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In Vitro Activity of Plazomicin Against Gram-Negative and Gram-Positive Pathogens Isolated from Patients in Canadian Hospitals in 2011: CANWARD Surveillance Study

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ABSTRACT

Background: Plazomicin is a next-generation aminoglycoside, synthetically derived from sisomicin, active against Gram-negative and Gram-positive organisms and currently in clinical development to treat serious bacterial infections. We determined the *in vitro* activity of plazomicin along with a variety of comparators versus Gram-negative and Gram-positive pathogens isolated from January to December 2011 from patients in medical and surgical wards, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals (CANWARD surveillance study).

Methods: Antimicrobial susceptibility testing was performed using in-house broth microdilution panels following the method recommended by CLSI.

Results: The activity of plazomicin and comparators is summarized below.

Organism (n)	MIC_{50}/MIC_{90} (µg/mL)				
	PLAZOMICIN	AMIKACIN	MEROPENEM	TIGECYCLINE	COLISTIN
E. coli All (646)	0.5/1 (≤0.12-2)*	2/4	≤0.03/≤0.03	0.25/0.5	0.25/0.5
E. coli Gent-R (77)	0.5/2 (≤0.12-2)	2/8	≤0.03/≤0.03	0.25/0.5	0.25/0.5
K. pneumoniae All (226)	0.25/0.5 (≤0.12-64)	≤1/≤1	≤0.03/≤0.03	0.5/1	0.25/0.5
K. pneumoniae Gent-R (4)#	0.25 (0.25-64)	2	≤0.03	1	0.5
E. cloacae All (104)	0.25/0.5 (≤0.12-1)	≤1/2	≤0.03/0.12	0.5/1	0.25/>16
E. cloacae Gent-R (7)#	0.5 (0.25-0.5)	≤1	0.12	0.5	0.25
S. marcescens All (69)	0.5/1 (0.25-4)	2/2	0.06/0.06	2/2	>16/>16
S. marcescens Gent-R (1)#	1	16	0.12	2	>16
K. oxytoca All (63)	0.25/0.5 (≤0.12-1)	≤1/≤1	≤0.0.3/≤0.03	0.5/1	0.25/0.5
K. oxytoca Gent-R (0)	-	-	-	-	-
P. mirabilis All (46)	2/4 (≤0.25-8)	2/4	0.06/0.06	4/8	16/>16
P. mirabilis Gent-R (3)#	4 (2-4)	4	0.06	8	>16
P. aeruginosa All (330)	4/16 (≤0.12->64)	4/8	0.5/4	16/>16	1/2
P. aeruginosa Gent-R (22)	16/>64 (2->64)	16/>64	4/32	16/>16	1/4
S. maltophilia All (62)	>64/>64 (2->64)	>64/>64	>32/>32	1/4	16/>16
S. maltophilia Gent-R (40)	64/>64 (8->64)	>64/>64	>32/>32	1/4	16/>16
A. baumannii All (12)	1/8 (0.5-16)	2/4	≤0.5/8	0.25/1	≤0.5/2
A. baumannii Gent-R (1)#	8	>64	>32	2	1
MRSA All (154)	1/1 (0.25-4)	16/32	4/32	0.12/0.25	>16/>16
MRSA Gent-R (3)#	1 (0.5-1)	16	2	0.12	>16
MRSE All (9)#	0.25 (0.25-4)	16	>32	0.25	>16
MRSE Gent-R (7)#	0.25 (0.25-4)	16	>32	0.25	>16

Gent-R, gentamicin-resistant (MIC ≥16µg/mL); #, median MIC; *, range; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

Conclusions: Plazomicin demonstrated potent *in vitro* activity against recent clinical isolates of *Enterobacteriaceae* including strains resistant to gentamicin as well as other antimicrobials including colistin. Plazomicin was active against staphylococci including gentamicin-resistant strains. Plazomicin activity against *P. aeruginosa* and *A. baumannii* was similar to amikacin. Versus MRSA and MRSE, plazomicin and tigecycline were the most active agents. Based on these results, plazomicin may demonstrate promise for the treatment of bacterial infections caused by resistant organisms.

