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Ceftaroline: A Novel Cephalosporin with Activity against Methicillin-resistant *Staphylococcus aureus*

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Ceftaroline (PPI 0903, formerly TAK-599), the active metabolite of a N-phosphono prodrug, ceftaroline fosamil, has been approved by the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. This antimicrobial agent binds to penicillin binding proteins (PBP) inhibiting cell wall synthesis and has a high affinity for PBP2a, which is associated with methicillin resistance. Ceftaroline is consistently active against multidrug-resistant *Streptococcus pneumoniae and Staphylococcus aureus*, including methicillin-resistant, vancomycin-intermediate, linezolid-resistant, and daptomycin-nonsusceptible strains. It possesses variable activity against *Enterobacteriaceae* and good activity against oral anaerobes. The drug is usually administrated intravenously at 600 mg every 12 h. Ceftaroline has low protein binding and is excreted by the kidneys and thus requires dose adjustments in individuals with renal failure. Clinical trials have demonstrated noninferiority when compared with vancomycin in the treatment of acute bacterial skin and skin structure infections and noninferiority when compared with ceftriaxone in the treatment of community-acquired bacterial pneumonia. Ceftaroline demonstrated a safety profile similar to that of comparator drugs in clinical trials.

Cephalosporins have been widely used for the treatment of a variety of infections since the introduction of "first generation" agents over 40 years ago [1]. These antibiotics have been a mainstay of therapy for gram-positive bacterial infections until the more recent increase in resistance to β-lactams among *Staphylococcus aureus*. Cephalosporins are now often replaced by vancomycin as empirical therapy for staphylococcal infections [2]. With the continued emergence of drug-resistant gram-positive organisms, alternative compounds are needed.

Ceftaroline (PPI 0903M, formerly TAK-599) is a new parenteral cephalosporin with antimicrobial activity against multidrug-resistant (MDR) gram-positive bacteria, including *S. aureus* strains with reduced susceptibility to methicillin and vancomycin and isolates of *Streptococcus pneumoniae* with reduced susceptibility to penicillins, erythromycin, and fluoroquinolones [3]. This new antibiotic has been approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP).

This article will review the chemistry, mode of action, antimicrobial activity, pharmacokinetics and pharmacodynamics, clinical indications, associated adverse events, and formulary considerations of ceftaroline.

CHEMISTRY

Ceftaroline is the active metabolite of an N-phosphono prodrug, ceftaroline fosamil [4]. This cephalosporin possesses an ethoxyiminoacetamido group in the C-7 moiety and a thio 5-membered heteroaromatic spacer group at position 3 (Figure 1). This water-soluble compound has good chemical stability and a molecular weight of 762.

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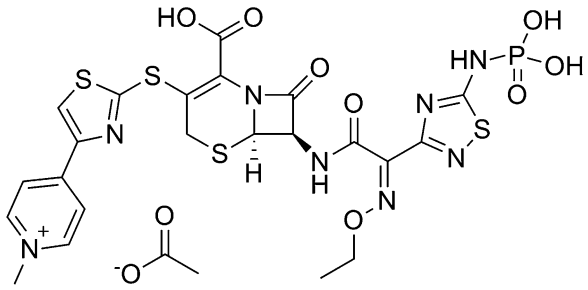

Figure 1. Chemical structure of ceftaroline fosamil acetate.

MODE OF ACTION

The antibacterial activity of cetaroline is similar to that of other β-lactams and occurs by binding to penicillin-binding proteins and thus interfering with cell wall synthesis.

Ceftaroline binds to PBP 1–4 and has an especially high affinity for PBP2a (mecA), which is associated with methicillin resistance. This unique affinity for PBP2a distinguishes ceftaroline from other cephalosporins. Ceftaroline binds to all 6 PBPs that have been identified in *S. pneumoniae* (PBP1A, 1B, 2x, 2A/B, and 3) [5] For the *Enterobacteriaceae,* the primary target is membrane PBPs, leading to transpeptidase and transglycosidase reactions in cell wall formation [6].

