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Antimicrobial Susceptibility Studies

Ceftaroline: clinical and microbiology experience with focus on methicillin-resistant *Staphylococcus aureus* after regulatory approval in the USA

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ABSTRACT

Ceftaroline fosamil was approved in 2010 by the United States Food and Drug Administration (USA-FDA) for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP). After approval, several studies and case reports have described the postmarketing clinical experience with ceftaroline in ABSSSIs and CABP and in patients with invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections, many of whom had failed prior antibiotics. Successful clinical outcomes observed among the majority of these patients were supported by preapproval and postapproval in vitro surveillance of ceftaroline activity using breakpoint criteria that have been harmonized between the USA-FDA and CLSI. MIC_{90} values/percentage of strains susceptible to ceftaroline has remained stable over the period 2009–2012. Taken together, these postapproval studies support the use of ceftaroline for ABSSSI as well as CABP. Importantly, these data also suggest that ceftaroline can be effective in patients with serious invasive MRSA infections who have failed other therapies.

1. Introduction

Ceftaroline fosamil (Teflaro®) was approved by the United States (USA) Food and Drug Administration (FDA) in October 2010 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP) (Corey et al., 2010a, 2010b; File et al., 2010, 2011; Low et al., 2011; Wilcox et al., 2010). Similarly, ceftaroline was also approved by the European Medicines Agency (EMA) in August 2012 (Zinforo®). These approvals were based on successful registrational phase 3 trials for each indication. Since the initial USA-FDA approval, several retrospective studies have described the clinical use of ceftaroline in patients with a variety of infections (including off-label use), particularly in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections. In this report, we will briefly summarize the clinical experience described with ceftaroline, with focus on patients with MRSA infections after completion of the registrational studies as well as the results of in vitro ceftaroline testing against recent (2009–2012) clinical strains from a USA resistance surveillance trial.

2. Postapproval microbiology surveillance

The antimicrobial activity and spectrum of ceftaroline (Frampton, 2013; Lodise and Low, 2012) have been followed closely for nearly a decade and in a prospective USA-based resistance surveillance program since 2008 (Flamm et al., 2012a, 2012b, 2014; Pfaller et al., 2014) monitoring nearly 100 medical centers. These results have been supplemented by the 2012 USA results from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program. This preapproval and postapproval resistance assessment survey collects thousands of clinical pathogens within and beyond the ceftaroline USA-FDA indications (Teflaro® Package Insert, 2012) each year in the USA; all strains forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) where CLSI reference broth microdilution tests are performed for ceftaroline and selected comparison agents (CLSI, 2012, 2014). Susceptibility interpretations utilize contemporary criteria (CLSI, 2014; Teflaro® Package Insert, 2012) and quality assurance limits (CLSI, 2014). Similar program components tabulate ceftaroline potencies in Europe, Latin America, and the Asia-Pacific regions (Farrell et al., 2013; Sader et al., 2013).

2.1. Ceftaroline activity against ABSSSI isolates

AWARE (USA) Program results for ABSSSI pathogens for 2009–2012 are shown in Table 1. Among 8903 *S. aureus* isolates sampled across all 9

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Table 1
Ceftaroline cumulative percentage inhibition results for 10,938 ABSSSI isolates of *S. aureus*, *E. coli*, and *K. pneumoniae* (AWARE Program, 2009–2012).[a]

Pathogen/surveillance year (no. tested)	Cum. % inhibited at MIC in μg/mL:										MIC (μg/mL)	
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16	50%	90%
S. aureus												
2009–2010 (1675)	<0.1	0.2	5.7	47.6	85.3	99.6[b]	100.0	-	-	-	0.5	1
2011 (1223)	0.1	0.4	8.3	48.1	84.5	99.5[b]	100.0	-	-	-	0.5	1
2012 (6085)	<0.1	0.4	5.0	46.9	85.8	99.3[b]	100.0	-	-	-	0.5	1
E. coli												
2009–2010 (223)	8.5	38.1	66.4	78.9	82.5[b]	86.1	87.4	87.9	90.1	100.0	0.12	8
2011 (217)	10.6	47.0	68.7	81.1	84.3[b]	87.1	88.5	89.4	89.9	100.0	0.12	16
2012 (647)	10.9	43.7	67.0	78.4	83.4[b]	86.4	87.4	87.9	88.7	100.0	0.12	16
K. pneumoniae												
2009–2010 (117)	6.0	34.2	67.5	75.2	79.5[b]	82.1	82.1	82.1	83.8	100.0	0.12	>16
2011 (150)	1.3	42.7	68.7	74.7	78.0[b]	81.3	82.7	84.7	86.0	100.0	0.12	>16
2012 (601)	4.0	30.1	60.1	76.4	84.5[b]	86.5	87.5	87.9	88.5	100.0	0.12	>16

[a] All results from reference MIC methods (CLSI, 2012, 2014).
[b] Susceptible breakpoint concentration (CLSI, 2014; Teflaro® Package Insert, 2012).

USA Census Regions, ceftaroline exhibited sustained potent activity with identical MIC_{50} and MIC_{90} results at 0.5 and 1 μg/mL, respectively, for all time periods, including prelaunch (2009–2010) and postapproval (2011–2012) intervals. At the ≤1 μg/mL susceptible breakpoint, 99.3–99.6% of *S. aureus* strains were inhibited, and all USA strains had ceftaroline MIC values at ≤2 μg/mL.

