

Ceftaroline fosamil - A new arrow in quiver against MRSA

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ABSTRACT

Staphylococcus aureus, a known pathogen for nosocomial infections, has developed resistance towards methicillin and related drugs. There are very few options available like Vancomycin, Linezolid, Daptomycin etc., for the treatment of MRSA infections which are associated toxicity and high costs. However, none of the beta-lactam antibiotic were effective against MRSA. Once methicillin resistance is developed by the bacteria, it is considered as resistant to many other Beta lactams including Cephems and Beta lactamase inhibitor combinations. Recent introduction of 'Ceftaroline fosamil' (Prodrug of active metabolite, Ceftaroline), a new broad spectrum cephalosporin often described as a 'Fifth Generation' cephalosporin, has created a considerable amount of expectation as an alternative for infections due to MRSA. Ceftaroline is used for the treatment of community-acquired pneumonia and acute skin and skin structure infection caused by susceptible organisms in adults >18 years of age. The safety of ceftaroline in paediatric population is not yet established. It is primarily eliminated by kidney and requires dose reduction in patients with renal impairment. It is approved by DCGI May 2016 for marketing in India.

Key words : Ceftaroline, 'Fifth Generation' cephalosporin, MRSA, Community-acquired pneumonia, acute skin and skin structure infection

Introduction :

Emergence of resistance to multiple antibiotics was a real paradox after the successful introduction of vast array of effective antimicrobial agents in early 1970s. As a consequence, understanding for the molecular mechanisms of antimicrobial resistance increased dramatically resulting in identification of novel drug targets.

Multidrug resistance is now the norm among the notable Gram positive bacteria like *Pneumococci*, *Enterococci* and *Staphylococci*. *S. aureus* is perhaps the pathogen of greatest concern because of its intrinsic virulence, its ability to cause a diverse array of life-threatening infections, and its capacity to adapt to different environmental conditions. As of now, *S. aureus* is the leading overall cause of nosocomial infections and, as more patients are treated outside the hospital setting, is an increasing concern in the community as well.

Penicillin, once an effective antimicrobial against *Staphylococcus aureus* has no place in the treatment of Staphylococcal infections in today's era. This is because of increased encounters with penicillinase producing strains of *S. aureus* in more than 90% of cases regardless of the clinical setting. This brought penicillinase stable penicillins like Methicillin, Oxacillin, Cloxacillin, Nafcillin into picture. However, as rapidly as new antibiotics were introduced, *Staphylococci* have developed efficient mechanisms to neutralize them¹.

S. aureus developed resistance towards methicillin and related drugs by virtue of *mecA* gene that encodes for altered penicillin binding protein 2a (PBP 2a OR PBP2'). Since PBPs are the main sites of action for beta lactam antibiotics, alteration at this target level does not allow binding of methicillin rendering the drug ineffective. Once methicillin resistance is developed by the bacteria, it is considered as resistant to many other Beta lactams including Cephems and Beta lactamase inhibitor combinations. This is because most cases of documented MRSA infections have responded poorly to Beta lactam therapy, or because convincing clinical data that document clinical efficacy for those agents have not been presented. Moreover, there are very few options available like Vancomycin, Linezolid, Daptomycin etc., for the

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treatment of MRSA infections which are associated with toxicity and high costs. The therapeutic outcome of infections that result from methicillin-resistant *S. aureus* (MRSA) is worse than the outcome of those that result from methicillin-sensitive strains. Hence, for clinicians, treating and preventing spread of these methicillin-resistant strains remains as an ongoing challenge.

Recent introduction of 'Ceftaroline fosamil' (Prodrug of active metabolite, Ceftaroline) a new broad spectrum cephalosporin often described as a 'Fifth Generation' cephalosporin, a prodrug of active metabolite, Ceftaroline, has engendered a considerable amount of expectation as an alternative to treat MRSA.

Antimicrobial action :

Ceftaroline fosamil is a fifth-generation cephalosporin with broad-spectrum activity against many Gram-positive and Gram-negative organisms. The antimicrobial activity of this drug is almost similar to Cefotaxime; however, it has an expanded spectrum of activity against Gram-positive bacteria that includes methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae*. *Enterococci* are generally resistant, but there may be some sensitivity shown by *Enterococcus faecalis*.

