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An open-label, non-randomised, phase 1, single-dose study to assess the pharmacokinetics of ceftaroline in patients with end-stage renal disease requiring intermittent haemodialysis

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ABSTRACT

For patients with normal renal function, the recommended ceftaroline fosamil dose is a 600 mg 1-h intravenous (i.v.) infusion every 12 h (q12h). In patients with a creatinine clearance of ≤30 mL/min, including those with end-stage renal disease (ESRD), the recommended dose is a 200 mg 1-h i.v. infusion q12h. This phase 1 study (NCT01664065) evaluated the pharmacokinetics, safety and tolerability of ceftaroline fosamil 200 mg 1-h i.v. infusion in patients with ESRD. Patients with ESRD ($n = 8$) participated in two treatment periods (ceftaroline fosamil 200 mg administered pre- and post-haemodialysis) separated by >1 week. Healthy volunteers ($n = 7$) received a single 600 mg dose of ceftaroline fosamil. Blood (pre- and post-haemodialysis) and dialysate samples were obtained for pharmacokinetic analysis. In patients with ESRD, the geometric mean [coefficient of variation (%CV)] plasma ceftaroline area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) following post-haemodialysis ceftaroline fosamil 200 mg infusion was 64.8 (38.9) μg·h/mL, similar to that in volunteers following a 600 mg infusion [62.7 (9.4) μg·h/mL]. Ceftaroline $AUC_{0-\infty}$ decreased by ca. 50% when infusion was initiated pre-haemodialysis. In the pre-haemodialysis treatment period, 80% of the ceftaroline fosamil dose was recovered in dialysate as ceftaroline (73%) and ceftaroline M-1 (7%). The frequency of adverse events was similar across patients with ESRD (pre- and post-haemodialysis) and volunteers (43%, 50% and 43% of subjects, respectively). Ceftaroline fosamil 200 mg 1-h i.v. infusion q12h, administered post-haemodialysis on dialysis days, is an appropriate dosage regimen for ESRD patients.

1. Introduction

Owing to the increasing prevalence of drug-resistant pathogens, infections such as community-acquired pneumonia (CAP) and complicated skin and soft-tissue infection (cSSTI) are becoming increasingly challenging to treat [1–3]. In patients with renal impairment, management of such infections is complicated further due to altered pharmacokinetic (PK) profiles of available antibacterial agents.

Ceftaroline fosamil, the prodrug of ceftaroline, is approved in the European Union for the treatment of adults with CAP and cSSTI, and elsewhere for similar indications [4,5]. Ceftaroline inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). It demonstrates in vitro activity against common Gram-positive and Gram-negative pathogens associated with the approved indications. Unlike most β-lactams, ceftaroline has high affinity for modified PBPs such as PBP2a and PBP2x, which confers in vitro activity against meticillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* [6,7]. Ceftaroline is ca. 20% bound to human plasma proteins and has a linear PK profile with no accumulation upon multiple dosing [8]. The recommended ceftaroline fosamil dose for patients with a creatinine clearance (CL_{Cr}) of >50 mL/min is a 600 mg 1-h intravenous (i.v.) infusion every 12 h (q12h) for 5–14 days (cSSTI) or 5–7 days (CAP). In patients with CL_{Cr} < 50 mL/min, the dose is adjusted to 400 mg q12h. In patients with $CL_{Cr} \leq 30$ mL/min, including those with end-stage renal disease (ESRD), the recommended dose is 200 mg q12h [4,5].

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Following i.v. infusion, ceftaroline fosamil is rapidly converted by plasma phosphatases to ceftaroline. A small proportion of ceftaroline is converted to the inactive metabolite ceftaroline M-1, both of which are predominantly renally cleared [8]. Impaired renal function affects the clearance of, and thereby plasma exposure to, ceftaroline [8]. This phase 1 study assessed the pharmacokinetics, safety and tolerability of ceftaroline fosamil in patients with ESRD receiving regular haemodialysis (HD).

2. Methods

2.1. Study design

This open-label, non-randomised, phase 1 study (ClinicalTrials.gov ID: NCT01664065) was conducted by Quintiles Drug Research Unit, Guy's Hospital (London, UK). The protocol was approved by an Independent Ethics Committee. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice. All subjects provided written informed consent.

2.2. Objectives

The objectives of this study were: (i) to characterise the pharmacokinetics of ceftaroline, ceftaroline fosamil and ceftaroline M-1 following single i.v. infusions of ceftaroline fosamil in patients with ESRD before and after scheduled HD and in matched volunteers with normal renal function; (ii) to characterise the clearance of ceftaroline by HD; and (iii) to evaluate the safety and tolerability of ceftaroline fosamil in patients with ESRD.

2.3. Subjects

Patients with ESRD and healthy volunteers were enrolled in this study. Patients with ESRD were in a stable physical condition consistent with ESRD, had CL_{Cr} < 15 mL/min (calculated using the Cockcroft–Gault formula) and haematocrit > 30%, required HD three to four times per week, and had received the same HD regimen for >1 month. Concomitant medications to treat medical conditions related to ESRD were permitted. Healthy volunteers (CL_{Cr} > 80 mL/min) were matched by sex, age (±5 years) and weight (±20%) to patients with ESRD.

