Antimicrobial Activity of Telavancin and Comparator Agents Tested Against Recently Isolated (2007) European *Staphylococcus aureus* and Coagulase-negative Staphylococci

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ABSTRACT

Objectives. Telavancin is an investigational, bactericidal lipoglycopeptide that is broadly active against Gram-positive pathogens and has completed clinical trials in complicated skin and soft tissue infections. Given concerns over the rapid emergence of resistance among staphylococci, including community-acquired strains, we compared the potency of telavancin versus other antimicrobials against contemporary oxacillin-susceptible (OX-S) and OX-resistant (OX-R) *Staphylococcus aureus* (SA) and coagulase-negative staphylococci (CoNS) collected as part of a European antimicrobial resistance surveillance programme.

Methods. Consecutive, non-duplicate patient isolates (n=2834) were submitted from 26 medical centres in Europe (10 countries), Turkey and Israel during 2007 (2202 SA [OX-R, 29.3%], 632 CoNS [OX-R, 76.1%]) and susceptibility tested using Clinical and Laboratory Standards Institute (M7-A7) broth microdilution methods.

Results. Compared with OX-S SA, telavancin MIC_{90} values varied by one dilution in OX-R SA (0.12 versus 0.25 mg/L, respectively; see **Table**), but was unchanged for OX-R CoNS (0.25 mg/L); all isolates were inhibited by ≤0.5 mg/L. Telavancin was 2-, 4- and 8-fold more potent (MIC_{90}) than daptomycin, vancomycin and linezolid, respectively, when testing SA, and 2-, 8- and 4-fold more potent, respectively, when testing CoNS. Among CoNS, telavancin was most active against *S. lugdunensis* (MIC_{50}, 0.06 mg/L) and least active against *S. warnerii* (MIC_{50}, 0.25 mg/L; 10 isolates each); MIC_{50} values for other species (*S. capitis* [20 isolates], *S. epidermidis* [316 isolates], *S. haemolyticus* [34 isolates] and *S. hominis* [59 isolates]) were all 0.12 mg/L. High levels of resistance to other agents were observed among OX-R SA and CoNS with respective resistance rates (%) as follows: erythromycin (69.8/68.0), clindamycin (30.0/29.7), gentamicin (19.7/37.9), levofloxacin (90.7/65.7), tetracycline (11.6/18.3) and trimethoprim/sulfamethoxazole (1.9/45.3).

Conclusions. Telavancin displayed higher potency than the other agents tested against SA and CoNS (MIC_{50} and MIC_{90} values for both, 0.12 and 0.25 mg/L), and inhibited all isolates at ≤0.5 mg/L. Telavancin exhibited similar potency for OX-S and -R strains. The continued and rapid emergence of resistant staphylococci, including community-acquired OX-R SA, necessitates the timely introduction of new therapeutic agents and longitudinal surveillance to assist in control efforts.

Table.

	MIC (mg/L)							
	Telavancin		Vancomycin		Levofloxacin		Linezolid	
Organism (n)	50%	90%	50%	90%	50%	90%	50%	90%
OX-S SA (1556)	0.12	0.12	1	1	≤0.5	≤0.5	1	2
OX-R SA (646)	0.12	0.25	1	1	>4	>4	1	2
OX-S CoNS (151)	0.12	0.25	1	2	≤0.5	≤0.5	0.5	1
OX-R CoNS (481)	0.12	0.25	2	2	4	>4	1	1

CoNS, coagulase-negative staphylococci; OX-S, oxacillin-susceptible; OX-R, oxacillin-resistant; SA, *Staphylococcus aureus*

INTRODUCTION

- Emergence of bacterial resistance is a significant global problem that complicates nosocomial infections, with increasing morbidity, mortality and costs of hospitalisation due to increased length of stay.
- Occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is especially problematic in intensive care units. Furthermore, the dramatic spread of community-associated MRSA infections (e.g., USA-300 clone), including into the hospital environment, has created a public health emergency that is challenging traditional infection control practices.

- Increased use of vancomycin in treating staphylococcal infections has driven vancomycin resistance among enterococci, especially *E. faecium*.
- Penicillin nonsusceptibility among strains of *Streptococcus pneumoniae* is increasing and currently exceeds 36% in the United States.
- The timely development and introduction of new agents active against these commonly occurring Gram-positive pathogens is sorely needed.
- Telavancin is an investigational, parenteral, semi-synthetic lipoglycopeptide that is broadly active against both aerobic and anaerobic Gram-positive bacteria, including MRSA and some vancomycin-resistant enterococci.[1–7]
- Bactericidal activity of telavancin is mediated both by interference with cell wall synthesis (similar to the glycopeptides) and by disruption of membrane function.[8]
- Efficacy and safety of telavancin have been demonstrated in Phase 2 and 3 complicated skin and skin structure clinical trials.[9–11] Phase 3 trials for nosocomial pneumonia have been recently completed.
- This poster summarises results of a European 2007 surveillance testing programme comparing the activity of telavancin and currently marketed glycopeptides with other antimicrobial agents against *S. aureus* and coagulase-negative staphylococci (CoNS) clinical isolates. The analysis includes evaluation of oxacillin (methicillin)-resistant (OX-R) and oxacillin-susceptible (OX-S) subsets for each of these groups.
- 2834 bacterial strains were tested by Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods with susceptibilities to comparator agents interpreted by CLSI breakpoint criteria (M100-S18 [2008][12]).

