Antimicrobial Spectrum of Activity of Telavancin and Comparator Agents Tested Against Methicillin-Resistant *Staphylococcus aureus* Recovered From United States and European Hospitals Over a 3-Year Sampling Period (2007–2009)

Rodrigo E. Mendes, Helio S. Sader*, Mike Janechek, Ronald N. Jones
JMI Laboratories, North Liberty, IA, USA

Contact information:
Helio S. Sader, PhD, MD
JMI Laboratories
North Liberty, IA 52317, USA
Phone: 319-665-3370
Fax: 319-665-3371
E-mail: helio-sader@jmilabs.com

ABSTRACT (REVISED)

Objectives. To monitor the activities of telavancin and comparators against methicillin-resistant *Staphylococcus aureus* (MRSA) collected from the United States (USA) and Europe over a 3-year period (2007–2009). Telavancin was recently approved in the USA and Canada for treatment of complicated skin and skin-structure infections (cSSSI) caused by Gram-positive pathogens in adult patients. This lipoglycopeptide has shown potent in vitro activity against staphylococci, including multidrug-resistant (MDR) strains.

Methods. 4077 and 1334 MRSA were collected from the USA (42 hospitals) and Europe (29 hospitals; 13 countries), respectively. Isolates were submitted to a coordinator monitoring laboratory where species identifications were confirmed by standard algorithms and Vitek 2, when necessary. Isolates were tested for susceptibility against telavancin and comparators by reference Clinical and Laboratory Standards Institute (CLSI) methods (M07-A8, 2009). Interpretive criteria were those from CLSI (M100-S20, 2010) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2009). Telavancin minimum inhibitory concentration (MIC) values were interpreted according to the breakpoint for susceptibility approved by the US Food and Drug Administration (FDA) for *S. aureus* (≤1 mg/L).

Results. MRSA were recovered from bacteremia (38.5%), SSSI (36.2%), pneumonia (18.0%) and other infection sites (7.3%). MRSA rates ranged from 56.2% in 2007 to 52.0% in 2009 in the USA, and from 28.3% in 2007 to 22.7% in 2008 in Europe. Among European countries, the MRSA rates varied considerably, ranging from 0.6% in Sweden to 64.7% in Greece. Telavancin was consistently active against MRSA from the USA and Europe over the study period (MIC_{90}, 0.25 mg/L; 100.0% susceptible; see **Table**). Resistance to teicoplanin was noted (0.5%) and these isolates were mostly from the USA (43.8%) and Turkey (17.5%). Daptomycin (MIC_{90}, 0.5 mg/L), linezolid (MIC_{90}, 2 mg/L) and trimethoprim/sulfamethoxazole (TMP/SMX; MIC_{90}, ≤0.5 mg/L) were also active against MRSA. Quinupristin/dalfopristin (Q/D) MIC_{90} values increased 1 doubling dilution among USA and European MRSA. Susceptibility rates to gentamicin were higher in the USA (≥95.6% susceptible) compared to Europe (80.8–86.9% susceptible).

	MIC_{90} (mg/L) / % susceptible[a]						
	USA (number tested)			Europe (number tested)			
Antimicrobial Agents	2007 (1560)	2008 (1277)	2009 (1240)	2007 (366)	2008 (650)	2009 (318)	Overall (5411)
Telavancin	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0	0.25/100.0
Vancomycin	1/99.9	1/100.0	1/100.0	1/100.0	1/100.0	1/100.0	1/100.0
Teicoplanin	≤2/99.9	≤2/99.9	≤2/99.9	≤2/99.7	≤2/100.0	≤2/99.4	≤2/99.9
Daptomycin	0.5/99.9	0.5/99.6	0.5/100.0	0.5/100.0	0.5/100.0	0.5/100.0	0.5/99.9
Linezolid	2/99.9	2/100.0	2/99.8	2/100.0	2/100.0	2/100.0	2/99.9
Q/D	0.5/99.8	0.5/99.4	1/99.6	0.5/98.9	1/98.9	1/99.7	0.5/99.5
TMP/SMX	≤0.5/97.4	≤0.5/99.0	≤0.5/98.3	≤0.5/99.5	≤0.5/98.9	≤0.5/98.1	≤0.5/98.3
Clindamycin	>2/63.0	>2/62.3	>2/67.3	>2/72.1	>2/62.9	>2/69.5	>2/64.8
Gentamicin	≤2/95.6	≤2/97.8	≤2/97.4	>8/86.9	>8/80.8	>8/86.8	≤2/93.6
Tetracycline	≤2/93.9	≤2/94.9	≤2/93.3	≤2/92.9	>8/80.9	≤2/93.4	≤2/92.3

[a]Interpretive criteria were those from EUCAST (2009), except for telavancin where the susceptible breakpoint approved by the US FDA for *S. aureus* (≤1 mg/L) was applied.

