Summary of Ceftaroline Fosamil Clinical Trial Studies and Clinical Safety

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In October 2010, the new cephalosporin, ceftaroline fosamil, was approved by the US Food and Drug Administration for therapy of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs). The active metabolite, ceftaroline, demonstrates in vitro activity against typical bacterial pathogens most often associated with CABP or ABSSSIs, including resistant Gram-positive pathogens such as multidrug-resistant Streptococcus pneumoniae and methicillin-resistant Staphylococcus aureus. The efficacy and safety of ceftaroline fosamil was assessed in 2 large phase 3 programs of randomized, double-blind, clinical trials for CABP and ABSSSIs. For both indications, therapy with ceftaroline fosamil was observed to be noninferior to the comparator agents (ceftriaxone for CABP and vancomycin plus aztreonam for ABSSSIs) at both a standard test of cure assessment time (8–15 days after discontinuation of study drug) and an early assessment time point (day 3 or 4 of study). In the integrated analysis of the trials for CABP (FOCUS 1 and 2), clinical cure rates for the ceftaroline group were numerically higher than those for the ceftriaxone group (for the clinically evaluable population 84.3% vs 77.7%; difference: 6.6%; 95% confidence interval, 1.6%–11.8%). Among patients with CABP caused by S. pneumoniae, clinical cure rates were markedly higher in the ceftaroline treatment group than in the ceftriaxone treatment group (59 of 69 [85.5%] vs 48 of 70 [68.6%], respectively). For the ABSSSI studies (CANVAS 1 and 2), microbiologically evaluable (ME) success rates were similar between the treatment groups. Notably, the clinical cure rates in ME patients with methicillin-resistant S. aureus ABSSSIs were 142 of 152 (93.4%) and 115 of 122 (94.3%), for ceftaroline and vancomycin plus aztreonam, respectively, and did not differ from those achieved in infections due to methicillin-susceptible S. aureus (93.0%–94.5%). Ceftaroline fosamil was well tolerated, with a safety profile similar to the comparator agents used in these phase 3 trials.

The emergence of antimicrobial resistance among pathogens of common infections is a significant concern. Resistance among Streptococcus pneumoniae and Staphylococcus aureus has become a major consideration when treating such infections as community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs). In addition to recommendations from treatment guidelines, these microbiological trends are important to consider during selection of antimicrobial treatment. Continued efforts to improve treatment options and outcomes for patients with these infections are warranted. Thus new options of effective therapy are welcomed.

In October 2010, the new cephalosporin, ceftaroline fosamil, was approved for therapy of ABSSSIs and CABP in the United States. Ceftaroline fosamil is the prodrug form of ceftaroline, a cephalosporin that demonstrates in vitro activity against typical bacterial pathogens most often associated with ABSSSIs or CABP, including resistant Gram-positive pathogens such as multidrug-resistant S. pneumoniae and methicillin-resistant S. aureus (MRSA). Ceftaroline exerts its...
antimicrobial therapy is usually administered initially [4]. Approximately 1.2 million patients who require admission to the hospital annually in the United States and for whom parenteral antimicrobial therapy is usually administered initially [4]. Community-acquired pneumonia refers to a recent US Food and Drug Administration (FDA)-approved indication of ceftaroline for CABP and may involve [6]. Community-acquired bacterial pneumonia refers to a recent US Food and Drug Administration (FDA)–derived definition that is designed to better identify patients most likely to have bacterial pneumonia (eg, S. pneumoniae, H. influenzae, S. aureus) and excludes those with a viral or “atypical” etiology [7]. Approval of ceftaroline for CABP was based on the results of clinical trials of the FOCUS program.

**FOCUS STUDIES**

**Design**

The FOCUS program was prospectively designed to include 2 similar (NCT00621504 and NCT00509106) phase 3, double-blind, randomized, multinational, multicenter studies that compared the efficacy and safety of intravenous ceftaroline with that of intravenous ceftriaxone administered for 5–7 days to adults who were hospitalized (but not admitted to an intensive care unit) with CABP of Pneumonia Outcomes Research Team (PORT) risk class 3 or 4 [8]. Inclusion criteria included an acute illness with radiographically confirmed CABP and at least 3 clinical signs or symptoms of lower respiratory tract infection. Patients were excluded if they received antimicrobial therapy within 4 days before randomization; had creatinine clearance of 30 mL/minute or lower; had an infection caused by a pathogen resistant to study medication, an atypical pathogen, or a pathogen other than a community-acquired bacterial pathogen; had risk factors for an MRSA infection (because ceftriaxone is not effective for this organism); or had pleural empyema. The 2 trials were similar in design except for the addition of 24 hours of adjunctive therapy with clarithromycin (2 doses) in study NCT00621504 to enhance enrollment of patients in North America, where treatment guidelines recommend adjunctive macrolide therapy. Potential confounding of the study results was minimized by limiting macrolide treatment to 24 hours.

