CASE REPORT

Ceftaroline Fosamil for Methicillin-Resistant *Staphylococcus aureus* Pulmonary Exacerbation in a Pediatric Cystic Fibrosis Patient

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Ceftaroline, an advanced generation cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), may present a new therapeutic alternative for treating lung infections among patients with cystic fibrosis. We report a case of ceftaroline therapy in a pediatric patient with cystic fibrosis, whose dose was increased from 9.7 mg/kg/dose every 12 hours to 10.8 mg/kg/dose every 8 hours by using pharmacokinetic analyses.

INDEX TERMS: ceftaroline, cystic fibrosis, pediatrics, pharmacodynamics, pharmacokinetics

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INTRODUCTION

Cystic fibrosis (CF) is the most common deadly genetic disease in Caucasian patients. CF is diagnosed in childhood, and optimal care is critical to survival into adulthood. Along with lung scarring and inflammation, infection is the principal manifestation of CF. Although *Pseudomonas aeruginosa* remains the most common pathogen found among CF patients, causing higher rates of complications, *Staphylococcus aureus*, particularly methicillin-resistant *S aureus* (MRSA) has gained increased attention. MRSA infection in CF patients has been associated with worsened baseline lung function, accelerated deterioration of lung function, and higher mortality than in CF patients without MRSA isolated from respiratory cultures.^{2–4}

Ceftaroline fosamil is a novel, advanced generation cephalosporin. It is the first cephalosporin with activity against MRSA, which is exerted through its 256-fold greater affinity for penicillin-binding protein 2a than other cephalosporins, which are rendered inactive by the presence of this protein.⁵ In addition to its activity against MRSA, ceftaroline is also active against

Enterobacteriaceae family members that do not harbor extended spectrum beta-lactamases or overproduce AmpC enzymes. Ceftaroline is available in its inactive pro-drug form ceftaroline fosamil, which is rapidly transformed to ceftaroline by phosphatase enzymes in plasma.⁶ Ceftaroline is currently approved for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia among adult patients. The recommended dose for adult patients with normal renal function is 600 mg intravenously (IV) every 12 hours, and dose reduction is recommended when creatinine clearance falls below 50 mL/min.⁷ There is currently very little known about optimal dosages of ceftaroline among pediatric patients, particularly those with CF.

We report a case of acute MRSA pulmonary exacerbation in a pediatric CF patient treated with ceftaroline, in which dosage selection was evaluated by using pharmacokinetic (PK) analyses.

CASE REPORT

A 6-year-old Caucasian male with a history of CF presented to the pediatric pulmonary clinic

complaining of increased cough and crackles upon auscultation. The patient was admitted for the management of an acute infectious exacerbation of CF and was given IV antibiotics. His condition had been diagnosed at 6 months of age by 2 positive sweat test results, and he was homozygous for the F508-del mutation. The patient had a history of multiple admissions and was acutely and chronically infected with MRSA. Additionally, previous cultures grew *Mycobacterium abscessus* from bronchoalveolar lavage (BAL) samples, for which he had received 2 courses of IV meropenem and tobramycin (selected because of a national shortage of amikacin) therapy along with oral clarithromycin for 6 weeks, followed by continued suppressive daily clarithromycin therapy and alternating months of inhaled tobramycin. Later, his cultures grew *M. avium* complex (MAC), and oral rifampin and ethambutol were added to the above regimen, as radiographic imaging and pulmonary function tests (PFTs) suggested MAC was pathogenic.

Throughout the recent course, prior to admission, the patient continued to have recurrent MRSA infection along with infections by Gram-negative *Achromobacter* and *Citrobacter* spp. Although the patient improved clinically during prolonged oral linezolid therapy, he developed vision complaints; however, ophthalmologic examination did not confirm optic neuritis (baseline evaluation before the initiation of ethambutol therapy was previously normal). Vancomycin therapy was attempted but resulted in severe red man syndrome without clinical improvement. Additionally, trimethoprim/sulfamethoxazole (TMP/SMX) monotherapy, 20 mg/kg/day, a high dose typically reserved for severe and invasive infections, did not improve his symptoms despite isolate susceptibility to both TMP/SMX and vancomycin (vancomycin minimum inhibitory concentrations [MICs] ranged between 0.5 and 2 mg/L; Microscan; American Hospital Supply)).

When the patient was admitted for the treatment course reported herein, his weight was 18.5 kg. Intravenous ceftazidime and gentamicin regimens were empirically initiated based on susceptibilities of his most recent Gram-negative organisms, as noted above. The patient's long-term antimycobacterial regimen was continued throughout his hospitalization, as were his other home medications including a multivitamin,

pancrelipase, dornase alfa, and 7% hypertonic saline nebulization.

