Ceftaroline fosamil: A novel anti-Methicillin-resistant Staphylococcus aureus cephalosporin

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) pose tremendous challenges to the health care system and have emerged as major concern both in and out of the hospital environment. It can cause serious infections including skin and soft tissue infections, wound infections, bacteremia, pneumonia, and endocarditis. Patients at hospitals with open wounds, invasive devices, and weakened immune systems are at greater risk of infection with MRSA. Another concern has been the emergence of highly virulent community-associated MRSA which cause skin infections, sepsis, toxic shock syndrome, and necrotizing pneumonia.[1] The preferred drugs for the treatment of MRSA infections include vancomycin and linezolid.[2] However, there have been many reports of strains of MRSA that have developed resistance to vancomycin.[1] This is an important concern since the already limited treatment options for serious MRSA infections may become more limited due to the increase in resistance to vancomycin. Although linezolid is highly active against MRSA, it is bacteriostatic and may result in adverse effects like thrombocytopenia and myelosuppression.[3] Complicated skin and skin structure infections (cSSSI), which are common in diabetes mellitus and peripheral vascular diseases, may also require coverage for MRSA as well as Gram-negative pathogens. The current situation indicates a need for continued development of effective antibacterials to combat-resistant infections.

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Ceftaroline fosamil is a prodrug form of a new semi-synthetic broad spectrum cephalosporin with bactericidal activity against MRSA and multidrug-resistant *Streptococcus pneumonia* and some Gram-negative organisms. It has been placed in a separate and unnamed subclass of the parenteral cephem class by the Clinical and Laboratory Standards Institute.[4] The ability of ceftaroline to bind the penicillin-binding protein (PBP)2a, an MRSA-specific protein, makes it unique among cephalosporins.[4] The efficacy of ceftaroline fosamil in the treatment of experimental endocarditis, pneumonia, myositis, and osteomyelitis has been demonstrated in animal models, while efficacy in the treatment of complicated skin and soft tissue infections and community-acquired pneumonia has been demonstrated in humans.[5]

ANTIBACTERIAL SPECTRUM

Ceftaroline fosamil is a broad spectrum cephalosporin with activity against many clinically important resistant Gram-positive bacteria as well as Gram-negative bacteria. *In vitro* studies showed that ceftaroline is active against methicillin-susceptible and methicillin-resistant isolates of *S. aureus* (MIC_{90s} of 0.25 and 1 mg/L, respectively). In addition, ceftaroline also retains activity against isolates with reduced susceptibility to vancomycin or linezolid (MIC_{90}, 2 mg/L).[6] Ceftaroline exhibited potent activity against *Streptococcus pyogenes, Streptococcus agalactiae*, and *Streptococcus pneumonia*. Among Gram-negative strains, ceftaroline is active against ceftazidime-susceptible isolates of *E. coli* and *Klebsiella pneumonia* and β-lactamase-positive and negative isolates of *Haemophilus influenzae*. However, ceftaroline is inactive against extended-spectrum β-lactamase (ESBL)-producing or AmpC-overexpressing *Enterobacteriaceae* and

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has limited activity against non-fermenting Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[7]

MECHANISM OF ACTION

β-Lactams, including cephalosporins, inhibit bacterial cell-wall synthesis by mimicking the terminal acyl-D-Ala-D-Ala portion of the peptidoglycan peptide chain, resulting in acylation of a serine residue in the active site of the PBPs. MRSA isolates have acquired an additional PBP gene known as *mecA* that encodes PBP (referred to as PBP2' or PBP2a), which is not inhibited by most β-lactam antibacterials. This enzyme will function as a surrogate transpeptidase that enables the organism to maintain cell wall biosynthesis at β-lactam concentrations that inhibit β-lactam-sensitive PBPs, thus conferring resistance to most members of this antibacterial class.[4,6] Ceftaroline has the ability to bind to PBP2a, demonstrating superior affinity (median inhibitory concentration [IC50] = 0.90 mg/mL) as compared with cefozopran and other β-lactams. In addition to that, ceftaroline also inhibits the biochemical activity of PBP2a more efficiently than imipenems or nitrocefin. The high affinity of ceftaroline for *S. aureus* PBPs correlates well with its low minimum inhibitory concentration (MIC) for MRSA or meticillin-susceptible *S. aureus* (MSSA) strains.[4,8]

PHARMACOKINETICS

After intravenous infusion, ceftaroline fosamil which is a prodrug is rapidly converted by plasma phosphatases to its bioactive metabolite, ceftaroline. In healthy volunteers, administration of intravenous ceftaroline 300 or 600 mg did not produce any drug accumulation. Moreover, the bioavailability by an intramuscular route was found to be similar to intravenous dose, indicating its potential to provide an alternative to the intravenous route in outpatient settings.[7,9] The volume of distribution of ceftaroline is 28.3 L, representing distribution into the total body water compartment, with a little effect by bodyweight changes. Plasma protein binding of ceftaroline is low (<20%). After conversion of ceftaroline fosamil in the plasma to the active metabolite, ceftaroline, a small fraction is converted to an inactive metabolite, ceftaroline-M-1. The half-life of active ceftaroline is 2.6 h and that of ceftaroline-M-1 metabolite is 4.51 h in healthy volunteers. Ceftaroline and ceftaroline-M-1 are eliminated primarily through kidney. Approximately half the dose of ceftaroline is excreted in the urine as active drug, with a small amount excreted in the urine as ceftaroline-M-1. Dosage adjustment may be needed in patients with moderate but not mild renal impairment (dose reduced to 400 mg instead of 600 mg).[4]

