eP435

Ceftazidime-Avibactam Activity Tested Against Select Gram-Negative Organisms from a Global Surveillance Programme (2011) in Relation to the Ceftazidime Epidemiologic Cut-off Value

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Abstract

Objectives: The effect of avibactam (AVI) on the activity of ceftazidime (CAZ) as measured by the CAZ-AVI MIC frequency distribution of select Gram-negative (GN) clinical isolates from the SENTRY Antimicrobial Surveillance Programme was compared to European Committee for Antimicrobial Susceptibility Testing (EUCAST) MIC epidemiological cut-off values (ECOFFs) listed for CAZ. CAZ-AVI, a combination of CAZ and the novel non-β-lactam β-lactamase inhibitor AVI, targets GN bacteria and is currently in clinical development.

Methods: The activity of CAZ-AVI and CAZ as measured in the 2011 SENTRY Antimicrobial Surveillance Programme for select GN bacteria for each region (Europe and Mediterranean, USA, Asia-Pacific, and Latin American region) was compared to ECOFF values from the EUCAST website (accessed at http://mic.eucast.org [14 November 2013]; see Abstract Table). Clinically relevant isolates were collected at medical centres from a variety of infection sites, including bloodstream, respiratory, skin and soft tissue, urinary and others. Susceptibility testing for CAZ and CAZ-AVI was conducted according to Clinical and Laboratory Standards Institute guidelines using validated dry-form broth microdilution panels. AVI was tested at a fixed concentration of 4 mg/L.

Results: For *Escherichia coli*, CAZ-AVI $MIC_{50/90}$ values ranged from 0.06–0.12/0.12–0.25 mg/L, respectively across all regions (EUCAST CAZ ECOFF, 0.5 mg/L). The CAZ MIC_{90} values for *E. coli* varied regionally from 2–>32 mg/L. For *Klebsiella pneumoniae*, CAZ-AVI MIC_{50} values were 0.12 mg/L in each region and MIC_{90} values ranged from 0.25–0.5 mg/L (EUCAST CAZ ECOFF, 0.5 mg/L). The MIC_{90} values for CAZ for *K. pneumoniae* were >32 mg/L in each region. The MIC_{90} for CAZ-AVI for *Enterobacter cloacae* ranged from 0.5–1 mg/L (EUCAST CAZ ECOFF, 1 mg/L). The MIC_{90} for CAZ in each region was >32 mg/L. The MIC_{90} for CAZ-AVI for *Citrobacter* spp. ranged from 0.25–0.5 mg/L (CAZ ECOFF, 1 mg/L). The MIC_{90} for CAZ in each region was >32 mg/L. *Morganella morganii* and *Proteus mirabilis* MIC_{90} values ranged from 0.06–0.25 mg/L and 0.06–0.12 mg/L, respectively, for CAZ-AVI (CAZ ECOFF values, 0.25 and 0.12 mg/L, respectively). MIC_{90} values for CAZ-AVI against *Serratia marcescens* were 0.5 mg/L for all regions (EUCAST CAZ ECOFF, 0.5 mg/L). *Haemophilus influenzae* MIC_{90} values ranged from ≤0.03–0.06 mg/L (EUCAST CAZ ECOFF, 0.5 mg/L). *Pseudomonas aeruginosa* MIC_{90} values for CAZ-AVI ranged from 8–16 mg/L while CAZ MIC_{90} values ranged from 32–>32 mg/L (EUCAST CAZ ECOFF, 8 mg/L). A total of 86.2–95.8% of *P. aeruginosa* isolates per region exhibited CAZ-AVI MIC values ≤8 mg/L (66.2–83.1% for CAZ only).

Conclusions: CAZ-AVI was highly active against select GN isolates from European, USA, Asia-Pacific, and Latin American regions. CAZ-AVI MIC_{90} values for most GN isolates were lowered to the ECOFF MIC value for CAZ alone or lower, demonstrating the beneficial effect of the addition of AVI.

