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In Vitro Activity of Tedizolid Against Canadian Clinical Gram-Positive Pathogens, Including hVISA and the CDC NARSA Strains

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REVISED ABSTRACT

Background: Tedizolid (TZD) is a novel oxazolidinone that has completed two clinical trials for treatment of acute bacterial skin and skin structure infections. TZD is active against Gram-positive (GP) pathogens, including methicillin-susceptible and –resistant *Staphylococcus aureus* (MSSA/MRSA). TZD shares the positive attributes of linezolid (LZD), along with greater potency, shorter dosing regimens and an improved tolerability profile.

Methods: Beginning in January 2013, 13 Canadian hospital laboratories submitted consecutive pathogens from blood, respiratory, urine and wound infections as part of the CANWARD 2013 study. To date, 1210 isolates have been collected. Antimicrobial susceptibility was performed on GP isolates in accordance with CLSI methods. PAP-proven heterogeneous-vancomycin (VAN)-resistant *S. aureus* (hVISA) from Canadian hospitals were also tested, as well as VISA and VAN-resistant *S. aureus* (VRSA) isolates from the CDC Network on Antimicrobial Resistance in *S. aureus* (NARSA).

Results: The table below shows the activity of TZD and comparators against NARSA VRSA and VISA isolates, as well as the first 205 CANWARD isolates:

Isolate Source	Organism (n)[a]	TZD MIC_{50}/MIC_{90}	Comparators (MIC_{50}/MIC_{90})			
			LZD	VAN	DAP	TGC
CANWARD 2013 Study	MRSA (30)	0.12/0.25	1/2	0.5/1	0.25/0.25	0.12/0.25
	MSSA (131)	0.12/0.25	1/2	0.5/1	0.25/0.25	0.12/0.25
	S. epidermidis (4)	0.06*	0.5*	1*	0.12*	0.12*
	E. faecalis (31)	0.25/0.25	2/2	1/2	0.5/1	0.12/0.12
	E. faecium (9)	0.25*	2*	1*	1*	0.06*
CANWARD 2007-2012	hVISA (8)	0.12*	1*	1*	0.25*	0.12*
CDC NARSA Collection	VISA (11)	0.12*	1*	2*	0.5*	0.25*
	VRSA (7)	0.25*	2*	32*	0.25*	0.12*

[a], n for which complete AST data available; LZD, linezolid; VAN, vancomycin; DAP, daptomycin; TGC, tigecycline; * median MIC value

Conclusion: From MIC_{90} values, TZD demonstrated in vitro activity that was equivalent to or more potent than LZD, VAN, DAP and TGC for GP pathogens isolated from Canadian hospitals. TZD also demonstrated potent activity against VISA and VRSA isolates from the CDC NARSA collection.

BACKGROUND

Tedizolid phosphate is a novel oxazolidinone prodrug which has completed clinical trials for treatment of acute bacterial skin and skin structure infections (ABSSSIs). Tedizolid phosphate is rapidly converted to the active moiety tedizolid in vivo [1, 2].The mechanism of action of tedizolid involves inhibition of protein synthesis through interaction with the bacterial 50S ribosomal subunit, effectively inhibiting protein translation [1, 3].

Tedizolid is active against all clinically relevant Gram-positive pathogens, including methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA/MRSA) and *Staphylococcus epidermidis* (MSSE/MRSE), *Enterococcus* species, as well as vancomycin- and linezolid-resistant organisms[1-3]. Tedizolid shares the positive attributes of linezolid, the first oxazolidinone approved for treatment of skin and skin structure infections. However, unlike linezolid, tedizolid phosphate is bactericidal in vivo [1, 2]. It also has a greater potency, shorter dosing regimens, an improved tolerability profile and low potential for resistance [1, 2].

This study evaluated the in vitro activity of tedizolid and relevant comparators against a recent cohort of Gram-positive organisms collected in Canada, as well as against a set of well-characterized isolates from the Centers for Disease Control's Network on Antimicrobial Resistance in *S. aureus* (NARSA) collection.

