Diagnostic Microbiology and Infectious Disease 93 (2019) 167–170

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

In vitro activity of telavancin against *Staphylococcus aureus* causing pneumonia or skin and skin structure infections with concomitant bloodstream infections in United States hospitals (2012–2016)

Leonard R. Duncan *, Robert K. Flamm, Helio S. Sader, Rodrigo E. Mendes

JMI Laboratories, North Liberty, IA 52317

ARTICLE INFO

Article history:
Received 29 June 2018
Received in revised form 18 September 2018
Accepted 23 September 2018
Available online 2 October 2018

Keywords:
Telavancin
Staphylococcus aureus
Bloodstream infection
SSSI
Pneumonia

ABSTRACT

Pneumonia and skin and skin structure infections (SSSIs) caused by *S. aureus* can lead to serious bloodstream infections (BSIs). This study reports on potent telavancin in vitro activity (MIC_{90}, 0.06 μg/mL; 100% susceptible) against 674 US *S. aureus* causing pneumonia or SSSI with associated BSI in hospitalized patients during 2012–2016.

Staphylococcus aureus is one of the most prevalent species that causes bloodstream infections (BSIs) (Laupland et al., 2004), with an annual incidence rate of 4.3–38.2 per 100,000 person-years in the United States (US) (Holland et al., 2014) and 26.1 per 100,000 person-years in several industrialized regions studied outside the United States (Laupland, et al., 2013). *S. aureus* BSIs (SABs) case fatality rates are reported to be 15–50% (Corey, 2009; Holland et al., 2014; Keynan and Rubinstein, 2013; Laupland, et al., 2013; Tong et al., 2015), and in one-third of patients, SAB is associated with complicated infections such as infective endocarditis, osteomyelitis, epidural abscess, and discitis (Corey, 2009; Cosgrove and Fowler, 2008).

Telavancin is a lipoglycopeptide antimicrobial agent with a dual mechanism of action that involves inhibition of peptidoglycan synthesis and disruption of bacterial cell membrane function (Higgins et al., 2005). Telavancin is approved in the United States for the treatment of adult patients with complicated skin and skin structure infections (SSSIs) and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *S. aureus* when alternative treatments are not suitable (VIBATIV Package Insert, 2016).

Several studies have reported positive results for telavancin in the treatment of SABs (Britt et al., 2018; Chaftari et al., 2016; Corey et al., 2015; Friedman et al., 2016; Reilly et al., 2017; Ruggero et al., 2015; Stryjewski et al., 2013, 2014; Wilson et al., 2017), and a phase 3 trial of patients with complicated *S. aureus* bacteremia and right-sided infective endocarditis is registered with clinicaltrials.gov under NCT02208063.

Reviews on the clinical management of *S. aureus* bacteremia emphasize the importance of identifying and eliminating the source of the bloodstream infection and initiating appropriate antimicrobial therapy (Cosgrove and Fowler, 2008; Jensen, 2002; Rongpharpi et al., 2014; Rubinstein, 2008; Tong et al., 2015). *S. aureus* SSSIs are a major source of SAB (~12–23% of cases), but respiratory tract infections, particularly for patients in intensive care, can also lead to SABs (9–10% of cases) (Jensen, 2002; Rubinstein, 2008; Tong et al., 2015; Wilson et al., 2011).

This study provides an analysis of the in vitro activity of telavancin and comparator antimicrobials tested against *S. aureus* isolates associated with pneumonia or SSSI with concomitant bloodstream infections in hospitalized patients in the United States from 2012 to 2016.