PURPOSE

To determine the *in vitro* activity of plazomicin along with aminoglycoside and non-aminoglycoside comparators versus Gram-negative and Gram-positive pathogens isolated from patients in medical and surgical wards, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals.

INTRODUCTION

Plazomicin (formerly ACHN-490) is a next-generation aminoglycoside that was synthetically derived from sisomicin by appending a hydroxy-aminobutyric acid (HABA) substituent at position 1 and a hydroxyethyl substituent at position 6' [1]. Plazomicin inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. Plazomicin demonstrates activity against both Gram-negative and Gram-positive bacterial pathogens, including isolates harboring all clinically relevant aminoglycoside-modifying enzymes. However, like other aminoglycosides, plazomicin is not active against bacterial isolates expressing ribosomal methyltransferases conferring aminoglycoside resistance. Plazomicin has been reported to demonstrate *in vitro* synergistic activity when combined with daptomycin or ceftobiprole versus methicillin-resistant *Staphylococcus aureus* (MRSA), heteroresistant vancomycin-intermediate *S. aureus* (hVISA), VISA, and vancomycin-resistant *S. aureus* (VRSA) and against *Pseudomonas aeruginosa* when combined with cefepime, doripenem, imipenem, or piperacillin-tazobactam. Results from a phase II randomized, double-blind study in patients with complicated urinary tract infection and acute pyelonephritis including cases with concurrent bacteremia comparing plazomicin 15mg/kg IV once daily for 5 days to levofloxacin 750mg IV for 5 days are anticipated in 2012. Animal and human studies to date have not reported nephrotoxicity or ototoxicity. Given reported increases in bacterial resistance to current antimicrobial agents and the lack of availability of new agents with novel mechanisms, plazomicin may become a welcomed addition to the antibacterial armamentarium pending further positive results from large-scale clinical trials and other required clinical studies.

MATERIALS & METHODS

Study Background and Bacterial Isolates: The isolates tested in this study were obtained from January to December 2011, inclusive, from an ongoing cross-Canada surveillance study (CANWARD 2011; 15 participant sites, www.can-r.ca) organized by the investigators [2,3]. The goal of the CANWARD 2011 study was to assess pathogens and antimicrobial resistance patterns associated with lower respiratory tract, skin/skin structure, urinary, and bacteremic infections in Canadian patients on medical wards, surgical wards, intensive care units, and presenting to emergency rooms and hospital clinics [2,3].

Antimicrobial Susceptibility Testing Methodology: Isolates were tested for antimicrobial susceptibilities using in-house prepared (Department of Clinical Microbiology, Health Sciences Centre, Winnipeg, Canada) 96-well broth microdilution panels according to CLSI M100-S21 (2011) guidelines [2,3].

The antimicrobial agents tested were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made, as described by the CLSI (M07-A8, 2009), in cation-adjusted Mueller-Hinton broth (MHB). Following two subcultures from frozen stock, the MICs of the antimicrobial agents for the isolates were determined by the CLSI broth microdilution method. Colony counts were performed periodically to confirm inocula. Quality control was performed using CLSI recommended (M100-S21) ATCC organisms including: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 27853.

RESULTS

Table 1. *In vitro* activity of Plazomicin and comparators versus Gram-negative bacilli

