International Journal of Research and Review
Vol. 9; Issue: 12; December 2022
Website: www.ijrrjournal.com
Review Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Review on Ceftaroline in the Treatment of Community Acquired Bacterial Pneumonia

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DOI: https://doi.org/10.52403/ijrr.20221253

ABSTRACT

Ceftaroline fosamil (ceftaroline) is approved by the United States Food and Drug Administration (FDA) for the treatment of community-acquired pneumonia (CAP). It is a fifth-generation cephalosporin having broad-spectrum efficacy against gram-positive bacteria such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP), as well as a variety of common gram-negative pathogens. Ceftaroline can bind to penicillin-binding protein (PBP)2a, an MRSA-specific PBP with minimal affinity for the majority of other β-lactam antibiotics. The drug is often given intravenously in doses of 600 mg every 12 hours for 5-7 days. Only a parenteral formulation of ceftaroline is commercially available, and the prodrug, ceftaroline fosamil, is rapidly and completely hydrolysed after intravenous administration. Ceftaroline was found to be noninferior to comparator agents in Phase II and Phase III clinical studies, with good clinical cure rates in the treatment of CAP. Ceftaroline is well tolerated, which is consistent with the cephalosporin class's safety and tolerability profile. In this review, we will evaluate the microbiological properties, pharmacological features, efficacy, safety, and tolerability of ceftaroline in the treatment of CAP.

Keywords: Ceftaroline, MRSA, CAP, efficacy.

INTRODUCTION

Community-acquired pneumonia (CAP) refers to an acute infection of the lungs that occurs outside of the hospital setting in a patient who has not recently been hospitalised.[1] It is a major threat and are associated with significant morbidity and mortality (especially in children and elderly patients.[2][3] with mortality rate ranges from 5% in outpatients to 30% in those admitted to an intensive care unit.[4] Similarly, 3 million children are diagnosed with community-acquired bacterial pneumonia (CABP) each year, with over 150,000 requiring hospitalisations, and the majority of these infections are caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP).[5] *Staphylococcus aureus* (S. aureus), including MRSA, has emerged as a cause of severe CAP in the last decade, with an increased risk of mortality compared to all-cause non-*S. aureus* CAP[6].MRSA infections have been reported all over the world, and their prevalence is increasing in both community and hospital settings, resulting in significant morbidity, mortality, duration of stay, and increased cost.[7][8] The ideal antibiotic for the treatment of CAP should have the following properties: (a) a broad spectrum of activity that includes the

majority of pathogens related to the infection; (b) documented safety and clinical efficacy in a wide range of patient populations; and (c) cost-effectiveness.[9] To choose appropriate empirical antimicrobial therapy, current guidelines recommend stratifying patients into groups based on the presence of specific risk factors and evaluating health care utilisation history. The adoption of these guidelines has significantly increased the success rate of CAP treatment. To choose appropriate empirical antimicrobial therapy, current guidelines recommend stratifying patients into groups based on the presence of specific risk factors and evaluating health care utilisation history. The adoption of these guidelines has significantly increased the success rate of CAP treatment.[10] The emergence and increasing prevalence of antimicrobial resistant strains of common pathogens has posed many challenges in the treatment of serious infections, such as CAP.[11] Ceftaroline fosamil, a fifth-generation cephalosporin with broad-spectrum activity against gram-positive pathogens including MRSA and PRSP, as well as many common gram-negative pathogens, is one of the most promising antibiotics recently marketed. Ceftaroline fosamil demonstrated clinical and bacteriological efficacy against CAP-causing bacteria.[12] Moreover, it demonstrated a satisfactory safety and tolerability profile during pre-marketing studies.[13] Ceftaroline was recently approved to treat community-acquired bacterial pneumonia in children aged > 2 months.[14] In this review, we will look at the pharmacological properties, safety, antimicrobial properties, efficacy, safety, and dosing of ceftaroline in the treatment of CAP patients.

