911163

In Vitro Activity of Ceftazidime-Avibactam Against Enterobacterales and *Pseudomonas aeruginosa* Collected in Latin America as part of the ATLAS Global Surveillance Program, 2017-2019

IHMA
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

K. M. Kazmierczak[1], M. L. N. de Figueiredo[2], E. V. Lemos Luengas[3], M. Baudrit Gonzalez[4], A. Quintana[5], P. Irani[6], G. G. Stone[7], D. F. Sahm[1]

[1]IHMA, Schaumburg, IL, USA; [2]Pfizer Brazil; [3]Pfizer Colombia; [4]Pfizer Central America and Caribbean; [5]Pfizer, Inc., New York, NY, USA; [6]Pfizer United Kingdom; [7]Pfizer Inc., Groton, CT, USA

Introduction

Ceftazidime - avibactam (CAZ-AVI) is a β-lactam/non - β-lactam β - lactamase inhibitor combination with *in vitro* activity against Enterobacterales and *Pseudomonas aeruginosa* carrying Class A, C and some Class D β-lactamases. We examined the *in vitro* activity of CAZ-AVI and comparators against isolates collected in Latin America as part of the ATLAS surveillance program.

Methods

Non-duplicate isolates of Enterobacterales (n=8416) and *P. aeruginosa* (n=2521) were collected in 10 countries in Central America (CAC; Costa Rica, Dominican Republic, Guatemala, Panama [2018-2019 only]) and South America (SA; Argentina, Brazil, Chile, Colombia, Mexico, Venezuela [2017-2019]). Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution. MIC values for all agents were interpreted using CLSI 2020 guidelines with the exception of tigecycline, which was interpreted using United States Food and Drug Administration breakpoints [1-3]. CAZ-AVI was tested at a fixed concentration of 4 µg/mL AVI. Isolates with meropenem (MEM) MICs ≥2 µg/mL (Enterobacterales) or ≥4 µg/mL (*P. aeruginosa*) were screened for β-lactamase genes [4,5].

Results

Table 1. *In vitro* activity of ceftazidime-avibactam and comparators against Enterobacterales isolates collected in Latin America

Region	Phenotype (n)	Drug/MIC$_{90}$ (µg/ml)/Percent susceptible (%)											
		CAZ-AVI		CAZ		MEM		TZP		AMK		TGC	
		MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S
Latin America	All (8416)	0.5	98.2	64	67.9	0.12	93.2	>64	82.7	8	96.2	1	97.2
	MEM-NS (570)	>128	74.7	>128	5.4	>16	0.0	>64	1.9	>32	70.2	2	95.6
Central America	All (1058)	0.5	94.9	128	69.9	0.12	94.3	64	85.4	8	95.8	1	98.1
	MEM-NS (60)	>128	10.0	>128	1.7	>16	0.0	>64	1.7	>32	48.3	2	98.3
Costa Rica	All (185)	0.5	98.4	64	75.7	0.12	98.4	32	88.7	4	98.9	1	99.5
	MEM-NS (3)	--	0.0	--	0.0	--	0.0	--	0.0	--	33.3	--	100
Dominican Republic	All (193)	0.25	100	32	75.1	≤0.06	100	8	95.3	8	96.4	2	97.9
	MEM-NS (0)	--	--	--	--	--	--	--	--	--	--	--	--
Guatemala	All (364)	>128	86.3	>128	58.2	16	85.2	>64	73.4	16	90.7	1	99.2
	MEM-NS (54)	>128	7.4	>128	1.9	>16	0.0	>64	1.9	>32	46.3	2	98.2
Panama	All (316)	0.5	99.7	64	76.6	≤0.06	99.1	16	91.5	4	99.7	1	96.2
	MEM-NS (3)	--	66.7	--	0.0	--	0.0	--	0.0	--	100	--	100
South America	All (7358)	0.5	98.6	64	67.6	0.12	93.1	>64	82.4	8	96.2	1	97.1
	MEM-NS (510)	>128	82.4	>128	5.9	>16	0.0	>64	2.0	>32	72.8	2	95.3
Argentina	All (1039)	0.5	98.9	64	71.7	0.25	91.6	>64	79.1	8	94.8	2	96.8
	MEM-NS (87)	4	92.0	>128	2.3	>16	0.0	>64	1.2	>32	65.5	2	97.7
Brazil	All (1646)	1	98.4	64	71.7	8	87.7	>64	78.0	8	96.5	2	97.5
	MEM-NS (202)	>128	87.6	>128	5.0	>16	0.0	>64	0.5	>32	79.7	2	97.0
Chile	All (805)	0.5	100	128	67.2	0.12	97.3	>64	84.5	8	96.8	1	97.4
	MEM-NS (22)	4	100	>128	0.0	2	0.0	>64	4.6	8	95.5	2	90.9
Colombia	All (1252)	0.5	98.9	64	72.1	0.5	91.5	>64	80.8	8	96.2	1	97.0
	MEM-NS (107)	32	89.7	>128	13.1	>16	0.0	>64	0.9	32	71.0	2	95.3
Mexico	All (1802)	0.5	98.2	128	55.3	0.12	96.7	32	86.2	8	96.7	1	96.6
	MEM-NS (59)	>128	49.2	>128	6.8	>16	0.0	>64	10.2	>32	67.8	4	86.4
Venezuela	All (814)	0.25	97.8	32	74.5	0.12	96.0	32	87.1	8	96.0	1	97.2
	MEM-NS (33)	>128	48.5	>128	0.0	>16	0.0	>64	0.0	>32	48.5	2	97.0

