1094

Antimicrobial Activity of Ceftaroline against Bacteria Isolated in 2008 from Community-acquired Respiratory Tract Infections in European Hospitals, including Methicillin-Resistant *Staphylococcus aureus*

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Amended Abstract

Objectives: To evaluate the potency and spectrum of ceftaroline tested against community-acquired respiratory tract infection (CARTI) pathogens. Ceftaroline, currently in phase III clinical development, is a novel N-phosphono prodrug cephalosporin that has high affinity for *S. aureus* PBP 2a and demonstrated bactericidal activity against methicillin-resistant *S. aureus* (MRSA) and other pathogens responsible for CARTI.

Methods: CARTI isolates (717) were consecutively collected in 2008 from 24 hospitals located in 10 European countries (EU), Turkey, and Israel. *S. aureus* isolates were obtained from patients with pneumonia occurring less than 72 hours after hospitalization. Susceptibility (S) was tested by CLSI broth microdilution method against ceftaroline and various antimicrobials used to treat CARTI.

Results: The potency of ceftaroline against 3 common pathogens associated with CARTI is summarized in the Table 1. Against *S. pneumoniae* (SPN), the activity of ceftaroline ($MIC_{50/90}$, ≤0.008/0.12 mg/L) was eight-, 16-, and 32-fold more potent than ceftriaxone ($MIC_{50/90}$, ≤0.25/1 mg/L), amoxicillin/clavulanate (A/C; $MIC_{50/90}$, ≤1/2 mg/L), and cefuroxime ($MIC_{50/90}$, ≤1/4 mg/L), respectively. Penicillin (PEN) resistance (R) was high among SPN; only 73.4% and 91.9% of strains were inhibited at ≤0.06 and ≤2 mg/L, respectively, whereas A/C inhibited 93.3% of strains at ≤2 mg/L. R was also high among the SPN isolates for erythromycin (33.6%), azithromycin (33.1%), tetracycline (27.5%), clindamycin (21.7%), and trimethoprim/sulfamethoxazole (17.0%). Ceftaroline was very active against *H. influenzae* (HI; $MIC_{50/90}$, ≤0.008/0.015 mg/L), and its activity was not adversely affected by beta-lactamase production. Ceftaroline ($MIC_{50/90}$, 0.25/0.5 mg/L) was eight- to 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L) and cefepime ($MIC_{50/90}$, 2/4 mg/L) against methicillin-susceptible *S. aureus* (MSSA). The highest ceftaroline MIC value among MRSA was 2 mg/L and 75.0% of all isolates were inhibited at ≤1 mg/L of ceftaroline. All non-MRSA Gram-positive cocci were ceftaroline susceptible at ≤0.5 mg/L (Table).

Conclusions: Bacterial pathogens recently collected (2008) from CARTI in EU medical centres were very S to ceftaroline, including community-acquired MRSA, PEN-R SPN, and other R strains. This favorable antimicrobial profile places ceftaroline as a promising and potentially effective therapeutic option in the treatment of CARTI in the EU.

Introduction

Ceftaroline fosamil (formerly PPI-0903 and TAK-599) is a *N*-phosphono-type prodrug cephalosporin. Its active form, ceftaroline, is released in vivo upon hydrolysis of the phosphonate group. This parenteral cephem has documented high affinity for PBP2a and potent in vitro activity against oxacillin (methicillin)-resistant *Staphylococcus aureus* (MRSA) and many other Gram-positive organisms, while retaining activity against many Gram-negative bacilli.

Community-acquired respiratory tract infections (CARTI), especially pneumonia (CAP), represent one of the main causes of morbidity and mortality among children and adults. The dominant bacterial causes of CARTI are *Streptococcus pneumoniae* and *Haemophilus influenzae*. In addition, community-acquired MRSA (CA-MRSA) has become an important cause of CARTI and other community-acquired infections. Thus, it has been recommended that empiric antimicrobial therapy for severe CARTI should provide antimicrobial coverage for multidrug-resistant (MDR) *S. pneumoniae*, β-lactamase-producing *H. influenzae* and MRSA.

In the present study, the potency and spectrum of ceftaroline and other antimicrobial agents used for the treatment of CARTI were evaluated *in vitro* against bacterial pathogens collected from patients with CARTI in European medical centers (2008).

