IDWeek 2018
Poster #1345

Comparative Activity of Plazomicin and Other Aminoglycosides against *Enterobacteriaceae* Isolates from Various Infection Sources from Hospitalized Patients in the United States

M CASTANHEIRA[1], JM STREIT[1], AW SERIO[2], KM KRAUSE[2], RK FLAMM[1]

[1]JMI Laboratories, North Liberty, Iowa, [2]Achaogen, South San Francisco, California

Mariana Castanheira, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: mariana-castanheira@jmilabs.com

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Amended Abstract

Background: Plazomicin is a next-generation aminoglycoside that was approved in June 2018 by the United States Food and Drug Administration for complicated urinary tract infections (cUTIs), including acute pyelonephritis due to certain *Enterobacteriaceae* (ENT) in patients who have limited or no alternative treatment options. We evaluated the activity of plazomicin and aminoglycosides against ENT isolates collected in US hospitals during 2014 to 2017 by site of infection.

Methods: A total of 8,510 ENT isolates were collected from bloodstream infections (2,133), pneumonia in hospitalized patients (1,826), skin and skin structure infections (1,155), intra-abdominal infections (IAIs; 731), UTIs (2,508), and other or unknown infection sites (157) in 71 US hospitals from 2014 to 2017. Isolates were susceptibility (S) tested by reference broth microdilution methods and results were interpreted using CLSI breakpoints.

Results: Plazomicin ($MIC_{50/90}$ ranges, 0.25–0.5/1–2 µg/mL) inhibited 98.8–99.9% of the ENT isolates at ≤4 µg/mL across all infection types (Figure 1). At ≤4 µg/mL, plazomicin inhibited 93.8–100% of the carbapenem-resistant ENT (CRE) isolates stratified by infection type. The S rates for amikacin ranged from 98.7–99.7% against ENT isolates overall. However, amikacin S rates for CRE ranged from 53.1% for UTI to 100% for IAI isolates. Gentamicin (89.2–93.6%S) and tobramycin (88.8–94.3%S) were slightly less active than plazomicin and amikacin against the ENT isolates stratified by infection source. Gentamicin S rates against CRE isolates ranged from 43.8–66.7% while tobramycin inhibited <45% of the CRE isolates from the different infection sources.

Conclusions: The activity of plazomicin and amikacin was similar against ENT isolates from US hospitals and did not vary by infection type; however, amikacin activity against CRE isolates varied by infection source while plazomicin remained active against CRE isolates regardless of infection source. These results highlight the potential role of plazomicin for treating serious infections caused by CRE.

Introduction

- Plazomicin is a semi-synthetic aminoglycoside developed from sisomicin that demonstrates activity against *Enterobacteriaceae*, including multidrug-resistant isolates, *Staphylococcus* spp. and some *Pseudomonas aeruginosa* isolates
- Plazomicin contains structural modifications that allow it to retain activity in the presence of aminoglycoside-modifying enzymes (AMEs)
  - AMEs are the most common resistance mechanism to aminoglycoside agents in gram-positive and -negative bacteria and confer resistance by aminoglycoside modification and subsequent inactivation
- Plazomicin was approved by the United States Food and Drug Administration (US FDA) in June 2018 for the treatment of complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Proteus mirabilis* in patients who have limited or no alternative treatment options
- We evaluated the activity of plazomicin and comparator antimicrobial agents against 8,510 *Enterobacteriaceae* isolates stratified by infection type collected in 71 US hospitals from 2014 to 2017 as part of the Antimicrobial Longitudinal Evaluation of Resistance Trends (ALERT) Program

Materials and Methods

- A total of 8,510 *Enterobacteriaceae* isolates collected from 71 US hospitals during 2014 to 2017 and identified as the cause of infection were included in the study; isolates were limited to 1 per patient episode
  - Isolates were collected from bloodstream infections (BSIs; 2,133), pneumonia in hospitalized patients (1,826), skin and skin structure infections (SSSIs; 1,155), intra-abdominal infections (IAIs; 731), urinary tract infections (UTIs; 2,508), and other or unknown infection sites (others; 157)
- Isolates were susceptibility tested using the reference broth microdilution method described by the Clinical and Laboratory Standards Institute (CLSI)
  - Categorical interpretations for all comparator agents were those in the CLSI M100 document (2018), EUCAST breakpoint tables (version 8.1, August 2018), or the US FDA website for plazomicin and tigecycline
  - Quality control (QC) was performed according to CLSI guidelines (M07, 2018), and all QC MIC results were within acceptable ranges as published in CLSI documents
- Extended-spectrum beta-lactamase (ESBL)-phenotype was defined as an MIC at ≥2 µg/mL for ceftriaxone, ceftazidime, or aztreonam (CLSI, 2018) for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 µg/mL
  - *Proteus mirabilis* and indole-positive Proteeae were categorized as CRE if doripenem and/or meropenem MIC values were at ≥2 µg/mL due to intrinsically elevated imipenem MIC values

