Antimicrobial Activity of Ceftaroline and Comparator Agents Against Contemporary (2010) *Streptococcus pneumoniae* from Europe and South Africa

DJ FARRELL, HS SADER, RK FLAMM, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

P1564

ECCMID 2012
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Objectives: To determine the activity of ceftaroline against recent (2010) *S. pneumoniae* (SPN) isolated in Europe (EU) and South Africa (SAF). Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a novel cephalosporin exhibiting broad-spectrum *in vitro* bactericidal activity against Gram-positive organisms including multidrug-resistant (MDR)-SPN, methicillin-resistant *S. aureus* and common Gram-negative enteric bacilli.

Methods: Susceptibility testing for ceftaroline and commonly used antimicrobials was performed by CLSI broth microdilution methodology on a total of 1,257 isolates from the 2010 Assessing Worldwide Antimicrobial Resistance Evaluation Programme (AWARE). Susceptibility interpretations for the comparators assessed in this study were performed using CLSI and EUCAST guidelines. Isolates were collected from patients in 55 medical centres in 19 EU countries, including Turkey and Israel. Additionally, twenty-two isolates were collected from 1 medical centre in SAF. MDR-SPN status was determined by resistance (R) to 2 or more classes of antimicrobials from penicillin (PEN; CLSI oral breakpoints), erythromycin (ERY), levofloxacin, tetracycline (TET) and trimethoprim-sulfamethoxazole (SXT).

Results: Ceftaroline was very active against PEN-susceptible (S) and non-MDR isolates, and retained potent activity against PEN-intermediate (I), PEN-R, and MDR isolates (Table 1). The highest ceftaroline MIC found was in one isolate at 0.5 mg/L (a MDR strain from Romania with a ceftriaxone (CRO) MIC of 4 mg/L). The ceftaroline MIC_{50} was at least four-fold higher in SAF isolates (0.03 mg/L) than in EU isolates (≤0.008 mg/L) due to the higher prevalence of MDR-SPN in the SAF region (54.5% vs. 26.8% in SAF vs. EU), however the MIC_{90} values were identical (0.12 mg/L for both; note the low number of SAF isolates [22]). Using CLSI oral PEN breakpoints, 26.0 and 72.7% of isolates were non-S for EU and SAF, respectively. By EUCAST breakpoints, 15.6% of all isolates were non-S to CRO (5.0% by CLSI non-meningitis breakpoints). Other antimicrobial resistances (CLSI) were: ERY, 23.6%; TET, 23.1%, SXT, 19.3%.

Conclusions: This study demonstrated the potent *in vitro* activity of ceftaroline against recent (2010) EU and SAF SPN isolates including MDR strains. These data suggest that ceftaroline fosamil may emerge as an important therapy for infections caused by SPN resistant to beta-lactams and other commonly used antimicrobials as well as MDR strains.

Introduction

Streptococcus pneumoniae is the dominant bacterial pathogen causing community-acquired bacterial pneumonia (CABP). The emergence of multidrug-resistant *S. pneumoniae* (MDR-SPN) is threatening the use of currently available β-lactams and agents from other antimicrobial classes. Inadequate (insufficient level of agent at the site of infection), inappropriate (pathogen resistant to agent) or delayed antimicrobial therapy is associated with increased morbidity and mortality, as well as increased length of hospital stay and escalating healthcare costs.

Ceftaroline fosamil is the prodrug form of ceftaroline, a novel broad-spectrum cephalosporin with *in vitro* activity against pathogens causing CABP, including MDR-SPN and methicillin-resistant *Staphylococcus aureus* (MRSA). In two phase 3 trials (NCT00509106; NCT00621504), ceftaroline fosamil was shown to be non-inferior to ceftriaxone for the treatment of patients with CABP requiring hospitalization. Ceftaroline fosamil has been approved by the United States Food and Drug Administration (USA-FDA) for CABP and acute bacterial skin and soft tissue infections.

In this study, we evaluated ceftaroline and comparator antimicrobial agents against 1,257 *S. pneumoniae* isolates associated with community-acquired respiratory tract infections collected in European and South African hospitals during 2010 as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance programme, a global ceftaroline study.

Materials and Methods

Organism Collection: A total of 1,257 pneumococcal isolates from the 2010 AWARE programme were tested. Susceptibility interpretations for the comparators assessed in this study were performed using Clinical and Laboratory Standards Institute (CLSI) and EUCAST guidelines. Ceftaroline test results were interpreted using criteria found in the USA-FDA-approved product package insert. Isolates were collected from patients in 55 medical centres in 19 European countries, including Turkey and Israel, and in South Africa (22 isolates, 1 medical centre). European countries (number of centres) were: Belgium (1), Czech Republic (1), France (5), Germany (7), Greece (2), Hungary (1), Israel (1), Italy (5), Netherlands (1), Poland (2), Portugal (1), Romania (1), Russia (5), Slovenia (1), Spain (7), Sweden (2), Turkey (5), United Kingdom (5), Ukraine (1). MDR-SPN status was determined by resistance to two or more classes of antimicrobials among penicillin (CLSI oral breakpoints), erythromycin, levofloxacin, tetracycline and trimethoprim/sulfamethoxazole (SXT).

