Clinical Medicine Reviews in Therapeutics

REVIEW

Ceftaroline for the Treatment of Complicated Skin and Skin-Structure Infections

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Abstract: Ceftaroline is novel "fifth generation" cephalosporin with broad acitivity, most notably including penicillinase-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline is inactive against *Pseudomonas spp,* other gram-negative non-fermenters, anaerobes and other multidrug resistant organisms. Ceftaroline has been evaluated for complicated skin and soft tissue infections in phase three clinical trials, CANVAS 1 and 2, which demonstrated non-inferiority to vancomycin and aztreonam. Infections evaluated included cellulitis, abscess, and skin and soft tissue ulcers. Decreased efficacy was noted in patient with *Enterococcus faecalis* and *Proteus mirabilis* infections. Ceftaroline is well tolerated with a favorable safety profile, and may play an important role in the future treating serious MRSA-related infections.

Keywords: ceftaroline, methicillin-resistant *Staphylococcus aureus* (MRSA), skin and soft tissue infections, cephalosporins

Clinical Medicine Reviews in Therapeutics 2012:4 123–129

doi: 10.4137/CMRT.S9284

This article is available from http://www.la-press.com.

Introduction

Complicated skin and skin-structure infections (cSSSIs) often require inpatient hospitalization for intravenous (IV) antibiotic administration and surgical intervention. As time has progressed, the cause of cSSSIs has shifted from common skin flora to more resistant organisms. Zervos et al retrospectively reviewed 449 patients with culture positive cSSSIs in a large Midwestern teaching hospital in the United States from 2005 through 2008. *Staphylococcus aureus* accounted for 66.4% cultures, with 74.8% of the *S. aureus* classified as methicillin-resistant *Staphylococcus aureus* (MRSA). *Streptococcus* species followed at 26.1%.[1] With an increasing prevalence of MRSA, initial anti-MRSA antibiotic coverage for cSSSI is becoming increasingly necessary for clinical success.

Ceftaroline (Teflaro, Forest Laboratories, Inc, New York, NY, USA) is a novel, parental broad-spectrum cephalosporin indicated for treatment of acute bacterial cSSSIs caused by susceptible isolates. Ceftaroline is United States Food and Drug Administration (FDA) approved for the treatment of cSSSIs due to MRSA, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Ceftaroline is administered by IV every twelve hours at a dose of 600 mg for an indicated duration of 5 to 14 days. Dosage adjustment is required in patients with a creatinine clearance less than 50 mL/min. No hepatic dose adjustment is known to be indicated at this time. Ceftaroline has only been approved for persons 18 years of age or older because studies have not been performed to date in the pediatric population.[2]

Mechanism of Action

Ceftaroline, a beta-lactam antibiotic, is bactericidal by targeting and binding penicillin-binding proteins (PBPs), inhibiting peptidoglycan cross-linking and subsequent cell wall synthesis. MRSA is known to contain the *mecA* structural gene, which alters penicillin-binding protein 2 (PBP2). This altered structure, known as PBP2a, has a low affinity for binding beta-lactams resulting in resistance.[3] Moison et al demonstrated ceftaroline's novel ability among beta-lactams to exhibit high binding affinity for PBP2a using a naturally occurring membrane fraction of MRSA cells. Furthermore, the major PBPs for S*treptococcus pneumonia* are1a, 1b, 2x, 2a/2b, and 3 with alterations in 1a, 2b, and 2x causing beta-lactam resistance. Similar studies also demonstrated ceftaroline's high binding affinity for these altered PBPs. The high affinity binding correlated with low mean inhibitory concentrations (MIC's) in the laboratory setting.[4] Ceftaroline overcomes previous beta-lactam resistance mechanisms by high affinity binding to the altered PBP of 1a, 2a, 2b, and 2x making it a therapeutic option for MRSA and penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae*.

