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Pharmacokinetic/pharmacodynamic analysis to evaluate ceftaroline fosamil dosing regimens for the treatment of community-acquired bacterial pneumonia and complicated skin and skin-structure infections in patients with normal and impaired renal function

A. Canut[a,b], A. Isla[c,d], A. Rodríguez-Gascón[c,d,*]

[a] Microbiology Service, Hospital Universitario de Álava, Servicio Vasco de Salud Osakidetza, Vitoria-Gasteiz, Spain
[b] Instituto de Investigación Sanitaria de Álava (BIOARABA), Servicio Vasco de Salud Osakidetza, Vitoria-Gasteiz, Spain
[c] Pharmacokinetics, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain
[d] Centro de Investigación Lascaray ikergunea, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain

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ABSTRACT

In this study, the probability of pharmacokinetic/pharmacodynamic target attainment (PTA) of ceftaroline against clinical isolates causing community-acquired bacterial pneumonia (CABP) and complicated skin and skin-structure infection (cSSSI) in Europe was evaluated. Three dosing regimens were assessed: 600 mg every 12 h (q12 h) as a 1-h infusion (standard dose) or 600 mg every 8 h (q8 h) as a 2-h infusion in virtual patients with normal renal function; and 400 mg q12 h as a 1-h infusion in patients with moderate renal impairment. Pharmacokinetic and microbiological data were obtained from the literature. The PTA and the cumulative fraction of response (CFR) were calculated by Monte Carlo simulation. In patients with normal renal function, the ceftaroline standard dose (600 mg q12 h as a 1-h infusion) can be sufficient to treat CABP due to ceftazidime-susceptible (CAZ-S) *Escherichia coli*, CAZ-S *Klebsiella pneumoniae*, meticillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (CFR > 90%). However, against meticillin-resistant *S. aureus* (MRSA), the CFR was 72%. In cSSSI, the CFR was also <80% for MRSA. Administration of ceftaroline 600 mg q8 h as a 2-h infusion or 400 mg q12 h as a 1-h infusion in patients with moderate renal insufficiency provided a high probability of treatment success (CFR ca. 100%) for most micro-organisms causing CABP and cSSSI, including MRSA and penicillin-non-susceptible *S. pneumoniae*. These results suggest that in patients with normal renal function, ceftaroline 600 mg q8 h as a 2-h infusion may be a better option than the standard dose, especially if the MRSA rate is high.

1. Introduction

Ceftaroline fosamil is a novel, parenteral, broad-spectrum, bactericidal, advanced-generation cephalosporin that shows potent activity against many bacteria owing to its high binding affinity to penicillin-binding proteins (PBPs), especially PBP2a in meticillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x in penicillin-resistant *Streptococcus pneumoniae* [1]. Recently, ceftaroline fosamil was approved in the USA and Europe as an intravenous (i.v.) treatment for patients with complicated skin and skin-structure infections (cSSSIs) and community-acquired bacterial pneumonia (CABP) [2]. Clinical trials have demonstrated non-inferiority in terms of cure rates (clinical and microbiological) compared with vancomycin in the treatment of cSSSI and compared with ceftriaxone in the treatment of CABP [3]. Ceftaroline demonstrated a safety profile similar to that of comparator drugs in clinical trials [3].

Ceftaroline is administered at a standard dose of 600 mg every 12 h (q12 h) as a 1-h i.v. infusion. Dose adjustment (400 mg q12 h) is proposed in patients with moderate and severe renal impairment, whilst no dosing regimen is proposed for end-stage renal disease [4]. A critical step in dose selection is an understanding

* Corresponding author. Present address: Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Paseo de la Universidad n° 7, 01006 Vitoria, Spain.
Tel.: +34 945 013 094; fax: +34 945 013 040.
E-mail address: alicia.rodriguez@ehu.es (A. Rodríguez-Gascón).

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of the pharmacokinetic/pharmacodynamic (PK/PD) goal for treatment, derived from PK/PD modelling, in order to maximise the likelihood of a favourable clinical/microbiological response as well as to minimise the probability of exposure-related toxicities [5]. Results of PK/PD analyses have increasingly been used to support drug development, both early in development to make decisions about dosing regimens and then in late-stage development to confirm these decisions [6].

For cephalosporin antibiotics, the PK/PD index that best relates to patient outcome is the fraction of time during the dosing interval for which the free drug concentration remains above the minimum inhibitory concentration (MIC) for the infecting pathogen(s) ($fT_{>MIC}$) [7]. With knowledge of the exposure targets necessary for optimal clinical response, Monte Carlo simulation can be used to combine pharmacokinetic, pharmacodynamic and microbiological data and inform dose selection [8].

