Ceftaroline Fosamil: An update

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INTRODUCTION

Microbial pathogens have an extraordinary capacity to develop resistance to antimicrobial agents.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prominent nosocomial pathogen causing community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (SSTIs). Cephalosporins are a class of Beta-lactam antibiotics with a broad spectrum of activity, proven efficacy and favourable safety profile, making it one of the most commonly prescribed classes of antimicrobials.[2] However, all the four generations are inactive against MRSA. Ceftaroline Fosamil, a fifth-generation Cephalosporin,[3] was synthesised by Takeda Pharmaceutical Co., Ltd and developed by Cerexa, Inc. and Forest Laboratories, Inc.,[2,4] and it gained the FDA approval in 2010. The Clinical and Laboratory Standards Institute, however, has considered it under a new subclass 'Cephalosporins with anti-methicillin-resistant *Staphylococcus aureus* activity'.[2,5] The 1, 3 thiazole ring attached to three-position of Cephalosporin nucleus and Oxime group in C7 Acyl moiety confers enhanced activity against MRSA.[2]

MECHANISM OF ACTION

The bactericidal action is mediated by binding to all forms of penicillin-binding proteins (PBPs; PBP2a and PBP2b, 2×, 1a), causing bacterial cell wall irregularities and eventually bacterial cell death. Activity on PBP2a and PBP2× confers increased activity against *S. aureus* and *Streptococcus pneumoniae*, respectively.[6]

ANTIBACTERIAL SPECTRUM

It is effective against resistant Gram-positive bacteria (e.g., *S. aureus* including MRSA, Methicillin-susceptible *S. aureus*, Vancomycin-resistant *S. aureus*, Vancomycin-intermediate *S. aureus*, coagulase-negative *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *S. pneumoniae*, *Streptococcus viridans, Streptococcus pyogenes*), Gram-negative bacteria (e.g., *Moraxella catarrhalis, Haemophilus influenza, Pasteurella multocida*) and a few anaerobes (Propionibacterium spp., *Peptostreptococcus* spp., non-difficile *Clostridium* spp., etc.). However, it is inactive against *Enterococcus faecium*, extended-spectrum β-lactamase and carbapenemase-producing strains, strains with stable de-repressed AmpC β-lactamase production, *Pseudomonas* spp. and most β-lactamase-producing Gram-negative anaerobes, including *Bacteroides fragilis* and *Prevotella* spp.[1,2,6]

PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE

It is a water-soluble prodrug, rapidly dephosphorylated to the active form, Ceftaroline, in plasma. Less than 20% of the drug is plasma protein bound. Elimination half-life is about 2.7 h, the maximum observed concentration is 21 μg/mL and the area under the concentration–time curve is 56 μg h/mL, with no appreciable accumulation. It is excreted through kidneys and dosage adjustment is recommended for patients with creatinine clearance ≤50 mL/min. Not metabolised by cytochrome P450 enzymes, so less propensity for drug–drug interactions. It exhibits time-dependent killing. The amount of time the serum concentration remains above the minimum inhibitory concentration represents the main pharmacodynamic predictor of efficacy.[6]

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PREPARATIONS, DOSAGE AND USES

It is available as 400 and 600 mg single-use vials of sterile powder. The reconstituted solution should be used within 6 h if stored at room temperature or within 24 h if refrigerated.[2] It is used in community-acquired bacterial pneumonia (600 mg intravenous [IV] over 1 h every 12 h for 5–7 days) and acute bacterial skin and skin structure infections including those caused by MRSA (600 mg IV over 1 h every 12 h for 5–14 days).[6]

ADVERSE EFFECTS

Diarrhoea, nausea, headache, rash and pruritus are the adverse effects. Data are incomplete regarding use in children and are considered as a category B drug in pregnancy.[1,2]

CLINICAL TRIALS

CANVAS I and II trials (randomised, double-blind, multinational Phase III trials) evaluated the efficacy of Ceftaroline for the treatment of SSTIs among 1378 subjects comparing Ceftaroline to Vancomycin ± Aztreonam in 2007. It was found that for treating SSTI, Ceftaroline (600 mg IV every 12 h) was non-inferior to Vancomycin (1 g IV every 12 h) plus Aztreonam (1 g IV every 8 h) administered for 5–14 days. In FOCUS I and II trials (randomised, double-blind, multicentric Phase III trials), 1228 hospitalised adults with moderate to severe CAP were randomised to Ceftaroline (600 mg IV every 12 h) or Ceftriaxone (1 g IV daily) for 5–7 days. The overall clinical and microbiological response rates were similar, demonstrating Ceftaroline to be efficacious, well tolerated and comparable in efficacy and adverse effects to Ceftriaxone in the treatment of CAP.[1]

CONCLUSION

Ceftaroline Fosamil, a new, broad spectrum Cephalosporin, is a promising approach towards combating MRSA-mediated infections and has been approved for use in CAP and complicated SSTIs.

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Conflicts of interest
There are no conflicts of interest.

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