A total of 674 *S. aureus* bloodstream infection isolates were collected from 22 sites located in the 9 US Census Bureau divisions as part of the SENTRY Antimicrobial Surveillance Program (https://www.jmilabs.com/sentry-surveillance-program/). The primary sites of infection that led to associated bacteremia were identified as: wound/drainage/ulcer (60%), lower respiratory tract (25%), skin and skin structure (11%), and abscess (4%). Isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) by each participating local

* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: leonard-duncan@jmilabs.com (L.R. Duncan).

https://doi.org/10.1016/j.diagmicrobio.2018.09.011

laboratory. Bacterial identification was confirmed by the reference monitoring laboratory using standard algorithms and supported by matrix assisted laser desorption time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Isolates were tested for susceptibility by the broth microdilution method following Clinical and Laboratory Standards Institute (CLSI) procedures (CLSI, 2018a). Testing for 2012–2014 isolates was performed using dry-form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These validated panels provided telavancin MIC results equivalent to the CLSI broth microdilution method, which includes 0.002% (v/v) polysorbate-80 in the testing medium (CLSI, 2018a). Testing for 2015–2016 isolates was performed using frozen-form panels manufactured by JMI Laboratories (North Liberty, Iowa) using cation-adjusted Mueller-Hinton broth supplemented with 0.002% (v/v) polysorbate-80 for telavancin. To ensure that an adequate number of cells were used for each testing event, bacterial inoculum densities were monitored by colony counts. CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212) were tested in parallel. All QC results were within published acceptable ranges (CLSI, 2018b).

MIC interpretations for telavancin and comparator agents were based on the current version of the CLSI (2018b) M100 document, as available. Methicillin-resistant *S. aureus* (MRSA) isolates were categorized as multidrug resistant (MDR) when a resistant phenotype to 3 or more drug classes in addition to oxacillin was observed. See Table 2 for the list of antimicrobial agents that were used to categorize isolates as MDR, using CLSI interpretive criteria.

Approximately one-half (49.4%) of the *S. aureus* included in the study displayed a methicillin-resistant phenotype (ie, oxacillin MIC value ≥4 μg/mL), and among these, 31.5% had an MDR phenotype (Table 1). Telavancin had MIC_{50} and MIC_{90} values of 0.03 and 0.06 μg/mL, respectively, against the overall collection and subsets of MRSA and MDR MRSA. All isolates were inhibited by telavancin at the susceptible breakpoint (≤0.12 μg/mL; Table 1) (CLSI, 2018b).

One limitation of this study is that we were unable to evaluate the in vitro activity of telavancin against vancomycin-intermediate *S. aureus* (VISA) isolates, because this phenotype is uncommon (Gomes et al., 2015;Mendes et al., 2015, 2017) and was absent from our isolate set. Indeed, only 5 *S. aureus* isolates had vancomycin MIC values of 2 μg/mL, and this subset remained susceptible to telavancin (MIC range, 0.06–0.12 μg/mL; Table 1). Previous reports have described the in vitro activity of telavancin against *S. aureus* isolates with vancomycin MIC values ≥2 μg/mL (Mendes et al., 2015, 2017).

Telavancin MIC_{90} values were 8-fold lower than daptomycin (100% susceptible; $MIC_{50/90}$, 0.25/0.5 μg/mL) and 16-fold lower than ceftaroline (95.9% susceptible; $MIC_{50/90}$, 0.5/1 μg/mL), linezolid (100% susceptible; $MIC_{50/90}$, 1/1 μg/mL), and vancomycin (100% susceptible; $MIC_{50/90}$, 1/1 μg/mL) against the complete isolate set (Table 2). Similar susceptibility rates and potency ratios were observed against the MRSA and MRSA MDR subsets for daptomycin, linezolid, and vancomycin. Ceftaroline was significantly less active against the MRSA MDR subset (78.6% susceptible) compared to the MRSA subset (92.5% susceptible).

The MRSA isolates were largely susceptible to gentamicin, tetracycline, and trimethoprim-sulfamethoxazole (95.2–96.1% susceptible; Table 2). However, of these comparator antimicrobials, only tetracycline exhibited a susceptibility value >90% against the MRSA MDR subset.

