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New antimicrobial alternatives in the treatment of pneumonia

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Ceftaroline in severe community-acquired pneumonia

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ABSTRACT

Severe community-acquired pneumonia (SCAP) is associated with high mortality. Factor such as early adequate antibiotic therapy, delay in intensive care unit (ICU) care and pneumonia caused by resistant pathogens are associated with worse outcomes in SCAP patients. Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against Gram-positive pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA] and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative organisms. The efficacy and safety for the treatment of pneumonia was evaluated in three randomized control trials were ceftaroline demonstrated superiority against ceftriaxone for the treatment of pneumonia in hospitalized patients with Pneumonia Severity Index (PSI) III – IV.

Keywords: severe community-acquired pneumonia; *Streptococcus pneumoniae*; *Staphylococcus aureus*; ceftaroline

INTRODUCTION

Severe CAP is associated with high morbidity and mortality [1]. The early detection of severe pneumonia and the timely, adequate antimicrobial therapy are critical in managing these cases that affect in great proportion to elderly adults and patients with chronic comorbidities [1]. Based on this observation, early, adequate antimicrobial therapy could reduce mortality in severe CAP.

Due to the growing microbial resistance and continued need for appropriate antimicrobial coverage, newer antibiotics have been investigated in CAP, with an ability to cover the most frequent pathogens in pneumonia and their resistances. Ceftaroline is one of this new generation cephalosporins, has broad-spectrum in vitro activity against Gram-positive pathogens (including methicillin-resistant *Staphylococcus aureus* [MRSA] and multidrug-resistant *Streptococcus pneumoniae*) and common Gram-negative pathogens. Ceftaroline is approved for their use in CAP in Europe and USA.

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MICROBIOLOGICAL PROFILE

Ceftaroline exhibits a greater binding affinity for penicillin-binding proteins (PBPs) and thus preventing the biosynthesis of the bacterial cell wall. Ceftaroline has high binding affinities to PBP 1- 3 and PBP-2A that mediates methicillin resistance in MRSA; and for PBP-1A, PBP-2A/B and PBP-2X that target *S. pneumoniae* including multidrug resistant strains.

Table 1 Antibacterial activity

Gram-positive bacteria	Gram-negative bacteria
Streptococcus pneumoniae	*Escherichia coli*
Staphylococcus aureus	*Klebsiella pneumoniae*
Methicillin-resistant *S. aureus* (MRSA)	*Haemophilus influenzae*
Methicillin-susceptible *S. aureus* (MSSA)	*Haemophilus parainfluenzae*
Vancomycin-intermediate *S. aureus* (VISA)	*Klebsiella oxytoca*
Vancomycin-resistant *S. aureus* (VRSA)	
Streptococcus pyogenes	*Morganella morganii*
Streptococcus agalactiae	*Moraxella catarrhalis*
Streptococcus anginosus group	
S. anginosus	
S. intermedius	
S. constellatus	

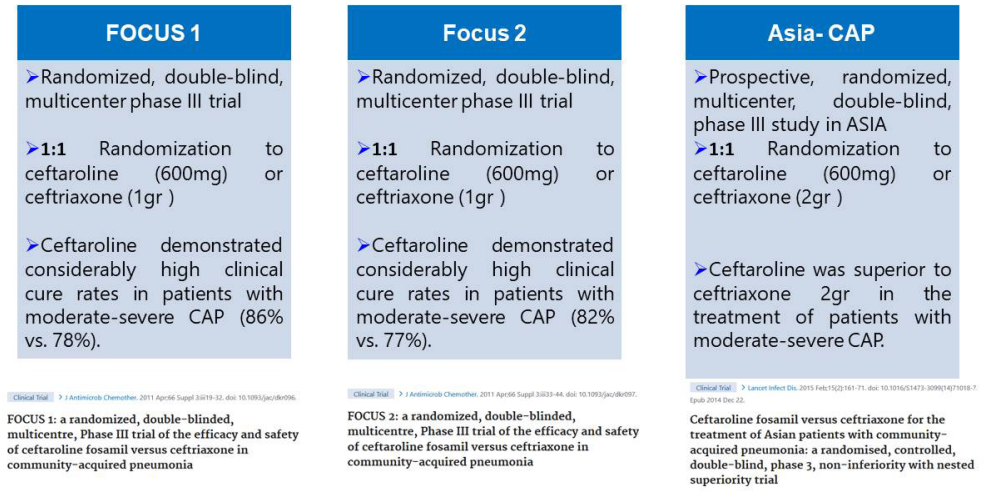

Figure 1 | **Ceftaroline fosamil: Clinical Experience**

Ceftaroline has demonstrated activity against a broad spectrum of gram-positive and gram-negative pathogens as show in table 1. However, ceftaroline does not have significant in vitro activity against extended-spectrum beta-lactamase (ESBL) producing microorganisms, AmpC-producing microorganisms, *Pseudomonas aeruginosa*, *Proteus* spp, *Prevotella* spp and *Bacteroide* spp.