The primary objective of these studies was to determine noninferiority in clinical cure rates of ceftaroline compared with ceftriaxone in the coprimary populations modified intent-to-treat efficacy (MITTE) (all patients were randomized, received study drug, and were PORT risk class 3 or 4) and clinically evaluable (CE) (MITTE population who also met all evaluability criteria) populations at the test of cure (TOC) (8–15 days after end of treatment). Patients remained hospitalized throughout the course of study drug therapy. Switch to oral therapy or to outpatient parenteral therapy was not permitted.

In addition to the standard TOC endpoint as described in the FOCUS trials, the FDA also specified and assessed post hoc clinical stability and symptom improvement on day 4 of study therapy [9]. For this analysis, the FDA MITT population included patients who received any amount of study therapy and had a baseline pathogen identified. These included patients with adequate sputum specimens or blood cultures that were positive for isolates of S. pneumoniae, H. influenzae, Moraxella catarrhalis, Streptococcus pyogenes, S. aureus, or Klebsiella pneumoniae [9]. There was no exclusion for resistant pathogens. The FDA endpoint for clinical success required patients to fulfill 2 criteria:

1. Clinical stability determined by temperature ≤37.8°C; heart rate ≤100 beats/minute; respiratory rate ≤24/minute; systolic blood pressure ≥90 mm Hg; room air oxygen saturation ≥90%, and normal mental status; and
2. Symptom improvement from baseline on at least 1 of the following components, and no worsening of any of the other components: cough; dyspnea; pleuritic chest pain; sputum production.

**Results**

As designed prestudy, data from the individual FOCUS trials were pooled for analysis of the combined population. For the TOC endpoint in the 2 FOCUS studies, there were 1053 total
patients in the MITTE population and 908 total patients in the CE population. Patient demographic and baseline characteristics were well matched between groups. The mean age was 61, and 38% of patients were classified as PORT risk class 4; most were enrolled in Europe (81%). A bacterial (excluding “atypical pathogen”) etiology (by sputum, blood cultures, or urinary antigen test) was documented in 26.1% of the MITTE population. The most common pathogens were S. pneumoniae (139), S. aureus (methicillin-susceptible; MSSA) (55), H. influenzae (44), K. pneumoniae (28), and E. coli (25). The 90% minimum inhibitory concentrations of these pathogens were S. pneumoniae: ceftaroline, ≤0.015 μg/mL, and ceftriaxone, 1 μg/mL; S. aureus: ceftaroline, 0.25 μg/mL, and ceftriaxone, 4 μg/mL; H. influenzae: ceftaroline, 0.03 μg/mL, and ceftriaxone, ≤0.015 μg/mL; K. pneumoniae: ceftaroline, 0.5 μg/mL, and ceftriaxone, 0.06 μg/mL; and E. coli: ceftaroline, 0.5 μg/mL, and ceftriaxone, 0.12 μg/mL. Mean duration of study drug treatment in the CE population was 6.6 days. A total of 309 patients were included in the FDA 4-day endpoint assessment of patients with confirmed bacterial CABP.

Clinical response at day 4 and clinical cure rates at the TOC visit in the combined population overall, as well as by PORT risk class and age, are presented in Table 1 and Figure 1. All numerical trends favored ceftaroline, and the 10% noninferiority margin was met for all the coprimary analysis populations. Among patients with CABP caused by S. pneumoniae, clinical cure rates were markedly higher in the ceftaroline group than in the ceftriaxone group (59 of 69 [85.5%] vs 48 of 70 [68.8%], respectively). The clinical success rates at TOC for the other common pathogens were S. aureus: ceftaroline, 72%, and ceftriaxone, 60%; H. influenzae: ceftaroline, 83%, and ceftriaxone, 83%; K. pneumoniae: ceftaroline, 93%, and ceftriaxone, 77%; and E. coli: ceftaroline, 83%, and ceftriaxone, 69%. The 30-day all-cause mortality was low at 2.4% in the ceftaroline groups and 2.0% in the ceftriaxone groups.

