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Antimicrobial Activity of Ceftaroline Combined with Avibactam Tested Against Contemporary (2012) Bacteria Collected from USA Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSIs)

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Abstract

Objective: To evaluate the activity of ceftaroline (CPT)-avibactam (AVI) tested against bacteria from ABSSSI collected in USA hospitals in 2012. CPT fosamil is a novel parenteral cephalosporin approved by the European Medicines Agency and USA Food and Drug Administration for treatment of complicated skin and soft tissue infections and ABSSSI, respectively, including those caused by MRSA. AVI is a novel non-β-lactam β-lactamase inhibitor of Ambler class A, C, and some D enzymes.

Methods: 5,140 isolates were consecutively collected in 2012 from 90 USA medical centres. Susceptibility (S) testing for CPT-AVI (AVI at fixed 4 mg/L), CPT alone and comparators was performed by CLSI broth microdilution methods. S interpretations were per EUCAST and CLSI breakpoints.

Results: The most common organisms were *S. aureus* (SA; 3,481; 50.5% MRSA), *E. coli* (EC; 444; 13.3% ESBL-phenotype), β-haemolytic streptococci (BHS; 389) and *Klebsiella* spp. (KSP; 338, 13.3% ESBL-phenotype and 5.3% meropenem [MER]-non-S). All EC, including ESBL-phenotype strains, were inhibited at CPT-AVI MIC values of only ≤0.5 mg/L (EUCAST and CLSI S breakpoint for CPT), and 99.3% of EC had CPT-AVI MIC ≤0.12 mg/L. CPT-AVI was also active against KSP (MIC_{90}, 0.25 mg/L), including ESBL-phenotype (MIC_{90}, 0.5 mg/L) and MER-non-S strains (MIC_{90}, 0.5 mg/L), and *Enterobacter* spp. (MIC_{90}, 0.25 mg/L), including ceftazidime (CAZ)-resistant (R) strains (MIC_{90}, 1 mg/L). Only 2 Enterobacteriaceae (0.2%) had CPT-AVI MIC at >1 mg/L, one *K. pneumoniae* and one *S. marcescens*, both with CPT-AVI MIC of 4 mg/L (see Table 1). All oxacillin-S (MSSA) and -R SA (MRSA) strains were inhibited at ≤0.5 and ≤2 mg/L of CPT-AVI respectively; and CPT MIC results were not adversely affected by the addition of AVI. CPT-AVI was 16-fold more active than ceftriaxone against MSSA. BHS, viridans group streptococci and coagulase-negative staphylococci were CPT-AVI-S with MIC_{90} values of ≤0.015, 0.03 and 0.5 mg/L, respectively.

Conclusions: CPT-AVI and CPT were the most potent β-lactam agents tested against staphylococci and streptococci collected from patients with ABSSSI in USA hospitals in 2012. MRSA was particularly S to CPT-AVI and CPT ($MIC_{50/90}$, 0.5/1 mg/L). CPT-AVI was also highly active against Enterobacteriaceae-producing KPC serine carbapenemase, various ESBL types, and AmpC (chromosomal or plasmid-mediated) enzymes. CPT-AVI demonstrated potent in vitro efficacy against resistant pathogens associated with ABSSSI in the USA.

Introduction

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin with notable *in vitro* bactericidal activity against organisms commonly responsible for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin-structure infections (ABSSSIs), including multidrug-resistant (MDR) *Streptococcus pneumoniae* and methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is also active against common Enterobacteriaceae species but, like many cephalosporins, has limited potencies against isolates producing extended-spectrum β-lactamases (ESBLs), cephalosporinases and carbapenemases. However, the spectrum of activity of ceftaroline can be expanded when combined with avibactam, a β-lactamase inhibitor.

Avibactam (formerly, NXL104) is a non-β-lactam β-lactamase inhibitor currently in clinical development with ceftazidime, ceftaroline and aztreonam. Avibactam protects β-lactams from hydrolysis by a variety of strains producing Ambler class A, C, and some D enzymes, including ESBLs and *Klebsiella pneumoniae* carbapenemase (KPC) β-lactamases. We report the *in vitro* activity of ceftaroline combined with avibactam (fixed concentration of 4 mg/L) tested against bacterial organisms from ABSSSI collected in USA hospitals in 2012, as part of a worldwide resistance surveillance programme.

Methods

A total of 5,140 bacterial isolates were collected from 90 medical centres distributed across all USA Census Regions for the Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) surveillance programme in 2012. Organisms were collected from clinical infections, as defined by local clinical criteria, and target numbers of strains for each of the requested bacterial species/genus were predetermined by study protocol. Species identification was performed at the participant medical centre and confirmed at the monitor laboratory (JMI Laboratories, North Liberty, Iowa, USA) using the Vitek2 System (bioMerieux, Hazelwood, Missouri, USA) or MALDI-TOF (Bruker Daltonics, Bremen, Germany) when necessary. Only one strain per patient infection episode was included in the surveillance study.

