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Antimicrobial Activity of the Novel Cephalosporin Ceftaroline Tested Against Gram-positive Organisms Causing Skin and Skin Structure Infections (SSSI) Isolated in USA and European Medical Centers in 2008

HS SADER, D BIEK, I CRITCHLEY, RN JONES

JMI Laboratories, North Liberty, IA; Cerexa, Alameda, CA

SIS 2009
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

Amended Abstract

Introduction: Ceftaroline is a novel, parenteral cephalosporin with broad-spectrum activity that encompasses many community- and hospital-acquired pathogens, including methicillin-resistant *S. aureus* (MRSA), multidrug-resistant streptococci, and commonly isolated (non-ESBL-producing) Enterobacteriaceae. We assessed the activity of ceftaroline and comparator agents tested against SSSI pathogens.

Methods: Clinically-significant strains (one per patient) of *S. aureus* (SA; 4,854 strains) and ß-haemolytic streptococci (ßHS; 429) were consecutively collected from more than 50 medical centers in the USA and Europe (EU). Strains of coagulase-negative staphylococci (CoNS; 821), *E. faecalis* (EF; 952) and viridans group streptococci (VGS; 161) were also evaluated. Susceptibility (S) testing was performed by reference CLSI broth microdilution methods against ceftaroline and >20 antimicrobials currently available for SSSI treatment.

Results: A total of 7,217 strains were tested. 54.9 and 25.8% of SA were MRSA in the USA and EU respectively. Ceftaroline was very active against oxacillin-S SA (MSSA; MIC_{90}, 0.25 µg/ml) and MRSA (MIC_{90}, 1-2 µg/ml). Ceftaroline was 16-fold more potent than ceftriaxone against MSSA and > 99% of MSSA were inhibited at ≤0.5 µg/ml of ceftaroline (highest MIC was only 1 µg/ml). The percentages of MRSA inhibited at 1 and 2 µg/ml of ceftaroline were 94.8 and 100.0% in the USA, and 85.9 and 99.8% in EU, respectively. ßHS was very S to ceftaroline and ≥99% of strains were inhibited at ≤0.03 µg/ml. Ceftaroline was also very active against CoNS, including methicillin-resistant strains, and eight- to 16-fold more potent than ceftriaxone against VGS. Vancomycin was very active against all organisms tested, except EF (92-99% S), while high rates of resistance to levofloxacin and clindamycin were observed among MRSA and CoNS.

Organism (no. tested)	CPT	CRO	LVX	CLI	SXT	VAN
	MIC_{90} (µg/ml)/% Susceptible					
MSSA						
USA(1276)	0.25[a]	4/>99	4/88	≤0.25/93	≤0.5/98	1/100
EU(1504)	0.25	4/>99	≤0.5/95	≤0.25/98	≤0.5/>99	1/100
MRSA						
USA(1551)	1	>32/0	>4/29	>2/65	≤0.5/99	1/100
EU(523)	2	>32/0	>4/15	>2/67	≤0.5/>99	1/100
ßHS						
USA(253)	0.03	≤0.25/>99	1/99	>2/87	≤0.5/NA	0.5/100
EU(176)	0.015	≤0.25/100	1/100	≤0.25/91	≤0.5/NA	0.5/100
CoNS						
USA(412)	0.5	>32/30	>4/47	>2/64	>2/60	2/100
EU(409)	1	>32/24	>4/44	>2/68	>2/62	2/100
EF						
USA(546)	8	>32/NA	>4/64	NA	NA	2/96
EU(406)	8	>32/NA	>4/71	NA	NA	2/99
VGS						
USA(77)	0.06	1/92	>4/84	≤0.25/92	2/94	0.5/100
EU(84)	0.25	2/89	1/98	>2/89	2/91	0.5/100

a. Breakpoints have not been established for CPT. CPT = ceftaroline; CRO = ceftriaxone; LVX = levofloxacin; CLI = clindamycin; SXT = co-trimoxazole; VAN = vancomycin; NA = not applicable.

