Diagnostic Microbiology and Infectious Disease 87 (2017) 133–138

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

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

Surveillance of tedizolid activity and resistance: In vitro susceptibility of Gram-positive pathogens collected over 5 years from the United States and Europe

Mekki Bensaci [a,*], Daniel Sahm [b]

[a] Merck and Co., Inc., Kenilworth, NJ, USA
[b] IHMA Inc., Schaumburg, IL, USA

ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 8 September 2016
Accepted 3 October 2016
Available online 8 October 2016

Keywords:
Oxazolidinones
Surveillance
Antibacterials

ABSTRACT

In vitro activity of tedizolid and comparators against 11,231 Gram-positive clinical isolates from the United States (84 centers) and Europe (115 centers) were summarized as part of the Surveillance of Tedizolid Activity and Resistance program between 2009 and 2013. Susceptibility testing was performed according to Clinical Laboratory and Standards Institute (CLSI) guidelines. Minimum inhibitory concentration (MIC) interpretations were based on CLSI and European Committee on Antimicrobial Susceptibility Testing criteria. Tedizolid inhibited 99.7% of all isolates at MIC ≤0.5 mg/L; activity was similar regardless of methicillin or vancomycin resistance phenotypes of *Staphylococcus aureus* and enterococci, respectively. Tedizolid MIC >1 mg/L was reported for 3 *S. aureus*, 4 coagulase-negative staphylococci, and 2 enterococcal isolates; all streptococci were inhibited at MIC ≤0.5 mg/L. Tedizolid was ≥4-fold more potent than linezolid against all groups, including resistant phenotypes. Tedizolid had potent/stable activity against a large, contemporary collection of Gram-positive clinical isolates, with low rates of resistance.

1. Introduction

Tedizolid phosphate, the prodrug of the oxazolidinone antibacterial tedizolid, is approved in the United States and a number of countries in the European Union for the treatment of acute bacterial skin and skin structure infections (ABSSSI) (Merck Sharp & Dohme Corp., 2015; Merck Sharp & Dohme Ltd., 2016). Two Phase 3 randomized, double-blind clinical trials in patients with ABSSSI demonstrated that the efficacy of tedizolid 200 mg once daily for 6 days was noninferior to that of linezolid 600 mg twice daily for 10 days and that tedizolid was well tolerated (Moran et al., 2014; Prokocimer et al., 2013).

Tedizolid exerts its antibacterial activity by binding to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis (Shaw et al., 2008). Multiple elements in the structure of tedizolid allow additional interactions and tighter binding at the target site, leading to a greater potency of tedizolid compared with linezolid (Locke et al., 2010a; Shaw et al., 2008). Based on MIC values that inhibited the growth of 90% of isolates (MIC_{90}), tedizolid is generally at least 4-fold more potent in vitro than linezolid against susceptible strains of staphylococci, streptococci, and enterococci, including methicillin- and vancomycin-resistant strains (Brown and Traczewski, 2010; Prokocimer et al., 2012; Schaadt et al., 2009; Shaw et al., 2008; Thomson and Goering, 2013).

Tedizolid also shows potent activity against certain linezolid-resistant strains (Livermore et al., 2009; Locke et al., 2010b; Shaw et al., 2008). Resistance to linezolid is not common (Mendes et al., 2014); however, several classes of resistance have been described for oxazolidinones. Chromosomal mutations that affect 23S rRNA or ribosomal proteins L3 and L4 account for the majority of linezolid-resistant strains (Long and Vester, 2012; Prystowsky et al., 2001; Tsiodras et al., 2001). Resistance to linezolid can also be conferred by the plasmid-borne chloramphenicol-florfenicol resistance gene (*cfr*), which leads to methylation of 23S RNA and obstructs the binding of multiple antibacterial agents (Kaminska et al., 2010; Locke et al., 2010b; Long et al., 2006; Smith and Mankin, 2008).