Other Gram-positive pathogens remained highly susceptible to ceftaroline using 2012 surveillance results (no. tested/MIC_{90} in μg/mL): *Streptococcus anginosus* (70/0.03), *Streptococcus pyogenes* or Group A (272/≤0.015), *Streptococcus agalactiae* or Group B (217/≤0.015), and Group C streptococci (35/0.03); data not shown. Similar data for *Escherichia coli* and *Klebsiella pneumoniae* (Table 1) show stable ceftaroline MIC_{50} results (0.12 μg/mL for both species for wild type population) and 78.0–84.3% susceptibility of these enteric bacilli at the current breakpoint of ≤0.5 μg/mL (CLSI, 2014; Teflaro® Package Insert, 2012). In fact, the ceftaroline susceptibility rates remained stable for *E. coli* (82.5 to 83.4%) and increased slightly for *K. pneumoniae* (79.5–84.5%) for 2009 versus 2012.

Various antimicrobial-resistant subgroups of *S. aureus* have been shown to be ceftaroline susceptible including MRSA, vancomycin intermediate susceptible (VISA), heterogeneous VISA, vancomycin-resistant, multidrug-resistant, and extensively drug-resistant strains (Farrell et al., 2012; Saravolatz et al., 2010). Also, ceftaroline appears to provide comparable activity to that of daptomycin, linezolid, and vancomycin in tests of MRSA in the extracellular and intracellular forms (Melard et al., 2013).

2.2. Ceftaroline activity against CABP isolates

Table 2 shows the activity of ceftaroline tested against 3 species commonly isolated from CABP. The data from 2009–2011 were supplemented with AWARE 2012 results from 878 *Streptococcus pneumoniae*, 380 *Haemophilus influenzae*, and 1652 *S. aureus* (50.7% MRSA) (Flamm et al., 2014). For the 4238 *S. pneumoniae* analyzed, the ceftaroline MIC_{50} and MIC_{90} remained stable or decreased slightly (1 doubling dilution for MIC_{90}) at 0.12–0.25 μg/mL. This level of potency is at least 8-fold greater than ceftriaxone, confirming previously reported USA results for pneumococcal isolates (Farrell et al., 2012; Jones et al., 2013a, 2013b).

H. influenzae (2179 isolates; Table 2) were susceptible to ceftaroline ($MIC_{50/90}$, ≤0.015/≤0.015–0.03 μg/mL), with all strains being categorized as susceptible at ≤0.5 μg/mL (CLSI, 2014; Teflaro® Package Insert, 2012). *S. aureus* isolated from the respiratory tract were comparably less inhibited (97.6 versus 97.3–98.8%) at the breakpoint concentration of ≤1 μg/mL for preapproval and postapproval samples, and all strains were susceptible to ≤2 μg/mL of ceftaroline (Table 2). *Moraxella catarrhalis* (119 strains) had ceftaroline $MIC_{50/90}$ results of 0.06/0.25 μg/mL (data not shown), and *E. coli* (MIC_{50}, 0.12 μg/mL) and *K. pneumoniae* (MIC_{50}, 0.12 μg/mL) had susceptibility rates at 75.5% and 77.2%, respectively.

2.3. In vitro testing of ceftaroline

Despite ceftaroline's availability in 3 years, few commercial reagents or systems are available to test it. Disk diffusion products (30-μg disk) and Etest strips are commercially available. However, another option for ceftaroline testing is via an interim application of a surrogate using another β-lactam to predict ceftaroline susceptibility. The tests of selected carbapenems and cephalosporins commonly present in commercial systems used by clinical microbiologists provide high confidence accuracy especially for *S. aureus* (including MRSA by using imipenem or

Table 2
Ceftaroline cumulative percentage inhibition results for 9156 respiratory tract isolates of *S. pneumoniae*, *H. influenzae*, and *S. aureus* (AWARE Program, 2009–2012).[a]

Pathogen/surveillance year (no. tested)	Cum. % inhibited at MIC in μg/mL:								MIC (μg/mL)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	50%	90%
S. pneumoniae										
2009–2010 (1707)	58.4	66.0	75.7	89.2	99.4	100.0[b]	-	-	≤0.015	0.25
2011 (1653)	57.0	66.4	75.7	92.1	98.9	100.0[b]	-	-	≤0.015	0.12
2012 (878)[a]	55.4	64.9	76.2	93.4	99.3	100.0[b]	-	-	≤0.015	0.12
H. influenzae										
2009–2010 (1027)	90.0	97.5	99.5	99.9	100.0	-[b]	-	-	≤0.015	≤0.015
2011 (772)	82.9	95.6	98.6	99.5	99.9	100.0[b]	-	-	≤0.015	0.03
2012 (380)[b]	84.2	95.8	99.2	100.0	-	-[b]	-	-	≤0.015	0.03
S. aureus										
2009–2010 (572)	0.0	0.2	0.5	4.2	49.3	77.3	97.6[b]	100.0	0.5	1
2011 (515)	0.0	0.0	0.4	10.7	52.4	82.3	98.8[b]	100.0	0.25	1
2012 (1652)	0.0	0.0	0.2	4.3	47.4	71.2	97.3[b]	100.0	0.5	1

[a] All results from reference MIC methods (CLSI, 2012, 2014).
[b] Susceptible breakpoint concentration (CLSI, 2014; Teflaro® Package Insert, 2012).