Isolates were tested for susceptibility to ceftaroline-avibactam (avibactam at a fixed concentration of 4 mg/L), ceftaroline and multiple comparator agents at a central (monitor) laboratory (JMI Laboratories) by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) document. Susceptibility interpretations were per EUCAST and CLSI breakpoints (CLSI, 2013; EUCAST, 2013). *E. coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" and "non-ESBL-phenotype" based on the CLSI screening criteria for ESBL production. Those isolates with positive ESBL screening test, ie. MIC of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam were categorized as "ESBL-phenotype" for the purpose of susceptibility testing results analysis.

Results

- The most common organisms were *S. aureus* (3,481; 50.5% MRSA), *E. coli* (444; 13.3% ESBL-phenotype), β-haemolytic streptococci (βHS; 389) and *Klebsiella* spp. (338, 13.3% ESBL-phenotype and 5.3% meropenem-non-susceptible [CLSI criteria])
- All *E. coli*, including ESBL-phenotype strains, were inhibited at ceftaroline-avibactam MIC values of only ≤0.5 mg/L (EUCAST and CLSI susceptible breakpoint for ceftaroline), and 99.3% of *E. coli* had ceftaroline-avibactam MIC ≤0.12 mg/L (Table 1)
- Ceftaroline-avibactam was highly active against *Klebsiella* spp. (MIC_{90}, 0.25 mg/L; Table 2), including ESBL-phenotype (MIC_{90}, 0.5 mg/L) and meropenem-non-susceptible strains (MIC_{90}, 0.5 mg/L), and *Enterobacter* spp. (MIC_{90}, 0.25 mg/L), including ceftazidime-non-susceptible strains (MIC_{90}, 1 mg/L; Table 1)
- Only two Enterobacteriaceae (0.2%) had ceftaroline-avibactam MIC at >1 mg/L, one *K. pneumoniae* and one *S. marcescens*, both with ceftaroline-avibactam MIC of 4 mg/L (Table 1)
- Antimicrobial activities of ceftaroline-avibactam, ceftaroline and comparator agents when tested against gram-negative organisms are summarized in Table 2
- All oxacillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA) strains were inhibited at ≤0.5 and ≤2 mg/L of ceftaroline-avibactam respectively (Table 1); and ceftaroline MIC results were not adversely affected by the addition of avibactam (data not shown)
- Ceftaroline-avibactam (MIC_{50} and MIC_{90}, 0.25 mg/L) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L; data not shown) against MSSA
- βHS, viridans group streptococci and coagulase-negative staphylococci were ceftaroline-avibactam-susceptible with MIC_{90} values of ≤0.015, 0.03 and 0.5 mg/L, respectively (Table 1).

Table 2. Antimicrobial activities of ceftaroline-avibactam, ceftaroline and comparator agents when tested against gram-negative organisms from skin and skin structure infections (USA, 2012).