Conclusions: SSSI Gram-positive pathogens recently (2008) isolated in USA and EU medical centers were very S to ceftaroline, including MRSA and fluoroquinolone-resistant ßHS. Ceftaroline appears to be a valuable agent for the treatment of organisms causing SSSI.

Introduction

Ceftaroline (formerly PPI-0903) is a broad-spectrum parenteral cephalosporin that has an enhanced Gram-positive spectrum, including bactericidal activity against methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA)[Brown and Traczewski, 2009; Ge et al., 2008; Kanafani and Corey, 2009]. Ceftaroline is currently in development for treatment of complicated skin and skin structure infections (cSSSI) and community-acquired pneumonia. Positive results have recently been reported from phase 3 investigations that compared the efficacy of ceftaroline to vancomycin plus aztreonam for treatment of cSSSI [Corey et al., 2008; Talbot et al., 2007].

S. aureus and *Streptococcus pyogenes* are considered the most important pathogens associated with SSSI. Ceftaroline demonstrates excellent in vitro activity against both of these species. Coagulase-negative staphylococci (CoNS), enterococci and viridans group streptococci are also considered to be relevant pathogens associated with some types of SSSI. Ceftaroline provides additional in vitro activity against these Gram-positive pathogens, including strains resistant to other drug classes and multidrug-resistant (MDR) isolates [Kanafani and Corey, 2009; Page 2006].

The objective of this study was to evaluate the antimicrobial activity and spectrum of ceftaroline and comparator agents tested against clinical bacterial isolates related to SSSI collected in medical institutions geographically dispersed throughout the USA and Europe.

Materials and Methods

The isolates tested in this study were collected from hospitalized patients in USA and European medical centers in 2008. There were 27 medical centers in the USA and 28 sites from 12 European countries that contributed isolates for analysis. A total of 7,217 isolates, 4,115 from USA and 3,102 from Europe, were evaluated. The collection included (no. of isolates from USA/Europe): *S. aureus* (2,827/2,027), ß-haemolytic streptococci (253/176) CoNS (412/409), *E. faecalis* (543/406), and viridans group streptococci (77/84).

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI) documents to determine the antimicrobial susceptibility of each organism [CLSI 2006]. Validated MIC panels manufactured by TREK Diagnostics (Cleveland, OH) were utilized. *S. aureus* and *E. faecalis* were tested in Mueller-Hinton (MH) broth and *Streptococcus* spp. were tested in MH broth supplemented with 3-5% lysed horse blood (M07-A8, 2009). Concurrent testing of quality control (QC) strains determined that proper test conditions and procedures were used. These strains included American Type Culture Collection (ATCC) strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based upon the CLSI guidelines or breakpoints; no criteria for ceftaroline susceptibility have been established [CLSI 2008].

