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 comparison 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 comparison 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 comparison 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 affection that appears in a patient with recently exposure [1].

Patients were classified in two cohorts:
- 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 target-ed treatment.

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

It was registered basal data as: comorbidity, initial data of ICU admission, outcomes in ICU and convention-al 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 semio-logy related with pneumonia or a clinical improvement that make unnecessary continue of any more antibiotic. A favorable clinical response was a resolute the symp-toms 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 pneu-monia 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 per-centage. 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 an-tibiotic, 82 with ceftriaxone (94.2%), 2 with piperacil-lin-tazobactam (2.2%), 2 with ceftepime (2.2%), and 1 with cloxacillin (1.1%). 110 patients received combine therapy (91.6%), 70 with quinolone (57.8%) and 40 with macrolide (33%).

**Table 1** shows basal characteristics, comorbidity, ini-

|                                | 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 | 7 (20.6%) | 12 (13.8%) | 0.356
Positive urine Antigens | 16 (47.1%) | 18 (20.7%) | 0.004

**Results**

- **Pneumococcus**
  - Ceftaroline: 17 (50%)
  - Other: 4 (11.8%)
  - Negative: 13 (38.2%)
- **Others**
  - Ceftaroline: 18 (20.7%)
  - Other: 22 (25.3%)
  - Negative: 47 (54%)

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].

| Severity scores, stay, clinical respond, and outcomes in Ceftaroline group versus another antibiotic. |
|---------------------------------------------------------------|
| **Ceftaroline** | **Another Antibiotic** | *p* |
| (N = 34) | (N = 87) (71.9%) | |
| 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 |

Discussion

Ceftaroline is a new cephalosporin with bactericidal 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 has 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 upon 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 Ceftriaxone 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 statistically significant results. 

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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