Activity of Aztreonam Combined with the Beta-lactamase Inhibitor Avibactam Tested against Metallo-β-lactamase-producing Organisms

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Abstract

Objective: To evaluate the in vitro activity of aztreonam (ATM) alone, ATM combined with avibactam (AVI) and comparator antimicrobial agents tested against a collection of metallo-beta-lactamase (MBL)-producing multidrug-resistant Gram-negative strains. The emergence of NDM-producing isolates has renewed discussions about the threat and limitations to therapeutic options for infections caused by MBL-producing organisms.

Methods: 133 MBL-producers (68 Enterobacteriaceae [ENT; 10 species], 47 *Pseudomonas* spp. [PSP] and 18 *Acinetobacter* spp. [ASP]) were susceptibility tested against ATM with and without AVI and comparator agents using reference broth microdilution method according to CLSI documents. Isolates produced 23 different MBL-types, including 13 IMP-variants, 9 VIM-types and NDM-1.

Results: ATM-AVI ($MIC_{50/90}$, 0.25/1 mg/L) was very active against MBL-producing ENT; inhibiting 67 of 68 (98.5%) at ≤2 mg/L (Table). Among different species, ATM-AVI MIC_{50} values were 1, 0.25, 0.12 and 0.06 mg/L for *E. coli* (6 strains), *K. pneumoniae* (24 strains), *E. cloacae* (25 strains) and other ENT, respectively. One NDM-1-producing *E. coli* had an ATM-AVI MIC of 8 mg/L. ATM-AVI ($MIC_{50/90}$, 0.25/1 mg/L) was the most active compound tested against ENT strains. Against PSP producing MBLs, the activity of ATM alone ($MIC_{50/90}$, 16/>64 mg/L) was similar to that of the ATM-AVI combination. All other compounds exhibited very limited activity against these organisms, with the exception of colistin ($MIC_{50/90}$, 1/2 mg/L; 100.0% susceptible by CLSI and EUCAST criteria). ATM-AVI ($MIC_{50/90}$, 32/64 mg/L), ATM alone ($MIC_{50/90}$, 32/>64 mg/L) and other beta-lactam agents tested exhibited limited activity against ASP. MIC values of ≥ two-doubling dilutions for ATM-AVI (>64 mg/L) compared to ATM alone (32 mg/L) were observed for three IMP-1-producing ASP.

Agent/organism (no. tested)	No. of organisms (cumulative %) inhibited at MIC (mg/L) of[a]: ≤0.5	1	2	4	8	16	32	≥64
Enterobacteriaceae (68)								
ATM-AVI	56(82.3)[b]	8(94.1)	3(98.5)	0(98.5)	1(100.0)	-	-	-
ATM	17(25.0)	2(27.9)	0(27.9)	1(29.4)	0(29.4)	5(36.8)	3(41.2)	40(100.0)
Pseudomonas spp. (47)								
ATM-AVI	-	-	3(6.4)	7(21.3)	6(34.0)	15(66.0)	8(83.0)	8(100.0)
ATM	-	-	1(2.1)	5(12.8)	4(21.3)	15(53.2)	7(68.1)	15(100.0)
Acinetobacter spp. (18)								
ATM-AVI	-	-	2(11.1)	1(16.7)	0(16.7)	4(38.9)	3(55.6)	8(100.0)
ATM	-	-	1(5.6)	0(5.6)	3(22.2)	2(33.3)	9(83.3)	3(100.0)

a. MIC_{50} values are underlined.
b. MIC_{50} is 0.25 mg/L.

Conclusions: ATM-AVI was generally active against a large collection of MBL-producing ENT strains, regardless of bacterial species or type of MBL produced. ATM-AVI inhibited 94.1% of the MBL-producing ENT compared to 27.9% for ATM alone. ATM-AVI activity against MBL-producing PSP and ASP was similar to that of ATM alone. MBL-producing strains represent a challenge to antimicrobial therapy and the combination ATM-AVI might be an option for the treatment of infections caused by these pathogens.