Results

- The MRSA rate was higher in the USA (54.9%) when compared to Europe (25.8%), and ceftaroline provided excellent potency against this organism with all isolates inhibited by ≤2 µg/ml (MIC_{90}, 1-2 µg/ml), except for one isolate from an European medical center which had a ceftaroline MIC of 4 µg/ml (Table 1).
- The percentages of MRSA inhibited at 1 and 2 µg/ml of ceftaroline were 94.8 and 100.0% in the USA, and 85.9 and 99.8% in Europe, respectively (Table 1). Ceftaroline and vancomycin (MIC_{50}, 1 µg/ml for both compounds) were highly active tested against MRSA. Linezolid was also very active but slightly less potent (MIC_{50} and MIC_{90}, 2 µg/ml) and resistance to this compound (MIC, ≥8 µg/ml) was observed in 2 MRSA isolates from the USA (Table 2).
- Methicillin (oxacillin)-susceptible *S. aureus* (MSSA) isolates exhibited slightly lower ceftaroline MIC values (MIC_{90}, 0.25 µg/ml) when compared to the MRSA strains (MIC_{90}, 1 µg/ml; Table 1).
- Ceftaroline was 16-fold more potent than ceftriaxone against MSSA (Tables 2 and 3) and 99.9% of MSSA were inhibited at ≤0.5 µg/ml of ceftaroline (highest MIC, 1 µg/ml; Table 1).
- Ceftaroline exhibited excellent activity (MIC_{90}, 0.015-0.03 µg/ml) against the ß-haemolytic streptococci (Tables 2 and 3). Ceftaroline was two- to four-fold more active than penicillin (MIC_{90}, 0.06 µg/ml) against these common pathogens, and 99.1% of strains were inhibited at ≤0.03 µg/ml of ceftaroline.
- Ceftaroline was the most active compound (MIC_{50}, 0.25-0.5 µg/ml and MIC_{90}, 0.5-1 µg/ml) tested against CoNS. Ceftaroline was two- to four-fold more active than linezolid and vancomycin (MIC_{50}, 1 µg/ml for both and MIC_{90}, 1 µg/ml for linezolid but 2 µg/ml for vancomycin), and 32- to 64-fold more active than ceftriaxone (MIC_{50}, 16 µg/ml and MIC_{90}, >32 µg/ml) against this pathogen (Tables 2 and 3). CoNS isolates resistant to linezolid (MIC, >8 µg/ml) were observed in USA and European medical centers.
- *E. faecalis* isolates had ceftaroline MIC_{50} and MIC_{90} values of 2 and 8 µg/ml, respectively (Tables 2 and 3).

Table 1. Frequency of occurrence of ceftaroline MIC values for *S. aureus* strains.

Organism/region (no. tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
	No. of strains (cumulative %) inhibited at ceftaroline MIC (µg/ml) of:									
MSSA										
USA (1,276)	1(0.1)	1(0.2)	1(0.2)	9(0.9)	51(4.9)	1,104(91.5)	108(99.9)	1(100.0)	-	-
Europe (1,504)	0(0.0)	0(0.0)	4(0.3)	14(1.2)	63(5.4)	1,277(90.3)	143(99.8)	3(100.0)	-	-
MRSA										
USA (1,551)	0(0.0)	0(0.0)	0(0.0)	1(0.1)	1(0.1)	17(1.2)	592(39.4)	859(94.8)	81(100.0)	-
Europe (523)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6(1.2)	157(31.2)	286(85.9)	73(99.8)	1(100.0)

Table 2. Antimicrobial activity of ceftaroline and comparator agents tested against bacterial isolates from USA medical centers.

