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Activity of Novel Oxazolidinone Tedizolid against Clinical Gram-Positive Pathogens Collected from Canadian Hospitals: CANWARD 2013-15

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ABSTRACT

Background: The novel oxazolidinone tedizolid (TZD) has been approved for the treatment of acute bacterial skin and skin structure infections. TZD demonstrates high antibacterial potency, and is active against Gram-positive pathogens including methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA/MRSA). TZD demonstrates numerous positive attributes, including 6-day short course therapy, once daily oral or intravenous dosing with no requirement for dose adjustment across a range of patient factors, a low potential for drug-drug interactions and a well-tolerated safety profile. Currently, TZD is being evaluated in Phase 3 trials for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia.
Methods: Beginning in January 2013, Canadian hospital laboratories (15 sites in 2013, 13 sites in 2014 and 2015) were asked to submit consecutive pathogens from blood, respiratory, urine and wound infections as part of the CANWARD 2013, 2014 and 2015 studies. Antimicrobial susceptibility testing was performed in accordance with CLSI guidelines.
Results: The table below demonstrates the activity of TZD (MIC, µg/mL) and select comparators against Canadian clinical Gram-positive pathogens tested to date during CANWARD 2013, 2014 and 2015 studies:

Organism (n)	Susceptibility*			TZD MIC_{50}/ MIC_{90}	TZD Range	Comparators (MIC_{50}/MIC_{90})			Fold Reduction in TZD MIC_{50}/ MIC_{90} vs. LZD MIC_{50}/MIC_{90}
	%S	%I	%R			LZD	VAN	DAP	
MRSA (417)	99.7	0.3	-	0.25/0.25	0.12-1	2/2	0.5/1	0.25/0.5	8/8
HA-MRSA (248)	99.4	0.6	-	0.25/0.5	0.12-1	2/2	1/1	0.25/0.5	8/4
CA-MRSA (169)	100	-	-	0.25/0.25	0.12-0.5	2/2	0.5/1	0.25/0.5	8/8
MSSA (1,851)	100	-	-	0.25/0.25	0.06-0.5	2/2	1/2	0.25/0.5	8/8
S. epidermidis (200)	NA	NA	NA	0.12/0.12	0.06-0.5	0.5/1	1/2	0.25/0.25	4/8
E. faecalis (308)	100	-	-	0.25/0.25	0.12-0.5	2/2	0.5/1	1/2	8/8
VAN-resistant *E. faecium* (25)	NA	NA	NA	0.25/0.5	0.12-2	2/4	>32/>32	2/2	8/8
VAN-susceptible *E. faecium* (105)	NA	NA	NA	0.25/0.5	0.12-0.5	2/2	0.5/1	2/2	8/4
S. agalactiae (178)	100	-	-	0.25/0.25	≤0.03-0.25	1/2	0.5/0.5	0.25/0.25	4/8
S. pneumoniae (462)	NA	NA	NA	0.12/0.25	≤0.03-0.5	1/2	0.25/0.25	0.12/0.12	8/8
S. pyogenes (137)	100	-	-	0.25/0.25	≤0.03-0.25	1/2	0.5/0.5	0.12/0.12	4/8

*, Interpretive breakpoints defined by CLSI; NA, breakpoints not available; HA, healthcare-associated; CA, community-associated; LZD, linezolid; VAN, vancomycin; DAP, daptomycin.

Conclusion: Based on MIC_{50} and MIC_{90} values, TZD demonstrated four to eight times greater activity than LZD, greater potency than VAN and equal or greater potency against DAP versus Gram-positive organisms isolated from Canadian hospitals in the surveillance period. The highest recorded MIC value for TZD was 2 µg/mL in a VAN-resistant *E. faecium*.

BACKGROUND

Tedizolid phosphate is a novel oxazolidinone antibacterial agent under investigation for the treatment of Gram-positive infections. In vivo, the tedizolid phosphate prodrug is rapidly converted by endogenous phosphatases to the active moiety, tedizolid [1]. Tedizolid has shown clinical efficacy and a favorable tolerability in the treatment of acute bacterial skin and skin structure infections (ABSSSI). Tedizolid has been approved for the treatment of ABSSSI, and is currently being evaluated in Phase 3 trials for the treatment of hospital-acquired and ventilator-associated Gram-positive pneumonia.