Introduction

The emergence of acquired metallo-β-lactamases (MBLs) among important Gram-negative pathogens, including members of the Enterobacteriaceae, *Pseudomonas aeruginosa,* and *Acinetobacter* spp. has highlighted a significant clinical problem that was recently aggravated by the worldwide dissemination of NDM-producing strains. MBLs, which are Ambler Class B enzymes and hydrolyze the β-lactam ring using a divalent cation as co-factor, are among the enzymes with broader spectrum of activity. MBLs can hydrolyze the vast majority of β-lactam agents available for clinical use, with the exception of monobactams. However, in many instances MBL-producing isolates are resistant to aztreonam due to the presence of other acquired β-lactamases, hyperexpression of the chromosomal cephalosporinase (AmpC), increased expression of efflux pumps and/or loss of outer membrane proteins.

Introduction-cont.

Avibactam (formerly NXL104) is a non-β-lactam β-lactamase inhibitor that inhibits Ambler classes A (eg, ESBL, KPC), C (AmpC), and some class D enzymes and like other β-lactamase inhibitors currently marketed or in clinical development, avibactam does not inhibit MBLs. However, due to the broad and potent inhibitory effect that avibactam has against serine-β-lactamases, a combination of this inhibitor with a monobactam might be a viable therapeutic option to treat infections caused by organisms that produce MBLs and have elevated MIC values against this β-lactam group due to the co-production of classes A, C or D enzymes.

In this study, we evaluated the activity of aztreonam-avibactam and comparator agents tested against 133 MBL-producing strains, including Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp. isolates producing 23 different MBL-types, including 13 IMP-variants, 9 VIM-types and NDM-1.

Materials and Methods

Bacterial strains. A total of 133 MBL-producing Gram-negative isolates were included in this study, including 68 Enterobacteriaceae (10 species), 47 *Pseudomonas* spp. and 18 *Acinetobacter* spp. Bacterial species producing MBLs included: *A. baumannii* (16), *A. lwoffii* (2), *A. radioresistens* (1), *Citrobacter freundii* (1), *C. koseri* (1), *Enterobacter aerogenes* (2), *E. cloacae* (25), *Escherichia coli* (6), *Klebsiella oxytoca* (4), *K. pneumoniae* (24), *Providencia rettgeri* (2), *P. stuartii* (1), *Pseudomonas aeruginosa* (44), *P. fluorescens/putida group* (3) and *Serratia marcescens* (2).

Isolates were collected during multicenter surveillance studies and only one isolate per patient from documented infections were included in these surveys. Isolates were collected from bloodstream, respiratory tract and skin and skin structures infections according to common protocols. Species identification was confirmed by standard biochemical tests and the Vitek 2 System (bioMerieux, Hazelwood, Missouri, USA), when necessary.

MBL-encoding genes were detected by various multiplex PCR reactions and all amplicons were sequenced on both strands using previously described methods. Isolates carried IMP (52 isolates), VIM (50) and NDM-1 (31) as described in Table 1.

Antimicrobial susceptibility testing. All isolates were tested for antimicrobial susceptibility using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012). Avibactam was tested in a fixed 4 mg/L concentration. Categorical interpretations were those found in CLSI; M100-S23 and quality control (QC) was performed using *E. coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *P. aeruginosa* ATCC 27853. All QC results for comparator agents were within specified ranges as published in CLSI documents.

