C2-1974

Antimicrobial Activity of Ceftaroline Tested Against Contemporary (2008) Bacteria Isolated From Community-Acquired Respiratory Tract Infections, Including Oxacillin- (Methicillin-) Resistant *Staphylococcus aureus*

H.S. Sader, T.R. Fritsche, R.N. Jones

JMI Laboratories, North Liberty, IA

Helio S. Sader, MD, PhD
JMI Laboratories
North Liberty, Iowa 52317
Phone: 319-665-3370
Fax: 319-665-3371
E-mail: helio-sader@jmilabs.com

Amended Abstract

Background: Ceftaroline is a new N-phosphono prodrug of an anti-MRSA cephalosporin that has high affinity for PBP 2a and demonstrated activity against MRSA and other pathogens responsible for community-acquired respiratory tract infections (CARTI). Ceftaroline, currently in phase III clinical development, was evaluated for potency against CARTI pathogens.

Methods: Isolates were consecutively collected from CARTI in hospitals from the USA (26) and Europe (EU; 28). Susceptibility was tested by the CLSI broth microdilution methods against ceftaroline and antimicrobials used to treat CARTI. *S. aureus* isolates were obtained from patients with pneumonia less than 72 h after hospitalization.

Results: Table 1 (amended in order to present results generated after the submission of the abstract) shows the potency of ceftaroline against 3 common pathogens associated with CARTI. The activity of ceftaroline ($MIC_{50/90}$, 0.008/0.12 µg/mL) was 8-fold more potent than ceftriaxone ($MIC_{50/90}$, ≤0.25/1 µg/mL) and 64-fold more potent than cefuroxime ($MIC_{50/90}$, ≤1/8 µg/mL) against *S. pneumoniae*. Penicillin resistance was high among *S. pneumoniae*; only 64.3% and 87.2% strains were inhibited at ≤0.06 and ≤2 µg/mL, respectively, while amoxicillin/clavulanate inhibited 86.8% at ≤2 µg/mL. Resistance was also high among the *S. pneumoniae* isolates for azithromycin (37.1%), clindamycin (20.3%), co-trimoxazole (22.5%), and tetracycline (25.6%). Ceftaroline was very active against *H. influenzae* (MIC_{90}, 0.015 µg/mL, including β-lactamase-positive strains (22.0%), and 16-fold more potent than ceftriaxone against oxacillin-susceptible *S. aureus*. The highest ceftaroline MIC value among MRSA was 4 µg/mL, and 85.2% of isolates were inhibited at ≤1 µg/mL of ceftaroline.

Conclusion: Ceftaroline exhibited high activity against bacterial pathogens from CARTI recently collected during 2008 in US and EU medical centers, including CA-MRSA and other resistant strains. Based on these results, ceftaroline appears to be a promising agent for the therapy of CARTI.

Introduction

- Ceftaroline is a novel, broad-spectrum cephalosporin with enhanced gram-positive activity that includes oxacillin (methicillin)-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is administered as a parenteral prodrug, ceftaroline fosamil, which is rapidly converted to the microbiologically active form in the bloodstream. Ceftaroline is being developed for the treatment of bacterial infections caused by gram-positive pathogens, including multidrug-resistant (MDR) staphylococci and streptococci, as well as common gram-negative species that are within the spectrum of this therapeutic agent. Ceftaroline has potent activity against *Haemophilus influenzae*, which is the leading gram-negative pathogen in community-acquired respiratory tract infections (CARTI) (Pfaller et al, 2001)
- The rates of MRSA and penicillin-resistant *Streptococcus pneumoniae*, including MDR isolates, continue to increase in many areas of the world. Ceftaroline has previously demonstrated excellent bactericidal activity against the leading pathogens associated with CARTI; it is active against MRSA and penicillin-resistant *S. pneumoniae* (Sader et al, 2005). Novel agents that target these resistant pathogens are needed for treating CARTI
- Phase 3 trials are in progress to evaluate safety and efficacy of ceftaroline in the treatment of community-acquired pneumonia (CAP) in adults compared with ceftriaxone
- The present study was conducted to assess the in vitro activity of ceftaroline compared with commonly prescribed antimicrobial agents used for the treatment of CARTI. Ceftaroline activity was evaluated against 3 significant bacterial pathogens associated with CARTI that were collected in 2008 from patients in the United States and Europe.

Materials and Methods

- Bacterial isolates tested in this study were obtained from patients in 27 medical centers located in the US and 28 in Europe during 2008. *S. pneumoniae* (703 strains) and *H. influenzae* (391 strains) were collected from clinically significant infections, including bloodstream and respiratory tract sources. *S. pneumoniae* isolates that were nonsusceptible to both penicillin and erythromycin were analyzed separately as an MDR subset (196 strains). A total of 142 *S. aureus* isolates (38.0% MRSA) were obtained from patients hospitalized with pneumonia within 72 hours post-admission to allow an analysis of strains that were likely to be of community origin
- Broth microdilution methods were used to determine the antimicrobial susceptibility of each organism using validated panels manufactured by TREK Diagnostics (Cleveland, OH). The Clinical and Laboratory Standards Institute (CLSI) recommendations were used for testing *S. aureus* in Mueller-Hinton (MH) broth, *S. pneumoniae* (MH supplemented with 3%-5% lysed horse blood), and *H. influenzae* using Haemophilus Test Media (M7-A7, 2006). Concurrent testing of quality control (QC) isolates determined that proper test conditions were used. These strains included American Type Culture Collection (ATCC) strains, *S. aureus* ATCC 29213, *H. influenzae* ATCC 49247, and *S. pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S18, 2008).

