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CLINICAL STUDY

Clinical Efficacy of Ceftaroline Fosamil in Patients with Severe Pneumonia in Intensive Care Unit

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Abstract

Objective: To evaluate our experience over the routine practice in the use of Ceftaroline fosamil (CF) as a treatment of severe community pneumonia in Intensive Care Unit (ICU) patients and to do a comparative with conventional antibiotics in terms of clinical efficacy.

Method: A retrospective observational study in ICU patients with were diagnosed of severe pneumonia and were treated at least 72 hours with CF in comparation with other antibiotics that are used usually for the treatment of pneumonia.

Results: We evaluate 121 patients. 34 of them (28.2%) were treated with CF and 87 (71.9%) with other antibiotic, ceftriaxone in their majority (94.2%). If we compared CF group vs. comparative group: age (55.1 ± 15.5 vs. 63.1 ± 15.2 years; $p = 0.01$), invasive mechanical ventilation (64.7% vs. 40.2%; $p < 0.01$), septic shock at admission (76.5% vs. 50.6%; $p < 0.001$), bacteremia (41.2% vs. 9.4%; $p < 0.001$). SOFA and FINE severity criteria at admission had higher scores in Ceftaroline group ($p = 0.01$). The rate of cure clinical criteria at 72 hours (82.4% vs. 54%; $p = 0.004$), criteria of clinical cure at end of treatment (97.1% vs. 75.9%; $p = 0.007$). There was no difference in early mortality and 30 days mortality, however the number of patient who died for pneumonia; 0% vs. 63.2%; $p = 0.007$.

Conclusion: In this study, the use of CF in the treatment of severe pneumonia in ICU, in comparative with conventional antibiotics, have been shown a higher clinical efficacy with better clinical respond in terms of early response and cure rate at end of treatment.

Keywords

Ceftaroline, Severe pneumonia, ICU, Antibiotics

Introduction

Severe community acquired pneumonia is entity with high mortality, it needs effective and early antibiotic therapy, and often the patients need admission in intensive care unit to receive respiratory support.

Appearance of new antibiotics have been expanding the therapeutic efficacy, that approves of Ceftaroline fosamil to treat community acquired pneumonia have allowed to use it as a part of usual therapeutic arsenal and it have shown an earlier clinic response and higher cure rate.

The goal of the study is to evaluate our experience with de use of Ceftaroline in patients with pneumonia and compare with conventional antibiotics in terms of clinical efficacy.

Material and Method

We did a retrospective evaluation of critical patients that were admitted in ICU in hospital Virgen de la Salud, in Toledo, Spain, with diagnosis of community acquired pneumonia (CAP) between January/2017 and December/2019, who were treated with antibiotics at least for 72 hours according to the choice of the physician in charge. The diagnosis of Pneumonia was reviewed and defined like all acute pulmonary infection with alveolar affectation that appears in a patient with recently exposure [1].

Patients were classified in two cohorts:

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- Those with Ceftaroline treatment: Initial dose 600 mg IV q8h (With renal adjustment if require) for 48-72 hours, and then 600 mg q12h or deescalate to targeted treatment.

- Those with another treatment (Not Ceftaroline): With habitual dosage.

It was registered basal data as: comorbidity, initial data of ICU admission, outcomes in ICU and conventional hospitalization. Severity was assessed with the SOFA on admission and the FINE. The severity of the infection was classified according to the third international consensus definition for sepsis and septic shock [2]. It was defined combination therapy as treatment with two or more antibiotics for at least a half of all treatment [3]. It was defined clinical cure as a disappear of all semiology related with pneumonia or a clinical improvement that make unnecessary continue of any more antibiotic. A favorable clinical response was a resolute the symptoms and signs: Early in the 3 first days. If symptoms and signs persist or make worse, or died occurs, it was defined as an unfavorable clinical response. The pneumonia associated die it was defined as symptoms and signs that persist and cause dead without another cause that justifies it.

Statistical analysis

Numerical variables are expressed like median ± standard deviation, and categoric variables like percentage. To comparative between Ceftaroline group and other antibiotic we use a Student´s T for numeric variables; for categoric variables we use Chi-square with Fisher´s test if didn´t meet the application conditions. We considered a significative result $p < 0.05$.