Tedizolid has potent activity against a wide range of Gram-positive pathogens, including methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA/MRSA) and *Staphylococcus epidermidis* (MSSE/MRSE), *Enterococcus* spp and *Streptococcus* spp [2]. Of note, tedizolid also shows activity against specific vancomycin- and linezolid-resistant organisms, including MRSA harbouring the *cfr* multi-drug resistance gene [3,4]. Tedizolid also possesses several other positive attributes, including a low potential for drug-drug interactions and a short, 6-day course for ABSSSI therapy. Studies support once daily dosing of tedizolid with both oral and intravenous formulations, without any need for dose adjustment across a range of patient factors [3-6]. Most recently, studies have suggested this treatment be extended to adolescents aged 12-17 in clinical trials [7].

The purpose of this study was to evaluate the in vitro activity of tedizolid and comparators linezolid, vancomycin and daptomycin against a cohort of clinical Gram-positive pathogens collected in Canada during 2013, 2014 and 2015.

MATERIALS & METHODS

Bacterial Isolates

Between January 2013 and December 2015, 9,891 isolates were collected as part of the CANWARD study assessing antimicrobial resistance and pathogen prevalence in Canadian hospitals. Each hospital site was asked to submit clinical isolates (consecutive, one per patient per infection site) from inpatients and outpatients with respiratory, wound, urine and bloodstream infections. Isolates were collected from patients attending hospital clinics, emergency rooms, surgical/medical wards and intensive care units. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where they were subcultured onto appropriate media and stocked in skim milk at -80°C.

Antimicrobial Susceptibility Testing

3,768 Gram-positive isolates were tested for antimicrobial susceptibilities. Following two subcultures from frozen stock, the in vitro activities of tedizolid and comparator agents linezolid, vancomycin and daptomycin were determined using broth microdilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [8]. Minimum inhibitory concentrations (MICs) were determined using custom-designed, in-house prepared 96-well broth microdilution panels. Quality control was performed using *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. MIC interpretive criteria were defined according to CLSI breakpoints [9].

CONCLUSIONS

1. Based on MIC_{90} values, tedizolid was 8-times more potent than linezolid and 2-4-times more potent than vancomycin and daptomycin against MSSA and CA-MRSA. Tedizolid was 4-times more potent than linezolid and had greater than or equal potency to that of vancomycin and daptomycin against HA-MRSA. Tedizolid was 8-times more potent than linezolid, 16-times more potent than vancomycin and twice as potent as daptomycin against *S. epidermidis*.
2. Tedizolid demonstrated 4-8-times greater potency than linezolid against *Streptococcus* species, based on MIC_{90} values. Tedizolid also demonstrated activity that was equivalent to or more potent than vancomycin against *Streptococcus* species.
3. Based on MIC_{90} values, the potency of tedizolid against *E. faecalis* was 8-times greater than linezolid, vancomycin and daptomycin. Tedizolid also demonstrated greater potency than all three comparators against both vancomycin-susceptible and -resistant *E. faecium*.

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RESULTS

Table 1. Activity of tedizolid and comparators against *Staphylococcus* spp. collected from CANWARD 2013-15.

Organism (n), Antimicrobial agent	MIC (µg/mL)					
	50%	90%	Range	%S	%I	%R
Methicillin-susceptible *S. aureus* (1,851)						
Tedizolid	0.25	0.25	0.06 – 0.5	100	-	-
Linezolid	2	2	≤ 0.12 – 4	100	-	-
Vancomycin	0.5	1	≤ 0.12 – 2	100	-	-
Daptomycin	0.25	0.5	0.06 – 1	100	-	-
Healthcare-associated Methicillin-resistant *S. aureus* (252)						
Tedizolid	0.25	0.5	0.12 – 1	99.6	0.4	-
Linezolid	2	2	0.5 – 4	100	-	-
Vancomycin	1	1	≤ 0.12 – 2	100	-	-
Daptomycin	0.25	0.5	0.12 – 1	100	-	-
Community-associated Methicillin-resistant *S. aureus* (171)						
Tedizolid	0.25	0.25	0.12 – 0.5	100	-	-
Linezolid	2	2	0.5 – 4	100	-	-
Vancomycin	0.5	1	0.5 – 4	99.4	0.6	-
Daptomycin	0.25	0.5	0.25 – 1	100	-	-
Methicillin-susceptible *S. epidermidis* (187)						
Tedizolid	0.12	0.12	0.06 – 0.5	NA	NA	NA
Linezolid	0.5	1	0.25 – 2	100	-	-
Vancomycin	1	2	≤ 0.12 – 2	100	-	-
Daptomycin	0.25	0.25	≤ 0.03 – 0.5	100	-	-
Methicillin-resistant *S. epidermidis* (17)						
Tedizolid	0.12*	-	0.06 – 0.12	NA	NA	NA
Linezolid	1*	-	0.5 – 1	100	-	-
Vancomycin	1*	-	1 – 2	100	-	-
Daptomycin	0.25*	-	0.12 – 0.5	100	-	-

* Median MIC value; NA, breakpoints not defined.