Results

- Ceftaroline demonstrated excellent activity against both methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates (Table 1). All MSSA strains were inhibited at ≤0.5 µg/mL. All MRSA isolates except 2 (3.7%) were inhibited by ≤2 µg/mL of ceftaroline. The highest ceftaroline MIC observed among MRSA was 4 µg/mL (Table 1)
- Ceftaroline (MIC_{90}, 0.25 µg/mL) was 16-fold more active than ceftriaxone (MIC_{90}, 4 µg/mL) against MSSA (Table 2). Ceftaroline retained good activity against MRSA isolates (MIC_{90}, 2 µg/mL), against which ceftriaxone was practically inactive (MIC range being 16 µg/mL->32 µg/mL; 0.0% susceptible)
- *S. pneumoniae* and *H. influenzae* isolates were highly susceptible to ceftaroline, with all strains having MIC values of ≤0.5 µg/mL (Table 1). Ceftaroline was the most potent antibiotic of all tested against *S. pneumoniae* and *H. influenzae*
- Ceftaroline (MIC_{90}, 0.12 µg/mL) was 8-fold more active than ceftriaxone (MIC_{90}, 1 µg/mL) and had 64-fold greater activity compared with either cefuroxime or cefdinir (MIC_{90}, 8 µg/mL) against the entire collection of *S. pneumoniae* isolates (Table 2)
- *S. pneumoniae* isolates that were not susceptible to both penicillin and erythromycin (multidrug-resistant) had slightly higher (2-fold) ceftaroline MIC values with a MIC_{90} of 0.25 µg/mL. Strains within this resistant subset of pneumococci were less susceptible to almost all comparators, including the cephalosporin agents
- All *H. influenzae* isolates, including those that were β-lactamase positive, were highly susceptible to ceftaroline (MIC_{90}, 0.015 µg/mL). Ceftaroline was 32- to 64-fold more potent than cefdinir and cefuroxime, respectively, against *H. influenzae* (Table 2).

Table 1. Activity of Ceftaroline Tested Against 1236 Bacterial Pathogens Associated With Community-Acquired Respiratory Tract Infections (CARTI)

	Cumulative % inhibited at ceftaroline MIC (µg/mL) of:									
Organism (no.)	**≤0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**
Streptococcus pneumoniae (703)	56.5	67.0	72.0	79.1	93.0	99.4	100.0	-	-	-
Haemophilus influenzae	79.3	95.1	97.2	99.2	99.7	100.0	-	-	-	-
β-Lactamase-negative (305)	84.6	98.0	98.7	99.7	99.7	100.0	-	-	-	-
β-Lactamase-positive (86)	60.5	84.9	91.9	97.7	100.0	-	-	-	-	-
Staphylococcus aureus										
Oxacillin-susceptible (88)	0.0	0.0	0.0	0.0	4.6	90.9	100.0	-	-	-
Oxacillin-resistant (54)	0.0	0.0	0.0	0.0	0.0	1.9	38.9	85.2	96.3	100.0

Table 2. Activity of ceftaroline and comparator agents when tested against *S. aureus*, *S. pneumoniae* and *H. influenzae*, including resistant phenotypes.