Organism (no. tested)	MIC 50%	MIC 90%	% Susceptible[a]	% Resistant[a]
S. aureus				
Oxacillin-susceptible (1,276)				
Ceftaroline	0.25	0.25	[b]	-
Ceftriaxone	4	4	99.7	0.0
Erythromycin	≤0.25	>4	63.3	36.1
Clindamycin	≤0.25	≤0.25	92.6	7.1
Levofloxacin	≤0.5	4	87.7	11.8
Gentamicin	≤2	≤2	99.1	0.9
TMP/SMX	≤0.5	≤0.5	98.3	1.7
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (1,551)				
Ceftaroline	1	1	-	-
Ceftriaxone	>32	>32	0.0	100.0
Erythromycin	>2	>4	6.8	92.6
Clindamycin	≤0.25	>2	64.9	35.0
Levofloxacin	>4	>4	28.7	51.8
Gentamicin	≤2	≤2	97.4	2.3
TMP/SMX	≤0.5	≤0.5	98.8	1.2
Linezolid	2	2	99.9	-
Vancomycin	1	1	100.0	0.0
ß-haemolytic streptococci (253)				
Ceftaroline	≤0.008	0.03	-	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Penicillin	≤0.015	0.06	100.0	0.0
Erythromycin	≤0.25	>2	72.7	26.1
Clindamycin	≤0.25	>2	87.4	12.2
Levofloxacin	≤0.5	1	98.8	0.8
Linezolid	1	1	100.0	-
Vancomycin	0.5	0.5	100.0	0.0
CoNS (412)				
Ceftaroline	0.25	0.5	-	-
Ceftriaxone	16	>32	29.9	70.1
Oxacillin	>2	>2	29.9	70.1
Erythromycin	>2	>2	34.0	65.8
Clindamycin	≤0.25	>2	63.8	34.5
Levofloxacin	4	>4	46.6	52.2
Gentamicin	≤2	>8	69.9	24.0
TMP/SMX	≤0.5	>2	59.7	40.3
Linezolid	1	1	98.5	-
Vancomycin	1	2	100.0	0.0
E. faecalis				
Vancomycin-susceptible (505)				
Ceftaroline	2	8	-	-
Ceftriaxone	>32	>32	-	-
Ampicillin	≤1	2	100.0	0.0
Erythromycin	>4	>4	7.9	68.1
Levofloxacin	1	>4	69.1	30.9
Gentamicin (HL)	≤500	>1000	73.5	26.5
Linezolid	1	2	100.0	0.0
Vancomycin	1	2	100.0	0.0
Vancomycin-resistant (25)				
Ceftaroline	4	8	-	-
Ceftriaxone	>32	>32	-	-
Ampicillin	≤1	2	100.0	0.0
Erythromycin	>4	>4	4.0	84.0
Levofloxacin	>4	>4	4.0	96.0
Gentamicin (HL)	>1000	>1000	29.2	60.8
Linezolid	1	2	100.0	0.0
Vancomycin	>16	>16	0.0	100.0
Viridans group streptococci (77)				
Ceftaroline	0.03	0.06	-	-
Ceftriaxone	≤0.25	1	92.2	3.9
Penicillin	0.06	1	76.6	5.2
Erythromycin	1	>2	45.6	54.5
Clindamycin	≤0.25	≤0.25	92.2	7.8
Levofloxacin	1	>4	84.4	14.3
Linezolid	1	1	100.0	-
Vancomycin	0.5	0.5	100.0	-

a. According to CLSI breakpoints [CLSI, 2008].
b. - = No breakpoint has been established by CLSI or US-FDA.
Abbreviations: TMP/SMX = trimethoprim/sulfamethoxazole; CoNS = coagulate-negative staphylococci; HL = high level resistance.

Table 3. Antimicrobial activity of ceftaroline and comparator agents tested against bacterial isolates from European medical centers.

