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Ceftaroline Activity Tested Against Pathogens Associated With Acute Bacterial Skin and Skin-Structure Infections (ABSSSI) Isolated From Latin American Medical Centers (2010)

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Abstract

Background: Ceftaroline is a new cephalosporin with activity against Gram-positive cocci, including methicillin-resistant *S. aureus* (MRSA) and Enterobacteriaceae species. The prodrug, ceftaroline fosamil is approved by the USA-FDA for treatment of ABSSSI.

Methods: 15 sites (5 countries) in 2010 contributed clinical isolates which were susceptibility tested using validated broth microdilution panels. Species associated with ABSSSI included *S. aureus* (1,259), ß-hemolytic streptococci (BHS; 199), *E. coli* (699) and *Klebsiella* spp. (509). CLSI, EUCAST and USA-FDA susceptibility criteria were applied.

Results: *S. aureus* ceftaroline MIC$_{50/90}$ were 0.25/2 µg/ml. Ceftaroline (MIC$_{90}$, 0.25 µg/ml) was 16-fold more active than ceftriaxone (MIC$_{90}$, 4 µg/ml) and 8-fold more active than linezolid (MIC$_{90}$, 2 µg/ml) against methicillin-susceptible *S. aureus* (MSSA). The highest ceftaroline MIC among MSSA strains was only 1 µg/ml with values ranging from 0.25 to 2 µg/ml (MIC$_{50/90}$, 1/2 µg/ml) among MRSA. *S. pyogenes* (MIC$_{90}$, ≤0.008 µg/ml) were slightly more susceptible to ceftaroline than *S. agalactiae* (MIC$_{90}$, 0.015 µg/ml). *E. coli* were generally susceptible to ceftaroline (MIC$_{50/90,}$ 0.12/>32 µg/ml) and the ceftaroline MIC$_{90}$ was 0.5 µg/ml for non-ESBL strains. *K. pneumoniae* and *K. oxytoca* exhibited similar susceptibility to ceftaroline among non-ESBL strains (MIC$_{90}$ 0.25 µg/ml). ESBL-producing Enterobacteriaceae had ceftaroline MIC$_{50}$ of >32 µg/ml.

Conclusions: Ceftaroline was active against *S. aureus*, with considerably greater activity compared to other ß-lactams against MRSA (all inhibited at ≤2 µg/ml). Ceftaroline was highly active against BHS and its activity against Enterobacteriaceae was similar to those of ceftazidime and ceftriaxone. Ceftaroline demonstrated potent *in vitro* activity against USA-FDA indicated species associated with ABSSSI from Latin America Hospitals.

Introduction

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin with *in vitro* bactericidal activity against Gram-positive organisms, including methicillin-susceptible (MS) and –resistant (MR) *Staphylococcus aureus* (SA), ß-hemolytic streptococci (including *Streptococcus pyogenes and S. agalactiae*), viridans group streptococci, *Streptococcus pneumoniae* (including multidrug-resistant [MDR] strains), as well as ceftriaxone-susceptible Enterobacteriaceae.

Ceftaroline demonstrated clinical (integrated clinical success rate of 92.7% in the microbiologically evaluable population) and microbiological efficacy (inhibiting 96.8% of all isolates at a ceftaroline MIC of ≤2 µg/ml) in two Phase 3 acute bacterial skin and skin structure infection (ABSSSI) trials conducted in Europe and the United States (USA); CANVAS 1 and CANVAS 2, registration numbers NCT00424190 and NCT00423657, and was shown to be non-inferior to vancomycin plus aztreonam. Ceftaroline fosamil is approved by the USA Food and Drug Administration (FDA) for community-acquired bacterial pneumonia (CABP) and ABSSSI. We evaluated ceftaroline and comparator antimicrobial agents tested against 2,666 pathogens associated with ABSSSI collected from patients in Latin American medical centers during 2010 as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study.

Materials and Methods

Organism collection: A total of 2,666 isolates of bacterial species associated with ABSSSI were evaluated. The organism collection included *S. aureus* (1,259), ß-hemolytic streptococci (199), *E. coli* (699) and *Klebsiella* spp. (509). The isolates were collected in 2010 from 15 medical centers located in five Latin American countries, including Argentina (two centers), Brazil (six centers), Chile (two centers), Colombia (one center) and Mexico (four centers).

Susceptibility testing methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) methods were performed to determine antimicrobial susceptibility of ceftaroline and comparator antimicrobials used to treat ABSSSI. Validated MIC panels were manufactured by ThermoFisher Scientific, Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). The isolates were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime MIC were ≥2 µg/ml were considered to be phenotype-positive for ESBL production (CLSI, 2012).

Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. Susceptibility percentages and validation of QC results were based on CLSI documents (M100-S22) and EUCAST (2012). USA-FDA interpretive criteria for ceftaroline susceptibility were used.