Respiratory cultures obtained upon the current admission indicated co-infection by *A. xylosoxidans* (susceptible only to TMP/SMX) and MRSA, which was susceptible to TMP/SMX, linezolid, vancomycin (MIC=1 mg/L [Microscan]) and ceftaroline (MIC = 1 mg/L [E-test; BioMerieux]). Ceftazidime and gentamicin were then discontinued, and TMP/SMX was initiated at a dose of 180 mg orally every 12 hours (19.5 mg/kg/day) to cover both MRSA and the resistant *Achromobacter xylosoxidans*. Considering the patient's history of treatment failures, intolerance to the limited alternative agents and enhanced TMP/SMX clearance described among CF patients,⁸ IV ceftaroline was initiated for enhanced anti-MRSA therapy at an initial dose of 180 mg IV every 12 hours (19.5 mg/kg/day), infused over 60 minutes. After reviewing a series of cases supporting an 8-hour dosage interval for eradication of MRSA bacteremia in adult patients⁹ and considering the anticipated large volume of distribution and rapid clearance¹⁰ in this patient, the dose was changed on the third day of therapy to 200 mg IV every 8 hours (32.4 mg/kg/day, approximately 10.8 mg/kg/dose), infused over 60 minutes. The patient was discharged home to complete a 3-week course of IV ceftaroline and oral TMP/SMX.

Ceftaroline serum concentrations were measured during each dosage regimen. On the third day of receiving ceftaroline 180 mg IV every 12 hours, concentrations drawn at 0.68, 2.75, and 4.63 hours postinfusion were 4.43, 0.7, and 0.17 mg/L, respectively. On the ninth day of receiving ceftaroline 200 mg IV every 8 hours, serum concentrations drawn at 0.3, 1.26, and 2.8 hours postinfusion were 6.09, 1.67, and 0.41 mg/L, respectively. Additional PK parameters are shown in the Table.

The calculated half-life ($t_{1/2}$) of 0.53 hours while the patient was receiving ceftaroline 200 mg IV every 8 hours is much shorter than the $t_{1/2}$ observed among adult patients in pre-clinical studies.^{7,11} Those adult patients had a mean calculated $t_{1/2}$ of 1.6 hours after receiving a single 600-mg dose and an even longer $t_{1/2}$ of 2.6 hours after receiving multiple doses of 600 mg IV every 12 hours. The only available data characterizing ceftaroline PK activity among pediatric patients indicates that drug clearance is similar to that in adults, but this information was limited to 7

Table. Pharmacokinetic Characterization Following Two Different Doses of Ceftaroline

PK Parameter	Dose Received	
	180 mg q 12 hr	200 mg q 8 hr
C_{max} (mg/L)	8.07	8.99
C_{min} (mg/L)	0.0002	0.0003
$t_{1/2}$ (hr)	0.785	0.530
Elimination rate constant (hr^{-1})	0.883	1.307
$T > MIC$ (hr)	2.37	1.68
% $T > MIC$	19.7	21

C_{max} , maximum serum concentration (peak); C_{min} , minimum serum concentration (trough); $t_{1/2}$, elimination half-life; MIC, minimum inhibitory concentration; $T > MIC$, duration of time during which serum concentration exceeded the minimum inhibitory concentration; % $T > MIC$, percentage of dosing interval during which serum concentration exceeded the MIC.

patients aged 12 to 17 years old who received a single dose of 8 mg/kg, maximum 600 mg. In comparison to the patients from which this pre-clinical data was derived, the patient described in this report was younger, had a diagnosis of CF, and had a much shorter $t_{1/2}$ despite receiving larger weight-based doses of ceftaroline.

When the patient described in this report was given the original dose of 180 mg IV every 12 hours (19.5 mg/kg/day), serum ceftaroline concentrations exceeded the MIC for only 19.7% of the dosage interval. However, this value remained very similar at 21% when the dose was changed to 200 mg IV every 8 hours (32.4 mg/kg/day). This minimal change in percentage of dosing interval during which serum concentration exceeded the MIC (% $T > MIC$) may be attributed to a notably shorter $t_{1/2}$ observed when the patient received the second regimen.

The patient was seen in clinic 9 days after discharge, and PFTs demonstrated improved lung function, with a forced expiratory volume in the first second (FEV-1) of 62% predicted from 55% predicted at the time of admission with resolution of crackles on exam.

SERUM DRUG ASSAY AND PK CHARACTERIZATION

The method used to quantify ceftaroline concentrations in human serum has been based on the plasma method developed and validated at Forest Research Institute.¹² This method has been subsequently qualified for use with human serum. The lower limit of quantitation for the assay was 50 ng/mL, and the upper limit was 50,000 ng/mL for ceftaroline, using the sample

volume of 50 microliters. Sample processing was based on protein precipitation with methanol. The diluted supernatant was injected into a liquid chromatography-tandem mass spectrometry system. The analytes of interest were detected by electrospray ionization mass spectrometry with multiple reaction monitoring of positive ions. The multiple reaction monitoring in positive mode used precursor $\rightarrow$ product ions m/z 605.0 $\rightarrow$ 209.0 for ceftaroline and m/z 608.1 $\rightarrow$ 212.0 for the d3-internal standard. The method was modified for use with human serum by diluting original plasma calibration standards and quality controls (QCs) 1:1 with blank human serum and diluting the serum clinical samples 1:1 with blank human plasma. The method has been qualified for use with human serum by performing one qualification run consisting of a single calibration curve, and QCs at 4 concentration levels in replicates of 6. The precision and accuracy of the qualified method has been evaluated on the basis of the QCs. The within-run precision was $\leq 3.2\%$ coefficient of variation across all 4 concentration levels, and the bias was $\leq 9.4\%$ difference from the nominal.