Eligible subjects were males and females aged 18–75 years, with a body mass index (BMI) of 18–35 kg/m^2 and weighing 50–110 kg. Exclusion criteria included: clinically significant disorders that could influence the results or the subject's ability to participate in the study; clinically significant abnormalities in clinical chemistry, haematology or urinalysis, other than what would be expected in patients with ESRD; clinically important electrocardiogram (ECG) abnormalities; a QT interval corrected for heart rate using Fridericia's formula of >500 ms or <340 ms; and allergy/hypersensitivity to β-lactams. Additional exclusion criteria for patients with ESRD included systolic blood pressure (SBP) <90 mmHg or >200 mmHg, diastolic blood pressure (DBP) <50 mmHg or >100 mmHg, or pulse rate <40 bpm or >110 bpm after 10 min supine rest; renal transplantation or renal carcinoma within 1 year of screening; or history of nephrectomy.

2.4. Treatments

Volunteers received a single ceftaroline fosamil 600 mg 1-h i.v. infusion. Patients with ESRD received two ceftaroline fosamil 200 mg 1-h i.v. infusions (post-HD and pre-HD) separated by >1 week. The post-HD infusion was given >1 h after HD and 48 h before the next HD session; the pre-HD infusion was given prior to a 4-h HD session; HD was initiated 15 ± 5 min after the end of infusion. Polyflux® 170H or 210H dialysers (Gambro AB, Lund, Sweden) were used, with a Polyamix® membrane made from a polymer blend of polyarylethersulfone, polyvinylpyrrolidone and polyamide [inner diameter, 215 μm; membrane wall thickness, 50 μm; and surface area, 1.7 m^2 (Polyflux® 170H) or 2.1 m^2 (Polyflux® 210H)]. HD lasted 4 h at a dialysate flow rate of 600–700 mL/min and a blood flow rate of 300–400 mL/min. The mean dialysate volume was 145 kg. During dialysis, an anticoagulant was used in the form of enoxaparin sodium (Clexane; Aventis Pharma Ltd., Sanofi Winthrop Industrie, Seine-Maritime, France) injection.

2.5. Pharmacokinetic assessments

The PK population comprised subjects who received at least one ceftaroline fosamil dose, had at least one measured concentration of any analyte in plasma or dialysate after infusion initiation, and had no major protocol deviations.

Blood samples for determination of ceftaroline, ceftaroline fosamil and ceftaroline M-1 were collected for all subjects pre-dose (within 1 h prior to infusion initiation) and at 20 min, 40 min, 1 h, 1 h 5 min, 1 h 15 min, 1 h 30 min, 2 h 15 min, 3 h 15 min, 4 h 15 min, 5 h 15 min, 8 h, 12 h and 24 h post-dose, as well as 36 h and 48 h post-dose for patients with ESRD only. For patients with ESRD (pre-HD), pooled dialysate was collected at hourly intervals during HD for determination of ceftaroline and ceftaroline M-1. Blood samples were collected pre-dose and 8 h after infusion initiation for determination of haematocrit, and at 1 h 30 min, 2 h 15 min, 3 h 15 min, 4 h 15 min and 5 h 15 min for determination of blood urea nitrogen (BUN) and serum creatinine. Blood samples obtained during and surrounding HD were collected from pre-dialyser and post-dialyser lines. Post-dialyser samples were collected within 1 min of respective pre-dialyser samples. Plasma samples were analysed for ceftaroline fosamil, ceftaroline and ceftaroline M-1 concentrations using validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) methods [9] by Covance Bioanalytical Services, LLC (Indianapolis, IN). Precision [coefficient of variation (%CV)] and accuracy (%bias) using three reference quality control (QC) samples in human plasma were, respectively, ≤6.2% and −2.0% to 4.2% for ceftaroline fosamil, ≤8.0% and −1.3% to 6.3% for ceftaroline, and ≤5.7% and −0.9% to 3.3% for ceftaroline M-1, indicating reliable performance. Incurred sample reproducibility was evaluated for the analytes in 36 samples. At least two-thirds of samples demonstrated a percentage change within ±20.0%, thus meeting acceptance criteria.

Human dialysate samples were analysed for ceftaroline and ceftaroline M-1 concentrations by Covance Bioanalytical Services, LLC using LC-MS/MS. Ceftaroline fosamil was not quantified as detection was not expected. Corresponding stable isotope-labelled internal standards were added to each 50 μL sample. Sensitivity was 4 ng/mL [lower limit of quantification (LLOQ)] to 2000 ng/mL (upper limit of quantification). Assay selectivity was assessed using blank matrix from six individuals' dialysate tested without added internal standard. Results demonstrated no significant interference in the chromatographic regions of interest for analytes (<20% of response from the single LLOQ used) and internal standard (<5% of internal standard response in the control zero sample). Interferences in the presence of multiple analytes was assessed using six replicates of QC-high samples (1500 ng/mL) spiked with ceftaroline or ceftaroline M-1, or each with internal standard. In ceftaroline-spiked samples, an interference peak was observed in the region of interest for ceftaroline M-1; however, the actual interference that contributed to the analysis was ≤1.9%, thus meeting acceptance criteria. Precision (%CV) and accuracy (%bias) using three reference QC samples were ≤6.4% and 0.8% to 6.7% for ceftaroline M-1,