Results

- Overall, aztreonam-avibactam (MIC_{50}, 0.25 mg/L and MIC_{90}, 1 mg/L; Tables 2, 3 and 4) was very active against MBL-producing Enterobacteriaceae strains and 67 of 68 (98.5%) had an aztreonam-avibactam MIC of ≤2 mg/L. One NDM-1-producing *E. coli* had an aztreonam-avibactam MIC of 8 mg/L.
- Aztreonam-avibactam (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; Table 4) was very active against 24 MBL-producing *K. pneumoniae* with the highest MIC value being only 1 mg/L (Table 2). Isolates were only 20.8 and 4.2% susceptible to aztreonam and piperacillin/tazobactam, respectively, and were all resistant to cefepime and meropenem (Table 4).
- The highest aztreonam-avibactam MIC value against MBL-producing *E. cloacae* was only 2 mg/L (MIC_{90}, 1 mg/L; Tables 2 and 4). MIC values for aztreonam (36.0% susceptible), piperacillin/tazobactam (16.0% susceptible), cefepime (20.0% susceptible) and meropenem (8.0% susceptible) were generally high according to CLSI criteria (Table 4).

Results-cont.

- Aztreonam-avibactam (MIC_{50}, 16 mg/L and MIC_{90}, 64 mg/L; Table 4) was the most active β-lactam compound tested against 47 MBL-producing *Pseudomonas* spp. strains and the activity of aztreonam alone (MIC_{50}, 16 mg/L and MIC_{90}, >64 mg/L; Tables 2 and 4) was similar to that of aztreonam-avibactam combination (Table 2). All other compounds, except colistin (100.0% susceptible) exhibited very limited activity against this species (Table 3).
- The activities of aztreonam-avibactam, aztreonam and comparators agents were very similar against IMP-producing (24 strains) and VIM-producing (23 strains) *P. aeruginosa* (Tables 3 and 4). These two groups exhibited similar susceptibility patterns to the comparator agents tested (Table 3).
- Against 18 *Acinetobacter* spp. strains producing IMP or VIM enzymes, aztreonam with and without avibactam (MIC_{50}, 32 mg/L and MIC_{90}, >64 mg/L for both) and the other β-lactam agents tested exhibited limited activity (Tables 2 and 4). A MIC value of ≥2 doubling dilutions for aztreonam-avibactam (>64 mg/L) compared to aztreonam alone (32 mg/L) were observed for three IMP-1 producing *Acinetobacter* spp. strains.

Table 1. Metallo-β-lactamase types and bacterial species tested during this study.

MBL (total no. of isolates)	Organism	No. of isolates by species	MBL (total no. of isolates)	Organism	No. of isolates by species
IMP-1 (29)	*A. baumannii*	9	VIM-1 (20)	*C. koseri*	1
	A. lwoffii	2		*E. aerogenes*	1
	A. radioresistens	1		*E. cloacae*	5
	E. cloacae	7		*K. pneumoniae*	9
	E. coli	1		*P. stuartii*	1
	K. pneumoniae	1		*P. aeruginosa*	3
	P. aeruginosa	7	VIM-2 (16)	*E. cloacae*	2
	P. fluorescens/putida	1		*K. oxytoca*	1
IMP-2 (2)	*P. aeruginosa*	2		*P. aeruginosa*	12
IMP-4 (2)	*E. cloacae*	1		*P. fluorescens/putida*	1
	S. marcescens	1	VIM-23 (2)	*E. cloacae*	1
IMP-7 (1)	*P. aeruginosa*	1		*K. oxytoca*	1
IMP-13 (3)	*P. aeruginosa*	3	VIM-4 (1)	*P. aeruginosa*	1
IMP-15 (3)	*P. aeruginosa*	3	VIM-5 (4)	*E. cloacae*	1
IMP-16 (2)	*P. aeruginosa*	1		*K. pneumoniae*	1
	P. fluorescens/putida	1		*P. aeruginosa*	2
IMP-18 (2)	*K. oxytoca*	1	VIM-6 (3)	*E. cloacae*	1
	P. aeruginosa	2		*P. aeruginosa*	2
IMP-19 (1)	*S. marcescens*	1	VIM-7 (2)	*P. aeruginosa*	2
IMP-21 (1)	*E. cloacae*	1	VIM-11 (1)	*P. aeruginosa*	1
IMP-26 (3)	*E. cloacae*	1	VIM-12 (1)	*E. aerogenes*	1
	K. oxytoca	1			
	K. pneumoniae	1			
IMP-29 (1)	*P. aeruginosa*	1			
IMP-33 (1)	*P. aeruginosa*	1			

Table 2. In vitro activity of aztreonam and aztreonam-avibactam activity tested against 133 metallo-β-lactamase producing strains grouped by organisms.