Organism (no. tested)	MIC 50%	MIC 90%	% Susceptible[a]	% Resistant[a]
S. aureus				
Oxacillin-susceptible (1,506)				
Ceftaroline	0.25	0.25	-[b]	-
Ceftriaxone	4	4	99.7	0.0
Erythromycin	≤0.25	>4	83.2	15.7
Clindamycin	≤0.25	≤0.25	97.7	2.2
Levofloxacin	≤0.5	≤0.5	94.8	4.4
Gentamicin	≤2	≤2	98.6	1.3
TMP/SMX	≤0.5	≤0.5	99.5	0.5
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (1,551)				
Ceftaroline	1	2	-	-
Ceftriaxone	>32	>32	0.0	100.0
Erythromycin	>2	>4	35.2	63.3
Clindamycin	≤0.25	>2	66.5	33.3
Levofloxacin	>4	>4	14.5	72.7
Gentamicin	≤2	>8	83.8	13.0
TMP/SMX	≤0.5	≤0.5	99.0	1.0
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
ß-haemolytic streptococci (176)				
Ceftaroline	≤0.008	0.015	-	-
Ceftriaxone	≤0.25	≤0.25	100.0	0.0
Penicillin	≤0.015	0.06	100.0	0.0
Erythromycin	≤0.25	>2	78.4	19.9
Clindamycin	≤0.25	≤0.25	90.9	.6
Levofloxacin	≤0.5	1	100.0	0.0
Linezolid	1	1	100.0	-
Vancomycin	0.5	0.5	100.0	0.0
CoNS (409)				
Ceftaroline	0.5	1	-	-
Ceftriaxone	16	>32	23.7	76.3
Oxacillin	>2	>2	23.7	76.3
Erythromycin	>2	>2	34.7	64.8
Clindamycin	≤0.25	>2	68.0	30.1
Gentamicin	≤2	>8	59.7	32.0
TMP/SMX	≤0.5	>2	62.1	37.9
Linezolid	1	1	99.5	-
Vancomycin	1	2	100.0	0.0
E. faecalis				
Vancomycin-susceptible (401)				
Ceftaroline	2	8	-	-
Ceftriaxone	>32	>32	-	-
Ampicillin	≤1	2	100.0	0.0
Erythromycin	>4	>4	7.9	68.1
Levofloxacin	1	>4	62.3	28.2
Gentamicin (HL)	≤500	>1000	71.3	28.7
Linezolid	2	2	100.0	0.0
Vancomycin	1	2	100.0	0.0
Vancomycin-resistant (6)				
Ceftaroline	4	NA	-	-
Ceftriaxone	>32	NA	-	-
Ampicillin	2	NA	100.0	0.0
Erythromycin	>4	NA	0.0	100.0
Levofloxacin	>4	NA	0.0	100.0
Gentamicin (HL)	>1000	NA	0.0	100.0
Linezolid	1	NA	100.0	0.0
Vancomycin	>16	NA	0.0	100.0
Viridans group streptococci (84)				
Ceftaroline	0.03	0.25	-	-
Ceftriaxone	≤0.25	2	89.3	4.9
Penicillin	0.06	2	77.4	8.3
Erythromycin	≤0.25	>2	57.1	36.9
Clindamycin	≤0.25	>2	88.1	11.9
Levofloxacin	1	1	97.6	1.2
Linezolid	1	1	100.0	-
Vancomycin	0.5	1	100.0	-

a. According to CLSI breakpoints [CLSI, 2008].
b. - = No breakpoint has been established by CLSI or US-FDA.
Abbreviations: TMP/SMX = trimethoprim/sulfamethoxazole; CoNS = coagulate-negative staphylococci; NA = not applicable.

- Vancomycin resistance was observed in 4.7 and 1.5% of *E. faecalis* strains from the USA and Europe, respectively. Ceftaroline had similar activity against vancomycin-resistant *E. faecalis* (MIC_{50}, 4 µg/ml and MIC_{90}, 8 µg/ml) compared to vancomycin-susceptible strains (MIC_{50}, 2 µg/ml and MIC_{90}, 8 µg/ml).
- Viridans group streptococci exhibited low ceftaroline MIC values with a MIC_{50} value of only 0.03 µg/ml and MIC_{90} values of 0.06 (USA) and 0.25 µg/ml (Europe; Tables 2 and 3). High rate of levofloxacin resistance (14.3%) was observed among viridans group streptococci from the USA (Table 2).

Conclusions

- Ceftaroline was highly active against the most common SSSI Gram-positive pathogens isolated in the USA and European medical centers, including MRSA.
- Ceftaroline demonstrated excellent activity against MRSA with 94.8 and 85.9% of strains in the USA and Europe, respectively, being inhibited at ≤1 µg/ml, and more than 99.9% inhibited by ≤2 µg/ml.
- Ceftaroline provides a significant potency advantage (≥ 16-fold) compared to ceftriaxone against the common Gram-positive pathogens associated with SSSI.
- Ceftaroline may have a significant role in the treatment of SSSI Gram-positive pathogens.

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Acknowledgement

This study was supported by Forest Laboratories, Inc.