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Clinical Study

Assessment of ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia due to *Streptococcus pneumoniae*: insights from two randomized trials☆,☆☆,☆☆☆,★,★★

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ABSTRACT

Ceftaroline fosamil resulted in higher cure rates than ceftriaxone in patients with community-acquired bacterial pneumonia in 2 randomized trials (FOCUS 1 and FOCUS 2). The present analysis examines the subgroup of patients with *Streptococcus pneumoniae* infection to determine whether the apparent difference in cure rates persists after adjusting for potential covariates. We retrospectively pooled subjects with *S. pneumoniae* isolated at baseline in the original studies and employed logistic regression to evaluate the independent relationship between clinical cure and treatment with ceftaroline. Covariates evaluated included demographics, severity of illness, bacteremia, and pathogen characteristics. The final cohort included 139 subjects (69 ceftaroline, 70 ceftriaxone). Unadjusted cure rates were 85.5% and 68.6% ($P = 0.009$) in the ceftaroline and ceftriaxone groups, respectively. After logistic regression, ceftaroline remained associated with higher cure rates. Our findings indicate that ceftaroline may result in improved outcomes of *S. pneumoniae* pneumonia. Formal clinical trials are warranted to confirm this hypothesis.

1. Introduction

Community-acquired bacterial pneumonia (CABP) is the leading cause of infectious disease-related death in the United States (Niederman et al., 2001; Xu et al., 2010). The clinical and economic burden associated with this disease is considerable (Adamuz et al., 2011; Jencks et al., 2009; Welte et al., 2012). CABP remains a leading cause of hospital admission (File and Marrie, 2010; Hall et al., 2010; Niederman, 2009), and rehospitalization is common following discharge after CABP (Adamuz et al., 2011; Jencks et al., 2009). *Streptococcus pneumoniae* continues to represent the predominant causative bacterial pathogen in CABP (Mandell et al., 2007; Richter et al., 2009), and the evolution in the prevalence of drug-resistant serotypes of *S. pneumoniae* may present clinical challenges for the treatment of patients infected with these strains (Cornick and Bentley, 2012; Gertz et al., 2010; Jones et al., 2010; Moore et al., 2008; Richter et al., 2009).

Ceftaroline fosamil is a broad-spectrum cephalosporin prodrug with bactericidal activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant *S. pneumoniae*, as well as select Gram-negative pathogens (Ge et al., 2008; Iizawa et al., 2004; Sader et al., 2005). In 2 pivotal, randomized, comparative clinical trials of the treatment of CABP, FOCUS 1 and FOCUS 2 (ceFtarOline Community-acquired pneUmonia trial vS ceftriaxone), ceftaroline fosamil was noninferior to ceftriaxone with respect to clinical cure rates. In the integrated analysis of the FOCUS trials, which pooled all subjects across the studies, the clinical cure rate among clinically evaluable (CE) patients was 84.3% in the ceftaroline fosamil group compared with 77.7% in the ceftriaxone

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group (File et al., 2010). In both studies, ceftaroline fosamil demonstrated noninferiority to ceftriaxone. As one would predict, *S. pneumoniae* represented the most commonly identified bacterial pathogen in the FOCUS trials. In both trials, clinical cure rates were numerically higher among patients with CABP caused by *S. pneumoniae* in persons randomized to ceftaroline fosamil (FOCUS 1: 88.9% versus 66.7%; FOCUS 2: 83.3% versus 70.0%, respectively) (File et al., 2011; Low et al., 2011). Because of these observations, we sought to better describe outcomes in subjects with CABP due to *S. pneumoniae*. Specifically, we aimed to conduct exploratory analyses examining the characteristics of the patients with CABP due to *S. pneumoniae* and the various serotypes recovered. We additionally focused on assessing the potential independent relationship between clinical cure rates for *S. pneumoniae* CABP and treatment with ceftaroline fosamil.

2. Methods

2.1. Study design and treatment

This study was supported by Forest Laboratories (New York, NY, USA). Cerexa (a wholly owned subsidiary of Forest Laboratories) was involved in the design, collection, analysis, interpretation of data, and decision to present these results. The FOCUS trials (NCT00621504 and NCT00509106) were global, double-blind, randomized, multicenter, multinational, noninferiority, phase III studies in patients hospitalized for moderate to severe CABP (Patient Outcomes Research Team [PORT] risk class III or IV) requiring intravenous (IV) antimicrobial therapy (File et al., 2010, 2011; Low et al., 2011). Prior to study initiation, all sites received approval from their institutional review board or independent ethics committee, and all patients provided written informed consent. Patients were randomized (1:1) to ceftaroline fosamil 600 mg IV q12h or ceftriaxone 1 g IV q24h for 5 to 7 days. Patients in FOCUS 1 also received 2 doses of oral clarithromycin 500 mg q12h on Day 1 to provide initial atypical pathogen coverage. The primary objective of the FOCUS studies was to determine noninferiority in the clinical cure rate of ceftaroline fosamil versus ceftriaxone evaluated at test of cure (TOC) (8 to 15 days post-therapy) in the CE and modified intent-to-treat efficacy (MITTE) populations. Safety was evaluated in the modified intent-to-treat (MITT) population.