MECHANISM OF ACTION

Following intravenous administration, plasma phosphatase rapidly converts the prodrug ceftaroline fosamil into the active metabolite ceftaroline.[15] Ceftaroline, like other β-lactam antibiotics, chemically reacts with penicillin-binding proteins (PBPs), forming stable, inactive acyl-enzymes that prevent further peptidoglycan cross-linking in the bacterial cell wall. The cell wall is weakened as a result, leading to lysis and cell death. [16] Because of its high affinity for PBP1-3 and PBP2, ceftaroline retains potent in vitro activity against MRSA, unlike currently marketed β-lactam antibiotics.[17] Ceftaroline binds to a variety of PBPs in *S. pneumoniae*, including PBP3, PBP1A, PBP2X, PBP1B, and PBP2A/B, all of which are primary targets for *S. pneumoniae*, including resistant strains.[16][17]

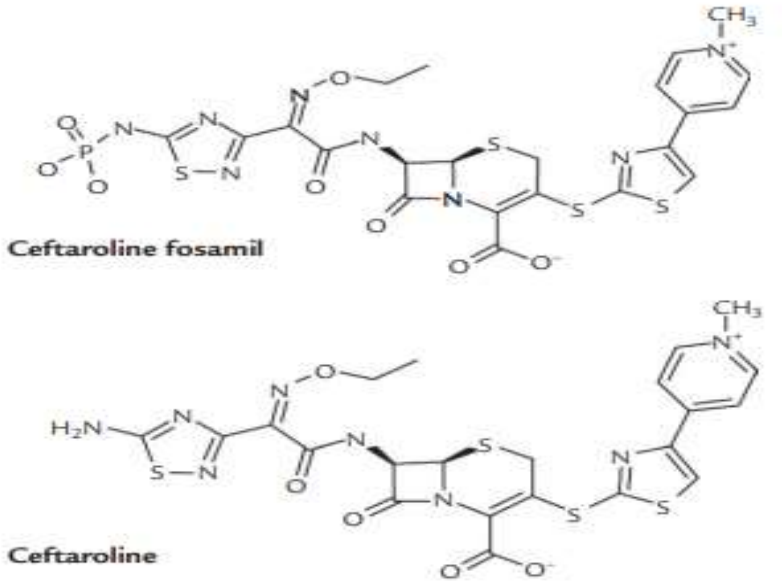

figure 1: Chemical structure of Ceftaroline fosamil and Ceftaroline

MICROBIOLOGIC ACTIVITY

Ceftaroline was found to be highly active in vitro against Gram-positive aerobes commonly associated with CAP. Ceftaroline, as shown in table I, has excellent antibacterial activity against *Staphylococcus aureus*, including MRSA. The ceftaroline MIC_{50} and MIC_{90} values for methicillin susceptible *S. aureus* (MSSA) isolates were 0.25 mg/L. The ceftaroline MIC_{50} and MIC_{90} values for MRSA isolates were 0.5 mg/L and 1.0 mg/L, respectively.[18] The MIC range for all *S aureus* isolates, which included isolates of MRSA, VRSA, was between 0.008≤ and 4 µg/mL.[19] Ceftaroline had low MICs against all streptococci species (table I). Ceftaroline is effective against *Streptococcus pneumoniae* isolates with varying degrees of penicillin resistance. Ceftaroline's MIC_{90} values against penicillin-susceptible, intermediate, and resistant strains of *Streptococcus pneumoniae* were 0.015, 0.06, and 0.25 mg/L, respectively.[20] Ceftaroline has in vitro activity against Gram negative pathogens such as *Moraxella catarrhalis* and *Haemophilus influenzae*, including β-lactamase-producing strains, which are common in CABP. It has antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae* isolates (MIC_{90} of 0.5 and 0.5 mg/L, respectively). In nonfermentative organisms such as *Pseudomonas aeruginosa*, ceftaroline has little to no activity ($MIC_{50/90}$ 16/>64 mg/L).[21]