Organism (N)	Ceftazidime-avibactam MIC in mg/L by region:[a] EMR MIC_{50}	EMR MIC_{90}	USA MIC_{50}	USA MIC_{90}	LATAM MIC_{50}	LATAM MIC_{90}	APAC MIC_{50}	APAC MIC_{90}	EUCAST ECOFF (CAZ) in mg/L
	(N=4,627)		(N=3,233)		(N=1,444)		(N=1,958)		
Enterobacteriaceae	0.06	0.25	0.12	0.25	0.12	0.25	0.12	0.25	NA
	(N=2,113)		(N=718)		(N=517)		(N=670)		
Escherichia coli	0.06	0.12	0.06	0.12	0.06	0.25	0.12	0.25	0.5
	(N=858)		(N=818)		(N=373)		(N=445)		
Klebsiella pneumoniae	0.12	0.5	0.12	0.25	0.12	0.5	0.12	0.25	0.5
	(N=428)		(N=379)		(N=172)		(N=219)		
Enterobacter cloacae	0.12	0.5	0.12	0.5	0.25	1	0.25	1	1
	(N=200)		(N=272)		(N=51)		(N=146)		
Citrobacter spp.	0.12	0.25	0.12	0.25	0.12	0.5	0.12	0.5	1
	(N=165)		(N=192)		(N=61)		(N=133)		
Morganella morganii	≤0.03	0.12	0.06	0.12	0.06	0.25	≤0.03	0.06	0.25
	(N=270)		(N=230)		(N=57)		(N=56)		
Proteus mirabilis	≤0.03	0.06	≤0.03	0.06	≤0.03	0.12	≤0.03	0.06	0.12
	(N=273)		(N=237)		(N=118)		(N=161)		
Serratia marcescens	0.12	0.5	0.12	0.5	0.12	0.5	0.12	0.5	0.5
	(N=1,137)		(N=213)		(N=517)		(N=612)		
Pseudomonas aeruginosa	2	16	2	8	2	16	2	8	8
	(N=758)		(N=909)		(N=126)		(N=323)		
Haemophilus influenzae	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	0.06	0.5

[a]Abbreviations: EMR, European and Mediterranean; LATAM, Latin America; APAC, Asia-Pacific

Introduction

The novel non-β-lactam β-lactamase inhibitor avibactam provides a broad-spectrum inhibition profile against both class A and class C enzymes, including extended spectrum β-lactamases and KPC serine carbapenemases, as well as activity against some class D enzymes. As avibactam has very limited intrinsic antibacterial activity, the activity profile of the ceftazidime-avibactam combination depends on the antibacterial activity of ceftazidime. Ceftazidime-avibactam has been shown to exhibit potent *in vitro* activity against Gram-negative bacteria including Enterobacteriaceae strains producing class A and C β-lactamases and *Pseudomonas aeruginosa*. Its activity has been confirmed in Phase II clinical trials for complicated urinary tract infections (cUTI) and complicated intraabdominal infections (cIAI). The ceftazidime-avibactam combination is in Phase III development for indications including cIAI, cUTI and nosocomial pneumonia.

The epidemiological cut-off value (ECOFF) is the value that characterises the upper-end of a wild-type minimal inhibitory concentration (MIC) distribution. The European Committee for Antimicrobial Susceptibility Testing (EUCAST) defines this MIC value in the form 'WT≤Xmg/L and provides the MIC distributions and corresponding ECOFF values on their website (http://mic.eucast.org/Eucast2/). A variety of information is taken into account when establishing susceptibility interpretive criteria/susceptibility breakpoints including pharmacokinetics/pharmacodynamics, clinical outcome information and analysis of MIC population distributions. The ECOFF value which defines the upper-limit of the wild-type population could be viewed as potentially defining the inherently "susceptible" population. This value can then be refined by the application of pharmacokinetic/pharmacodynamic and clinical outcome information to define clinical breakpoints.

The aim of this study was to evaluate the activity of ceftazidime-avibactam and comparator agents against contemporary clinical isolates collected in a global antibacterial surveillance programme during 2011 and to evaluate the MIC frequency distributions in relation to the ECOFFs for ceftazidime.

Materials and Methods

Clinically relevant isolates were collected at medical centres in Europe and the Mediterranean region (EMR), USA, Latin America (LATAM) and Asia-Pacific (APAC) from a variety of infection sites, including bloodstream, respiratory, skin and soft tissue, urinary and others. Susceptibility testing by broth microdilution was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines in cation-adjusted Mueller-Hinton broth in validated dry-form panels manufactured by ThermoFisher Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA), to determine the antimicrobial susceptibility of ceftazidime-avibactam and comparator agents. *Haemophilus influenzae* were tested in *Haemophilus* test medium (M07-A9, 2012). Avibactam was tested at a fixed concentration of 4 mg/L. Isolates with an extended spectrum β-lactamase (ESBL) phenotype were defined as a MIC ≥2 mg/L for any one of ceftriaxone, or ceftazidime, or aztreonam (CLSI, 2014).

