal agents, especially fluoroquinolones, with concomitant increases in resistance mutations to these agents. There is an urgent need for the development and introduction into clinical practice of new agents active against these commonly occurring Gram-positive species.
- Telavancin is an investigational, parenteral, semi-synthetic lipoglycopeptide that is broadly active against both aerobic and anaerobic Gram-positive bacteria, including streptococci, methicillin-resistant *Staphylococcus aureus* (MRSA), and some vancomycin-resistant enterococci.[1–4]
- Bactericidal activity of telavancin is mediated both by interference with cell wall synthesis (similar to the glycopeptides) and by disruption of membrane function.[5]
- Efficacy and safety of telavancin have been demonstrated in Phase 2 and 3 cSSSI clinical trials.[6–8] Phase 3 trials for nosocomial pneumonia have been completed.

- This poster summarises results of an international surveillance testing programme comparing the activity of telavancin and currently marketed glycopeptides with other antimicrobial agents against streptococcal clinical isolates (VGS, beta-haemolytic streptococci and *S. pneumoniae*, including multidrug-resistant strains).
- 1005 streptococcal isolates 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

- 1005 non-duplicate, consecutive streptococcal clinical isolates were submitted from >60 medical centres located in North America, Latin America and Europe as part of international surveillance programmes for 2004–2006.
- Isolates originated from patients with documented bloodstream, respiratory tract or skin and soft tissue infections.
- The distribution of leading species included 100 each of *S. anginosus* (also known as *S. milleri*), *S. constellatus*, *S. intermedius*, *S. mitis*, *S. oralis*, *S. agalactiae* (Group B), *S. dysgalactiae* subsp. *equisimilis* (Group C), Group G beta-haemolytic streptococci and 205 *S. pneumoniae*. The *S. pneumoniae* strains included pan-susceptible strains (16 total) and those with defined resistant patterns (189 total; see **Table 4** for resistant phenotype descriptions).
- Identifications were confirmed by the central monitor (JMI Laboratories, Iowa, USA).

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 streptococci. Testing was by the broth microdilution method using commercially prepared and validated panels (TREK Diagnostics, Ohio, USA) in cation-adjusted Mueller-Hinton broth supplemented with 2–5% lysed horse blood.
- Interpretation of MIC results was in accordance with published CLSI breakpoint criteria.[9,10]
- Quality control strains utilised included *S. pneumoniae* ATCC 49619.

RESULTS

- 99.8% of tested VGS had telavancin MIC values of ≤0.06 mg/L (**Tables 1** and **2**). MIC_{50} and MIC_{90} values for *S. anginosus*, *S. constellatus*, *S. mitis* and *S. oralis* were 0.03 mg/L; the MIC_{90} value for *S. intermedius* was 0.06 mg/L and the highest telavancin MIC was 0.25 mg/L.
- Serogroups B, C and G beta-haemolytic streptococci had the same modal telavancin MIC (0.03 mg/L), but MIC_{90} results varied from 0.03 mg/L for Group C isolates to 0.06 mg/L for Group B and G isolates. All beta-haemolytic streptococci were inhibited by ≤0.12 mg/L (**Tables 1** and **3**).
- Against *S. pneumoniae*, telavancin had a pronounced modal MIC at 0.015 mg/L (also the MIC_{50} and MIC_{90}; **Table 3**); 99.5% of MIC values were either 0.008 or 0.015 mg/L (highest MIC).
- No difference was observed in the telavancin MIC_{90} results (0.015 mg/L) among the various *S. pneumoniae* resistance phenotypes (**Table 4**).
- Telavancin MIC values did not correlate with mechanisms of resistance found for beta-lactams, macrolides, tetracyclines, fluoroquinolones or trimethoprim/sulfamethoxazole.
- Overall, >99% of telavancin MIC values were within three doubling dilution steps (0.015–0.06 mg/L) for the tested streptococci.

Table 1. Telavancin activity tested against 1005 recent streptococcal isolates by reference (Clinical and Laboratory Standards Institute) broth microdilution methods

	Number inhibited at each telavancin MIC (mg/L)									MIC (mg/L)	
Group/organism (n tested)	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%	90%
All streptococci (1005)	1	2	80	304	543	73	1	1	0	0.03	0.03
Viridans group streptococci											
S. anginosus (100)	1	1	1	20	68	9	0	0	0	0.03	0.03
S. constellatus (100)	0	0	0	17	76	7	0	0	0	0.03	0.03
S. intermedius (100)	0	0	0	29	59	11	0	1	0	0.03	0.06
S. mitis (100)	0	0	2	43	48	7	0	0	0	0.03	0.03
S. oralis (100)	0	0	0	16	79	5	0	0	0	0.03	0.03
Beta-haemolytic streptococci											
Group B (100)	0	0	0	1	83	16	0	0	0	0.03	0.06
Group C (100)	0	0	0	26	69	5	0	0	0	0.03	0.03
Group G (100)	0	0	0	25	61	13	1	0	0	0.03	0.06
S. pneumoniae											
All (205)	0	1	77	127	0	0	0	0	0	0.015	0.015

