IDWEEK 2012
845

Antimicrobial Activity of Ceftaroline Combined with Avibactam Tested Against Bacteria Collected from Patients with Acute Bacterial Skin and Skin Structure Infections in USA Medical Centers (2011)

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Abstract

Background: Ceftaroline, the active form of ceftaroline fosamil, is a broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive cocci (GPC), including MRSA, and common Enterobacteriaceae (ENT). Avibactam is a novel non-β-lactam β-lactamase inhibitor of Ambler class A, C, and some D enzymes. Ceftaroline-avibactam was tested against recent (2011) clinical isolates from acute bacterial skin and skin structure infections (ABSSSI).

Methods: 6648 isolates were consecutively collected in 2011 from 67 USA medical centers representing all 9 Census Regions (4-10 centers/region). Susceptibility testing for ceftaroline-avibactam (avibactam at fixed 4 μg/mL), ceftaroline and comparators was performed by CLSI broth microdilution methods.

Results: The most frequently isolated organisms were *S. aureus* (SA; 2898; 51.5% MRSA), β-haemolytic streptococci (BHS; 1233), *E. coli* (440; 12.7% ESBL-phenotype), *Klebsiella* spp. (409; 16.6% ESBL-phenotype and 5.4% meropenem-non-susceptible), coagulase-negative staphylococci (CoNS; 340), viridans group streptococci (VGS; 264) and *Enterobacter* spp. (188; 18.1% ceftazidime-non-susceptible). Ceftaroline-avibactam was 16-fold more active than ceftriaxone against methicillin-susceptible SA and inhibited all MRSA at ≤2 μg/mL. BHS, VGS and CoNS were ceftaroline-avibactam-susceptible with MIC_{90} values of ≤0.03, 0.06 and 0.5 μg/mL, respectively. Ceftaroline activity against GPC was not adversely impacted by the addition of avibactam. All *E. coli*, including ESBL-phenotype strains, were inhibited at ceftaroline-avibactam MIC values of only ≤0.5 μg/mL. Ceftaroline-avibactam was also active against *Klebsiella* spp. (MIC_{90}, 0.12 μg/mL), including ESBL-phenotype and meropenem-non-susceptible strains (MIC_{90}, 1 μg/mL for both subsets). Highest ceftaroline-avibactam MIC among ceftazidime-non-susceptible ESP was only 1 μg/mL.

Conclusions: Ceftaroline-avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci collected from patients with ABSSSI in USA hospitals evaluated in this study during 2011. MRSA was particularly S to ceftaroline-avibactam and ceftaroline ($MIC_{50/90}$, 0.5/1 μg/mL). Ceftaroline-avibactam was also highly active against ENT-producing KPC serine carbapenemase, various ESBL types, and AmpC (chromosomal- or plasmid-mediated) enzymes. Ceftaroline-avibactam demonstrated potent in vitro efficacy against resistant pathogens associated with ABSSSI in the USA.

Introduction

β-lactams are among the most prescribed antimicrobial agents in the community and hospital settings. However, increasing resistance, mainly due to the emergence and dissemination of β-lactamases, has limited the utility of this class of agents. Ceftaroline fosamil is a new cephalosporin prodrug approved by the United States of America Food and Drug Administration (USA-FDA) in 2010 for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs), including ABSSSI caused by methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). More recently (August 28, 2012), the European Medicines Agency (EMA) approved ceftaroline fosamil for treatment of adults with complicated skin and soft tissue infections and community-acquired pneumonia. Ceftaroline, the active form of ceftaroline fosamil, is also active against most Enterobacteriaceae species but, like other cephalosporins, has limited activity against isolates producing extended-spectrum β-lactamases (ESBLs), cephalosporinases and carbapenemases.