Quality control (QC) testing was performed using the QC strains: *Escherichia coli* ATCC 25922 and ATCC 35218, *P. aeruginosa* ATCC 27853, and *H. influenzae* ATCC 49247 and 49766. QC results were within published CLSI guidelines (M100-S24).

Results

- Ceftazidime-avibactam $MIC_{50/90}$ values ranged from 0.06–0.12/0.25 mg/L for the 4,627 Enterobacteriaceae; ceftazidime $MIC_{50/90}$ values ranged from 0.12–0.25/16–>32 mg/L (Table 1).
- For *E. coli*, ceftazidime-avibactam $MIC_{50/90}$ values ranged from 0.06–0.12/0.12–0.25 mg/L, respectively, across all regions (European Committee on Antimicrobial Susceptability Testing [EUCAST] ceftazidime ECOFF, 0.5 mg/L). The ceftazidime MIC_{90} values for *E. coli* varied regionally from 2–>32 mg/L (USA and APAC, respectively; Table 1). Figure 1 shows that in the presence of avibactam the ceftazidime MIC distribution was shifted to lower MIC values such that 98.9% of MIC values were at or below the ECOFF value for ceftazidime as opposed to 73.3% for ceftazidime alone.

Table 1. Regional MIC_{50} and MIC_{90} values for ceftazidime-avibactam and ceftazidime for select Gram-negative bacteria in comparison to ECOFF values

Antimicrobial agent (N)	EMR MIC_{50}	EMR MIC_{90}	USA MIC_{50}	USA MIC_{90}	LATAM MIC_{50}	LATAM MIC_{90}	APAC MIC_{50}	APAC MIC_{90}	EUCAST ECOFF (ceftazidime) in mg/L
Enterobacteriaceae	N=4,627		N=3,233		N=1,444		N=1,958		NA
CAZ-AVI	0.06	0.25	0.12	0.25	0.12	0.25	0.12	0.25	
Ceftazidime	0.25	32	0.12	16	0.25	>32	0.25	>32	
E. coli	N=2,113		N=718		N=517		N=670		0.5
CAZ-AVI	0.06	0.12	0.06	0.12	0.06	0.25	0.12	0.25	
Ceftazidime	0.12	16	0.12	2	0.25	32	1	>32	
K. pneumoniae	N=858		N=818		N=373		N=445		0.5
CAZ-AVI	0.12	0.5	0.12	0.25	0.12	0.5	0.12	0.25	
Ceftazidime	2	>32	0.12	>32	2	>32	0.5	>32	
E. cloacae	N=428		N=379		N=172		N=219		1
CAZ-AVI	0.12	0.5	0.12	0.5	0.25	1	0.25	1	
Ceftazidime	0.25	>32	0.25	>32	2	>32	0.5	>32	
Citrobacter spp.	N=200		N=272		N=51		N=146		1
CAZ-AVI	0.12	0.25	0.12	0.25	0.12	0.5	0.12	0.5	
Ceftazidime	0.25	>32	0.25	>32	0.5	>32	0.5	>32	
M. morganii	N=165		N=192		N=61		N=133		0.25
CAZ-AVI	≤0.03	0.12	0.06	0.12	0.06	0.25	≤0.03	0.06	
Ceftazidime	0.12	16	0.12	16	0.25	16	0.12	16	
P. mirabilis	N=270		N=230		N=57		N=56		0.125
CAZ-AVI	≤0.03	0.06	≤0.03	0.06	≤0.03	0.12	≤0.03	0.06	
Ceftazidime	0.06	1	0.06	0.12	0.06	2	0.06	0.25	
S. marcescens	N=273		N=237		N=118		N=161		0.5
CAZ-AVI	0.12	0.5	0.12	0.5	0.12	0.5	0.12	0.5	
Ceftazidime	0.12	0.5	0.25	0.5	0.12	16	0.25	0.25	
P. aeruginosa	N=1,137		N=213		N=517		N=612		8
CAZ-AVI	2	16	2	8	2	16	2	8	
Ceftazidime	4	>32	2	32	4	>32	4	>32	
H. influenzae	N=758		N=909		N=126		N=323		0.5
CAZ-AVI	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	0.06	
Ceftazidime	0.06	0.12	0.06	0.12	0.06	0.12	0.06	0.12	

