Poster # P1356

Analysis of the activity of telavancin tested against a global collection of *Staphylococcus aureus* clinical isolates responsible for documented hospital-acquired pneumonia (2014)

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ABSTRACT

Background: Telavancin is approved in the United States for use in hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by *S. aureus*, including MRSA when other alternatives are not suitable. Telavancin is also approved in the European Union for nosocomial pneumonia (NP), including ventilator associated pneumonia (VAP) caused by MRSA when other alternatives are not suitable. This study evaluated telavancin *in vitro* activity against *S. aureus* causing HABP in patients hospitalized in a worldwide network of medical centres.

Methods: A total of 1,722 *S. aureus* isolates recovered from medical centers belonging to a surveillance network in North America (1,189), Europe (329), Latin America (128) and Asia-Pacific (APAC) regions (76) were included. Isolates deemed responsible for HABP/VABP per local guidelines were submitted to a central laboratory and subjected to bacterial identification and susceptibility testing (reference broth microdilution). MIC breakpoint interpretation used the FDA (telavancin), CLSI and/or EUCAST criteria. MRSA isolates displaying resistance phenotype to at least three additional classes of drugs were considered multidrug-resistant (MDR).

Results: Telavancin had consistent MIC_{50} and MIC_{90} values (0.03 and 0.06 mg/L, respectively) against the overall *S. aureus* population and each of the resistance subsets analysed. A slightly higher MIC_{50} result was noted for telavancin against those isolates displaying a vancomycin MIC of 2 mg/L compared with those with a vancomycin MIC of ≤1 mg/L. Telavancin (MIC_{50}/MIC_{90}, 0.03-0.06/0.06 mg/L) showed MIC_{50} and MIC_{90} results 16- to 32-fold lower than linezolid (MIC_{50}/MIC_{90}, 1/1 mg/L) and vancomycin (MIC_{50}/MIC_{90}, 1/1 mg/L) against the overall MRSA or MDR subsets, with equivalent results when these isolates were stratified by geographical region. Telavancin (100.0% susceptible) and linezolid, teicoplanin, trimethoprim-sulfamethoxazole and vancomycin had *in vitro* coverage against the overall MRSA (96.1 - 100.0% susceptible) or MDR groups (92.7 - 100.0% susceptible). Trimethoprim-sulfamethoxazole had a lower susceptibility rate (77.3% susceptible) against MDR isolates from Europe compared to isolates from other geographic regions (90.9 - 94.5% susceptible), while tetracycline varied from 93.9 - 97.0% in Latin America to 82.6 - 88.9% in North America, 54.5 - 59.1% in Europe and 12.5% in the APAC region. Only telavancin (MIC_{50}/MIC_{90}, 0.06/0.06 mg/L; 100.0% susceptible) and linezolid (MIC_{50}/MIC_{90}, 1/1 mg/L; 93.3% susceptible) remained highly active with no trend for decreased susceptibility against *S. aureus* exhibiting vancomycin MIC of 2 mg/L, while 100.0 and 86.7% of these isolates were considered susceptible to teicoplanin based on CLSI and EUCAST breakpoints, respectively.

Conclusions: Telavancin (100.0% susceptible) demonstrated potent *in vitro* activity against a global and contemporary (2014) collection of *S. aureus* isolates causing HABP, regardless of resistance phenotype/subset, including isolates with vancomycin MIC of 2 mg/L. This *in vitro* activity was consistently greater than comparator agents.

INTRODUCTION

Hospital-acquired bacterial pneumonia (HABP) is the second most common nosocomial infection in the United States (USA) and is a leading cause of mortality among hospital-acquired infections. The rate of HABP has been reported to be between 5 and 10 cases per 1,000 admissions in the USA, with the incidence of ventilator-associated bacterial pneumonia (VABP) being much higher. Rates for HABP in Europe have been estimated to be approximately 3 cases per 1,000 admissions. The mortality rate for HABP is high, reaching >50% for VABP in some settings despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide range of preventive measures.