Avibactam (previously known as NXL104) is a new non-β-lactam β-lactamase inhibitor currently in clinical development. Avibactam efficiently protects β-lactams from hydrolysis by a variety of strains producing Ambler class A, C, and some D enzymes, including ESBLs and KPC enzymes (carbapenemases). Thus, the addition of avibactam protects ceftaroline activity against resistance that many Enterobacteriaceae strains have developed to broad-spectrum cephalosporins due to the production of β-lactamases. We report the in vitro activity of ceftaroline combined with avibactam (fixed concentration of 4 μg/mL) tested against bacterial organisms isolated in USA medical centers in 2011, as part of a worldwide surveillance program.

Methods

Organisms collection: A total of 6,648 isolates were tested as listed in Table 1. Sixty-seven medical centers from all 9 USA census regions (4 to 10 centers per region) contributed clinical isolates in 2011. Organisms were consecutively collected from patients with skin and skin structure infections and target numbers of strains for each of the requested bacterial species/genus were predetermined in the study protocol. Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, Iowa, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance study.

Susceptibility testing: Isolates were tested for susceptibility to ceftaroline-avibactam and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) and CLSI interpretations were based on M100-S22 breakpoints. *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime MIC values were ≥2 μg/mL were considered to be phenotype-positive for ESBL production (CLSI, 2012), and *Klebsiella* spp. isolates with a meropenem MIC value ≥2 μg/mL were considered meropenem-non-susceptible. Ceftaroline interpretations followed the breakpoint criteria established by the USA-FDA. Ceftaroline was combined with avibactam at a fixed concentration of 4 μg/mL. β-haemolytic streptococci were tested in Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood, whereas the other organisms were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control strains assured proper test conditions.

Results

- The most frequently isolated organisms were *S. aureus* (2,898; 51.5% MRSA), β-haemolytic streptococci (1,233), *E. coli* (440; 12.7% ESBL-phenotype), *Klebsiella* spp. (409; 16.6% ESBL-phenotype and 5.4% meropenem-non-susceptible), coagulase-negative staphylococci (CoNS; 340), viridans group streptococci (264) and *Enterobacter* spp. (188; 18.1% ceftazidime-non-susceptible)
- Ceftaroline-avibactam (MIC_{50} and MIC_{90}, 0.25 μg/mL) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 μg/mL) and four- to eight-fold more active than linezolid ($MIC_{50/90}$, 1/2 μg/mL) when tested against oxacillin- (methicillin-) susceptible *S. aureus* (MSSA; data not shown). The highest ceftaroline-avibactam MIC value among MSSA strains was only 0.5 μg/mL and 94.0% of strains were inhibited at a ceftaroline-avibactam MIC of ≤0.25 μg/mL (Table 1)
- Against MRSA ($MIC_{50/90}$, 0.5/1 μg/mL), 97.9% and 100.0% of strains were inhibited at ceftaroline-avibactam MIC values of ≤1 μg/mL and ≤2 μg/mL, respectively (Table 1)
- Ceftaroline-avibactam was very potent against β-haemolytic streptococci with the MIC_{90} at ≤0.03 μg/mL (Tables 1 and 2)
- Ceftaroline-avibactam was also active against CoNS and viridans group streptococci with MIC_{90} values of 0.5 and 0.06 μg/mL, respectively (Tables 1 and 2)
- All *E. coli* isolates were susceptible to ceftaroline-avibactam ($MIC_{50/90,}$ ≤0.03/0.06 μg/mL) when breakpoints established by the USA-FDA for ceftaroline tested alone (≤0.5 μg/mL) were applied. Furthermore, ceftaroline-avibactam exhibited potent activity against *E. coli* strains with an ESBL-phenotype ($MIC_{50/90,}$ 0.06/0.25 μg/mL; Table 1)
- Ceftaroline-avibactam was active against *Klebsiella* spp. ($MIC_{50/90}$, 0.06/0.12 μg/mL), including strains with an ESBL-phenotype ($MIC_{50/90}$, 0.12/1 μg/mL) and those with reduced susceptibility to carbapenems ($MIC_{50/90}$, 0.5/1 μg/mL; Table 1). Among ESBL-phenotype *Klebsiella* spp., 32.4% of strains exhibited decreased susceptibility (MIC, ≥2 μg/mL) to meropenem (Table 2)
- Among *Enterobacter* spp. strains, 97.9 and 100.0% were inhibited by ceftaroline-avibactam at ≤0.5 and ≤1 μg/mL, respectively (Table 1). Meropenem ($MIC_{90,}$ ≤0.12 μg/mL; 97.9% susceptible) and tigecycline ($MIC_{90,}$ 0.5 mg/L; 98.9% susceptible) were also very active against *Enterobacter* spp. (Table 2). Among ceftazidime-non-susceptible (MIC, ≥8 μg/mL) *Enterobacter* spp. strains, 88.2 and 100.0% of strains were inhibited at ceftaroline-avibactam MIC values of ≤0.5 and ≤1 μg/mL, respectively (Table 1).