Conclusions. Telavancin exhibited sustained potency when tested against MRSA from the USA and Europe over a 3-year surveillance period. Vancomycin, daptomycin, linezolid, and quinupristin/dalfopristin were also active against the tested contemporary strains; however, telavancin showed overall MIC_{90} values at least 2-fold lower when compared to these agents. These data emphasize the importance of continued longitudinal surveillance to monitor the activities of marketed antimicrobial agents, mainly against MDR strains.

INTRODUCTION

- Methicillin resistance among *Staphylococcus aureus* (MRSA) currently occurs in approximately 70% of the isolates recovered from United States (USA) intensive care units and to a lesser extent in Europe.[1]
- Hospital-acquired MRSA isolates usually display resistance phenotypes to other classes of antimicrobial agents, such as macrolides, lincosamides, and fluoroquinolones, limiting the therapeutic options.[2]
- A community-acquired (CA) MRSA clone (USA300) has recently emerged and disseminated in the USA and elsewhere.[3]
  - USA300 isolates have been identified in a variety of community populations[1,2] and are currently responsible for approximately 80% of the skin and skin-structure infections (SSSI) in the USA.[3]
  - CA-MRSA isolates have also been implicated in severe infections, such as pneumonia, sepsis, and necrotizing fasciitis.[4]
- This change in the MRSA epidemiology has modified the empirical therapies utilized in recent years, including a greater use of vancomycin for the treatment of staphylococcal infections.[2]
- However, poor clinical responses to vancomycin therapy associated with infections caused by isolates displaying elevated vancomycin minimum inhibitory concentration (MIC) values (>1 mg/L) have been reported.[5]
- Telavancin, an intravenous semi-synthetic lipoglycopeptide, was approved in the USA and Canada for the treatment of complicated SSSI (cSSSI) caused by susceptible Gram-positive organisms, including MRSA, in adult patients.[6]
- Telavancin is under regulatory review for the treatment of nosocomial pneumonia in the USA and Europe. In addition, this drug is also under regulatory review for the treatment of complicated skin and soft tissue infections in Europe.
- The aim of this study was to monitor the activities of telavancin and comparator agents tested against MRSA clinical isolates collected from the USA and Europe over a 3-year period (2007–2009).

MATERIALS AND METHODS

Bacterial strain collection

- A total of 4077 and 1334 non-duplicate MRSA were collected from the USA (42 hospitals) and Europe (29 hospitals; 13 countries), respectively, as part of the international telavancin surveillance program.
- Isolates were submitted to a monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) according to a prevalence mode design. MRSA originated mostly from bacteremia (38.5%), SSSI (36.2%), pneumonia (18.0%), and other less prevalent infection sites (7.3%).
- Species identifications were confirmed by the monitoring laboratory using standard algorithms and the automated Vitek 2 system (bioMérieux, Hazelwood, Missouri, USA), when necessary.

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by using the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations.[7]
- Susceptibility testing was performed using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth.
- Validation of the MIC values was performed by concurrent testing of CLSI-recommended (M100-S20, 2010)[8] quality control (QC) strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213.
- Interpretation of MIC results was in accordance with published CLSI (M100-S20)[8] and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2009)[9] breakpoint criteria. Telavancin susceptible breakpoint for *S. aureus* (≤1 mg/L) approved by the US Food and Drug Administration (FDA) was applied.[6]
- *S. aureus* isolates included in this investigation were those displaying oxacillin MIC values >2 mg/L, as determined by the reference broth microdilution method (CLSI; M100-S20, 2010). In addition, methicillin-susceptible *S. aureus* (MSSA) were included for comparison purposes.

