Broad In Vitro Activity Analysis of Tedizolid Compared with Other Agents against a Global Collection of Gram-Positive Isolates Causing Bloodstream Infections (2014–2016)

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INTRODUCTION

- Tedizolid is an oxazolidinone derivative that exhibits potency greater than linezolid when tested against a broad array of gram-positive cocci, including those exhibiting multidrug-resistance phenotypes, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and some linezolid-resistant phenotypes
- Importantly, tedizolid demonstrates activity against linezolid-resistant gram-positive isolates harboring the horizontally transmissible *cfr* gene, but similar to linezolid, both agents are affected by the presence of certain mutations in the 23S rRNA and *optrA*
- Tedizolid is approved to treat acute bacterial skin and skin structure infections (ABSSSI) in the United States and countries in Europe and other regions
- This study assessed the in vitro activities of tedizolid and comparator agents tested against gram-positive isolates responsible for bloodstream infections (BSI) in hospitalized patients in the United States, Europe, Latin America, and the Asia-Pacific region (APAC)

MATERIALS AND METHODS

Bacterial Isolates

- A total of 7,284 non-duplicate, single-patient gram-positive isolates were included (Table 1)
  - Isolates were part of the Surveillance of Tedizolid Activity and Resistance (STAR) Program during 2014–2016 for the United States, Europe, Latin America, and the APAC region
  - Participating sites included 31 medical centers in the United States; 20 European countries/regions (40 sites), including Russia (3 sites), Turkey (2 sites), and Israel (1 site); 4 countries in Latin America (8 sites); and 8 countries in the APAC region (16 sites)
- Isolates were initially identified by the participating laboratory and submitted to a central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) where bacterial identifications were confirmed using standard algorithms and supported by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial Susceptibility Testing

- Isolates were susceptibility tested by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- MIC reading for tedizolid and linezolid was performed according to the CLSI guidelines—ie, the first well at which trailing begins without regard to pinpoint trailing in the wells
- Quality assurance was performed by concurrently testing CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* 29212, and *Streptococcus pneumoniae* ATCC 49619)
  - All QC results were within published acceptable ranges

Table 1. Tedizolid activity against the main organisms and groups of isolates responsible for BSI

Organism / organism group†	No. of isolates inhibited at MIC in µg/mL (cumulative %)									MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>1	50%	90%
Staphylococcus aureus (4,042)		1 <0.1	28 0.7	938 23.9	2,789 92.9	286 100.0				0.12	0.12
MSSA (2,677)		1 <0.1	13 0.5	550 21.1	1,904 92.2	209 100.0				0.12	0.12
MRSA (1,365)			15 1.1	388 29.5	885 94.4	77 100.0				0.12	0.12
Enterococcus spp. (1,758)			8 0.5	93 5.7	999 62.6	633 98.6	20 99.7	3 99.9	2 100.0	0.12	0.25
E. faecalis (1,089)			3 0.3	36 3.6	583 57.1	456 99.0	11 100.0			0.12	0.25
Vancomycin-susceptible (1,067)			2 0.2	35 3.5	569 56.8	450 99.0	11 100.0			0.12	0.25
Vancomycin-resistant (22)			1 4.5	1 9.1	14 72.7	6 100.0				0.12	0.25
E. faecium (620)			4 0.6	54 9.4	385 71.5	164 97.9	8 99.2	3 99.7	2 100.0	0.12	0.25
Vancomycin-susceptible (371)			3 0.8	22 6.7	235 70.1	104 98.1	5 99.5	2 100.0		0.12	0.25
Vancomycin-resistant (249)			1 0.4	32 13.3	150 73.5	60 97.6	3 98.8	1 99.2	2 100.0	0.12	0.25
S. pneumoniae (373)			3 0.8	15 4.8	264 75.6	91 100.0				0.12	0.25
VGS (388)	1 0.3	1 0.5	8 2.6	81 23.5	270 93.0	27 100.0				0.12	0.12
Streptococcus anginosus group (72)	1 1.4	1 2.8	3 6.9	27 44.4	37 95.8	3 100.0				0.12	0.12
BHS (723)				41 5.7	557 82.7	125 100.0				0.12	0.25

† MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; VGS = viridans group streptococci; and BHS = beta-hemolytic streptococci.

- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (2017) and EUCAST (2017)
  - Tedizolid breakpoints for *Streptococcus anginosus* group were applied to viridans group streptococci (VGS), while those for *Streptococcus agalactiae* and *Streptococcus pyogenes* (CLSI) were applied to β-hemolytic streptococci (BHS)

RESULTS

- *S. aureus* was the most common gram-positive pathogen (4,042 isolates; 33.8% MRSA) responsible for BSI followed by *E. faecalis* (1,089 isolates; 2.0% VRE), BHS (723 isolates), *E. faecium* (620 isolates; 40.2% VRE), VGS (388 isolates), and *S. pneumoniae* (373 isolates) (Table 1)
- Overall, tedizolid showed identical MIC_{50} results (0.12 mg/L) regardless of pathogen, group, or antimicrobial susceptibility phenotype (Tables 1 and 2)
- All isolates (100.0%) of methicillin-susceptible *S. aureus* (MSSA), MRSA, *E. faecalis* (CLSI), and BHS were susceptible to tedizolid (Tables 1 and 2)
- Tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L; 100.0/100.0% susceptible [CLSI/EUCAST]), tetracycline ($MIC_{50/90}$, ≤0.5/1 mg/L; 93.1/90.9% susceptible [CLSI/EUCAST]), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.7/99.7% susceptible [CLSI/EUCAST]), ceftaroline ($MIC_{50/90}$, 1/1 mg/L; 90.3/90.3% susceptible [CLSI/EUCAST]), linezolid ($MIC_{50/90}$, 1/1 mg/L; 100.0/100.0% susceptible [CLSI/EUCAST]), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0/100.0% susceptible [CLSI/EUCAST]) also had acceptable activity (>90% susceptible) against MRSA (Table 2)
- Tedizolid (MIC_{90}, 0.25 mg/L) and tigecycline (MIC_{90}, 0.12 mg/L) were the most potent agents tested against *E. faecalis* (Table 2)
  - Although linezolid (MIC_{90}, 2 mg/L), daptomycin (MIC_{90}, 1 mg/L), ampicillin (MIC_{90}, 2 mg/L), and vancomycin (MIC_{90}, 2 mg/L) were consistently active against *E. faecalis*, these agents had MIC_{90} values 4- to 16-fold higher than tedizolid and tigecycline
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) was also active against *E. faecium*, including VRE ($MIC_{50/90}$, 0.12/0.25 mg/L; 98.8% inhibited by ≤0.5 mg/L [Table 1]); linezolid ($MIC_{50/90}$, 1/2 mg/L; 98.9/99.2% susceptible [CLSI/EUCAST]), and daptomycin ($MIC_{50/90}$, 2/2 mg/L; 99.4% susceptible [CLSI]), were also active against this species
- Tedizolid (MIC_{90}, 0.12–0.25 mg/L), ceftaroline (MIC_{90}, 0.12 mg/L), and vancomycin (MIC_{90}, 0.25–0.5 mg/L) had the lowest MIC_{90} values against *S. pneumoniae* and VGS (Table 2)
- Ceftaroline (MIC_{90}, ≤0.015 mg/L), penicillin (MIC_{90}, ≤0.06 mg/L), tigecycline (MIC_{90}, 0.06 mg/L), daptomycin (MIC_{90}, 0.25 mg/L), and tedizolid (MIC_{90}, 0.25 mg/L) were the most potent antimicrobials against BHS

Table 2. Antimicrobial activity of tedizolid and comparator agents against main organisms and groups of isolates responsible for BSI