Antimicrobial agent/ organism (no. tested)	No. of organisms (cumulative %) inhibited at MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Enterobacteriaceae (68)													
E. coli (6)													
Aztreonam	-	-	-	-	-	-	-	-	-	1(16.7)	0(16.7)	1(33.3)	4(100.0)
Aztreonam-avibactam	-	-	2(33.0)	0(33.3)	0(33.3)	2(66.7)	1(83.3)	0(83.3)	1(100.0)	-	-	-	-
E. cloacae (25)													
Aztreonam	-	3(12.0)	1(16.0)	2(24.0)	1(28.0)	2(36.0)	0(36.0)	0(36.0)	0(36.0)	2(44.0)	3(56.0)	5(76.0)	6(100.0)
Aztreonam-avibactam	3(12.0)	5(32.0)	5(52.0)	2(60.0)	5(80.0)	3(92.0)	2(100.0)	-	-	-	-	-	-
K. pneumoniae (24)													
Aztreonam	-	2(8.3)	1(12.5)	2(20.8)	0(20.8)	0(20.8)	0(20.8)	0(20.8)	0(20.8)	0(20.8)	0(20.8)	4(37.5)	15(100.0)
Aztreonam-avibactam	1(4.7)	5(25.0)	4(41.7)	9(79.2)	4(95.8)	1(100.0)	-	-	-	-	-	-	-
Others (13)[a]													
Aztreonam	1(7.7)	2(23.1)	0(23.1)	1(30.8)	1(38.5)	0(38.5)	0(38.5)	1(46.2)	0(46.2)	2(61.5)	0(61.5)	2(76.9)	3(100.0)
Aztreonam-avibactam	3(23.1)	4(58.9)	1(61.5)	2(76.9)	1(84.6)	2(100.0)	-	-	-	-	-	-	-
Pseudomonas spp. (47)[b]													
Aztreonam	-	-	-	-	-	-	1(2.1)	5(12.8)	4(21.3)	15(53.2)	7(68.1)	7(83.0)	8(100.0)
Aztreonam-avibactam	-	-	-	-	-	-	3(6.4)	7(21.3)	6(34.0)	15(66.0)	8(83.0)	4(91.5)	4(100.0)
P. aeruginosa (44)													
Aztreonam	-	-	-	-	-	-	1(2.3)	5(13.6)	4(22.7)	15(56.8)	4(65.9)	7(81.8)	8(100.0)
Aztreonam-avibactam	-	-	-	-	-	-	3(6.8)	7(22.7)	6(36.4)	15(70.5)	6(83.0)	3(90.9)	4(100.0)
Acinetobacter spp. (18)													
Aztreonam	-	-	-	-	-	-	1(5.6)	0(5.6)	3(22.2)	2(33.3)	9(83.3)	3(100.0)	-
Aztreonam-avibactam	-	-	-	-	-	-	2(11.1)	1(16.7)	0(16.7)	4(38.9)	3(55.6)	5(83.3)	3(100.0)

a. Includes *Citrobacter freundii* (1), *C. koseri* (1), *E. areogenes* (2), *K. oxytoca* (4), *Providencia rettgeri* (2), *P. stuartii* (1) and *Serratia marcescens* (2).
b. Includes *P. aeruginosa* (44) and *P. fluorescens/putida* (3).

Table 3. In vitro activity of aztreonam and aztreonam-avibactam activity tested against 130 metallo-β-lactamase producing strains grouped by organisms and enzyme families (*P. fluorescens/putida* isolates were not included in this analysis).