ANTIMICROBIAL ACTIVITY

Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA), *Staphylococcus epidermidis* (both methicillin sensitive and resistant), and other coagulase negative staphylococci, including *Staphylococcus lugdunensi, Staphylococcus hominis*, and *Staphylococcus hemolyticus* (Table 1) [7, 8]. Ceftaroline is active against MRSA strains, including Panton Valentine-leukocidin (PVL)-producing strains, as well as strains that are resistant to other classes of antimicrobial agents, such as glycopeptides, daptomycin, clindamycin, sulfamethoxazole-trimethoprim, and linezolid [8].

In vitro studies have also demonstrated high potency of ceftaroline against β-hemolytic streptococci and *S. pneumoniae* strains that are resistant to available parenteral cephalosporins, including ceftriaxone and cefotaxime. Ceftaroline had a minimum inhibitory concentration (MIC) of 0.5 μg/mL against 120 cefotaxime-resistant (MIC ⩾ 4 μg/mL) *S. pneumoniae* strains and laboratory-cloned R6 strains with penicillin-binding protein mutations [9]. The excellent activity of ceftaroline against *S. pneumoniae* strains that exhibit resistance to penicillin, amoxicillin, and cefotaxime has been demonstrated in the United States and Europe [9, 10].

Table 1. Comparative in vitro MIC 90s of Ceftaroline and Other Comparators against Gram-Positive Bacteria

Organism (no. of isolates tested)	Ceftaroline[a]	Vancomycin	Daptomycin	Ceftriaxone	Linezolid	Erythomycin
Staphaylococcus aureus						
MSSA (348)	0.25	1	0.5	NA	2	NA
MRSA (92)	1	1	1	NA	2	NA
VISA (20)	1	8	4	NA	2	NA
VRSA (10)	0.5	>64	1	NA	2	NA
Coagulase-negative staphylococci						
Methicillin susceptible (201)	0.12	2	4	NA	2	NA
Methicillin resistant (299)	0.5	2	>32	NA	2	NA
Enterococcus faecalis						
Vancomycin susceptible (157)	4	2	1	NA	2	NA
Vancomycin resistant(25)	4	>16	1	NA	2	NA
Enterococcus faecium (157)	>16	>16	4	NA	2	NA
Streptococcus pyogenes						
Erythromycin susceptible(91)	<.008	0.5	NA	<.008	1	0.06
Erythromycin resistant (10)	<.015	0.5	NA	0.12	1	>16
Streptococcus agalactiae (59)	0.015	0.5	NA	0.12	1	0.06
Streptococcus pneumoniae						
Penicillin sensitive (202)	0.015	0.5	NA	0.06	1	0.5
Penicillin intermediate (103)	0.06	0.5	NA	0.5	1	>16
Penicillin resistant (296)	0.12	0.5	NA	0.12	1	>16

NOTE. Adapted from [7, 8]. MIC_{90} values are given as μg/mL. MIC_{90},90% minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*; NA, not applicable.; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.

[a] Ceftaroline MIC breakpoints areas follows: *S. aureus* ⩽ 1 for skin isolates only, S. *pneumoniae* ⩽ 0.25 μg/mL for community-acquired bacterial pneumonia isolates only, *Streptococcus pyogenes* ⩽ 0.015 for skin isolates only, and *Streptococcus agalactiae* ⩽0 .03 μg/mL for skin isolates only.

Although the in vitro activity suggests that ceftaroline might be effective against vancomycin-resistant *Enterococcus faecalis* (not *Enterococcus faecium*), to date, there is little clinical experience to support the in vivo efficacy of ceftaroline against these strains.

Ceftaroline has variable activity against many gram-negative *Enterobacteriaceae* (Table 2) [7]. It is not active against β-lactamase–producing, AMP C –derepressed Enterobacteriaceae or most nonfermentative gram-negative bacilli, including *Pseudomonas aeruginosa* [7].

Ceftaroline possesses anti-anaerobic activity similar to that of amoxicillin-clavulanate against gram-positive anaerobes and 4- to 8-fold greater activity than that of ceftriaxone [11]. Ceftaroline does not have good activity against members of the *Bacteroides fragilis* group, but it is active against β-lactamase–negative strains, including *Actinomycees* species, *Proprionibacterium, Eubacterium, Clostriium perfringens, Clostridium ramosum*, and *Clostridium innocuum*.

