Plazomicin Activity against Contemporary Clinical Isolates Collected in USA Hospitals

C-613

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ICAAC 2015
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ABSTRACT

Background: Plazomicin (PLZ) is a next generation aminoglycoside, stable against aminoglycoside modifying enzymes commonly detected among bacterial organisms. This compound is currently being investigated in two Phase 3 clinical trials. We evaluated the activity of PLZ and comparators tested against 2,490 clinical isolates collected in USA hospitals during 2014.

Methods: 2,291 Enterobacteriaceae (ENT), 115 Gram-positive, 49 *P. aeruginosa* (PSA) and 35 *A. baumannii* (ACB) were susceptibility (S) tested using reference broth microdilution method. CLSI and EUCAST interpretative criteria were applied.

Results: PLZ ($MIC_{50/90}$, 0.5/2 µg/mL) inhibited 85.3 and 95.3% of the ENT isolates at ≤1 and ≤2 µg/mL, respectively. PLZ was active against *E. coli* (EC; $MIC_{50/90}$, 1/2 µg/mL), *K. pneumoniae* (KPN; $MIC_{50/90}$, 0.5/0.5 µg/mL) and *K. oxytoca* (KOX; $MIC_{50/90}$, 0.5/1 µg/mL), including isolates displaying an ESBL-phenotype (97.1, 98.7 and 100.0% inhibited at ≤2 µg/mL, respectively). All *E. cloacae* (n=50), *E. aerogenes* (n=62) and *C. koseri* (n=77) isolates displayed PLZ MIC results ≤2 µg/mL and *C. freundii* (n=80) and *Serratia* spp. (n=54) had only 1 and 2 isolates with MIC values at 4 µg/mL, respectively. PLZ MIC results for *M. morgannii* (n=72), *Providencia* spp. (n=94) and *Proteus* spp. (n=147) were slightly higher (MIC_{50} and MIC_{90} ranges, 1-2 and 4-8 µg/mL) when compared to other ENT species. Among 28 isolates displaying PLZ MIC values ≥4 µg/mL were 2 EC, 2 KPN, 2 KOX with MIC results ≥64 µg/mL and 2 *P. mirabilis* and 19 Indole-positive *Proteae* with MIC values ranging from 4 to 64 µg/mL. PLZ ($MIC_{50/90}$, 0.5/1 µg/mL) inhibited 47/48 (97.9%) carbapenem-resistant ENT (CRE) at ≤2 µg/mL. The highest PLZ MIC value for *S. aureus* ($MIC_{50/90}$, 0.5/0.5 µg/mL) was 1 µg/mL and for coagulase-negative staphylococci ($MIC_{50/90}$, 0.12/0.25 µg/mL) was 2 µg/mL. PLZ displayed limited activity against *E. faecalis* ($MIC_{50/90}$, 64/128 µg/mL) and *S. pneumoniae* ($MIC_{50/90}$, 32/64 µg/mL). PLZ MIC results for PSA ($MIC_{50/90}$, 4/16 µg/mL) ranged from 0.5 to 32 µg/mL and from 0.5 to >128 µg/mL for ACB ($MIC_{50/90}$, 2/32 µg/mL).

Conclusions: PLZ displayed good activity against contemporary ENT species, including ESBL-producers and CRE, and staphylococci. MIC results were slightly higher for PSA and ACB, but limited options are available to treat these organisms.

INTRODUCTION

The worldwide emergence of multidrug-resistant (MDR) organisms, including carbapenem-resistant Enterobacteriaceae (CRE) that are often multidrug-resistant and pan- or extremely-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* highlights the need for new therapeutic options to treat infections. Furthermore, the Infectious Diseases Society of America (IDSA) recognized the urgent need of monitoring initiatives and new therapeutic options for the group of organisms known as ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* species) that includes the Gram-negative organisms described above as well as troublesome Gram-positive species.

New therapeutic options for Gram-positive organisms have been approved for clinical therapy in the USA and Europe and more recently, a few antimicrobials with coverage for Gram-negative organisms have been cleared for patient treatment. However, the development of new agents with Gram-negative coverage is important since the adequacy of empiric treatment (before microbiology laboratory results are available) is critical for successful outcomes.

Plazomicin is a next-generation aminoglycoside that is stable in the presence of most aminoglycoside modifying enzymes (AME) and has activity against Gram-negative pathogens and *Staphylococcus* spp., including methicillin-resistant (MRSA) isolates. In this study, we evaluated the activity of plazomicin and comparator antimicrobial agents tested against a collection of 2,490 clinical isolates collected in USA hospitals (2014).