Materials and Methods

Bacterial Isolates

The isolates were consecutively collected from CARTI patients in 28 medical centers from 12 European countries in 2008 through the Ceftaroline Longitudinal Assessment of Spectrum and Susceptibility (CLASS) Program. Only one isolate per patient was included. The collection included: *S. pneumoniae* (447), *H. influenzae* (199) and *S. aureus* (71). *S. aureus* isolates were obtained from patients with pneumonia occurring less than 72 hours after hospitalization.

Susceptibility Testing

The isolates were tested for susceptibility to ceftaroline and many comparator agents by broth microdilution methods using validated panels manufactured by TREK Diagnostics (Cleveland, Ohio) and following the Clinical and Laboratory Standards Institute (CLSI) recommendations (M07-A8, 2009). *S. pneumoniae* was tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood *H. influenzae* was tested in Haemophilus Test Media while *S. aureus* was tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains determined that proper test conditions were applied. These strains included *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and *S. aureus* ATCC 29213.

Results

- Table 1 summarizes the ceftaroline MIC distributions for the year 2008 CARTI organisms. Ceftaroline activity against *S. pneumoniae* varied according to the susceptibility of this organism to penicillin, but all subsets of organisms were very susceptible to ceftaroline (≤0.5 mg/L).
- Ceftaroline MIC distributions among β-lactamase-producing *H. influenzae* were very similar to those of β-lactamase-negative strains (Table 1).
- MRSA strains were very susceptible to ceftaroline with MIC values ranging from 0.5 to 2 mg/L. Among methicillin-susceptible *S. aureus,* ceftaroline MIC results were either 0.25 or 0.5 mg/L (Table 1).
- Ceftaroline was very active against penicillin-susceptible ($MIC_{50/90}$, ≤0.008/0.015 mg/L), -intermediate ($MIC_{50/90}$, 0.03/0.06 mg/L) and -resistant ($MIC_{50/90}$, 0.12/0.25 mg/L) *S. pneumoniae* (Table 2). The highest ceftaroline MIC value was only 0.5 mg/L (Table 1).

Table 1. Ceftaroline MIC distributions for isolates from CARTI collected in Europe in 2008.

	Cumulative % inhibited at ceftaroline MIC (mg/L) of:									
Organism (no. tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
S. pneumoniae										
Penicillin-susceptible[a] (328)	85.1	97.0	98.5	99.7	99.7	100.0	-	-	-	-
Penicillin-intermediate[a] (41)	4.9	19.5	53.7	87.8	97.6	100.0	-	-	-	-
Penicillin-resistant[a] (78)	0.0	1.3	2.6	6.4	71.8	98.7	100.0	-	-	-
H. influenzae										
β-lactamase-negative (170)	86.5	99.4	99.4	100.0	-	-	-	-	-	-
β-lactamase-positive (29)	65.5	96.6	100.0	-	-	-	-	-	-	-
S. aureus										
Oxacillin-susceptible (47)	0.0	0.0	0.0	0.0	0.0	85.1	100.0	-	-	-
Oxacillin-resistant (24)	0.0	0.0	0.0	0.0	0.0	0.0	29.2	75.0	100.0	-

a. Penicillin breakpoints of ≤0.06 and ≥2 mg/L were applied.

- Ceftaroline (MIC_{90}, 0.12 mg/L) was eight-, 16- and 32-fold more active than ceftriaxone (MIC_{90}, 1 mg/L), amoxicillin/clavulanate (MIC_{90}, 2 mg/L), and cefuroxime (MIC_{90}, 4 mg/L), respectively, when tested against the entire collection of *S. pneumoniae* isolates (Table 2).
- Penicillin-resistant *S. pneumoniae* (MIC, ≥2 mg/L) strains exhibited high resistance rates to most antimicrobial agents tested, including amoxicillin/clavulanate (25.6%), azithromycin (84.4%), tetracycline (73.1%) and trimethoprim/sulfamethoxazole (22.2%). Furthermore, only 48.7% of strains were susceptible to ceftriaxone (Table 2).
- When tested against penicillin-resistant (MIC, ≥2 mg/L) *S. pneumoniae*, ceftaroline ($MIC_{50/90}$, 0.12/0.25 mg/L) was eight- to 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 2 mg/L) and 32-fold more potent than either cefuroxime ($MIC_{50/90}$, 4/8 mg/L) or amoxicillin/clavulanate ($MIC_{50/90}$, 2/8 mg/L; Table 2).
- Ceftaroline was highly active against β-lactamase-negative and -positive *H. influenzae* isolates (MIC_{90}, 0.015 mg/L, for both groups).
- MSSA strains were very susceptible to ceftaroline (Tables 1 and 2). Although higher ceftaroline MIC values were observed for MRSA strains, all strains were inhibited by ≤2 mg/L of ceftaroline (Table 1).
- Ceftaroline ($MIC_{50/90}$, 0.25/0.5 mg/L) was eight to 16-fold more active than ceftriaxone ($MIC_{50/90}$, 4/4 mg/L) against MSSA (Table 2). In addition, ceftaroline retained good activity against MRSA (MIC_{90}, 2 mg/L), while ceftriaxone showed poor activity (MIC_{50}, >32 mg/L) against this subset (0.0% susceptible). MRSA also exhibited high rates of resistance to clindamycin (33.3%), erythromycin (79.2%) and levofloxacin (95.8%; Table 2)

