

In Vitro Activity of Tedizolid against Gram-Positive Pathogens Isolate in Canadian Hospitals: CANWARD 2013-15

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ABSTRACT

Background: Tedizolid (TZD) is a novel oxazolidinone that has been approved for the treatment of acute bacterial skin and skin structure infections. Additionally, it is currently being evaluated in Phase 3 trials for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia. TZD is active against Gram-positive pathogens, including methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA/MRSA). TZD demonstrates high antibacterial potency, as well as numerous other positive attributes, including short course therapy, once daily oral or intravenous dosing with no requirement for dose adjustment in renal or hepatic dysfunction, a low potential for drug-drug interactions and a well-tolerated safety profile.

Methods: Beginning in January 2013, 15 Canadian hospital laboratories 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 methods.

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 up to April 2015:

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	
MRSA (293)	99.7	0.3	-	0.25/0.25	0.12-1	2/2	0.5/1	8/8
HA-MRSA (179)	99.4	0.6	-	0.25/0.5	0.12-1	2/2	1/1	8/4
CA-MRSA (114)	100	-	-	0.25/0.25	0.12-0.5	2/2	0.5/1	8/8
MSSA (1,247)	100	-	-	0.25/0.25	0.06-0.5	2/2	1/2	8/8
<i>S. epidermidis</i> (129)	NA	NA	NA	0.12/0.12	0.06-0.5	0.5/1	1/2	4/8
<i>E. faecalis</i> (215)	100	-	-	0.25/0.25	0.12-0.5	2/2	>32/>32	8/8
VAN-resistant <i>E. faecium</i> (20)	NA	NA	NA	0.25/0.5	0.12-2	2/4	0.5/1	8/8
VAN-susceptible <i>E. faecium</i> (69)	NA	NA	NA	0.25/0.5	0.12-0.5	2/2	0.5/0.5	8/4
<i>S. agalactiae</i> (124)	100	-	-	0.25/0.25	≤0.03-0.25	1/2	0.25/0.25	4/8
<i>S. pneumoniae</i> (328)	NA	NA	NA	0.12/0.25	≤0.03-0.5	1/2	0.5/0.5	8/8
<i>S. pyogenes</i> (87)	100	-	-	0.25/0.25	≤0.03-0.25	1/2	0.5/0.5	4/8

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

Conclusion: Based on MIC₅₀ and MIC₉₀ values, TZD demonstrated four to eight times greater activity than LZD and greater potency than VAN 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 prodrug that 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. In vivo, tedizolid phosphate is rapidly converted by endogenous phosphatases to the active moiety, tedizolid¹.

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. Of note, tedizolid also shows activity against specific vancomycin- and linezolid-resistant organisms²⁻⁴. Tedizolid possesses several positive attributes, including a low potential for drug-drug interactions and a short, 6-day course for ABSSSI therapy^{2,3}. Studies also support once daily dosing of tedizolid with both oral and intravenous formulations, without any need for dose adjustment across a range of patient factors^{1,5}.

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

MATERIALS & METHODS

Bacterial Isolates

Between January 2013 and July 2015, 8,201 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

2,983 Gram-positive isolates were tested for antimicrobial susceptibilities. Following two subcultures from frozen stock, the in vitro activities of tedizolid and comparator agents linezolid and vancomycin were determined using broth microdilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines⁶. 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 for linezolid and vancomycin were defined according to CLSI breakpoints⁷. Tedizolid data was analyzed using FDA approved breakpoints.

CONCLUSIONS

- Based on MIC₉₀ values, tedizolid was 8-times more potent than linezolid and 4-times more potent than vancomycin against MSSA and CA-MRSA. Tedizolid was 8-times more potent than both linezolid and vancomycin against HA-MRSA. Tedizolid was 8-times more potent than linezolid and 16-times more potent than vancomycin against *S. epidermidis*.
- Tedizolid demonstrated 8-times greater potency than linezolid against *Streptococcus* species, based on MIC₉₀ values. Tedizolid also demonstrated activity that was equivalent to or more potent than vancomycin against *Streptococcus* species.
- Based on MIC₉₀ values, the potency of tedizolid against *E. faecalis* was 8-times greater than both linezolid and vancomycin. Tedizolid also demonstrated greater potency than linezolid and vancomycin 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)			%S	%I	%R
	50%	90%	Range			
Methicillin-susceptible <i>S. aureus</i> (1,539)						
Tedizolid ^a	0.25	0.25	0.06 – 0.5	100	-	-
Linezolid	2	2	≤ 0.12 - 4	100	-	-
Vancomycin	0.5	1	≤ 0.12 - 2	100	-	-
Healthcare-associated Methicillin-resistant <i>S. aureus</i> (215)						
Tedizolid ^a	0.25	0.5	≤ 0.03 – 1	99.5	0.5	-
Linezolid	2	2	0.25 – 4	100	-	-
Vancomycin	1	2	≤ 0.12 – 2	100	-	-
Community- associated Methicillin- resistant <i>S. aureus</i> (141)						
Tedizolid ^a	0.25	0.25	0.12 – 0.5	100	-	-
Linezolid	2	2	1 – 4	100	-	-
Vancomycin	0.5	1	0.5 – 2	100	-	-
Methicillin-susceptible <i>S. epidermidis</i> (120)						
Tedizolid	0.12	0.12	0.06 – 0.5	NA	NA	NA
Linezolid	0.5	1	0.5 – 2	100	-	-
Vancomycin	1	2	≤ 0.12 – 2	100	-	-
Methicillin-resistant <i>S. epidermidis</i> (14)						
Tedizolid	0.12*	-	0.06 – 0.25	NA	NA	NA
Linezolid	1*	-	0.5 – 1	100	-	-
Vancomycin	2*	-	1 – 2	100	-	-