MATERIALS & METHODS

Bacterial Isolates

Between January and July 2013, 1890 isolates were collected as part of the CANWARD 2013 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. In addition, 11 vancomycin-intermediate *S. aureus* (VISA) and 7 vancomycin-resistant *S. aureus* (VRSA) from the Centers for Disease Control's Network on Antimicrobial Resistance in *S. aureus* (NARSA) collection were tested, as well as 8 population analysis profiling (PAP)-proven heterogenous-vancomycin resistant (hVISA) collected as part of the CANWARD 2007-12 study.

Antimicrobial Susceptibility Testing

Of the 1890 specimens received, 576 Gram-positive pathogens were tested for antimicrobial susceptibilities. Following two subcultures from frozen stock, the in vitro activities of tedizolid and comparator agents linezolid, vancomycin, daptomycin and tigecycline were determined using broth microdilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [4]. 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 and *E. faecalis* ATCC 29212. MIC interpretive criteria were defined according to CLSI breakpoints [5]. Tigecycline MIC values were interpreted using FDA breakpoints.

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RESULTS

Table 1. Activity of tedizolid and comparators against Gram-positive organisms collected from CANWARD 2013.

Organism (n), Antimicrobial agent	MIC (µg/mL) 50%	90%	Range	%S	%I	%R
Methicillin-susceptible *S. aureus* (373)						
Tedizolid	0.25	0.25	0.06 – 1	NA	NA	NA
Linezolid	2	2	0.5 – 16	99.7	-	0.3
Vancomycin	0.5	1	≤ 0.12 - 2	100	-	-
Daptomycin	0.25	0.25	0.06 – 1	100	-	-
Tigecycline[a]	0.12	0.25	0.06 – 1	100	-	-
Methicillin-resistant *S. aureus* (106)						
Tedizolid	0.25	0.25	0.12 – 0.5	NA	NA	NA
Linezolid	2	2	1 – 4	100	-	-
Vancomycin	0.5	1	0.5 – 1	100	-	-
Daptomycin	0.25	0.25	0.12 – 0.5	100	-	-
Tigecycline[a]	0.12	0.25	0.12 – 0.5	100	-	-
Methicillin-susceptible *S. epidermidis* (13)						
Tedizolid	0.12*	-	0.06 – 0.5	NA	NA	NA
Linezolid	1*	-	0.5 – 2	100	-	-
Vancomycin	1*	-	≤ 0.12 – 2	100	-	-
Daptomycin	0.25*	-	0.06 – 0.25	100	-	-
Tigecycline[a]	0.12*	-	≤ 0.03 – 0.25	NA	NA	NA
Methicillin-resistant *S. epidermidis* (2)						
Tedizolid	0.12*	-	0.12 – 0.12	NA	NA	NA
Linezolid	1*	-	1 – 1	100	-	-
Vancomycin	2*	-	2 – 2	100	-	-
Daptomycin	0.38*	-	0.25 – 0.5	100	-	-
Tigecycline[a]	0.25*	-	0.25 – 0.25	NA	NA	NA

Organism (n), Antimicrobial agent	MIC (µg/mL) 50%	90%	Range	%S	%I	%R
Vancomycin-susceptible *Enterococcus faecium* (19)						
Tedizolid	0.25*	-	0.12 – 0.25	NA	NA	NA
Linezolid	2*	-	1 – 2	100	-	-
Vancomycin	0.5*	-	0.5 – 2	-	-	100
Daptomycin	1*	-	1 – 2	100	-	-
Tigecycline[a]	0.12*	-	0.06 – 0.25	NA	NA	NA
Vancomycin-resistant *Enterococcus faecium* (5)						
Tedizolid	0.25*	-	0.12 – 0.25	NA	NA	NA
Linezolid	2*	-	1 – 2	100	-	-
Vancomycin	> 32*	-	32 – >32	-	-	100
Daptomycin	1*	-	1 – 2	100	-	-
Tigecycline[a]	0.12*	-	0.06 – 0.25	NA	NA	NA
Enterococcus faecalis (54)						
Tedizolid	0.25	0.25	0.12 – 0.5	NA	NA	NA
Linezolid	2	2	0.5 – 4	96.3	3.7	-
Vancomycin	1	2	0.5 – 2	100	-	-
Daptomycin	0.5	1	0.12 – 4	100	-	-
Tigecycline[a]	0.12	0.12	0.06 – 0.25	100	-	-

