Update of the Telavancin *In vitro* Activity against *Staphylococcus aureus* and Coagulase-negative Staphylococci, Including Isolates with Decreasing Susceptibility for Comparator Agents in European Hospitals (2013)

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ABSTRACT

Objectives. To provide an update on the telavancin *in vitro* activity tested against *S. aureus* and coagulase-negative staphylococci (CoNS) with decreased susceptibility to anti-Gram-positive agents. Telavancin is approved in the USA for the treatment of skin and skin-structure infections, and in the USA and Europe (MRSA only) for hospital-acquired and ventilator-associated bacterial pneumonia, when alternative treatments are not suitable.

Methods. 2169 *S. aureus* and 381 CoNS isolates were collected from 31 sites located in 15 European countries, and Russia, Turkey and Israel. Isolates were submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Program for 2013. Identification was confirmed by MALDI-TOF and susceptibility testing was performed by CLSI methods. MIC interpretation used the FDA (telavancin), CLSI and/or EUCAST criteria. Isolates were grouped according to susceptibility results for vancomycin and teicoplanin. Isolates displaying resistance phenotype to methicillin and at least three classes of drugs (except for daptomycin; non-susceptible phenotypes were included) were considered as multidrug-resistant (MDR).

Results. Overall, telavancin showed MIC_{50} and MIC_{90} results of 0.03 and 0.06 mg/L, respectively, against *S. aureus*, methicillin-susceptible and -resistant isolates. Telavancin inhibited these isolates at the FDA breakpoint for susceptibility (i.e. ≤0.12 mg/L). *S. aureus* exhibiting vancomycin MICs of 2 mg/L had MIC_{50} results for telavancin and daptomycin 2-fold higher than those isolates with vancomycin MICs at ≤1 mg/L. Telavancin ($MIC_{50/90}$, 0.03/0.06 mg/L; 100.0% susceptible) had MIC_{50} and MIC_{90} results 8-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% susceptible) and at least 16-fold lower than vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/1 mg/L; 99.4% susceptible) against MDR isolates of *S. aureus*. Other comparators had decreased activity (1.7 – 74.9% susceptible) against MDR *S. aureus*, except for trimethoprim-sulfamethoxazole (96.1% susceptible). Telavancin had MIC_{50}, MIC_{90} and MIC_{100} values of 0.03, 0.06 and 0.12 mg/L against all CoNS, respectively. CoNS exhibiting vancomycin MIC of 2 mg/L had MIC_{50} results for telavancin and daptomycin 2-fold higher than those isolates with vancomycin MICs at ≤1 mg/L. Similarly, MIC_{50} results for telavancin, vancomycin and daptomycin against CoNS with teicoplanin MICs of 8-16 mg/L were 2-fold higher than those isolates with teicoplanin MICs at ≤4 mg/L. Only telavancin (100.0% susceptible [*S. aureus* breakpoint]), vancomycin (100.0% susceptible), daptomycin (100.0% susceptible) and linezolid (98.9% susceptible) were active against MDR isolates of CoNS. However, telavancin had MICs at least 8-fold lower than these comparators. Other tested agents had limited coverage against these MDR isolates, including teicoplanin (79.3% susceptible; EUCAST criteria).

Conclusions. Telavancin had potent *in vitro* activity against this contemporary (2013) collection of *S. aureus* and CoNS isolates, including less susceptible and MDR subsets from European hospitals and adjacent geographic regions. In addition, telavancin demonstrated *in vitro* activity greater than comparators against this challenge set of organisms.