In conclusion, telavancin displayed potent in vitro activity against *S. aureus* causing pneumonia or SSSIs with associated BSIs in hospitalized patients during 2012–2016. All *S. aureus* isolates (including MRSA MDR) were susceptible to telavancin, and telavancin was consistently more potent than comparator agents. These in vitro results for telavancin, combined with recent pharmacokinetic and pharmacodynamic data that suggest the current dosing regimen of telavancin is optimized to obtain drug exposures sufficient to treat *S. aureus* (Lepak et al., 2017), support the further investigation of telavancin as a candidate for the treatment of bacteremia.

Acknowledgments

The authors thank L. Flanigan and J. Oberholser (JMI Laboratories) for their assistance in manuscript preparation.

Funding Information

This study was performed by JMI Laboratories and supported by Theravance Biopharma R&D, Inc.

JMI Laboratories contracted to perform services in 2017 for Achaogen, Allecra Therapeutics, Allergan, Amplyx Pharmaceuticals, Antabio, API, Astellas Pharma, AstraZeneca, Athelas, Basilea Pharmaceutica, Bayer AG, BD, Becton, Dickinson and Co., Boston Pharmaceuticals, CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Entasis Therapeutics, Inc., Geom Therapeutics, Inc., GSK, Iterum Pharma, Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., MicuRx Pharmaceuticals, Inc., N8 Medical, Inc., Nabriva Therapeutics, Inc., NAEJA-RGM, Novartis, Paratek Pharmaceuticals, Inc., Pfizer, Polyphor, Ra Pharma, Rempex, Riptide Bioscience Inc., Roche, Scynexis, Shionogi, Sinsa Labs Inc., Skyline Antiinfectives, Sonoran Biosciences, Spero Therapeutics, Symbiotica, Synlogic, Synthes Biomaterials, TenNor Therapeutics, Tetraphase, The

Table 1
Antimicrobial activity and minimal inhibitory concentration (MIC) distributions for telavancin tested against *S. aureus* isolates from the United States causing SSSI or pneumonia with concomitant bloodstream infection.

Organism/organism group (no. of isolates)	No. of isolates and cumulative % inhibited at MIC (μg/mL) of:				MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12		
Staphylococcus aureus (674)	50 (7.4)	526 (85.5)	97 (99.9)	1 (100.0)	0.03	0.06
Methicillin-susceptible (341)	31 (9.1)	263 (86.2)	46 (99.7)	1 (100.0)	0.03	0.06
Vancomycin MIC, 2 μg/mL (3)			2 (66.7)	1 (100.0)	NA	
Vancomycin MIC, <2 μg/mL (338)	31 (9.2)	263 (87.0)	44 (100.0)		0.03	0.06
Methicillin-resistant (333)	19 (5.7)	263 (84.7)	51 (100.0)		0.03	0.06
MDR[a] (105)	6 (5.7)	78 (80.0)	21 (100.0)		0.03	0.06
Vancomycin MIC, 2 μg/mL (2)			2 (100.0)		NA	
Vancomycin MIC, <2 μg/mL (331)	19 (5.7)	263 (85.2)	49 (100.0)		0.03	0.06

[a] MDR, multidrug-resistant, defined as MRSA (methicillin-resistant *S. aureus*) resistant to 3 or more additional antimicrobial classes; NA, not applicable.

Table 2
Antimicrobial activity of telavancin and comparator agents tested against *S. aureus* isolates from the United States causing SSSI or pneumonia with concomitant bloodstream infection.

