Diagnostic Microbiology and Infectious Disease 88 (2017) 184–187

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

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

Activity of telavancin against Gram-positive pathogens isolated from bone and joint infections in North American, Latin American, European and Asia-Pacific nations

Ronald N. Jones [a], Robert K. Flamm [a], Mariana Castanheira [a], Helio S. Sader [a], Jennifer I. Smart [b], Rodrigo E. Mendes [a,*]

[a] JMI Laboratories, North Liberty, Iowa, US
[b] Theravance Biopharma US, Inc., South San Francisco, CA, US

ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 2 March 2017
Accepted 4 March 2017
Available online 8 March 2017

Keywords:
Telavancin
Osteomyelitis
Gram-positive
S. aureus
Surveillance

ABSTRACT

Telavancin was tested against a worldwide collection of Gram-positive pathogens (967) isolated from bone and joint infections (BJI). Most BJI isolates were from the United States (US) (49.9%) followed by Europe (26.4%), Latin America (LATAM; 14.4%), and Asia-Pacific (APAC; 9.3%). Organisms were tested by broth microdilution susceptibility methods. *S. aureus* (66.4%; range of 48.9% in APAC to 71.2% in LATAM) was the most common pathogen and had a 35.7% methicillin resistance (MRSA) rate and telavancin $MIC_{50/90}$ of 0.03/0.06 μg/mL (100% susceptible). MRSA isolates that were daptomycin resistant (0.2%) were telavancin susceptible. CoNS (12.1% of BJI) had telavancin $MIC_{50/90}$ at 0.06/0.06 μg/mL, and 13.7% were teicoplanin resistant. Enterococci had telavancin $MIC_{50/90}$ at 0.12/0.25 μg/mL, but telavancin inhibited vancomycin-susceptible isolates at ≤0.25 μg/mL. All streptococci were telavancin susceptible (MIC_{90}, 0.03–0.06 μg/mL). The in vitro results presented here warrant further investigations to access the role of telavancin for BJI/osteomyelitis treatment caused by Gram-positive cocci.

1. Introduction

Telavancin, a once-daily dosed lipoglycopeptide, has been approved for use in the United States (US), Canada, and Europe (EU) for designated infections caused by Gram-positive organisms (Corey et al., 2014; Masterton et al., 2015; VIBATIV Package Insert, 2016). In the US, this intravenous agent is used for complicated skin and skin structure infections (cSSSI) and hospital acquired (HABP) or ventilator-associated bacterial pneumonias (VABP), all of which may occur with or without concomitant bacteremia (VIBATIV Package Insert, 2016). Organisms susceptible to telavancin include *Staphylococcus aureus* and methicillin-resistant (MRSA) isolates, β-hemolytic *Streptococcus* spp. (*S. agalactiae* and *S. pyogenes*), *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis* (Mendes et al., 2015a, 2015b, 2015c, 2015d). Several clinical studies are ongoing or completed in pediatric and adult patients and through the Telavancin Observational Use Registry (TOUR™) to capture real-world use of telavancin, including bone and joint infections (BJI) due to *S. aureus* (NCT02288234). Several case studies have reported successfully treating BJI using telavancin alone or in combination (Brinkman et al., 2012; Twilla et al., 2011) and favorable outcomes in osteomyelitis in vivo animal models (Chan et al., 2015; Yin et al., 2009).

This investigation assessed the in vitro activity of telavancin using the recently modified broth microdilution method (0.002% polysorbate-80) when tested against a global surveillance collection of Gram-positive pathogens cultured during 2011–2014 (Mendes et al., 2015a). Organisms in all clinical specimens caused BJI, according to the submitting institutions located on 5 continents (4 geographic regions).

2. Materials and methods

2.1. Organisms

A total of 967 BJI isolates were cultured in the US, EU, Latin America (LATAM), and the Asia-Pacific (APAC) regions during 2011–2014, with 217 to 284 sampled BJI isolates per year. *S. aureus* (642) was the most common pathogen observed followed by coagulase-negative *Staphylococcus* spp. (CoNS; 117), β-hemolytic streptococci (βHS; 106), enterococci (65; including 44 *E. faecalis* and 19 *E. faecium*), and viridans group streptococci (VGS; 37 from 13 species groups). Isolates were categorized further by geographic region and additionally by patient age groups (≤17 and ≥18 years old).

* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: rodrigo-mendes@jmilabs.com (R.E. Mendes).

http://dx.doi.org/10.1016/j.diagmicrobio.2017.03.003

The participating laboratory initially performed the bacterial identification, which were confirmed by the monitoring laboratory using standard algorithms supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

2.2. Antimicrobial susceptibility test methods

Isolates were tested for susceptibility by the broth microdilution method following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document (CLSI, 2015). Testing was performed using reference panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, US). These panels provided telavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80 (CLSI, 2016; Mendes et al., 2015a; Ross et al., 2014). Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Concurrent testing of CLSI-recommended quality control (QC) reference strains *S aureus* ATCC 29213 and *E. faecalis* ATCC 29212 (CLSI, 2016; Ross et al., 2014) assured the MIC values obtained. MIC breakpoint interpretation used concurrent CLSI and EUCAST criteria (CLSI, 2016; http://www.eucast.org/clinical_breakpoints/, 2016; VIBATIV Package Insert, 2016).

3. Results

3.1. BJI pathogens sampled

Tables 1–3 list the 5 major groups of Gram-positive organisms associated with BJI. Staphylococci, *S. aureus* (642; 66.4%) and CoNS (117; 12.1%) were the dominant pathogens followed by the streptococci (143; 14.8%) and enterococci (65; 6.7% including 4 species). The methicillin (oxacillin) resistance (MR) rates were 35.7% and 64.1% for *S. aureus* and CoNS, respectively (Tables 1–3). β-hemolytic and viridans group streptococci were quite diverse by species (17 species groups) with the most numerous being *S. pyogenes* (27 isolates) and *S. agalactiae* (49 isolates). The main enterococcal species were *E. faecalis* (44 isolates) and *E. faecium* (19 isolates); see Table 1.

3.2. Telavancin activity tested against all BJI isolates

Table 1 exhibits the uniform monomodal activity of telavancin MIC results when tested against the BJI organism collection for the staphylococci and streptococci. Excluding the enterococci, telavancin inhibited all BJI pathogens at ≤0.12 μg/mL with the MIC_{90} results varying from 0.03 μg/mL (VGS) to 0.06 μg/mL for all other species groups. *Enterococcus* spp. MIC values for telavancin were bimodal (0.12 and 1 μg/mL); MIC values of 1 or 2 μg/mL were from 6 *E. faecium* isolates with a VanA resistance phenotype (vancomycin and teicoplanin MIC values of >4 μg/mL and >8 μg/mL), respectively. A total of 90.8% of enterococci (59 of 65 isolates) or all vancomycin-susceptible enterococci had a telavancin MIC at ≤0.25 μg/mL; i.e. susceptible using available CLSI criteria for vancomycin-susceptible *E. faecalis* (CLSI, 2016). All BJI pathogens except the 6 vancomycin-resistant *E. faecium* (VRE) had telavancin MIC results at ≤0.25 μg/mL (susceptible). Telavancin was 16-fold more active than vancomycin versus the entire BJI isolate sample (Fig. 1).

3.3. Telavancin potencies compared to other Gram-positive organism active agents

Telavancin was compared to numerous other antimicrobials active against Gram-positive pathogens. When tested against *S. aureus* and using the MIC_{50} statistics, telavancin (MIC_{50}, 0.03 μg/mL) was up to 8-fold more potent than daptomycin, clindamycin, erythromycin, and levofloxacin (Table 2) and up to 16-fold more active than vancomycin, gentamicin, and linezolid. The percentage of pathogen susceptibility (100%) favored telavancin, vancomycin and trimethoprim-sulfamethoxazole compared to daptomycin (99.8%), gentamicin (94.5–95.3%), and other tested alternative agents (57.6–95.2%). Similarly, telavancin was active ($MIC_{50/90}$, 0.06/0.06 μg/mL) against the CoNS species.