INTRODUCTION

- Staphylococcal species are important human pathogens, and while methicillin-resistant *Staphylococcus aureus* (MRSA) has remained a major public health problem worldwide, coagulase-negative staphylococci (CoNS) has undoubtedly become the most common cause of bacteremia related to indwelling devices. These pathogens are often associated with hospital-acquired infections and have challenged the clinically available antimicrobial therapies due to the resistance nature of these isolates.
- In addition, the emergence and rise of community-acquired MRSA infections have contributed to these therapeutic challenges.
- Telavancin is a parenteral semi-synthetic lipoglycopeptide approved in 2009 in the USA and Canada for the treatment of adults with complicated skin and soft tissue infections caused by susceptible organisms.[1,2]
- Subsequently, telavancin was granted approval in the USA and Europe for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus* (MRSA only in Europe) when alternative treatments are not suitable.[1,3]
- This study provides an update on the telavancin *in vitro* activity tested against *S. aureus* and CoNS displaying decreased susceptibility to anti-Gram-positive agents.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 2169 *S. aureus* and 381 CoNS isolates were included. These isolates originated from 31 medical sites located in 15 European countries (Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Slovenia, Spain, Sweden, UK and Ukraine) and Russia, Turkey and Israel.
- These isolates were recovered mostly from skin and soft tissue (46.0%), lower respiratory tract (16.0%) and blood (16.0%) specimens and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Program during 2013.
- Isolates were initially identified by the participating laboratory and identification confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document.[4]
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event.
- Affirmation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212).
- Expected telavancin minimum inhibitory concentration (MIC) ranges when tested against ATCC strains were those available in the current M100-S25 document, as follows:[5]
  - *S. aureus* ATCC 29213 (0.03–0.12 mg/L) and *E. faecalis* ATCC 29212 (0.03–0.12 mg/L).
- All QC results were within published acceptable ranges.
- MIC interpretations for telavancin applied the breakpoint criteria available in the product package insert (2014),[1] as follows: *S. aureus* at ≤0.12 mg/L for susceptible (also applied for CoNS). The European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) breakpoint criteria were applied for comparator agents, as available.[6]
- Isolates were grouped according to MIC results for vancomycin and teicoplanin. Isolates displaying resistance phenotype to methicillin and at least three classes of drugs (except for daptomycin; non-susceptible phenotypes were included) were considered as multidrug-resistant (MDR).

RESULTS

- Telavancin showed $MIC_{50/90}$ results of 0.03 and 0.06 mg/L, respectively, against methicillin-susceptible *S. aureus* and MRSA isolates. Similar $MIC_{50/90}$ results (ie, 0.03 and 0.06 mg/L, respectively) were also obtained against *S. aureus* isolates displaying an MDR phenotype (**Table 1**).
- *S. aureus* exhibiting vancomycin MIC values at the breakpoint for susceptibility (ie, 2 mg/L) had MIC_{50} results for telavancin and daptomycin two-fold higher than those observed for isolates with vancomycin MIC results at ≤1 mg/L (**Table 1** and **2**). However, telavancin inhibited all isolates at ≤0.06 mg/L (**Table 1**).
- Overall, telavancin ($MIC_{50/90}$, 0.03/0.06 mg/L; 100.0% susceptible) had $MIC_{50/90}$ results eight-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% susceptible) and at least 16-fold lower than vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/1 mg/L; 99.4% susceptible) against MDR isolates of *S. aureus*.
- Other comparator agents had decreased activity (1.7–74.9% susceptible) against MDR *S. aureus*, except for trimethoprim-sulfamethoxazole (96.1% susceptible) (data not shown).
- Telavancin had $MIC_{50/90/100}$ values of 0.03, 0.06 and 0.12 mg/L against all CoNS, respectively. CoNS exhibiting vancomycin MIC of 2 mg/L had MIC_{50} results for telavancin and daptomycin two-fold higher than those isolates with vancomycin MIC values at ≤1 mg/L.
- Similarly, MIC_{50} results for telavancin, vancomycin and daptomycin against CoNS with teicoplanin MIC results of 8–16 mg/L were two-fold higher than those isolates with teicoplanin MIC values at ≤4 mg/L. Still, these agents demonstrated high antimicrobial susceptibility rates (98.9–100.0%) against these isolates (**Table 2**).
- Only telavancin (100.0% susceptible [*S. aureus* breakpoint]), vancomycin (100.0% susceptible), daptomycin (100.0% susceptible) and linezolid (98.9% susceptible) were active against MDR isolates of CoNS. However, telavancin had MIC results at least eight-fold lower than these comparators. Other tested agents had limited coverage against MDR isolates, including teicoplanin (79.3% susceptible; EUCAST criteria).

Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against 2550 contemporary (2013) staphylococcal clinical isolates from European and adjacent geographic regions, as part of the SENTRY Antimicrobial Surveillance Program

