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Activity of Tedizolid against Gram-Positive Clinical Isolates Causing Infections in Europe and Surrounding Areas (2014-2015)

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Abstract

Background: Tedizolid is currently approved to treat acute bacterial skin and skin structure infections (ABSSSI), with a Phase 3 clinical trial in nosocomial pneumonia ongoing. Activities of tedizolid and comparator agents were evaluated against gram-positive isolates responsible for SSSI, pneumonia, and bloodstream infections.

Material/methods: A total of 8,268 nonduplicate, single-patient gram-positive isolates were collected from 20 European countries/regions (39 sites), including Russia (3 sites), Turkey (2 sites), and Israel (1 site). Isolates were submitted to a monitoring laboratory as part of the Surveillance of Tedizolid Activity and Resistance (STAR) program. Identification was confirmed and susceptibility testing was performed by CLSI methods. MIC interpretation used EUCAST criteria.

Results: Overall, tedizolid showed similar MIC_{50} results (0.12 mg/L) regardless of pathogen/group or infection type. Exceptions were noted for coagulase-negative staphylococci (CoNS), *Enterococcus faecalis*, and viridans group streptococci (VGS) causing SSSI, against which tedizolid had MIC_{50} values of 0.06, 0.25, and 0.06 mg/L, respectively. Similar tedizolid MIC_{50} and MIC_{90} results ($MIC_{50/90}$, 0.12/0.12 mg/L) were obtained against methicillin-resistant *Staphylococcus aureus* (MRSA). Daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L) also had consistent MIC results against *S. aureus* across infection types. Tedizolid exhibited MIC_{90} values 4- to 16-fold lower than daptomycin (MIC_{90}, 0.5 mg/L), ceftaroline (MIC_{90}, 1 mg/L), linezolid (MIC_{90}, 1 mg/L), and vancomycin (MIC_{90}, 2 mg/L) against CoNS (52.8%–72.6% methicillin-resistant) and 32- to 64-fold lower than teicoplanin (MIC_{90}, 4-8 mg/L). Only tedizolid, linezolid, and daptomycin were consistently active against enterococci. 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 *Streptococcus pneumoniae* and VGS, whereas ceftaroline (MIC_{90}, ≤0.015 mg/L), penicillin (MIC_{90}, ≤0.06 mg/L), ceftriaxone (MIC_{90}, ≤0.06–0.12 mg/L), and tedizolid (MIC_{90}, 0.12 mg/L) were the most potent against β-haemolytic streptococci. Tedizolid MIC values were also consistent against tested pathogens for both years.

Conclusion: Overall, tedizolid consistently displayed activity greater than comparator agents against gram-positive isolates from Europe, regardless of infection type.

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 linezolid-resistant phenotypes[1]
- Importantly, tedizolid demonstrates activity against linezolid-resistant gram-positive isolates harbouring 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*[2]
- Tedizolid is currently approved to treat acute bacterial skin and skin structure infections (ABSSSI) in the United States and Europe[3,4]
  - Tedizolid is currently in clinical development to treat nosocomial pneumonia with an ongoing Phase 3 clinical trial (NCT02019420), and it's being investigated for bone and joint infections (NCT03009045) and diabetic wound infections (NCT02620787)[1,5]
- This study assessed the in vitro activities of tedizolid and comparator agents tested against gram-positive isolates responsible for SSSI, pneumonia, and bloodstream infections (BSI) in hospitalized patients in Western and Eastern European countries, Russia, and the Middle East

Materials and Methods

- A total of 8,268 nonduplicate, single-patient gram-positive isolates were included
  - These isolates were collected from 20 European countries/regions (39 sites), including Russia (3 sites), Turkey (2 sites), and Israel (1 site)
  - Isolates were part of the Surveillance of Tedizolid Activity and Resistance (STAR) Program during 2014–2015 for Europe and adjacent regions
- 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)
- Isolates were susceptibility tested by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document[6]
- 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[7]
- Quality assurance was performed by concurrently testing CLSI-recommended QC reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* 29212)[7]
  - All QC results were within published acceptable ranges
- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (2016)[7] and EUCAST (2016)[8]