CLINICAL TRIALS

Ceftaroline fosamil was studied for its efficacy and safety in comparison with other standard treatments in cSSSI and in community acquired pneumonia (CAP) in various clinical trials. Talbot *et al*.[10] performed a randomized, observer-blinded study to evaluate the safety and efficacy of ceftaroline versus standard therapy in treating cSSSI. Adult patients with cSSSI (n = 100) requiring intravenous therapy were randomized to receive intravenous ceftaroline, 600 mg every 12 h or intravenous vancomycin, 1 g every 12 h with or without adjunctive aztreonam (1 g every 8 h) for 7–14 days. At the end of the study, 61 patients were clinically evaluable for ceftaroline and 27 for standard therapy (total of 88 clinically evaluable), and 96.7% of patients were clinically cured with ceftaroline compared with 88.9% of those treated with standard therapy. In the microbiologically evaluable population, the microbiological success rate was 95.2% (40/42) for ceftaroline and 85.7% (18/21) for the standard therapy group. Of the five patients from each treatment group who were confirmed to have MRSA infections, four of five patients treated with ceftaroline and five of five patients treated with standard therapy achieved clinical cures. Ceftaroline exhibited a very favorable safety and tolerability profile, consistent with that of older cephalosporins.

CANVAS 1 and CANVAS 2, another two similar phase 3 randomized, double-blind, multicenter trials, also compared ceftaroline fosamil monotherapy with vancomycin plus aztreonam in cSSSI. CANVAS 1 trial reported that clinical cure rates were similar for ceftaroline fosamil and vancomycin plus aztreonam (91.1%, 288/316 versus 93.3%, 280/300) and for MRSA cSSSI was 95.1% (78/82) for ceftaroline fosamil and 95.2% (59/62) for vancomycin plus aztreonam. Clinical cure rates of 92.2%, 271/294 versus 92.1%, 269/292 was observed in the CANVAS 2 study. The microbiological success rate and adverse events were also similar for ceftaroline fosamil and vancomycin. Ceftaroline was concluded to be noninferior to the standard therapy of vancomycin plus aztreonam in treating patients with cSSSI caused by both Gram-positive and Gram-negative pathogens.[11,12]

File *et al*. evaluated ceftaroline for the treatment of CAP in two randomized, double-blind, multicenter trials, namely FOCUS 1 and FOCUS 2.[13] Patients hospitalized with Pneumonia Outcomes Research Team risk class III or IV CAP requiring intravenous therapy were randomized to 600 mg of ceftaroline every 12 h or 1 g of ceftriaxone every 24 h for 5–7 days. Patients in FOCUS 1 received two doses of oral clarithromycin (500 mg) every 12 h on day 1. In the integrated analysis, 614 patients received ceftaroline and 614 received ceftriaxone. Of the clinically evaluable patients treated with ceftaroline, 84.3% achieved clinical cure, compared with

77.7% of ceftriaxone-treated patients. Clinical cure rates in the modified intent-to-treat efficacy population were 82.6% versus 76.6% for ceftaroline and ceftriaxone. Clinical cure rates for the ceftaroline group were numerically higher than those for the ceftriaxone group with good tolerance and safety profile.

ADVERSE EFFECTS

The adverse effects produced by ceftaroline fosamil were generally mild in severity. They include nausea, headache, pruritus, and rash which infrequently require discontinuation of therapy. Occurrence of *Clostridium difficile*-induced diarrhea was rare with this novel cephalosporin.[4,10] Moreover, there was neither evidence of hepatic, renal, or cardiac toxicity nor any infection- or antimicrobial-related fatalities during the study period. Ceftaroline fosamil should not be used in patients with sensitivities to cephalosporin antibiotics. No clinically significant drug interactions were reported during clinical trials.[11,12]

CURRENT STATUS

The U.S. FDA has granted approval for ceftaroline fosamil (teflaro) on October 2010, to treat adults with community acquired bacterial pneumonia and acute bacterial skin and skin structure infections, including MRSA. The dose of ceftaroline fosamil recommended is 600 mg intravenously, every 12 h for patients with normal renal function or mild renal dysfunction. The drug formulation of ceftaroline fosamil available is in a powder form for intravenous administration as 400 mg and 600 mg vials.[14] This drug is not yet available in India.

CONCLUSIONS

The increased incidence of resistant bacterial infections necessitates novel antibacterial agents for their clinical management. Ceftaroline fosamil 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. Ceftaroline monotherapy was generally safe, well tolerated, and had a favorable 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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