^a Interpretive breakpoints defined by FDA; * Median MIC value; NA, breakpoints not defined.

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

Organism (n), Antimicrobial agent	MIC (µg/mL)			%S	%I	%R
	50%	90%	Range			
Vancomycin- susceptible <i>Enterococcus faecium</i> (81)						
Tedizolid	0.25	0.5	0.12 – 0.5	NA	NA	NA
Linezolid	2	2	0.25 – 4	95.1	4.9	-
Vancomycin	0.5	1	0.12 – 2	100	-	-
Vancomycin-resistant <i>Enterococcus faecium</i> (21)						
Tedizolid	0.25	0.5	0.12 – 1	NA	NA	NA
Linezolid	2	4	1 – 4	90.5	9.5	-
Vancomycin	> 32	> 32	32 – >32	-	-	100
<i>Enterococcus faecalis</i> (264)						
Tedizolid ^a	0.25	0.25	0.12 – 0.5	100	-	-
Linezolid	2	2	0.5 – 4	98.9	1.1	-
Vancomycin	1	2	0.5 – 2	100	-	-

^a Interpretive breakpoints defined by FDA; NA, breakpoints not defined.

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

Organism (n), Antimicrobial agent	MIC (µg/mL)			%S	%I	%R
	50%	90%	Range			
<i>Streptococcus agalactiae</i> (124)						
Tedizolid ^a	0.25	0.25	≤ 0.03 – 0.25	100	-	-
Linezolid	2	2	1 – 2	100	-	-
Vancomycin	0.5	0.5	0.25 – 1	100	-	-
<i>Streptococcus pneumoniae</i> (328)						
Tedizolid	0.12	0.5	≤ 0.03 – 0.5	NA	NA	NA
Linezolid	1	2	≤ 0.12 – 2	100	-	-
Vancomycin	0.25	0.25	≤ 0.12 – 0.5	100	-	-
<i>Streptococcus pyogenes</i> (87)						
Tedizolid ^a	0.12	0.25	0.03 – 0.5	100	-	-
Linezolid	1	2	0.25 – 4	97.7	-	2.3
Vancomycin	0.25	0.5	0.25 – 0.5	100	-	-

^a Interpretive breakpoints defined by FDA; 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 (1,539)	-	2 (0.1)	409 (26.6)	1,052 (68.4)	76 (4.9)	-
HA-MRSA (215)	1 (0.5)	-	39 (18.1)	146 (67.9)	28 (13.0)	1 (0.5)
CA-MRSA (141)	-	-	51 (36.2)	88 (62.4)	2 (1.4)	-
MSSE (120)	-	22 (18.3)	90 (75.0)	6 (5.0)	2 (1.7)	-
MRSE (14)	-	2 (14.3)	11 (78.6)	1 (7.1)	-	-
<i>E. faecalis</i> (264)	-	-	19 (7.2)	221 (83.7)	24 (9.1)	-
VS <i>E. faecium</i> (81)	-	-	8 (9.9)	58 (71.6)	15 (18.5)	-
VR <i>E. faecium</i> (21)	-	-	2 (9.5)	12 (57.1)	6 (28.6)	1 (4.8)
<i>S. agalactiae</i> (124)	1 (0.8)	3 (2.4)	45 (36.3)	75 (60.5)	-	-
<i>S. pneumoniae</i> (328)	31 (9.5)	80 (24.4)	161 (49.1)	55 (16.8)	1 (0.3)	-
<i>S. pyogenes</i> (87)	5 (5.7)	16 (18.4)	47 (54.0)	18 (20.7)	1 (1.1)	-

VR, vancomycin-resistant; VS, vancomycin-susceptible.

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