1093

Ceftaroline Activity Tested Against Common Organisms Causing Skin and Skin-Structure Infections in European Medical Centres During 2008

RN JONES, GJ MOET, HS SADER

JMI Laboratories, North Liberty, Iowa, USA

ECCMID 2009

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

Amended Abstract*

Objectives: To assess the activity of ceftaroline and comparator agents tested against SSSI pathogens. Ceftaroline is the bioactive metabolite of ceftaroline fosamil, a *N*-phosphonoamino water-soluble cephalosporin prodrug. Ceftaroline is active against methicillin-resistant *S. aureus* (MRSA) and other resistant pathogens and is under evaluation for treatment of skin and skin-structure infections (SSSI) in clinical trials.
Methods: Unique (1 per patient) clinically significant isolates of *S. aureus* (2168), beta-haemolytic streptococci (BHS; 172), viridans group streptococci (VGS; 86), and *E. faecalis* (409) were consecutively collected from 24 medical centers in 10 European (EU) countries, Turkey and Israel in 2008. The strains were tested for susceptibility (S) by the CLSI broth microdilution method (M07-A8; M100-S19) against ceftaroline and numerous antimicrobials currently available for SSSI treatment.
Results: 25.4% of *S. aureus* isolates were MRSA. Ceftaroline was very active against methicillin-susceptible *S. aureus* (MSSA; MIC_{90}, 0.25 mg/L) and MRSA (MIC_{90}, 2 mg/L). Against MSSA, ceftaroline was 16-, eight- and four-fold more potent than ceftriaxone (CRO), linezolid (LZD) and vancomycin (VAN), respectively. The highest ceftaroline MIC among MSSA was 1 mg/L, and 90.9 and 99.8% of strains were inhibited at ≤0.25 and ≤0.5 mg/L, respectively. Among MRSA, **99.3%** of strains were inhibited at 2 mg/L of ceftaroline. All MRSA strains with ceftaroline MICs of >2 mg/L (**4 strains at 4 mg/L**) were found in Greece (**1 medical centre**). MRSA showed high rates of resistance (R) to levofloxacin (LEV; 84.4%) and clindamycin (CLI; 35.1%). Against BHS, ceftaroline was 64- and 32-fold more potent than LZD and VAN, respectively, and all strains were inhibited at ≤0.06 mg/L of ceftaroline. VGS were very S to ceftaroline, while 79.1 and 90.7% of strains were S to penicillin and CRO, respectively. More than 90% of *E. faecalis*, including all VAN-R isolates (VRE) were inhibited by ≤8 mg/L of ceftaroline. Four of 5 VRE were from Greece.

	MIC_{90} (mg/L)/% Susceptible					
Organism (no.)	Ceftaroline	CRO	LEV	CLI	LZD	VAN
MSSA (1617)	0.25/NA	4/99.8	≤0.5/94.6	≤0.25/98.0	2/100.0	1/100.0
MRSA (551)	2/NA	>32/0.0	>4/14.5	>2/64.3	2/100.0	1/100.0
BHS (172)	0.015/NA	≤0.25/100.0	≤0.25/100.0	1/90.7	1/100.0	0.5/100.0
VGS (86)	0.25/NA	0.5/90.7	≤0.25/97.7	2/88.4	1/100.0	0.5/100.0
E. faecalis (409)	8/NA	>32/NA	>2/71.4	>4/NA	2/100.0	2/98.8

a. NA = not assigned.

Conclusions: Ceftaroline demonstrated broad-spectrum and high activity against the most common SSSI Gram-positive pathogens, including MRSA, isolated in EU medical centres in 2008. This favourable antimicrobial profile demonstrates that ceftaroline is a promising anti-MRSA therapeutic option in the treatment of SSSI.

* Changes from the original abstract are shown in bold and reflect results obtained after its submission.

Introduction

Ceftaroline is a novel parenteral cephalosporin with broad-spectrum of antimicrobial activity, which includes methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is the bioactive metabolite of ceftaroline fosamil, a *N*-phosphonoamino water-soluble cephalosporin prodrug, and is currently being developed for treatment of complicated skin and skin structure infections (cSSSI) and community-acquired pneumonia. Encouraging results have recently been reported from phase 3 investigations that compared the efficacy of ceftaroline to vancomycin plus aztreonam for treatment of cSSSI.

Ceftaroline demonstrates excellent in vitro activity against *S. aureus* and β-haemolytic streptococci (*Streptococcus pyogenes*), which are considered the most important pathogens associated with SSSI. 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. In the present study we evaluate the antimicrobial activity and spectrum of ceftaroline and comparator agents tested against clinical bacterial isolates related to SSSI collected in European medical centres in 2008.