There are limited data that suggest synergy of ceftaroline with tobramycin against MRSA. In studies of *P. aeruginosa,* ceftaroline when combined with amikacin was synergistic. When combined with meropenem and aztreonam, ceftaroline demonstrated synergy against *Escherichia coli* at *Enterobacter cloacae* and indifference against other gram-negative strains [12].

PHARMACOKINETICS

Following parenteral administration, ceftaroline fosamil is rapidly converted by bloodstream phosphatase enzymes to ceftaroline. At the end of a 1-hour intravenous infusion of 600 mg of ceftaroline, maximum serum concentrations (C_{max}) of ~20 mg/L are obtained. The same dose with intramuscular administration will produce a C_{max} of 8.5 mg/L at 2 h after administration [13]. This cephalosporin exhibits linear pharmacokinetics and has a serum half-life (t½) of 1.6 h (for a single dose) to 2.7 h (following multiple doses). Ceftaroline has a volume of distribution (V_d; ~20 L) that is similar to that of other parenteral cephalosporins. Plasma protein binding is ~20% [14].

Ceftaroline undergoes some metabolism via hydrolysis of its β-lactam ring to form an inactive, open-ring metabolite (ceftaroline M-1). The cyp_{450} system does not appear to be a significant metabolic pathway for ceftaroline, which implies that this drug has a low potential for drug-drug interactions.

Table 2. Comparative in vitro MIC 90s of Ceftaroline and Other Comparators against Gram-negative Bacteria

Organism (no. of isolates tested)	Ceftaroline[a]	Ceftazidime	Ceftriaxone	Imipenem	Levofloxacin	Piperacillin-tazobactm
Enterobacteriaceae						
Ceftazidime susceptible (833)	1	0.5	0.25	1	4	4
Ceftazidime resistant (220)	>16	>32	>16	4	>16	>64
Citrobacter freundii						
Ceftazidime susceptible (50)	0.25	1	0.5	1	1	4
Ceftazidime resistant (33)	>16	>32	>16	1	16	>64
Enterobacter cloacae						
Ceftazidime susceptible (50)	1	1	0.12	0.5	≤.003	2
Ceftazidime resistant (35)	>16	>32	>16	1	16	>64
Escherichia coli						
Ceftazidime Susceptible (345)	0.5	0.25	0.12	0.25	16	4
Ceftazidime resistant (63)	>16	>32	>16	1	>16	>64
Klebsiella pneumoniae						
Ceftazidime susceptible (210)	0.25	0.25	0.12	0.5	0.25	8
Ceftazidime resistant (66)	>16	>32	>32	16	>16	>64
Proteus mirabilis (58)	4	0.12	0.12	4	16	1
Providencia species (27)	>16	4	2	2	16	>16
Serratia marcescens (59)	16	1	4	1	1	16
Acinetobacter species						
Imipenem susceptible (47)	16	>32	>16	0.5	>16	>64
Imipenem resistant (16)	>16	>32	>16	32	>16	>64
Pseudomonas aeruginosa (20)	>32	8	>32	8	>4	16
Stenotrophomonas maltophilia (10)	>32	>16	>32	>8	2	>256

NOTE. Adapted from [7]. MIC_{90} values are given as μg/mL. MIC_{90},90% minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*; NA, not applicable.; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.

[a] Ceftaroline breakpoints are as follows: Enterobacteriaceae sensitive ≤ 0.5, intermediate =1, and resistant ≥ 2 μg/mL for community-acquired bacterial pneumonia (CABP) and skin isolates. *Haemophilus influenzae* ≤ 0.12 μg/mL for CABP isolates only.

