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Ceftaroline: An Alternative Broad Spectrum Antibiotic for Pediatric Infections

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Ceftaroline was approved by the Food and Drug Administration (FDA) on November 1, 2010 for adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) caused by susceptible bacteria. On May 31, 2016, the FDA extended the approval to include children 2 months of age and older.[1,2] Ceftaroline offers the advantage of a broad spectrum of activity, with efficacy against SSSI caused by methicillin-resistant *Staph. aureus* (MRSA) and other difficult to treat infections, in addition to a relatively mild adverse effect profile. A number of recent papers describe the studies that were done to support the FDA indication for use in infants, children, and adolescents. These papers, as well as new reviews of the drug and case reports of its adverse effect profile, add to our understanding of the role for this agent in the treatment of pediatric infections.

Mechanism of Action and Spectrum of Activity

Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil.[1-3] The prodrug is converted to active ceftaroline by plasma phosphate enzymes. As with other cephalosporins, the antibacterial activity of ceftaroline is the result of binding to essential penicillin-binding proteins (PBPs) to inhibit bacterial cell wall synthesis. Ceftaroline exhibits enhanced activity for mutated PBPs, including the mecA gene-encoded mutant PBP2a seen in MRSA, PBP2x associated with multi-drug resistant *Strep. pneumoniae*, PBP1A, and PBP2b. The resulting efficacy of ceftaroline, particularly in treating MRSA and beta-lactam resistant *Strep. pneumoniae*, has led some authors to refer to it as the first "5th generation" cephalosporin.[1]

Ceftaroline is indicated for the treatment of ABSSI cause by methicillin-sensitive and methicillin-resistant strains of *Staph. aureus*, *Strep. pyogenes*, *Strep. agalactiae*, *E. coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. It is approved for CABP caused by *Strep. pneumoniae*, methicillin-sensitive *Staph. aureus*, *E. coli*, *Haemophilus influenzae*, *Klebsiella pneumonia*, and *Klebsiella oxytoca*. Criteria for interpreting susceptibility based on minimum inhibitory concentrations and disk diffusion zone diameters is available in the manufacturer's prescribing information.[3,4]

In vitro testing suggests that ceftaroline may also be effective against *Strep. dysgalactiae*, *Citrobacter koseri*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Proteus mirabilis*, and *Haemophilus parainfluenzae;* however, there are not adequate clinical studies to support their use in these infections at this time. Ceftaroline is not active against Gram negative bacteria that produce extended spectrum beta-lactamases (ESBLs).[3,4]

The development of ceftaroline-resistant MRSA isolates has been documented in several case reports in adults. In 2016, Cannavino and colleagues reported a case of ceftaroline-resistant MRSA in a 4-year-old girl with cystic fibrosis (CF) after 22 ceftaroline courses over a period of 30 months.[5] The authors hypothesize that subinhibitory concentrations of the drug in the thick mucus of the airways in patients with CF may have supported the development of genetic mutations leading to resistance.

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Pharmacokinetics

Following IV administration of ceftaroline fosamil, peak concentrations of active ceftaroline

occur within approximately 5 minutes.[3] The mean maximum concentrations (C_{max}) in adults given a 600 mg dose are approximately 32.5 ± 4.82 mcg/mL after a 5 minute infusion and 17.4 ± 3.87 mcg/mL after a 60 minute infusion. Ceftaroline exhibits little binding to serum proteins (20%) and has a steady state volume of distribution in adults of 20.3 L (range 18.3-21.6 L). It undergoes hydrolysis to an inactive metabolite, with both the remaining unchanged ceftaroline and the M-1 metabolite eliminated by glomerular filtration. The average rate of ceftaroline clearance in adults is 5.56 ± 0.20 L/hr. Clearance is prolonged in patients with moderate to severe renal impairment. Hepatic impairment does not appear to have an effect on its clearance.

The pharmacokinetic profile of ceftaroline was evaluated in five pediatric studies. Two were single dose studies; the first was conducted in seven adolescents with normal renal function who received a single 8 mg/kg IV dose. While the volume of distribution and clearance were similar to adult values, the C_{max} in the adolescents was 10% lower than adult values and the area under the concentration-time curve (AUC) was 23% lower. A second pharmacokinetic study in children from 28 days to 12 years of age was conducted to guide dosing recommendations for younger children. Three additional studies were performed in conjunction with prospective, randomized, comparator-controlled clinical trials. Serum samples from more than 300 children taking part in these studies were used in a population pharmacokinetic analysis using nonlinear mixed-effects modeling.[6] The results of this pharmacokinetic model confirm the appropriateness of the current dosing recommendations for ceftaroline in the pediatric population.