Results

- Plazomicin was active against 97.0% of the *Enterobacteriaceae* isolates included in this study using the current US FDA approved breakpoint (Figure 1)
  - Plazomicin activity ranged from 94.3% to 98.5% among the different infection types with greater activity against BSIs and lower activity against SSSIs
  - Among comparator antimicrobial agents, tigecycline, meropenem, and amikacin inhibited 98.0%, 98.2%, and 99.1% of the isolates
- Plazomicin was active against 97.9% of the CRE isolates, including all isolates from BSIs, IAIs, and UTIs at the US FDA breakpoint (Figure 2)
  - Overall, the activity of amikacin against CRE was 69.2% and ranged from 53.1% for UTI isolates to 100% against IAI isolates
  - Gentamicin activity ranged from 43.8% to 66.7% against CRE isolates, and tobramycin inhibited <45% of the CRE isolates from the different infection sources (data not shown)
- Overall, plazomicin was active against 94.9% of the 632 isolates nonsusceptible to any 2 of amikacin, gentamicin, or tobramycin by applying the CLSI breakpoints (Figure 3)
  - The activity of plazomicin ranged from 71.4% of the 7 isolates from other infection types to 100.0% of the 45 IAI isolates
  - Amikacin and gentamicin inhibited 92.1% and 7.9% of the isolates nonsusceptible to 2 aminoglycosides, respectively, and all isolates were tobramycin-resistant

Conclusions

- Plazomicin was active against most CRE isolates whereas the activity of amikacin, gentamicin, and tobramycin was variable against these isolates
- Plazomicin displayed activity against isolates nonsusceptible to 2 of the most commonly used aminoglycosides that include amikacin, gentamicin, and tobramycin
- In summary, plazomicin is an active agent against *Enterobacteriaceae* isolates from different infection types, regardless of resistance to carbapenems and resistance to other aminoglycosides

Acknowledgements

This study was performed by JMI Laboratories and supported by Achaogen, which included funding for services related to preparing this poster.

This project has been funded in whole or in part with Federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO100201000046C.

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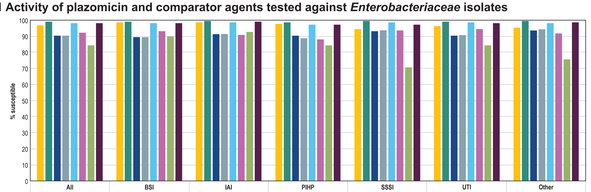
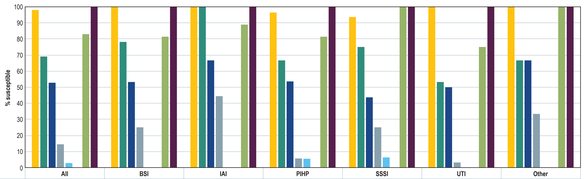
Figure 1 Activity of plazomicin and comparator agents tested against *Enterobacteriaceae* isolates



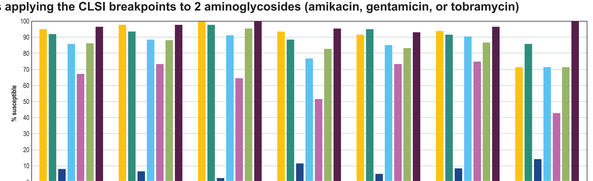
	All	BSI	IAI	PIHP	SSSI	UTI	Other
Plazomicin	97.0	98.5	98.4	97.5	94.3	96.2	95.5
Amikacin	99.1	99.3	99.7	98.7	99.4	98.9	99.4
Gentamicin	90.5	89.2	91.2	90.5	92.9	90.2	93.6
Tobramycin	90.5	89.4	91.4	88.8	93.7	90.7	94.3
Meropenem	98.2	98.3	98.4	97.1	98.6	98.6	98.1
Piperacillin-tazobactam	92.3	92.9	90.7	88.2	93.7	94.5	91.7
Colistin	84.3	89.7	92.7	84.3	70.6	84.3	75.5
Tigecycline	98.0	98.3	99.3	97.4	97.1	98.3	98.7

Figure 2 Activity of plazomicin and comparator agents tested against carbapenem-resistant *Enterobacteriaceae* isolates



	All	BSI	IAI	PIHP	SSSI	UTI	Other
Plazomicin	97.9	100	100	96.3	93.8	100	100
Amikacin	69.2	78.1	100	66.7	75.0	53.1	66.7
Gentamicin	52.7	53.1	66.7	53.7	43.8	50.0	66.7
Tobramycin	14.4	25.0	44.4	5.6	25.0	3.1	33.3
Meropenem	2.7	0	0	5.6	6.2	0	0
Piperacillin-tazobactam	0	0	0	0	0	0	0
Colistin	82.8	81.2	88.9	81.5	100	75.0	100
Tigecycline	100	100	100	100	100	100	100

Figure 3 Activity of plazomicin and comparator agents tested against *Enterobacteriaceae*-nonsusceptible isolates applying the CLSI breakpoints to 2 aminoglycosides (amikacin, gentamicin, or tobramycin)



	All	BSI	IAI	PIHP	SSSI	UTI	Other
Plazomicin	94.9	97.8	100	93.7	91.7	93.9	71.4
Amikacin	92.1	93.4	97.8	88.7	95.0	91.6	85.7
Gentamicin	7.9	6.6	2.2	11.3	5.0	8.4	14.3
Meropenem	85.8	88.5	91.1	76.7	85.0	90.5	71.4
Piperacillin-tazobactam	67.2	73.1	64.4	51.6	73.3	74.9	42.9
Colistin	86.3	88.3	95.6	83.0	83.1	86.6	71.4
Tigecycline	96.7	97.8	100	95.6	93.3	96.6	100

Note: All isolates were tobramycin-resistant