Ceftaroline and accompanying metabolites are primarily eliminated by the kidneys (mean ceftaroline clearance, 9.6 L/h). Following a single 600-mg dose, ~65% of the active drug is excreted in the urine in healthy subjects. The elimination of ceftaroline is altered in patients with diminished renal function, and dosage adjustments are recommended when the patient's creatinine clearance level is <50 mL/min. Patients undergoing hemodialysis exhibit significantly increased serum concentrations of ceftaroline, compared with those in patients with health renal function [15]. The serum t½ of ceftaroline increases to ~6 h in these patients. The mean recovery of ceftaroline in dialysate during a 4-h hemodialysis session is ~22% of the administered dose. The systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment.

PHARMACODYNAMICS

The duration of exposure (ie, the duration that the serum concentration is >MIC) determines the degree of antimicrobial activity for time-dependent (concentration-independent) agents [16]. In a neutropenic murine model, the %t >MIC best correlated with ceftaroline efficacy [17]. In addition, the mean %t >MIC for a 2-log reduction in multiple bacteria was 50%, 45%, and 54% for *S. pneumoniae, S. aureus,* and gram-negative bacilli (*E. coli* and *Klebsiella pneumoniae*), respectively, in these models.

In an in vitro hollow-fiber model, concentrations of ceftaroline were compared with those of vancomycin for activity against strains of heterogeneous vancomycin-intermediate *S. aureus* [18]. In this model, ceftaroline exhibited superior killing, compared with that of vancomycin, and no difference in antimicrobial activity was observed between 2 ceftaroline dosing intervals (every 8 h vs every 12 h). Moreover, emergence of drug-resistant isolates was not observed following ceftaroline exposure.

Several studies of ceftaroline in a rabbit endocarditis model have been conducted [19–21]. After a 4-day treatment regimen mimicking a human infusion of 600 mg every 12 h, ceftaroline demonstrated excellent bactericidal activity (at least a 6-log colony-forming unit/g decrease) against 2 strains of MRSA [19]. Ceftaroline exhibited similar killing in aortic valve vegetations, compared with vancomycin, against a vancomycin-sensitive strain of MRSA (ceftaroline MIC, 1 mg/L; vancomycin MIC, 1mg/L) and superior bactericidal activity against an hetero-resistant vancomycin intermediate Staphylococcus aureus (hVISA) strain (ceftaroline MIC, 2 mg/L; vancomycin MIC, 4 mg/L). In a similar investigation, ceftaroline exhibited a greater reduction in bacterial titers in vegetations, compared with that of vancomycin, against vancomycin-susceptible (ceftaroline MIC, 2 mg/L; vancomycin MIC, 2 mg/L) and vancomycin-resistant (ceftaroline MIC, 1 mg/L; vancomycin MIC, ⩾256 mg/L) strains of *E. faecalis* [20]. In a study comparing administration of ceftaroline and teicoplanin against a strain of MRSA (ceftaroline MIC, 1 mg/L; teicoplanin MIC, 0.5 mg/L), similar bactericidal activity was observed in aortic valve vegetations [21]. After 4 days of this dosage regimen, ceftaroline (C_{max} = 15.8 mg/L) sterilized 8 of 10 vegetations, compared with 6 of 10 vegetations that were sterilized with teicoplanin. A higher dose (40 mg/kg) of ceftaroline (C_{max} = 37.9 mg/L) was not statistically more effective and a lower dose (5 mg/kg) was statistically inferior to the 20-mg/kg dose in decreasing bacterial titers in vegetations.

In a rabbit acute osteomyelitis model, the antibacterial activity of ceftaroline was compared with that of linezolid and vancomycin against 2 strains of MRSA [22]. After 4 days of treatment, bacterial titers were determined in joint fluid, bone marrow, and bone specimens. Against 1 strain of MRSA (ceftaroline MIC, 1 mg/L,; vancomycin MIC, 1 mg/L; linezolid MIC, 2 mg/L), bacterial titers after vancomycin treatment were not different than in control specimens for all 3 tissues. Ceftaroline and linezolid demonstrated similar decreases in bacterial titers in bone marrow and bone specimens. Ceftaroline was the only drug to exhibit significant activity in joint fluid. Similar findings were observed against a VISA strain, with the exception that all 3 drugs exhibited significant antibacterial activity in joint fluid, compared with controls.