Although, Ceftaroline has good activity against many Gram-negative organisms, *Pseudomonas aeruginosa*, *Acinetobacter spp.* and *Stenotrophomonas maltophilia* have decreased susceptibility. Ceftaroline is not active against Gram-negative bacteria producing extended spectrum beta-lactamases (ESBLs).

Ceftaroline has poor activity against Gram-negative anaerobes such as *Bacteroides fragilis* and *Prevotella spp.*; however, Gram-positive anaerobes such as *Propionibacterium spp.* and *Peptostreptococcus spp.* are highly susceptible.

With reference to clinically important pathogens responsible for community acquired bacterial pneumonia, Ceftaroline has good activity against Gram positive organisms like *S. pneumoniae*, *S. aureus*, and *Streptococcus pyogenes*, and Gram

negative pathogens *Haemophilus influenzae*, *Moraxella catarrhalis*. In addition, the microorganism responsible for skin and skin structure infections like *S. aureus* and *S. pyogenes*, are also susceptible to Ceftaroline.

Pharmacokinetics :

Ceftaroline fosamil is a water soluble prodrug. It rapidly gets converted to its active biologic form Ceftaroline after intravenous infusion. Mean peak plasma concentration of 19 µg/ml can be achieved in 1 hour after intravenous infusion of Ceftaroline in a dose of 600 mg,

It gets metabolized to its metabolite, Ceftaroline M-1, which is microbiologically inactive and both parent compound and its metabolite excreted mainly through kidney and very less through faeces. The elimination half-life of Ceftaroline is about 2.66 hours.

Clinical Pharmacokinetics² :

Ceftaroline is primarily eliminated by kidney. Hence, it requires dose reduction in patients with moderate to severe renal impairment, end-stage renal disease (ESRD) patients including patients on dialysis. The dosage in patient with renal impairment are calculated using the Cockcroft-Gault formula (*See Table 2*).

In addition, risk of adverse reactions may be greater in patients with impaired renal function. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should be based on renal function.

It has elimination half-life of 2.66 hours i.e. short half-life. Hence, this drug is given as intravenous infusion.

Mechanism of action :

Ceftaroline is a bactericidal drug. Its bactericidal action is similar to other cephalosporin and mediated through binding to essential penicillin-binding protein. Methicillin resistance is associated with PBP 2A, for which most β-lactams have low affinity. However, ceftaroline has a high affinity for

staphylococcal PBPs 1, 2 and 3, and for MRSA PBP2A, which correlates with low ceftaroline MICs for MRSA (MIC range, 0.52 mg/L). The high binding affinity of ceftaroline for Streptococcus pneumoniae PBPs (2X, 2A, 2B and 3) also corresponds to low MICs (MICs for strains tested ranged from 0.008 to 2 mg/L)³.

Preparation :

Ceftaroline fosamil is available as acetate salt for intravenous infusion to be given over a period of 1 hour. Doses are expressed in terms of equivalent amount of Ceftaroline fosamil : 1.11 gm of Ceftaroline fosamil acetate is equivalent to about 1 gm of Ceftaroline fosamil. Ceftaroline fosamil is available in 600 mg single use vial of sterile powder. The vial contents should be reconstituted with 20 mL of sterile water and further diluted in 250 mL of normal saline, 5% dextrose solution, 2.5% dextrose and 0.45% sodium chloride solution, or Lactated Ringer's Injection. The resulting solution should be used within 6h if stored at room temperature or within 24 h if refrigerated.

Uses and administration :

Ceftaroline is used for the treatment of community-acquired pneumonia and acute skin and skin structure infection caused by susceptible organisms

in adults >18 years of age. It may be of particular use for skin infection caused by MRSA. The usual dose is 600 mg every 12 hour. The recommended treatment schedule of ceftaroline for its indications is depicted in **Table 1**. However, the duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

Dosage regimen in patients with renal impairment :

In patients with renal impairment, the following intravenous doses of Ceftaroline fosamil are recommended, according to creatinine clearance.