CAZ-AVI, ceftazidime-avibactam

- Ceftazidime-avibactam MIC_{50} values for *Klebsiella pneumoniae* were 0.12 mg/L in each region and MIC_{90} values ranged from 0.25–0.5 mg/L (Table 1; EUCAST ceftazidime ECOFF, 0.5 mg/L). The MIC_{90} values for ceftazidime for *K. pneumoniae* were >32 mg/L in each region (Table 1). Figure 2 shows a downward shift of ceftazidime MIC values in the presence of avibactam. A total of 93.4% of ceftazidime-avibactam MIC values from the global 2011 surveillance programme were at or below the EUCAST ECOFF value of 0.5 mg/L (Figure 2). Only 60.1% of ceftazidime MIC values in the absence of avibactam were ≤0.5 mg/L (Figure 2).
- Avibactam decreased the regional *Enterobacter cloacae* ceftazidime MIC_{90} values to a MIC value ≤1 mg/L (the EUCAST ECOFF value for ceftazidime alone). The $MIC_{50/90}$ for ceftazidime-avibactam for *E. cloacae* ranged from 0.12–0.25/0.5–1 mg/L (Table 1). The regional $MIC_{50/90}$ for CAZ ranged from 0.25–2/>32 mg/L (Table 1). A total of 96.6% of all ceftazidime-avibactam MIC values were less than or equal to the ceftazidime ECOFF while only 65.8% of ceftazidime MICs were less than or equal to the ceftazidime ECOFF.
- Regional ceftazidime-avibactam $MIC_{50/90}$ values for *Citrobacter* spp. ranged from 0.12/0.25–0.5 mg/L (Table 1). These regional MIC_{90} values were two- to four-fold lower than the EUCAST ECOFF for ceftazidime alone, 1 mg/L. The regional ceftazidime $MIC_{50/90}$ values ranged from 0.25–0.5/>32 mg/L (Table 1). A total of 98.7% of all ceftazidime-avibactam MIC values were less than or equal to the ceftazidime ECOFF while only 76.8% of ceftazidime MICs were less than or equal to the ceftazidime ECOFF.
- Avibactam reduced the ceftazidime $MIC_{50/90}$ values for *Morganella morganii* to ≤0.03–0.06/0.06–0.25 mg/L (Table 1). The EMR and USA regional ceftazidime-avibactam MIC_{90} value of 0.12 mg/L was two-fold lower than the ceftazidime EUCAST ECOFF (0.25 mg/L). A total of 98.7% of all ceftazidime-avibactam MIC values were less than or equal to the ceftazidime ECOFF while only 65.0% of ceftazidime MICs were less than or equal to the ceftazidime ECOFF.

Figure 1. MIC distribution for the global collection of *E. coli* (4,018) for ceftazidime-avibactam and ceftazidime compared to the EUCAST *E. coli* ceftazidime MIC distribution

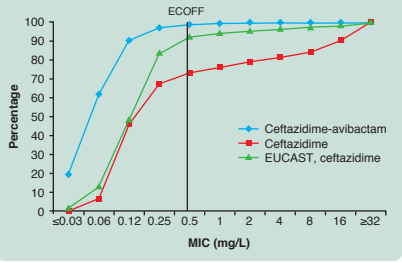


Figure 2. MIC distribution for the global collection of *K. pneumoniae* (2,494) for ceftazidime-avibactam and ceftazidime compared to the EUCAST *K. pneumoniae* ceftazidime MIC distribution

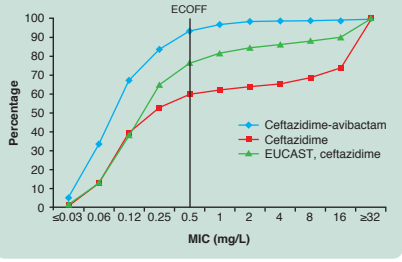
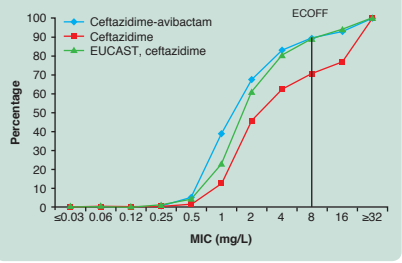


Figure 3. MIC distribution for the global collection of *P. aeruginosa* (2,479) for ceftazidime-avibactam and ceftazidime compared to the EUCAST *P. aeruginosa* ceftazidime MIC distribution