Ceftaroline has been compared with ceftriaxone and vancomycin against strains of *S. pneumoniae* in a rabbit meningitis model [23]. Peak ceftaroline levels in the cerebral spinal fluid (CSF) were 3.2 mg/L after the first dose (40 mg/kg), and its CSF penetration was 14% ± 5%. Treatment with ceftaroline produced greater reductions in counts of penicillin susceptible *S. pneumoniae* compared to ceftriaxone and ceftaroline was superior to vancomycin against penicillin resistant S. *pneumoniae*.

CLINICAL EXPERIENCE

Ceftaroline has been investigated in humans for the treatment of CABP and ABSSSIs. There have been 2 Phase 2 cSSSI studies and 4 Phase 3 studies, including 2 each involving ABSSSI (Ceftaroline versus Vancomycin in Skin and Skin-structure Infection [CANVAS] 1 and 2) and CABP (FOCUS1 and 2) [24–26]. On the strength of these studies, the US Food and Drug Administration (FDA) approved ceftaroline for the treatment of CABP and ABSSSI, including MRSA infections. The available clinical data in these indications will be reviewed. Studies in pediatrics have not been completed, so the recommendations for clinical use are limited to adult patients.

ABSSSI

A Phase 2 randomized, observer-blinded study that compared ceftaroline with vancomcyin with or without aztreonam was

performed in a cohort of adults with ABSSSI [24]. Ceftaroline was administered at a dosage of 600 mg every 12 h, vancomycin was administered at a dosage of 1 g every 12 h, and aztreonam was administered at a dosage of 1 g every 8 h. The primary outcome was clinical cure at a test-of-cure (TOC) visit 8–14 days after treatment, and secondary outcomes included microbiologic success rate at TOC and clinical relapse rate at 21–28 days after treatment. A total of 100 patients were recruited and randomized 2:1 (ceftaroline:standard therapy) at 15 clinical sites. There were a total of 88 patients who were clinically evaluable (CE) and 63 patients who were microbiologically evaluable (ME). The groups were similar in terms of types of infections and duration of treatment (mean duration of 7.8 days in the ceftaroline group and 8.0 days in the standard therapy group), and 7 patients who received standard therapy received aztreonam for a mean of 5.1 days. Cure rates for the CE (96.7% in the ceftaroline group vs 88.9% in the standard therapy group) and ME (95.2% in the ceftaroline group vs 85.7% in the standard therapy group) patients were similar. Among the 63 ME patients, *S. aureus* was the most common pathogen (found in 74.6% of cases), although most of these infections (76.6%) were due to MSSA.

The 2 CANVAS studies were randomized, double-blind, comparative efficacy and safety studies with identical designs [24]. Patients again received 600 mg of ceftaroline followed by normal saline placebo or received 1 g of vancomycin followed by 1 g of aztreonam. The ceftaroline dose was adjusted to 400 mg for patients with creatinine clearance levels of 30–50 mL/min, and the vancomycin dose was adjusted according to institutional guidelines. In addition to the CE and ME groups, the CANVAS studies also included the microbiological modified intent-to-treat (mMITT) population. Patients were excluded from the ME population if *P. aeruginosa* or anaerobic bacteria were identified at baseline. Among 1396 randomized patients, 1202 were CE and 914 were ME. This group included modified intent-to-treat patients who had $\geqslant$1 bacterial pathogen isolated at baseline. Most patients were hospitalized at study entry (78.2%), and the median age was 48 years. The groups were similar in terms of underlying rates of diabetes mellitus, peripheral vascular disease, bacteremia (4% overall), mean duration of therapy (8.3 and 8.4 days, respectively), and need to undergo surgery for infection (14.9% overall).