Metabolism

Ceftaroline fosamil is the water-soluble prodrug of ceftaroline. When administered via IV, it is quickly converted into the active drug, ceftaroline, by plasma phosphatases.[5] Ceftaroline is weakly protein bound, with an average of 20% protein distribution. When incubated with pooled human liver microsomes, ceftaroline was metabolically stable (<12% metabolic turnover), indicating that ceftaroline is not a substrate for the CYPP450 enzymes.[3] Ceftaroline is primarily excreted by the renal system, and, thus, dosage is decreased with declining glomerular filtration rates and creatinine clearance (CrCl). Approximately 50% of the dose of ceftaroline is excreted as active drug in the urine.[6] Ge et al studied normal volunteers and patients with mild and moderate renal dysfunction.[7,8] A single 600 mg dose of IV ceftaroline in subjects with mild renal impairment (CrCl > 50 to ≤80 mL/min, n = 6) resulted in a geometric mean area under the curve (AUC) that was 19% higher than normal subjects. When 400 mg of ceftaroline was administered to hemodialysis patients 1 hour after hemodialysis, the geometric mean AUC was 167% higher than normal subjects. In patients on hemodialysis for end-stage renal disease (ESRD), ceftaroline should be administered after hemodialysis, as 21.6% was recovered in the dialysate after a 400 mg dose was given 4 hours prior to hemodialysis session.[3,7,8] No dosage adjustment is necessary in patients with hepatic impairment Table 1.

Pharmacokinetic Profile

Ceftaroline is a bactericidal drug that demonstrates time-dependent killing similar to other beta-lactams. Andes et al evaluated ceftaroline in a murine thigh infection model and showed that the

pharmacokinetic-pharmacodynamic (PK-PD) index that best correlated with efficacy was the time above the MIC (R^2 = 84% to 88% for *S. pneumoniae, S. aureus*, and *E. coli*).[9] The study compared mice treated with 5 days of intraperitoneal cyclophosphamide prior to inoculation of 0.1 mL of $10^{6.6}$ to $10^{8.7}$ CFU/mL of 11 different organisms with mice who were inoculated without pretreatment cyclophosphamide. MSSA, MRSA, penicillin-sensitive, penicillin-intermediate, and penicillin-resistant *S. pneumoniae,* two *E. coli* strains, and two *Klebsiella pneumoniae* strains were used in the study. Two hours after bacterial inoculation, the mice were treated with different doses of ceftaroline and then evaluated. The investigators found that increasing the peak concentration of the drug did not result in more killing. More drug was required to kill organisms in the neutropenic model although it was not statistically significant. *S. aureus* did exhibit a post-antibiotic effect, while *S. pneumoniae* did not. This could possibly prevent bacterial re-growth when the ceftaroline levels fall below the MIC.[3] The pharmacodynamics principal suggested with these experiments was that ceftaroline should be dosed based on the time the drug concentration remains above the MIC (%T > MIC).

Ceftaroline is not thought to accumulate after doses, as exemplified in PK studies in healthy adults. The AUC after administration of 600 mg IV of ceftaroline every 12 hours for 14 days was reported as 56.8 and 56.2 mg·h/L.[10] Per Riccobene et al, intramuscular injection had roughly equivalent systemic exposure as IV infusion in healthy adults.[11]

Clinical studies

Ceftaroline was FDA approved on October 29, 2010, for cSSSIs based on ceftaroline versus vancomycin in clinical trials of cSSSI, otherwise known as the CANVAS 1 (NCT00424190) and CANVAS 2 (NCT00423657) trials. These were phase 3 international multicenter randomized double-blind comparative efficacy and safety studies with identical designs and protocols. The trials compared ceftaroline with vancomycin plus aztreonam for 5 to 14 days in adult patients hospitalized with cSSSI. One hundred and eleven study centers participated in Western and Eastern Europe, Latin America, and the United States. CANVAS 1 and CANVAS 2 were designed for combined analysis.[12]