Clinical Experience in Pediatrics

The manufacturer submitted a series of clinical studies showing the safety and efficacy of ceftaroline in pediatric patients to gain approval for use in children from the FDA and the European Medicines Agency. Cannavino and colleagues enrolled 161 children with CABP in a multicenter, randomized comparator-controlled trial.[7] Patients in the 34 study centers were randomized in a 3:1 ratio to receive ceftaroline or ceftriaxone for a minimum of 72 hours or 3 study days, at which point the patients could be switched to oral amoxicillin/clavulanate, and a maximum of 14 days. Patients were stratified by age into four cohorts: 2 to 23 months, 2 years to < 6 years, 6 to < 12 years, and 12 to < 18 years. Patients younger than 6 months of age received a dose of 8 mg/kg every 8 hours, while older patients weighing 33 kg or less received 12 mg/kg and those weighing more than 33 kg received 400 mg every 8 hours. All doses were infused over 60 minutes. Patients in the ceftriaxone group received a dose of 75 mg/kg/day (maximum 4 g/day) divided and given every 12 hours using a 30-minute infusion.

In the modified intent-to-treat population of 143 children, clinical cure rates at test of cure were 87.9% for ceftaroline and 88.9% for ceftriaxone, with a treatment difference of -1.0 (95% CI -11.5, 14.1). While the study supported the efficacy of ceftaroline in this cohort of children, it was not powered to identify a statistically significant difference from standard treatment. Rates of adverse effects were similar, with 10% of the ceftaroline group and 8% of the ceftriaxone group experiencing a drug-related adverse effect. Serious adverse effects were infrequent, occurring in six patients in the ceftaroline group (5%) and 1 patient in the ceftriaxone group (3%). The most frequently reported adverse effect was diarrhea. In the 112 patients with a negative Direct Coombs' test at baseline, 19 (17%) of patients in the ceftaroline group and 1 of the 37 patients in the ceftriaxone group seroconverted during treatment. There were no cases of hemolytic anemia.

The pediatric CABP indication was further supported by the study conducted by Blumer and colleagues in 40 children between 2 and 17 years of age.[8] This randomized parallel-group study compared ceftaroline to the combination of ceftriaxone and vancomycin in the treatment of complicated CABP infections. The median duration of treatment prior to switching to a more narrow-spectrum antibiotic was 9 days (range 2 to 19 days) in the ceftaroline group and 7.5 days (5-13 days) in the ceftriaxone/vancomycin group. Clinical response rates in the modified intent-to-treat population were 82.8% and 77.8% in the two groups, respectively, with a treatment difference of 5% (95% CI -19.9, 40.3). Drug-related adverse effects were reported in seven ceftaroline patients and four patients in the comparator group. Two patients in the ceftaroline group discontinued treatment; one for elevated serum transaminases and one for a rash and pruritus. Direct Coombs' test seroconversion was reported in 6/23 (26%) ceftaroline patients. As in the previous study, there were no reports of hemolytic anemia.

The efficacy and safety of ceftaroline in pediatric ABSSSI was established in a study by Korczowski and colleagues.[9] One hundred sixty-

three children between 2 and 17 years of age were randomized to receive either vancomycin or cefazolin (with or without aztreonam) for a period of 5 to 14 days. Efficacy was assessed in the 159 patients in the modified intent-to-treat population. As in the CABP studies, clinical cure rates at the test of cure visit (8-15 days after the end of treatment) were similar between the groups: 94.4% in the ceftaroline group and 86.5% in the combined comparator group, with a treatment difference of 7.9 (95% CI -1.2, 20.2). There were no clinical failures reported in the ceftaroline group and only one case in the comparator group. The only serious drug-related adverse effect reported was hypersensitivity in a patient in the ceftaroline group. Direct Coombs' test seroconversion was documented in 17 of the 99 (17%) previously negative patients. There were no cases of hemolytic anemia reported.

