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Review Article

Ceftaroline: A novel broad spectrum cephalosporin with activity against methicillin resistant Staphylococcus aureus

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Abstract

Ceftaroline is a novel fifth-generation cephalosporin, which exhibits broad-spectrum activity against Gram-positive bacteria, including MRSA and extensively-resistant strains, such as vancomycin-intermediate S. Aureus(VISA), heteroresistant VISA (hVISA), and vancomycin resistant S. Aureus (VRSA). Ceftaroline has a favorable tolerability profile and broad in vitro activity against resistant Gram-positive and common Gram-negative organisms. It received approval from the United States (US) Food Drug Administration (FDA) and European Commission for the treatment of adult patients with community acquired pneumonia (CAP) and complicated skin and soft tissue infections. Ceftaroline has the ability to bind to penicillin-binding protein (PBP)2a, an MRSA-specific PBP that has low affinity for most other beta-lactam antibacterials. Ceftaroline has a volume of distribution of 0.37L/kg (28.3L), low protein binding (<20%) and a serum half-life of 2.6 hours. No drug accumulation occurs with multiple doses and elimination occurs primarily through renal excretion (49.6%).

Key Words: ceftaroline, cephalosporin, antibiotic, methicillin resistant Staphylococcus aureus

INTRODUCTION

Ceftaroline is a fifth generation cephalosporin, with broad spectrum of activity against gram positive and gram-negative bacteria, including contemporary gram-positive phenotypes, such as methicillin-resistant Staphylococcus aureus (MRSA), multidrug resistant Streptococcus pneumoniae and penicillin resistant S. Pneumoniae. Microbial pathogens have an extraordinary capacity to develop resistance to antimicrobial agents. Within the last two decades, resistance has escalated, occasionally at seemingly exponential rates, threatening to outpace the ability to counter with more potent antimicrobial agents, methicillin-resistant Staphylococcus aureus (MRSA), first isolated in the 1960s, became a prominent nosocomial pathogen over the past three decades. The advent of community-associated MRSA (CA-MRSA), which arose novo outside the healthcare environment, has dramatically heightened the importance of MRSA. Today, MRSA is the leading cause of community-acquired skin and soft tissue infections (SSTI) and a cause of necrotizing pneumonia. The dramatic escalation in MRSA, which is now globally ubiquitous, coupled to intrinsic resistance to many of the existing antimicrobial agents, renders this an enormous public health issue. MRSA has also recently exhibited an inexorable creep in minimum inhibitory concentrations (MIC) to the standard intravenous antibiotic (vancomycin) utilized in its management. In addition, S. aureus strains with vancomycin-intermediate resistance (VISA), heteroresistance (hVISA), and vancomycin resistance (VRSA) have been described. These resistant strains are associated with increased morbidity and mortality above that of methicillin-sensitive Staphylococcus aureus (MSSA), and often require surgical intervention coupled to a sparse selection of suitable antimicrobial therapy. Resistance has become an increasing problem across the country and globe. This rampant spread of resistance has led to institutions implementing antibiotic stewardship programs in hopes of preserving the usefulness of available antimicrobials. Even with these efforts, the need for new agents is clear as vancomycin-resistant S.aureus infections and other pan-resistant infections have been found in the United States. In October 2010, the FDA approved ceftaroline, a “fifth generation” cephalosporin that is the first beta-lactam approved with activity against MRSA. Ceftaroline has FDA approved indications for treating acute bacterial sinus and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Ceftaroline is a novel fifth-generation parenteraloximino...
cephalosporin with bactericidal activity against MRSA. In contrast to most of the aforementioned MRSA antimicrobials, ceftaroline exhibits broad-spectrum activity against many of the important community-acquired Gram-positive and Gram-negative pathogens. Importantly, it has activity against MDR Gram-positive bacteria, including MRSA, VISA, hVISA and VRSA. It also has efficacy against respiratory bacterial pathogens such as *Streptococcus pneumoniae* (including multidrug-resistant strains), *Haemophilus influenza*, and *Moraxella catarrhalis*. Mirroring other broad-spectrum cephalosporins, ceftaroline does not possess activity against extensively-resistant Gram-negative bacteria and exhibits limited activity against most non-fermentative Gram-negative bacilli (e.g. *Pseudomonas aeruginosa*, *Acinetobacter spp.*) and many anaerobic species.  