There were no differences in cure rates between the groups in the CE (91.6% for the ceftaroline group vs 92.7% for the vancomycin-aztreonam group) or ME (92.3% vs 93.7%) populations. The cure rates for patients with bacteremia were also similar (84.6% for the ceftaroline vs 100% for the vancomycin-aztreonam group) despite a higher proportion of *S. aureus* bacteremias among the ceftaroline group (18 cases vs 9 cases). The treatment groups had similar cure rates by type of infection, including cellulitis (93.0% in the ceftaroline group vs 91.4% in the vancomycin-aztreonam group) and major abscess (91.1% in the ceftaroline group vs 94.1% in the vancomycin/-aztreonam group). There were also no differences in cure rates among the 271 patients (36.9%) with MRSA infection. Among the mMITT population with gram-negative isolates at baseline (including *E. coli, P. aeruginosa, Proteus mirabilis,* and *K. pneumoniae* isolates), cure rates were 84.1% with ceftaroline and 85.2% with vancomycin-aztreonam. Thus, ceftaroline had similar efficacy to the comparator group in treating overall infections, gram-positive infections, and gram-negative infections.

Community-acquired Bacterial Pneumonia

The two FOCUS studies were international, multicenter, randomized, double-blind studies that compared the safety and efficacy of ceftaroline and ceftriaxone in a cohort of hospitalized patients with CABP [26]. Patients with Pneumonia Outcomes Research Team (PORT) risk classes I, II, and V were excluded [27]. Patients received either ceftaroline 600 mg every 12 h or ceftriaxone 1 g every day in both studies. All FOCUS 1 trial patients were also given two 500-mg doses of oral clarithromycin. Treatment was given for 5–7 days, all patients were inpatients, and no switches to oral regimens were permitted. Patients were excluded if they had a creatinine clearance level of $<$30 mL/min, had known or suspected infection due to atypical pathogens (including *Legionella* species) or MRSA, had empyema, or were immunosuppressed (including patients with end-stage liver disease, human immunodeficiency virus infection, or neutropenia). Patients underwent baseline microbiologic testing, including sputum and blood cultures, determination of acute and convalescent titers for atypical pathogens, and urine *Legionella* antigen tests. The ceftaroline dosage was adjusted to 400 mg every 12 h for patients with creatinine clearance levels of 30–50 mL/min.

A total of 1240 patients were randomized in FOCUS 1 and 2, and 614 patients received ceftaroline and ceftriaxone. The groups were similar in terms of age, underlying lung disease, PORT class, and presence of renal insufficiency. In FOCUS1, ceftaroline was associated with higher success rates than was ceftriaxone in the CE (86.6% vs 78.2%; 95% confidence interval [CI], 1.4%–15.4%), ME (89.9% vs 76.1%; 95% CI, 1.3%–26.4%), and mMITTE (88.0% vs 75.0%; 95% CI, 0.7%–25.2%) populations. In the integrated FOCUS 1 and 2 analysis, clinical cure rates were 6.7% (95% CI, 1.6%–11.8%) and 6.0% (95% CI, 1.4%–10.7%) higher for ceftaroline than for ceftriaxone in the CE and MITTE populations. In the ME and mMITTE populations, cure rates were 85.1% and 83.6%, respectively, for ceftaroline and 75.5% and 75.0% for ceftriaxone. The integrated cure rates for *S. pneumoniae* were 85.5% for ceftaroline and 68.6% for ceftriaxone. Among 55 patients with *S. aureus* identified as a pathogen, the ceftaroline cure rate was 72.0%

and ceftriaxone cure rate was 60%. There were no differences in cure rates among patients with bacteremia with respect to age, renal impairment, or the presence of mixed typical/atypical infections. The relapse rates were <2% in both groups. In patients with multidrug-resistant *S. pneumoniae* pneumonia, treatment with ceftaroline cured all 4 patients, and treatment with ceftriaxone cured only 2 of 9 patients. Thus, ceftaroline was noninferior to ceftriaxone in all populations and showed numerical superiority in a number of the populations. The lower ceftaroline MICs, compared with ceftriaxone MICs, for the most commonly identified pathogens likely contributed to the results (ceftaroline MICs of ≤ 0.015 and 0.25 for *S. pneumoniae* and *S. aureus*, respectively, compared with 1 and 4, respectively, for ceftriaxone).