RESULTS

- MRSA rates in the USA were 56.2% in 2007, 51.8% in 2008, and 52.0% in 2009, while European MRSA rates over the same period were 28.3, 26.0, and 22.7%, respectively. Rates of methicillin resistance among *S. aureus* in European countries varied considerably, ranging from 0.6% in Sweden to 64.7% in Greece (data not shown).
- Overall, telavancin was consistently active ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible; **Table 1**) against MRSA from the USA and Europe over the study period. In addition, telavancin $MIC_{50/90}$ results (0.12/0.25 mg/L) tested against MRSA were equivalent to those observed among the control group (MSSA; $MIC_{50/90}$, 0.12/0.25 mg/L).
- Vancomycin (MIC_{90}, 1 mg/L), teicoplanin (MIC_{90}, ≤2 mg/L), daptomycin (MIC_{90}, 0.5 mg/L), and linezolid (MIC_{90}, 2 mg/L) were also very active (≥99.4% susceptible) when tested against MRSA from the USA and Europe (**Table 2**).
- A total of 183 (3.4%) MRSA displayed elevated vancomycin MIC values (≥2 mg/L) and the majority of isolates (82.0%) were from the USA (**Table 1**). The telavancin $MIC_{50/90}$ values (0.25/0.5 mg/L) when tested against these strains were only 2-fold higher than the control MSSA and MRSA groups ($MIC_{50/90}$, 0.12/0.25 mg/L).
- Resistance to teicoplanin (0.5% of total) was noted among isolates from both continents when the EUCAST breakpoint was applied (≤2 mg/L for susceptibility; **Table 2**). These teicoplanin-resistant *S. aureus* were mostly from the USA (43.8%) and Turkey (17.5%).
- Daptomycin MIC_{50} results tested against MRSA from the USA and Europe increased from 0.25 mg/L during 2007 and 2008 to 0.5 mg/L in 2009, whereas linezolid MIC_{50} values increased from 1 mg/L during 2007 to 2 mg/L in 2008 and 2009 (data not shown).
- Quinupristin/dalfopristin MIC_{50} values (0.5 mg/L) did not vary, while the MIC_{90} values increased 1 doubling dilution among USA and European MRSA during the study interval (MIC_{90}, 0.5–1 mg/L; **Table 2**).
- Fluoroquinolones (levofloxacin), macrolides (erythromycin), and lincosamides (clindamycin) were not active against tested MRSA isolates (**Table 2**).
- Gentamicin, tetracycline, and trimethoprim/sulfamethoxazole demonstrated a good antimicrobial coverage (93.3–99.0% susceptible; **Table 2**) against MRSA collected from the USA, whereas gentamicin showed suboptimal susceptibility rates when tested against MRSA strains from Europe (80.8–86.9% susceptible).

CONCLUSIONS

- Telavancin demonstrated potent activity ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible) and inhibited all *S. aureus* from the USA and Europe at ≤0.5 mg/L. In addition, telavancin was very potent ($MIC_{50/90}$, 0.25/0.5 mg/L) against isolates with decreased susceptibility to vancomycin (≥2 mg/L).
- No difference in telavancin potencies (MIC_{50}) was observed among geographic regions or years, while comparator agents, such as daptomycin, linezolid, and quinupristin/dalfopristin showed increases in the MIC_{50} or MIC_{90} values during the study interval.
- Telavancin (MIC_{90}, 0.25 mg/L) exhibited 2- to 8-fold greater potency (MIC_{90}) than daptomycin (MIC_{90}, 0.5 mg/L), vancomycin (MIC_{90}, 1 mg/L), and linezolid (MIC_{90}, 2 mg/L).
- These data emphasize the importance of continued longitudinal surveillance to monitor the activities of newly marketed antimicrobial agents, especially against prevalent multidrug-resistant (MDR) strains.

Table 1. Antimicrobial activity of telavancin tested against MRSA and those isolates with reduced susceptibility to vancomycin (MIC, ≥2 mg/L) recovered from the USA and Europe (2007–2009). Telavancin MIC distribution for methicillin-susceptible isolates are shown for comparison purposes