Table 1: I**nvitro antimicrobial activity of ceftaroline against clinical isolates of common Gram-positive and Gram-negative organisms**

Organism	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (µg/mL)
Staphylococcus aureus			
MSSA [18][19]	0.25	0.25	≤ 0.008 to 1
MRSA [18][21]	0.5	1.0	0.12–2
CA-MRSA [17][22][23]	0.5	0.5	0.25-1
VISA/hVISA [18][22][23]	1.0	2.0	0.25-4.0
VRSA [18][31]	0.5	1.0	≤ 0.12-2.0
Streptococcus pneumoniae			
Penicillin resistant [20]	0.12	0.25	≤ 0.008-0.5
Penicillin-intermediate [24][25][26]	0.015	0.06	≤ 0.008-0.25
Penicillin susceptible [25][26]	≤ 0.008	0.015	≤ 0.008-0.5
Moraxella catarrhalis [24]	0.12	0.25	≤ 0.016-1.0
Haemophilus influenzae [28]	≤ 0.06	≤ 0.06	≤ 0.06- 0.25
β-lactamase positive [24][25]	≤ 0.015	≤ 0.03	≤ 0.008-2.0
β-lactamase-negative [24][25][26]	≤ 0.008	≤ 0.01	≤ 0.008-1.0
Klebsiella pneumoniae[28]	≤ 0.12	0.5	≤0.12-128
Escherichia coli [28]	≤ 0.12	0.5	≤0.12 - >128
Enterobacter cloacae [28]	≤ 0.12	32	≤0.12 - >128
Pseudomonas aeruginosa [24][28]	16	> 64	0.25 to > 128

Abbreviations: MIC: minimum inhibitory concentration; MSSA:*methicillin-susceptible Staphylococcus aureus*; CA-MRSA: community acquired *methicillin-resistant Staphylococcus aureus*; VISA/hVISA: vancomycin-intermediate *S. aureus*/hetero-resistant *S. aureus* ; VRSA: vancomycin resistant *S. aureus*.

PHARMACOKINETICS

Understanding pharmacokinetics is critical for optimising antimicrobial doses so that the drugs are used effectively and pathogens do not develop resistance to them.[29] There are no absorption data in the literature, and only a parenteral formulation of ceftaroline with regulatory approval for intravenous administration is available.[30] The prodrug ceftaroline fosamil is rapidly metabolised into active ceftaroline after intravenous administration, as demonstrated in in vitro studies using phosphatase inhibitors.[31] The in vitro conversion half-life of ceftaroline fosamil to ceftaroline was determined to be 19 minutes, which is consistent with the in vivo half-life reported in healthy volunteers receiving single or multiple ascending doses of ceftaroline fosamil.[32] Ceftaroline has a volume of distribution of 28.3 L (0.37 L/kg; range 0.31-0.45 L/kg) that represents distribution into the total body water compartment.[33] It has a low plasma protein binding (20%) and is not distributed

