Official journal of the Spanish Society of Chemotherapy

Update on antimicrobial pharmacotherapy

Alex Soriano

Ceftaroline

Servicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona

Revista Española de Quimioterapia
doi:10.37201/req/s01.08.2021

ABSTRACT

Community-acquired pneumonia (CAP) is one of the leading causes of admission to emergency departments. Ceftaroline is a fifth-generation cephalosporin with a potent *In vitro* activity against *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus,* the three most important pathogens causing CAP. Three randomized and double-blind clinical trials compared the efficacy of ceftaroline versus ceftriaxone in patients with CAP and the results of each trial and a meta-analysis, concluded the superiority of ceftaroline in terms of clinical success. In particular, the major difference was observed among patients with CAP caused by *S. aureus.* Accordingly, ceftaroline has been included as a first-line option in the recent clinical guidelines for the management of CAP.

Keywords: Community-acquired pneumonia, clinical cure, *S. pneumoniae*, *S. aureus*, ceftaroline

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the leading causes of emergency department care and hospital admission. The most recent guidelines for the management of this entity were published in 2019 by two American Societies[1] and among the most notable changes is the incorporation of ceftaroline as a first-line option for the treatment of CAP in patients with a severe infection, but without risk factors for *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA). For this reason, we are going to summarize the main characteristics of this fifth-generation cephalosporin.

Correspondence:
Alex Soriano
Servicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona, Spain.
E-mail: asoriano@clinic.ub.es

MECHANISM OF ACTION

Like all beta-lactams, ceftaroline inhibits the transpeptidase activity of PBPs, including PBP1a, PBP2b and PBP2x of *Streptococcus pneumoniae* responsible of penicillin resistance, as well as PBP2a of MRSA. In the latter case, inhibition is produced by an allosteric effect consisting in the binding of a ceftaroline molecule at a point distant from the active centre inducing a conformational change in PBP2a that now allows the binding of another molecule of ceftaroline at the active centre leading to the inhibition of this enzyme. The in vitro activity exhibited by ceftaroline is bactericidal and time-dependent [2].

SPECTRUM

It is active against Gram-positive microorganisms including viridans group streptococci, ß-haemolytics and *S. pneumoniae* with a MIC_{90} < 0.25 mg/L. It is of note its activity against third-generation cephalosporin-resistant strains of pneumococcus. A study of strains from around the world collected between 2015 and 2016 showed that ceftaroline was the ß-lactam with the highest intrinsic activity (lowest MIC) against pneumococcus [3]. For *S. aureus* and coagulase-negative *Staphylococcus*, ceftaroline has a MIC_{90} < 0.5 mg/L, although for MRSA strains the MIC_{90} is 2 mg/L. Its activity against other Gram-positive cocci such as enterococcus is moderate (*E. faecalis*) or they are resistant (*E. faecium*).

Against Gram-negative bacilli, its activity is superimposable to that of a third-generation cephalosporin. For *Haemophilus influenzae* and *Moraxella* the MIC_{90} is < 0.12 mg/L and for the susceptible Enterobacterales < 0.5 mg/L. Extended-spectrum beta-lactamase (ESBL) and AmpC-producing strains are resistant to ceftaroline. *P. aeruginosa* and other non-fermenting Gram-negative bacilli are resistant. Activity against anaerobic microorganisms is limited to Gram-positive cocci (*Peptococcus* and *Peptostreptococcus*), while Gram-negative bacilli (*Prevotella*, *Bacteroides*) are resistant.

The breakpoint for susceptibility proposed by EUCAST for *S. pneumoniae* is ≤ 0.25 mg/L, for *H. influenzae* ≤ 0.03 mg/L, for *S. aureus* ≤0.5 mg/L (1 mg/L in case of pneumonia) and for Enterobacterales ≤ 0.5 mg/L.

The association with daptomycin is often synergistic against MRSA and the association with ampicillin may be synergistic against *E. faecalis* [4].

PHARMACOKINETICS AND PHARMACODYNAMICS

It is administered intravenously in a 60-minute infusion that allows a maximum serum concentration of 28 mg/L with 600 mg. It has a half-life of 2.5h and the protein binding is 15-20%. About 20% is metabolized in the liver but it does not modify the activity of cytochrome P-450 isoenzymes. Elimination is mostly urinary (90%) and 64% in active form. Although data are scarce, diffusion to cerebrospinal fluid is 5-9% of the serum concentration, corresponding to 1-2 mg/L.

The pharmacodynamic parameter that predicts its clinical efficacy is the time that the antibiotic free fraction remains above the MIC between two consecutive doses (*f*T > MIC). The value required to obtain a 2-log reduction in bacterial load is 35% for *S. aureus* and 51% for *S. pneumoniae*. In both cases the probability of achieving these values with the 600 mg/12h dose infused over 60 minutes is >90% for the cut-off points established by EUCAST [5].