Table 2. Activity of tedizolid and comparators against *Streptococcus* spp. collected from CANWARD 2013-15.

Organism (n), Antimicrobial agent	MIC (µg/mL)					
	50%	90%	Range	%S	%I	%R
Streptococcus agalactiae (178)						
Tedizolid	0.25	0.25	≤ 0.03 – 0.25	100	-	-
Linezolid	1	2	0.5 – 2	100	-	-
Vancomycin	0.5	0.5	0.25 – 1	100	-	-
Daptomycin	0.25	0.25	0.06 – 0.5	100	-	-
Streptococcus pneumoniae (462)						
Tedizolid	≤ 0.03	0.25	≤ 0.03 – 0.5	NA	NA	NA
Linezolid	0.25	1	≤ 0.12 – 2	100	-	-
Vancomycin	≤ 0.12	0.25	≤ 0.12 – 0.5	100	-	-
Daptomycin	0.06	0.12	≤ 0.03 – 0.5	NA	NA	NA
Streptococcus pyogenes (137)						
Tedizolid	0.12	0.25	≤ 0.03 – 0.5	100	-	-
Linezolid	1	2	≤ 0.12 – 4	98.5	-	1.5
Vancomycin	0.25	0.5	≤ 0.12 – 0.5	100	-	-
Daptomycin	0.06	0.12	≤ 0.03 – 0.12	100	-	-

NA, breakpoints not defined.

Table 3. Activity of tedizolid and comparators against *Enterococcus* spp. collected from CANWARD 2013-15.

Organism (n), Antimicrobial agent	MIC (µg/mL)					
	50%	90%	Range	%S	%I	%R
Vancomycin-susceptible *Enterococcus faecium* (105)						
Tedizolid	0.25	0.5	0.12 – 0.5	NA	NA	NA
Linezolid	2	2	0.25 – 4	97.1	2.9	-
Vancomycin	0.5	1	0.25 – 2	100	-	-
Daptomycin	2	2	≤ 0.03 – 4	100	-	-
Vancomycin-resistant *Enterococcus faecium* (25)						
Tedizolid	0.25	0.5	0.12 – 1	NA	NA	NA
Linezolid	2	2	1 – 4	92.0	8.0	-
Vancomycin	> 32	> 32	32 – >32	-	-	100
Daptomycin	2	2	0.25 – 4	100	-	-
Enterococcus faecalis (308)						
Tedizolid	0.25	0.25	0.12 – 0.5	100	-	-
Linezolid	2	2	0.5 – 4	99.0	1.0	-
Vancomycin	1	2	0.5 – 2	100	-	-
Daptomycin	1	2	≤ 0.03 – 4	100	-	-

NA, breakpoints not defined.

Table 4. MIC distribution of tedizolid against Gram-positive cocci collected from CANWARD 2013-15.

Organism (n)	Number (percentage) at each MIC					
	≤ 0.03	0.06	0.12	0.25	0.5	1
MSSA (1,851)	-	3 (0.2)	508 (27.4)	1,258 (68.0)	82 (4.4)	-
HA-MRSA (215)	-	-	52 (20.6)	170 (67.5)	29 (11.5)	1 (0.4)
CA-MRSA (171)	-	-	62 (36.3)	107 (62.6)	2 (1.2)	-
MSSE (187)	-	30 (16.0)	143 (76.5)	12 (6.4)	2 (1.1)	-
MRSE (17)	-	1 (5.9)	16 (94.1)	-	-	-
E. faecalis (308)	-	-	24 (7.8)	258 (83.8)	26 (8.4)	-
VS *E. faecium* (105)	-	-	11 (10.5)	76 (72.4)	18 (17.1)	-
VR *E. faecium* (25)	-	-	3 (12.0)	15 (60.0)	6 (24.0)	1 (4.0)
S. agalactiae (178)	1 (0.6)	4 (2.2)	81 (45.5)	92 (51.7)	-	-
S. pneumoniae (462)	39 (8.4)	95 (20.6)	244 (52.8)	83 (18.0)	1 (0.2)	-
S. pyogenes (137)	9 (6.6)	28 (20.4)	76 (55.5)	23 (16.8)	1 (0.7)	-

HA, healthcare-associated; CA, community-associated; VS, vancomycin-susceptible; VR, vancomycin-resistant.

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