Use in paediatric population and pregnancy :

Ceftaroline is approved only for use in adult population (>18 years of age). The safety and effectiveness of this drug in paediatric population has not yet been established. Ceftaroline fosamil has been classified as pregnancy category B.

Adverse effects and precautions :

It promotes colonization and super infection with resistant organism. *Clostridium difficile* associated diarrhoea (CDAD), ranging in severity from mild diarrhoea to fatal colitis, has been reported. Therefore, careful evaluation is warranted if diarrhoea occurs.

Table 1 : Treatment schedule of Ceftaroline for its indications⁵

Infection	Dosage	Frequency	Infusion (time)	Recommended duration of total antimicrobial treatment
Acute bacterial skin and skin structure infection	600 mg	Every 12 hours	1	5-14 days
Community acquired bacterial pneumonia	600 mg	Every 12 hours	1	5-7 days

Table 2 : Dosage regimen in patients with renal impairment

Creatinine clearance (ml/min)	Dosage regimen
> 50	No dosage adjustment necessary
> 30 and = 50	400 mg every 12 hours
= 15 and = 30	300 mg every 12 hours
< 15 (End-stage renal disease), including Haemodialysis#	200 mg every 12 hours

#For patients on haemodialysis, the doses should be given after the dialysis run.

Severe hypersensitivity is reported with Ceftaroline. Hence, it is cautioned to use Ceftaroline with all precaution in the similar line with other cephalosporin, especially in patients with known hypersensitivity.

Direct Coombs' test seroconversion has been reported with Ceftaroline. If anaemia develops during or after therapy, a diagnostic workup for drug-induced haemolytic anaemia should be performed and consideration given to discontinuation of Ceftaroline.

Approval status in India :

Ceftaroline is approved for marketing in India as Injection 600mg/vial (Date of Approval : 09.05.2016). In India, presently, it is only approved for the treatment of adult (= 18 years of age) patients with community-acquired bacterial pneumonia⁴. However, as per USFDA Label, it was approved by USFDA in 2010 and approved indications are acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults >18 years of age⁵.

Ceftaroline vs Other antimicrobials⁶ :

The safety and efficacy of Ceftaroline was compared with Vancomycin in a Phase-III clinical trial in Skin and Skin Structure Infections (Ceftaroline Versus Vancomycin in Skin and Skin Structure Infections - CANVAS trial). It was a noninferiority double blind, randomized, active controlled design. Similarly, efficacy and safety of Ceftaroline was compared with Ceftriaxone in community acquired pneumonia (CAP) in a Phase III, doubleblinded, randomized, multinational, multicenter trial (ceftaroline Community-acquired pneumonia trial versus ceftriaxone - FOCUS Trial).

These clinical trials showed that ceftaroline was noninferior to Vancomycin plus aztreonam in the treatment of cSSTIs and to ceftriaxone in the treatment of CAP. Ceftaroline achieved demonstrated high bactericidal activity and substantiated high clinical cure rates which was comparable with their respective controlled arm.

The most potential advantage of Ceftaroline, over other β -lactam antibiotic, is its activity against MRSA. In addition, there are no reports on development of resistance in the FOCUS and

CANVAS trials. One potential disadvantage of ceftaroline compared with other broad spectrum antibacterial agents is its lack of coverage of Gram-negative organisms, particularly those producing β -lactamases including AmpC, extended-spectrum β -lactamase (ESBL), and *K. pneumoniae* carbapenemase (KPC). The disadvantage of FOCUS and CANVAS trial is that these trial showed only noninferiority as opposed to superiority to its comparator. There is lack of clinical trial data as far as efficacy of Ceftaroline in patients with MRSA pneumonia. Hence, at present, superiority of Ceftaroline over other antimicrobial active against MRSA cannot be commented. However, it is definitely a new arrow in quiver against MRSA.

Key points :

- Fifth generation parenteral cephalosporin
- Clinically useful activity against methicillin-resistant *Staphylococcus aureus* (MRSA)
- Approved and marketed in India for Community acquired bacterial pneumonia (CABP) in adults > 18 years' age.
- Dose reduction required in renal failure.
- Not yet approved for paediatric use.
- Pregnancy Category B

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