MATERIALS AND METHODS

Bacterial isolates: A total of 2,490 clinical isolates, including 2,291 Enterobacteriaceae, 115 Gram-positive organisms, 49 *P. aeruginosa* and 50 *Acinetobacter* spp. were consecutively collected in 69 USA hospitals during 2014. These non-duplicate isolates, considered clinically significant, were recovered from bloodstream infections (587 isolates), pneumonia in hospitalized patients (586), skin/soft tissue infections (209), urinary tract infections (828), intra-abdominal infections (261) and other or unknown specimen sites (45). Species identification was confirmed by standard biochemical tests and using the MALDI-TOF Biotyper (Bruker Daltonics, Billerica, Massachusetts, USA) according to the manufacturer instructions, where necessary.

Susceptibility testing: Plazomicin was tested by reference broth microdilution testing methods according to the Clinical and Laboratories Standards Institute (CLSI document) guidelines (M07-A10). Comparator antimicrobial agents were tested using validated dry-form panels (ThermoFisher Scientific Inc., Cleveland, Ohio, USA). CLSI (M100-S25, 2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015) breakpoint interpretive criteria were applied, where available. USA-FDA breakpoints were applied for tigecycline.

Quality control (QC) was assured by testing *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published ranges.

E. coli, *Klebsiella* spp. and *Proteus mirabilis* isolates displaying the CLSI criteria for an ESBL-phenotype (MIC, >1 µg/mL for aztreonam and/or ceftazidime and/or ceftriaxone) were grouped as the ESBL-phenotype. CRE was defined as any isolate displaying imipenem (*Proteus mirabilis* and indole-positive *Proteae* were not included due to the intrinsically elevated MIC values) and/or meropenem MIC values at ≥2 µg/mL CLSI criteria [2015].

RESULTS

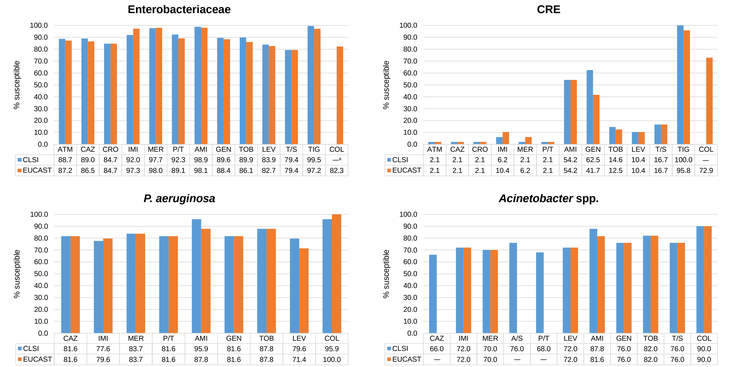
- Plazomicin (MIC_{50} and MIC_{90}, 0.5 and 2 µg/mL) had MICs ≤1 and ≤2 µg/mL against 85.3 and 95.3% of the 2,291 Enterobacteriaceae isolate, respectively. There are no approved interpretive criteria for plazomicin, but tentatively applying the CLSI susceptibility breakpoints for gentamicin/tobramycin (≤4 µg/mL) and amikacin (≤16 µg/mL) for comparison purposes only, would provide plazomicin susceptibility rates of 98.8 and 99.6% against these isolates. (**Table 1**).
- All but one CRE isolate (47/48; 97.9%) was inhibited by plazomicin (MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL) at ≤2 µg/mL and this compound was more potent than amikacin, gentamicin and tobramycin against CRE isolates ($MIC_{50/90}$, 16/32, 2/>32 and >8/>8 µg/mL, respectively; data not shown). CRE isolates displayed low susceptibility rates against comparator agents and tigecycline and colistin were the only agents to inhibit >70.0% of the isolates (**Figure 1**).
- Among Enterobacteriaceae species, plazomicin inhibited 687/689 (99.7%) of the *E. coli* isolates (MIC_{50} and MIC_{90}, 1 and 2 µg/mL) at ≤4 µg/mL, including isolates displaying an ESBL-phenotype. This compound inhibited 782 of 784 *K. pneumoniae* (MIC_{50} and MIC_{90}, 0.5 and 0.5 µg/mL) and 180 of 182 *K. oxytoca* (MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL) at ≤4 µg/mL.
- Plazomicin inhibited all *E. cloacae* (n=50; MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL), *E. aerogenes* (n=62; MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL), *C. koseri* (n=77; MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL), *C. freundii* (n=80; MIC_{50} and MIC_{90}, 0.5 and 1 µg/mL), and *Serratia marcescens* (n=54; MIC_{50} and MIC_{90}, 1 and 2 µg/mL) at ≤ 4 µg/mL, (**Table 1**).
- Against 49 *P. aeruginosa* isolates tested, plazomicin activity (MIC_{50} and MIC_{90}, 4 and 16 µg/mL) was two-fold less potent when compared to the activity of amikacin ($MIC_{50/90}$, 2/16 µg/mL), gentamicin ($MIC_{50/90}$, 2/16 µg/mL) and tobramycin ($MIC_{50/90}$, 2/8 µg/mL; data not shown).
- Plazomicin inhibited 76.0% of the *Acinetobacter* spp. isolates at ≤4 µg/mL, the current CLSI breakpoint for gentamicin (applied for comparison purposes only). These isolates were highly resistant to comparator antimicrobial agents (**Figure 1**).
- All *S. aureus* isolates, including the MRSA, were inhibited by ≤1 µg/mL of plazomicin (MIC_{50} and MIC_{90}, 0.5 and 0.5 µg/mL). Coagulase-negative staphylococci (MIC_{50} and MIC_{90}, 0.12 and 0.25 µg/mL) were inhibited by ≤2 µg/mL of plazomicin.
- The activity of plazomicin was limited against *E. faecalis* (MIC_{50} and MIC_{90}, 64 and 128 µg/mL) and *S. pneumoniae* (MIC_{50} and MIC_{90}, 64 and 64 µg/mL); see **Table 1**.