Table 2. Antimicrobial activity of telavancin and selected comparison agents against viridans group streptococci collected as part of the SENTRY Antimicrobial Surveillance Programme (2004–2006)

Organism (n tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	% Susceptible/ resistant, by category*
S. anginosus (100)				
Telavancin	0.03	0.03	0.002–0.06	– / –
Vancomycin	0.5	0.5	0.25–1	100.0 / –
Ceftriaxone	0.12	0.25	≤0.03–2	99.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	93.0 / 7.0
Daptomycin	0.12	0.25	≤0.03–0.5	100.0 / –
Erythromycin	≤0.25	2	≤0.25–>2	86.0 / 14.0
Levofloxacin	0.5	1	≤0.06–>8	99.0 / 1.0
Linezolid	0.5	1	≤0.06–1	100.0 / –
Penicillin	≤0.03	0.06	≤0.03–2	98.0 / 0.0
Tetracycline	0.25	8	≤0.06–>8	77.0 / 22.0
S. constellatus (100)				
Telavancin	0.03	0.03	0.015–0.06	– / –
Vancomycin	0.5	1	0.25–1	100.0 / –
Ceftriaxone	0.25	0.5	≤0.03–>4	94.0 / 6.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	93.0 / 7.0
Daptomycin	0.25	0.25	≤0.03–0.5	100.0 / –
Erythromycin	≤0.25	2	≤0.25–>2	84.0 / 15.0
Levofloxacin	0.5	1	≤0.06–4	99.0 / 0.0
Linezolid	0.5	1	≤0.06–2	100.0 / –
Penicillin	≤0.03	0.12	≤0.03–>4	91.0 / 5.0
Tetracycline	0.25	>8	≤0.06–>8	77.0 / 21.0
S. intermedius (100)				
Telavancin	0.03	0.06	0.015–0.25	– / –
Vancomycin	0.5	0.5	0.25–1	100.0 / –
Ceftriaxone	0.12	0.5	≤0.03–4	96.0 / 2.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	92.0 / 7.0
Daptomycin	0.25	0.5	≤0.03–1	100.0 / –
Erythromycin	≤0.25	>2	≤0.25–>2	68.0 / 32.0
Levofloxacin	0.5	1	≤0.06–>8	95.0 / 5.0
Linezolid	0.5	1	0.25–2	100.0 / –
Penicillin	0.06	1	≤0.03–>4	75.0 / 4.0
Tetracycline	0.5	>8	≤0.06–>8	64.0 / 29.0
S. mitis (100)				
Telavancin	0.03	0.03	0.008–0.06	– / –
Vancomycin	0.5	0.5	0.25–1	100.0 / –
Ceftriaxone	0.06	4	≤0.03–>4	87.0 / 11.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	91.0 / 9.0
Daptomycin	0.25	0.5	≤0.03–1	100.0 / –
Erythromycin	0.5	>2	≤0.25–>2	47.0 / 50.0
Levofloxacin	1	1	0.25–>8	96.0 / 4.0
Linezolid	0.5	1	0.25–1	100.0 / –
Penicillin	0.06	4	≤0.03–>4	74.0 / 12.0
Tetracycline	0.25	>8	≤0.06–>8	69.0 / 29.0
S. oralis (100)				
Telavancin	0.03	0.03	0.015–0.06	– / –
Vancomycin	0.5	0.5	0.25–0.5	100.0 / –
Ceftriaxone	0.06	1	≤0.03–>4	92.0 / 5.0
Clindamycin	≤0.25	>2	≤0.25–>2	89.0 / 11.0
Daptomycin	0.5	1	≤0.03–1	100.0 / –
Erythromycin	≤0.25	>2	≤0.25–>2	50.0 / 47.0
Levofloxacin	1	2	0.25–>8	95.0 / 5.0
Linezolid	1	1	0.25–>8	99.0 / –
Penicillin	≤0.03	2	≤0.03–>4	75.0 / 8.0
Tetracycline	0.25	>8	≤0.06–>8	75.0 / 23.0

*Criteria as published by the CLSI (2008)
–, no breakpoint established

Table 3. Antimicrobial activity of telavancin and selected comparison agents against beta-haemolytic streptococci and *S. pneumoniae* collected as part of the SENTRY Antimicrobial Surveillance Programme (2004–2006)