The goal of this study was to evaluate the probability of attaining targeted pharmacodynamic exposure of intravenously administered ceftaroline against different clinical isolates causing CABP and cSSSI. Three dosing regimens were evaluated: 600 mg q12 h as a 1-h infusion in simulated patients with normal renal function (standard dose); 400 mg q12 h as a 1-h infusion in simulated patients with moderate renal impairment; and 600 mg every 8 h (q8 h) as a 2-h infusion in simulated patients with normal renal function, since in a recent phase 1 clinical trial [9] this dosing regimen was also administered to healthy volunteers.

2. Methods

The methodology included the following steps: (i) dosing regimen selection and acquisition of pharmacokinetic data; (ii) microbiological data acquisition; and (iii) Monte Carlo simulation of different i.v. dosing regimens of ceftaroline fosamil in two patient populations, namely patients with normal renal function and patients with moderate renal impairment. Monte Carlo simulation allowed us to estimate the probability of target attainment (PTA), defined as the probability that at least a specific value of a PK/PD index is achieved at a certain MIC, and to calculate the cumulative fraction of response (CFR), defined as the expected population PTA for a specific drug dose and a specific population of micro-organisms [10].

Table 1
Mean ± standard deviation pharmacokinetic parameters of ceftaroline from published studies in patients with normal renal function and in patients with moderate renal impairment [11–13].

Group	V (L)	CL (L/h)	f_u
Normal renal function	20.39 ± 4.87	8.10 ± 1.54	0.8
Moderate renal insufficiency	20.39 ± 4.87	4.44 ± 0.54	0.8

V, volume of distribution; CL, total body clearance; f_u, unbound fraction.

2.1. Dosing regimen selection and acquisition of pharmacokinetic data

Three dosing regimens were evaluated: i.v. administration of 600 mg ceftaroline q12 h infused over 1 h and 600 mg q8 h infused over 2 h for patients with normal renal function [creatinine clearance (CL_{Cr}) of 80–120 mL/min]; and 400 mg q12 h infused over 1 h for patients with moderate renal impairment (CL_{Cr} of 30–50 mL/min).

Pharmacokinetic parameters were obtained from published studies [11–13]. Pharmacokinetic studies were identified using PubMed, the National Library of Medicine's search engine for the Medline® database. Studies were included if they evaluated the selected dosing regimens after multiple-dose administration and provided the mean and standard deviation for the pharmacokinetic parameters of interest for each patient group. Pharmacokinetic parameters (volume of distribution and clearance values and their variability in the different groups of patients) from non-compartmental analysis were selected. Table 1 shows the pharmacokinetic parameters of ceftaroline [total body clearance (CL), volume of distribution (V) and unbound fraction (f_u)] used to estimate the $fT_{>MIC}$.

2.2. Acquisition of microbiological data

Susceptibility data for ceftaroline fosamil against pathogens associated with CABP and cSSSI in Europe were obtained from

Table 2
Activity of ceftaroline against bacteria associated with community-acquired bacterial pneumonia isolated in Europe in 2008–2009 [14].

Organism	% of strains inhibited at a ceftaroline MIC (mg/L) of										
	≤0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	≥8
Escherichia coli											
All	0.1	0.4	9.0	31.0	22.6	12.2	6.3	3.9	1.7	1.2	11.5
CAZ-S	0.1	0.5	10.1	34.9	25.4	13.4	6.7	4.3	1.5	1.0	2.1
CAZ-R						2.3	3.1	0.8	3.9	3.1	86.7
Klebsiella pneumoniae											
All	0.3	0.0	4.8	30.2	21.3	6.6	4.5	2.7	1.5	0.6	27.5
CAZ-S	0.4	0.0	6.7	42.1	29.6	9.2	6.3	3.8	1.7	0.0	0.4
CAZ-R									1.1	2.1	96.8
Enterobacter cloacae	0.6	0.0	0.0	6.5	12.9	27.1	11.0	1.9	0.6	1.3	38.1
Staphylococcus aureus											
All				0.5	3.2	53.4	19.0	18.0	5.8		
MSSA				0.8	4.7	76.7	17.8				
MRSA						3.3	21.7	56.7	18.3		
Streptococcus pneumoniae											
All	63.0	10.3	4.5	4.7	12.3	4.9	0.2				
PEN-S	68.5	11.2	4.9	5.1	8.0	2.2					
PEN-NS					61.1	36.1	2.8				
Haemophilus influenzae	82.8	16.3	0.5	0.5							
Moraxella catarrhalis	8.2	7.5	37.3	32.1	14.2	0.7					

MIC, minimum inhibitory concentration; CAZ-S, ceftazidime-susceptible; CAZ-R, ceftazidime-resistant (ESBL phenotype; MIC ≥ 2 mg/L); ESBL, extended-spectrum β-lactamase; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*; PEN-S, penicillin-susceptible (MIC ≤ 2 mg/L); PEN-NS, penicillin-non-susceptible (MIC ≥ 4 mg/L).

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