	MIC (mg/L)		No. (cumulative %) inhibited at telavancin MIC (mg/L)[bc]			
Organism (no. tested)	**50%**	**90%**	**≤0.015**	**0.03**	**0.06**	**0.12**
S. aureus (2169)	0.03	0.06	135 (6.2)	**1518 (76.2)**	515 (>99.9)	1 (100.0)
MSSA (1669)	0.03	0.06	108 (6.5)	**1165 (76.3)**	395 (99.9)	1 (100.0)
MRSA (500)	0.03	0.06	27 (5.4)	**353 (76.0)**	120 (100.0)	–
Vancomycin (MIC, ≥2 mg/L; 15)	0.06	0.06	0 (0.0)	3 (20.0)	**12 (100.0)**	–
Vancomycin (MIC, ≤1 mg/L; 2154)	0.03	0.06	135 (6.3)	**1515 (76.6)**	503 (>99.9)	1 (100.0)
MDR (179)	0.03	0.06	11 (6.1)	**117 (71.5)**	51 (100.0)	–
Non-MDR (1990)	0.03	0.06	124 (6.2)	**1401 (76.6)**	464 (99.9)	1 (100.0)
Coagulase-negative staphylococci[F] (381)	0.03	0.06	64 (16.8)	141 (53.8)	**169 (98.2)**	7 (100.0)
MSCoNS (83)	0.03	0.06	16 (19.3)	**34 (60.2)**	32 (98.8)	1 (100.0)
MRCoNS (298)	0.03	0.06	48 (16.1)	107 (52.0)	**137 (98.0)**	6 (100.0)
Vancomycin (MIC, ≥2 mg/L; 177)	0.06	0.06	4 (2.3)	56 (33.9)	**110 (96.0)**	7 (100.0)
Vancomycin (MIC, ≤1 mg/L; 204)	0.03	0.06	60 (29.4)	**85 (71.1)**	59 (100.0)	–
Teicoplanin (MIC, ≥8 mg/L; 53)	0.06	0.06	0 (0.0)	16 (30.2)	**34 (94.3)**	3 (100.0)
Teicoplanin (MIC, ≤4 mg/L; 328)	0.03	0.06	64 (19.5)	125 (57.6)	**135 (98.8)**	4 (100.0)
MDR (177)	0.06	0.06	17 (9.6)	67 (47.5)	**89 (97.7)**	4 (100.0)
Non-MDR (204)	0.03	0.06	47 (23.0)	74 (59.3)	**80 (98.5)**	3 (100.0)

MDR = multidrug-resistant (ie, isolates displaying resistance phenotype to methicillin and at least three classes of drugs, except for daptomycin; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MRSA = methicillin-resistant *S. aureus*; non-susceptible phenotypes); MSCoNS = methicillin-susceptible coagulase-negative staphylococci; MSSA = methicillin-susceptible *S. aureus*.
[b]Modal MIC values are shown in bold.
[c]Includes *S. capitis* (16 strains), *S. caprae* (four strains), *S. cohnii* (one strain), *S. epidermidis* (222 strains), *S. haemolyticus* (49 strains), *S. hominis* (41 strains), *S. lugdunensis* (21 strains), *S. pasteuri* (one strain), *S. pettenkoferi* (one strain), *S. saprophyticus* (eight strains), *S. schleiferi* (one strain), *S. sciuri* (two strains), *S. simulans* (seven strains), *S. warneri* (five strains), and *S. xylosus* (two strains).

Table 2. Antimicrobial activity and spectrum of telavancin and comparator agents tested against staphylococcal clinical isolates from European and adjacent geographic regions, as part of the 2013 SENTRY Antimicrobial Surveillance Program

	$MIC_{50/90}$ (mg/L) and % susceptible[d] for each agent														
Species/Group (no. tested)	**Telavancin**			**Vancomycin**			**Daptomycin**			**Linezolid**			**Clindamycin**		
Phenotype	**50%**	**90%**	**%S**	**50%**	**90%**	**%S**	**50%**	**90%**	**%S**	**50%**	**90%**	**%S**	**50%**	**90%**	**%S**
S. aureus (2169)	0.03	0.06	100.0	1	1	100.0	0.25	0.25	>99.9	1	1	>99.9	≤0.25	≤0.25	90.7
MSSA (1669)	0.03	0.06	100.0	1	1	100.0	0.25	0.25	99.9	1	1	100.0	≤0.25	≤0.25	97.7
MRSA (500)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	1	99.8	≤0.25	>2	67.4
Vancomycin (MIC, ≥2 mg/L; 15)	0.06	0.06	100.0	2	2	100.0	0.5	0.5	93.3	1	1	100.0	≤0.25	>2	80.0
Vancomycin (MIC, ≤1 mg/L; 2154)	0.03	0.06	100.0	1	1	100.0	0.25	0.25	100.0	1	1	>99.9	≤0.25	≤0.25	90.8
MDR (179)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	1	99.4	>2	>2	12.8
Non-MDR (1990)	0.03	0.06	100.0	1	1	100.0	0.25	0.25	100.0	1	1	100.0	≤0.25	≤0.25	97.7
Coagulase-negative staphylococci[F] (381)	0.03	0.06	100.0	1	2	100.0	0.25	0.5	99.5	0.5	1	99.5	≤0.25	>2	66.9
MSCoNS (83)	0.03	0.06	100.0	1	2	100.0	0.25	0.5	98.8	0.5	1	100.0	≤0.25	≤0.25	98.8
MRCoNS (298)	0.03	0.06	100.0	1	2	100.0	0.25	0.5	99.7	0.5	1	99.3	≤0.25	>2	58.1
Vancomycin (MIC, ≥2 mg/L; 177)	0.06	0.06	100.0	2	2	100.0	0.5	0.5	98.9	0.5	1	98.9	≤0.25	>2	54.2
Vancomycin (MIC, ≤1 mg/L; 204)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	0.5	1	100.0	≤0.25	>2	77.9
Teicoplanin (MIC, ≥8 mg/L; 53)	0.06	0.06	100.0	2	2	100.0	0.5	0.5	100.0	0.5	1	96.2	≤0.25	>2	54.7
Teicoplanin (MIC, ≤4 mg/L ;328)	0.03	0.06	100.0	1	2	100.0	0.25	0.5	99.4	0.5	1	100.0	≤0.25	>2	68.9
MDR (177)	0.06	0.06	100.0	2	2	100.0	0.5	0.5	100.0	0.5	1	98.9	>2	>2	33.9
Non-MDR (204)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	99.0	0.5	1	100.0	≤0.25	≤0.25	95.6