Results

- *S. aureus* was the most common gram-positive pathogen responsible for BSI and SSSI (Tables 1–3), and MRSA rates were higher among *S. aureus* responsible for BSI (26.0%) compared to those causing pneumonia (25.8%) or SSSI (20.7%; data not shown)
- Most pathogens or groups of pathogens exhibited similar susceptibility profiles among infection types, except for coagulase-negative staphylococci (CoNS) and viridans group streptococci (VGS), in which isolates causing BSI tended to be less susceptible to β-lactam agents compared to isolates causing SSSI (Table 4)
- Overall, tedizolid showed similar MIC_{50} results (0.12 mg/L) regardless of pathogen/group or infection type, except for CoNS, *E. faecalis*, and VGS causing SSSI, against which tedizolid had MIC_{50} values of 0.06, 0.25, and 0.06 mg/L, respectively (Tables 1–3)
- Tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), ceftaroline ($MIC_{50/90}$, 1/1-2 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L) also had consistent MIC results against MRSA across infection types (Table 4)
- Against CoNS, tedizolid and tigecycline (MIC_{90}, 0.12 mg/L for both) exhibited MIC_{90} values 4- to 16-fold lower than daptomycin (MIC_{90}, 0.5 mg/L), ceftaroline (MIC_{90}, 1 mg/L), linezolid (MIC_{90}, 1 mg/L), and vancomycin (MIC_{90}, 2 mg/L) and 32- to 64-fold lower than teicoplanin (MIC_{90}, 4-8 mg/L; Table 4)
- 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 4)
  - Although linezolid (MIC_{90}, 1 mg/L), daptomycin (MIC_{90}, 2 mg/L), ampicillin (MIC_{90}, 1–2 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_{90}, 0.12–0.25 mg/L), ceftaroline (MIC_{90}, 0.06–0.12 mg/L), and vancomycin (MIC_{90}, 0.25–0.5 mg/L) had the lowest MIC_{90} values against *Streptococcus pneumoniae* and VGS (Table 4)
- Ceftaroline (MIC_{90}, ≤0.015 mg/L), penicillin (MIC_{90}, ≤0.06 mg/L), tigecycline (MIC_{90}, 0.06 mg/L), ceftriaxone (MIC_{90}, ≤0.06–0.12 mg/L), and tedizolid (MIC_{90}, 0.12 mg/L) were the most potent antimicrobials against β-haemolytic streptococci

Conclusions

- Organisms causing SSSI tended to exhibit a more susceptible antimicrobial susceptibility profile when compared to those causing BSI or pneumonia, which may be associated with a greater number of community pathogens (a more naïve population) causing SSSI
- Overall, tedizolid displayed consistent in vitro potencies when tested against gram-positive pathogens or groups of pathogens in Europe, Russia, and the Middle East, regardless of infection type
- The in vitro activity of tedizolid was similar or greater than comparator agents against gram-positive isolates causing infections in European and adjacent medical centres

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Table 1 Tedizolid activity against the main organisms and groups of isolates responsible for bloodstream infections

Organism / organism group	No. of isolates at MIC (mg/L; cumulative %)									MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>1	50%	90%
S. aureus (1,078)			9 (0.8%)	295 (28.2%)	733 (96.2%)	41 (100.0%)				0.12	0.12
MRSA (280)			3 (1.1%)	89 (32.9%)	178 (96.4%)	10 (100.0%)				0.12	0.12
MSSA (798)			6 (0.8%)	206 (26.6%)	555 (96.1%)	31 (100.0%)				0.12	0.12
CoNS (445)	2 (0.4%)	0 (0.4%)	11 (2.9%)	205 (49.0%)	219 (98.2%)	7 (99.8%)	0 (99.8%)	0 (99.8%)	1 (100.0%)	0.12	0.12
E. faecalis (309)				14 (4.5%)	182 (63.4%)	111 (99.4%)	2 (100.0%)			0.12	0.25
E. faecium (201)			1 (0.5%)	21 (10.9%)	146 (83.6%)	30 (98.5%)	2 (99.5%)	0 (99.5%)	1 (100.0%)	0.12	0.25
Vancomycin-susceptible *E. faecium* (162)			1 (0.6%)	15 (9.9%)	118 (82.7%)	26 (98.8%)	2 (100.0%)			0.12	0.25
Vancomycin-resistant *E. faecium* (39)				6 (15.4%)	28 (87.2%)	4 (97.4%)	0 (97.4%)	0 (97.4%)	1 (100.0%)	0.12	0.25
S. pneumoniae (123)		2 (1.6%)	4 (4.9%)	89 (77.2%)	28 (100.0%)					0.12	0.25
VGS (144)		4 (2.8%)	40 (30.6%)	95 (96.5%)	5 (100.0%)					0.12	0.12
BHS (175)			16 (9.1%)	146 (92.6%)	13 (100.0%)					0.12	0.12