The distribution of pathogens causing HABP can vary within units in the same hospital, as well as from institution to institution, both within countries and between nations. However, methicillin-resistant *Staphylococcus aureus* (MRSA) is commonly responsible for HABP among patients in USA and European intensive care units (ICU). Although there has been a general decline in the rates of MRSA bacteraemia in certain European countries, MRSA was reported to cause 16% of HABP.

Telavancin is approved in the USA for HABP and VABP due to *S. aureus* (methicillin-susceptible [MSSA] and MRSA) when other alternatives are unsuitable, and in Europe for treatment of MRSA nosocomial pneumonia when other alternatives are unsuitable. This study reports an updated *in vitro* activity analysis for telavancin and comparator agents against *S. aureus* causing HABP in patients hospitalized in a worldwide network of medical centres.

MATERIALS AND METHODS

- **Bacterial strain collection.** A total of 1,722 *S. aureus* isolates recovered from medical centres belonging to a surveillance network in North America (1,189), Europe (329), Latin America (128) and Asia-Pacific (APAC) regions (76) were included. All isolates were deemed responsible for HABP/VABP per local guidelines. Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Program during 2014. 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. Testing was performed using panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, USA). These panels provide telavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% Polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Affirmation of the MIC values was performed by concurrent testing of CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212). MIC breakpoint interpretation used current CLSI and EUCAST criteria. MRSA isolates displaying resistance phenotype to at least three classes of drugs other than β-lactam agents were considered multidrug-resistant (MDR).

RESULTS

- MRSA and MDR rates among *S. aureus* from the USA, Europe, APAC and Latin America respectively were, as follows (% MRSA/% MDR): 43.8/45.1%, 25.8/25.9%, 47.4/66.6% and 39.1/66.0% (data not shown).
- Telavancin had consistent MIC_{50} and MIC_{90} values (0.03 and 0.06 mg/L, respectively) against the *S. aureus* population and each of the resistance subsets analysed (**Table 1**). A slightly higher MIC_{50} result was noted for telavancin against those isolates displaying a vancomycin MIC of 2 mg/L compared with those with a vancomycin MIC of ≤1 mg/L.
- Telavancin (100.0% susceptible) and linezolid, teicoplanin, trimethoprim-sulfamethoxazole and vancomycin had *in vitro* coverage against the MRSA (96.1 - 100.0% susceptible) or MDR groups (92.7 - 100.0% susceptible; **Table 2**).
- Telavancin (MIC_{50}/MIC_{90}, 0.03-0.06/0.06 mg/L) showed MIC_{50} and MIC_{90} results 16- to 32-fold lower than linezolid (MIC_{50}/MIC_{90}, 1/1 mg/L) and vancomycin (MIC_{50}/MIC_{90}, 1/1 mg/L) against the MRSA or MDR subsets (**Table 2**).
- Similar susceptibility results were obtained for telavancin (100.0% susceptible), vancomycin (100.0% susceptible), and linezolid (98.7 - 100.0% susceptible) when tested against MRSA and MDR isolates stratified by geographical region (**Figures 1 and 2**).
- MDR phenotypes among *S. aureus* isolates from the USA, Europe and Latin America were dominantly due to clindamycin, erythromycin and levofloxacin resistance (**Figure 2**), whereas among isolates from the APAC region resistance to clindamycin, erythromycin, levofloxacin, gentamicin and tetracycline was commonly observed.
- Trimethoprim-sulfamethoxazole had a lower susceptibility rate (77.3% susceptible) against MDR isolates from Europe compared to isolates from other geographic regions (90.9 - 94.5% susceptible), while tetracycline varied from 93.9 - 97.0% in Latin America to 82.6 - 88.9% in North America, 54.5 - 59.1% in Europe and only 12.5% in the APAC region (**Figure 2**).
- Only telavancin (MIC_{50}/MIC_{90}, 0.06/0.06 mg/L; 100.0% susceptible) and linezolid (MIC_{50}/MIC_{90}, 1/1 mg/L; 93.3% susceptible) remained highly active with no trend toward decreased susceptibility against *S. aureus* exhibiting vancomycin MIC of 2 mg/L, while 100.0% and 86.7% of these isolates were considered susceptible to teicoplanin based on CLSI and EUCAST breakpoints, respectively (**Table 2**).