**Ceftaroline: Mode of action**  
The antibacterial activity of ceftaroline is similar to that of other beta-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). For the *Enterobacteriaceae*, the primary target is membrane PBPs, leading to transpeptidase and transglycosidase reactions in cell wall formation.  

**Dosing and Uses**  
- Community-Acquired Bacterial Pneumonia: 600mg IV q12h; infuse over 1 h for 5-7 days.  
- Acute bacterial skin and skin structure infections, including MRSA: 600 mg IV q12h; infuse over 1 h for 5-14 days.  

Renal impairment:  
- CrCl 31-50 mL/min: 400 mg IV q12h  
- CrCl 15-30 mL/min: 300 mg IV q12h  
- ESRD (including hemodialysis): 200mg IV q12h  

**Pharmacokinetics**  
Following parenteral administration, ceftarolinefosamil (prodrug) is rapidly converted by blood stream phosphatase enzymes to ceftaroline. At the end of a 1-hour intravenous infusion 600mg 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. This cephalosporin exhibits linear pharmacokinetics and has a serum half-life of 1.6 h (for a single dose) to 2.7 h (following multiple doses). Ceftaroline has a volume of distribution ($V_d$) of 20L which is similar to that of other parenteral cephalosporins. Plasma protein binding is ~20%. Ceftaroline undergoes some metabolism via hydrolysis of its beta-lactam ring to form an inactive, open-ring metabolite (ceftaroline M-1). The CYP450 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. Ceftaroline and accompanying metabolites are primarily eliminated by the kidneys. Following a single 600mg 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.  

**Anti-microbial activity**  
Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA), staphylococcus epidermidis, and other coagulase negative *staphylococci*, including *staphylococcus lugdunensis*, *staphylococcus hominis*, and *staphylococcus hemolyticus*. Ceftaroline is active against MRSA strains, including panto 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. In vitro studies have also demonstrated high potency of ceftaroline against beta haemolytic streptococci and *S. pneumoniae* strains that are resistant to available parenteral cephalosporins, including ceftriaxone and cefotaxime. Ceftaroline had a minimum inhibitory concentration (MIC) of 0.5g/mL against 120 cefotaxime-resistant (MIC>4g/Ml) *S. pneumoniae* strains and laboratory –cloned R6 strains with penicillin-binding protein mutations. 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. Although the in vitro activity suggests that ceftaroline might be effective against vancomycin –resistant *Enterococcus faecalis*, 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*. It is not active against beta lactamase producing, AMP C-depressed *Enterobacteriaceae* or most nonfermentative gram-negative bacilli, including *Pseudomonas aeruginosa*. Ceftaroline possesses anti-anaerobic activity similar to that of amoxicillin-clavulananateganistgram-positive anaerobes and 4 to 8 fold greater activity than that of ceftriaxone. Ceftaroline does not have good activity against members of the Bacteroidesfragilis group, but it is active against beta-lactamase negative strains, including *Actinomyceces* species, *Propronibacterium, Eubacterium, Clostridiumperfringens*, *Clostridium ramosum*and *Clostridium innoculum*.  

**Ceftarolinefosamil clinical trial studies and clinical safety**  
The efficacy and safety of ceftarolinefosamil (prodrug) was assessed in 2 large phase 3 programs of randomized, double-blind, clinical trials for CABP and ABSSSIs. For both indications, therapy with ceftarolinefosamil was observed to be noninferior to the comparator agents (ceftiraxone 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 (CAVAS 1 and 2), microbiologically evaluable success rates were similar between treatment groups. Notably, the clinical cure rates in microbiologically evaluable 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%). Ceftarolinefosamil was well tolerated; with a safety profile similar to the comparator agents used in these phase 3 trials.

CONCLUSION
The increased incidence of resistant bacterial infections necessitates novel antibacterial agents for their clinical management. Ceftaroline is such an emerging agent which showed its usefulness in the empirical treatment of patients with a variety of presentations of cSSSIs, including those caused by MRSA and CAP. Ceftarolinemonotherapy was generally safe, well tolerated, and had a favourable pharmacokinetic profile without any reported drug interaction. Its usefulness against vancomycin resistant *Staphylococcus aureus* has to be evaluated in clinical trials. It is only the passage of time and the cumulative experience with ceftaroline use that will fully elucidate the complete efficacy and safety profile of this agent.

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