Organism (no tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	%S / %I / %R CLSI[a]	EUCAST[a]
E. coli (444)					
Ceftaroline-avibactam	0.03	0.06	≤0.015 – 0.5	- / - / -	- / - / -
Ceftaroline	0.12	32	≤0.015 – >32	83.3 / 2.7 / 14.0	83.3 / 0.0 / 16.7
Ceftriaxone	≤0.06	>8	≤0.06 – >8	87.4 / 0.0 / 12.6	87.4 / 0.0 / 12.6
Ceftazidime	0.12	4	0.03 – >32	90.8 / 1.5 / 7.7	87.8 / 3.0 / 9.2
Piperacillin/tazobactam	2	8	≤0.5 – >64	96.4 / 2.5 / 1.1	94.6 / 1.8 / 3.6
Meropenem	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	67.3 / 0.6 / 32.1	67.3 / 0.0 / 32.7
Gentamicin	≤1	>8	≤1 – >8	88.5 / 0.2 / 11.3	87.2 / 1.3 / 11.5
Klebsiella spp.[b] (338)					
Ceftaroline-avibactam	0.06	0.25	≤0.015 – 4	- / - / -	- / - / -
Ceftaroline	0.12	>32	≤0.015 – >32	83.4 / 3.0 / 13.6	83.4 / 0.0 / 16.6
Ceftriaxone	≤0.06	>8	≤0.06 – >8	87.9 / 0.6 / 11.5	87.9 / 0.6 / 11.5
Ceftazidime	0.12	8	0.03 – >32	88.8 / 1.7 / 9.5	88.2 / 0.6 / 11.2
Piperacillin/tazobactam	2	64	≤0.5 – >64	88.8 / 1.7 / 9.5	82.8 / 6.0 / 11.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	94.7 / 0.3 / 5.0	95.0 / 1.7 / 3.3
Levofloxacin	≤0.12	4	≤0.12 – >4	89.6 / 1.2 / 9.2	88.4 / 1.2 / 10.4
Gentamicin	≤1	2	≤1 – >8	92.6 / 2.7 / 4.7	92.3 / 0.3 / 7.4
Enterobacter spp.[c] (102)					
Ceftaroline-avibactam	0.12	0.25	≤0.015 – 1	- / - / -	- / - / -
Ceftaroline	0.25	>32	≤0.015 – >32	76.5 / 5.9 / 17.6	76.5 / 0.0 / 23.5
Ceftriaxone	0.25	>8	≤0.06 – >8	80.4 / 2.0 / 17.6	80.4 / 2.0 / 17.6
Ceftazidime	0.25	>32	0.03 – >32	83.3 / 0.0 / 16.7	81.4 / 1.9 / 16.7
Piperacillin/tazobactam	4	64	≤0.5 – >64	87.1 / 5.0 / 7.9	78.2 / 8.9 / 12.9
Meropenem	≤0.06	≤0.06	≤0.06 – 4	99.0 / 0.0 / 1.0	99.0 / 1.0 / 0.0
Levofloxacin	≤0.12	0.5	≤0.12 – >4	97.0 / 1.0 / 2.0	92.1 / 4.9 / 3.0
Gentamicin	≤1	≤1	≤1 – >8	98.0 / 1.0 / 1.0	98.0 / 0.0 / 2.0
Citrobacter spp.[d] (77)					
Ceftaroline-avibactam	0.06	0.12	≤0.015 – 0.5	- / - / -	- / - / -
Ceftaroline	0.12	16	0.03 – >32	84.4 / 1.3 / 14.3	84.4 / 0.0 / 15.6
Ceftriaxone	0.12	8	≤0.06 – >8	85.7 / 1.3 / 13.0	85.7 / 1.3 / 13.0
Ceftazidime	0.25	16	0.06 – >32	87.0 / 2.6 / 10.4	85.7 / 1.3 / 13.0
Piperacillin/tazobactam	4	32	1 – >64	89.6 / 6.5 / 3.9	83.1 / 6.5 / 10.4
Meropenem	≤0.06	≤0.06	≤0.06 – >8	97.4 / 0.0 / 2.6	97.4 / 1.3 / 1.3
Levofloxacin	≤0.12	1	≤0.12 – >4	92.2 / 1.3 / 6.5	92.2 / 0.0 / 7.8
Gentamicin	≤1	≤1	≤1 – >8	92.2 / 1.3 / 6.5	92.2 / 0.0 / 7.8
Serratia marcescens (51)					
Ceftaroline-avibactam	0.5	1	0.12 – 4	- / - / -	- / - / -
Ceftaroline	1	4	0.25 – >32	31.4 / 43.1 / 25.5	31.4 / 0.0 / 68.6
Ceftriaxone	0.25	2	≤0.06 – >8	86.3 / 3.9 / 9.8	86.3 / 3.9 / 9.8
Ceftazidime	0.25	0.5	0.06 – >32	94.1 / 0.0 / 5.9	94.1 / 0.0 / 5.9
Piperacillin/tazobactam	2	16	≤0.5 – >64	94.1 / 3.9 / 2.0	88.2 / 5.9 / 5.9
Meropenem	≤0.06	≤0.06	≤0.06 – 2	98.0 / 2.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.25	2	≤0.12 – >4	92.2 / 1.9 / 5.9	82.4 / 9.8 / 7.8
Gentamicin	≤1	2	≤1 – >8	98.0 / 0.0 / 2.0	96.1 / 1.9 / 2.0
Morganella morganii (27)					
Ceftaroline-avibactam	0.06	0.25	≤0.015 – 1	- / - / -	- / - / -
Ceftaroline	0.25	>32	0.03 – >32	66.7 / 0.0 / 33.3	66.7 / 0.0 / 33.3
Ceftriaxone	≤0.06	4	≤0.06 – >8	85.2 / 3.7 / 11.1	85.2 / 3.7 / 11.1
Ceftazidime	0.25	16	0.06 – >32	85.2 / 3.7 / 11.1	74.1 / 11.1 / 14.8
Piperacillin/tazobactam	≤0.5	8	≤0.5 – >64	96.3 / 0.0 / 3.7	92.6 / 3.7 / 3.7
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	70.4 / 18.5 / 11.1	66.7 / 3.7 / 29.6
Gentamicin	≤1	>8	≤1 – >8	77.8 / 0.0 / 22.2	77.8 / 0.0 / 22.2

a. Criteria as published by the CLSI (2013) and EUCAST (2013).
b. Includes: *Klebsiella oxytoca* (83 strains) and *K. pneumoniae* (255 strains).
c. Includes: *Enterobacter aerogenes* (18 strains) and *E. cloacae* (84 strains)
d. Includes: *Citrobacter freundii* (35 strains), *C. koseri* (40 strains) and unspeciated *Citrobacter* (2 strains).