Organism/ antimicrobial agent	MIC (mg/L)		CLSI†			EUCAST†		
	50%	90%	%S	%I	%R	%S	%I	%R
MSSA (2,677)								
Tedizolid	0.12	0.12	100.0	0.0	0.0	100.0	—	0.0
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Ceftaroline	0.25	0.25	100.0	0.0	0.0	100.0	—	0.0
Clindamycin	≤0.25	≤0.25	96.8	<0.1	3.1	96.5	0.3	3.2
Daptomycin	0.25	0.5	99.9	—	—	99.9	—	0.1
Erythromycin	0.25	>8	78.7	4.9	16.4	79.2	1.8	19.0
Levofloxacin	0.25	0.5	91.6	0.3	8.1	91.6	—	8.4
Tetracycline	≤0.5	≤0.5	96.6	0.5	3.0	95.4	0.4	4.2
Tigecycline‡	0.06	0.12	100.0	—	—	100.0	—	0.0
TMP-SMX§	≤0.5	≤0.5	99.6	—	0.4	99.6	0.1	0.3
Vancomycin	0.5	1	100.0	0.0	0.0	100.0	—	0.0
MRSA (339)								
Tedizolid	0.12	0.12	100.0	0.0	0.0	100.0	—	0.0
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Ceftaroline	1	1	90.3	9.7	0.0	90.3	—	9.7
Clindamycin	≤0.25	>2	70.1	0.3	29.6	69.9	0.2	29.9
Daptomycin	0.25	0.5	99.7	—	—	99.7	—	0.3
Erythromycin	>8	>8	20.1	5.0	74.9	21.0	1.5	77.5
Levofloxacin	<1	>8	71.6	2.2	26.1	71.6	—	28.4
Tetracycline	≤0.5	1	93.1	1.0	5.9	90.9	1.7	7.4
Tigecycline‡	0.06	0.12	100.0	—	—	100.0	—	0.0
TMP-SMX§	≤0.5	≤0.5	96.2	—	3.8	96.2	0.6	3.2
Vancomycin			100.0	0.0	0.0	100.0	—	0.0
E. faecalis (1,089)								
Tedizolid	0.12	0.25	100.0	—	—	—	—	—
Linezolid	1	2	99.8	0.2	0.0	100.0	—	0.0
Ampicillin	1	2	100.0	—	0.0	99.9	0.1	0.0
Daptomycin	1	1	100.0	—	—	—	—	—
Levofloxacin	1	>8	68.3	0.8	30.9	69.1	—	30.9
Tigecycline‡	0.06	0.12	100.0	—	—	100.0	0.0	0.0
Vancomycin	1	2	98.0	0.1	1.9	98.0	—	2.0
E. faecium (620)								
Tedizolid	0.12	0.25	—	—	—	—	—	—
Linezolid	1	2	98.9	0.3	0.8	99.2	—	0.8
Ampicillin	>8	>8	11.1	—	88.9	10.3	0.8	88.9
Daptomycin	2	2	99.4	—	—	—	—	—
Levofloxacin	>4	>4	7.9	4.0	88.1	11.9	—	88.1
Vancomycin	1	>16	59.8	0.8	39.4	59.8	—	40.2
S. pneumoniae (373)								
Tedizolid	0.12	0.25	—	—	—	—	—	—
Linezolid	1	1	100.0	—	—	100.0	0.0	0.0
Ceftaroline	≤0.015	0.12	100.0	—	—	99.7	—	0.3
Clindamycin	≤0.25	>1	86.1	0.3	13.7	86.3	—	13.7
Erythromycin	≤0.12	>2	67.3	0.8	31.9	67.3	0.8	31.9
Levofloxacin	1	1	98.9	0.0	1.1	98.9	—	1.1
Tetracycline	≤0.5	>4	81.8	0.8	17.4	81.8	0.8	17.4
TMP-SMX	≤0.5	>4	74.8	9.1	16.1	79.9	4.0	16.1
Penicillin	≤0.06	1	73.5 73.5 96.2	18.2 — 3.8	8.3 26.5¶ 0.0††	73.5 73.5	— 22.8	26.5‡‡ 3.8§§
Vancomycin	0.25	0.25	100.0	—	—	100.0	—	0.0
VGS (388)□□								
Tedizolid	0.12	0.12	100.0	—	—	100.0	—	0.0
Linezolid	1	1	100.0	—	—	—	—	—
Clindamycin	≤0.25	>2	86.9	1.3	11.8	88.2	—	11.8
Daptomycin	0.25	0.5	100.0	—	—	—	—	—
Erythromycin	≤0.12	>4	51.3	1.8	46.9	—	—	—
Levofloxacin	1	2	91.7	1.1	7.2	—	—	—
Tetracycline	≤0.5	>8	64.2	2.1	33.7	—	—	—
Tigecycline‡	≤0.015	0.06	100.0	—	—	—	—	—
TMP-SMX	≤0.5	≤0.5	—	—	—	—	—	—
Vancomycin	0.5	0.5	100.0	—	—	100.0	—	0.0
BHS (723)¶¶								
Tedizolid	0.12	0.25	100.0	—	—	100.0	—	0.0
Linezolid	1	1	100.0	—	—	100.0	0.0	0.0
Ceftaroline	≤0.015	≤0.015	100.0	—	—	100.0	—	0.0
Clindamycin	≤0.25	>2	82.0	0.6	17.4	82.6	—	17.4
Daptomycin	0.12	0.25	100.0	—	—	100.0	—	0.0
Erythromycin	≤0.12	>4	69.9	0.8	29.3	69.9	0.8	29.3
Levofloxacin	0.5	1	99.4	0.1	0.5	99.4	—	0.6
Tetracycline	4	>8	48.8	1.6	49.6	48.6	0.2	51.2
Tigecycline‡	0.03	0.06	100.0	—	—	100.0	0.0	0.0
Vancomycin	0.25	0.5	100.0	—	—	100.0	—	0.0
Penicillin	≤0.06	≤0.06	100.0	—	—	100.0	—	0.0