Results

121 patients with CAP were admitted during de study period; 34 (28.1%) were treated with Ceftaroline fosamil and 87 (71.9%) were treated with another antibiotic, 82 with ceftriaxone (94.2%), 2 with piperacillin-tazobactam (2.2%), 2 with cefepime (2.2%), and 1 with cloxacillin (1.1%). 110 patients received combinate therapy (91.6%), 70 with quinolone (57.8%) and 40 with macrolide (33%).

Table 1 shows basal characteristics, comorbidity, ini-

Table 1: Basal data, comorbidity, initial clinical and microbiological data in patients with Ceftaroline and another antibiotic.

	Ceftaroline (N = 34) (28.1%)	**Another Antibiotic (N = 87) (71.9%)**	**p**
Sex male	20 (58.8%)	65 (74.7%)	0.09
Age (years)	55.1 ± 15.5	63.1 ± 15.2	0.01
Institutionalized	0	4 (4.6%)	0.204
Comorbidity			
Smoke	12 (35.3%)	21 (24.1%)	0.216
Diabetes mellitus	8 (23.5%)	18 (20.7%)	0.732
Alcohol abuse	0	4 (4.6%)	0.204
Neoplasm	3 (8.8%)	2 (2.3%)	0.105
COPD	7 (20.6%)	21 (24.1%)	0.677
Asthma	2 (5.9%)	0	0.023
Chronic hepatopathy	4 (11.8%)	7 (8%)	0.522
Corticoids	2 (5.9%)	11 (12.6%)	0.280
Immunosuppressor therapy	2 (5.9%)	6 (6.9%)	0.840
Initial data in ICU			
Type of sepsis			
Sepsis	8 (23.5%)	43 (49.4%)	
Septic shock	26 (76.5%)	44 (50.6%)	0.01
Mechanical Ventilation	22 (64.7%)	35 (40.2%)	0.01
Vasoactive drugs	28 (82.4%)	44 (50.6%)	0.001
Procalcitonin (ng/ml)	23.6 ± 28.5	11.8 ± 23.6	0.025
Procalcitonin at third day (ng/ml)	6.9 ± 7.2	6.4 ± 11.1	0.803
ICU associated treatment			
Macrolide	18 (90%)	22 (45.8%)	0.001
Quinolone	13 (86.7%)	57 (78.1%)	0.453
Corticoids	9 (26.5%)	27 (31.4%)	0.596
Microbiological data			

Positive blood culture	14 (41.2%)	8 (9.4%)	< 0.001
Positive Bronquial secretion culture positivo	7 (20.6%)	12 (13.8%)	0.356
Positive urine Antigens	16 (47.1%)	18 (20.7%)	0.004
Results			
Pneumococcus	17 (50%)	18 (20.7%)	
Others	4 (11.8%)	22 (25.3%)	
Negative	13 (38.2%)	47 (54%)	0.005

Another antibiotic group includes treatment with ceftriaxone, piperacillin tazobactam, cefepime or cloxacillin. Quantitative data are expressed like median ± standard deviation and categoric data like percentage. COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit [2].

Table 2: Severity scores, stay, clinical respond, and outcomes in Ceftaroline group versus another antibiotic.

	Ceftaroline (N = 34) (28.1%)	**Another Antibiotic (N = 87) (71.9%)**	p
Severity of clinical presentation			
SOFA at admission	7.6 ± 2.9	5.6 ± 3.01	0.001
FINE	4.4 ± 0.7	3.6 ± 1.2	0.001
Stay			
Stay in ICU (days)	18.9 ± 15.5	9.4 ± 12.8	0.001
Stay in hospital (days)	28.9 ± 20.4	17.01 ± 19.1	0.003
Clinical response			
Cure criteria: End of treatment	33 (97.1%)	66 (75.9%)	0.007
Clinical improvement in 72 hours	28 (82.4%)	47 (54%)	0.004
Mortality			
Hospital death	6 (17.6%)	22 (25.3%)	0.370
Early death (< 3 days)	1 (25%)	8 (36.4%)	0.660
Death at 30 days	3 (75%)	12 (80%)	0.827
Related Mortality	0	12 (63.2%)	0.007

Another group includes treatment with ceftriaxone, piperacillin-tazobactam, cefepime or cloxacillin. Quantitative data are expressed like median ± standard deviation and categoric data like percentage; SOFA: Sequential Failure Assessment Score; ICU: Intensive care unit.

tial data in ICU and microbiological data in relation with Ceftaroline versus another antibiotic. Table 2 shows results of comparative between the 2 groups (Ceftaroline and another antibiotic) according to scores, stay and clinical evolution.