Materials and Methods

Bacterial Isolates

Unique (one per patient) clinically significant isolates of *S. aureus* (2,168; 25.4% MRSA), coagulase-negative staphylococci (CoNS; 423; 76.1% oxacillin-resistant), β-haemolytic streptococci (172), viridans group streptococci (86), and *Enterococcus faecalis* (409) were consecutively collected in 2008 from 24 medical centers in 10 European countries, Turkey and Israel.

Susceptibility Testing

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI) documents to determine the antimicrobial susceptibility of each organism. Validated MIC panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) 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. The following American Type Culture Collection (ATCC) strains were tested: *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.

Results

- Ceftaroline was very active against methicillin-susceptible *S. aureus* (MSSA; MIC_{90}, 0.25 mg/L). The highest ceftaroline MIC was 1 mg/L, and 99.8% of strains were inhibited at ≤0.5 mg/L (Table 1).
- Ceftaroline (MIC_{50} and MIC_{90}, 0.25 mg/L) was 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L), eight-fold more potent than linezolid (MIC_{50} and MIC_{90}, 2 mg/L) and four-fold more potent than vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) when tested against MSSA (Table 2).
- Resistance to oxacillin (MRSA) was observed in 25.4% of *S. aureus* isolates and ceftaroline was very active against these organisms (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; Table 2). All MRSA strains, except for four isolates from a unique medical center in Greece, were inhibited at ≤2 mg/L of ceftaroline. Molecular typing results revealed that these four strains were clonally related.
- Ceftaroline (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L), vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) and linezolid (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) were very active against MRSA. MRSA showed high rates of resistance to levofloxacin (84.4%), erythromycin (64.1%) and clindamycin (14.9%; Table 2)
- Ceftaroline exhibited excellent activity (MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.015 mg/L) against the β-haemolytic streptococci (Table 2). Ceftaroline was four-fold more active than penicillin (MIC_{90}, 0.06 mg/L) against these common pathogens, and 100.0% of strains were inhibited at ≤0.06 mg/L of ceftaroline (Table 1).
- Ceftaroline was the most active compound (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L) tested against CoNS. Ceftaroline was two- to four-fold more active than linezolid (MIC_{50} and MIC_{90}, 1 mg/L) and vancomycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L), and ≥32-fold more active than ceftriaxone (MIC_{50}, 16 mg/L and MIC_{90}, >32 mg/L) against this pathogen (Table 2).
- More than 90% of *E. faecalis*, including all vancomycin-resistant isolates (VRE) were inhibited by ≤8 mg/L of ceftaroline (MIC_{50}, 2 mg/L; Table 2). Four of 5 VRE were from Greece.
- Viridans group streptococci exhibited low ceftaroline MIC values with a MIC_{50} value of only 0.015 mg/L and MIC_{90} of 0.25 mg/L. Furthermore, only 79.1 and 90.7% of strains were susceptible to penicillin and ceftriaxone, respectively (Table 2).

Table 1. Frequency of occurrence of ceftaroline MIC values for all organisms tested.

	No. (cumulative %) of isolates inhibited at ceftaroline MIC (mg/L) of:								
Organisms (no. tested)	≤0.06	0.12	0.25	0.5	1	2	4	8	>8
S. aureus (2,168)	19 (0.9)	67 (4.0)	1,392 (68.2)	303 (82.2)	304 (96.2)	77 (99.8)	4 (100.0)	-	-
Oxacillin-susceptible (1,617)	19 (1.2)	67 (5.3)	1,383 (90.9)	145 (99.8)	3 (100.0)	-	-	-	-
Oxacillin-resistant (551)	0 (0.0)	0 (0.0)	9 (1.6)	158 (30.3)	301 (84.9)	79 (99.3)	4 (100.0)	-	-
β-haemolytic streptococci (172)	172 (100.0)	-	-	-	-	-	-	-	-
Coagulase-neg. staphylococci (423)	66 (15.6)	37 (24.4)	105 (49.2)	129 (79.7)	47 (90.8)	31 (98.1)	8 (100.0)	-	-
E. faecalis (409)	2 (0.5)	1 (0.7)	1 (1.0)	7 (2.7)	143 (37.7)	141 (72.1)	20 (77.0)	56 (90.7)	38 (100.0)
Viridans group streptococci (86)	76 (88.4)	1 (89.5)	3 (93.0)	3 (96.5)	2 (98.8)	0 (98.8)	0 (98.8)	0 (98.8)	1 (100.0)

Table 2. Activity of ceftaroline and comparator agents tested against bacterial isolates from European medical centers.

