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Ceftaroline Activity Against Clinical Isolates of *Staphylococcus aureus*, Including Methicillin-resistant Strains (MRSA), from United States Hospitals

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Abstract

Introduction: Ceftaroline (CPT) is a novel, parenteral, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms, including MRSA and multidrug-resistant *Streptococcus pneumoniae* (MDRSP), as well as common Gram-negative pathogens. CPT is in late-stage clinical development for treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia. *S. aureus* is the main cause of cSSSI. We assessed the activity of CPT tested against *S. aureus* from USA hospitals.

Methods: 6,626 unique clinical *S. aureus* strains, consecutively collected from 40 USA medical centers in 2008-2009, plus 10 molecularly characterized USA300-0114 strains (from cSSSI) were tested for susceptibility (S) against CPT and various comparator agents by CLSI broth microdilution methods.

Results: 53.4% of *S. aureus* were MRSA. CPT was very active against methicillin-S strains (MSSA) and MRSA with MIC_{90}s of 0.25 and 1 μg/mL, respectively. All MRSA were inhibited at ≤2 μg/mL of CPT (see Table). CPT was eight- to 16-fold more potent than ceftriaxone ($MIC_{50/90}$, 4/4 μg/mL) and cefepime ($MIC_{50/90}$, 2/4 μg/mL against MSSA. MRSA showed high resistance rates to erythromycin (92.5%), levofloxacin (71.3%) and clindamycin (34.7%), but remained 100.0% S to linezolid ($MIC_{50/90}$, 2/2 μg/mL), vancomycin ($MIC_{50/90}$, 1/1 μg/mL) and daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL). CPT was four- to eight-fold more active than linezolid or vancomycin and showed activity similar to daptomycin when tested against MRSA. All USA300-0114 strains were PVL positive, had SCC*mec* type IVa and were highly CPT-S (MIC range, 0.5-1 μg/mL).

Abstract Table

	Cumulative % inhibited at CPT MIC of:					
Organism (no.)	**≤.06**	**.12**	**.25**	**.5**	**1**	**2**
MSSA (3,089)	0.8	6.4	90.3	99.8	100	-
MRSA (3,537)	0.0	0.1	1.4	40.6	95.2	100
USA300 (10)	0.0	0.0	0.0	50.0	100	-

Conclusions: CPT was highly active against a large collection of MSSA and MRSA strains recently isolated in USA hospitals, including representative strains of the pandemic USA300 clone. CPT represents a very promising therapeutic option for treatment of cSSSI infections, including those caused by MRSA.

Introduction

Ceftaroline fosamil is the prodrug of ceftaroline, a novel, broad-spectrum cephalosporin that has bactericidal activity against resistant Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*, as well as common Gram-negative pathogens. Ceftaroline fosamil is currently in late-stage clinical development for the treatment of complicated skin and skin structure infections (cSSSIs) and community-acquired bacterial pneumonia. Encouraging results have been reported from phase 3 investigations that compared the efficacy of ceftaroline with vancomycin plus aztreonam for the treatment of cSSSI.

Ceftaroline demonstrates excellent in vitro activity against both *S. aureus* and *Streptococcus pyogenes*, the two most important pathogens associated with cSSSI. Coagulase-negative staphylococci (CoNS), enterococci, and viridans group streptococci are pathogens also associated with cSSSI. Ceftaroline provides in vitro activity against these Gram-positive pathogens, including strains resistant to other drug classes and multidrug-resistant isolates.

The objective of this study was to evaluate the antimicrobial activity of ceftaroline and multiple comparator agents when tested against current (2008-2009) clinical *S. aureus* isolates collected in medical centers throughout the United States (USA).

Methods

A total of 40 medical centers geographically distributed throughout the USA contributed 6626 unique, consecutively collected clinical *S. aureus* isolates from hospitalized patients from 2008 to 2009. In addition, a molecularly characterized set of 10 *S. aureus* isolates from cSSSI with a USA300-0114 type were also tested.

Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods were performed to determine the antimicrobial activity of ceftaroline and 13 comparison agents on validated MIC panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton (MH) broth (M07-A8, 2009).

Concurrent testing of quality control (QC) strains assured that proper test conditions and procedures were used. These strains included American Type Culture Collection (ATCC) strains: *S. aureus* ATCC 29213, *Enterococcus 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