Antimicrobial agent/ group/enzyme (no. tested)	No. of organisms (cumulative %) inhibited at MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Enterobacteriaceae (68)													
IMP-producers (17)													
Aztreonam	-	2(11.8)	0(11.8)	4(35.3)	1(41.2)	0(41.2)	0(41.2)	0(41.2)	0(41.2)	2(52.9)	1(58.8)	4(82.4)	3(100.0)
Aztreonam-avibactam	1(5.9)	5(35.3)	4(58.8)	0(58.8)	4(82.4)	3(100.0)	-	-	-	-	-	-	-
NDM-producers (25)													
Aztreonam	1(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	0(4.0)	5(24.0)	19(100.0)
Aztreonam-avibactam	3(12.0)	2(20.0)	3(32.0)	9(68.0)	2(76.0)	4(92.0)	1(96.0)	0(96.0)	1(100.0)	-	-	-	-
VIM-producers (26)													
Aztreonam	-	5(19.3)	2(26.9)	1(30.8)	1(34.6)	2(42.3)	0(42.3)	1(46.2)	0(46.2)	3(57.7)	2(65.4)	3(76.9)	6(100.0)
Aztreonam-avibactam	3(11.5)	7(38.5)	5(57.7)	4(73.1)	4(88.5)	1(92.3)	2(100.0)	-	-	-	-	-	-
P. aeruginosa (44)													
IMP-producers (21)													
Aztreonam	-	-	-	-	-	-	1(4.8)	4(23.8)	2(33.3)	4(52.4)	3(66.7)	6(95.3)	1(100.0)
Aztreonam-avibactam	-	-	-	-	-	-	2(9.5)	5(33.3)	2(42.9)	5(66.7)	2(76.2)	3(90.5)	2(100.0)
VIM-producers (23)													
Aztreonam	-	-	-	-	-	-	-	1(4.3)	2(13.0)	11(60.9)	1(65.2)	1(67.6)	7(100.0)
Aztreonam-avibactam	-	-	-	-	-	-	1(4.3)	2(13.0)	4(30.4)	10(73.9)	4(91.5)	0(91.5)	2(100.0)
Acinetobacter spp. (18)													
IMP-producers (12)													
Aztreonam	-	-	-	-	-	-	1(8.3)	0(8.3)	3(33.3)	2(50.0)	6(100.0)	-	-
Aztreonam-avibactam	-	-	-	-	-	-	2(16.7)	1(25.0)	0(25.0)	3(50.0)	0(50.0)	3(75.0)	3(100.0)
NDM-producers (6)													
Aztreonam	-	-	-	-	-	-	-	-	-	-	3(50.0)	3(100.0)	-
Aztreonam-avibactam	-	-	-	-	-	-	-	-	-	1(16.7)	3(66.7)	2(100.0)	-