Because of its more compact A-ring hydroxymethyl chain, these conformational changes do not affect tedizolid binding; hence, it retains activity against linezolid-resistant *cfr*-bearing strains (Locke et al., 2010a; Shaw et al., 2008). Recently, a novel oxazolidinone resistance gene (*optrA*) was identified in *Enterococcus faecium* and *Enterococcus faecalis* isolates from China that confers transferable resistance or elevated MICs (when no clinical breakpoints were available) to

Abbreviations: ABSSSI, Acute bacterial skin and skin structure infections; BHS, β-hemolytic streptococci; *cfr*, Chloramphenicol-florfenicol resistance gene; CLSI, Clinical Laboratory and Standards Institute; CoNS, Coagulase-negative streptococci; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IHMA, International Health Management Associates; MIC, Minimum inhibitory concentration; MRSA, Methicillin resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; *optrA*, Oxazolidinone resistance gene; STAR, Surveillance of Tedizolid Activity and Resistance; VGS, Viridans group streptococci; VR, Vancomycin resistant; VS, Vancomycin susceptible.

* Corresponding author: Tel.: +1-781-860-8067; fax: +1-267-305-6529.
E-mail address: Mekki.Bensaci@merck.com (M. Bensaci).

http://dx.doi.org/10.1016/j.diagmicrobio.2016.10.009

oxazolidinones (linezolid and tedizolid) and phenicols (chloramphenicol and florfenicol) (Wang et al., 2015). Whether this resistance mechanism is confirmed, remains to be elucidated. The Surveillance of Tedizolid Activity and Resistance (STAR) study is an ongoing program that compares the in vitro activity of tedizolid and other antibacterial agents against a variety of clinically relevant Gram-positive pathogens and monitors the emergence of resistance. Herein, we report 5 years of STAR program surveillance data (2009–2013) on more than 11,000 isolates collected in the United States and Europe.

2. Methods

2.1. Collection of bacterial isolates

Antibacterial susceptibility testing was conducted by Eurofins Global Central Laboratory (Chantilly, VA, USA) and International Health Management Associates (IHMA), Inc. (Schaumburg, IL, USA). A total of 11,231 nonduplicate, nonconsecutive isolates of staphylococci, streptococci, and enterococci were collected from multiple locations in the United States and Europe, including samples from bloodstream infection, pneumonia in hospitalized patients, skin/soft tissue infection, urinary tract infection, intra-abdominal infection, and respiratory tract infection. The distribution of pathogen species is shown in Table 1. Of the 11,231 isolates, 8912 were collected from 84 hospitals across 9 US census regions and 2319 were collected from 115 sites in 21 European countries.

2.2. Susceptibility testing

Upon receipt of the isolates, species identification was confirmed by Matrix Assisted Laser Desorption Ionization Biotyper (Bruker, Fremont, CA, USA) using the MBT Compass library RUO 5989. Susceptibility testing was performed by broth microdilution in accordance with the guidelines of the Clinical Laboratory and Standards Institute (CLSI) M07-A9 (Clinical and Laboratory Standards Institute, 2012a) and CLSI M100-S22 (Clinical and Laboratory Standards Institute, 2012b) and in accordance with the standard operating procedures at the testing laboratories. Quality control and interpretation of results were performed in accordance with CLSI M100-S22 methods. The MICs of isolates with tedizolid MIC values >0.5 mg/L or linezolid MIC values >4 mg/L were reconfirmed by broth microdilution testing in accordance with CLSI guidelines.

Isolates were tested with MIC panels (ThermoFisher Scientific, Cleveland, OH, USA, and IHMA) of antibiotics appropriate for their class (as listed in Table 2). MIC interpretations for tedizolid were based on CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria. The following CLSI breakpoints were applied: ≤0.5 mg/L (susceptible), 1 mg/L (intermediate) and ≥2 mg/L (resistant) for *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA] isolates); ≤0.5 mg/L (susceptible) for *Enterococcus faecalis*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*; and ≤0.25 mg/L (susceptible) for *Streptococcus anginosus* group isolates (ie, *S. anginosus, S. intermedius*, and *S. constellatus*) (Merck Sharp & Dohme Corp., 2015). The following EUCAST breakpoints were applied (Merck Sharp & Dohme Ltd., 2016): ≤0.5 mg/L (susceptible) and >0.5 mg/L (resistant) for *Staphylococcus* spp. and BHS (β-hemolytic streptococci; groups A, B, C, and G); and ≤0.25 mg/L (susceptible) and >0.25 mg/L (resistant) for *S. anginosus* group isolates. Susceptibility results for comparator agents were interpreted according to CLSI and EUCAST criteria (Clinical and Laboratory Standards Institute, 2015; European Committee on Antimicrobial Susceptibility Testing, 2015).