ADVERSE EVENTS

Safety data on ceftaroline derived from 1305 patients treated with ceftaroline in Phase 3 trials are summarized in Table 3. Ceftaroline demonstrated a safety profile similar to that of comparator drugs. Allergic reactions to ceftaroline occurred in only 1.9% of patients who received it in the CANVAS studies, and there were no differences between ceftaroline and comparator drugs in terms of cardiac toxicity. Although seroconversion to a positive direct Coombs' test result was seen more frequently among ceftaroline-treated patients than among those treated with comparator drugs (10.7% vs 4.4%), the frequency of drug-induced hemolytic anemia was not higher (1.2% vs 1.3%). In Phase 3 studies, 3 cases of *Clostridium difficile* infection were noted, including 2 in ceftaroline-treated patients and 1 in a patient treated with a comparator drug.

FORMULARY ISSUES

Ceftaroline is a new broad-spectrum cephalosporin with improved in vitro activity against gram positive cocci, such as penicillin resistant Streptococcus pneumoniae and MRSA. This greater antimicrobial spectrum, compared with that of older agents, such as ceftriaxone, enhances the usefulness of this antibiotic for the treatment of cSSSI and CABP. Alternatively, ceftaroline does not have good in vitro activity against several important gram-negative pathogens, such as *P. aeruginosa* and extended-spectrum β-lactamase–producing organisms, and will not be a suitable alternative to ceftazidine or cefepime for empirical treatment of suspected gram-negative nosocomial infection. In addition, it should not be used alone in treating ABSSSI due to mixed gram-negative anaerobic pathogens if *B. fragilis* is suspected.

Ceftaroline has a prolonged serum half-life without extensive protein binding. These pharmacokinetic parameters, in conjunction with pharmacodynamic studies, support twice-daily dosing against bacteria with MIC ≤ 1 mg/L [28]. This dosing schedule will not be an advantage in the hospital or in outpatient parenteral antimicrobial therapy, compared with available alternative agents. Ceftaroline can be diluted in common solutions and is compatible with most drugs via Y-site coadministration. Incompatible agents include amphotericin B and caspofungin. Although there is no oral formulation of ceftaroline, it has excellent bioavailability by intramuscular administration.

Ceftaroline is well tolerated and has an adverse effect profile similar to that of other cephalosporins. This involves the risk of diarrhea, including *C. difficile* infection. Unlike some cephalosporins, ceftaroline can be administered via intramuscular dosing without causing significant pain. Although there are no controlled trials of ceftaroline in pregnant women, toxicity studies in animals did not find adverse effects on offspring. Based on these findings, the FDA has given ceftaroline a category B designation for use in pregnancy.

An acquisition cost of ~$80/day for ceftaroline allows for favorable comparisons to other newer agents for the treatment of ABSSSI and CABP. Although more costly than other parenteral cephalosporins, fluoroquinolones and vancomycin, ceftaroline would be less expensive than single-drug or combination-drug therapy utilizing newer agents, such as linezolid, daptomycin, or tigecycline, to treat MRSA.

Table 3. Treatment-emergent Adverse Events in Phase 3 Trials

	Percentage of subjects with adverse event, by trial			
Variable	CANVAS		FOCUS	
Adverse event	Ceftaroline	Vancomycin-aztreonam	Ceftaroline	Ceftriaxone
Nausea	5.9	5.1	2.3	2.3
Headache	5.2	4.5	3.4	1.5
Diarrhea	4.9	3.8	4.2	2.6
Rash	3.2	2.5	…	…
Any	44.7	47.5	47.0	45.7
Discontinuation due to adverse event	3.0	4.8	4.4	4.1

In summary, ceftaroline represents the first cephalosporin to be approved for the treatment of MRSA infections with an efficacy profile that is similar to that of comparative agents in the treatment of ABSSSI and to ceftriaxone in the treatment of CABP. In the integrated analysis of 2 studies of CABP, ceftaroline was superior to comparator drugs. Its limited activity against many problem gram-negative pathogens will not earn it a place in the treatment of serious hospital-associated gram-negative infections. The potential for the development of resistance to ceftaroline among MRSA strains will be determined over time. This agent has a good safety profile and is a welcome addition to the antimicrobial armamentarium of the infectious disease physician.

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