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

Table 2. Activity of tedizolid and comparators against VISA and VRSA from the CDC NARSA collection and hVISA collected from CANWARD 2007-12.

Organism (n), Antimicrobial agent	MIC (µg/mL) Median	Range	%S	%I	%R
NARSA VISA (11)					
Tedizolid	0.12	0.12 – 0.25	NA	NA	NA
Linezolid	1	1 – 2	100	-	-
Vancomycin	2	1 – 4	81.8	18.2	-
Daptomycin	0.25	0.25 – 1	100	-	-
Tigecycline[a]	0.12	0.12 – 0.5	100	-	-
NARSA VRSA (7)					
Tedizolid	0.25	0.12 – 0.25	NA	NA	NA
Linezolid	2	1 – 2	100	-	-
Vancomycin	32	16 – >32	-	-	100
Daptomycin	0.25	0.12 – 0.25	100	-	-
Tigecycline[a]	0.12	0.12 – 0.5	100	-	-
CANWARD hVISA (8)					
Tedizolid	0.12	0.06 – 0.25	NA	NA	NA
Linezolid	1	0.5 – 2	100	-	-
Vancomycin	1	0.5 – 2	100	-	-
Daptomycin	0.25	0.12 – 0.5	100	-	-
Tigecycline[a]	0.12	0.06 – 0.25	100	-	-

[a] Interpretive breakpoints defined by FDA; NA, breakpoints not defined.

Table 3. MIC distribution of tedizolid against Gram-positive cocci collected from CANWARD 2013, CDC NARSA isolates and hVISA collected from CANWARD 2007-12.

Organism (n)	Number (percentage) at each MIC 0.06	0.12	0.25	0.5	1
MSSA (373)	2 (0.5)	137 (36.7)	215 (57.6)	19 (5.1)	1 (0.3)
MRSA (106)		35 (33.0)	66 (62.3)	4 (3.8)	
MSSE (13)	3 (23.1)	8 (61.5)	1 (7.7)	1 (7.7)	
MRSE (2)		2 (100)			
E. faecalis (54)		13 (24.1)	39 (72.2)	3 (5.6)	
VS *E. faecium* (19)		2 (10.5)	13 (68.4)	4 (21.1)	
VR *E. faecium* (5)		1 (20.0)	4 (80.0)		
CANWARD hVISA (8)	1 (12.5)	5 (62.5)	2 (25.0)		
NARSA VISA (11)		7 (63.6)	4 (36.4)		
NARSA VRSA (7)		3 (42.9)	4 (57.1)		

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

CONCLUSIONS

1. Based on MIC_{90} values, tedizolid was 8-times more potent than linezolid and showed activity that was equivalent to or greater than vancomycin, daptomycin and tigecycline against MSSA and MRSA.
2. Tedizolid showed activity that was equivalent to or more potent than linezolid, vancomycin, daptomycin and tigecycline against MSSE and MRSE.
3. Based on MIC_{90} values, the potency of tedizolid was 8-times greater than linezolid against *E. faecalis*. Tedizolid was more potent than linezolid, vancomycin and daptomycin against all *Enterococcus* species.
4. Tedizolid had superior activity to linezolid, vancomycin and daptomycin against CANWARD 2007-12 collected hVISA and CDC NARSA VISA isolates. Against CDC NARSA VRSA isolates, tedizolid was more active than linezolid and vancomycin.

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