Susceptibility Testing: Isolates were susceptibility tested against ceftaroline and comparator agents by reference broth microdilution methods as described by CLSI M07-A9 (2012). CLSI interpretations for comparators were based on M100-S22 breakpoints and EUCAST breakpoints (2012); in the absence of CLSI breakpoints for ceftaroline, USA-FDA breakpoints were applied. *S. pneumoniae* were tested in Mueller-Hinton broth supplemented with 2.5-5% lysed horse blood. Concurrent testing of the quality control (QC) *S. pneumoniae* ATCC 49619 was performed. All QC results were within published ranges.

Results

- Ceftaroline was very active against all 1,257 *S. pneumoniae*, inhibiting all strains at ≤0.5 mg/L (Table 1). The highest ceftaroline MIC found was for one isolate at 0.5 mg/L (a MDR strain from Romania with a ceftriaxone MIC of 4 mg/L).
- Compared with other β-lactams, ceftaroline was the most active agent tested against *S. pneumoniae* (MIC_{90}, 0.12 mg/L) demonstrating eight-fold greater potency than ceftriaxone (MIC_{90}, 1 mg/L), 16-fold greater potency than penicillin and amoxicillin/clavulanate (MIC_{90}, both 2 mg/L) and 32-fold greater potency than cefuroxime (MIC_{90}, 4 mg/L; Table 2).
- The MIC range of ceftaroline was lower against penicillin-susceptible *S. pneumoniae* (≤0.008 to 0.06 mg/L), than against penicillin-resistant strains (0.06-0.5 mg/L; Tables 1 and 2).
- Ceftaroline was very active (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L) against MDR-SPN with all 318 isolates inhibited at a MIC of ≤0.5 mg/L (Table 1).
- The activity of ceftaroline against penicillin-resistant *S. pneumoniae* (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L) was eight- and 32-fold greater than the activities of ceftriaxone (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) and amoxicillin/clavulanic acid (MIC_{50}, 2 mg/L and MIC_{90}, 8 mg/L), respectively (Table 2).
- By EUCAST criteria, 15.6% of all isolates were non-susceptible to ceftriaxone. Ceftriaxone non-susceptibility ranged from only 0.1% in penicillin-susceptible isolates to 11.6% in penicillin-intermediate isolates to >97.0% (with 2.7% resistance) in the penicillin-resistant population (Table 2).
- Overall, moderate rates of resistance (CLSI/EUCAST) were observed for erythromycin (23.6/23.6%), clindamycin (15.8/15.8%), tetracycline (23.1/23.8%) and trimethoprim/sulfamethoxazole (19.3/19.3%). However, resistance to these agents was greatly increased in penicillin-resistant strains, e.g. erythromycin resistance was 73.6% (Table 2). Levofloxacin resistance was low overall (1.0%) and in the penicillin-resistant isolates was more elevated at 2.2%.

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against contemporary (2010) European and South African *S. pneumoniae* associated with respiratory tract infections