Subjects with cSSSI were randomized if their clinical condition required hospitalization or treatment in the emergency department with IV antibacterial agents and at least 5 continued days of IV antibacterial agents. Patients had to be 18 years of age or older with greater than 3 signs of clinical infection. Infectious signs were defined as purulent or seropurulent discharge or drainage, erythema, fluctuance, heat or localized warmth, pain or tenderness to palpation, temperature greater than 38 °C or hypothermia, white blood cell (WBC) count > 10,000 cells/μL, or >10% immature neutrophils irrespective of WBC count. Two clinical scenarios were tested. The first was defined as subjects with diabetes mellitus treated with medications or documented peripheral vascular disease in the setting of lower extremity cellulitis or abscess. The second scenario encompassed cSSSI involving the deep soft tissue or requiring significant surgical intervention. Written informed consent was obtained.

Subjects were excluded if they had received greater than 24 hours of antimicrobial treatment within 96 hours prior to randomization, save for patients with evidence of clinical and microbiological failure on the current regimen after 48 hours of therapy. Pathogens resistant to vancomycin or aztreonam were excluded, as were known *Pseudomonas* isolates, anaerobes, fungal, viral, and parasitic pathogens. Also excluded were patients requiring extensive surgical intervention such as amputation or patients with diagnosed osteomyelitis, endocarditis, necrotizing fasciitis, gangrene, burns, septic arthritis, and human or animal bites. In addition, patients requiring high-dose corticosteroid therapy or concomitant antimicrobial therapy could not be randomized.

A total of 1396 patients were randomized to either receive ceftaroline 600 mg IV every 12 hours plus saline placebo or vancomcyin 1 g IV every 12 hours and aztreonam 1 g IV every 12 hours. Dosage adjustments were made to the vancomycin based on institutional guidelines or local prescribing practices. Ceftaroline was dose-reduced by an unblinded pharmacist to 400 mg IV every 12 hours if the subject's creatinine clearance was 50 mL/min or less. Subjects with a creatinine clearance of less than 30 were excluded, as were patients on hemodialysis. Site investigators were allowed to discontinue IV aztreonam or saline placebo if a gram-negative pathogen was neither suspected nor identified.

Table 1. Dosage of ceftaroline in patients with renal impairment.

Estimated CrCl (mL/min)	Recommended dosage
>50	No adjustment necessary
>30 to ≤50	400 mg IV (over 1 hour) every 12 hours
≥15 to ≤30	300 mg IV (over 1 hour) every 12 hours
ESRD, including HD	200 mg IV (over 1 hour) every 12 hours

Adapted from package insert.[2]

The modified intent-to-treat (MITT) population consisted of 693 patients treated with ceftaroline and 685 patients treated with vancomycin and aztreonam, for a total of 1378 patients. The MITT group was primarily used to assess safety, while the clinically evaluable (CE) population was analyzed for efficacy. The CE population (n = 1202) was defined as an MITT population who met clinical disease criteria for cSSSI, received a minimum amount of study drug, and for whom outcome information was available. Secondary analysis was performed on the microbiological modified intent-to-treat (mMITT) population and microbiologically evaluable population (ME). The mMITT (n = 1062) was defined as MITT patients who met clinical disease criteria for cSSSI and had ≥1 bacterial pathogen isolated from blood or infected tissue. The ME population (n = 914) included the CE group with ≥1 bacterial pathogen isolated at enrollment. Baseline cultures with monomicrobial *Pseudomonas* species infection or anaerobic organisms led to subject exclusion from the ME population.