Telavancin had very low MIC_{50} values for the streptococci associated with BJI at ≤0.015–0.03 μg/mL (Table 2). This level of activity was 4-fold greater than daptomycin when tested against BHS species (MIC_{50}, 0.12 μg/mL) and 32-fold greater versus the VGS species. Vancomycin was 16- to 32-fold less active than telavancin when tested against these *Streptococcus* species (Table 2). Macrolides (erythromycin 48.6–67.9% susceptible), clindamycin (81.1–84.8%) and the tetracyclines (45.7–67.6%) had the most compromised streptococci coverage.

Enterococci were generally less susceptible to telavancin ($MIC_{50/90}$, 0.12/0.25 μg/mL) compared to the other Gram-positive pathogens monitored. However, telavancin (MIC_{50}, 0.12 μg/mL) inhibited all vancomycin-susceptible enterococci at ≤0.25 μg/mL and was 8-fold more active than daptomycin, vancomycin, ampicillin and linezolid (MIC_{50}, 1 μg/mL). All isolates with telavancin MICs at >0.25 μg/mL were *E. faecium* (not indicated for treatment) and had co-resistances to vancomycin and teicoplanin (Table 2).

Table 1
Telavancin activity tested against 967 Gram-positive pathogens causing bone and joint infections (BJI) during 2011—2014 worldwide.

BJI pathogen[a]/Subset (no. tested)	No. isolates (cum. %) inhibited by telavancin at MIC (μg/mL):[f]								MIC (μg/mL)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	50%	90%
S. aureus (642)	34 (5.3)	366 (62.3)	242 (100.0)	–	–	–	–	–	0.03	0.06
methicillin-susceptible (413)	25 (6.1)	240 (64.2)	148 (100.0)	–	–	–	–	–	0.03	0.06
methicillin-resistant (229)	9 (3.9)	126 (59.0)	94 (100.0)	–	–	–	–	–	0.03	0.06
CoNS (117)[b]	19 (16.2)	34 (45.3)	64 (100.0)	–	–	–	–	–	0.06	0.06
Enterococci (65)[c]	7 (10.8)	4 (16.9)	16 (41.5)	31 (89.2)	1 (90.8)	0 (90.8)	4 (96.9)	2 (100.0)	0.12	0.25
βHS (106)[d]	48 (45.3)	39 (82.1)	16 (97.2)	3 (100.0)	–	–	–	–	0.03	0.06
VGS (37)[e]	19 (51.4)	15 (91.9)	3 (100.0)	–	–	–	–	–	≤0.015	0.03

[a] CoNS – coagulase-negative staphylococci, βHS – beta-hemolytic streptococci, and VGS – viridans group streptococci.
[b] Organisms include: unspeciated CoNS (3), *Staphylococcus capitis* (9), *S. cohnii* (1), *S. caprae* (2), *S. epidermidis* (72), *S. haemolyticus* (5), *S. hominis* (5), *S. lugdunensis* (12), *S. pettenkoferi* (1), *S. pseudintermedius* (1), *S. simulans* (2), and *S. warneri* (4).
[c] Organisms include: *Enterococcus avium* (1), *E. faecalis* (44), *E. faecium* (19), and *E. gallinarum* (1), and isolates with a telavancin MIC value at >0.25 μg/mL were *E. faecium* with a VanA-phenotype.
[d] Organisms include: *Streptococcus pyogenes* (27), *S. agalactiae* (49), Group C *Streptococcus* (3), Group G *Streptococcus* (10) and *S. dysgalactiae* (17).
[e] Organisms include: *Streptococcus constellatus* (2), *S. cristatus* (1), *S. gordonii* (3), *S. anginosus* group (1), *S. mitis* group (5), *S. mitis/oralis* (4), *S. parasanguinis* (2), *S. salivarius* (2), *S. anginosus* (7), *S. mitis* (1), *S. oralis* (6), *S. sanguinis* (2), and unspeciated VGS (1).
[f] All indicated species where telavancin breakpoints are available (i.e. *S. aureus*, vancomycin-susceptible *E. faecalis, I. pyogenes, S. agalactiae, S. dysgalactiae* and *S. anginosus* group) and were susceptible to vancomycin were also susceptible telavancin.