Organism (no. tested) / antimicrobial agent	MIC (µg/mL)			%		
	50%	90%	Range	S	I	R
E. coli (646)						
Plazomicin	0.5	1	≤0.12 - 4	,a	-	-
Amikacin	2	4	≤1 - 32	99.7	0.3	0.0
Colistin	0.25	0.5	≤0.06 - >16	-	-	-
Gentamicin	≤0.5	32	≤0.5 - >32	87.5	0.6	11.9
Meropenem	≤0.03	≤0.03	≤0.03 - 1	100.0	0.0	0.0
Tigecycline	0.25	0.5	0.12 - 2	100.0	0.0	0.0
Gentamicin-Resistant *E.coli* (77)						
Plazomicin	0.5	1	≤0.12 - 2	-	-	-
Amikacin	2	8	≤1 - 32	98.7	1.3	0.0
Colistin	0.25	0.5	0.5 - 4	-	-	-
Gentamicin	32	>32	16 - >32	0.0	0.0	100.0
Meropenem	≤0.03	≤0.03	≤0.03	100.0	0.0	0.0
Tigecycline	0.25	0.5	0.25 - 1	100.0	0.0	0.0
K. pneumoniae (226)						
Plazomicin	0.25	0.5	≤0.12 - >64	-	-	-
Amikacin	≤1	≤1	≤1 - >64	96.6	0.0	0.4
Colistin	0.25	0.5	0.12 - >16	-	-	-
Gentamicin	≤0.5	≤0.5	≤0.5 - >32	98.2	0.0	1.8
Meropenem	≤0.03	≤0.03	≤0.03 - 0.12	100.0	0.0	0.0
Tigecycline	0.5	1	0.06 - 4	96.9	3.1	0.0
Gentamicin-Resistant *K. pneumoniae* (4)						
Plazomicin			0.25 - >64	-	-	-
Amikacin			≤1 - >64	75.0	0.0	25.0
Colistin			0.25 - 0.5	-	-	-
Gentamicin			16 - >32	0.0	0.0	100.0
Meropenem			≤0.03 - 0.06	100.0	0.0	0.0
Tigecycline			0.5 - 1	100.0	0.0	0.0
E. cloacae (104)						
Plazomicin	0.25	0.5	≤0.12 - 1	-	-	-
Amikacin	≤1	2	≤1 - 16	100.0	0.0	0.0
Colistin	0.25	>16	≤0.12 - >16	-	-	-
Gentamicin	≤0.5	≤0.5	≤0.5 - >32	93.3	0.0	6.7
Meropenem	≤0.03	0.12	≤0.03 - 2	99.0	1.0	0.0
Tigecycline	0.5	1	0.25 - 8	95.2	2.9	1.9
Gentamicin-Resistant *E. cloacae* (7)						
Plazomicin			0.25 - 0.5	-	-	-
Amikacin			≤1 - 2	100.0	0.0	0.0
Colistin			0.25 - 1	-	-	-
Gentamicin			32 - >32	0.0	0.0	100.0
Meropenem			≤0.03 - 0.5	100.0	0.0	0.0
Tigecycline			0.5 - 4	85.7	14.3	0.0
S. marcescens (69)						
Plazomicin	0.5	1	0.25 - 4	-	-	-
Amikacin	2	2	≤1 - 16	100.0	0.0	0.0
Colistin	>16	>16	0.5 - >16	-	-	-
Gentamicin	≤0.5	1	≤0.5 - >32	98.6	0.0	1.4
Meropenem	0.06	0.06	≤0.03 - 0.12	100.0	0.0	0.0
Tigecycline	2	2	1 - 4	94.1	5.9	0.0
Gentamicin-Resistant *S. marcescens* (1)						
Plazomicin			1	-	-	-
Amikacin			16	100.0	0.0	0.0
Colistin			>16	-	-	-
Gentamicin			>32	0.0	0.0	100.0
Meropenem			0.12	100.0	0.0	0.0
Tigecycline			2	100.0	0.0	0.0
K. oxytoca (63)						
Plazomicin	0.25	0.5	≤0.12 - 1	-	-	-
Amikacin	≤1	≤1	≤1 - 2	100.0	0.0	0.0
Colistin	0.25	0.5	0.25 - >16	-	-	-
Gentamicin	≤0.5	≤0.5	≤0.5 - 1	100.0	0.0	0.0
Meropenem	≤0.03	≤0.03	≤0.03 - 0.06	100.0	0.0	0.0
Tigecycline	0.5	1	≤0.12 - 1	100.0	0.0	0.0
P. mirabilis (46)						
Plazomicin	2	4	0.25 - 8	-	-	-
Amikacin	2	4	≤1 - 8	100.0	0.0	0.0
Colistin	16	>16	8 - >16	-	-	-
Gentamicin	≤0.5	1	≤0.5 - >32	93.5	0.0	6.5
Meropenem	0.06	0.06	≤0.03 - 0.12	100.0	0.0	0.0
Tigecycline	4	8	1-8	23.9	63.0	13.0
Gentamicin-Resistant *P. mirabilis* (3)						
Plazomicin			2-4	-	-	-
Amikacin			2-4	100.0	0.0	0.0
Colistin			>16	-	-	-
Gentamicin			16 - >32	0.0	0.0	100.0
Meropenem			≤0.03 - 0.12	100.0	0.0	0.0
Tigecycline			4 - 8	0.0	33.3	66.7