	MIC		%	%		MIC		%	%
Organism (no. tested)	50%	90%	susceptible[a]	resistant[a]	Organism (no. tested)	50%	90%	susceptible[a]	resistant[a]
S. aureus					CoNS (423)				
Oxacillin-susceptible (1,617)					Ceftaroline	0.5	1	-	-
Ceftaroline	0.25	0.25	-[b]	-	Ceftriaxone	16	>32	23.9	76.1
Ceftriaxone	4	4	99.8	0.0	Oxacillin	>2	>2	23.9	76.1
Erythromycin	≤0.25	>4	84.0	14.8	Erythromycin	>4	>4	35.2	64.3
Clindamycin	≤0.25	≤0.25	98.0	1.9	Clindamycin	≤0.25	>2	67.4	30.3
Levofloxacin	≤0.5	≤0.5	94.6	5.1	Levofloxacin	4	>4	44.7	53.0
Gentamicin	≤2	≤2	98.6	1.4	Gentamicin	≤2	>8	59.3	31.9
TMP/SMX	≤0.5	≤0.5	99.5	0.5	TMP/SMX	≤0.5	>2	62.9	37.1
Linezolid	2	2	100.0	-	Linezolid	1	1	99.5	-
Vancomycin	1	1	100.0	0.0	Vancomycin	1	2	100.0	0.0
Oxacillin-resistant (551)					*E. faecalis* (409)				
Ceftaroline	1	2	-	-	Ceftaroline	2	8	-	-
Ceftriaxone	>32	>32	0.0	100.0	Ceftriaxone	>32	>32	-	-
Erythromycin	>4	>4	34.3	64.1	Ampicillin	≤1	2	100.0	0.0
Clindamycin	≤0.25	>2	64.2	35.2	Erythromycin	>4	>4	3.7	59.2
Levofloxacin	>4	>4	14.5	84.4	Levofloxacin	1	>4	71.1	28.6
Gentamicin	≤2	>8	81.3	14.9	Gentamicin (HL)	≤500	>1000	70.8	29.2
TMP/SMX	≤0.5	≤0.5	98.7	1.3	Linezolid	1	2	100.0	0.0
Linezolid	1	2	100.0	-	Vancomycin	1	2	98.8	1.2
Vancomycin	1	1	100.0	0.0					
					Viridans group streptococci (86)				
β-haemolytic streptococci (253)					Ceftaroline	0.015	0.25	-	-
Ceftaroline	≤0.008	0.015	-	-	Ceftriaxone	≤0.25	1	90.7	5.8
Ceftriaxone	≤0.25	≤0.25	100.0	-	Penicillin	0.06	1	79.1	7.0
Penicillin	≤0.015	0.06	100.0	0.0	Erythromycin	≤0.25	>2	59.3	34.9
Erythromycin	≤0.25	>2	79.1	19.2	Clindamycin	≤0.25	>2	88.4	11.6
Clindamycin	≤0.25	≤0.25	90.7	8.7	Levofloxacin	1	>4	97.7	1.2
Levofloxacin	≤0.5	1	100.0	0.0	Linezolid	1	1	100.0	-
Linezolid	1	1	100.0	-	Vancomycin	0.5	1	100.0	-
Vancomycin	0.5	0.5	100.0	0.0					

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.

Conclusions

- Ceftaroline demonstrated broad-spectrum and high activity against the most common SSSI Gram-positive pathogens, including MRSA, isolated from European medical centres in 2008.
- Ceftaroline provides a significant potency advantage (≥16-fold) compared to ceftriaxone against the common Gram-positive pathogens associated with SSSI.
- This favorable antimicrobial profile demonstrates that ceftaroline is a promising anti-MRSA therapeutic option in the treatment of SSSI.

References

1. Clinical and Laboratory Standards Institute (2009). *M07-A8, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - eighth edition.* Wayne, PA. CLSI.
2. Clinical and Laboratory Standards Institute (2009). *M100-S19, Performance standards for antimicrobial susceptibility testing, 19th informational supplement.* Wayne, PA. CLSI.
3. Corey R, Wilcox M and Talbot GH (2008). CANVAS-1: randomized, double-blinded phase 3 study (P903-06) of the efficacy and safety of ceftaroline vs vancomycin plus aztreonam in complicated skin and skin structure infections (cSSSI). *48th ICAAC, October 25-28, 2008.*
4. Ge Y, Biek D, Talbot GH and Sahm DF (2008). In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. *Antimicrob. Agents Chemother.* 52:3398-3407.
5. Kanafani ZA and Corey GR (2009). Ceftaroline: a cephalosporin with expanded Gram-positive activity. *Future Microbiol.* 4:25-33.
6. Talbot GH, Thye D, Das A and Ge Y (2007). Phase 2 study of ceftaroline versus standard therapy in the treatment of complicated skin and skin structure infections. *Antimicrob. Agents Chemother.* 51:3612-3616.

Acknowledgement

This study was supported by Forest Laboratories, Inc.