- Regional ceftazidime-avibactam MIC_{90} values for *Proteus mirabilis* ranged from 0.06–0.12 mg/L (Table 1). The highest regional value of 0.12, which was equal to the EUCAST ECOFF value for ceftazidime (0.125 mg/L), occurred in LATAM (Table 1). Ceftazidime $MIC_{50/90}$ values ranged from 0.06/0.12–2 mg/L (Table 1). The highest ceftazidime MIC_{90} value occurred in LATAM isolates (Table 1). A total of 98.7% of all ceftazidime-avibactam MIC values were less than or equal to the ceftazidime ECOFF while 89.7% of ceftazidime MICs were less than or equal to the ceftazidime ECOFF.
- Ceftazidime-avibactam $MIC_{50/90}$ values against *Serratia marcescens* in each region were 0.12/0.5 mg/L (Table 1) whereas ceftazidime $MIC_{50/90}$ values ranged from 0.12–0.25/0.25–16 mg/L (highest regional MIC_{90} value: 16 mg/L, LATAM). The EUCAST ECOFF value for *S. marcescens* was 0.5 mg/L (Table 1). A total of 97.2% of all ceftazidime-avibactam MIC values were less than or equal to the ceftazidime ECOFF while 90.1% of ceftazidime MICs were less than or equal to the ceftazidime ECOFF.
- Avibactam reduced the ceftazidime $MIC_{50/90}$ values for *H. influenzae* to ≤0.03/≤0.03–0.06 mg/L (Table 1). The EUCAST ECOFF value for *H. influenzae* was 0.5 mg/L (Table 1).
- Regional *P. aeruginosa* $MIC_{50/90}$ values for ceftazidime-avibactam ranged from 2/8–16 mg/L while ceftazidime $MIC_{50/90}$ values ranged from 2–4/32–>32 mg/L (EUCAST ceftazidime ECOFF, 8 mg/L). EMR and LATAM were the regions which demonstrated the highest ceftazidime-avibactam MIC_{90} (16 mg/L; Table 1). For all regions combined, 89.2% of isolates exhibited a ceftazidime-avibactam MIC value ≤8 mg/L compared to 70.1% for ceftazidime alone (Figure 3). A total of 86.2–95.8% of *P. aeruginosa* isolates per region exhibited ceftazidime-avibactam MIC values ≤8 mg/L (66.2–83.1% for ceftazidime only from the global surveillance programme). In the EMR, 86.2% of *P. aeruginosa* isolates exhibited a MIC value ≤8 mg/L and in LATAM, 89.2%. The regional differences in the activity of ceftazidime and ceftazidime-avibactam activity may be due to varying prevalences of *P. aeruginosa* with resistance mechanisms such as the elevated number of strains harbouring the metallo-β-lactamase VIM-2 as noted by Castanheira et al. in various European countries in 2011.

Conclusions

Ceftazidime-avibactam was highly active against select Gram-negative isolates from the EMR, USA, LATAM and APAC regions. Regional MIC_{90} values for ceftazidime-avibactam against Enterobacteriaceae were ≤1 mg/L, which is the susceptible EUCAST breakpoint for Enterobacteriaceae for ceftazidime alone. For *P. aeruginosa*, the regional MIC_{90} values for the USA and APAC for ceftazidime-avibactam were ≤8 mg/L. In the EMR and LATAM, 86.2 and 89.2% of isolates exhibited MIC values ≤8 mg/L, respectively. These regional differences presumably are reflective of a differing prevalence of resistant strains/mechanisms. Ceftazidime MIC values in the presence of avibactam for most Gram-negative isolates were lowered to MIC values that were equal to or lower than the EUCAST ceftazidime ECOFF MIC value, demonstrating the beneficial effect of the addition of avibactam.

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CAZ-AVI Phase II and III study numbers

Phase II CAZ-AVI studies in cIAI and cUTI: NCT00752219 and NCT00690378, respectively.
Phase III CAZ-AVI studies in cIAI: NCT01726023, NCT01499290 and NCT01500239.
Phase III CAZ-AVI studies in cUTI: NCT01595438 and NCT01599806.
Phase III CAZ-AVI study in nosocomial pneumonia: NCT01808092.

This study was funded by AstraZeneca, and JMI Laboratories received compensation fees for services in relation to preparing the abstract/poster, which was also funded by AstraZeneca. Poster typesetting was provided by Prime Medica Ltd, Knutsford, Cheshire, UK, funded by AstraZeneca. Presented at the 24th European Society of Clinical Microbiology and Infectious Diseases (ECCMID), 10–13 May 2014, Barcelona, Spain.