Streptococcus pneumoniae was the most commonly isolated pathogen in the FOCUS trials, consistent with the epidemiologic perspective of CABP and previously conducted registration trials of antimicrobial agents. Ceftaroline was efficacious against CABP caused by S. pneumoniae and in the subset of those patients with S. pneumoniae bacteremia. Ceftaroline achieved clinical cure in all 4 patients with multidrug-resistant S. pneumoniae, whereas ceftriaxone achieved cure in 2 of 9 patients. A possible explanation of the differences in clinical cure rates for S. pneumoniae with ceftaroline vs ceftriaxone is their respective affinities for S. pneumoniae PBPs and resulting significantly lower MIC values. Ceftaroline has a higher affinity for PBP2x, which is the primary determinant of beta-lactam resistance in S. pneumoniae [10]. Of interest, the second most common pathogen identified in the FOCUS studies was MSSA. This is consistent with the finding of other recent studies suggesting that MSSA has emerged as a relatively common cause of CABP [11]. Of note, patients with known or suspected MRSA pneumonia were excluded from the study because ceftriaxone is inactive against this pathogen. Future studies are planned to assess the efficacy of ceftaroline for MRSA CABP.

The results of the FOCUS trials demonstrated that 600 mg of ceftaroline administered every 12 hours for 5–7 days to initially hospitalized adults (who were not hospitalized in an intensive care unit) with CABP of PORT risk class 3 or 4 is an efficacious, well-tolerated treatment. Although the FOCUS studies were not designed as superiority studies, the results suggested a benefit of ceftaroline over ceftriaxone.

In summary, analysis of the 2 FOCUS trials demonstrates that ceftaroline is efficacious and well tolerated for treatment of

### Table 1. Results of FOCUS Studies: Clinical Cure Rates by Study Population at 4 Day Food and Drug Administration Assessment and Test-of-Cure Visit

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Ceftaroline</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Day FDA assessment</td>
<td>106/154* (69.3%)</td>
<td>93/155 (59.9%)</td>
</tr>
<tr>
<td>TOC (8–15 days post-treatment), MITTE populationa</td>
<td>479/580 (82.6%)</td>
<td>439/573 (76.6%) (95% CI, 1.4%–10.7%)</td>
</tr>
<tr>
<td>TOC (8–15 days post-treatment), CEPopulationb</td>
<td>387/459 (84.3%)</td>
<td>349/449 (77.7%) (95% CI, 1.6%–11.8%)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>15/21 (71.4%)</td>
<td>10/17 (58.8%)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>59/69 (85.5%)</td>
<td>48/70 (68.8%)</td>
</tr>
<tr>
<td>PORT class 3</td>
<td>249/287 (86.8%)</td>
<td>217/274 (79.2%)</td>
</tr>
<tr>
<td>PORT class 4</td>
<td>138/172 (80.2%)</td>
<td>132/175 (75.4%)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>195/232 (84.1%)</td>
<td>177/219 (80.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: CE, clinically evaluable; CI, confidence interval; FDA, Food and Drug Administration; MITTE, modified intent-to-treat efficacy; PORT, Pneumonia Outcomes Research Team; TOC, test-of-cure.

*a MITTE = all patients were randomized, received study drug, and were PORT risk class 3 or 4;

b CE = met all evaluable criteria.
c XY, number with successful response/total number evaluated.
CABP (PORT risk class 3 or 4) [5]. As a β-lactam agent, ceftaroline is not effective against the pathogens of atypical pneumonia (M. pneumoniae, C. pneumoniae, L. pneumophila), and combination therapy often with a macrolide is recommended for empirical therapy of patients requiring admission to the hospital [6].

**ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS**

One of the prominent challenges in management of ABSSSIs (formerly known as complicated skin and skin structure infections) in today’s hospital environment is the changing pattern of susceptibility of S. aureus. Over the past decade, there has been a significant increase in the prevalence of severe ABSSSIs requiring hospitalization and caused by community-acquired MRSA. Methicillin-resistant S. aureus is now the leading cause of purulent skin and soft tissue infection in emergency departments in the United States [12] Cefaroline was evaluated for efficacy and safety in ABSSSIs in the 2 CANVAS (CeftArolNe Versus VAncomycin in Skin and Skin Structure Infections) studies [13–15].