Organism (n tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	% Susceptible/ resistant, by category*
Group B streptococci (100)				
Telavancin	0.03	0.06	0.015–0.06	– / –
Vancomycin	0.5	0.5	0.25–0.5	100.0 / –
Ceftriaxone	0.06	0.06	≤0.03–0.12	100.0 / –
Clindamycin	≤0.25	>2	≤0.25–>2	83.0 / 17.0
Daptomycin	0.12	0.25	≤0.03–0.25	100.0 / –
Erythromycin	≤0.25	>2	≤0.25–>2	65.0 / 35.0
Levofloxacin	0.5	1	0.25–>8	99.0 / 1.0
Linezolid	1	1	0.5–1	100.0 / –
Penicillin	≤0.03	0.06	≤0.03–0.06	100.0 / –
Tetracycline	>8	>8	0.12–>8	14.0 / 85.0
Group C streptococci (100)				
Telavancin	0.03	0.03	0.015–0.06	– / –
Vancomycin	0.25	0.5	0.25–0.5	100.0 / –
Ceftriaxone	≤0.03	≤0.03	≤0.03–0.25	100.0 / –
Clindamycin	≤0.25	≤0.25	≤0.25–>2	97.0 / 2.0
Daptomycin	≤0.03	0.06	≤0.03–0.25	100.0 / –
Erythromycin	≤0.25	0.5	≤0.25–>2	88.0 / 8.0
Levofloxacin	0.5	0.5	≤0.06–1	100.0 / 0.0
Linezolid	0.5	1	0.5–2	100.0 / –
Penicillin	≤0.03	≤0.03	≤0.03–0.06	100.0 / –
Tetracycline	0.25	>8	≤0.06–>8	77.0 / 19.0
Group G streptococci (100)				
Telavancin	0.03	0.06	0.015–0.12	– / –
Vancomycin	0.25	0.25	0.25–0.5	100.0 / –
Ceftriaxone	≤0.03	≤0.03	≤0.03–0.12	100.0 / –
Clindamycin	≤0.25	≤0.25	≤0.25–>2	96.0 / 4.0
Daptomycin	≤0.03	0.06	≤0.03–0.25	100.0 / –
Erythromycin	≤0.25	2	≤0.25–>2	76.0 / 22.0
Levofloxacin	0.5	0.5	0.25–8	97.0 / 3.0
Linezolid	0.5	1	0.5–1	100.0 / –
Penicillin	≤0.03	≤0.03	≤0.03	100.0 / –
Tetracycline	4	>8	0.12–>8	48.0 / 44.0
S. pneumoniae (205)				
Telavancin	0.015	0.015	0.004–0.015	– / –
Vancomycin	0.25	0.25	≤0.12–0.5	100.0 / –
Ceftriaxone	1	2	≤0.03–>4	86.3 / 3.4
Clindamycin	>2	>2	≤0.25–>2	45.9 / 53.2
Daptomycin	0.12	0.12	≤0.03–0.5	– / –
Erythromycin	>2	>2	≤0.25–>2	39.5 / 60.5
Levofloxacin	1	1	0.5–>8	95.1 / 4.9
Linezolid	1	1	0.25–1	100.0 / –
Penicillin	2	4	≤0.03–>4	26.8 / 55.6†
Tetracycline	>8	>8	≤0.06–>8	40.5 / 59.5
Trimethoprim/ sulfamethoxazole	4	>4	≤0.5–>4	41.0 / 57.1

*Criteria as published by the CLSI (2008)
†Criteria as published by the CLSI (2008) for penicillin parenteral (meningitis)
–, no breakpoint established

Table 4. Telavancin MIC results for pneumococcal strains having nine different patterns of resistance (205 strains)

	MIC (mg/L)		
Resistance pattern (n tested)	50%	90%	Range
Pan-S (16)	0.015	0.015	0.008–0.015
Penicillin-NS (30)	0.008	0.015	0.008–0.015
Penicillin and cefuroxime-NS (10)	0.015	0.015	0.008–0.015
Erythromycin-R (10)	0.008	0.015	0.008–0.015
Levofloxacin-R (10)	0.015	0.015	0.008–0.015
Tetracycline-R (10)	0.015	0.015	0.008–0.015
Trimethoprim/sulfamethoxazole-R (11)	0.015	0.015	0.004–0.015
Erythromycin, clindamycin, tetracycline-R (10)	0.015	0.015	0.008–0.015
Multidrug-R (98)*	0.015	0.015	0.008–0.015
All strains (205)	0.015	0.015	0.004–0.015

S, susceptible; R, resistant; NS, nonsusceptible
*Multidrug-R, resistance to penicillin, cefuroxime, clindamycin, erythromycin, tetracycline and trimethoprim/sulfamethoxazole (six drug classes)

CONCLUSIONS

- Telavancin was highly potent against contemporary isolates of VGS and beta-haemolytic streptococci (serogroups B, C and G; MIC_{90} results, 0.03–0.06 mg/L) and various resistance phenotypes of *S. pneumoniae* (MIC_{90}, 0.015 mg/L) including multidrug-resistant (six drug classes) isolates (**Table 4**).
- Reference MIC values for telavancin occurred across a very narrow range (>99.0% within three log_2 dilution steps) for each streptococcal group tested. Only two strains had a telavancin MIC >0.06 mg/L.
- This *in vitro* assessment suggests that telavancin is a promising, potent agent for treating infections caused by these pathogenic streptococci.

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