Poster #C-766

In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) and Comparators Against Gram-Negative Pathogens Isolated from Patients in Canadian Hospitals in 2009-2013: CANWARD Surveillance Study

P. LAGACÉ-WIENS[1,2], H. ADAM[1,2], A. DENISUIK[1], M. BAXTER[1], J. KARLOWSKY[1,2], P. J. SIMNER[2], R. VASHISHT[1], A. WALKTY[1,2], D. HOBAN[1,2], G. G. ZHANEL[1]
and the Canadian Antimicrobial Resistance Alliance
[1]University of Manitoba, [2]Diagnostic Services of Manitoba, Winnipeg, Canada

Philippe Lagacé-Wiens
L4025-409 Taché Ave.
Winnipeg, MB, CANADA
+204-237-2483
plagacewiens@dsmanitoba.ca

www.can-r.ca

ABSTRACT (REVISED)

Background: Avibactam, a non-β-lactam beta-lactamase inhibitor of Ambler class A, C and some class D enzymes, is currently being studied in combination with ceftazidime. We determined the in vitro activity of ceftazidime (CAZ) with avibactam (at a fixed 4 μg/mL concentration) and comparators versus Gram-negative pathogens, including extended-spectrum β-lactamase producing (ESBL) and AmpC-producing (AmpC) strains isolated from January 2009 to December 2013 from patients in medical and surgical wards, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals.
Methods: Antimicrobial susceptibility testing was performed using in-house broth microdilution panels following CLSI recommendations (M07-A9). CAZ susceptibility breakpoints were used for CAZ-AVI. Cephalosporin-resistant *Escherichia coli* and *Klebsiella* sp. strains were genetically characterized for ESBL-production using PCR and sequence analysis.
Results: The activity of CAZ-AVI and comparators is summarized in the tables.
Conclusions: CAZ-AVI demonstrated potent in vitro activity against recent clinical isolates of *Enterobacteriaceae*, including those with acquired resistance to oximinocephalosporins by a variety of mechanisms including ESBL production. MIC_{90} of CAZ-AVI against *Pseudomonas aeruginosa* was comparable to meropenem and 4 fold lower than CAZ alone. The susceptibility rate of CAZ-resistant *P. aeruginosa* to ceftazidime-avibactam was considerably greater than susceptibility to meropenem or piperacillin-tazobactam. Activity against *Acinetobacter baumannii* was not improved compared to CAZ alone. CAZ-AVI may be useful for the treatment of infections caused by oximinocephalosporin and piperacillin-tazobactam-resistant *Enterobacteriaceae* and *P. aeruginosa*.

INTRODUCTION

Antimicrobial resistance is a growing problem among Gram-negative isolates worldwide. Multi-drug resistant (MDR) *P. aeruginosa*, ESBL-, KPC- and AmpC-producing *Enterobacteriaceae*, and MDR *Acinetobacter* spp. can cause severe infections and treatment choices are limited. Avibactam is a broad-spectrum non-β-lactam β-lactamase inhibitor being studied in combination with ceftazidime to restore the parent drug activity against a wide range of cephalosporin-resistant Gram-negative pathogens expressing Ambler class A and C, and some class D, β-lactamases (1).

MATERIALS & METHODS

Isolates were collected as part of the CANWARD 2009, to 2013 studies occurring between January 2009 and December 2013. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. Only species with >100 isolates submitted and *A. baumannii* were considered in this study. A total of 8663 Gram-negative bacilli and 87 *A. baumannii* isolates were included. Susceptibility testing was done by broth microdilution in accordance with the CLSI M07-A9 document (2). Serial dilutions of ceftazidime with and without a fixed concentration of 4 μg/mL avibactam, piperacillin-tazobactam, ceftriaxone, meropenem and tigecycline were included on the panel. The susceptibility breakpoints for the ceftazidime-avibactam combination have not been established but were considered to be the same as those for ceftazidime.

RESULTS

TABLE 1: MIC_{50} and MIC_{90} for all isolates and cephalosporin-resistant isolates for ceftazidime-avibactam and comparators.

	MIC_{50}/MIC_{90} (μg/mL)					
Organism (n)	Ceftazidime-Avibactam	Ceftazidime	Ceftriaxone	Meropenem	Tigecycline	Pipercallin-tazobactam
Escherichia coli (3915)	0.12/0.25	≤0.25/1	≤0.25/≤0.25	≤0.03/≤0.03	0.25/0.5	2/4
E. coli CRO-R (300)	0.12/0.5	32/>32	64/>64	≤0.03/0.06	0.5/1	4/16
E. coli ESBL (223)	0.12/0.25	16/>32	>64/>64	≤0.03/≤0.03	0.5/1	4/16
Pseudomonas aeruginosa (1825)	2/8	4/32	16/>64	0.5/8	16/>16	4/64
P. aeruginosa CAZ-R (215)	8/>16	>32/>32	>64/>64	4/32	>16/>16	128/512
Klebsiella pneumoniae (1288)	0.12/0.5	≤0.25/1	≤0.25/≤0.25	≤0.03/≤0.03	1/2	2/8
K. pneumoniae CRO-R (55)	0.5/2	>32/>32	>64/>64	0.06/1	1/2	8/512
K. pneumoniae ESBL (50)	0.5/1	32/>32	64/>64	≤0.03/0.12	1/2	8/256
Enterobacter cloacae (512)	0.25/1	0.5/>32	≤0.25/>64	≤0.03/0.12	0.5/1	2/64
E. cloacae CRO-R (123)	0.5/2	>32/>32	>64/>64	0.06/0.25	1/2	32/128
Serratia marcescens (323)	0.25/0.5	≤0.25/0.5	≤0.25/1	0.06/0.06	2/4	≤1/4
Klebsiella oxytoca (336)	0.12/0.5	≤0.25/0.5	≤0.25/1	≤0.03/≤0.03	0.5/1	2/128
Proteus mirabilis (311)	≤0.06/0.12	≤0.25/≤0.25	≤0.25/≤0.25	0.06/0.12	8/16	≤1/≤1
Enterobacter aerogenes (153)	0.25/0.5	0.5/32	≤0.25/16	≤0.03/0.12	1/2	4/32
Acinetobacter baumannii (87)	8/>16	8/>32	8/64	0.5/1	0.5/1	≤1/64