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

Table 2 Tedizolid activity against the main organisms and groups of isolates responsible for pneumonia

Organism / organism group	No. of isolates at MIC (mg/L; cumulative %)						MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	50%	90%
S. pneumoniae (1,150)		4 (0.3%)	5 (0.8%)	84 (8.1%)	830 (80.3%)	227 (100.0%)	0.12	0.25
S. aureus (916)			8 (0.9%)	181 (20.6%)	687 (95.6%)	40 (100.0%)	0.12	0.12
MRSA (236)			5 (2.1%)	53 (24.6%)	173 (97.9%)	5 (100.0%)	0.12	0.12
MSSA (680)			3 (0.4%)	128 (19.3%)	514 (94.9%)	35 (100.0%)	0.12	0.12

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*

Table 3 Tedizolid activity against the main organisms and groups of isolates responsible for skin and skin structure infections

Organism / organism groups	No. of isolates at MIC (mg/L; cumulative %)						MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	50%	90%
S. aureus (2,370)		1 (<0.1%)	0 (<0.1%)	19 (0.8%)	509 (22.3%)	1,714 (94.6%)	127 (100.0%)	0.12	0.12
MRSA (490)				6 (1.2%)	127 (27.1%)	338 (96.1%)	19 (100.0%)	0.12	0.12
MSSA (1,880)		1 (<0.1%)	0 (<0.1%)	13 (0.7%)	382 (21.1%)	1,376 (94.3%)	108 (100.0%)	0.12	0.12
CoNS (284)				19 (6.7%)	147 (58.5%)	116 (99.3%)	2 (100.0%)	0.06	0.12
E. faecalis (250)					3 (2.0%)	110 (46.0%)	135 (100.0%)	0.25	0.25
E. faecium (110)					6 (5.5%)	76 (74.5%)	28 (100.0%)	0.12	0.25
Vancomycin-susceptible *E. faecium* (83)					5 (6.0%)	55 (72.3%)	23 (100.0%)	0.12	0.25
Vancomycin-resistant *E. faecium* (27)					1 (3.7%)	21 (81.5%)	5 (100.0%)	0.12	0.25
VGS (74)				5 (6.8%)	35 (54.1%)	34 (100.0%)		0.06	0.12
BHS (382)					39 (10.2%)	320 (94.0%)	23 (100.0%)	0.12	0.12

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

Table 4 Antimicrobial activity of tedizolid and comparator agents against main organisms and groups of isolates responsible for human infections in Europe and adjacent regions

Organism (no. tested) / antimicrobial agent	MIC_{50}, MIC_{90}, and % susceptible (EUCAST/CLSI)[1] by infection type											
	BSI (no. tested)			Pneumonia (no. tested)				SSSI (no. tested)				
MRSA	(280)			(236)				(490)				
Tedizolid	0.12	0.12	100.0	100.0	0.12	0.12	100.0	100.0	0.12	0.12	100.0	100.0
Linezolid	1	1	100.0	100.0	1	1	100.0	100.0	1	1	100.0	100.0
Ceftaroline	1	2	78.9	78.9	1	2	74.6	74.6	1	1	91.9	91.9
Clindamycin	≤0.25	>2	73.3	73.7	≤0.25	>2	68.4	68.9	≤0.25	>2	72.1	72.3
Daptomycin	0.25	0.5	99.6	99.6	0.25	0.5	100.0	100.0	0.25	0.5	100.0	100.0
Erythromycin	>8	>8	30.7	30.0	>8	>8	29.7	29.2	>8	>8	33.3	32.9
Levofloxacin	>4	>4	14.3	14.3	>4	>4	8.6	8.6	>4	>4	17.8	17.8