FOLLOW-UP

Three months later, the patient again received a 14-day course of ceftaroline, 200 mg IV every 8 hours, and his FEV-1 increased to 60% predicted from 39% predicted at hospital admission. This was repeated another 3 months later, and his FEV-1 improved from 18% predicted to 55% predicted. The patient then did not require re-hospitalization for another 4 months, at which time when he was seen in clinic with an FEV-1

Figure. Change in lung function after ceftaroline treatment.
FEV-1, forced expiratory volume in the first second.

of 33% predicted, he was admitted for a fourth course of ceftaroline at the same dose as the previous admissions, after which his FEV-1 improved to 54% predicted (Figure). When admitted for the fourth course of ceftaroline, the patient had gained approximately 2 kg since the initiation of the first course of therapy.

DISCUSSION

Antimicrobial agents administered to CF patients exhibit altered PK parameters. Among the beta-lactam antimicrobials, the most pronounced of these alterations is an increase in total body clearance.^{10, 13} CF patients typically have a relatively small proportion of adipose tissue, yielding an increased lean body mass per kilogram of bodyweight which results in an increased volume of distribution for hydrophilic antimicrobial agents such as ceftaroline, which primarily distribute into the total body water compartment.¹⁴ Although decreased protein binding as a function of low albumin is typically seen in undernourished patients experiencing acute exacerbations, this is less likely to influence ceftaroline clearance because this agent demonstrates low (<20%) protein binding. The anticipated increased volume of distribution and rate of clearance are compounded by viscid mucus, further impeding the ability of antimicrobials to penetrate to their desired site of activity.^{10,13} Additionally, because glomerular hyperfiltration is common, pediatric CF patients typically exhibit more rapid clearance of agents like ceftaroline, which are dependent on renal elimination.¹⁴

Information guiding pediatric ceftaroline dose selection is limited to the US Food and Drug Administration Briefing Document for the September 2010 Anti-Infective Drugs Advisory Committee Meeting, which provides single-dose PK characterization of ceftaroline as studied in 7 patients ages 12 to 17 years old.^{7,11} In that study, adolescent patients received a single dose of ceftaroline 8 mg/kg, not to exceed 600 mg. The pharmacokinetic parameters of the adolescent patients were compared to those of adult patients who received a single dose of ceftaroline, 600 mg. In a comparison between adults and adolescents, both the volumes of distribution and elimination $t_{1/2}$ were similar. Differences were observed, however, in peak concentrations (C_{max}) and area under the concentration-time curve at 24 hours (AUC_{24}). The mean ceftaroline C_{max} of adolescent patients was 10% lower than the mean ceftaroline C_{max} of adult patients after a single 600-mg dose. The mean ceftaroline AUC_{24} of adolescent patients after a single 8 mg/kg dose was 23% lower than the mean ceftaroline AUC_{24} of adult patients after a single 600-mg dose.

Ceftaroline, like other beta-lactam agents, exhibits time-dependent killing and requires maintenance of serum drug concentration above the MIC for a given percentage of the dosing interval (%T > MIC). For activity against *Staphylococcus* spp, %T > MIC of 30% and 50% is needed for bacteriostatic and bactericidal activity, respectively.^{15,16} Despite the clinical improvement of the patient described in this case, his suboptimal %T > MIC of 21% may warrant consideration of more aggressive dosages, perhaps with a further

shortened interval, to achieve the targeted %T > MIC that will provide optimal antimicrobial effectiveness.

This patient's clinical improvement may not be entirely attributed to his treatment with ceftaroline, as he received concomitant TMP/SMX to which his MRSA isolates were susceptible. However, upon follow-up ceftaroline treatment, similar clinical improvements were realized without concomitant anti-MRSA therapy. The same dose of approximately 10 mg/kg/dose IV every 8 hours was used with clinical success upon repeated treatment courses. Until data from larger studies are available, this clinical experience along with a modest improvement in drug exposure supports the consideration of this dosing strategy for the treatment of infectious exacerbations of CF among pediatric patients requiring ceftaroline therapy.

To summarize, we report the case of a pediatric CF patient with an extensive history of MRSA pulmonary infection successfully managed with ceftaroline. Our pharmacokinetic analysis and clinical experience suggest that high weight-based doses of ceftaroline given more frequently may be needed to optimize outcomes among pediatric CF patients. To our knowledge, this is the first report providing PK characterization of 2 different dosing strategies. Larger studies are needed to evaluate dosing and to guide future decisions regarding the role of ceftaroline for MRSA pulmonary infection among pediatric CF patients.

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Abbreviations BAL, bronchoalveolar lavage; CF, cystic fibrosis; FEV-1, forced expiratory volume in the first second; IV, intravenous; MAC, *Mycobacterium avium* complex; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PFTs, pulmonary function tests; PK, pharmacokinetic; QCs, quality controls; TMP/SMX, trimethoprim/sulfamethoxazole.

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