Efficacy of Human Simulated Exposures of Ceftaroline Administered at 600 Milligrams Every 12 Hours against Phenotypically Diverse *Staphylococcus aureus* Isolates[▽]

Rebecca A. Keel,¹ Jared L. Crandon,¹ and David P. Nicolau^{1,2*}

Center for Anti-Infective Research and Development¹ and Division of Infectious Diseases,² Hartford Hospital, Hartford, Connecticut

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Ceftaroline exhibits bactericidal activity against Gram-positive pathogens, including methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus*, as well as common Gram-negative pathogens. This study evaluated the efficacy of human simulated exposures of ceftaroline against *S. aureus* in both the neutropenic and immunocompetent mouse thigh infection models. Twenty-six *S. aureus* isolates (4 MSSA, 22 MRSA) with ceftaroline MICs ranging from 0.125 to 4 $\mu\text{g/ml}$ were collected. All isolates were tested in the neutropenic model and a subset of 13 MRSA isolates were tested in the immunocompetent model. Two hours after inoculation, a ceftaroline regimen that simulated the percentage of the dosing interval that free-drug concentrations remained above the MIC of the infecting organism ($fT > \text{MIC}$) of humans administered ceftaroline at 600 mg every 12 h (q12h) infused over 1 h was given. The change in $\log_{10}$ CFU/ml after 24 h of treatment was analyzed relative to the 0- and 24-h controls for neutropenic and immunocompetent mice, respectively. The human simulated regimen resulted in efficacy against all isolates tested in both infection models. In the neutropenic model, a 0.95 to 3.28 $\log_{10}$ CFU/ml reduction was observed when compared with the 0-h control, whereas for the immunocompetent model, all isolates obtained a $>1 \log_{10}$ CFU/ml reduction ($\log_{10}$ CFU/ml reduction range: 1.06 to 2.43) in bacterial density. Irrespective of immune competency, a reduction in bacterial density was observed at the highest MIC of 4 $\mu\text{g/ml}$ ($fT > \text{MIC}$ of 27.5%). Human simulated exposures of ceftaroline 600 mg q12h provided predictable efficacy against all tested *S. aureus* isolates in the mouse thigh model independent of immune status. These data support the clinical utility of ceftaroline against *S. aureus*, including MRSA, with MICs of $\leq 4 \mu\text{g/ml}$.

Acute bacterial skin and skin structure infections are frequently caused by Gram-positive organisms, including *Staphylococcus aureus* (18). Furthermore, methicillin resistance among *S. aureus* (methicillin-resistant *S. aureus* [MRSA]) has been steadily increasing in both the hospital and community settings. Recent surveys report that 50 to 60% of the *S. aureus* isolates from skin and soft tissue infections are MRSA (16), which has posed a therapeutic challenge to clinicians. Additionally, the number of hospitalizations due to bacterial skin and skin structure infections has been rising (6, 10), which may be due to the growing incidence in community-acquired MRSA (17). As a result of this changing epidemiology and limited therapeutic options available to the clinician due to both the emergence of resistance and the potential for drug toxicities, new therapies targeted at MRSA are needed.

Ceftaroline, the active form of the prodrug ceftaroline fosamil, is a novel broad-spectrum cephalosporin which exhibits bactericidal activity against Gram-positive pathogens, including MRSA, as well as common Gram-negative pathogens. As with other beta-lactams, ceftaroline exhibits antimicrobial activity by binding to penicillin-binding proteins and ultimately inhibiting the biosynthesis of the bacterial cell wall (3). Traditionally, beta-lactams have lacked efficacy against MRSA due

to the presence of PBP 2a penicillin-binding protein, for which they have low binding affinity; however, ceftaroline has a high affinity to for all staphylococcal penicillin-binding proteins, including PBP 2a protein, resulting in bactericidal effects against MRSA (11, 15). Recently, ceftaroline fosamil was approved in the United States for acute bacterial skin and skin structure infections as well as community-acquired bacterial pneumonia at a dose of 600 mg every 12 h as a 1-h intravenous infusion.

The objective of this study was to evaluate the efficacy of human simulated exposures of ceftaroline 600 mg administered as an IV infusion over 1 h every 12 h in both the neutropenic and immunocompetent murine thigh infection models by using *S. aureus* exhibiting a range of ceftaroline MICs.