Discussion

Ceftaroline is a new cephalosporin with bactericide effect against Gram positive pathogens (include *Streptococcus pneumoniae* penicillin-resistant and *Staphylococcus aureus* methicillin-resistant), Gram negative pathogens (Haemophilus influenzae, Moraxella Catarrhalis, etc.), and cephalosporin-sensitive Enterobacteria. Their union to blood proteins is low (20% vs. 90% for ceftriaxone), which favors penetration on epithelial lining liquid [4,5]. This excellent penetration in lungs have been led to use it in the empiric and targeted treatment of community acquired pneumonia [6,7]. Ceftaroline is 16 times more powerful against *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA), 6 times more powerful against *Streptococcus pneumoniae* compared with ceftriaxone, even with higher minimum inhibitory concentrations for penicillin, and 4 to 8 times more powerful against Moraxella catarrhalis in comparative with ceftriaxone [8]. All the studies *in vitro* and animal models shown a better activity against *Streptococcus pneumoniae* and *Staphylococcus aureus* including MRSA and PVL- producing strain in simulating models of pneumonia. All of this can be justified by the better affinity of the Ceftaroline for penicillin binding proteins (PBP) in comparative with ceftriaxone, especially for PBP 2a [9]. In addition of this excellent activity *in vitro*, it has been shown that the prolonged exposure to Ceftaroline fosamil does not implies the appearance of resistance for the most microorganisms that can cause CAP, and neither have been described cross-resistance with another antibiotic families [7].

Its approval for the treatment of pneumonia in adults was based y two third phase clinical trials (FOCUS 1 and 2) that shown Ceftaroline was non-inferior to empiric standard treatment, with comparable security profile [10,11]. Subsequently appear studies that point to better efficacy than comparative antibiotic, with earlier clinical respond and better rate of clinical cure. This

has a special interest in ICU patients which need faster activity in front to major severity.

We review the differences between uses of Ceftaroline versus another antibiotic in ICU patients with CAP in our usual practice. There is a selection bias, because our Ceftaroline group was younger but more serious (greater SOFA, FINE, Procalcitonin at admission, and use of vasoactive drugs). Some patients of Ceftaroline group proceeded of hospitalization plant which were have treated with another antibiotic, with bad clinical outcome and who required ICU admission, and Ceftaroline was a rescue therapy. We believe that it was reserved the "new antibiotic" for young people with poor outcomes. This involves longer stay in ICU and in hospitalization plant for the Ceftaroline group. Despite more severity and the presence of patients with rescue therapy in Ceftaroline group, it was obtained a better early clinical respond (First 72 hours), 50% better, better healing rate and lower mortality rate, all of these with statistically significant results. Our results match with another studies than compare Ceftaroline fosamil with ceftriaxone in the treatment of PAC in inpatient with risk class PORT III-IV [12-14]. In the integrated FOCUS-1 and FOCUS-2 the cure rate for the clinically evaluable population was 84.3% in the Ceftaroline group, compared to 77.7% in ceftriaxone, what it means a difference of 6.7% (confidence interval [CI] of 95%, 1.6-11.8). Results in the microbiologically evaluable population were similar: 85.1% for Ceftaroline versus 75.5% for Ceftriaxone. In patients with bacteremia the cure was 71% for Ceftaroline and 58.8% for ceftriaxone. Healing was earlier in the Ceftaroline group, on the fourth day 69.5% of patients in the Ceftaroline group compared to 59.4% of the ceftriaxone group had achieved the stability defined by the normalization of vital signs and improvement in at least 1 of the 4 guiding symptoms (cough, dyspnea, pleuritic pain, and sputum production). Among patients with *S. pneumoniae* infection this better response was more marked; Ceftaroline 73%, ceftriaxone 56% [15].

On the other hand, in our study, the fact that in some patients of Ceftaroline group had previously started another antimicrobial with poor clinical response, could have obscured the results in this group, but nevertheless the clinical improvement obtained with respect to comparator treatment continues to be maintained.

Our study has the disadvantage of being retrospective and not as homogeneous as you would like, but it show Ceftaroline fosamil acts in the usual clinical practice of patients with severe NAC who enter ICU and shows us a path that seems to provide good results in that group of patients.

In conclusion, in our study the use of Ceftaroline fosamil in the treatment of severe NAC entering ICU, in relation to other conventional antibiotics used, has demonstrated superior clinical efficacy with an earlier favorable clinical response and higher cure rate at the end of treatment.

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