Results

- Ceftaroline was very active against *S. aureus* (MIC$_{50}$, 0.25 µg/ml and MIC$_{90}$, 2 µg/ml). When tested against MSSA (MIC$_{50}$ and MIC$_{90}$, 0.25 µg/ml), 97.5% of strains were inhibited at a ceftaroline MIC of only ≤0.25 µg/ml (Table 1).
- Against MRSA, ceftaroline MIC values ranged from 0.25 to 2 µg/ml (MIC$_{50}$, 1 µg/ml and MIC$_{90}$, 2 µg/ml) and 68.3% of strains were inhibited at a ceftaroline MIC of ≤1 µg/ml (Table 1). Ceftaroline activity against MRSA was comparable to that of linezolid (MIC$_{50}$ and MIC$_{90}$, 1 µg/ml) and vancomycin (MIC$_{50}$ and MIC$_{90}$, 1 µg/ml; Table 2). Clindamycin (81.3% and 81.5% resistant by CLSI and EUCAST criteria, respectively), erythromycin (86.6% and 87.1% resistant) and levofloxacin (82.5% resistant) exhibited limited activity against MRSA strains, while vancomycin, linezolid, daptomycin and tigecycline showed complete coverage (100.0% susceptibility) against this organism (Table 2).
- Ceftaroline was very potent against ß-hemolytic streptococci. *S. pyogenes* strains (MIC$_{50}$ and MIC$_{90}$, ≤0.008 µg/ml) were slightly more susceptible to ceftaroline than *S. agalactiae* strains (MIC$_{50}$ and MIC$_{90}$, 0.015 µg/ml), and the highest ceftaroline MIC among ß-hemolytic streptococci was only 0.03 µg/ml (Tables 1 and 2).
- *E. coli* isolates were generally susceptible to ceftaroline (MIC$_{50,}$ 0.12 µg/ml). Among non-ESBL strains, 95.9% and 98.5% of strains were inhibited at ceftaroline MIC of ≤0.5 and ≤1 µg/ml, respectively (Tables 1 and 2). An ESBL-phenotype was observed in 27.8% of *E. coli* strains, and ESBL-phenotype strains were less susceptible to ceftaroline (MIC$_{50/90}$ 32/>32 µg/ml) and all other cephalosporins tested such as ceftriaxone and ceftazidime (data not shown).
- High rates of ESBL-phenotypes were observed among *K. pneumoniae* (55.3%) and *K. oxytoca* (32.4%). Non-ESBL strains of these two species exhibited similar susceptibility to ceftaroline (MIC$_{90}$, 0.25 µg/ml), while ESBL-producing strains had ceftaroline MIC$_{50}$ of >32 µg/ml (Tables 1 and 2). Decreased susceptibility to meropenem (MIC, ≥2 µg/ml) was observed in 19.3% of ESBL-phenotype *K. pneumoniae* but none of the ESBL-phenotype *K. oxytoca* (data not shown).

Table 1. *Summary of Ceftaroline Activity Tested Against Pathogens Associated with ABSSSI from Latin American Medical Centers (2010).*