Organism group/ susceptibility subset (no. tested) Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible[a]	% resistant[a]
S. aureus					
Oxacillin-susceptible (88)					
Ceftaroline	0.25	0.25	0.12-0.5	-[b]	-
Ceftriaxone	4	4	2-16	98.9	0.0
Erythromycin	≤0.25	>2	≤0.25->2	69.3	30.7
Clindamycin	≤0.25	≤0.25	≤0.25->2	95.5	4.5
Levofloxacin	≤0.5	≤0.5	≤0.5->4	90.9	8.0
Gentamicin	≤2	≤2	≤2->8	95.5	4.5
Tetracycline	≤2	≤2	≤2->8	98.9	1.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0	0.0
Vancomycin	1	1	0.5-2	100.0	0.0
Oxacillin-resistant (54)					
Ceftaroline	1	2	0.25-4	-	-
Ceftriaxone	>32	>32	16->32	0.0	72.2
Erythromycin	>2	>2	≤0.25->2	11.1	88.9
Clindamycin	≤0.25	>2	≤0.25->2	57.4	42.6
Levofloxacin	>4	>4	≤0.5->4	14.8	85.2
Gentamicin	≤2	8	≤2->8	88.9	7.4
Tetracycline	≤2	≤2	≤2->8	90.7	9.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5-2	100.0	0.0
Vancomycin	1	1	0.5-2	100.0	0.0
S. pneumoniae					
All isolates (703)					
Ceftaroline	≤0.008	0.12	≤0.008-0.5	-	-
Ceftriaxone	≤0.25	1	≤0.25-8	90.5	1.3
Cefuroxime	≤1	8	≤1->8	74.5	25.5
Cefdinir	≤0.06	8	≤0.06->8	74.4	23.3
Penicillin (oral, penicillin V)[c]	≤0.03	4	≤0.03->4	64.3	21.1
Penicillin (parenteral, nonmeningitis)[d]	≤0.03	4	≤0.03->4	87.2	0.5
Amoxicillin/clavulanate	≤1	8	≤1-16	86.8	10.4
Erythromycin	≤0.06	>8	≤0.06->8	62.7	37.1
Clindamycin	≤0.25	>2	≤0.25->2	79.5	20.3
Levofloxacin	1	1	≤0.5->4	99.3	0.6
Tetracycline	≤2	>8	≤2->8	74.0	25.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	68.4	22.5
Penicillin/erythromycin-non-susceptible isolates (196)[e]					
Ceftaroline	0.12	0.25	≤0.008-0.5	-	-
Ceftriaxone	1	2	≤0.25-8	68.9	3.6
Cefuroxime	4	>8	≤1->8	24.5	68.9
Cefdinir	8	>8	≤0.06->8	23.0	69.4
Penicillin (parenteral, nonmeningitis)[d]	2	4	0.12->4	56.1	1.5
Amoxicillin/clavulanate	2	8	≤1-16	56.1	36.7
Clindamycin	>2	>2	≤0.25->2	42.4	57.6
Levofloxacin	1	1	≤0.5->4	98.0	2.6
Tetracycline	>8	>8	≤2->8	30.6	69.4
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	23.6	61.5
H. influenzae					
β-lactamase-negative (305)					
Ceftaroline	≤0.008	0.015	≤0.008-0.25	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-1	100.0	-
Cefuroxime	≤1	2	≤1-8	99.7	0.0
Cefdinir	0.12	0.5	≤0.06-2	99.0	-
Ampicillin	≤1	≤1	≤1	100.0	0.0
Amoxicillin-clavulanate	≤1	≤1	≤1-4	100.0	0.0
Azithromycin	1	2	≤0.5->4	98.0	-
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0	-
Tetracycline	≤2	≤2	≤2	100.0	0.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	81.3	15.7
β-lactamase-positive (86)					
Ceftaroline	≤0.008	0.015	≤0.008-0.12	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Cefuroxime	≤1	2	≤1-8	97.7	0.0
Cefdinir	0.25	0.5	≤0.06-2	97.7	-
Ampicillin	16	>16	2->16	0.0	100.0
Amoxicillin/clavulanate	≤1	≤1	≤1-4	100.0	0.0
Azithromycin	1	2	≤0.5-4	100.0	-
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0	-
Tetracycline	≤0.5	>8	≤0.25->8	93.0	5.8
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	75.6	24.4

[a]Susceptibility criteria of the CLSI (M100-S18, 2008) were used where available.
[b]- = no breakpoint criteria have been recommended by the CLSI.
[c]According to CLSI breakpoints (M100-S18, 2008) for oral penicillin (penicillin V).
[d]According to CLSI breakpoints (M-100-S18, 2008) for parenteral penicillin to treat nonmeningeal pneumococcal infections.
[e]Strains with penicillin MIC at ≥ 0.12 µg/mL and erythromycin MIC at ≥ 0.5 µg/mL (CLSI, 2008).

Conclusions

- Ceftaroline was highly active against CARTI isolates of *S. aureus*, *S. pneumoniae* and *H. influenzae* recently collected (2008) in the United States and Europe
- Ceftaroline showed excellent in vitro activity against MRSA (MIC_{90} = 2 µg/mL), for which marketed β-lactams are only weakly active. In addition, ceftaroline was significantly more active (≥16-fold) compared with ceftriaxone against MSSA
- Substantially greater activity (8- to 64-fold) was also observed for ceftaroline compared with the other cephalosporins against *S. pneumoniae* and *H. influenzae*. Ceftaroline was the most active antimicrobial tested, regardless of class, against these species
- The in vitro activity of ceftaroline against respiratory isolates demonstrated in this study suggests that ceftaroline has the potential to be a very promising antimicrobial agent for treatment of CARTI.

Selected References

Clinical and Laboratory Standards Institute. M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition. Wayne, PA: CLSI; **2006**.

Clinical and Laboratory Standards Institute. M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement. Wayne, PA: CLSI; **2008**.

Page MG. Anti-MRSA β-lactams in development. Curr Opin Pharmacol **2006**;6:480-5.

Pfaller MA, Enhrhardt AF, Jones RN. Frequency of pathogen occurrence and antimicrobial susceptibility among community-aquired respiratory tract infections in the respiratory surveillance program study. Am J Med **2001**;111(Suppl 9A):4S-12S.

Sader HS, Fritsche TR, Kaniga K, et al. Antimicrobial activity and spectrum of PPI-0903M (T-91825), a novel cephalosporin, tested against a worldwide collection of clinical strains. Antimicrob Agents Chemother **2005**;49:3501-12.

Acknowledgments

Supported by Forest Laboratories Inc.