Table 2. Activity of ceftaroline and comparator agents tested against the main pathogens responsible for community-acquired respiratory tract infections in USA and European medical centers (2008).

Organism group/ Susceptibility subset (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% susceptible[a]	% resistant[a]
S. pneumoniae				
All isolates (447)				
Ceftaroline	≤0.008	0.12	-[b]	-
Ceftriaxone	≤0.25	1	90.8	0.7
Cefuroxime	≤1	4	79.8	18.6
Penicillin	≤0.03	2	73.4(91.9)[c]	17.4(0.0)[c]
Amox/clav[d]	≤1	2	93.3	4.5
Erythromycin	≤0.25	>2	66.4	33.6
Azithromycin	≤0.5	>4	66.0	33.1
Clarithromycin	≤0.25	>32	66.4	32.4
Clindamycin	≤0.25	>2	77.6	21.7
Levofloxacin	1	1	97.1	2.7
Linezolid	1	1	100.0	-
Tetracycline	≤2	>8	71.8	27.3
Trim/sulfa[d]	≤0.5	>2	71.1	17.0
Pen.-susceptible[e] (328)				
Ceftaroline	≤0.008	0.015	-[c]	-
Ceftriaxone	≤0.25	≤0.25	100.0	0.0
Cefuroxime	≤1	≤1	99.4	0.0
Amox/clav[d]	≤1	≤1	100.0	0.0
Erythromycin	≤0.25	>2	81.7	18.3
Azithromycin	≤0.5	>4	81.4	18.0
Clarithromycin	≤0.25	>32	81.7	17.6
Clindamycin	≤0.25	≤0.25	81.7	17.6
Levofloxacin	1	1	97.3	2.4
Linezolid	1	1	100.0	-
Tetracycline	≤2	>8	85.1	14.0
Trim/sulfa[d]	≤0.5	2	85.7	7.0
Pen.-intermediate[e] (41)				
Ceftaroline	0.03	0.12	-	-
Ceftriaxone	≤0.25	0.5	97.6	2.4
Cefuroxime	≤1	4	73.2	17.1
Amox/clav[d]	≤1	≤1	100.0	0.0
Erythromycin	>2	>2	43.9	56.1
Azithromycin	>4	>4	41.5	56.1
Clarithromycin	2	>32	43.9	56.1
Clindamycin	≤0.25	>2	63.4	34.1
Levofloxacin	1	1	100.0	0.0
Linezolid	1	1	100.0	-
Tetracycline	≤2	>8	51.2	46.3
Trim/sulfa[d]	≤0.5	>2	56.1	34.2
Pen.-resistant[e] (78)				
Ceftaroline	0.12	0.25	-	-
Ceftriaxone	2	2	48.7	2.6
Cefuroxime	4	8	1.3	97.4
Amox/clav[d]	2	8	62.8	25.6
Erythromycin	>2	>2	14.1	85.9
Azithromycin	>4	>4	14.3	84.4
Clarithromycin	>32	>32	14.3	81.8
Clindamycin	1	>2	46.2	52.6
Levofloxacin	1	1	94.9	5.1
Linezolid	0.5	1	100.0	-
Tetracycline	≤2	>8	26.9	73.1
Trim/sulfa[d]	2	>2	18.0	50.0
H. influenzae				
All isolates (199)				
Ceftaroline	≤0.008	0.015	-	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Cefuroxime	≤1	2	100.0	0.0
Amox/clav[d]	≤1	≤1	100.0	0.0
Azithromycin	1	2	98.5	-
Clarithromycin	8	16	88.4	1.0
Levofloxacin	≤0.5	≤0.5	100.0	-
Tetracycline	≤2	≤2	98.5	1.0
β-lact-negative (170)				
Ceftaroline	≤0.008	0.015	-	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Cefuroxime	≤1	2	100.0	0.0
Amox/clav[d]	≤1	≤1	100.0	0.0
Azithromycin	1	2	98.2	-
Clarithromycin	8	16	87.6	1.2
Levofloxacin	≤0.5	≤0.5	100.0	-
Tetracycline	≤2	≤2	99.4	0.0
β-lact.-positive (29)				
Ceftaroline	≤0.008	0.015	-	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Cefuroxime	≤1	≤1	100.0	0.0
Amox/clav[d]	≤1	≤1	100.0	0.0
Azithromycin	1	2	100.0	-
Clarithromycin	4	8	93.1	0.0
Levofloxacin	≤0.5	≤0.5	100.0	-
Tetracycline	≤2	≤2	93.1	6.9
S. aureus				
All isolates (71)				
Ceftaroline	0.25	1	-	-
Ceftriaxone	4	>32	64.8	33.8
Oxacillin	0.5	>2	66.2	33.8
Amox/clav[d]	≤1	>16	66.2	33.8
Erythromycin	≤0.25	>4	59.2	40.8
Clindamycin	≤0.25	>2	85.9	14.1
Levofloxacin	≤0.5	>4	63.4	35.2
Tetracycline	≤2	≤2	98.5	1.0
Trim/sulfa[d]	≤2	≤2	91.5	8.5
Vancomycin	1	1	100.0	0.0
Oxacillin-susceptible (47)				
Ceftaroline	0.25	0.5	-	-
Ceftriaxone	4	4	97.9	0.0
Amox/clav[d]	≤1	≤1	100.0	0.0
Erythromycin	≤0.25	>4	78.7	21.3
Clindamycin	≤0.25	≤0.25	95.7	4.3
Levofloxacin	≤0.5	≤0.5	93.6	4.3
Tetracycline	≤2	≤2	95.7	4.3
Trim/sulfa[d]	≤0.5	≤0.5	100.0	0.0
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (24)				
Ceftaroline	1	2	-	-
Ceftriaxone	>32	>32	0.0	100.0
Amox/clav[d]	>16	>16	0.0	100.0
Erythromycin	>4	>4	20.8	79.2
Clindamycin	≤0.25	>2	66.7	33.3
Levofloxacin	>4	>4	4.2	95.8
Tetracycline	≤2	>8	83.3	16.7
Trim/sulfa[d]	≤0.5	2	100.0	0.0
Vancomycin	1	1	100.0	0.0