MATERIALS AND METHODS

Bacterial strain collection

- 2834 non-duplicate, consecutive staphylococcal clinical isolates were submitted from 26 medical centres located in Europe as part of the international telavancin surveillance programme for 2007.
- Isolates originated from patients with documented bloodstream (49.7%), respiratory tract (32.0%) or skin and soft tissue infections (18.3%).
- Isolates included 2202 *S. aureus* strains (646 [29.3%] OX-R) and 632 CoNS (481 [76.1%] OX-R).
- 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 the indicated pathogen.
- Testing was by the CLSI broth microdilution method (M7-A7 [2006][13]) 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 (M100-S18 [2008][12]) criteria.
- Quality control strains utilised included *S. aureus* ATCC 29213.

RESULTS

- Telavancin was highly active against European *S. aureus* and CoNS, inhibiting all isolates by ≤0.5 mg/L (MIC_{50} and MIC_{90} results, 0.12 and 0.25 mg/L, respectively; **Tables 1** and **2**).
- Compared with OX-S *S. aureus*, telavancin MIC_{90} values for OX-R *S. aureus* increased by one dilution (0.12 versus 0.25 mg/L, respectively); no difference was detected between OX-S and OX-R CoNS (MIC_{90} values, 0.25 mg/L).

Table 1. Antimicrobial activity of telavancin against staphylococcal species/groups and resistant subsets submitted as part of a 2007 European surveillance programme

	Cumulative % inhibited at each telavancin MIC (mg/L)					
Group/organism (n tested)	≤0.015	0.03	0.06	0.12	0.25	0.5
S. aureus (2202)	0	<1	14	89	>99	100
Oxacillin-susceptible (1556)	0	<1	13	91	>99	100
Oxacillin-resistant (646)	0	0	17	84	>99	100
Coagulase-negative staphylococci (632)	<1	1	21	88	>99	100
Oxacillin-susceptible (151)	0	2	26	88	>99	100
Oxacillin-resistant (481)	<1	<1	20	88	>99	100
S. capitis (20)	5	5	25	100	–	–
S. epidermidis (316)	0	0	20	90	>99	100
S. haemolyticus (34)	0	6	18	65	97	100
S. hominis (59)	0	0	37	97	100	–
S. lugdunensis (13)	0	0	69	100	–	–
S. saprophyticus (13)	0	0	8	54	100	–
S. warnerii (10)	0	0	0	30	90	100

- Telavancin was 2-, 4- and 8-fold more potent (MIC_{90} results) than daptomycin, vancomycin and linezolid, respectively, when testing *S. aureus*, and 2-, 8- and 4-fold more potent, respectively, when testing CoNS (**Table 2**).
- Among CoNS isolates, telavancin was most active against *S. lugdunensis* (MIC_{50}, 0.06 mg/L) and least active against *S. warnerii* (MIC_{50}, 0.25 mg/L; **Table 2**). MIC_{50} values for other species (*S. capitis*, *S. epidermidis*, *S. haemolyticus* and *S. hominis*) were all 0.12 mg/L.
- High levels of resistance to other agents were observed among OX-R *S. aureus* and OX-R CoNS with respective resistance rates (%) as follows: erythromycin (69.8/68.0), clindamycin (30.0/29.7), gentamicin (19.7/37.9), levofloxacin (90.7/65.7), tetracycline (11.6/18.3) and trimethoprim/sulfamethoxazole (1.9/45.3).

CONCLUSIONS

- Telavancin displayed higher activity than other tested agents against European *S. aureus* and CoNS (MIC_{50} and MIC_{90} values for both, 0.12 and 0.25 mg/L) isolates and inhibited all strains tested at ≤0.5 mg/L.
- Potency (MIC_{50} results) of telavancin against OX-S and OX-R strains was identical for both *S. aureus* and CoNS.
- Among CoNS isolates, telavancin was slightly less active (MIC_{50}, 0.25 mg/L) against *S. warnerii* and more active (MIC_{50}, 0.06 mg/L) against *S. lugdunensis*.
- The continued and rapid emergence of resistant staphylococci, including community-acquired MRSA, necessitates the timely introduction of new therapeutic agents and longitudinal surveillance to assist in control efforts.