Continent	MIC (mg/L)		Number (cumulative %) inhibited at telavancin MIC (mg/L) of:					
Pathogen or year (number tested)	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5
North America								
MSSA (overall; 3551)	0.12	0.25	3(<0.1)	15(0.5)	258(7.8)	2353(74.0)	869(98.5)	53(100.0)
MRSA (overall; 4077)	0.12	0.25	2(<0.1)	2(0.1)	138(3.5)	2679(69.2)	1163(97.7)	93(100.0)
2007 (1560)	0.12	0.25	0(0.0)	1(0.06)	98(6.3)	1284(88.6)	171(99.6)	6(100.0)
2008 (1277)	0.25	0.25	2(0.2)	1(0.3)	11(1.1)	589(47.2)	634(96.9)	40(100.0)
2009 (1240)	0.12	0.25	0(0.0)	0(0.0)	29(2.3)	806(67.3)	358(96.2)	47(100.0)
MRSA (vancomycin ≥2 mg/L; 150)	0.25	0.5	0(0.0)	0(0.0)	2(1.3)	32(22.7)	85(79.3)	31(100.0)
Europe								
MSSA (overall; 3859)	0.12	0.25	0(0.0)	9(0.2)	186(5.0)	2577(71.8)	1063(99.4)	24(100.0)
MRSA (overall; 1334)	0.12	0.25	0(0.0)	1(<0.1)	96(7.3)	833(69.7)	391(99.0)	13(100.0)
2007 (366)	0.12	0.25	0(0.0)	0(0.0)	61(16.7)	264(88.8)	40(99.7)	1(100.0)
2008 (650)	0.12	0.25	0(0.0)	1(0.1)	20(3.2)	359(58.5)	264(99.1)	6(100.0)
2009 (318)	0.12	0.25	0(0.0)	0(0.0)	15(4.7)	210(70.7)	87(98.1)	6(100.0)
MRSA (vancomycin ≥2 mg/L; 33)	0.25	0.5	0(0.0)	0(0.0)	1(3.0)	9(30.3)	18(84.8)	5(100.0)

MIC, minimum inhibitory concentration; MSSA, methicillin (oxacillin)-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

Table 2. Antimicrobial activity of telavancin and comparator antimicrobial agents against MRSA clinical isolates (2007–2009)

	MIC 90% (mg/L) / % susceptible by CLSI/EUCAST[a]								
Continent	2007			2008			2009		
Antimicrobial agent	MIC 90%	CLSI	EUCAST	MIC 90%	CLSI	EUCAST	MIC 90%	CLSI	EUCAST
North America									
Telavancin[b]	0.25	100.0		0.25	100.0		0.25	100.0	
Vancomycin	1	99.9	99.9	1	100.0	100.0	1	100.0	100.0
Teicoplanin	≤2	100.0	99.9	≤2	100.0	99.9	≤2	100.0	99.9
Daptomycin	0.5	99.9	99.9	0.5	99.6	99.6	0.5	100.0	100.0
Linezolid	2	99.9	99.9	2	100.0	100.0	2	99.8	99.8
Q/D	0.5	99.8	99.8	0.5	99.4	99.4	1	99.6	99.6
Levofloxacin	>4	28.6	28.6	>4	25.9	25.9	>4	30.4	30.4
Erythromycin	>2	7.2	7.3	>2	5.7	6.0	>2	7.6	7.6
Clindamycin	>2	63.4	63.0	>2	62.7	62.3	>2	67.6	67.3
Gentamicin	≤2	95.6	95.6	≤2	97.8	97.8	≤2	97.4	97.4
Tetracycline	≤2	94.2	93.9	≤2	96.1	94.9	≤2	94.6	93.3
TMP/SMX	≤0.5	97.4	97.4	≤0.5	99.0	99.0	≤0.5	98.3	98.3
Europe									
Telavancin[b]	0.25	100.0		0.25	100.0		0.25	100.0	
Vancomycin	1	100.0	100.0	1	100.0	100.0	1	100.0	100.0
Teicoplanin	≤2	100.0	99.7	≤2	100.0	100.0	≤2	100.0	99.4
Daptomycin	0.5	100.0	100.0	0.5	100.0	100.0	0.5	100.0	100.0
Linezolid	2	100.0	100.0	2	100.0	100.0	2	100.0	100.0
Q/D	0.5	98.9	98.9	1	98.9	98.9	1	99.7	99.7
Levofloxacin	>4	9.6	9.6	>4	12.8	12.8	>4	9.1	9.1
Erythromycin	>2	27.3	28.4	>2	32.2	33.4	>2	33.3	34.3
Clindamycin	>2	72.4	72.1	>2	64.2	62.9	>2	70.1	69.5
Gentamicin	>8	86.9	86.9	>8	80.8	80.8	>8	86.8	86.8
Tetracycline	≤2	92.9	92.9	>8	80.9	80.9	≤2	94.0	93.4
TMP/SMX	≤0.5	99.5	99.5	≤0.5	98.9	98.9	≤0.5	98.1	98.1

MIC, minimum inhibitory concentration; Q/D, quinupristin/dalfopristin; TMP/SMX, trimethoprim/sulfamethoxazole.
[a]Criteria for susceptibility as published by the Clinical and Laboratory Standards Institute (M100-S20, 2010) and European Committee on Antimicrobial Susceptibility Testing (2009).
[b]For telavancin, the US FDA approved susceptible breakpoint for *S. aureus* (≤1 mg/L) was applied.

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