Organism	No. of Isolates	No. of isolates (%) inhibited at ceftaroline MIC value (µg/ml) of: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC$_{50}$	MIC$_{90}$
S. aureus	1259	--	--	--	2 (0.2)	73 (6.0)	610 (54.5)	132 (65.0)	262 (85.8)	180 (100.0)	--	--	--	--	--	0.25	2
MSSA	692	--	--	--	2 (0.3)	73 (10.8)	600 (97.5)	16 (99.8)	1 (100.0)	--	--	--	--	--	--	0.25	0.25
MRSA	567	--	--	--	--	--	10 (1.8)	116 (22.3)	261 (68.3)	180 (100.0)	--	--	--	--	--	1	2
ß-hemolytic streptococci	199	72 (36.2)	115 (94.0)	12 (100.0)	--	--	--	--	--	--	--	--	--	--	--	0.015	0.015
S. pyogenes	68	65 (95.6)	3 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.008	≤0.008
S. agalactiae	131	7 (5.3)	112 (90.8)	12 (100.0)	--	--	--	--	--	--	--	--	--	--	--	0.015	0.015
Escherichia coli	699	--	1 (0.1)	46 (6.7)	175 (31.7)	157 (54.2)	67 (63.8)	39 (69.4)	14 (71.4)	10 (72.8)	6 (73.7)	14 (75.7)	7 (76.7)	6 (77.6)	157 (100.0)	0.12	>32
non ESBL	505	--	1 (0.2)	46 (9.3)	175 (44.0)	157 (75.1)	67 (88.4)	38 (95.9)	13 (98.5)	6 (99.7)	1 (99.9)	1 (100.0)	--	--	--	0.12	0.5
ESBL phenotype	194	--	--	--	--	--	--	1 (0.5)	1 (1.0)	4 (3.1)	5 (5.7)	13 (12.4)	7 (16.0)	6 (19.1)	157 (100.0)	>32	>32
Klebsiella pneumoniae	468	1 (0.2)	2 (0.6)	9 (2.5)	111 (26.2)	43 (35.4)	24 (40.5)	10 (42.6)	5 (43.7)	5 (44.8)	4 (45.7)	10 (47.8)	7 (49.3)	5 (50.4)	232 (100.0)	32	>32
non ESBL	209	1 (0.5)	2 (1.5)	9 (5.8)	111 (58.9)	43 (79.5)	23 (90.5)	10 (95.3)	5 (97.7)	3 (99.0)	2 (100.0)	--	--	--	--	0.06	0.25
ESBL phenotype	259	--	--	--	--	--	1 (0.4)	0 (0.4)	0 (0.4)	2 (1.2)	2 (2.0)	10 (5.8)	7 (8.5)	5 (10.4)	232 (100.0)	>32	>32
Klebsiella oxytoca	37	--	--	2 (5.4)	10 (32.4)	8 (54.0)	4 (64.8)	1 (67.5)	0 (67.5)	0 (67.5)	1 (70.2)	1 (72.9)	1 (75.6)	1 (78.3)	8 (100.0)	0.12	>32
non ESBL	25	--	--	2 (8.0)	10 (48.0)	8 (80.0)	4 (96.0)	1 (100.0)	--	--	--	--	--	--	--	0.12	0.25
ESBL phenotype	12	--	--	--	--	--	--	--	--	--	1 (8.3)	1 (16.6)	1 (24.9)	1 (33.2)	8 (100.0)	>32	>32

Table 2. *Activity of Ceftaroline and Comparator Agents when Tested Against Bacterial Organisms Associated with Skin and Skin Structure Infections from Latin American Medical Centers (2010).*

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) MIC$_{50}$	MIC$_{90}$	Range	%S / %R[a] CLSI	EUCAST
Staphylococcus aureus (1,259)					
Ceftaroline	0.25	2	0.06 – 2	85.7[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	55.0 / 45.0	55.0 / 45.0
Ceftriaxone	4	>8	≤0.06 – >8	55.0 / 45.0	55.0 / 45.0
Erythromycin	0.5	>4	≤0.25 – >4	50.3 / 47.8	50.3 / 48.8
Clindamycin	≤0.25	>2	≤0.25 – >2	61.7 / 38.1	61.4 / 38.3
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	1	≤0.25 – >8	91.9 / 7.2	90.2 / 8.4
Tigecycline	0.06	0.25	≤0.03 – 0.5	100.0[c] / -	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	60.8 / 38.4	60.8 / 38.4
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	96.7 / 3.3	96.7 / 2.9
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MSSA (692)					
Ceftaroline	0.25	0.25	0.06 – 1	100.0[b] / -	- / -
Ceftriaxone	4	4	≤0.06 – 8	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>4	≤0.25 – >4	81.1 / 16.0	81.1 / 17.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.1 / 2.7	96.5 / 2.9
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	89.3 / 9.1	88.7 / 11.1
Tigecycline	0.06	0.25	≤0.03 – 0.5	100.0[c] / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.0 / 2.3	97.0 / 2.3
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.8 / 1.2	98.8 / 1.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MRSA (567)					
Ceftaroline	1	2	0.25 – 2	68.3[b] / -	- / -
Erythromycin	>4	>4	≤0.25 – >4	12.7 / 86.6	12.7 / 87.1
Clindamycin	>2	>2	≤0.25 – >2	18.5 / 81.3	18.5 / 81.5
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	1	≤0.25 – >8	95.1 / 4.9	92.1 / 5.1
Tigecycline	0.06	0.25	≤0.03 – 0.5	100.0[c] / -	100.0 / 0.0
Levofloxacin	>4	>4	≤0.5 – >4	16.8 / 82.5	16.8 / 82.5
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	94.2 / 5.8	94.2 / 5.3
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
S. pyogenes (68)					
Ceftaroline	≤0.008	≤0.008	≤0.008 – 0.015	100.0[b] / -	- / -
Penicillin	≤0.03	≤0.03	≤0.03	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	≤0.25 – >4	95.6 / 4.4	95.6 / 4.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.6 / 4.4	95.6 / 4.4
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤0.25	>8	≤0.25 – >8	80.9 / 19.1	80.9 / 19.1
Tigecycline	≤0.03	≤0.03	≤0.03 – 0.06	100.0[c] / -	100.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5 – 4	98.5 / 0.0	92.6 / 1.5
TMP/SMX[d]	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
S. agalactiae (131)					
Ceftaroline	0.015	0.015	≤0.008 – 0.03	100.0[b] / -	- / -
Penicillin	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	≤0.25 – >4	90.1 / 8.4	90.1 / 8.4
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.7 / 5.3	94.7 / 5.3
Vancomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	17.6 / 82.4	17.6 / 82.4
Tigecycline	≤0.03	≤0.03	≤0.03 – 0.06	100.0[c] / -	100.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5 – >4	98.5 / 1.5	96.2 / 1.5
TMP/SMX[d]	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Daptomycin	0.12	0.25	0.12 – 0.5	100.0 / -	100.0 / 0.0
Escherichia coli (699)					
Ceftaroline	0.12	>32	0.015 – >32	69.4[b] / 28.6	- / -
Ceftriaxone	≤0.06	>8	≤0.06 – >8	72.7 / 26.9	72.7 / 26.9
Ceftazidime	0.25	32	0.03 – >32	79.1 / 17.3	74.5 / 20.9
Ampicillin/sulbactam	16	>16	≤2 – >16	38.0 / 38.4	- / 62.0
Piperacillin/tazobactam	2	16	≤0.5 – >64	91.1 / 3.0	83.4 / 8.9
Tigecycline	0.12	0.25	≤0.03 – 1	100.0[c] / 0.0	100.0 / 0.0
Gentamicin	≤1	>8	≤1 – >8	81.4 / 17.5	81.1 / 18.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	58.8 / 38.8	58.8 / 41.2
Meropenem	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Klebsiella spp.[e] (509)					
Ceftaroline	16	>32	≤0.008 – >32	44.6[c] / 54.4	- / -
Ceftriaxone	8	>8	≤0.06 – >8	47.0 / 52.7	47.0 / 52.7
Ceftazidime	2	>32	0.03 – >32	54.8 / 40.1	49.5 / 45.2
Ampicillin/sulbactam	>16	>16	≤0.25 – >16	40.3 / 54.8	- / 59.7
Piperacillin/tazobactam	4	>64	≤0.5 – >64	63.1 / 27.9	57.0 / 36.9
Tigecycline	0.25	1	0.06 – 4	98.6[c] / 0.0	95.3 / 1.4
Gentamicin	≤1	>8	≤1 – >8	65.6 / 30.6	64.6 / 34.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	61.3 / 37.5	58.7 / 38.7
Meropenem	≤0.12	1	≤0.12 – >8	90.2 / 8.4	91.6 / 5.3