**CANVAS STUDIES**

**Design**

The CANVAS studies were 2 phase 3, randomized, double-blind, clinical trials (NCT00423657 and NTC00424190) that evaluated the safety and efficacy of 5–14 days of 600 mg ceftaroline given every 12 hours in comparison with a combination of 1 g of vancomycin given every 12 hours plus 1 g of aztreonam given every 12 hours for the treatment of ABSSSIs [13–15]. The CANVAS 1 and CANVAS 2 studies had identical designs and protocols and recruited 1378 patients in a total of 110 study centers in Europe, Latin America, and the United States between February and December 2007 [13–15]. Thus, patient recruitment occurred after the emergence of MRSA as a prime pathogen in ABSSSI, notably in community settings [16–18]. The studies were designed to determine non-inferiority in the clinical cure rate achieved with ceftaroline monotherapy (693 patients) compared with vancomycin and aztreonam combination therapy (685 patients) in the CE (n = 610 and 592) and modified intent-to-treat (MITT) (n = 693 and 685) populations. Patients were excluded if they had received >24 hours of antimicrobial treatment within 96 hours prior to randomization, unless there was evidence of therapy failure or antibacterial resistance or if creatinine clearance was <30 mL/minute. Other key exclusions included patients with suspected P. aeruginosa or anaerobic infection and those with decubitus ulcer, diabetic foot ulcer, ulcer associated with peripheral vascular disease accompanied by osteomyelitis, or extensive burns.

**Results**

Baseline characteristics of the treatment groups were comparable. The median age of patients was 48 years, 78% were hospitalized at study entry, 55% had ≥2 signs or symptoms (erythema, swelling, tenderness, or warmth) classified as severe, and 4% were bacteremic. As expected, the major infection types in the study were cellulitis, major abscess requiring surgical intervention, infected wound, and infected ulcer.
Table 2. Results of CANVAS Studies: Clinical Cure Rates for Clinically Evaluable Population at the Test-of-Cure Visit and for Subgroups According to Type of Infection and Presence of Diabetes Mellitus, Peripheral Vascular Disease, or Bacteremia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ceftaroline</th>
<th>Vancomycin Plus Aztreonam</th>
<th>Difference (Ceftaroline – Vancomycin Plus Aztreonam) % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All clinically evaluable</td>
<td>559/610 (91.6)</td>
<td>549/592 (92.7)</td>
<td>−1.1 (−4.2 to 2.0)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>213/229 (93.0)</td>
<td>222/243 (91.4)</td>
<td>1.7 (−3.4 to 6.7)</td>
</tr>
<tr>
<td>Major abscess</td>
<td>184/202 (91.1)</td>
<td>177/188 (94.1)</td>
<td>−3.0 (−8.5 to 2.3)</td>
</tr>
<tr>
<td>Infected wound</td>
<td>73/84 (86.9)</td>
<td>65/73 (89.0)</td>
<td>−2.1 (−12.8 to 8.7)</td>
</tr>
<tr>
<td>Infected ulcer</td>
<td>48/53 (90.6)</td>
<td>47/50 (94.0)</td>
<td>−3.5 (−15.4 to 8.2)</td>
</tr>
<tr>
<td>Infected burn</td>
<td>25/25 (100.0)</td>
<td>18/18 (100.0)</td>
<td>0.0 (−13.6 to 17.9)</td>
</tr>
<tr>
<td>Infected bite</td>
<td>9/9 (100.0)</td>
<td>9/9 (100.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>4/5 (80.0)</td>
<td>9/9 (100.0)</td>
<td>−20.0</td>
</tr>
<tr>
<td><strong>Underlying comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>96/110 (87.3)</td>
<td>100/110 (90.9)</td>
<td>−3.6 (−12.3 to 5.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>80/90 (88.9)</td>
<td>75/84 (89.3)</td>
<td>−0.2 (−10.0 to 9.7)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>22/26 (84.6)</td>
<td>21/21 (100.0)</td>
<td>−15.4 (−33.8 to 1.5)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>16/18 (88.9)</td>
<td>9/9 (100.0)</td>
<td>−11.1 (−33.2 to 5.7)</td>
</tr>
<tr>
<td>MRSA</td>
<td>6/7 (85.7)</td>
<td>2/2 (100.0)</td>
<td>−14.3 (−53.5 to 58.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant S. aureus.