Table 1. Antimicrobial activity and MIC distributions for telavancin when tested against 1,722 *S. aureus* clinical isolates, as part of the international telavancin surveillance program.

Organism/Phenotype[a]	MIC (mg/L)		Number (cumulative %) inhibited at telavancin MIC (mg/L) of:			
(number tested)	50%	90%	≤0.015	0.03	0.06	0.12
S. aureus (1,722)	0.03	0.06	112 (6.5)	1179 (75.0)	427 (99.8)	4 (100.0)
MSSA (1,030)	0.03	0.06	71 (6.9)	708 (75.6)	251 (100.0)	
MRSA (692)	0.03	0.06	41 (5.9)	471 (74.0)	176 (99.4)	4 (100.0)
MDR (314)	0.03	0.06	18 (5.7)	184 (64.3)	109 (99.0)	3 (100.0)
Non-MDR (378)	0.03	0.06	23 (6.1)	287 (82.0)	67 (99.7)	1 (100.0)
Vancomycin MIC ≤1 mg/L (1,707)	0.03	0.06	111 (6.5)	1174 (75.3)	419 (99.8)	3 (100.0)
Vancomycin MIC=2 mg/L (15)	0.06	0.06	1 (6.7)	5 (40.0)	8 (93.3)	1 (100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant, defined as MRSA (methicillin [oxacillin]-resistant) resistant to three or more drug classes in addition to β-lactam agents.

CONCLUSIONS

- Telavancin demonstrated potent *in vitro* activity (100.0% susceptible) against a global and contemporary (2014) collection of *S. aureus* isolates causing HABP, regardless of resistance phenotype/subset, including isolates with decreased susceptibility to vancomycin.
- MRSA and MDR rates were lowest among isolates from Europe and highest among those from the APAC region. In addition, MRSA and MDR isolates from APAC and Latin America demonstrated lowest susceptibility rates to clindamycin, erythromycin and gentamicin.
- Telavancin *in vitro* activity against MRSA and MDR isolates was consistently greater than comparator agents. This data supports the use of telavancin for treatment of patients with HABP/VABP caused by *S. aureus*, regardless of resistance phenotype or reduced susceptibility to vancomycin.

ACKNOWLEDGEMENTS

- The research and publication process was supported by Theravance Biopharma Antibiotics, Inc. Poster production support was coordinated by AlphaBioCom, funded by Theravance Biopharma Antibiotics, Inc.

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Table 2. Antimicrobial activity of telavancin and comparator agents tested against a global collection of MRSA and MDR clinical isolates responsible for documented hospital-acquired pneumonia (2014).