Warnings and Precautions

Ceftaroline is contraindicated in patients with a known sensitivity to it or other cephalosporins. Hypersensitivity reactions, including anaphylaxis, are possible following ceftaroline use. A history of allergic reactions to any beta-lactam antibiotics, including penicillins, cephalosporins, and carbepenems, should be obtained from the patient or family and the risk for cross sensitivity should be considered prior to initiating treatment with ceftaroline.[3]

As with other antibiotics, use of ceftaroline may place the patient at risk for *Clostridium difficile*-associated diarrhea. Ceftaroline may also produce seroconversion to a positive direct Coombs' test. This has been reported in 11% to 17% of children and adults receiving the drug during phase 3 trials. Any patient developing anemia while receiving ceftaroline should be evaluated for a potential drug-induced hemolytic anemia, and treatment should be discontinued.[1-3]

Adverse Effects

The safety profile of ceftaroline in children was evaluated in three clinical trials. These trials, one in ABSSSI and two CABP infections, enrolled a total of 257 children from 2 months to 18 years of age in the ceftaroline group and 102 children in the comparator groups. Significant drug-related adverse effects were documented in 10 patients (4%) receiving ceftaroline and 3 (3%) in the comparator groups. Discontinuation of therapy occurred in 3.9% and 2% of patients in the two groups, respectively. The most commonly reported adverse effects with ceftaroline in this pooled analysis were diarrhea (in 8% of patients), rash (7%), vomiting (5%), nausea (3%), and fever (3%). The most common reason for discontinuation in patients given ceftaroline was rash.[3]

While not a common adverse effect, beta-lactam antibiotics can produce myelosuppression. Clinicians should be aware of the risk for leukopenia and agranulocytosis with ceftaroline.[10,11] Several cases have been reported in the literature since the drug's approval. In 2015, Varada and colleagues published a retrospective medication safety review of ceftaroline in two hospitals.[10] A total of 29 patients from the Washington site and 587 patients at the San Diego site were treated during the evaluation period. At the Washington site, five patients developed a rash and two patients developed agranulocytosis. At the San Diego site, most patients received ceftaroline for less than 48 hours before being transitioned to more narrow-spectrum antibiotics. Of the 37 patients who were given a full treatment course, two developed agranulocytosis. All four patients with agranulocytosis, defined as an absolute neutrophil count (ANC) of zero, responded to discontinuation of the drug and treatment with granulocyte colony-stimulating factor (G-CSF). Treatment with G-CSF ranged from 2 to 8 days, with resolution in all cases. The authors proposed that the risk of ceftaroline-induced agranulocytosis was greater in patients receiving every 8 hour dosing rather than every 12 hours, and in those treated for more than 14 days.

A case of ceftaroline-induced agranulocytosis in a 14-year-old was recently reported by Shirley and Froh at the University of Virginia.[11] The patient presented with a decline in lung function associated with a cystic fibrosis-related pulmonary exacerbation. Her sputum culture grew methicillin-resistant *Staph. aureus* and *Stenotrophomonas maltophilia*. After failing to respond clinically to high-dose trimethoprim-sulfamethoxazole and minocycline, treatment was changed to ceftaroline 400 mg (8.5 mg/kg) every 8 hours. White blood cell count and ANC were normal at that time. On the 8th day of treatment, she developed a transient rash and fever. Ceftaroline was discontinued on day 10 when her ANC had declined from 4,350 cell/μL to 990 cell/μL. By day 12, her ANC was zero. After two days of G-CSF, her ANC rapidly returned to normal and she defervesced. Based on their experience, the authors recommend regular monitoring of cell counts and differentials in all pediatric patients receiving ceftaroline until more is known about this adverse effect.

Drug Interactions

There have been no drug interactions identified with ceftaroline at this time. It does not serve as a substrate, inhibitor, or inducer of cytochrome P450 enzymes and has no effect on the QTc interval.[3]

Availability and Cost

Ceftaroline fosamil injection (Teflaro®) is available in 400 mg and 600 mg single-dose 20 mL vials. The powder must be reconstituted and further diluted prior to administration. The average wholesale price per vial is $192.28, regardless of vial size.[3,12]

