P945

Antimicrobial Activity of Ceftaroline Tested Against Common Pathogens Causing Complicated Skin and Soft Tissue Infections in European Medical Centres in 2009

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Abstract

Objective: To assess the activity of ceftaroline and comparator agents tested against pathogens responsible for complicated skin and soft tissue infections (cSSTI). Ceftaroline, the active component of the prodrug ceftaroline fosamil, demonstrates bactericidal activity against Gram-positive organisms, including methicillin-resistant *S. aureus* (MRSA), and common Gram-negative pathogens associated with cSSTI.

Methods: Clinically significant, unique (1 per patient) isolates of *S. aureus* (n=1985; 24.6% MRSA) and β-haemolytic streptococci (BHS; n=388) were collected consecutively from 27 medical centres in 11 European (EU) countries, Turkey and Israel in 2009. Isolates were tested and interpreted for susceptibility (S) by CLSI broth microdilution methods (M07-A8; M100-S21) to ceftaroline and numerous comparator antimicrobials currently available for cSSTI treatment.

Results: Ceftaroline was very active against all *S. aureus* (24.6% MRSA; highest MIC, 2 mg/L). Oxacillin-S *S. aureus* (MSSA; MIC_{50} and MIC_{90}, 0.25 mg/L) had lower MICs than MRSA ($MIC_{50/90}$, 1/2 mg/L). Against MSSA, ceftaroline was 2-, 4-, 8-, 16- and 16-fold more potent than daptomycin (DAP), vancomycin (VAN), linezolid (LZD), ceftriaxone (CRO) and cefepime (CPM), respectively. MRSA isolates demonstrated 100.0% S to LZD, VAN, DAP and tigecycline, but high resistance to levofloxacin (LEV; 89.4%), erythromycin (ERY; 65.6%) and clindamycin (CLI; 32.1%). Against BHS, all isolates were inhibited at ≤0.03 mg/L of ceftaroline, with the greatest activity (MIC_{90}) observed against group A (≤0.008 mg/L), followed by other BHS (0.015 mg/L) and group B (0.03 mg/L). Ceftaroline was 8-, 16-, 32- and 32-fold more potent than DAP, VAN, LZD and LEV, respectively, against BHS. The lowest S rates among BHS isolates were observed against CLI (90.2%) and ERY (82.5%).

Organism (no. tested)	Cumulative % inhibited at ceftaroline MIC (mg/L) of: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
S. aureus									
MSSA (1496)	0.1	0.1	0.1	0.9	10.6	92.7	99.9	100.0	-
MRSA (489)	0.0	0.0	0.0	0.0	0.0	2.7	43.2	83.6	100.0[a]
BHS									
Group A (115)	94.8	99.1	100.0	-	-	-	-	-	-
Group B (196)	4.6	75.0	100.0	-	-	-	-	-	-
Other BHS (77)	84.4	94.8	100.0	-	-	-	-	-	-

[a]Clonal occurrences

Conclusion: Ceftaroline demonstrated strong broad-spectrum activity against the most common cSSTI pathogens (*S. aureus*, including MRSA and BHS) isolated from patients in EU medical centres in 2009. These data warrant continued clinical evaluation of ceftaroline as a therapeutic agent for cSSTI.

Introduction

Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil, an N-phosphonoamino water-soluble cephalosporin. Ceftaroline fosamil has been recently approved by the United States Food and Drug Administration (USA-FDA) for the treatment of complicated skin and soft tissue infections (cSSTIs) and community-acquired bacterial pneumonia.

Ceftaroline has demonstrated excellent *in vitro* activity against *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) and *Streptococcus pyogenes*, which are considered the most common organisms associated with cSSTI. Ceftaroline is also active against coagulase-negative staphylococci, *Enterococcus faecalis* and viridans group streptococci, which are occasional causes of cSSTI.

As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) programme, a global ceftaroline surveillance study, we evaluated the antimicrobial activity of ceftaroline and several comparator agents tested against clinical isolates of *S. aureus* and β-haemolytic streptococci collected in medical institutions throughout Europe.

Materials and methods

Clinically significant, consecutively collected, non-duplicate isolates from patients hospitalized in 27 medical centres in 2009 were utilized for this study. A total of 2373 isolates were collected from 11 European countries, including Belgium, France, Germany, Ireland, Italy, Poland, Portugal, Spain, Sweden, Switzerland, UK, plus Israel and Turkey. The organism collection included: *S. aureus* (n= 1985; 24.6% MRSA) and β-haemolytic streptococci (n=388; 29.6% *S. pyogenes* [Group A]).

Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine antimicrobial susceptibility of ceftaroline and 11 comparators. Validated MIC panels were manufactured by TREK Diagnostics (Cleveland, Ohio, USA). *S. aureus* strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB). β-haemolytic streptococci were tested in CA-MHB supplemented with 3-5% lysed horse blood (M07-A8, 2009).

Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S21) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2011). No interpretive criteria for ceftaroline susceptibility have been established by CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Table 1. *Occurrences of ceftaroline MIC values for S. aureus and β-haemolytic streptococci collected from medical centres in 11 countries in Europe, Israel and Turkey in 2009*

Organism (no. tested)	No. of strains (cumulative %) inhibited at ceftaroline MIC (mg/L) ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
S. aureus (1985)	1 (0.1)	0 (0.1)	0 (0.1)	13 (0.7)	145 (8.0)	1240 (70.5)	306 (85.9)	200 (96.0)	80 (100.0)
MSSA (1496)	1 (0.1)	0 (0.1)	0 (0.1)	13 (0.9)	145 (10.6)	1227 (92.7)	108 (99.9)	2 (100.0)	-
MRSA (489)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.7)	198 (43.2)	198 (83.6)	80 (100.0)
β-haemolytic streptococci (388)	183 (47.2)	151 (86.1)	54 (100.0)	-	-	-	-	-	-
Group A (115)	109 (94.8)	5 (99.1)	1 (100.0)	-	-	-	-	-	-
Group B (196)	9 (4.6)	138 (75.0)	49 (100.0)	-	-	-	-	-	-
Other groups[a] (77)	65 (84.4)	8 (94.8)	4 (100.0)	-	-	-	-	-	-

[a]Includes Group C (n=17), Group F (n=4), Group G (n=35), *S. dysgalactiae* (n=20) and *S. equisimilis* (n=1).

Table 2. *Antimicrobial activity of ceftaroline and comparator agents tested against S. aureus and β-haemolytic streptococci collected from medical centres in 11 European countries, Israel and Turkey in 2009*

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (n=1985)					
Ceftaroline[b]	0.25	1	≤0.008 – 2	- / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	75.4 / 24.6	75.4 / 24.6
Ceftriaxone	4	>32	1 – >32	75.4 / 24.6	75.4 / 24.6
Cefepime	2	>16	0.5 – >16	80.9 / 16.3	75.4 / 24.6
Imipenem	≤0.12	4	≤0.12 – >8	91.4 / 6.9	75.4 / 24.6
Erythromycin	0.5	>2	≤0.25 – >2	70.8 / 29.2[c]	71.6 / 28.1
Clindamycin	≤0.25	0.5	≤0.25 – >2	90.2 / 9.5	89.5 / 9.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	74.0 / 25.7	74.0 / 25.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Linezolid	2	2	0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
MSSA (n=1496)					
Ceftaroline[b]	0.25	0.25	≤0.008 – 1	- / -	- / -
Ceftriaxone	4	4	1 – 16	100.0 / 0.0	100.0 / 0.0
Cefepime	2	4	0.5 – 8	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	83.0 / 17.0[c]	83.8 / 15.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.6 / 2.1	97.1 / 2.4
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.9 / 4.9	94.9 / 4.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	99.2 / 0.8	99.2 / 0.8
Linezolid	2	2	0.12 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
MRSA (n=489)					
Ceftaroline[b]	1	2	0.25 – 2	- / -	- / -
Ceftriaxone	>32	>32	4 – >32	0.0 / 100.0	0.0 / 100.0
Cefepime	>16	>16	2 – >16	0.0 / 100.0	0.0 / 100.0
Imipenem	2	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	33.5 / 66.5[c]	34.4 / 65.6
Clindamycin	≤0.25	>2	≤0.25 – >2	67.5 / 32.1[c]	66.5 / 32.5
Levofloxacin	>4	>4	≤0.5 – >4	10.0 / 89.4	10.0 / 89.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	96.3 / 3.7	96.3 / 3.7
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[d]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (n=388)					
Ceftaroline[b]	0.015	0.03	≤0.008 – 0.03	- / -	- / -
Penicillin	0.03	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.5 / 16.0	82.5 / 16.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.2 / 8.5	91.5 / 9.5
Levofloxacin	≤0.5	1	≤0.5 – >4	99.7 / 0.3	93.0 / 0.3
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Tigecycline[d]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0