into erythrocytes, which decreases slightly from 28% to 14% as concentrations increase from 1 to 50 µg/mL. The mean steady-state volume of distribution of ceftaroline fosamil 600mg was similar to the volume of distribution (20.3 L) in healthy adult male volunteers after a single radiolabelled dose.[35] A small percentage of ceftaroline is further hydrolyzed to form microbiologically inactive metabolites, such as ceftaroline M-1.[35] Ceftaroline and ceftaroline M-1 have average half-lives of 2.6 and 4.5 hours, respectively.[33] Furthermore, as it undergoes little hepatic metabolism, it does not appear to be a substrate of the cytochrome CYP450 system and is therefore unlikely to cause significant CYP450-related drug-drug interactions.[29] Drug accumulation does not occur after multiple doses of ceftaroline with dose administration intervals of 12 or 24 hours for 5-14 days. Ceftaroline and ceftaroline-M-1 are primarily eliminated via renal excretion, with average renal clearances for ceftaroline of 95.6 mL/min (single dose) and 86.7 mL/min (daily dose) (multiple doses). [33] Within 48 hours of receiving a single radiolabelled dose of ceftaroline fosamil 600 mg, approximately 88% of the radioactivity was recovered in the urine and 6% in the faeces. Approximately 64% of the radioactivity recovered in urine was excreted as ceftaroline, with the remaining 2% excreted as ceftaroline M-1.[21] Ceftaroline fosamil and ceftaroline have very few drug interactions. It has predictable pharmacokinetic parameters, like other renally eliminated cephalosporins: within the single-dose range of 50-1000 mg, ceftaroline has linear pharmacokinetics, with maximum concentration (C_{max}) and area under the concentration-time curve (AUC) increasing approximately in proportion to doses.[36] Each intermittent haemodialysis session eliminates an estimated 21% of a dose. As a result, renal and intermittent haemodialysis dose adjustments are required.[29] Children aged 2 months to 12 years and adolescents aged 12 to 18 years with a bodyweight of 33 kg require dosage adjustments. Ceftaroline fosamil's safety and efficacy in children aged birth to 2 months have not been established. Ceftaroline pharmacokinetics in patients with hepatic impairment have not been studied. Ceftaroline's systemic clearance is not expected to be significantly affected by hepatic impairment because it does not appear to undergo significant hepatic metabolism. [34] Ceftaroline pharmacokinetics are altered to a clinically significant extent in paediatric and adult patients with varying degrees of renal impairment, with dosage adjustments required in adult and paediatric patients with moderate to severe renal impairment with $CL_{CR} \leq 50$mL/min. Pharmacokinetic parameters did not differ clinically between people with mild renal impairment (CL_{CR} > 50-80 mL/min) and adults with normal renal function (CL_{CR} >80 mL/min). When compared to adults with normal renal function, those with moderate (CL_{CR} >30-50 mL/min) or severe (CL_{CR} ≤30 mL/min) renal impairment had significantly higher systemic exposure to ceftaroline, with area under the plasma concentration time curve increasing by 52 and 104%, $t_{1/2}$ increasing by 58 and 67%, and renal clearance decreasing by 65 and 84%.[37] When comparing adults with end-stage renal disease (ESRD) on haemodialysis to adults with normal renal function, similar changes in the pharmacokinetic profile of ceftaroline were observed. [38]

PHARMACODYNAMICS

The current ceftaroline dose of 600 mg intravenously every 12 hours is based on pharmacodynamic studies comparing target organism MICs to concentrations obtained after ceftaroline dosing.[38] Ceftaroline, like other β-lactam antimicrobials, is bactericidal time-dependent, with the percentage of time the unbound drug concentration exceeds the MIC (fT>MIC) having the greatest impact on bactericidal activity against *Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae* and MRSA.[32] With the exception of

staphylococci, β-lactams have a minimal post antibiotic effect on most bacteria. Similarly, ceftaroline had a minimal post antibiotic effect on *S. pneumoniae* and *E. coli* but a longer post antibiotic effect on *S. aureus* (0.8-7.2 hours).[36] Furthermore, when the free drug concentration exceeded the MIC for 30% and 40% of the dosing interval, respectively, ceftaroline was found to be bacteriostatic for staphylococci and gram-negative bacilli. Ceftaroline, on the other hand, had bactericidal activity against staphylococci and gram-negative bacilli when %T>MIC was 50% and 60%, respectively. [39]

DOSAGE AND ADMINISTRATION

Recommended Dosage in Adult Patients

The recommended dosage of ceftaroline for CABP is 600 mg administered every 12 hours by intravenous (IV) infusion over 5 to 60 minutes in patients ≥ 18 years of age 5-7 days.[34]