- The methicillin (oxacillin)-resistance (MRSA) rate was 53.4% among the 6626 *S. aureus* strains collected from cSSSI within the 40 USA medical centers. Ceftaroline provided excellent activity against these strains, with all isolates inhibited by ≤2 μg/mL (Table 1)
- Ceftaroline was very active against methicillin (oxacillin)-susceptible *S. aureus* (MSSA) isolates, with 4-fold lower ceftaroline $MIC_{50/90}$ values (0.25/0.25 μg/mL) when compared with the MRSA strains (1/1 μg/mL; Tables 1 and 2)
- A sample of molecularly characterized USA300-0114 community-acquired (CA) MRSA strains from cSSSI were confirmed to possess Panton-Valentine leukocidin (PVL) and staphylococcal chromosome cassette (SCC)*mec* type IVa and demonstrated low MICs for ceftaroline (range 0.5-1 μg/mL; Table 1)
- Against MSSA, ceftaroline (MIC_{50} and MIC_{90}, 0.25 μg/mL) was 8- to 16-fold more potent than ceftriaxone (MIC_{50} and MIC_{90}, 4 μg/mL) and cefepime (MIC_{50} and MIC_{90}, 2/4 μg/mL; Table 2); 99.8% of strains were inhibited at ≤0.5 μg/mL of ceftaroline (highest MIC, 1 μg/mL; Table 1)
- Ceftaroline exhibited excellent activity against MRSA (MIC_{90}, 1 μg/mL) that was ≥32-fold more potent than ceftriaxone (MIC_{90}, >32 μg/mL) and cefepime (MIC_{90}, >16 μg/mL; Table 2)
- Among non-β-lactam comparators, MRSA strains showed the highest resistance rates for erythromycin (92.5%), followed by levofloxacin (71.2%) and clindamycin (34.7%). The highest susceptibility rates were observed for vancomycin (100.0%), followed by tigecycline (99.9%), linezolid and daptomycin (99.8%), and trimethoprim/sulfamethoxazole (98.4%; Table 2)
- Ceftaroline demonstrated better potency (MIC_{90}, 1 μg/mL) than linezolid (MIC_{90}, 2 μg/mL) and was similar in potency to vancomycin (MIC_{90}, 1 μg/mL), daptomycin (MIC_{90}, 0.5 μg/mL), but was 4-fold less active than tigecycline (MIC_{90}, 0.25 μg/mL) when tested against MRSA isolated from cSSSI (Table 2)
- MSSA strains were significantly less resistant than MRSA strains for erythromycin (33.8 vs 92.5%), levofloxacin (10.3 vs 71.2%), and clindamycin (6.0 vs 34.7%; Table 2)

Table 1. Frequency of Occurrence of Ceftaroline MIC Values for USA *S. aureus* Strains in 2008-2009

	No. of strains (cumulative %) inhibited at ceftaroline MIC (μg/mL) of:						
Organism/ (no. tested)	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**
S. aureus							
All strains (6,626)	2 (0.1)	21 (0.4)	174 (3.0)	2,639 (42.9)	1,681 (68.2)	1,937 (97.5)	169 (100.0)[a]
MSSA (3,089)	2 (0.2)	21 (0.8)	171 (6.4)	2,592 (90.3)	294 (99.8)	6 (100.0)	-
MRSA (3,537)	-	-	3 (0.1)	47 (1.4)	1,387 (40.6)	1,931 (95.2)	169 (100.0)[a]
USA300 type (10)	-	-	-	-	5 (50.0)	5 (100.0)	-

a. Only 2.5% of all *S. aureus* had a MIC at 2 μg/mL.

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against *S. aureus* Isolates from USA Medical Centers Isolated in 2008-2009

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% Susceptible/ % Resistant[a]
All strains (6626)				
Ceftaroline	0.5	1	≤0.008 – 2	- / -
Oxacillin	>2	>2	≤0.25 – >2	46.6 / 53.4
Ceftriaxone	16	>32	≤0.25 – >32	46.6 / 53.4
Cefepime	4	>16	0.25 – >16	46.6 / 53.4
Erythromycin	>2	>2	≤0.25 – >2	34.3 / 65.1
Clindamycin	≤0.25	>2	≤0.25 – >2	78.3 / 21.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	56.6 / 42.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5
Linezolid	2	2	≤0.06 – >8	99.9 / 0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -
Tigecycline[b]	0.12	0.25	≤0.03 – 1	>99.9 / -
Methicillin-susceptible (3089)				
Ceftaroline	0.25	0.25	≤0.008 – 1	- / -
Ceftriaxone	4	4	0.5 – 32	99.4 / 0.0
Cefepime	2	4	0.25 – 16	99.9 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	65.5 / 33.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	93.7 / 6.0
Levofloxacin	≤0.5	4	≤0.5 – >4	89.1 / 10.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.7 / 1.3
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -
Methicillin-resistant (3537)				
Ceftaroline	1	1	0.12 – 2	- / -
Erythromycin	>2	>2	≤0.25 – >2	7.1 / 92.5
Clindamycin	≤0.25	>2	≤0.25 – >2	64.9 / 34.7
Levofloxacin	>4	>4	≤0.5 – >4	28.2 / 71.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.4 / 1.6
Linezolid	2	2	0.25 – >8	99.8 / 0.2
Vancomycin	1	1	0.25 – 2	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 4	99.8 / -
Tigecycline[b]	0.12	0.25	≤0.03 – 1	99.9 / -

a. Criteria as published by the CLSI [2010]. β-lactam susceptibility should be directed by the oxacillin test results. No criteria for ceftaroline susceptibility have been established.
b. US FDA breakpoints were applied [Tygacil Product Insert, 2005].
CLSI = Clinical and Laboratory Standards Institute; FDA = Food and Drug Administration.

Conclusions

- Ceftaroline was highly active against this large collection of recent (2008-2009) MSSA and MRSA strains isolated from cSSSI in USA medical centers
- Against the small set of representative strains of the pandemic USA300 clone of community-acquired MRSA, ceftaroline demonstrated excellent activity, with all strains inhibited by ≤1 μg/mL
- Based on the broad-spectrum coverage and excellent MRSA activity, ceftaroline fosamil represents a promising option for the treatment of cSSSIs, including those caused by MRSA

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