The MITT population was predominately male. Over 70% of the population was Caucasian. The United States and Europe represented 90% of the patients with approximately 10% enrolled from Latin America. The median age in both the ceftaroline and vancomycin plus aztreonam group was 48 years; 18.1% of the population was 65 years or older. In addition, 30% of the population was obese, defined as a body mass index (BMI) greater than 30. Diabetes mellitus and peripheral vascular disease were distributed equally across both groups: approximately 18% of patients were diabetic, and 14% of patients had been diagnosed with peripheral vascular disease. Less than 5% of each group were injection drug users. Approximately 40% of patients in each group had received prior antimicrobial therapy in. Cellulitis was the most common diagnosis at 35.9% in the ceftaroline group and 39.9% in the vancomycin plus aztreonam group. Major abscess was the second most common at 34% in both groups. The median length and width of the infectious site was identical in both groups at 15 cm long and 10 cm wide. Regarding surgical intervention, the groups were basically equal with the vancomycin plus aztreonam group requiring surgical intervention in 1% to 2% more of the population. Moderate renal impairment (CrCl > 30 to ≤50 mL/min) affected 3.6% of patients.

Efficacy

Efficacy was established at the test of cure visit, which occurred 8 to 15 days after the last dose of study drug. Clinical cure was defined as total resolution of all signs or symptoms, or enough improvement that no additional antibiotic therapy was warranted. Relapse was defined as a clinically cured patient who returned to the last follow-up visit (21–35 days after the last dose of study drug) with signs or symptoms of infection.

In the integrated analysis, efficacy was similar in all groups with the exception of gram-negative only infection. Ceftaroline was 85.3% effective in gram-negative only infections versus 100% cure in the aztreonam group. The integrated analysis was designed as a non-inferiority study. The predefined lower limit of the 95% CI was above −10%.

Among clinical syndrome subsets, clinical cure rates were similar for cellulitis, major abscess, infected wound, ulcer, burn, and bite. There was a difference noted among bacteremic patients. In the ceftaroline group, 22/26 (84.6%) patients were cured clinically in contrast to 21/21 (100%) patients in the vancomycin plus aztreonam group. The difference was −15.4 (−33.8 to 1.5). The four clinical failures in the bacteremia group were due to 2 adverse events, *c diff* infection and rash. Need for surgical intervention is not an adverse event. In three of the patients with clinical failure, *S. aureus* (MRSA and MSSA) were isolated from 2 patients, and *Streptococcus anginosus* was isolated from one. All blood cultures had cleared on ceftaroline therapy.

When the results were drilled down by organism, in the ME population and mMITT population, cure rates were relatively similar for *S. aureus*, *Streptococcus*

Table 2. Integrated analysis of CANVAS 1 and 2: clinical cure rates by analysis population at test-of cure visit.

Population	Cure rate	
	Ceftaroline	Vancomycin + aztreonam
Clinically evaluable	559/610 (91.6%)	549/592 (92.7%)
MITT	595/693 (85.9%)	586/685 (85.5%)
Microbiologically evaluable	434/468 (92.7%)	421/446 (94.4%)
Gram positive only	348/371 (93.8%)	330/350 (94.3%)
Gram negative only	29/34 (85.3%)	24/24 (100%)

Adapted from Intergrated Analysis of Canvas 1 and 2.[12]
Abbreviation: MITT, modified intent to treat.

species, *Escherichia coli*, and *Klebsiella pneumoniae*. The results did differ with cure rates for *Enterococcus faecalis* and *Proteus mirabilis*. In the ME population, 80% of the patients with *E. faecalis* were cured on ceftaroline versus 91.7% patients in the vancomycin plus aztreonam group. Patients with infection secondary to *P mirabilis* had a larger discrepancy between the two treatment groups: 66.7% cure rate in the ceftaroline group versus 95.2% in the vancomycin plus aztreonam group.[12] A retrospective review of CANVAS 1 and 2 was performed by Friedland et al to evaluate day 3 clinical end points for acute bacterial skin and skin structure infections (ABSSSI).[13] This was performed as the FDA issued a draft guidance document *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* in 2010 that recommended a primary endpoint of clinical response at 48 to 72 hours after initiation of therapy.[14] The CANVAS 1 and CANVAS 2 studies were not designed to assess this endpoint. Therefore a retrospective study was performed with a portion (57.8%) of the MITT population in CANVAS 1 and CANVAS 2. Friendland et al defined the study population as the exploratory modified intent-to-treat (E-MITT) population, which included all randomized patients who received any study drug, had a cellulitis $\geq$ 75 cm^2, a major abscess with erythema $\geq$ 5 cm, or an infected wound as well as patients with diabetes mellitus or peripheral vascular disease with a lower extremity abscess or cellulitis. Infected burns and ulcers were excluded from the analysis.