CLINICAL EFFICACY

A meta-analysis of 3 clinical trials in patients with CAP and with similar inclusion criteria summarized the clinical efficacy of ceftaroline. In two studies, the comparator was ceftriaxone at a dose of 1g/24h and in the third 2g/24h. The outcome variable in all 3 studies was clinical cure defined as resolution of symptoms without modification of antibiotic 8-15 days after completion of treatment. The conclusion of the meta-analysis is that ceftaroline was superior to ceftriaxone in both the intention-to-treat and clinically evaluable populations [6]. The results were consistent across the different sub-analyses according to age, co-morbidity and PORT scale. In addition, the percentage difference in clinical cure rate was approximately 10 points higher in the ceftaroline arm in cases with documented *S. pneumoniae* and Gram-negative bacilli (*E. coli, K. pneumoniae*) infections, but reached a difference of more than 20 points in those patients with S. aureus isolation. A subsequent analysis including only the two studies using the 1g of ceftriaxone as a comparator assessed the time to recovery of the two treatment options and showed that a significantly higher percentage of patients in the ceftaroline arm reached clinical stability earlier [7]. These data support the incorporation of ceftaroline in the recent clinical guidelines for the management of CAP. On the other hand, not many data are available in patients with severe pneumonia (criteria for ICU admission), but recently our group reported at the congress of the Spanish Society of Infectious Diseases and Clinical Microbiology our experience in patients with these characteristics and through a case-control study we were able to observe a decrease in in-hospital mortality among patients who received ceftaroline.

ADVERSE EVENTS

The main adverse effects are related to skin hypersensitivity reactions and gastrointestinal disturbances (diarrhea, nausea). In 10% of patients the Coombs' test becomes positive without evidence of hemolysis. Neutropenia has been reported in patients receiving more than 3 weeks of treatment.

CONCLUSION

Empirical treatment of moderate or severe CAP requiring hospital admission or 24h of observation should include a ß-lactam. Ceftaroline is an alternative that has demonstrated greater clinical efficacy than ceftriaxone in several clinical trials. The greatest difference between the two options has been seen in patients with *S. aureus* infection, which is to be expected given the low intrinsic activity of ceftriaxone against this pathogen. This makes ceftaroline the ß-lactam of choice when *S. aureus* is suspected (e.g. co-infection with influenza virus). The greater benefit observed in patients with moderate CAP, a prevalence of *S. pneumoniae* strains with intermediate susceptibility to ceftriaxone of 10% in many areas of the world [3] and a higher incidence of *S. aureus* among severe forms of CAP suggest that treatment of patients with severe CAP should include ceftaroline for at least the first 48-72h until microbiological results are available. Further studies on its efficacy in this population group are needed in the future.

CONFLICTS OF INTEREST

AS has received honoraria for lectures and advisory boards from Pfizer, MSD, Shionogi, Menarini, Angelini and Gilead.

REFERENCES

1. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67. doi: 10.1164/rccm.201908-1581ST.
2. Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: A Novel Cephalosporin with Activity against Methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis. 2011;52(9):1156-63. doi: 10.1093/cid/cir147
3. Sader HS, Mendes RE, Le J, Denys G, Flamm RK, Jones RN. Antimicrobial Susceptibility of Streptococcus pneumoniae from North America, Europe, Latin America, and the Asia-Pacific Region: Results From 20 Years of the SENTRY Antimicrobial Surveillance Program

(1997-2016). Open Forum Infect Dis. 2019;6(Suppl 1):S14-S23. doi: 10.1093/ofid/ofy263.

4. Smith JR, Barber KE, Raut A, Aboutaleb M, Sakoulas G, Rybak MJ. β-Lactam combinations with daptomycin provide synergy against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. J Antimicrob Chemother. 2015;70(6):1738-43. doi: 10.1093/jac/dkv007.
5. Cristinacce A, Wright JG, Stone GG, Hammond J, McFadyen L, Raber S. A Retrospective Analysis of Probability of Target Attainment in Community-Acquired Pneumonia: Ceftaroline Fosamil Versus Comparators. Infect Dis Ther. 2019;8(2):185-198. doi: 10.1007/s40121-019-0243-4.
6. Taboada M, Melnick D, Iaconis JP, Sun F, Zhong NS, File TM, et al. Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2016;71(4):862-70. doi: 10.1093/jac/dkv415.
7. Lodise TP, Anzueto AR, Weber DJ, Shorr AF, Yang M, Smith A, et al. Assessment of time to clinical response, a proxy for discharge readiness, among hospitalized patients with community-acquired pneumonia who received either ceftaroline fosamil or ceftriaxone in two phase III FOCUS trials. Antimicrob Agents Chemother. 2015;59(2):1119-26. doi: 10.1128/AAC.03643-14.