Table 4. Activity of aztreonam alone and in combination with avibactam (fixed 4 mg/L) and comparator antimicrobial agents when tested against 130 MBL-producing Gram-negative isolates (*P. fluorescens/putida* isolates were not included in this analysis).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All Enterobacteriaceae (68)					
Aztreonam-avibactam	0.25	1	≤0.03 – 8	- / -	- / -
Aztreonam	64	>64	≤0.03 – >64	29.4 / 70.6	27.9 / 70.6
Piperacillin/tazobactam	>256	>256	2 – >256	14.7 / 72.1	8.8 / 85.3
Cefepime	>64	>64	1 – >64	11.8 / 80.9	1.5 / 91.2
Meropenem	8	>32	0.25 – >32	5.9 / 80.9	19.1 / 47.1
Ciprofloxacin	4	>16	≤0.008 – >16	30.9 / 57.4	25.0 / 69.1
Tigecycline[b]	0.5	4	0.12 – 8	89.7 / 1.5	77.9 / 10.3
Colistin	0.5	>16	0.25 – >16	- / -	83.8 / 16.2
K. pneumoniae (24)					
Aztreonam-avibactam	0.25	0.5	≤0.03 – 1	- / -	- / -
Aztreonam	>64	>64	0.06 – >64	20.8 / 79.2	20.8 / 79.2
Piperacillin/tazobactam	>256	>256	4 – >256	4.2 / 91.7	4.2 / 95.8
Cefepime	>64	>64	16 – >64	0.0 / 91.7	0.0 / 100.0
Meropenem	16	>32	2 – >32	0.0 / 79.2	20.8 / 62.5
Ciprofloxacin	16	>16	0.015 – >16	16.7 / 75.0	12.5 / 83.3
Tigecycline[b]	1	4	0.25 – 8	87.5 / 4.2	70.8 / 12.5
Colistin	0.5	1	0.25 – 1	- / -	100.0 / 0.0
E. cloacae (25)					
Aztreonam-avibactam	0.12	1	≤0.03 – 2	- / -	- / -
Aztreonam	32	>64	0.06 – >64	36.0 / 64.0	36.0 / 64.0
Piperacillin/tazobactam	256	>256	4 – >256	16.0 / 64.0	8.0 / 84.0
Cefepime	>64	>64	1 – >64	20.0 / 80.0	4.0 / 84.0
Meropenem	8	32	1 – >32	8.0 / 76.0	24.0 / 28.0
Ciprofloxacin	1	>16	≤0.008 – >16	52.0 / 36.0	44.0 / 48.0
Tigecycline[b]	0.5	2	0.25 – 4	96.0 / 0.0	84.0 / 4.0
Colistin	0.5	>16	0.25 – >16	- / -	80.0 / 20.0
P aeruginosa (44)					
Aztreonam-avibactam	16	64	2 – >64	- / -	- / -
Aztreonam	16	>64	2 – >64	21.3 / 46.8	0.0 / 46.8
Piperacillin/tazobactam	64	256	4 – >256	23.4 / 46.8	23.4 / 76.6
Cefepime	>64	>64	8 – >64	2.1 / 87.2	2.1 / 97.9
Meropenem	>32	>32	4 – >32	0.0 / 95.7	0.0 / 93.6
Ciprofloxacin	16	>16	0.06 – >16	12.8 / 80.9	12.8 / 87.2
Tigecycline[b]	8	16	2 – >16	- / -	- / -
Colistin	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Acinetobacter spp. (18)					
Aztreonam-avibactam	32	>64	2 – >64	- / -	- / -
Aztreonam	32	64	2 – 64	22.2 / 66.7	- / -
Piperacillin/tazobactam	>256	>256	≤0.12 – >256	38.9 / 61.1	- / -
Cefepime	64	>64	0.5 – >64	11.1 / 72.2	- / -
Meropenem	>32	>32	0.5 – >32	16.7 / 77.8	11.1 / 77.8
Ciprofloxacin	>16	>16	0.06 – >16	33.3 / 55.6	33.3 / 66.7
Tigecycline[b]	0.5	2	0.12 – 4	- / -	- / -
Colistin	0.5	16	0.25 – 16	88.9 / 11.1	88.9 / 11.1

a. Criteria as published by the CLSI [2013] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].

Conclusions

- Aztreonam-avibactam was very active against this large collection of metallo-β-lactamase producing Enterobacteriaceae strains, regardless of the bacterial species or type of metallo-β-lactamase produced.
- Aztreonam-avibactam activity against metallo-β-lactamase producing *Pseudomonas* spp. and *Acinetobacter* spp. was most similar to that of aztreonam when tested alone.
- Avibactam was able to restore aztreonam activity against the vast majority of metallo-β-lactamase producing strains of Enterobacteriaceae, but had limited effect against metallo-β-lactamase producing *Pseudomonas* spp. and *Acinetobacter* spp.

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