Pharmacokinetic-Pharmacodynamic Analyses for Efficacy of Ceftaroline Fosamil in Patients with Community-Acquired Bacterial Pneumonia

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Pharmacokinetic-pharmacodynamic (PK-PD) analyses for efficacy using Phase 3 data from patients treated with ceftaroline fosamil 600 mg IV q12h for 5-7 days for community-acquired bacterial pneumonia (CABP) were conducted. High clinical and microbiological success rates (84.7% and 86.3%, respectively) and f %T>MIC values (98.4% had f %T>MIC ≥ 63.3) were observed among 124 microbiologically evaluable patients. As a result, significant PK-PD relationships could not be identified. These data provide support for the ceftaroline fosamil 600 mg IV q12h dosing regimen to treat patients with CABP.
Results of pharmacokinetic-pharmacodynamic (PK-PD) analyses have increasingly been used to support drug development, both early in development to make decisions about dose and then in late stage development to confirm these decisions (1). Such analyses were carried out for ceftaroline fosamil, a water-soluble prodrug of ceftaroline (2). Ceftaroline is a broad-spectrum cephalosporin with activity against pathogens commonly associated with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*, respectively. Ceftaroline fosamil is approved by the FDA for the treatment of patients with ABSSSI and CABP and for similar such indications in Europe (3, 4, 5).

Using data from ceftaroline-treated patients with ABSSSI enrolled in two Phase 2 and two Phase 3 studies, PK-PD analyses for efficacy were carried out (2). Results of these analyses demonstrated a relationship between ceftaroline exposure, as measured by the percent of time during the dosing interval that free-drug steady-state concentrations remain above the MIC (\(t\% \text{T}>\text{MIC}\)), and microbiological response. Given that ceftaroline fosamil 600 mg intravenous (IV) every 12 hours (q12h) provided exposures associated with the upper plateau of the PK-PD relationship identified for efficacy, these data provided support for this dosing regimen for the treatment of patients with ABSSSI. The objective of the analyses described herein was to conduct similar such PK-PD analyses for efficacy using data from two Phase 3 studies in patients with CABP.
(ClinicalTrials.gov registration numbers NCT00621504 and NCT00509106) in which the efficacy and safety of ceftaroline fosamil 600 mg IV q12h was evaluated (6, 7).

In each of the above-described Phase 3 studies, patients received two consecutive infusions of 300 mg IV ceftaroline fosamil q12h, each infused over 30 minutes for a total dose of 600 mg and total infusion time of 60 minutes, with dose adjustments in patients with moderate renal impairment. The total duration of treatment was 5 to 7 days.

Patients were eligible for inclusion if they were at least 18 years of age with CABP and if they required initial hospitalization or emergency room care and treatment with IV antimicrobial agents. Patients were also required to have radiographic evidence of pneumonia, acute illness with at least three clinical signs or symptoms consistent with lower respiratory tract infection, and PORT Risk Class III or IV. Additional details regarding the inclusion and exclusion criteria for these studies are provided elsewhere (6, 7).

Patients were evaluated for clinical and microbiological response at the Test-of-Cure visit, which occurred 8-15 days post-therapy. Clinical response was classified as a cure if there was total resolution of all signs and symptoms of CABP or improvement such that further antimicrobial therapy was not necessary. Patients were classified as failure if persistence, incomplete resolution or worsening in signs and symptoms of CABP that required further antimicrobial therapy, discontinuation of study medication, or death, wherein CABP was considered causative, occurred. Microbiological response was
classified as favorable if the baseline pathogen was eradicated or presumed eradicated and unfavorable if baseline pathogen persisted or was presumed to persist.

Ceftaroline fosamil and ceftaroline plasma concentrations were collected on Day 3 of therapy (approximately 15 minutes prior to a dose, within 5 minutes following the end of the second consecutive 30 minutes infusion between 1 and 3 hours after the end of the second infusion, and between 4 and 8 hours after the end of the second infusion) from a subset of patients who participated in each of the two Phase 3 studies. The final population pharmacokinetic (PK) models for ceftaroline fosamil and ceftaroline were used to generate steady-state ceftaroline concentrations during the 12-hour dosing interval. Free-drug concentrations for ceftaroline were determined using a protein binding estimate of 20% and used in the calculation of \( f \%T>MIC \), the PK-PD index most predictive of ceftaroline efficacy based on pre-clinical data. It should be noted that only 28 CABP patients with PK data collected were in the ME population. In order to utilize data for all patients with CABP in the ME population for the PK-PD analyses, \( f \%T>MIC \) values were also calculated for patients without PK data (n=96) using the population PK models for ceftaroline fosamil and ceftaroline and patient covariate data as prior information.