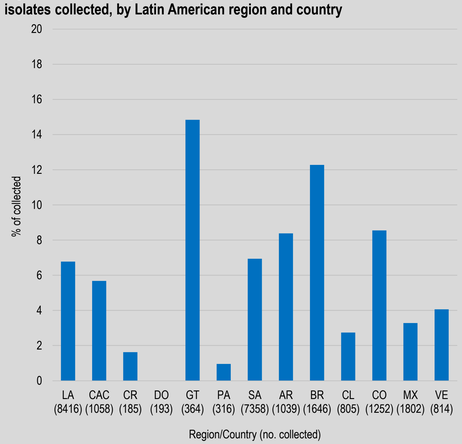
Latin America was divided in two subregions for this analysis: Central America (Costa Rica, Dominican Republic, Guatemala, Panama) and South America (Argentina, Brazil, Chile, Colombia, Mexico, Venezuela). CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; TGC, tigecycline; %S, percent susceptible; MEM-NS, meropenem non-susceptible (MIC ≥2 µg/ml); --, MIC$_{90}$ was not calculated for n<10 isolates.

Table 2. *In vitro* activity of ceftazidime-avibactam and comparators against *P. aeruginosa* isolates collected in Latin America

Region	Phenotype (n)	Drug/MIC$_{90}$ (µg/ml)/Percent susceptible (%)									
		CAZ-AVI		CAZ		MEM		TZP		AMK	
		MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S
Latin America	All (2521)	32	87.0	64	71.5	>8	66.9	>64	69.1	>32	82.1
	MEM-NS (835)	64	61.9	>128	35.3	>8	0.0	>64	28.6	>32	52.3
Central America	All (348)	8	92.2	32	81.6	>8	78.2	>64	79.3	>32	85.9
	MEM-NS (76)	128	65.8	>128	44.7	>8	0.0	>64	31.6	>32	48.7
Costa Rica	All (55)	4	96.4	32	81.8	8	85.5	64	81.8	8	98.2
	MEM-NS (8)	--	87.5	--	87.5	--	0.0	--	75.0	--	87.5
Dominican Republic	All (64)	4	98.4	8	93.8	1	92.2	16	96.9	32	87.5
	MEM-NS (5)	--	80.0	--	60.0	--	0.0	--	60.0	--	80.0
Guatemala	All (149)	8	90.6	64	75.8	>8	71.8	>64	71.8	>32	79.2
	MEM-NS (42)	64	66.7	64	38.1	>8	0.0	>64	21.4	>32	33.3
Panama	All (80)	16	87.5	32	82.5	>8	73.8	64	77.5	32	88.8
	MEM-NS (21)	>128	52.4	>128	38.1	>8	0.0	>64	28.6	>32	57.1
South America	All (2173)	32	86.1	128	69.9	>8	65.1	>64	67.5	>32	81.5
	MEM-NS (759)	64	61.5	>128	34.4	>8	0.0	>64	28.3	>32	52.7
Argentina	All (308)	8	97.4	64	75.0	>8	72.4	>64	69.8	>32	85.1
	MEM-NS (85)	8	91.8	64	36.5	>8	0.0	>64	20.0	>32	55.3
Brazil	All (425)	8	95.3	64	78.6	>8	72.9	>64	73.7	16	90.8
	MEM-NS (115)	32	86.1	128	62.6	>8	0.0	>64	47.8	>32	78.3
Chile	All (257)	32	77.4	128	58.0	>8	53.3	>64	57.6	>32	77.0
	MEM-NS (120)	32	51.7	>128	18.3	>8	0.0	>64	16.7	>32	56.7
Colombia	All (384)	16	87.5	128	71.4	>8	67.7	>64	69.3	>32	85.9
	MEM-NS (124)	64	62.1	128	35.5	>8	0.0	>64	29.0	>32	60.5
Mexico	All (562)	64	80.3	>128	64.4	>8	57.7	>64	64.1	>32	74.6
	MEM-NS (238)	>128	55.0	>128	32.8	>8	0.0	>64	31.1	>32	42.9
Venezuela	All (237)	32	76.0	64	71.3	>8	67.5	>64	69.6	>32	74.3
	MEM-NS (77)	128	26.0	>128	18.2	>8	0.0	>64	16.9	>32	23.4