Recommended Dosage in Paediatric Patients

Ceftaroline dosage in paediatric patients is determined by the child's age and weight. Ceftaroline is infused intravenously every 8 hours for 5 to 60 minutes. The recommended treatment duration is 5-7 days. The recommended dose for patients aged 2 months to 2 years is 8 mg/kg every 8 hours. The dosage for patients aged > 2 years to 18 years and weighing ≤ 33 kg is 12 mg/kg every 8 hours. The dosage for patients aged 2 to 18 years and weighing more than 33 kg is 400 mg every 8 hours or 600 mg every 12 hours.[40]

Dosage Adjustments in Patients with Renal Impairment

Adults: No dosage adjustment is required if CL_{CR} is greater than 50 mL/min. For patients with creatinine clearance is >30 but ≤50 mL/min, the recommended dose is 400 mg IV (over 5 to 60 minutes) every 12 hours. If the creatinine clearance is s ≥15 but ≤30 mL/min, the dose should be adjusted to 300 mg IV (over 5 to 60 minutes) every 12 hours. In the case of end-stage renal disease (CL_{CR} <15 mL/min.), a dose of 200 mg IV (over 5 to 60 minutes) every 12 hours is recommended.[29][36]

Since ceftaroline is hemodialyzable, it should be administered after haemodialysis-on-haemodialysis days.[36] In the case of paediatric patients, no dosage adjustment is required if CL_{CR} is greater than 50 mL/min/1.73 m2, as estimated by the Schwartz equation. There is not enough data to recommend a dosage regimen for paediatric patients with CL_{CR}<50 mL/min/1.73 m2.[40]

THERAPEUTIC EFFICACY

Ceftaroline's efficacy and safety in the treatment of community-acquired bacterial pneumonia were assessed in two multicentre, double-blind, randomised phase III studies called Ceftaroline Community-acquired Pneumonia versus Ceftriaxone in Hospitalized Patients (FOCUS) 1 and FOCUS2. [29] The key objective of these trials was to evaluate non-inferiority of ceftaroline in clinical cure rates compared to ceftriaxone in clinically evaluable and modified intent-to-treat efficacy groups.[41] Clinical cure was defined as the absence of all signs and symptoms of pneumonia or improvement to the point that no additional antimicrobial medication was required. Patients were also required to be fever-free over 24 hours, with CAP signs and symptoms returning to baseline levels.[41] There were 1228 adult patients in each of these phase III studies (ceftaroline, n = 614 against ceftriaxone, n = 614). Baseline characteristics were similar between groups with moderate to severe CAP (PORT risk class III or IV), requiring hospitalisation and treatment with IV antimicrobials. Patients were randomly assigned to either ceftaroline (600 mg intravenously every 12 hours) or ceftriaxone (1 gm intravenously daily) for 5-7 days [35]. Importantly, individuals who were not admitted to the hospital (PORT I and II) or immediately to the intensive care unit (ICU) were excluded from the studies (PORT V).[39] Patients with significant renal

impairment, risk factors for hospital acquired infections, known or suspected infections with atypical microorganisms, risk factors for positive cultures for MRSA and immunosuppression were also excluded.[39] The only difference between these two trials was the participants in FOCUS 1 got two clarithromycin doses on day1. Overall clinical cure rates for ceftaroline and ceftriaxone were similar, at 84% and 78%, respectively, whereas overall microbiological response rates were 87% and 81%, respectively. Ceftaroline had an 86% clinical response rate and ceftriaxone had a 69.5% clinical response rate against *Streptococcus pneumoniae* isolates.[41] Clinical cure was achieved in 83% of patients treated with ceftaroline, compared to 7% of patients treated with ceftriaxone in the modified intent-to-treat efficacy group. During the research, there were 27 reported deaths: 15 (2.4%) in the ceftaroline group and 12 (2.0%) in the ceftriaxone group.[39] *Staphylococcus aureus* was the second most prevalent pathogen identified, accounting for 14.3% of all isolates. Ceftaroline had a clinical cure rate of 72% and ceftriaxone had a cure rate of 56% for *S. aureus*. Only two MRSA isolates were found among the *S. aureus* isolates, and both were in the ceftriaxone trial group. The low incidence of MRSA is likely due to both the pathogen's low frequency of occurrence and the exclusion criteria of the FOCUS 1 and FOCUS 2 investigations.[42] Furthermore, the integrated analysis revealed a statistically significant trend toward ceftaroline enhancing clinical cure rates. These findings firmly support the efficacy and safety of ceftaroline therapy in hospitalised, non-ICU CAP patients, leaving questions about efficacy in other groups unsolved. [39]