(Table 2). The median infection area was 156 and 150 cm² for the ceftaroline and comparator groups, respectively. A pathogen was recovered in 76% of patients, most commonly S. aureus, with MRSA accounting for 40% and 34% in the ceftaroline and combination treatment groups, respectively. Gram-negative potential pathogens were isolated in 21% of cases but usually as part of a polymicrobial lesion; polymicrobial infections that included a Gram-positive potential pathogen occurred in 28% of patients.

The mean treatment duration for patients in the CE population was approximately 8 days for both treatment groups. Clinical cure rates were similar for ceftaroline and combination treatment groups in the CE (91.6% vs 92.7%) and MITT (85.9% vs 85.5%) populations. Microbiologic success rates were similar between the treatment groups. Notably, the clinical cure rates in microbiologically evaluable patients with MRSA ABSSSIs were 93.4% and 94.3%, respectively, and did not differ from those achieved in infections due to MSSA (93.0%–94.5%). The rates of adverse events, discontinuations because of an adverse event, serious adverse events, and deaths were similar between treatment groups; nausea, headache, and diarrhea occurred in 4%–6% of patients, and pruritus occurred in 3.5% of ceftaroline cases vs 8.2% of comparator cases (not significant difference, see next section).

Inclusion of cases with cutaneous abscesses in the study was justified on the basis that antimicrobial therapy is recommended if abscesses are large, surrounded by extensive cellulitis, or accompanied by systemic symptoms [19]. Importantly, the efficacy of ceftaroline was similar after reanalysis of the data for the noncutaneous abscess patients alone. Also, clinical cure rates were similar regardless of infection type (including cellulitis, major abscess, and infected wound) and in patients with common comorbidities such as diabetes mellitus or peripheral vascular disease (Table 2). Clinical cure rates were similar in patients infected with a single pathogen or multiple pathogens. In those classified as having polymicrobial infection, ceftaroline was as efficacious as the combination treatment group (91.9% vs 96.4% [difference: −4.2; 95% confidence interval, −10.5 to 1.5]), although the significance of individual organisms in such cases is often unclear. Nevertheless, ceftaroline does offer the potential to avoid the need to use combination treatment if there is a concern that Gram-positive and/or Gram-negative pathogens are present. Ceftaroline is not active against P. aeruginosa, but this remains a very uncommon pathogen in ABSSSIs.

As part of its review of ceftaroline, the FDA defined a key sensitivity endpoint of clinical response in those patients with cessation of spread of the lesion from baseline along with absence of fever at the day 3 assessment [20]. This additional (poststudy defined) endpoint reflects the criteria set by the FDA to assure the robustness of a noninferiority margin when comparing antimicrobial treatment options for ABSSSIs. In addition, the FDA reanalyzed treatment response, having determined that patients who had an EOT assessment on day 3, which was assessed by an investigator as a clinical failure, could not be classified as a clinical responder. The regulatory
With lesion size ≥ 75 cm² having 1 of the following infection types: major abscess with ≥5 cm of surrounding erythema, wound infection, deep/extensive cellulitis, or lower extremity ABSsSIs in patients with diabetes mellitus or peripheral vascular disease) appeared to be robust.

In conclusion, the CANVAS 1 and 2 studies demonstrated that ceftaroline achieved high clinical cure and microbiologic success rates, being efficacious against ABSsSIs caused by MRSA and other common ABSsSI pathogens, and is well tolerated. Clinically, the observation that clinical cure rates in microbiologically evaluable patients with MRSA ABSsSIs did not differ from those achieved in infections due to MSSA is important because treatment of ABSsSIs is invariably empiric and presentation characteristics are not reliable to distinguish cases caused by MSSA as opposed to MRSA [21]. Cefaroline therefore has the potential to be used as monotherapy for the empirical treatment of ABSsSIs.

Clinical Safety
With few exceptions, the cephalosporin group of antimicrobials is well tolerated. Common adverse effects fall into several general categories, such as hypersensitivity reactions, gastrointestinal disturbances, hematologic changes, hepatotoxicity, nephrotoxicity, neurotoxicity, and superinfections. In large, clinical, phase 3 studies [8, 13–15], ceftaroline was well tolerated with no unexpected safety concerns [22, 23]. The adverse event profiles in patients aged ≥65 years and in patients aged <65 years were similar. Moreover, its safety profile was observed to be similar to the comparator agents, ceftriaxone and vancomycin plus aztreonam in these trials.