MATERIALS AND METHODS

Antimicrobial test agents. Analytical-grade ceftaroline fosamil (lot FMD-CEF-030 [Forest Laboratories, Inc., New York, NY]) and ceftaroline (lot FMD-CEF-035 [Forest Laboratories, Inc., New York, NY]) were used for the *in vivo* and *in vitro* analyses, respectively. Immediately prior to each *in vivo* experiment, ceftaroline fosamil was weighed and reconstituted with a solution of 1.9% L-arginine (lot L0003043 [Forest Laboratories, Inc., New York, NY]) in sterile water and then further diluted in normal saline to achieve the desired concentration. The ceftaroline solution was stored under refrigeration and discarded 24 h after reconstitution.

Bacterial isolates. Twenty-six clinical isolates of *S. aureus* (twenty-two MRSA and four methicillin-susceptible *S. aureus* [MSSA] isolates) with various phenotypic and genotypic profiles were used in this study. Ceftaroline MICs were determined by broth microdilution according to CLSI guidelines (4) and genotypes were determined by standard methods (13, 14). Isolates were stored at -80°C in double-strength skim milk (Remel, Lenexa, KS) and then subcultured twice onto Trypticase soy agar with 5% sheep blood (Becton, Dickinson, and Co., Sparks, MD) and grown for 18 to 24 h at 35°C prior to use in the experiments.

* Corresponding author. Mailing address: FCCP, FIDSA, Center for Anti-Infective Research and Development, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102. Phone: (860) 545-3941. Fax: (860) 545-3992. E-mail: dnicola@harthosp.org.

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Neutropenic thigh infection model. Specific-pathogen-free, female ICR mice weighing approximately 22 g each were obtained from Harlan Sprague-Dawley, Inc. (Indianapolis, IN) and utilized throughout these experiments. The study was reviewed and approved by the Hartford Hospital Institutional Animal Care and Use Committee. Animals were maintained and used in accordance with National Research Council recommendations and were provided food and water *ad libitum*. For the immunocompromised studies, mice were rendered transiently neutropenic by intraperitoneal injections of cyclophosphamide (Baxter, Deerfield, IL) at 150 mg/kg and 100 mg/kg given 4 days and 1 day, respectively, prior to inoculation. A single intraperitoneal injection of uranyl nitrate at 5 mg/kg was given 3 days prior to inoculation to induce a predictable degree of renal impairment (1) and reduce drug clearance.

A suspension of each isolate was freshly prepared from the second subculture of each organism and diluted in normal saline to achieve a final inoculum of 10^7 CFU/ml. Each thigh was inoculated intramuscularly with 0.1 ml of inoculum 2 h prior to the initiation of antimicrobial therapy.

Immunocompetent thigh infection model. Mice utilized in the immunocompetent studies underwent the same procedure as neutropenic mice but without the use of cyclophosphamide prior to inoculation. In addition, 0.1 ml of a final inoculum of 10^8 CFU/ml was used to produce the thigh infection.

Pharmacokinetic studies and determination of dosing regimen. Using pharmacokinetic parameters calculated by our group in a previous study of ceftaroline in neutropenic mice, a human simulated dosing regimen of ceftaroline was determined (19). In brief, the pharmacokinetic parameters from single doses of ceftaroline were calculated utilizing a one-compartment model with first-order input and elimination (WinNonlin version 5.2, Pharsight, Mountain View, CA). Mean pharmacokinetic parameters were calculated from the individual parameter estimates and were used in the current study to determine a dosing regimen in mice that simulated the percentage of the dosing interval that the free drug concentration remains above the MIC of the infecting organism ($fT > MIC$) of ceftaroline observed in humans following ceftaroline at 600 mg administered every 12 h (q12h) as a 1-hour infusion across a range of MICs. The human concentration-time profile of ceftaroline to be simulated was derived from phase 1 multiple-dose studies in healthy human volunteers (7). The protein binding values for ceftaroline were 20% in humans (7) and 35% in mice (2).

Confirmatory pharmacokinetic studies were conducted in both neutropenic and immunocompetent infected mice prior to the use of these regimens in pharmacodynamic analyses to ensure that target exposures (i.e., $fT > MIC$) were achieved with the simulated dosing regimen in both models. Infected, immunocompetent mice were administered the derived human-simulated dosing regimen and blood samples were collected via cardiac puncture from groups of six mice at eight time points over the 12-h dosing interval. Additionally, groups of six neutropenic mice were included at select time points in order to confirm appropriate targets were achieved in immunocompromised mice. Serum samples were separated by centrifugation and stored at -80°C until analysis. Ceftaroline concentrations were analyzed by Eurofins Medinet, Inc. (Chantilly, VA) using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The upper and lower limits of quantification for the ceftaroline assay were 20 $\mu\text{g/ml}$ and 0.0075 $\mu\text{g/ml}$, respectively ($R > 0.999$). The intraday percentage coefficients of variation (CVs) for ceftaroline quality control samples of 16 $\mu\text{g/ml}$ and 0.015 $\mu\text{g/ml}$ were $<10\%$ and the interday % CVs were $<6\%$.