Organism (no. tested) / antimicrobial agent	MIC_{50}, MIC_{90}, and % susceptible (EUCAST/CLSI)[1] by infection type											
	BSI (no. tested)			Pneumonia (no. tested)				SSSI (no. tested)				
Tecoplanin	≤2	≤2	99.3	100.0	≤2	≤2	98.7	100.0	≤2	≤2	99.6	100.0
Tetracycline	≤0.5	>8	85.7	86.5	≤0.5	≤0.5	92.3	92.3	≤0.5	8	86.7	86.9
Tigecycline	0.06	0.12	100.0	100.0	0.06	0.12	100.0	100.0	0.06	0.12	100.0	100.0
TMP-SMX	≤0.5	≤0.5	99.3	99.3	≤0.5	≤0.5	97.5	97.5	≤0.5	≤0.5	99.2	99.2
Vancomycin	0.5	1	100.0	100.0	0.5	1	100.0	100.0	0.5	1	100.0	100.0
S. pneumoniae	(123)				(1,150)							
Tedizolid	0.12	0.25	—	—	0.12	0.25	—	—				
Linezolid	1	1	100.0	100.0	1	1	100.0	100.0				
Ceftaroline	≤0.015	0.12	100.0	100.0	≤0.015	0.12	99.4	99.8				
Ceftriaxone	≤0.06	1	85.4	94.3	≤0.06	1	84.2	94.3				
Clindamycin	≤0.25	>1	82.9	82.9	≤0.25	>1	80.7	79.7				
Erythromycin	≤0.12	>2	75.6	75.6	≤0.12	>2	72.0	72.0				
Levofloxacin	1	1	98.4	98.4	1	1	98.3	98.3				
Penicillin	≤0.06	2	70.7	92.7	≤0.06	2	67.3	95.4				
Tetracycline	≤0.5	>4	78.0	78.0	≤0.5	>4	73.7	73.7				
TMP-SMX	≤0.5	>4	73.2	68.3	≤0.5	>4	76.3	69.5				
Vancomycin	0.25	0.25	100.0	100.0	0.25	0.25	100.0	100.0				
CoNS	(445)								(284)			
Tedizolid	0.12	0.12	99.8	—					0.06	0.12	100.0	—
Linezolid	0.5	1	99.8	99.8					0.5	1	100.0	100.0
Ceftaroline	0.25	1	—	—					0.25	1	—	—
Clindamycin	≤0.25	>2	72.1	73.9					≤0.25	>2	79.6	81.0
Daptomycin	0.5	0.5	100.0	100.0					0.25	0.5	100.0	100.0
Erythromycin	>8	>8	36.0	36.0					2	>8	49.6	48.9
Levofloxacin	4	>4	42.0	42.0					0.25	>4	62.0	62.0
Oxacillin	>2	>2	27.4	27.4					1	>2	47.2	47.2
Tecoplanin	≤2	8	86.3	99.6					≤2	4	90.8	98.2
Tetracycline	≤0.5	>8	82.2	86.5					≤0.5	>8	83.0	86.2
Tigecycline	0.06	0.12	100.0	—					0.06	0.12	100.0	—
TMP-SMX	≤0.5	>4	68.8	68.8					≤0.5	>4	76.1	76.1
Vancomycin	1	2	100.0	100.0					1	2	100.0	100.0
E. faecalis	(309)								(250)			
Tedizolid	0.12	0.25	—	—					0.25	0.25	—	—
Linezolid	1	1	100.0	100.0					1	1	100.0	100.0
Ampicillin	1	2	100.0	100.0					1	1	99.6	100.0
Daptomycin	1	2	—	100.0					1	2	—	100.0
Erythromycin	>16	>16	—	4.7					>16	>16	—	9.0
Levofloxacin	2	>4	63.6	61.9					1	>4	72.9	72.9
Tecoplanin	≤2	≤2	98.4	98.4					≤2	≤2	99.2	99.2
Tetracycline	>8	>8	—	21.6					>8	>8	—	20.6
Tigecycline	0.06	0.12	100.0	100.0					0.06	0.12	100.0	100.0
Vancomycin	1	2	98.4	98.4					1	2	98.8	98.8
E. faecium	(201)								(110)			
Tedizolid	0.12	0.25	—	—					0.12	0.25	—	—