MDR = multidrug-resistant (ie, isolates displaying resistance phenotype to methicillin and at least three classes of drugs, except for daptomycin; non-susceptible phenotypes); MRCoNS = methicillin-resistant coagulase-negative staphylococci; MRSA = methicillin-resistant *S. aureus*; MSCoNS = methicillin-susceptible coagulase-negative staphylococci; MSSA = methicillin-susceptible *S. aureus*; S = susceptible.
[d]Telavancin breakpoint against *S. aureus* according to the labeling supplement for the product VIBATIV® (ie, ≤0.12 mg/L for susceptible; also applied for CoNS). Breakpoint criteria for comparator agents were those from EUCAST.
[f]Includes *S. capitis* (16 strains), *S. caprae* (four strains), *S. cohnii* (one strain), *S. epidermidis* (222 strains), *S. haemolyticus* (49 strains), *S. hominis* (41 strains), *S. lugdunensis* (21 strains), S. *pasteuri* (one strain), *S. pettenkoferi* (one strain), S. *saprophyticus* (eight strains), *S. schleiferi* (one strain), *S. sciuri* (two strains), *S. simulans* (seven strains), *S. warneri* (five strains), and *S. xylosus* (two strains).

CONCLUSIONS

- Invasive infections caused by *S. aureus* isolates exhibiting elevated vancomycin MIC results (ie, 2 mg/L) have been reported to be refractory to vancomycin monotherapy, despite being considered susceptible according to the breakpoints established by international regulatory agencies.
- Telavancin inhibited all *S. aureus* at the U.S. Food and Drug Administration breakpoint for susceptibility (ie, ≤0.12 mg/L), a concentration approximately eight- and 64-fold lower than the predicted free (unbound) trough (~1 mg/L) and peak (~8 mg/L) levels in plasma, respectively, that is achieved following standard once-daily administration of the recommended dosage.
- Similar potencies were documented for telavancin against CoNS, including less susceptible and MDR subsets from European hospitals and adjacent geographic regions. In addition, telavancin demonstrated *in vitro* activity greater than comparators against this challenge set of organisms.

REFERENCES

1. VIBATIV® [package insert]. South San Francisco, CA: Theravance, Inc.; 2009. Available at: http://www.vibativ.com. Accessed March 19 2015.
2. Health Canada. PRVIBATIV®. Available at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2010_vibativ_107792-eng.pdf, 2010. Accessed March 19 2015.
3. Clinigen Healthcare Ltd. VIBATIV: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001240/WC500115364.pdf, 2014. Accessed March 19 2015.
4. Clinical and Laboratory Standards Institute 2015. *Approved Standard* M07-A10: Tenth edition. Wayne, PA, USA. Accessed March 19 2015.
5. Clinical and Laboratory Standards Institute 2015. M100-S25. 25th *Informational Supplement*. Wayne, PA, USA.
6. European Committee on Antimicrobial Susceptibility Testing 2015. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed March 19 2015.
7. Mendes RE, et al. *Diagn Microbiol Infect Dis.* 2015.

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