In vivo efficacy as assessed by bacterial density. Twenty-six clinical *S. aureus* isolates were utilized in the neutropenic thigh infection model; 13 of these isolates were also evaluated in the immunocompetent model to assess the efficacy of a human-simulated dosing regimen both with and without the presence of an intact immune system. Two hours after inoculation, groups of three mice were administered the human simulated regimen of ceftaroline over a 24-h period as 0.2-ml subcutaneous injections. Control mice were administered normal saline at the same volume, route, and frequency as the treatment regimen. Groups of three untreated control mice were euthanized by CO_2 exposure, followed by cervical dislocation just prior to the initiation of therapy (0 h). All other treatment and control mice were sacrificed 24 h after the initiation of therapy. Mice that did not survive to 24 h were harvested at the time of expiration. Following sacrifice, thighs were removed and homogenized individually in 5 ml of normal saline. Serial dilutions of thigh homogenate were plated onto Trypticase soy agar with 5% sheep blood for determination of bacterial density. Efficacy, defined as the change in bacterial density, was calculated as the change in $\log_{10}$ CFU/ml obtained for ceftaroline-treated mice after 24 h from 0-h control mice for the neutropenic thigh infection model. To control for the impact of the host, efficacy in the immunocompetent model was calculated as the change in $\log_{10}$ CFU/ml obtained for ceftaroline-treated mice after 24 h relative to the 24-h immunocompetent control mice. An E_{max} model was derived using the Hill equation to describe the relationship between the pharmacokinetic and pharmacodynamic

target ($fT > MIC$) and efficacy. The 80% effective index (EI_{80}), EI_{50} , $1 \log_{10}$ and $2 \log_{10}$ reductions in bacterial density, and stasis exposure values were calculated from the composite curve of all *S. aureus* isolates.

RESULTS

Bacterial isolates. The genotypic and phenotypic profiles for all 26 *S. aureus* isolates evaluated in this study are listed in Table 1. The ceftaroline MICs for the isolates ranged from 0.125 to 4 $\mu\text{g/ml}$.

Pharmacokinetic determination. Based on the pharmacokinetic parameters determined in mice receiving a single dose of ceftaroline, multiple descending doses were administered over the 12-h dosing interval to simulate the human pharmacodynamic profile (i.e., $fT > MIC$). The free concentration-time profiles of ceftaroline 600 mg every 12 h as a 1-h infusion in humans as well as the murine regimen are presented in Fig. 1. The human simulated regimen of ceftaroline utilized in mice matched the pharmacodynamic parameter, $fT > MIC$, in humans up to a MIC of 32 $\mu\text{g/ml}$ (Table 2). Additionally, the free peak concentration and the area under the free concentration-time curve of the human simulated murine regimen of ceftaroline (17.3 $\mu\text{g/ml}$ and 44.5 $\mu\text{g} \cdot \text{h/ml}$, respectively) were similar to those observed in humans (16.9 $\mu\text{g/ml}$ and 41.1 $\mu\text{g} \cdot \text{h/ml}$, respectively). Moreover, the concentrations observed with the human simulated murine regimen were similar between the neutropenic and immunocompetent models at select time points verifying appropriate target attainments in each infection model (Fig. 1).

In vivo efficacy. The mean ($\pm$ standard deviation) bacterial density for 0-h mice at the start of dosing was $5.74 \pm 0.18 \log_{10}$ CFU/ml per thigh in the neutropenic mice and $6.84 \pm 0.16 \log_{10}$ CFU/ml in immunocompetent mice. The respective mean bacterial densities of control mice at 24 h were 7.98 ± 0.65 and $6.88 \pm 0.60 \log_{10}$ CFU/ml. The mice that received treatment all survived to the 24-h time point; however, a number of control mice failed to survive to 24 h due to the aggressive virulence of the isolates. Bacterial densities obtained from these animals were similar to those in mice that survived to 24 h and were included in the data analysis.