Table 1. Antimicrobial activity of plazomicin tested against the main organisms, organism groups, and resistant subsets of isolates from USA hospitals tested during 2014.

Organism	No. of isolates tested	No. of isolates inhibited at plazomicin MIC values in µg/mL (cumulative %)													MIC (µg/mL)	
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	50%	90%
Enterobacteriaceae	2291	--	10 (0.4)	259 (11.7)	1152 (62.0)	534 (85.3)	229 (95.3)	79 (98.8)	8 (99.1)	10 (99.6)	2 (99.7)	2 (99.7)	1 (99.8)	5 (100.0)	0.5	2
CRE[a]	48	--	2 (4.2)	11 (27.1)	25 (79.2)	7 (93.8)	2 (97.9)	0 (97.9)	0 (97.9)	0 (97.9)	0 (97.9)	0 (97.9)	0 (97.9)	1 (100.0)	0.5	1
Escherichia coli	689	--	--	11 (1.6)	254 (38.5)	350 (89.3)	66 (98.8)	6 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	2 (100.0)	1	2
ESBL-phenotype *E. coli*	104	--	--	1 (1.0)	42 (41.3)	48 (87.5)	10 (97.1)	1 (98.1)	0 (98.1)	0 (98.1)	0 (98.1)	0 (98.1)	0 (98.1)	2 (100.0)	1	2
Klebsiella pneumoniae	784	--	8 (1.0)	204 (27.0)	543 (96.3)	22 (99.1)	4 (99.6)	1 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	2 (100.0)	0.5	0.5
ESBL-phenotype *K. pneumoniae*	127	--	3 (2.4)	37 (31.5)	72 (88.2)	11 (96.9)	2 (98.4)	0 (98.4)	0 (98.4)	0 (98.4)	0 (98.4)	0 (98.4)	0 (98.4)	2 (100.0)	0.5	1
Klebsiella oxytoca	182	--	--	12 (6.6)	143 (85.2)	20 (96.2)	4 (98.4)	1 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	1 (99.5)	1 (100.0)	0.5	1
ESBL-phenotype *K. oxytoca*	23	--	--	1 (4.3)	17 (78.3)	5 (100.0)									0.5	1
Proteus mirabilis	63	--	--	--	--	9 (14.3)	43 (82.5)	9 (96.8)	2 (100.0)						2	4
Enterobacter cloacae	51	--	--	3 (5.9)	40 (84.3)	7 (98.0)	1 (100.0)								0.5	1
Enterobacter aerogenes	62	--	--	3 (4.8)	43 (74.2)	15 (98.4)	1 (100.0)								0.5	1
Morganella morganii	72	--	--	--	1 (1.4)	19 (27.8)	25 (62.5)	19 (88.9)	3 (93.1)	2 (95.8)	2 (98.6)	1 (100.0)			2	8
Citrobacter koseri	77	--	1 (1.3)	22 (29.9)	46 (89.6)	5 (96.1)	3 (100.0)								0.5	1
Citrobacter freundii	80	--	--	4 (5.0)	62 (82.5)	11 (96.2)	2 (98.8)	1 (100.0)							0.5	1
Serratia marcescens	53	--	--	--	8 (15.1)	36 (83.0)	8 (98.1)	1 (100.0)							1	2
Proteus vulgaris	84	--	--	--	3 (3.6)	29 (38.1)	40 (85.7)	11 (98.8)	0 (98.8)	1 (100.0)					2	4
Providencia spp.	94	--	1 (1.1)	0 (1.1)	9 (10.6)	11 (22.3)	32 (56.4)	30 (88.3)	3 (91.5)	7 (98.9)	0 (98.9)	1 (100.0)			2	8
Pseudomonas aeruginosa	49	--	--	--	1 (2.0)	1 (4.1)	5 (14.3)	23 (61.2)	11 (83.7)	4 (91.8)	4 (100.0)				4	16