SAFETY AND TOLERABILITY

Ceftaroline appears to be safe and well-tolerated based on clinical trial results to date. Considering ceftaroline is a cephalosporin, it has caused severe hypersensitivity reactions in individuals who are sensitive to cephalosporins and in certain people who are allergic to penicillin. As a result, prior to administering ceftaroline, a thorough history of previous antibiotic allergies should be obtained.[35] In the integrated FOCUS studies of CABP (FOCUS 1 and 2), the most common side-effects occurring in more than 2% of people receiving ceftaroline fosamil were diarrhoea (4.2%), headache (3.4%), insomnia (3.1%), and phlebitis (2.8%).[43] At a dose of 1,500 mg, ceftaroline fosamil showed no clinically relevant effect on the QT interval.[44] Although animal studies reveal no evidence of teratogenicity, no controlled trials in pregnant or lactating women have been done.[43] Rare cases of eosinophilic pneumonia and neutropenia have been recorded in patients taking lengthier courses of ceftaroline; both outcomes have previously been associated to cephalosporin use.[34] As ceftaroline is excreted through the kidneys, studies in healthy young people have revealed that it has no effect on faecal microbiota after seven days. In a study conducted by Panagiotidis, G *et al*, The number of *Escherichia coli* strains was reduced slightly, while the number of *enterococci and Candida albicans* strains was unaffected. During the first seven days, the numbers of bifidobacteria and lactobacilli decreased moderately, but the quantity of *clostridia* increased. There was no effect on the number of Bacteroides bacteria. There were no novel aerobic or anaerobic microorganisms discovered to be resistant to ceftaroline (MIC $\geq$ 4 mg/liter). Ceftaroline showed no noticeable effect on the human intestinal microflora.[45] There has been no systematic research on drug-drug interactions with ceftaroline to yet. Ceftaroline's metabolism through the kidneys likely results in minimal inhibition of CYP450 system, implying a low tendency for drug- drug interactions metabolised by this system.[35]

CONCLUSION

Ceftaroline, the active form of ceftaroline fosamil, a new fifth-generation

cephalosporin, is a safe and effective therapy option for non-ICU hospitalised patients with CABP. Its effectiveness against modern resistant Gram-positive phenotypes, such as MRSA, CA-MRSA hVISA, VISA, VRSA, daptomycin-non-susceptible *Staphylococcus. aureus*, and penicillin- and cephalosporin-resistant *Streptococcus. pneumoniae*, appears to be most promising. Clinical studies have shown that ceftaroline fosamil has the same effectiveness as comparator medications in the treatment of CABP. Ceftaroline fosamil is also approved to treat adults with *S. pneumoniae* CABP, including instances with concurrent bacteraemia. ceftaroline is currently indicated CABP at a recommended dosage of 600 mg every 12 h in patients with normal renal function and is typically well tolerated, with a toxicity profile similar to other cephalosporins but a considerably higher risk of neutropenia with prolonged courses of treatment.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Ashitha Ephrem, Shahada Ali, A.R. Shabaraya. A review on Ceftaroline in the treatment of community acquired bacterial pneumonia. *International Journal of Research and Review*. 2022; 9(12): 473-481.
DOI: *https://doi.org/10.52403/ijrr.20221253*

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