In total, 797 patients were included in the E-MITT population, 397 in the ceftaroline group, and 400 in the vancomycin plus aztreonam group. Responders were classified as patients with absence of fever (temperature $\leq$ 37.6 °C) and baseline lesion stability on clinical day 3. If the investigator deemed the patient a clinical failure on day 3 or information was missing or inadequate, then the subject was deemed a non-responder. Patient characteristics were similar to the integrated analysis of CANVAS 1 and CANVAS 2, with the majority of the population being male and white. Forty-four percent of the E-MITT population had a fever (defined as temperature $\geq$ 38 °C). Cellulitis was the primary classification in 54.2% of the ceftaroline group and 60.2% in the vancomycin plus aztreonam group. Abscess was the second most common, followed by infected wound and then infected bite.

The clinical response rate on day 3 was similar in both groups. The ceftaroline group had a clinical response of 296/400 (74.6%), while 263 (66.2%) patients were deemed clinical responders in the vancomycin plus aztreonam group (P = 0.018). Since the day 3 clinical response was not a preplanned end point, only a portion of the population could be included in the E-MITT analysis.

A phase 2 study was performed prior to the CANVAS 1 and CANVAS 2 trials. It was a randomized, observer blinded study conducted at 15 clinical sites in the United States, Russia, South America, and South Africa. The phase 2 and 3 study protocols were roughly similar, with a few changes. The same inclusion criteria were present for the CANVAS trials, but instead of lumping all signs of infection together, the phase 2 study broke inclusion criteria into 2 local signs of cSSSI plus 1 systemic sign (oral temperature $>$ 38 °C, WBC $>$ 10,000 cells/mm^3, or $>$10% immature neutrophils). Subjects were randomized (2:1) to receive ceftaroline 600 mg IV every 12 hours or vancomycin 1 g IV every 12 hours. Aztreonam 1 g IV every 8 hours (different dose than phase 3) was allowed in addition to vancomycin in the standard therapy group if a gram-negative pathogen was suspected. The standard therapy group was allowed to be switched to a penicillinase-resistant penicillin after 72 hours if a gram-positive pathogen was isolated and susceptible. Test of cure visit was performed at 8 to 14 days after last dose of study drug.[15]

The MITT population (67 patients) was utilized for safety analysis. In the ceftaroline group, 88% of patients were cured. Eighty-one percent of patients were cured in the standard therapy group. Seven

Table 3. Clinical response at day 3 in the E-MITT population.

Drug	Responder		Nonresponder	
	Ceftaroline	Vancomycin plus aztreonam	Ceftaroline	Vancomycin plus aztreonam
Patients	296/400 (74.0%)	263/397 (66.2%)	104/400 (26.0%)	134/397 (33.8%)

Adapted from Freidland et al.[13]
Abbreviation: E-MITT, exploratory modified intent to treat.

patients received aztreonam in the standard therapy group. Five patients were bacteremic. In the ceftaroline group, one MSSA bacteremia and 1 MRSA bacteremia occurred. Both were cured. The standard therapy group had 3 bacteremias: 2 MSSA and 1 *Streptococcus agalactaie*. The latter was not cured.

Safety

In the phase 2 study, five serious adverse events were reported, 3 in the ceftaroline group (recurrent skin infection, gangrene, and pulmonary edema) and 2 in the standard therapy group (interstitial nephritis and reinfection). Death was not reported.[12] Safety was thoroughly analyzed in CANVAS 1 and CANVAS 2.