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Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against *S. aureus* and coagulase-negative staphylococci

Organism (n tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	% Susceptible/resistant, by category*
S. aureus (2202)				
Telavancin	0.12	0.25	0.03–0.5	– / –
Vancomycin	1	1	0.25–2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2–4	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	1	2	0.5–8	>99.9 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–>2	99.8 / 0.1
Levofloxacin	≤0.5	>4	≤0.5–>4	69.0 / 30.7
Erythromycin	≤0.25	>2	≤0.25–>2	69.1 / 30.4
Clindamycin	≤0.25	>2	≤0.25–>2	89.3 / 10.7
Tetracycline	≤2	≤2	≤2–>8	93.0 / 6.9
Oxacillin	0.5	>2	≤0.25–>2	70.7 / 29.3
Oxacillin-susceptible (1556)				
Telavancin	0.12	0.12	0.03–0.5	– / –
Vancomycin	1	1	0.25–2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2–4	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	1	2	0.5–2	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–1	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5–>4	94.1 / 5.8
Erythromycin	≤0.25	>2	≤0.25–>2	85.7 / 14.1
Clindamycin	≤0.25	≤0.25	≤0.25–>2	97.3 / 2.7
Tetracycline	≤2	≤2	≤2–>8	95.1 / 4.9
Oxacillin-resistant (646)				
Telavancin	0.12	0.25	0.06–0.5	– / –
Vancomycin	1	1	0.25–2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2–4	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	1	2	0.5–8	99.8 / –
Quinupristin-dalfopristin	0.5	0.5	≤0.25–>2	99.4 / 0.5
Levofloxacin	>4	>4	≤0.5–>4	8.5 / 90.7
Erythromycin	>2	>2	≤0.25–>2	29.1 / 69.8
Clindamycin	≤0.25	>2	≤0.25–>2	70.0 / 30.0
Tetracycline	≤2	>8	≤2–>8	87.9 / 11.6
Coagulase-negative staphylococci (632)				
Telavancin	0.12	0.25	≤0.015–0.5	– / –
Vancomycin	1	2	0.25–4	100.0 / 0.0
Teicoplanin	≤2	4	≤2–>16	97.9 / 0.3
Daptomycin	0.25	0.5	≤0.06–2	99.8 / –
Linezolid	1	1	0.25–2	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–>2	99.1 / 0.8
Levofloxacin	4	>4	≤0.5–>4	44.6 / 51.6
Erythromycin	>2	>2	≤0.25–>2	40.0 / 59.7
Clindamycin	≤0.25	>2	≤0.25–>2	76.3 / 23.4
Tetracycline	≤2	>8	≤2–>8	82.4 / 17.1
Oxacillin	>2	>2	≤0.25–>2	23.9 / 76.1
Oxacillin-susceptible (151)				
Telavancin	0.12	0.25	0.03–0.5	– / –
Vancomycin	1	2	0.25–2	100.0 / 0.0
Teicoplanin	≤2	4	≤2–16	99.3 / 0.0
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	0.5	1	0.25–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	≤0.25	≤0.25–1	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5–>4	92.1 / 6.6
Erythromycin	≤0.25	>2	≤0.25–>2	66.9 / 33.1
Clindamycin	≤0.25	≤0.25	≤0.25–>2	96.0 / 3.3
Tetracycline	≤2	>8	≤2–>8	86.8 / 13.2
Oxacillin-resistant (481)				
Telavancin	0.12	0.25	≤0.015–0.5	– / –
Vancomycin	2	2	0.25–4	100.0 / 0.0
Teicoplanin	≤2	4	≤2–>16	97.5 / 0.4
Daptomycin	0.25	0.5	≤0.06–2	99.8 / –
Linezolid	1	1	0.25–2	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–>2	98.8 / 1.0
Levofloxacin	4	>4	≤0.5–>4	29.7 / 65.7
Erythromycin	>2	>2	≤0.25–>2	31.6 / 68.0
Clindamycin	≤0.25	>2	≤0.25–>2	70.1 / 29.7
Tetracycline	≤2	>8	≤2–>8	81.1 / 18.3
S. capitis (20)				
Telavancin	0.12	0.12	≤0.015–0.12	– / –
Vancomycin	1	1	0.25–2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Daptomycin	0.5	1	≤0.06–1	100.0 / –
Linezolid	1	1	0.25–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	1	≤0.25–1	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5–>4	80.0 / 20.0
Erythromycin	≤0.25	>2	≤0.25–>2	70.0 / 30.0

Table 2 - cont. Antimicrobial activity of telavancin and comparator antimicrobial agents against *S. aureus* and coagulase-negative staphylococci - cont.