Table 1. Summary of Ceftaroline-avibactam Activity Tested Against Pathogens Associated with ABSSSI from USA Medical Centers (2011)

Organism/subset (no. tested)	Cumulative % inhibited at ceftaroline-avibactam MIC (μg/mL) of: ≤0.03	0.06	0.12	0.25	0.5	1	2
Gram-positive cocci							
S. aureus (2898)	0.1	0.3	7.3	47.1	85.9	98.9	100.0
MSSA (1406)	0.1	0.8	15.0	94.0	100.0	–	–
MRSA (1492)	–	–	0.1	2.8	72.6	97.9	100.0
β-haemolytic streptococci (1233)	98.5	100.0	–	–	–	–	–
CoNS (340)	7.7	27.4	44.1	83.8	98.5	99.7	100.0
Viridans gr. streptococci (264)	82.6	92.4	95.8	97.0	99.2	100.0	–
Gram-negative bacilli							
E.coli (440)	63.9	92.5	98.0	99.3	100.0	–	–
non-ESBL-phenotype (384)	46.6	68.2	96.4	99.2	100.0	–	–
ESBL-phenotype (56)	33.9	66.1	89.3	96.6	100.0	–	–
Klebsiella spp. (409)	32.3	74.3	90.0	94.6	97.8	99.5	100.0
non-ESBL-phenotype (341)	35.8	82.7	97.1	99.1	100.0	–	–
ESBL-phenotype (68)	14.7	32.4	54.4	72.1	86.8	97.1	100.0
Meropenem-non-susceptible (22)	9.1	13.6	27.3	40.9	68.2	90.9	100.0
Enterobacter spp. (188)	11.7	35.6	73.9	92.0	97.9	100.0	–
Ceftazidime-susceptible (154)	14.3	41.6	85.1	97.4	100.0	–	–
Ceftazidime-non-susceptible (34)	–	8.8	23.5	67.7	88.2	100.0	–

Table 2. Activity of Ceftaroline-avibactam, Ceftaroline and Comparator Antimicrobial Agents when Tested Against Bacterial Organisms Associated with ABSSSI from USA Medical Centers (2011)