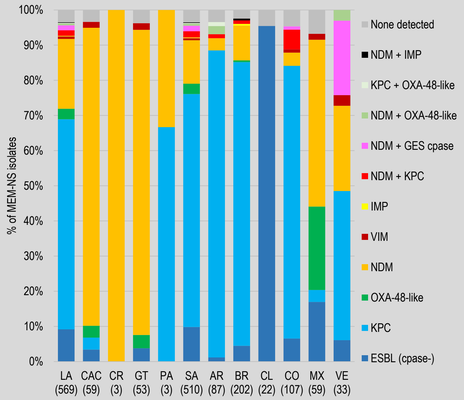
Latin America was divided in two subregions for this analysis: Central America (Costa Rica, Dominican Republic, Guatemala, Panama) and South America (Argentina, Brazil, Chile, Colombia, Mexico, Venezuela). CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; %S, percent susceptible; MEM-NS, meropenem non-susceptible (MIC ≥4 µg/ml); --, MIC$_{90}$ was not calculated for n<10 isolates.

Figure 1. Percentage of meropenem non-susceptible Enterobacterales isolates collected, by Latin American region and country



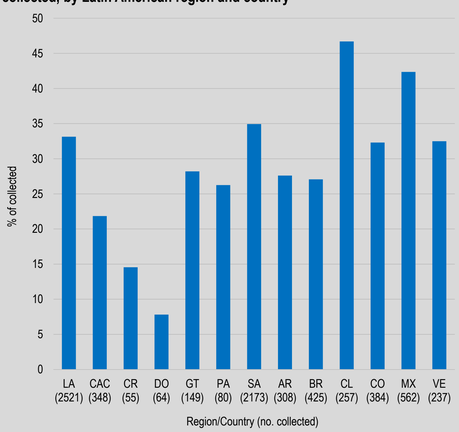
LA, Latin America; CAC, Central American countries; CR, Costa Rica; DO, Dominican Republic; GT, Guatemala; PA, Panama; SA, South America; AR, Argentina; BR, Brazil; CL, Chile; CO, Colombia; MX, Mexico; VE, Venezuela

Figure 2. Distribution of resistance mechanisms among meropenem non-susceptible Enterobacterales isolates



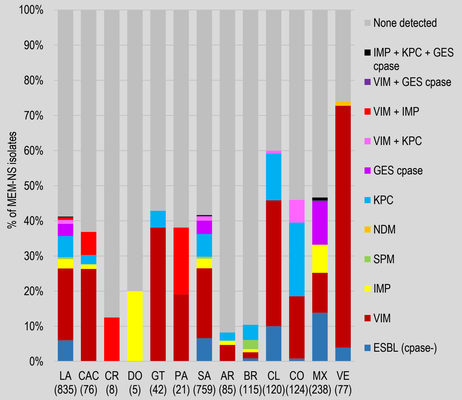
LA, Latin America; CAC, Central American countries; CR, Costa Rica; GT, Guatemala; PA, Panama; SA, South America; AR, Argentina; BR, Brazil; CL, Chile; CO, Colombia; MX, Mexico; VE, Venezuela; Cpase, carbapenemase; None detected, no gene encoding an acquired β-lactamase was detected by PCR. ESBL (cpase-) included isolates carrying CTX-M-type and SHV-type ESBLs. No MEM-NS Enterobacterales were collected in the Dominican Republic during the surveyed time period.

Figure 3. Percentage of meropenem non-susceptible *P. aeruginosa* isolates collected, by Latin American region and country



LA, Latin America; CAC, Central American countries; CR, Costa Rica; DO, Dominican Republic; GT, Guatemala; PA, Panama; SA, South America; AR, Argentina; BR, Brazil; CL, Chile; CO, Colombia; MX, Mexico; VE, Venezuela

Figure 4. Distribution of resistance mechanisms among meropenem non-susceptible *P. aeruginosa* isolates



LA, Latin America; CAC, Central American countries; CR, Costa Rica; DO, Dominican Republic; GT, Guatemala; PA, Panama; SA, South America; AR, Argentina; BR, Brazil; CL, Chile; CO, Colombia; MX, Mexico; VE, Venezuela; Cpase, carbapenemase; None detected, no gene encoding an acquired β-lactamase was detected by PCR. ESBL (cpase-) included isolates carrying ESBL-like GES and PER-type β-lactamases.