a. Susceptibility criteria of the CLSI (M100-S19, 2009) were used where available.
b. - = no breakpoint criteria have been recommended by the CLSI.
c. According to CLSI breakpoints (M100-S19, 2009) for parental penicillin (nonmeningitis).
d. Amox/clav = Amoxicillin/clavulanate; Trim/sulfa = Trimethoprim/sulfamethoxazole.
e. According to CLSI breakpoints (M100-S19, 2009) for oral penicillin (penicillin V), i.e. susceptible ≤0.06 mg/L, intermediate 0.12-1 mg/L, and resistant ≥2 mg/L.

Conclusions

- Bacterial pathogens recently (2008) collected from patients with CARTI in European medical centers (including MRSA and *S. pneumoniae* resistant to amoxicillin/ clavulanate and/or ceftriaxone), were very susceptible to ceftaroline.
- Ceftaroline activity was routinely greater (eight- to 128-fold) compared to other cephalosporins when tested against *S. pneumoniae* and *H. influenzae* isolates.
- Ceftaroline showed significant activity against MRSA and a major potency advantage (≥16-fold) compared to ceftriaxone against MSSA.
- This favorable antimicrobial profile demonstrates that ceftaroline is a promising agent for the treatment of CARTI in Europe, including those caused by MRSA and other important Gram-positive organisms.

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