CAZ-AVI: Ceftazidime-avibactam, CRO-R: Ceftriaxone-resistant; CAZ-R: Ceftazidime-resistant; ESBL: Extended spectrum β-lactamase-producing

TABLE 2: Percent susceptible for all isolates and cephalosporin-resistant isolates to ceftazidime-avibactam and comparators.

	% Susceptible					
Organism (n)	Ceftazidime-Avibactam[1]	Ceftazidime[2]	Ceftriaxone[2]	Meropenem[2]	Tigecycline[3]	Pipercallin-tazobactam[2]
Escherichia coli (3915)	99.9%	94.2%	92.2%	100%	100%	97.8%
E. coli CRO-R (300)	99.3%	29.7%	0%	99.7%	100%	92.0%
E. coli ESBL (223)	99.6%	33.6%	1.8%	99.6%	100%	94.2%
Pseudomonas aeruginosa (1825)	94.4%	82.7%	N/A	82.0%	N/A	84.7%
P. aeruginosa CAZ-R (215)	65.6%	0%	N/A	48.4%	N/A	11.2%
Klebsiella pneumoniae (1288)	99.8%	96.2%	95.3%	99.6%	95.6%	97.4%
K. pneumoniae CRO-R (55)	94.5%	16.4%	0%	90.9%	90.9%	65.5%
K. pneumoniae ESBL (50)	98.0%	98.0 %	24.0%	96.0%	90%	
Enterobacter cloacae (512)	99.4%	78.3%	73.8%	99.0%	95.9%	86.%
E. cloacae CRO-R (123)	97.6%	11.4%	0%	95.9%	90.2%	42.3%
Serratia marcescens (323)	100%	99.4%	93.5%	99.7%	80.1%	95.4%
Klebsiella oxytoca (336)	100%	98.8%	92.3%	100%	99.4%	88.4%
Proteus mirabilis (311)	100%	99.4%	98.1%	100%	10.9%	100%
Enterobacter aerogenes (153)	98.7%	76.5%	72.5%	99.3%	95.4%	89.5%
Acinetobacter baumannii (87)	60.9%	79.3%	54.0%	94.3%	N/A	83.9%

CRO-R: Ceftriaxone resistant; CAZ-R: Ceftazidime resistant; ESBL: Extended spectrum β-lactamase-producing
[1]Breakpoints not yet defined, CLSI M100-S24 (3) breakpoints for ceftazidime were used.
[2] CLSI M100-S24 (3) breakpoints.
[3]FDA breakpoints

CONCLUSIONS

Avibactam reduced MIC_{50} and MIC_{90} of ceftazidime for all organisms tested except *A. baumannii* and *S. marcescens*.

Avibactam restored the activity of ceftazidime for all *Enterobacteriaceae* with acquired resistance to ceftriaxone.

Avibactam resulted in a 2-fold reduction in MIC_{50} and 4-fold reduction in MIC_{90} compared with ceftazidime alone for *P. aeruginosa*.

If ceftazidime breakpoints are used for ceftazidime-avibactam, susceptibility rates are >99% for all *Enterobacteriaceae* (76.5-99.2% for ceftazidime alone), 94.4% for *P. aeruginosa* (82.7% for ceftazidime alone) and 60.9% for *A. baumannii* (79.3% for ceftazidime alone).

If ceftazidime breakpoints are used for ceftazidime-avibactam, susceptibility rates are comparable with meropenem for *Enterobacteriaceae*, superior to meropenem for *P. aeruginosa* and inferior to meropenem for *A. baumannii.*

ACKNOWLEDGMENTS

We acknowledge the contributions of the directors and technologists of the contributing site microbiology laboratories.

This study was supported in part Abbott Laboratories Ltd, Affinium, Astellas, AstraZeneca, Cerexa/Forest, Cubist, Merck Canada, Pfizer, Sunovion, and The Medicines Company.

REFERENCES

1. Lagacé-Wiens et al. Activity of NXL104 in Combination with β-Lactams against Genetically Characterized *Escherichia coli* and *Klebsiella pneumoniae* Isolates Producing Class A Extended-Spectrum β-Lactamases and Class C β-Lactamases. Antimicrob. Agents Chemother. 55:2434-2437.
2. CLSI. *Methods for Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth Edition.* CLSI document M07-A9. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
3. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement.* CLSI document M100-S24. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.