Organism (number tested)/ Antimicrobial agent[a]	MIC (mg/L)			% Susceptible/%Intermediate/%Resistant[b]					
	Range	50%	90%	CLSI			EUCAST		
MRSA (692)									
Telavancin	≤0.015 — 0.12	0.03	0.06	100.0	-	-[c]	100.0	-	0.0
Clindamycin	≤0.25 — >2	≤0.25	>2	56.6	0.4	42.9	56.1	0.6	43.4
Erythromycin	≤0.12 — >16	>16	>16	14.5	6.5	79.0	15.1	1.0	83.9
Gentamicin	≤1 — >8	≤1	>8	88.2	0.4	11.4	87.6	-	12.4
Levofloxacin	≤0.12 — >4	>4	>4	18.6	0.4	80.9	18.6	0.4	80.9
Linezolid	≤0.12 — >8	1	1	99.6	-	0.4	99.6	-	0.4
Oxacillin	>2 — >2	>2	>2	0.0	-	100.0	0.0	-	100.0
Teicoplanin	≤2 — 8	≤2	≤2	100.0	0.0	0.0	98.6	-	1.4
Tetracycline	≤0.5 — >8	≤0.5	8	89.7	0.6	9.7	86.7	2.7	10.6
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	96.1	-	3.9	96.1	0.6	3.3
Vancomycin	0.25 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
MDR (314)									
Telavancin	≤0.015 — 0.12	0.03	0.06	100.0	-	-	100.0	-	0.0
Clindamycin	≤0.25 — >2	>2	>2	6.4	1.0	92.7	5.4	1.0	93.6
Erythromycin	1 — >16	>16	>16	0.0	3.2	96.8	1.0	0.3	98.7
Gentamicin	≤1 — >8	≤1	>8	76.4	1.0	22.6	75.5	-	24.5
Levofloxacin	0.25 — >4	>4	>4	0.6	0.0	99.4	0.6	0.0	99.4
Linezolid	≤0.12 — >8	1	1	99.0	-	1.0	99.0	-	1.0
Oxacillin	>2 — >2	>2	>2	0.0	-	100.0	0.0	-	100.0
Teicoplanin	≤2 — 8	≤2	≤2	100.0	0.0	0.0	97.1	-	2.9
Tetracycline	≤0.5 — >8	≤0.5	>8	81.8	0.6	17.5	76.4	5.1	18.5
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	92.7	-	7.3	92.7	1.3	6.1
Vancomycin	0.25 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
***S. aureus* with vancomycin MIC = 2 mg/L (15)**									
Telavancin	≤0.015 — 0.12	0.06	0.06	100.0	-	-	100.0	-	0.0
Clindamycin	≤0.25 — >2	>2	>2	40.0	0.0	60.0	40.0	0.0	60.0
Erythromycin	0.25 — >16	>16	>16	33.3	6.7	60.0	33.3	0.0	66.7
Gentamicin	≤1 — >8	≤1	>8	73.3	6.7	20.0	73.3	-	26.7
Levofloxacin	≤0.12 — >4	>4	>4	40.0	0.0	60.0	40.0	0.0	60.0
Linezolid	0.25 — >8	1	1	93.3	-	6.7	93.3	-	6.7
Oxacillin	≤0.25 — >2	>2	>2	46.7	-	53.3	46.7	-	53.3
Teicoplanin	≤2 — 8	≤2	4	100.0	0.0	0.0	86.7	-	13.3
Tetracycline	≤0.5 — >8	≤0.5	>8	86.7	0.0	13.3	66.7	20.0	13.3
TMP-SMX	≤0.5 — >4	≤0.5	4	86.7	-	13.3	86.7	6.7	6.7

a. MRSA = methicillin-resistant *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole; MDR = multidrug resistance (defined as MRSA resistant to three or more drug classes in addition to β-lactam agents).
b. Breakpoint criteria according to CLSI (M100-S26, 2016) and EUCAST, as available.
c. - = Breakpoint not available.

Figure 1. Percentage of susceptibility for telavancin and comparator agents (EUCAST criteria) tested against a collection of MRSA isolates recovered from four geographic regions.

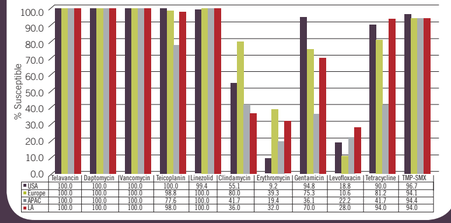

Figure 2. Percentage of susceptibility for telavancin and comparator agents (EUCAST criteria) tested against a collection of MRSA isolates displaying a MDR phenotype recovered from four geographic regions.