Organism (no. tested) / antimicrobial agent	MIC (µg/mL)			%		
	50%	90%	Range	S	I	R
P. aeruginosa (330)						
Plazomicin	4	16	≤0.12 - >64	-	-	-
Amikacin	4	8	≤1 - >64	94.5	2.7	2.7
Colistin	1	2	0.25 - 16	95.5	1.5	3.0
Gentamicin	1	8	≤0.5 - >32	88.2	4.5	7.3
Meropenem	0.5	4	≤0.03 - >32	84.2	6.1	9.7
Tigecycline	16	>16	0.25 - >16	-	-	-
Gentamicin-Resistant *P. aeruginosa* (22)						
Plazomicin	2	>64	2 - >64	-	-	-
Amikacin	≤1	>64	≤1 - >64	54.6	13.6	31.8
Colistin	0.25	4	0.25 - 8	91.0	4.5	4.5
Gentamicin	>32	>32	16 - >32	0.0	0.0	100.0
Meropenem	4	>32	0.06 - >32	50.0	22.7	27.3
Tigecycline	16	>16	4 - >16	-	-	-
S. maltophilia (62)						
Plazomicin	>64	>64	2 - >64	-	-	-
Amikacin	>64	>64	4 - >64	-	-	-
Colistin	16	>16	0.25 - >16	-	-	-
Gentamicin	32	>32	1 - >32	-	-	-
Meropenem	>32	>32	32 - >32	-	-	-
Tigecycline	1	4	0.25 - 8	-	-	-
Gentamicin-Resistant *S. maltophilia* (40)						
Plazomicin	>64	>64	8 - >64	-	-	-
Amikacin	>64	>64	32 - >64	-	-	-
Colistin	16	>16	1 - >16	-	-	-
Gentamicin	32	>32	16 - >32	-	-	-
Meropenem	>32	>32	32 - >32	-	-	-
Tigecycline	1	4	0.25 - 8	-	-	-
A. baumannii (12)						
Plazomicin	≤0.06	≤0.06	≤0.06 - 0.12	-	-	-
Amikacin	≤1	4	≤1 - >64	91.7	0.0	8.3
Colistin	0.5	1	0.25 - 1	100.0	0.0	0.0
Gentamicin	≤0.5	8	≤0.5 - >32	83.4	8.3	8.3
Meropenem	0.12	2	0.12 - >32	91.7	0.0	8.3
Tigecycline	0.25	1	0.12 - 2	100.0	0.0	0.0
Gentamicin-Resistant *A. baumannii* (1)						
Plazomicin		8		-	-	-
Amikacin		>64		0.0	0.0	100.0
Colistin		1		100.0	0.0	0.0
Gentamicin		>32		0.0	0.0	100.0
Meropenem		>32		0.0	0.0	100.0
Tigecycline		2		100.0	0.0	0.0

* – no breakpoints; S, susceptible; I, intermediate; R, resistant.

Bacterial Isolates Collected: 3,557 clinical isolates were collected for CANWARD 2011.