Table 2. *(Cont)*

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Group A streptococci (n=115)					
Ceftaroline[b]	≤0.008	≤0.008	≤0.008 – 0.03	- / -	- / -
Penicillin	≤0.015	≤0.015	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	≤0.25 – >2	91.3 / 7.0	91.3 / 7.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.7 / 4.3	95.7 / 4.3
Levofloxacin	≤0.5	2	≤0.5 – 2	100.0 / 0.0	88.7 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Tigecycline[d]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Group B streptococci (n=196)					
Ceftaroline[b]	0.015	0.03	≤0.008 – 0.03	- / -	- / -
Penicillin	0.06	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	79.6 / 19.4	79.6 / 19.4
Clindamycin	≤0.25	>2	≤0.25 – >2	86.2 / 11.8	88.2 / 11.8
Levofloxacin	1	1	≤0.5 – 2	100.0 / 0.0	95.4 / 0.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.25	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Tigecycline[d]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Other β-haemolytic streptococci (n=77)[e]					
Ceftaroline[b]	≤0.008	0.015	≤0.008 – 0.03	- / -	- / -
Penicillin	≤0.015	0.03	≤0.015 – 0.06	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	76.6 / 20.8	76.6 / 20.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.2 / 6.5	93.5 / 6.5
Levofloxacin	≤0.5	1	≤0.5 – >4	98.7 / 1.3	93.5 / 1.3
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	≤0.06	0.25	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Tigecycline[d]	0.06	0.12	≤0.03 – 0.25	100.0 / -	100.0 / 0.0

R=resistant; S=susceptible. [a]According to CLSI and EUCAST breakpoints [CLSI, 2011]. [b]No breakpoint has been established by CLSI or EUCAST. [c]Non-susceptible category was used instead of resistant. [d]US-FDA breakpoints were applied [Tygacil Package Insert, 2010]. [e]Includes: Group C (n=17), Group F (n=4) and Group G (n=35) β-haemolytic streptococci, *S. dysgalactiae* (n=20) and *S. equisimilis* (n=1).

Results

- Ceftaroline exhibited activity against methicillin-susceptible *S. aureus* (MSSA) isolates (MIC_{50} and MIC_{90}, 0.25 mg/L) and MRSA isolates ($MIC_{50/90}$, 1/2 mg/L). The highest MIC results observed among MSSA and MRSA were 1 and 2 mg/L, respectively (Tables 1 and 2).
- Ceftaroline was 16-fold more potent than ceftriaxone and 8-fold more potent than cefepime when tested against MSSA. All tested agents were ≥94.9% susceptible against MSSA, except erythromycin (83.0-83.8% susceptible; Table 2).
- The most potent agents against MRSA were: ceftaroline ($MIC_{50/90}$, 1/2 mg/L; 100% inhibited at ≤2 mg/L), linezolid ($MIC_{50/90}$, 2/2 mg/L; 100% susceptible), vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100% susceptible), and tigecycline ($MIC_{50/90}$, 0.12/0.25 mg/L; 100% susceptible) (Tables 1 and 2). In contrast, only 10.0% of MRSA strains were susceptible to levofloxacin (Table 2).
- Against β-haemolytic streptococci, ceftaroline demonstrated greater potency ($MIC_{50/90}$, 0.015/0.03 mg/L) than penicillin ($MIC_{50/90}$, 0.03/0.06 mg/L) and ceftriaxone (MIC_{50} and MIC_{90}, ≤0.25 mg/L). Decreased susceptibility was observed only with erythromycin (82.5% susceptible) and clindamycin (90.2-91.5% susceptible; Table 2).
- Amongst β-haemolytic streptococci, ceftaroline was slightly more potent against Group A strains ($MIC_{50/90}$, ≤0.008/≤0.008 mg/L) when compared to Group B ($MIC_{50/90}$, 0.015/0.03 mg/L) and other β-haemolytic streptococci ($MIC_{50/90}$, ≤0.008/0.015 mg/L; Table 2).

Conclusions

- Ceftaroline demonstrated broad-spectrum activity against *S. aureus* (including MRSA) and β-haemolytic streptococci isolated from patients in medical centres from 11 European countries, plus Israel and Turkey in 2009.
- Activity of ceftaroline against *S. aureus* was similar to that of vancomycin, daptomycin and linezolid; activity against β-haemolytic streptococci was similar to that of penicillin and ceftriaxone.
- These data warrant continued clinical evaluations of ceftaroline as a therapeutic agent for cSSTI.

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