Acinetobacter spp.	50	1 (2.0)	0 (2.0)	3 (8.0)	7 (22.0)	8 (38.0)	16 (70.0)	3 (76.0)	5 (86.0)	2 (90.0)	2 (94.0)	0 (94.0)	1 (96.0)	2 (100.0)	2	16
Staphylococcus aureus	34	--	--	7 (20.6)	26 (97.1)	1 (100.0)									0.5	0.5
MRSA[b]	15	--	--	4 (26.7)	10 (93.3)	1 (100.0)									0.5	0.5
Coagulase-negative staphylococci	35	13 (37.1)	14 (77.1)	6 (94.3)	1 (97.1)	0 (97.1)	1 (100.0)								0.12	0.25
MRCoNS[c]	27	8 (29.6)	12 (74.1)	5 (92.6)	1 (96.3)	0 (96.3)	1 (100.0)								0.12	0.25
Enterococcus spp.	26	--	--	--	--	--	3 (11.5)	1 (15.4)	5 (34.6)	1 (38.5)	2 (46.2)	11 (88.5)	3 (100.0)		64	128
Enterococcus faecalis	17	--	--	--	--	--	--	--	1 (5.9)	0 (5.9)	2 (17.6)	11 (82.4)	3 (100.0)		64	128
Streptococcus pneumoniae	31	--	--	--	--	--	--	--	--	1 (3.2)	14 (48.4)	16 (100.0)			64	64

a. CRE = carbapenem-resistant Enterobacteriaceae.
b. MRSA = methicillin-resistant *Staphylococcus aureus*.
c. MRCoNS = methicillin-resistant Coagulase-negative staphylococci.

Figure 1. Percentage of susceptibility for comparator antimicrobial agents using the CLSI and EUCAST breakpoint criteria for the main groups of Gram-negative organisms from the USA.



a. "---" interpretive criteria is not available. Abbreviations: ATM= aztreonam; A/S = ampicillin-sulbactam; CAZ= ceftazidime; CRO= ceftriaxone; IMI= imipenem; MER= meropenem; P/T= piperacillin-tazobactam; GEN= gentamicin; AMI= amikacin; LEV= levofloxacin; TOB= tobramycin; T/S= trimethoprim-sulfamethoxazole; TIG= tigecycline; COL= colistin.

CONCLUSIONS

- Plazomicin demonstrated potent in vitro antibacterial activity against Enterobacteriaceae, including CRE and isolates displaying an ESBL-phenotype. Furthermore, this aminoglycoside was more active than other compounds from the same class against CRE isolates.
- Plazomicin was less potent against *P. aeruginosa* and *Acinetobacter* spp. isolates, which were also more resistant to many comparator agents, when compared to Enterobacteriaceae isolates.
- Against Gram-positive isolates, the activity of plazomicin was best against *Staphylococcus* spp., including MRSA; but limited against *Enterococcus* spp. and *S. pneumoniae*.
- Plazomicin displays potent in vitro activity against clinically important groups of MDR organisms and has the potential to address an area of high unmet need.

ACKNOWLEDGEMENT

This study was sponsored by an investigational grant from Achaogen.

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