Organism/antimicrobial agent (no. tested)	MIC (μg/mL) MIC_{50}	MIC_{90}	%S / %R CLSI[a]	EUCAST[a]
Staphylococcus aureus (2,898)				
Ceftaroline-avibactam	0.5	1	- / -	- / -
Ceftaroline[b]	0.5	1	99.6 / -	- / -
Ceftriaxone	8	>8	48.5 / 51.5	48.5 / 51.5
Oxacillin	>2	>2	48.5 / 51.5	48.5 / 51.5
Erythromycin	>2	>2	37.3 / 61.4	37.4 / 62.1
Clindamycin	≤0.25	>2	87.6 / 12.3	87.3 / 12.4
Levofloxacin	≤0.5	>4	64.1 / 33.9	64.1 / 33.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.8 / 1.2	98.8 / 1.0
Tigecycline[c]	0.06	0.25	100.0 / -	100.0 / 0.0
Linezolid	1	2	>99.9 / <0.1	>99.9 / <0.1
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Coagulase-negative staphylococci (340)				
Ceftaroline-avibactam	0.25	0.5	- / -	- / -
Ceftaroline	0.25	0.5	- / -	- / -
Ceftriaxone	4	>8	34.7 / 65.3	34.7 / 65.3
Oxacillin	1	>2	34.7 / 65.3	34.7 / 65.3
Erythromycin	>2	>2	40.9 / 57.1	41.5 / 58.2
Clindamycin	≤0.25	>2	69.7 / 28.2	68.2 / 30.3
Levofloxacin	≤0.5	>4	66.2 / 31.8	66.2 / 31.8
Trimethoprim/sulfamethoxazole	≤0.5	>2	70.0 / 30.0	70.0 / 30.0
Tigecycline[c]	0.06	0.25	- / -	100.0 / 0.0
Linezolid	0.5	1	99.1 / 0.9	99.1 / 0.9
Vancomycin	1	2	100.0 / 0.0	99.4 / 0.6
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (1,233)				
Ceftaroline-avibactam	≤0.03	≤0.03	- / -	- / -
Ceftaroline	≤0.015	0.03	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	100.0 / -	100.0 / 0.0
Penicillin	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	68.5 / 30.9	68.5 / 30.9
Clindamycin	≤0.25	>2	83.2 / 16.6	83.4 / 16.6
Levofloxacin	≤0.5	1	99.0 / 0.6	95.2 / 1.0
Tetracycline	≤2	>8	52.5 / 46.4	51.9 / 47.5
Tigecycline[c]	≤0.03	0.06	100.0 / -	100.0 / 0.0
Linezolid	1	1	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Daptomycin	≤0.06	0.25	100.0 / -	100.0 / 0.0
Viridans group streptococci (264)				
Ceftaroline-avibactam	≤0.03	0.06	- / -	- / -
Ceftaroline	0.03	0.06	- / -	- / -
Ceftriaxone	≤0.25	0.5	94.7 / 2.7	91.7 / 8.3
Penicillin	≤0.06	0.25	86.4 / 2.3	90.5 / 2.3
Erythromycin	≤0.25	>2	57.2 / 38.6	- / -
Clindamycin	≤0.25	>2	87.5 / 10.2	89.8 / 10.2
Levofloxacin	≤0.5	2	94.7 / 3.8	- / -
Tetracycline	≤2	>8	63.3 / 31.4	- / -
Tigecycline[c]	≤0.03	0.06	100.0 / -	- / -
Linezolid	1	1	100.0 / -	- / -
Vancomycin	0.5	1	100.0 / -	100.0 / 0.0
Daptomycin	0.25	1	99.6 / -	- / -