Table 1. Summary of ceftaroline-avibactam tested against common pathogens isolated from skin and skin structure infections in USA hospitals (2012).

Organism (no. tested)/ antimicrobial agent	no. of isolates (cumulative %) inhibited at ceftaroline-avibactam MIC (mg/L) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	MIC_{50}	MIC_{90}
S. aureus (3481)	-	1 (<0.1)	15 (0.5)	241 (7.4)	1448 (49.0)	1433 (90.2)	324 (99.5)	19 (100.0)	-	0.5	0.5
MSSA (1723)	-	1 (<0.1)	15 (0.9)	241 (14.9)	1410 (96.8)	56 (100.0)	-	-	-	0.25	0.25
MRSA (1757)	-	-	-	-	38 (2.2)	1377 (80.5)	324 (98.9)	19 (100.0)	-	0.5	1
β-haemolytic strep. (389)	374 (96.1)	14 (99.7)	1 (100.0)	-	-	-	-	-	-	≤0.015	≤0.015
CoNS (185)	2 (1.1)	14 (8.7)	43 (31.9)	19 (42.2)	87 (89.2)	20 (100.0)	-	-	-	0.25	0.5
Viridans group strep (46)	17 (37.0)	26 (93.5)	3 (100.0)	-	-	-	-	-	-	0.03	0.03
E. coli (444)	116 (26.1)	216 (74.8)	103 (98.0)	6 (99.3)	2 (99.8)	1 (100.0)	-	-	-	0.03	0.06
Non-ESBL-phenotype[a] (385)	110 (28.6)	195 (79.2)	78 (99.5)	2 (100.0)	-	-	-	-	-	0.03	0.06
ESBL-phenotype[a] (59)	6 (10.2)	21 (45.8)	25 (88.1)	4 (94.9)	2 (98.3)	1 (100.0)	-	-	-	0.06	0.12
Klebsiella spp. (338)	6 (1.8)	103 (32.3)	153 (77.5)	38 (88.8)	26 (96.5)	11 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.06	0.25
non-ESBL-phenotype[a] (293)	2 (2.1)	99 (35.9)	144 (85.0)	26 (93.9)	15 (99.0)	3 (100.0)	-	-	-	0.06	0.12
ESBL-phenotype[a] (45)	-	4 (8.9)	9 (28.9)	12 (55.6)	11 (80.0)	8 (97.8)	0(97.8)	0(97.8)	1 (100.0)	0.12	0.5
meropenem-non-susc.[b] (18)	-	-	-	4 (22.2)	8 (66.7)	5 (94.4)	0 (94.4)	0 (94.4)	1 (100.0)	0.25	0.5
Enterobacter spp. (102)	4 (3.8)	7 (10.8)	26 (36.3)	38 (75.5)	17 (90.2)	8 (98.0)	2 (100.0)	-		0.12	0.25
Ceftazidime-susc.[c] (85)	4 (4.7)	7 (12.9)	26 (43.5)	37 (87.1)	10 (98.8)	1 (100.0)	-	-		0.12	0.25
Ceftazidime-non-susc[c] (17)	-	-	-	1 (5.9)	7 (47.1)	7 (88.2)	2 (100.0)	-		0.5	1
Citrobacter spp. (77)	2 (2.6)	13 (19.5)	42 (74.0)	16 (94.8)	3 (98.7)	1 (100.0)	-	-		0.06	0.12
M. morganii (27)	3 (11.1)	10 (48.2)	6 (70.4)	5 (88.9)	1 (92.6)	1 (96.3)	1 (100.0)	-		0.06	0.25
S. marcescens (51)	-	-	-	4 (7.8)	6 (19.6)	26 (70.6)	14 (98.0)	0 (98.0)	1 100.0)	0.5	1

a. ESBL phenotype defined as a MIC ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam (CLSI, 2013).
b. Meropenem MIC of ≥2 mg/L (CLSI, 2013).
c. Ceftazidime susceptible at MIC of ≤4 mg/L and non-susceptible at MIC of ≥8 mg/L (CLSI, 2013).
Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus* and CoNS = coagulase-negative staphylococci.

Conclusions

- Ceftaroline-avibactam was highly active against ESBL-phenotype and carbapenem-non-susceptible Enterobacteriaceae
- Ceftaroline-avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci
- MRSA was particularly susceptible to ceftaroline-avibactam and ceftaroline ($MIC_{50/90}$, 0.5/1 mg/L)
- Ceftaroline-avibactam demonstrated potent *in vitro* activity against resistant pathogens associated with ABSSSI in the USA.

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