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All *S. pneumoniae* (1,257)					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.5	99.9 / -	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 4	95.0 / 0.4	84.4 / 0.4
Cefuroxime	≤0.12	4	≤0.12 – >16	82.1 / 16.7	81.2 / 17.9
Penicillin[b]	≤0.03	2	≤0.03 – >4	94.1 / 0.2	- / -
Penicillin[c]	≤0.03	2	≤0.03 – >4	73.2 / 14.5	73.2 / 5.9
Amoxicillin/clavulanate	≤1	2	≤1 – >8	92.9 / 4.3	- / -
Erythromycin	≤0.06	>8	≤0.06 – >8	76.2 / 23.6	76.2 / 23.6
Clindamycin	≤0.25	>1	≤0.25 – >1	83.6 / 15.8	84.2 / 15.8
Tetracycline	0.5	>8	≤0.25 – >8	76.2 / 23.1	75.8 / 23.8
Levofloxacin	1	1	≤0.5 – >4	99.0 / 1.0	99.0 / 1.0
TMP/SMX[d]	≤0.5	>4	≤0.5 – >4	70.8 / 19.3	77.2 / 19.3
Penicillin-susceptible *S. pneumoniae* (920)					
Ceftaroline	≤0.008	≤0.008	≤0.008 – 0.06	100.0 / -	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 1	100.0 / 0.0	99.9 / 0.0
Cefuroxime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Penicillin[b]	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / 0.0	- / -
Penicillin[c]	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / 0.0	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – >8	99.8 / 0.2	- / -
Erythromycin	≤0.06	≤0.06	≤0.06 – >8	91.7 / 8.0	91.7 / 8.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >1	95.2 / 4.6	95.4 / 4.6
Tetracycline	≤0.25	8	≤0.25 – >8	89.1 / 10.0	88.9 / 10.9
Levofloxacin	1	1	≤0.5 – >4	99.6 / 0.4	99.6 / 0.4
TMP/SMX[d]	≤0.5	2	≤0.5 – >4	84.7 / 7.6	89.5 / 7.6
Penicillin-intermediate *S. pneumoniae* (155)					
Ceftaroline	0.03	0.12	≤0.008 – 0.12	100.0 / -	- / -
Ceftriaxone	0.25	1	≤0.06 – 2	99.4 / 0.0	88.4 / 0.0
Cefuroxime	0.5	4	≤0.12 – 4	72.3 / 19.4	65.2 / 27.7
Penicillin[b]	0.25	1	0.12 – 1	100.0 / 0.0	- / -
Penicillin[c]	0.25	1	0.12 – 1	0.0 / 0.0	0.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Erythromycin	2	>8	≤0.06 – >8	42.6 / 57.4	42.6 / 57.4
Clindamycin	≤0.25	>1	≤0.25 – >1	60.0 / 38.1	61.9 / 38.1
Tetracycline	>8	>8	≤0.25 – >8	40.0 / 60.0	38.7 / 60.0
Levofloxacin	1	1	≤0.5 – >4	97.4 / 2.6	97.4 / 2.6
TMP/SMX[d]	1	>4	≤0.5 – >4	46.5 / 36.1	56.1 / 36.1
Penicillin-resistant *S. pneumoniae* (182)					
Ceftaroline	0.12	0.25	0.06 – 0.5	99.5 / -	- / -
Ceftriaxone	1	2	0.5 – 4	65.9 / 2.7	2.7 / 2.7
Cefuroxime	8	16	2 – >16	0.0 / 98.9	0.0 / 100.0
Penicillin[b]	2	4	2 – >4	59.3 / 1.1	- / -
Penicillin[c]	2	4	2 – >4	0.0 / 100.0	0.0 / 40.7
Amoxicillin/clavulanate	2	8	≤1 – >8	52.2 / 28.6	- / -
Erythromycin	>8	>8	≤0.06 – >8	26.4 / 73.6	26.4 / 73.6
Clindamycin	>1	>1	≤0.25 – >1	45.1 / 53.8	46.2 / 53.8
Tetracycline	>8	>8	≤0.25 – >8	41.8 / 57.7	41.2 / 58.2
Levofloxacin	1	1	≤0.5 – >4	97.8 / 2.2	97.8 / 2.2
TMP/SMX[d]	4	>4	≤0.5 – >4	21.4 / 63.7	33.5 / 63.7

a. Criteria as published by CLSI [2012] and EUCAST [2012]; USA-FDA criteria for ceftaroline.
b. Criteria as published by CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
c. Criteria as published by CLSI [2012] for 'Penicillin (oral penicillin V)'.
d. Trimethoprim/sulfamethoxazole.

Conclusions

- Ceftaroline was the most potent β-lactam agent tested with eight-fold greater potency than the next most potent β-lactam (ceftriaxone) or other agent (levofloxacin) demonstrated.
- Overall, moderate rates of resistance to erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole were found. However, high rates of resistance were demonstrated against these antimicrobial agents in the penicillin-resistant and MDR populations. Levofloxacin resistance was low overall.
- These data demonstrate the good *in vitro* activity of ceftaroline against contemporary *S. pneumoniae*, including MDR-SPN, from Europe and South Africa.

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Acknowledgment

This study at JMI Laboratories was supported by an Educational/Research grant from AstraZeneca, and the authors received compensation fees for services in relation to preparing the abstract/poster, which was funded by AstraZeneca

Table 1. Summary of ceftaroline activity tested against contemporary (2010) European and South African *S. pneumoniae* associated with respiratory tract infections

Group/phenotype (no. tested)	No. of organisms (cumulative %) inhibited at ceftaroline MIC (mg/L) of: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
All isolates (1257)	836 (66.5)	104 (74.8)	56 (79.2)	67 (84.6)	160 (97.3)	33 (99.9)	1 (100.0)	≤0.008	0.12
Penicillin-susceptible (920)[a]	831 (90.3)	73 (98.3)	11 (99.5)	5 (100.0)	-	-	-	≤0.008	≤0.008
Penicillin-intermediate (155)[a]	5 (3.2)	31 (23.2)	45 (52.3)	50 (84.5)	24 (100.0)	-	-	0.03	0.12
Penicillin-resistant (182)[a]	-	-	-	12 (6.6)	136 (81.3)	33 (99.5)	1 (100.0)	0.12	0.25
MDR (318)[b]	42 (13.2)	38 (25.2)	23 (32.4)	42 (45.6)	140 (89.6)	32 (99.7)	1 (100.0)	0.12	0.25
Non-MDR (939)	794 (84.5)	66 (91.6)	33 (95.1)	25 (97.8)	20 (99.9)	1 (100.0)	-	≤0.008	0.015

a. Criteria for S/I/R were according to CLSI oral penicillin V breakpoints (MIC, ≤0.06/0.12 - 1/≥2 mg/L).
b. MDR-SPN status was determined by resistance to two or more classes of antimicrobials from penicillin (CLSI oral breakpoints), erythromycin, levofloxacin, tetracycline and trimethoprim/sulfamethoxazole (SXT).