Dosing Recommendations

The recommended dose of ceftaroline in adults is 600 mg given IV every 12 hours, with duration of 5-14 days for ABSSSI or 5-7 days for CABP. Dosing for pediatric patients is the same for both ABSSSI and CABP. Patients 2 months up to 2 years of age should receive 8 mg/kg every 8 hours, while those 2-18 years of age who weigh 33 kg or less should receive a dose of 12 mg/kg every 8 hours. Children weighing more than 33 kg should receive either 400 mg every 8 hours or the adult dose of 600 mg every 12 hours. The recommended duration of treatment for both ABSSKI and CABP is 5-14 days.[3]

No dosing adjustment is needed in children and adults with mild renal impairment (a creatinine clearance > 50 mL/min/1.73m^2 or 50 mL/min). In adults with moderate renal impairment (creatinine clearance 30-50 mL/min), the dose of ceftaroline should be reduced to 400 mg every 12 hours. In patients with severe impairment (creatinine clearance 15-30 mL/min), a dose of 300 mg every 12 hours is recommended. Patients with end-stage renal disease should receive 200 mg ceftaroline every 12 hours. There are no dosing recommendations available for pediatric patients with moderate to severe renal impairment.[3]

Ceftaroline may be infused over 5 to 60 minutes. It may be diluted to a concentration of 4 to 12 mg/mL with normal saline, 5% dextrose, 0.45% sodium chloride, or lactated Ringer's solution. The diluted solution is stable for up to 6 hours at room temperature or 24 hours when refrigerated.[3]

Summary

Several pre-approval and post-marketing studies have been published in the past 3 years demonstrating the safety and efficacy of ceftaroline in infants, children, and adolescents. These studies are useful in defining the role of this broad spectrum antibiotic in treating bacterial pneumonia and skin and skin structure infections, but additional studies are needed to evaluate its use in other infections, such as osteomyelitis. Continued monitoring will also be necessary to identify developing resistance patterns. At this time, ceftaroline is best reserved for infections that have proven refractory to standard therapies.

References

1. Yim J, Molloy LM, Newland JG. Use of ceftaroline fosamil in children: review of current knowledge and its application. Infect Dis Ther 2017;6:57-67.
2. Corey A, So TY. Current clinical trials on the use of ceftaroline in the pediatric population. Clin Drug Investig 2016; DOI: 10.1007/s40261-017-0523-2.
3. Teflaro prescribing information. Forest Pharmaceuticals, Inc, Allergan. May 2016. Available at: https://www.allergan.com/assets/pdf/teflaro_pi (accessed 5/13/2017).
4. Pfaller MA, Mendes RE, Castanheira M, et al. Ceftaroline activity tested against bacterial isolates causing community-acquired respiratory tract infections and skin and skin structure infections in pediatric patients from United States hospitals: 2012-2014. Pediatr Infect Dis J 2017;36:486-91.
5. Cannavino CR, Mendes RE, Sader HS, et al. Evolution of ceftaroline-resistant MRSA in a child with cystic fibrosis following repeated antibiotic exposure. Pediatr Infect Dis J 2016;35(7):813-5.
6. Riccobene TA, Khariton T, Knebel W, et al. Population PK modeling and target attainment simulations to support dosing of ceftaroline fosamil in pediatric patients with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. J Clin Pharmacol 2017;57(3):345-55.
7. Cannavino CR, Nemeth A, Korczowski B, et al. A randomized, prospective study of pediatric patients with community-acquired pneumonia treated with ceftaroline versus ceftriaxone. Pediatr Infect Dis J 2016;35(7):752-9.
8. Blumer JL, Ghonghadze T, Cannavino C, et al. A multicenter, randomized, observer-blinded, active-controlled study evaluating the safety and effectiveness of ceftaroline compared with ceftriaxone plus vancomycin in pediatric patients with complicated community-acquired bacterial pneumonia. Pediatr Infect Dis J 2016;35(7):760-6.
9. Korczowski B, Antadze T, Giorgobiani M, et al. A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety and efficacy of ceftaroline versus comparator in pediatric patients with acute bacterial skin and skin structure infection. Pediatr Infect Dis J 2016;35(8):e239-e247.
10. Varada NL, Sakoulas G, Lei LR, et al. Agranulocytosis with ceftaroline high-dose monotherapy or combination therapy with clindamycin. Pharmacotherapy 2015;35(6):608-612.
11. Shirley DT, Froh DK. Agranulocytosis in a pediatric patient treated with ceftaroline. J Pediatr Infect Dis Society 2016;5(2):e5-e8.
12. Micromedex 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (accessed 5/15/2017).

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