- 1463 (41.1%) were from blood, 1372 (38.6%) from respiratory sources, 374 (10.5%) were from urine, and 349 (9.8%) were from wounds
- 1958 (55.0%) collected from male patients; 1599 (45%) female patients
- 444 (12.5%) from patients ≤ 17 years of age, 1532 (43.1%) 18-64 years, and 1581 (44.4%) ≥ 65 years
- 986 (27.7%) were from patients on medical wards, 841 (23.6%) from emergency rooms, 802 (22.6%) from intensive care units, 638 (17.9%) from hospital clinics, and 290 (8.2%) from surgical wards

Table 2. *In vitro* activity of Plazomicin and comparators versus Gram-positive cocci

Organism (no. tested) / antimicrobial agent	MIC (µg/mL)			%		
	50%	90%	Range	S	I	R
MSSA (643)						
Plazomicin	0.5	1	≤0.12 - 1	,a	-	-
Amikacin	4	4	≤1 - 32	99.8	0.2	0.0
Colistin	>16	>16	1 - >16	-	-	-
Gentamicin	≤0.5	≤0.5	≤0.5 - >32	98.6	0.0	1.4
Meropenem	0.12	0.25	≤0.06 - 4	100.0	0.0	0.0
Tigecycline	0.12	0.5	0.06 - 0.5	100.0	0.0	0.0
MRSA (154)						
Plazomicin	1	1	0.25 - 4	-	-	-
Amikacin	16	32	2 - >64	74.7	20.8	4.5
Colistin	>16	>16	>16 - >16	-	-	-
Gentamicin	≤0.5	≤0.5	≤0.5 - 32	97.4	0.6	1.9
Meropenem	4	32	0.5 - >32	0.0	0.0	100.0
Tigecycline	0.12	0.25	0.06 - 2	99.4	-	-
Gentamicin-Resistant MRSA (3)						
Plazomicin			0.5 - 1	-	-	-
Amikacin			8 - >64	66.7	0.0	33.3
Colistin			>16	-	-	-
Gentamicin			>32	0.0	0.0	100.0
Meropenem			0.5 - >32	66.7	0.0	33.3
Tigecycline			0.12 - 0.5	100.0	0.0	0.0
MSSE (72)						
Plazomicin	0.25	0.5	≤0.12 - 4	-	-	-
Amikacin	≤1	16	≤1 - >64	94.4	1.4	4.2
Colistin	>16	>16	1 - >16	-	-	-
Gentamicin	≤0.5	>32	≤0.5 - >32	52.8	8.3	38.9
Meropenem	2	32	0.06 - >32	65.3	12.5	22.2
Tigecycline	0.12	0.25	≤0.03 - 1	-	-	-
MRSE (9)						
Plazomicin	0.25	4	0.25 - 4	-	-	-
Amikacin	16	>64	≤1 - >64	66.7	11.1	22.2
Colistin	>16	>16	>16 - >16	-	-	-
Gentamicin	>32	>32	8 - >32	0.0	22.2	77.8
Meropenem	32	>32	16 - >32	0.0	0.0	100.0
Tigecycline	0.12	0.25	0.06 - 0.25	-	-	-
Gentamicin-Resistant MRSE (7)						
Plazomicin			0.25 - 4	-	-	-
Amikacin			≤1 - >64	71.4	0.0	28.6
Colistin			>16	-	-	-
Gentamicin			8 - >32	0.0	12.5	88.5
Meropenem			16 - >32	0.0	0.0	100.0
Tigecycline			0.06 - 0.25	100.0	0.0	0.0

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSSE, methicillin-susceptible *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*; * – no breakpoints; S, susceptible; I, intermediate; R, resistant

CONCLUSIONS

- Plazomicin demonstrated potent *in vitro* activity against recent clinical isolates of *Enterobacteriaceae*, including strains resistant to gentamicin as well as other antimicrobials including colistin.
- Plazomicin activity against *P. aeruginosa* and *A. baumannii* was similar to amikacin.
- Plazomicin was active against staphylococci including gentamicin-resistant strains.
- Versus MRSA and MRSE plazomicin demonstrated excellent activity.
- Plazomicin demonstrates promise for the treatment of bacterial infections caused by resistant organisms.

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