29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P1154 *In vitro* activity of aztreonam-avibactam against MBL-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates collected during the ATLAS Global Surveillance Program 2015-2017

Meredith Hackel*[1], Sibylle Lob[1], Krystyna Kazmierczak[1], Boudewijn Dejonge[2], Dan Sahm[1]

[1] IHMA, Inc., Schaumburg, United States, [2] Pfizer, Inc., Cambridge, United States

Background: Aztreonam-avibactam is in development for use against infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), especially isolates carrying metallo-β-lactamases (MBLs). Aztreonam is refractory to hydrolysis by MBLs but is inactivated by Class A (KPC, extended-spectrum β-lactamases) and plasmid-mediated or stably-derepressed chromosomally-encoded Class C serine β-lactamases. Avibactam inhibits the activities of Class A, C, and some Class D β-lactamases that are frequently co-carried with MBLs. This study evaluated the *in vitro* activity of aztreonam-avibactam and comparators against MBL-positive isolates of *Enterobacteriaceae* and *P. aeruginosa* collected globally in 2015-2017.

Materials/methods: 43591 *Enterobacteriaceae* and 12265 *P. aeruginosa* isolates were collected from 168 medical centres in 35 countries. Susceptibility testing was performed by CLSI broth microdilution. Aztreonam-avibactam was tested at a fixed concentration of 4 mg/L avibactam. PCR and sequencing of β-lactamase genes was performed on meropenem MIC >1 mg/L (*Enterobacteriaceae*) or MIC >2 mg/L (*P. aeruginosa*).

Results: Genes encoding MBLs were detected in 417 *Enterobacteriaceae* (222 *Klebsiella* spp., 82 *Enterobacter* spp., 41 *Citrobacter* spp., 39 Proteeae, 29 *Escherichia coli*, 3 *Serratia marcescens,* 1 *Raoultella ornithinolytica*) and 525 *P. aeruginosa* isolates. The highest proportion of MBL-positive isolates among collected *Enterobacteriaceae* was found in Romania (23/292, 7.9%), Greece (64/1433, 4.5%), Philippines (50/1363, 3.7%), and Thailand (41/1184, 3.5%); among *P. aeruginosa*, the highest proportion was found in Russia (75/365, 20.5%), Chile (53/304, 17.4%), Venezuela (49/309, 15.9%), and Greece (45/329, 13.7%). >90% of *Enterobacteriaceae* isolates co-carried MBLs and one or more Class A or Class C β-lactamases able to hydrolyze aztreonam, resulting in MIC_{90} values of ≥128 mg/L for this agent (Table). In contrast, aztreonam-avibactam demonstrated potent *in vitro* activity against these MBL-positive isolates of *Enterobacteriaceae*, with MIC_{90} values of 0.5 mg/L against NDM-, IMP- and VIM-positive isolates (Table). All 417 MBL-positive *Enterobacteriaceae* isolates were inhibited by ≤8 mg/L of aztreonam-avibactam. Aztreonam-avibactam showed limited activity against MBL-positive *P. aeruginosa*.

		Cumulative percentage of isolates inhibited at each MIC (mg/L)												
Organism (n)[a]	**Drug**	**≤0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**>128**
Enterobacteriaceae															
All MBL-positive (417)	ATM	2.2	5.0	7.4	13.2	15.8	17.0	18.9	21.3	24.9	29.5	37.9	52.3	73.4	**100**
	ATM-AVI	11.8	26.6	57.3	85.6	**94.0**	97.1	98.8	99.3	100					
NDM-positive (266)	ATM	3.4	5.3	7.1	10.5	13.5	15.4	16.5	17.7	20.7	24.4	31.2	40.2	63.5	**100**
	ATM-AVI	12.8	25.6	57.9	86.8	**94.7**	96.6	98.1	98.9	100					
VIM-positive (120)	ATM	0.8	3.3	5.8	15.8	18.3	18.3	20.8	24.2	28.3	34.2	45.8	71.7	**90.8**	100
	ATM-AVI	11.7	25.8	55.0	83.3	**91.7**	98.3	100							
IMP-positive (32)	ATM		12.5	18.8	28.1	28.1	28.1	34.4	43.8	50.0	56.3	65.6	81.3	**90.6**	100
	ATM-AVI	6.3	40.6	62.5	84.4	**96.9**	96.9	100							
P. aeruginosa															
All MBL-positive (525)	ATM				0.8	0.8	0.8	1.7	8.8	22.7	55.8	80.0	**90.5**	93.5	100
	ATM-AVI		0.2	0.4	0.8	1.3	1.3	2.7	13.3	33.7	69.3	**90.1**	96.8	98.5	100

MBL-positive, gene encoding a metallo-β-lactamase (MBL) was detected by PCR; ATM, aztreonam; ATM-AVI, aztreonam-avibactam; MIC_{90} is indicated in bold font.
[a] Includes isolates co-carrying class A, C, and D β-lactamases and one isolate co-carrying an NDM and VIM enzyme.

Conclusions: Aztreonam-avibactam was highly active *in vitro* against genotypically identified MBL-containing *Enterobacteriaceae*, regardless of serine β-lactamase co-carriage, species or country of isolation. The emergence and increasingly widespread dissemination of MBLs among *Enterobacteriaceae* warrants further development of aztreonam-avibactam for the treatment of infections caused by CRE.