Organism/antimicrobial agent (no. tested)	MIC (μg/mL) MIC_{50}	MIC_{90}	%S / %R CLSI[a]	EUCAST[a]
Escherichia coli (440)				
Ceftaroline-avibactam	≤0.03	0.06	- / -	- / -
Ceftaroline[b]	0.12	8	83.4 / 13.4	- / -
Ceftriaxone	≤0.25	8	89.3 / 10.7	89.3 / 10.7
Ceftazidime	≤1	2	91.1 / 8.2	89.3 / 8.9
Piperacillin/tazobactam	2	8	94.8 / 3.0	92.3 / 5.2
Meropenem	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤2	>8	88.6 / 11.1	87.3 / 11.4
Levofloxacin	≤0.5	>4	70.0 / 29.1	69.8 / 30.0
Tigecycline[c]	0.12	0.25	100.0 / 0.0	100.0 / 0.0
Klebsiella spp. (409)				
Ceftaroline-avibactam	0.06	0.12	- / -	- / -
Ceftaroline[b]	0.12	>16	81.4 / 16.1	- / -
Ceftriaxone	≤0.25	>8	84.6 / 14.4	84.6 / 14.4
Ceftazidime	≤1	>16	86.8 / 12.5	85.1 / 13.2
Piperacillin/tazobactam	2	>64	87.0 / 10.8	83.6 / 13.0
Meropenem	≤0.12	≤0.12	94.6 / 5.1	94.9 / 4.4
Gentamicin	≤2	≤2	92.9 / 5.1	91.4 / 7.1
Levofloxacin	≤0.5	>4	88.0 / 10.5	86.3 / 12.0
Tigecycline[c]	0.25	0.5	98.8 / 0.0	96.1 / 1.2
ESBL phenotype *Klebsiella* spp. (68)				
Ceftaroline-avibactam	0.12	1	- / -	- / -
Ceftaroline[b]	>16	>16	1.5 / 94.1	- / -
Ceftriaxone	>8	>8	7.4 / 86.8	7.4 / 86.8
Ceftazidime	>16	>16	20.6 / 75.0	10.3 / 79.4
Piperacillin/tazobactam	>64	>64	25.0 / 63.2	16.2 / 75.0
Meropenem	≤0.12	>8	67.6 / 30.9	69.1 / 26.5
Gentamicin	≤2	>8	61.8 / 27.9	52.9 / 38.2
Levofloxacin	>4	>4	36.8 / 60.3	32.4 / 63.2
Tigecycline[c]	0.5	2	95.6 / 0.0	86.8 / 4.4
Enterobacter spp. (188)				
Ceftaroline-avibactam	0.12	0.25	- / -	- / -
Ceftaroline[b]	0.25	>16	73.4 / 21.3	- / -
Ceftriaxone	≤0.25	>8	77.1 / 21.8	77.1 / 21.8
Ceftazidime	≤1	>16	81.9 / 17.0	78.7 / 18.1
Piperacillin/tazobactam	2	64	83.5 / 8.5	81.4 / 16.5
Meropenem	≤0.12	≤0.12	97.9 / 1.1	98.9 / 0.5
Gentamicin	≤2	≤2	94.7 / 4.8	94.1 / 5.3
Levofloxacin	≤0.5	≤0.5	94.1 / 4.3	93.1 / 5.9
Tigecycline[c]	0.25	0.5	98.9 / 0.0	97.3 / 1.1
Ceftazidime-non-susceptible *Enterobacter* spp. (34)				
Ceftaroline-avibactam	0.25	1	- / -	- / -
Ceftaroline[b]	>16	>16	0.0 / 100.0	- / -
Ceftriaxone	>8	>8	0.0 / 97.1	0.0 / 97.1
Ceftazidime	>16	>16	0.0 / 94.1	0.0 / 100.0
Piperacillin/tazobactam	64	>64	11.8 / 47.1	2.9 / 88.2
Meropenem	≤0.12	0.5	91.2 / 5.9	94.1 / 2.9
Gentamicin	≤2	>8	76.5 / 23.5	76.5 / 23.5
Levofloxacin	≤0.5	>4	79.4 / 17.6	76.5 / 20.6
Tigecycline[c]	0.25	1	100.0 / 0.0	97.1 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012]. β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied [Teflaro Package Insert, 2012].
c. USA-FDA breakpoints were applied [Tygacil Product Insert, 2011].

Conclusions

- Ceftaroline-avibactam and ceftaroline were the most potent β-lactam agents tested against staphylococci and streptococci collected from patients with skin and skin structure infections in the USA hospitals evaluated in the present study (2011)
- MRSA was particularly susceptible to ceftaroline-avibactam and ceftaroline ($MIC_{50/90}$, 0.5/1 μg/mL)
- Ceftaroline-avibactam was also highly active against Enterobacteriaceae with an ESBL-phenotype and *Klebsiella* spp. strains with decreased susceptibility to meropenem (possibly producing KPC serine carbapenemases)
- In summary, ceftaroline-avibactam demonstrated very potent in vitro efficacy against resistant Gram-positive and -negative pathogens associated with skin and skin structure infections in the USA.

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Acknowledgments

This study was supported by Forest Laboratories, Inc. Forest Laboratories, Inc., was involved in the study design and in the decision to present these results. Forest Laboratories, Inc., had no involvement in the analysis, collection, and interpretation of data. Scientific Therapeutics Information, Inc., provided editorial coordination, which was funded by Forest Research Institute, Inc.