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-lactam susceptibility should be directed by the oxacillin test results.
b. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Teflaro® Prescribing Information, 2012].
c. In the absence of CLSI breakpoints, USA-FDA breakpoints were applied [Tygacil® Prescribing Information, 2011].
d. TMP/SMX = trimethoprim/sulfamethoxazole.
e. Includes: *Klebsiella oxytoca* (37 strains), *K. ozaenae* (2 strains), *K. pneumoniae* (468 strains), *K. terrigena* (1 strain), and unspeciated *Klebsiella* (1 strain).

Conclusions

- Ceftaroline was active against *S. aureus*, with considerably greater activity compared with other ß-lactams against MRSA (all inhibited at ≤2 µg/ml). Ceftaroline was 16-fold more active than ceftriaxone against MSSA.
- Ceftaroline was highly active against ß-hemolytic streptococci (MIC$_{90}$, ≤0.008-0.015 µg/ml) and its activity against Enterobacteriaceae was similar to that of ceftriaxone and ceftazidime.
- In summary, ceftaroline demonstrated potent *in vitro* activity against USA-FDA indicated species associated with ABSSSI collected from Latin American hospitals in 2010.

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References

1. Biek D, Critchley IA, Riccobene TA, Thye DA (2010). Ceftaroline fosamil: A novel broad-spectrum cephalosporin with expanded anti-Gram-positive activity. *J Antimicrob Chemother* 65 Suppl 4: iv9-iv16.
2. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement.* Wayne, PA: CLSI.
4. Corey GR, Wilcox MH, Talbot GH (2010). CANVAS 1: The first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 65 Suppl 4: iv41-51.
5. European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012.
6. Jones RN, Mendes RE, Sader HS (2010). Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: Results from an international surveillance study. *J Antimicrob Chemother 65 Suppl* 4: iv17-iv31.
7. Teflaro® Prescribing Information (2012). Available at http://www.frx.com/pi/Teflaro_pi.pdf. Accessed June 2012.
8. Tygacil® Prescribing Information (2011). Available at www.tygacil.com. Accessed June 2012.
9. Wilcox MH, Corey GR, Talbot GH (2010). CANVAS 2: The second Phase III, randomized double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 65: iv53-iv65.