Group (no. tested)/agent	Antimicrobial activity (μg/mL)			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
All isolates (674)						
Telavancin	0.03	0.06	≤0.015 to 0.12	100.0		
Ceftaroline	0.5	1	0.12 to 2	95.9	4.1	0.0
Clindamycin	≤0.25	>2	≤0.25 to >2	82.9	0.1	16.9
Daptomycin	0.25	0.5	≤0.12 to 1	100.0		
Erythromycin	>8	>8	≤0.12 to >8	40.4	4.2	55.5
Gentamicin	≤1	≤1	≤1 to >8	97.8	0.0	2.2
Levofloxacin	0.25	>4	≤0.12 to >4	59.2	1.5	39.3
Linezolid	1	1	≤0.12 to 2	100.0		0.0
Oxacillin	2	>2	≤0.25 to >2	50.6		49.4
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	96.4	0.7	2.8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	97.5		2.5
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0
MSSA (341)						
Telavancin	0.03	0.06	≤0.015 to 0.12	100.0		
Ceftaroline	0.25	0.25	0.12 to 0.5	100.0	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	95.9	0.0	4.1
Daptomycin	0.25	0.5	≤0.12 to 1	100.0		
Erythromycin	0.25	>8	≤0.12 to >8	69.2	5.3	25.5
Gentamicin	≤1	≤1	≤1 to >8	99.4	0.0	0.6
Levofloxacin	0.25	4	≤0.12 to >4	88.3	0.9	10.9
Linezolid	1	1	0.25 to 2	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	97.7	0.3	2.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	99.1		0.9
Vancomycin	0.5	1	0.25 to 2	100.0	0.0	0.0
MRSA (333)						
Telavancin	0.03	0.06	≤0.015 to 0.06	100.0		
Ceftaroline	0.5	1	0.25 to 2	92.5	7.5	0.0
Clindamycin	≤0.25	>2	≤0.25 to >2	69.7	0.3	30.0
Daptomycin	0.25	0.5	≤0.12 to 1	100.0		
Erythromycin	>8	>8	≤0.12 to >8	10.8	3.0	86.2
Gentamicin	≤1	≤1	≤1 to >8	96.1	0.0	3.9
Levofloxacin	4	>4	≤0.12 to >4	29.4	2.1	68.5
Linezolid	1	1	≤0.12 to 2	100.0		0.0
Tetracycline	≤0.5	1	≤0.5 to >8	95.2	1.2	3.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	95.8		4.2
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0
MDR MRSA (105)						
Telavancin	0.03	0.06	≤0.015 to 0.06	100.0		
Ceftaroline	1	2	0.25 to 2	78.6	21.4	0.0
Clindamycin	>2	>2	≤0.25 to >2	11.4	0.0	88.6
Daptomycin	0.25	0.5	≤0.12 to 0.5	100.0		
Erythromycin	>8	>8	>8 to >8	0.0	0.0	100.0
Gentamicin	≤1	>8	≤1 to >8	89.5	0.0	10.5
Levofloxacin	>4	>4	≤0.12 to >4	1.9	0.0	98.1
Linezolid	1	1	0.5 to 2	100.0		0.0
Tetracycline	≤0.5	2	≤0.5 to >8	92.4	1.9	5.7
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	87.6		12.4
Vancomycin	1	1	0.5 to 1	100.0	0.0	0.0

Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug resistant (defined as MRSA resistant to 3 or more additional drug classes).
[a] Criteria as published by CLSI (2018b).

Medicines Company, Theravance Biopharma, VenatoRx Pharmaceuticals, Inc., Wockhardt, Yukon Pharma, Zai Laboratory, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