Common allergic reactions to cephalosporins, such as rash, urticaria, serum sickness, and anaphylaxis, have been reported in frequencies varying between 1% and 3% in large patient populations. In the population who received ceftaroline in phase 3 studies, rash occurred in 3% of patients. Urticaria and anaphylaxis were also rarely reported. These studies excluded patients with a history of hypersensitivity to β-lactam agents, so no cross-reactivity information was obtained. In spite of this absence of data, it is important to remember that approximately 2% of patients without a history of penicillin allergy may have a reaction to a cephalosporin [24].

Parenteral cephalosporins have been associated with gastrointestinal disturbances such as nausea, vomiting, and diarrhea. In addition, ceftriaxone may precipitate in the bile and cause biliary sludge and gallstones, especially in children. Approximately 5% of patients who received ceftaroline in phase 3 studies developed diarrhea. Although ceftaroline does not significantly impact human intestinal flora in healthy subjects, 2 cases of Clostridium difficile–associated diarrhea developed in ceftaroline-treated patients with ABSsSIs [22, 25]. In contrast to ceftriaxone, ceftaroline does not have high biliary excretion, and acute cholecystitis has not been associated with its use.

Hematologic toxicity is occasionally associated with cephalosporin therapy, although eosinophilia can occur in up to 4% of patients. Neutropenia and thrombocytopenia are uncommon side effects of cephalosporin therapy. Similar findings have also been observed with ceftaroline. Older cephalosporins such as cefoperazone and cefotetan are known to cause prolongation of the prothrombin time, especially in patients with renal insufficiency [26]. These agents contain an N-methyl-thiotetrazole moiety that interferes with the synthesis of vitamin K–dependent clotting factors in the liver. Cefaroline does not possess this 3-position side chain and has not been associated with hypoprothrombinemia. A positive Coombs’ test has been associated with all cephalosporins, and frequencies vary with different agents. In phase 3 trials, conversion to a positive Coombs’ test occurred in approximately 11% of patients treated with ceftaroline and 4.4% treated with comparators, but none developed hemolytic anemia [22, 23].

The newer cephalosporins are rarely nephrotoxic and do not appear to increase the risk of aminoglycoside nephrotoxicity [27]. In the phase 3 clinical trials, a >50% decrease in creatinine clearance occurred in ≤1% of patients treated with ceftaroline. Acute renal failure was infrequently reported (<1%); none of the renal abnormalities were attributed to ceftaroline. Furthermore, none of these patients were receiving an aminoglycoside.

Cephalosporin neurotoxicity is uncommon, but these drugs are known to cause tremor, confusion, encephalopathy, nonconvulsive status epilepticus, and seizures [28]. Patients with renal insufficiency are at the greatest risk. Although headache (3.4%–5.2%) and dizziness (2%) have occurred in patients receiving ceftaroline, no serious neurologic toxicity has been associated with its use in clinical trials [22, 23]. It is important to note that patients with severe renal impairment (creatinine clearance ≤30 mL/minute) were excluded from these phase 3 studies.

Clinical hepatotoxicity with cephalosporin antibiotics is rare, although there are occasional reports of self-limited cholestatic or mixed injury [29]. However, disturbances in liver tests are observed in 1%–7% of patients. Ceftriaxone, which is predominantly excreted in the bile, has also been associated with biliary sludge or pseudolithiasis due to the precipitation of a calcium salt of this compound. Liver function abnormalities occurred in approximately 2.5% of patients who received ceftaroline in phase 3 clinical trials. These usually involved
elevations in alanine aminotransferase or aspartate aminotransferase; the incidence was lower than that seen with comparator agents [22]. No cases of pseudolithiasis were reported.

Overall, about 3% of patients who received ceftaroline discontinued treatment due to an adverse event in phase 3 studies [22, 23]. Allergic reactions were the most common reason for discontinuation of this parenteral cephalosporin. Serious adverse effects were not related to ceftaroline therapy with the exception of 1 patient with moderate vomiting that lead to severe fatigue [22]. The clinical safety of ceftaroline at higher than FDA-recommended daily doses remains unknown; however, preliminary investigations in healthy subjects have not revealed any serious untoward events [30].

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