Linezolid	1	1	99.5	99.5					1	1	100.0	100.0
Ampicillin	>8	>8	5.0	5.0					>8	>8	8.2	10.0
Daptomycin	2	4	—	100.0					2	4	—	100.0
Erythromycin	>16	>16	—	2.7					>16	>16	—	6.6
Levofloxacin	>4	>4	7.0	5.0					>4	>4	14.5	10.9
Teicoplanin	≤2	>16	83.6	84.6					≤2	>16	82.7	82.7
Tetracycline	≤1	>8	—	53.2					>8	>8	—	43.6
Vancomycin	≤0.5	>16	80.6	80.6					≤0.5	>16	75.5	75.5
VGS	(144)								(74)			
Tedizolid	0.12	0.12	—	—					0.06	0.12	—	—
Linezolid	0.5	1	—	100.0					0.5	1	—	100.0
Amoxicillin-clavulanate	≤1	2	75.5	—					≤1	≤1	89.9	—
Ceftaroline	≤0.015	0.12	—	—					≤0.015	0.06	—	—
Ceftriaxone	0.12	1	83.2	90.2					≤0.25	>2	95.7	95.7
Clindamycin	≤0.25	>2	88.8	88.8					≤0.25	>2	87.0	85.5
Daptomycin	0.25	1	—	99.3					0.25	1	—	100.0
Erythromycin	≤0.12	>4	—	54.9					≤0.12	>4	—	66.2
Levofloxacin	1	2	—	94.4					0.5	1	—	94.2
Penicillin	≤0.06	2	75.7	66.7					≤0.06	0.25	90.5	83.8
Tetracycline	≤0.5	>8	—	75.5					≤0.5	>8	—	69.4
Vancomycin	0.5	0.5	100.0	100.0					0.5	0.5	100.0	100.0
BHS	(175)								(382)			
Tedizolid	0.12	0.12	100.0	—					0.12	0.12	100.0	—
Linezolid	1	1	100.0	100.0					1	1	100.0	100.0
Amoxicillin-clavulanate	≤1	≤1	100.0	100.0					≤1	≤1	100.0	100.0
Ceftaroline	≤0.015	≤0.015	100.0	100.0					≤0.015	≤0.015	100.0	100.0
Ceftriaxone	≤0.06	0.12	100.0	100.0					≤0.06	≤0.06	100.0	100.0
Clindamycin	≤0.25	>2	86.6	85.4					≤0.25	≤0.25	90.2	90.2
Daptomycin	0.12	0.25	100.0	100.0					0.12	0.25	100.0	100.0
Erythromycin	≤0.12	>4	81.0	81.0					≤0.12	4	84.3	84.3
Levofloxacin	0.5	1	97.5	98.7					0.5	1	97.8	99.4
Penicillin	≤0.06	≤0.06	100.0	100.0					≤0.06	≤0.06	100.0	100.0
Teicoplanin	≤2	≤2	100.0	—					≤2	≤2	100.0	—
Tetracycline	≤0.5	>8	51.6	51.6					≤0.5	>8	54.0	55.0
Tigecycline	0.03	0.06	100.0	100.0					0.03	0.06	100.0	100.0
Vancomycin	0.25	0.5	100.0	100.0					0.25	0.5	100.0	100.0

MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-haemolytic streptococci; VGS = viridans group streptococci; TMP-SMX = trimethoprim-sulfamethoxazole; BSI = bloodstream infection; SSSI = skin and skin structure infection

[1] Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2016) and CLSI (2016), as available. Penicillin MIC interpretation against *S. pneumoniae* applied the parenteral CLSI (nonmeningitis) breakpoint. MIC interpretation for tigecycline utilized the FDA breakpoints (results under the CLSI column). '—' breakpoint not available.