Results

- CAZ-AVI demonstrated potent *in vitro* activity against Enterobacterales collected in Latin America (LA) overall and in the Central American (CAC) and South American (SA) subregions (95-99% susceptible) that was comparable to or exceeded the activity of comparators including meropenem, amikacin and tigecycline. On the country level, percentages of susceptibility to CAZ-AVI were >97% in all countries except Guatemala (86% susceptible) (Table 1).
- 6.8% of Enterobacterales collected in LA tested as meropenem-non-susceptible (MEM-NS). Percentages of MEM-NS isolates ranged from 0% (Dominican Republic) to 14.8% (Guatemala) (Figure 1).
- CAZ-AVI retained good activity against MEM-NS Enterobacterales collected in SA (82% susceptible; 6.9% of collected isolates) (Table 1, Figure 1). In this subregion, susceptibility to CAZ-AVI was >87% for all countries except Mexico and Venezuela (49% susceptible), where 49% and 52% of isolates, respectively, carried NDM-type or VIM-type metallo-β-lactamases (MBLs) (Table 1, Figure 2).
- Activity was reduced against MEM-NS isolates from CAC (10% susceptible; 5.7% of collected isolates) that included a high proportion of isolates carrying predominantly NDM-type MBLs (Guatemala, 88.7%; Costa Rica, 100% (n=3)) (Table 1, Figure 2).
- Among *P. aeruginosa*, CAZ-AVI showed greater activity than the tested comparators against overall isolates (86-92% susceptible) collected in LA and in the two subregions. On the country level, percentages of susceptibility to CAZ-AVI were >87% in 7 of 10 countries surveyed, with the lowest values observed for Chile and Venezuela (76-77% susceptible) (Table 2).
- 33% of *P. aeruginosa* collected in LA were MEM-NS. Percentages of MEM-NS isolates ranged from 7.8% (Dominican Republic) to 46.7% (Chile) (Figure 3).
- CAZ-AVI showed greater activity than the tested comparators against MEM-NS *P. aeruginosa* (61-66% susceptible) collected in LA overall and in the two subregions. Percentages of susceptibility ≥80% were observed for isolates collected in Argentina, Brazil, Costa Rica, and Dominican Republic (Table 2).
- Susceptibilities below the regional average (26-55% susceptible) were observed among isolates from Chile, Mexico, Panama, and Venezuela, which included higher proportions of MBL-positive (VIM-type, IMP-type, NDM-type) and GES carbapenemase-positive isolates (Figure 4).

Conclusions

CAZ-AVI showed potent *in vitro* activity against overall isolates of Enterobacterales and *P. aeruginosa* collected from patients in Latin America. Activity was also good against MEM-NS isolates from countries that did not included a high proportion of MBL-positive isolates.

The regional and country prevalence of different carbapenem-resistance mechanisms must be considered when evaluating treatment options; however, CAZ-AVI could provide a valuable therapeutic option for treatment of infections caused by Enterobacterales and *P. aeruginosa* in Latin America.

References

1. Clinical and Laboratory Standards Institute. 2018. M07-A11. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standards – Eleventh Edition*. Clinical and Laboratory Standards Institute, Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2020. M100-S30. *Performance standards for antimicrobial susceptibility testing, thirtieth informational supplement*. Clinical and Laboratory Standards Institute, Wayne, PA.
3. Pfizer, Inc. 2016. *Tygacil (tigecycline) prescribing information*. Pfizer, Inc., Collegeville, PA.
4. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm DF. 2015. *Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013*. Antimicrob Agents Chemother 59:3606-3610.
5. Nichols WN, de Jonge BLM, Kazmierczak KM, Karlowsky JA, Sahm DF. 2016. *In vitro susceptibility of global surveillance isolates of Pseudomonas aeruginosa to ceftazidime-avibactam (INFORM 2012 to 2014)*. Antimicrob Agents Chemother 60:4743-4749.

Disclosures

This study was sponsored by Pfizer. AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. IHMA received financial support from Pfizer in connection with the study and the development of this poster. K. Kazmierczak and D. Sahm are employees of IHMA. G. Stone, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer. M. Figueiredo, E Luengas, M Gonzalez, A. Quintana, and P. Irani are employees of Pfizer.