To support the use of population mean predicted \( f \%T>MIC \) as a surrogate for individual predicted \( f \%T>MIC \) values, the bias and precision of these exposure measures were examined for all patients with PK data by assessing the distribution of the percent predicted error (PE%) and the absolute predicted error (|PE|), respectively.
was calculated as the population mean predicted f %T>MIC value minus the individual predicted f %T>MIC value multiplied by 100 and then divided by the individual predicted f %T>MIC. Among the 28 patients in the ME population with PK data, median (min, max) values for PE% and |PE%| were 0% (-19.59%, 9.09%) and 0% (0%, 19.59%), respectively. The coefficient of determination ($r^2$) for the relationship between population mean predicted and individual predicted f %T>MIC values was 0.974. Given these findings, population mean predicted f %T>MIC represented a reasonable surrogate for individual predicted f %T>MIC for those ME patients who did not have PK data. Thus, using individual predicted and population mean predicted f %T>MIC values, PK-PD analyses were carried out using data from all of the ME patients (n=124).

Among the 124 ME patients evaluated, the median (min, max) age, creatinine clearance, and weight was 59 (21, 99) years, 69.0 (30.2, 188) mL/min/1.73 m$^2$, and 70.0 (36.0, 160) kg, respectively. Percentages of patients in PORT risk class III and IV were 59.7% and 40.3%, respectively. A total of 35 patients had $S.\ pneumoniae$ isolated at baseline. Other pathogens isolated at baseline included $Enterobacteriaceae$ spp. (n=45) and $Haemophilus influenzae$ or $Haemophilus parainfluenzae$ (n=30). Percentages of successful clinical and microbiological response were 84.7% and 86.3%, respectively. A total of 108 (87.1%) patients had f %T>MIC equal to 100; 91.1% of patients had f %T>MIC ≥ 91.7 and 98.4% of patients had f %T>MIC ≥ 63.3. Minimum, MIC$_{50}$, MIC$_{90}$, and maximum values upon which f %T>MIC values were based were ≤ 0.004, 0.03, 0.5, and 16 mg/L, respectively.
PK-PD analyses were conducted using the software program, R version 2.4.1 (11). Chi-square or Fisher’s exact test for %T>MIC assessed as categorical independent variables and logistic regression for %T>MIC assessed as a continuous independent variable were used to evaluate univariable relationships for clinical and microbiological response. Categorical variables for %T>MIC were constructed using classification and regression tree (CART) analysis to derive dichotomous variables. Breakpoint pairs that split continuous %T>MIC into three groups were also assessed to investigate potential non-linearity, with an optimal pair chosen based on that which achieved the greatest statistical significance when comparing three groups of at least ten patients in each group.

Despite the evaluation of all patients in the ME population, results of univariable analyses failed to demonstrate significant relationships between clinical or microbiological response and %T>MIC. However, given the limited number of failures and predominantly high %T>MIC values, PK-PD relationships for efficacy, even if present, would have been difficult to identify. Given these findings and that the rate of bactericidal activity of β-lactams has been shown to be maximized at low multiples of the MIC (approximately 4-8 X MIC) based on historical in vivo (12) and prospective clinical data from infected patients recently described by Tam et al. (13), additional univariable analyses were carried out using the percent of time during the dosing interval that free-drug steady-state concentrations remain above various threshold (f %T>threshold) values. The threshold values represented multiples of the MIC. Those chosen for further evaluation, 4 to 64 times the MIC, were selected to achieve a
reasonable scatter of data across the $\text{%T} >$ threshold range from 0 to 100. However, the results of these analyses also failed to reveal significant PK-PD relationships.

In conclusion, high percentages of clinical and microbiological success and high $\text{f \%T} > \text{MIC}$ values were observed among ME patients. Failure to identify relationships between $\text{f \%T} > \text{MIC}$ and response was not surprising since the exposure range based on the ceftaroline fosamil dosing regimen administered and the MIC distribution for pathogens resulted in a narrow range of high $\text{f \%T} > \text{MIC}$ values; the majority of patients (91.1%) had $\text{f \%T} > \text{MIC}$ values ranging from 91.7 to 100. The results described herein together with non-clinical $\text{f \%T} > \text{MIC}$ targets for *S. pneumoniae* (9) suggest that patients had exposures associated with the upper plateau of the PK-PD relationship for efficacy. Thus, these data provide support for the adequacy of exposure of ceftaroline fosamil 600 mg IV q12h to treat patients with CABP.
References


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