References

Britt NS, Tirmizi S, Ritchie DJ, Topal JE, McManus D, Nizet V, et al. Telavancin for refractory MRSA bacteraemia in intermittent haemodialysis recipients. J Antimicrob Chemother 2018;73:764–7.
Chaftari AM, Hachem R, Jordan M, Garoge K, Al Halmal Z, El Zakhem A, et al. Case-control study of telavancin as an alternative treatment for gram-positive bloodstream infections in patients with cancer. Antimicrob Agents Chemother 2016;60:239–44.
Clinical and Laboratory Standards Institute (CLSI). M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. eleventh ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018a.
Clinical and Laboratory Standards Institute (CLSI). M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2018b.
Corey GR. *Staphylococcus aureus* bloodstream infections: definitions and treatment. Clin Infect Dis 2009;48(Suppl. 4):S254–9.
Corey GR, Rubinstein E, Stryjewski ME, Bassetti M, Barriere SL. Potential role for telavancin in bacteremic infections due to gram-positive pathogens: focus on *Staphylococcus aureus*. Clin Infect Dis 2015;60:787–96.
Cosgrove SE, Fowler Jr VG. Management of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 2008;46(Suppl. 5):S386–93.
Friedman B, Bressler A, Cleveland K, Lat A, Helgeson M, Sherman C, et al. Telavancin observational use registry: preliminary results for bacteremia and endocarditis. Crit Care Med 2016;44(Suppl. 12):248.
Gomes DM, Ward KE, LaPlante KL. Clinical implications of vancomycin heteroresistant and intermediately susceptible *Staphylococcus aureus*. Pharmacotherapy 2015;35:424–32.
Higgins DL, Chang R, Debabov DV, Leung J, Wu T, Krause KM, et al. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2005;49:1127–34.
Holland TL, Arnold C, Fowler Jr VG. Clinical management of *Staphylococcus aureus* bacteremia: a review. JAMA 2014;312:1330–41.
Jensen AG. Importance of focus identification in the treatment of *Staphylococcus aureus* bacteraemia. J Hosp Infect 2002;52:29–36.
Keynan Y, Rubinstein E. *Staphylococcus aureus* bacteremia, risk factors, complications, and management. Crit Care Clin 2013;29:547–62.
Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. Crit Care Med 2004;32:992–7.

Laupland KB, Lyytikainen O, Sogaard M, Kennedy KJ, Knudsen JD, Ostergaard C, et al. The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect 2013;19:465–71.

Lepak AJ, Zhao M, Andes DR. Comparative pharmacodynamics of telavancin and vancomycin in the neutropenic murine thigh and lung infection models against *Staphylococcus aureus*. Antimicrob Agents Chemother 2017;61, e00281.

Mendes RE, Farrell DJ, Flamm RK, Sader HS, Jones RN. Analysis of vancomycin susceptibility testing results for presumptive categorization of telavancin. J Clin Microbiol 2015;53:2727–30.

Mendes RE, Sader HS, Smart JI, Castanheira M, Flamm RK. Update of the activity of telavancin against a global collection of *Staphylococcus aureus* causing bacteremia, including endocarditis (2011-2014). Eur J Clin Microbiol Infect Dis 2017;36:1013–7.

Reilly J, Jacobs MA, Lat A, Osmukhina A, Castaneda-Ruiz B. Clinical experience with telavancin for the treatment of patients with bacteremia and endocarditis: Preliminary results from the telavancin observational use registry (TOUR™). ID Week, October 4-8 San Diego, CA, USA: # 1861; 2017.

Rongpharpi SR, Duggal S, Kalita H, Duggal AK. *Staphylococcus aureus* bacteremia: targeting the source. Postgrad Med 2014;126:167–75.

Rubinstein E. *Staphylococcus aureus* bacteraemia with known sources. Int J Antimicrob Agents 2008;32(Suppl. 1):S18–20.

Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis. Infect Dis 2015;47:379–84.

Stryjewski ME, Barriere SL, Rubinstein E, Genter FC, Lentnek AL, Magana-Aquino M, et al. Telavancin versus vancomycin for bacteraemic hospital-acquired pneumonia. Int J Antimicrob Agents 2013;42:367–78.

Stryjewski ME, Lentnek A, O'Riordan W, Pullman J, Tambyah PA, Miro JM, et al. A randomized phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. BMC Infect Dis 2014;14:289.

Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler Jr VG. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603–61.

VIBATIV Package Insert. Package Insert. Available at http://www.vibativ.com, 2016.

Wilson J, Guy R, Elgohari S, Sheridan E, Davies J, Lamagni T, et al. Trends in sources of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: data from the national mandatory surveillance of MRSA bacteraemia in England, 2006-2009. J Hosp Infect 2011;79:211–7.

Wilson SE, Graham DR, Wang W, Bruss JB, Castaneda-Ruiz B. Telavancin in the treatment of concurrent *Staphylococcus aureus* bacteremia: a retrospective analysis of ATLAS and ATTAIN studies. Infect Dis Ther 2017;6:413–22.