Table 1
Distribution of organisms collected as part of the STAR program in the United States and Europe, 2009–2013.

	United States	Europe	Total
Staphylococcus aureus	6237	1576	7813
MRSA	2858	376	3234
MSSA	3379	1200	4579
CoNS[a]	504	119	623
BHS	1148	321	1469
Streptococcus agalactiae	568	147	715
Streptococcus pyogenes	530	154	684
Other BHS[b]	50	20	70
VGS[c]	30	21	51
Enterococci	993	282	1275
E. faecalis	702	166	868
E. faecium	267	105	372
Other enterococci[d]	24	11	35
Total	8912	2319	11,231

BHS = β-hemolytic streptococci; CoNS = coagulase-negative staphylococci; MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; VGS = viridans group streptococci.

[a] CoNS include *S. capitis*, *S. caprae*, *S. cohnii*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. intermedius*, *S. pasteuri*, *S. pettenkoferi*, *S. saprophyticus*, *S. schleiferi*, *S. sciuri*, *S. simulans*, *S. warneri*, and *S. xylosus*.

[b] Other BHS include group C, group F, and group G streptococci.

[c] VGS include *S. anginosus*, *S. constellatus*, and nonspeciated *Streptococcus*.

[d] Other enterococci include *E. casseliflavus*, *E. durans*, *E. gallinarum*, *E. mundtii*, *E. raffinosus*, and nonspeciated enterococci.

3. Results

3.1. Overall activity of tedizolid from 2009 to 2013

Over the 5 years tested, tedizolid maintained excellent activity against key target pathogens, including strains with resistant phenotypes. Table 2 shows the activity profile of tedizolid and comparators against target pathogens. Table 3 shows the cumulative percentage of isolates inhibited at each tedizolid MIC value; for comparison, the cumulative percentages of isolates inhibited at each linezolid MIC value are shown in Table 4. Tedizolid MIC values ranged from ≤0.008 to 4 mg/L, and 99.7% of 11,231 isolates were inhibited at MIC ≤0.5 mg/L. Based on MIC_{90}, tedizolid was 4- to 8-fold more potent than linezolid. Tedizolid was active against Gram-positive strains that were resistant to commonly used antibacterial agents.

3.2. Activity of tedizolid against S. aureus

Tedizolid had highly potent activity against *S. aureus* isolates over the 5 years of surveillance, with MIC_{50} and MIC_{90} values 0.25 and 0.5 mg/L, respectively, and modal MIC 0.25 mg/L. Of 7813 isolates, 0.2% were nonsusceptible to tedizolid MIC >0.5 mg/L. For linezolid, the MIC ranged from 0.12 to 8 mg/L, and MIC_{50} and MIC_{90} were both 2 mg/L. Tedizolid was active against *S. aureus* that was resistant to clindamycin, erythromycin, levofloxacin, and trimethoprim/sulfamethoxazole.

Tedizolid maintained activity against *S. aureus* regardless of methicillin susceptibility, with MIC_{50} and MIC_{90} values 0.25 mg/L and 0.5 mg/L, respectively, against both MRSA and methicillin-resistant *Staphylococcus aureus* (MSSA). In comparison, linezolid MIC_{50} and MIC_{90} were 2 mg/L against either MRSA or MSSA. Limited anti-MRSA activity was also reported for clindamycin, erythromycin, and levofloxacin. The proportion of MRSA was higher among *S. aureus* isolates from the United States (45.8%) than among those from Europe (23.9%).

Of 7813 *S. aureus* isolates, 19 were nonsusceptible to tedizolid (based on both CLSI and EUCAST breakpoints), with MIC >0.5 mg/L. Of these tedizolid nonsusceptible isolates, 14 (all with tedizolid MIC 1 mg/L) remained susceptible to linezolid according to CLSI breakpoints, with MICs of 1 mg/L (4 isolates), 2 mg/L (4 isolates), or 4 mg/L (6 isolates). Based on CLSI breakpoints, 16/19 nonsusceptible isolates were considered to have intermediate susceptibility to tedizolid since their MIC was 1 mg/L (CLSI intermediate category defined as MIC = 1 mg/L); however, these isolates were considered resistant based on EUCAST-approved breakpoints (resistant category defined as MIC >0.5 mg/L). The remaining three nonsusceptible isolates were tedizolid