2.2. Microbiologic assessment

Microbiological samples were collected from the respiratory tract (induced or expectorated sputum, pleural fluid, or bronchoalveolar lavage), blood, and urine (for pneumococcal and *Legionella* [serogroup 1] urinary antigen testing). Susceptibility testing was performed by broth microdilution tests and Kirby-Bauer disk diffusion tests, in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. All *S. pneumoniae* isolates were serotyped at a central laboratory using commercial group and type-specific antisera. Multidrug-resistant *S. pneumoniae* (MDRSP) were defined as isolates with resistance to 2 or more antimicrobial classes. If *S. pneumoniae* was only identified by urine antigen testing, then it was considered a CABP pathogen.

2.3. Subgroup analyses

This analysis evaluated the population of patients with *S. pneumoniae* isolated as a baseline pathogen. All authors had access to and reviewed the per-pathogen outcome data provided by Forest Laboratories. The following results are summarized: 1) baseline characteristics including relevant risk factors; 2) overall clinical cure and favorable microbiological response rates at TOC; 3) clinical cure rates according to method of pathogen identification (positive by urinary antigen only versus positive by culture, which included *S. pneumoniae* isolates identified by either respiratory or blood specimen); 4) clinical cure rates by *S. pneumoniae* baseline ceftaroline fosamil or ceftriaxone MIC and serotype; 5) clinical cure rates for patients with bacteremia caused by *S. pneumoniae*; and 6) odds ratios (ceftaroline fosamil/ceftriaxone) of clinical cure adjusted for relevant risk factors derived from the logistic regressions.

2.4. Statistics

Continuous variables were reported as mean ± the standard deviation. The *F* test from the general linear model with effect for protocol and treatment was used to compare mean age between treatment groups. Categorical data were expressed as frequency distributions, and the Cochran Mantel Haenszel (CMH) stratified by protocol was used to compare treatment groups.

An initial evaluation of pooled data comparing treatment groups suggested an advantage of ceftaroline fosamil over ceftriaxone in the subgroup of subjects with CABP due to *S. pneumoniae*. To further investigate the favorable clinical cure rate among patients treated with ceftaroline fosamil, additional exploratory analyses were conducted to compare cure rates between the 2 treatment arms (ceftaroline fosamil versus ceftriaxone) while accounting for baseline characteristics that could be considered predictive of the outcome.

We performed multiple logistic regression analysis to identify clinical risk factors that were associated with clinical outcome (SAS Institute, Cary, NC, USA). All risk factors, including potential interactions with treatment effects that were significant at the 0.10 level in the univariate logistic analysis (adjusted for protocol only), were included in the corresponding multivariable logistic analysis. All statistical tests were 2-sided, and a P value <0.05 was determined to represent statistical significance. The Hosmer–Lemeshow test was used to assess goodness of fit in selecting the model that best described the data.

3. Results

3.1. Baseline demographics and characteristics

Baseline demographics and characteristics for the subset of patients who had *S. pneumoniae* identified as a baseline pathogen (modified microbiological intent-to-treat efficacy [mMITTE] population) are shown in Table 1. The final cohort for this analysis included 139 subjects. The baseline characteristics of persons treated with ceftaroline fosamil were similar to those of patients treated with ceftriaxone. Specifically, with respect to severity of illness, 50.7% of persons in the ceftaroline fosamil group had a PORT score of IV as compared to 47.1% in the ceftriaxone group. Most patients met the criteria for the systemic inflammatory response syndrome (SIRS) (85.5% ceftaroline fosamil versus 84.3% ceftriaxone). Severe pneumonia as classified based on the modified American Thoracic Society (ATS) criteria occurred in 31.9% and 45.7% of ceftaroline fosamil and ceftriaxone subjects, respectively. Table 1 outlines the individual modified ATS criteria incidence. As noted, no criteria were significantly imbalanced. There was no difference either in the rates of bacteremia between the 2 treatment arms. No patient was enrolled as a prior antibiotic failure; prior antibiotic use consisted only of a single dose of a short-acting antibiotic in select patients (Table 1). Overall, baseline demographics in patients whose pathogens were identified solely by urinary antigen were similar to those in the general mMITTE population.

Of the *S. pneumoniae* identified, 13 were MDRSP (4 in the ceftaroline fosamil group and 9 in the ceftriaxone group). Identification of *S. pneumoniae* was made solely by positive urinary antigen for 40.6% (28/69) and 44.3% (31/70) of the ceftaroline fosamil and ceftriaxone groups, respectively (Table 2). Coinfection with an atypical pathogen