Organism (n tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	% Susceptible/resistant, by category*
S. capitis (20) – cont.				
Clindamycin	≤0.25	>2	≤0.25–>2	85.0 / 15.0
Tetracycline	≤2	≤2	≤2–>8	90.0 / 10.0
Oxacillin	≤0.25	>2	≤0.25–>2	60.0 / 40.0
S. epidermidis (316)				
Telavancin	0.12	0.25	0.06–0.5	– / –
Vancomycin	2	2	0.5–4	100.0 / 0.0
Teicoplanin	≤2	4	≤2–16	98.4 / 0.0
Daptomycin	0.25	0.5	≤0.06–2	99.7 / –
Linezolid	0.5	1	0.25–2	100.0 / –
Quinupristin-dalfopristin	≤0.25	≤0.25	≤0.25–>2	98.1 / 1.6
Levofloxacin	4	>4	≤0.5–>4	36.7 / 58.9
Erythromycin	>2	>2	≤0.25–>2	35.8 / 64.2
Clindamycin	≤0.25	>2	≤0.25–>2	72.2 / 27.5
Tetracycline	≤2	>8	≤2–>8	80.1 / 19.0
Oxacillin	>2	>2	≤0.25–>2	18.4 / 81.6
S. haemolyticus (34)				
Telavancin	0.12	0.25	0.03–0.5	– / –
Vancomycin	1	2	0.25–4	100.0 / 0.0
Teicoplanin	≤2	16	≤2–>16	85.3 / 2.9
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	0.5	1	0.5–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–0.5	100.0 / 0.0
Levofloxacin	>4	>4	≤0.5–>4	29.4 / 70.6
Erythromycin	>2	>2	≤0.25–>2	23.5 / 76.5
Clindamycin	≤0.25	>2	≤0.25–>2	82.4 / 17.6
Tetracycline	≤2	>8	≤2–>8	88.2 / 11.8
Oxacillin	>2	>2	≤0.25–>2	20.6 / 79.4
S. hominis (59)				
Telavancin	0.12	0.12	0.06–0.25	– / –
Vancomycin	1	2	0.5–2	100.0 / 0.0
Teicoplanin	≤2	4	≤2–16	98.3 / 0.0
Daptomycin	0.25	0.5	≤0.06–1	100.0 / –
Linezolid	1	1	0.5–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–0.5	100.0 / 0.0
Levofloxacin	2	>4	≤0.5–>4	44.1 / 47.5
Erythromycin	>2	>2	≤0.25–>2	28.8 / 71.2
Clindamycin	≤0.25	>2	≤0.25–>2	78.0 / 20.3
Tetracycline	≤2	>8	≤2–>8	66.1 / 33.9
Oxacillin	>2	>2	≤0.25–>2	16.9 / 83.1
S. lugdunensis (13)				
Telavancin	0.06	0.12	0.06–0.12	– / –
Vancomycin	1	1	0.5–1	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Daptomycin	0.25	0.25	0.12–0.25	100.0 / –
Linezolid	0.5	1	0.25–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5–>4	92.3 / 7.7
Erythromycin	≤0.25	>2	≤0.25–>2	76.9 / 23.1
Clindamycin	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Tetracycline	≤2	≤2	≤2	100.0 / 0.0
Oxacillin	0.5	1	≤0.25–1	100.0 / 0.0
S. saprophyticus (13)				
Telavancin	0.12	0.25	0.06–0.25	– / –
Vancomycin	1	2	0.5–2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Daptomycin	0.25	0.5	0.12–1	100.0 / –
Linezolid	1	1	0.5–2	100.0 / –
Quinupristin-dalfopristin	0.5	0.5	≤0.25–1	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5–>4	69.2 / 30.8
Erythromycin	>2	>2	≤0.25–>2	46.2 / 53.8
Clindamycin	≤0.25	>2	≤0.25–>2	84.6 / 15.4
Tetracycline	≤2	≤2	≤2–>8	92.3 / 7.7
Oxacillin	1	>2	≤0.25–>2	7.7 / 92.3
S. warnerii (10)				
Telavancin	0.25	0.25	0.12–0.5	– / –
Vancomycin	1	2	1–2	100.0 / 0.0
Teicoplanin	≤2	4	≤2–8	100.0 / 0.0
Daptomycin	0.5	1	0.25–1	100.0 / –
Linezolid	1	1	0.5–1	100.0 / –
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25–1	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5–>4	80.0 / 20.0
Erythromycin	≤0.25	>2	≤0.25–>2	70.0 / 30.0
Clindamycin	≤0.25	>2	≤0.25–>2	80.0 / 20.0
Tetracycline	≤2	≤2	≤2	100.0 / 0.0
Oxacillin	≤0.25	>2	≤0.25–>2	50.0 / 50.0

*Criteria as published by the CLSI (2008)

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