Over 1300 patients were included in the safety analysis, with the most common side effects in the ceftaroline group noted as nausea (5.9%), headache (5.2%), diarrhea (4.9%), and pruritus (3.5%). Severe treatment-emergent adverse events (TEAE) were reported in 3.8% of ceftaroline patients and 4.5% in the vancomycin plus aztreonam group.

A larger percentage of patients receiving vancomycin plus aztreonam discontinued the study drug 4.2% versus 3.0% in the ceftaroline group. Ceftaroline caused less hepatic TEAEs (2.7% versus 4.2%) than in the vancomycin plus aztreonam group. All renal TEAEs were higher in the ceftaroline group at 1.3% versus 0.7%. No patients in the ceftaroline group developed QT prolongation, although it is unclear what the frequency of electrocardiographic testing was. Positive direct Coombs' tests were more common in the ceftaroline group at 11.6% of patients. No patients in either group developed hemolytic anemia. A seizure disorder was reported in 1 ceftaroline patient. Overall, ceftaroline appears to be safe and well-tolerated, akin to other cephalosporins.[16]

Place in Therapy

Ceftaroline has been demonstrated to be a safe and effective antibacterial for cSSSI caused by MRSA, *S. pneumoniae*, other *Streptococcus* species, and some enteric gram-negative organisms. Ceftaroline does not treat infections secondary to *Pseudomonas aeruginosa,* anaerobic bacteria, or multidrug resistant organisms, such as vancomcyin-resistant *enterococcus*, extended spectrum beta-lactamase producing bacteria or carbapenemase producing organisms. The data show a decreased effectiveness against *Proteus mirabilis* and *Enterococcus fecaelis*. Unfortunately, when choosing an empiric antibiotic, selective coverage of gram-negative organisms proves to be a disadvantage. The CANVAS 1 and CANVAS 2 studies show fewer efficacies when treating bacteremia, but those data are limited. The methodology of CANVAS 1 and CANVAS 2 also excluded patients with infections that required surgical intervention such as septic knee, osteomyelitis, or large abscess.

Ceftaroline's main advantage over standard cephalosporins is the additional coverage of MRSA and penicillinase-resistant *S. pneumoniae*. The twice daily dosing schedule transitions conveniently to the outpatient setting. Dosing adjustments are easily calculated based on CrCl, and serum levels do not need to be followed. Ceftaroline also operates under the pharmacodynamic principle of other beta-lactams (%T $>$ MIC). These types of pharmacodynamics have the potential to be manipulated when higher MICs are encountered by extending the dosing interval, preserving clinical efficacy in the ever-shrinking arsenal of antimicrobials.

Conclusion

Ceftaroline is a novel cephalosporin with MRSA and penicillinase-resistant *S. pneumoniae* coverage. It adequately serves a population of patients requiring IV therapy for undifferentiated cellulitis, with

the benefit of empirically treating MRSA.[5] Safety concerns are minimal. Ceftaroline was not proven to be as efficacious as vancomycin plus aztreonam for bacteremia in a limited number of patients. Cure rates were lower in patients with *Proteus mirabilis* and *Enterococcal* sp infections. The drug's advantage appears to be in treating gram-positive cSSSI at this time. Ceftaroline is a fantastic addition to the arsenal against the fight of MRSA but otherwise should be reserved for patients with cSSSIs not requiring surgical debridement unless culture and susceptibility results are known. Further studies are needed to investigate utility in other clinical syndromes such as bacteremia and infections requiring surgical debridement.

Author Contributions

Conceived and designed the experiments: NA. Analysed the data: NA. Wrote the first draft of the manuscript: CL. Contributed to the writing of the manuscript: CL, SIM. Agree with manuscript results and conclusions: CL, SIM. Jointly developed the structure and arguments for the paper: CL, SIM. Made critical revisions and approved final version: SIM. All authors reviewed and approved of the final manuscript.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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