PHARMACOLOGIC CHARACTERISTICS (PK/PD)

Ceftaroline is a time-depend antibiotic, whose best predictor of bacteriological and clinical efficacy is the percentage of time that the free drug concentration remains above the minimal inhibitory concentration (MIC) of the microorganism over the dosing interval (mean %f T >MIC). For the reduction of 2-log in bacterial load of *S. aureus* is 35%. In the case of *S. pneumoniae* the value required is 51%. With a dose of 600mg/12h infused over 60 minutes the probability of achieving these values for *S. aureus* and *S. pneumoniae* is >90% for the cut-off points established by EUCAST.

Plasma protein binding of ceftaroline is approximately 20% and terminal elimination half-life approximately 2.5 hours. Ceftaroline is primarily eliminated by the kidneys. The dose should be adjusted when creatinine clearance (CrCL) is ≤50 mL/min. The recommended durations of treatment are 5-7 days for CAP.

CLINICAL EXPERIENCE

The efficacy of ceftaroline in CAP was investigated in three double-blind, multinational, phase 3 trials (FOCUS 1 [2], FOCUS 2 [3] and Asian Trial [4]) in adult patients (aged>18 years) hospitalized with Pneumonia Severity Index (PSI) risk class III or IV (Figure 1). In the FOCUS 1 and 2 trials a dosage of 1gr of ceftriaxone was given, whereas in the Asian trial 2 gr of ceftriaxone was given. CAP cases causes by pathogens resistant to ceftriaxone were excluded (including MRSA).

The objective in all trials was determination of the non-inferiority of ceftaroline to ceftriaxone in terms of the clinical cure (defined as resolution of all signs and symptoms of pneumonia or improvement such that no further antimicrobial therapy was necessary) rate at the test of cure (TOC) visit in the modified intent-to-treat (MITTE) and clinically evaluable (CE) population.

Ceftaroline was well tolerated in all the trials and demonstrated non-inferiority to ceftriaxone in the MITTE and CE populations for the primary end point of clinical cure at the TOC visit (8–15 days after end of therapy).

In the integrated analysis, of the CE patients treated with ceftaroline, 84% achieved clinical cure, compared with 78% of ceftriaxone-treated patients. Clinical cure rates in the MITTE population were 83% versus 77% for ceftaroline and ceftriaxone. Ceftaroline and ceftriaxone were well tolerated; rates of adverse events, serious adverse events, deaths, and premature discontinuations caused by an adverse event were similar in both treatment groups [5].

In a meta-analysis of three trials including 1916 CAP patients, ceftaroline (600mg/8h) was superior to ceftriaxone (1–2 g /24 h) for 5–7 days in the MITT population (OR: 1.66; 95% CI 1.34, 2.06; $P < 0.001$) and in the CE (OR: 1.65; 95% CI 1.26, 2.16; $P < 0.001$) populations [6].

A subsequent analysis quantify the time to a clinical response, a proxy for the time to discharge readiness, among CAP patients including in the FOCUS 1 and FOCUS 2 trials. The results of the study showed that patients who received Ceftaroline were found to have shorter overall times to a clinical response and clinical stability relative to patients who received ceftriaxone [7].

The current ATS/IDA guidelines [8] and the update of the SEPAR guidelines [9] for the management of CAP patients incorporate ceftaroline as one of the ß-lactams recommended for the treatment of hospitalized patients with CAP.

Recently, our group published a case-control study were ceftaroline was mainly prescribed in cases with severe pneumonia (67% vs. 56%, p0.215) with high suspicion of *S. aureus* infection (9% vs. 0%, p 0.026). Patients who received ceftaroline had a longer length of hospital stay (13 days vs. 10 days, p0.007), while an increased risk of in-hospital mortality was observed in the patients who received ceftriaxone compared to the patients in the ceftaroline group (13% vs. 21%, HR 0.41; 95% CI 0.18 to 0.62, p 0.003). This study reported that the use of ceftaroline in hospitalized patients with severe CAP was associated with a decreased risk of in-hospital mortality [10].

The great bactericidal activity of ceftaroline against *S. pneumoniae* and *S. aureus*, makes it an excellent therapeutic option in the treatment of cases of severe CAP.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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