† Criteria as published by CLSI (2017) and EUCAST (2017). Tedizolid breakpoints for *Streptococcus anginosus* group were applied to viridans group streptococci (VGS), while those for *Streptococcus agalactiae* and *Streptococcus pyogenes* (CLSI) were applied to β-hemolytic streptococci (BHS)
‡ Breakpoints from US FDA Package Insert.
§ TMP-SMX = trimethoprim-sulfamethoxazole.
‖ Using oral breakpoints
¶ Using parenteral, meningitis breakpoints
†† Using parenteral, non-meningitis breakpoints
‡‡ Using meningitis breakpoints
§§ Using non-meningitis breakpoints
□□ Organisms include: *Streptococcus anginosus* (48), *S. anginosus* group (14), *S. australis* (5), *S. bovis* group (5), *S. constellatus* (6), *S. cristatus* (1), *S. equinus* (1), *S. gallolyticus* (39), *S. gordonii* (16), *S. infantarius* (1), *S. infantis* (1), *S. intermedius* (4), *S. lutetiensis* (7), *S. massiliensis* (1), *S. mitis* (4), *S. mitis* group (67), *S. mitis/oralis* (39), *S. mutans* (5), *S. oralis* (30), *S. parasanguinis* (23), *S. salivarius* (20), *S. salivarius* group (13), *S. salivarius/vestibularis* (5), *S. sanguinis* (29), *S. vestibularis* (4)
¶¶ Organisms include: *S. agalactiae* (340), *S. dysgalactiae* (135), *S. pyogenes* (248)

CONCLUSIONS

- Overall, tedizolid was highly active when tested against this global collection of gram-positive pathogens causing BSI or groups of pathogens
- Tedizolid retained activity against MRSA, VRE, and other resistant gram-positive organisms causing BSI
  - This feature holds special importance against *E. faecium*, as isolates causing BSI have become as prevalent as *E. faecalis*
- A favorable pharmacodynamic profile along with potent in vitro activity may suggest tedizolid is a promising candidate for treating BSI caused by gram-positive isolates, especially VRE *E. faecium*

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