The ceftaroline human simulated regimen produced a 0.95 to $\geq 3 \log_{10}$ CFU/ml reduction after 24 h against all isolates in the neutropenic thigh infection model (Fig. 2). In the immunocompetent model, a $\geq 1 \log_{10}$ reduction in CFU/ml from the 24-h controls was observed (Fig. 2). Irrespective of immune competency, a reduction in bacterial density was observed at the highest MIC of 4 mg/L equivalent to an $fT > MIC$ exposure of 27.5%. The EI_{80} , EI_{50} , and stasis targets ($fT > MIC$) in the neutropenic thigh infection were 28.3, 9.7, and 9.3%, respectively. For a $1 \log_{10}$ and $2 \log_{10}$ reduction in bacterial density, an $fT > MIC$ of 19.3 and 70.5% was required (Fig. 3).

DISCUSSION

The treatment of MRSA infections poses a therapeutic challenge to clinicians. Ceftaroline, which is administered as the prodrug ceftaroline fosamil, exhibits extended activity against Gram-positive pathogens, including MRSA, as well as activity against common Gram-negative pathogens. Clinical trials (5) have demonstrated similar cure rates between ceftaroline and

TABLE 1. Genotypic and phenotypic profiles of the *Staphylococcus aureus* test isolates for ceftaroline and other compounds^a

<i>S. aureus</i> isolate	Genotype/clone	PVL	Country	MIC ($\mu\text{g/ml}$)			
				CPT	VAN	DAP	LZD
25923	MSSA	ND	USA	0.125	ND	ND	ND
29213	MSSA	ND	USA	0.125	1	0.5	4
54	HA-MRSA/USA100	ND	USA	0.5	1	0.39 ^b	ND
141	HA-MRSA/USA100	ND	Unknown	0.5	1	ND	4
152	HA-MRSA/USA100	Neg	Unknown	0.5	1	0.5	2
156	CA-MRSA/USA300	Neg	USA	0.5	1	0.5	2
446	HA-MRSA/USA100	ND	USA	0.5	1 ^b	0.25 ^b	0.75 ^b
56	HA-MRSA/USA100	ND	USA	1	1	1	8
426	HA-MRSA/USA100	ND	Unknown	1	ND	ND	ND
456	HA-MRSA/USA100	ND	USA	1	256	ND	ND
460	CA-MRSA	Neg	France	1	1	0.5	2
464	CA-MRSA	Neg	Germany	1	0.5	0.25	2
465	MSSA	Neg	Poland	1	0.5	0.25	1
466	MSSA	Neg	Germany	1	2	0.5	2
449	HA-MRSA/USA100	ND	USA	2	2	0.5	1
461	HA-MRSA	Neg	Italy	2	1	1	2
462	HA-MRSA	Neg	Netherlands	2	0.5	0.25	2
463	HA-MRSA	Neg	Germany	2	2	1	2
467	HA-MRSA Rhine Hesse	Neg	Germany	2	1	0.25	2
468	HA-MRSA Southern Germany	Neg	Italy	2	1	1	2
470	HA-MRSA EMRSA-16	Neg	UK	2	0.5	0.5	2
471	HA-MRSA EMRSA-15	Neg	Italy	2	1	0.5	2
473	HA-MRSA Brazilian/Hungarian	Neg	Greece	4	1	0.25	1
474	HA-MRSA Brazilian/Hungarian	Neg	Greece	4	1	0.5	1
475	HA-MRSA Brazilian/Hungarian	Neg	Greece	4	1	0.5	1
476	HA-MRSA Brazilian/Hungarian	Neg	Greece	4	1	0.25	2

^a Phenotypic profiles (MICs) were determined by broth microdilution unless otherwise noted. CPT, ceftaroline; VAN, vancomycin; DAP, daptomycin; LZD, linezolid; ND, not determined; Neg, negative; MSSA, methicillin-susceptible *S. aureus*; CA-MRSA, community-acquired methicillin-resistant *S. aureus*; HA-MRSA, hospital-acquired methicillin-resistant *S. aureus*; PVL, Pantone-Valentine leukocidin.

^b MIC determined by Etest.

vancomycin plus aztreonam for the treatment of complicated skin and skin structure infections. Our study objective was to determine the efficacy of a human simulated regimen of ceftaroline against *S. aureus*, in particular MRSA, with a range of MIC values in a murine thigh infection model. This human simulated regimen resulted in efficacy against all isolates tested

FIG. 1. Free concentration-time profile for ceftaroline at 600 mg in humans (solid line) with 40% CV (dotted line) and mice (dashed line). Shown are actual obtained mean ceftaroline values ($\pm$ standard deviation) in immunocompetent mice (black triangles) and neutropenic mice (white diamonds).

in both the neutropenic and immunocompetent models of infection.

The pharmacodynamic parameter that best predicts efficacy for the beta-lactams is $fT > \text{MIC}$ (8); thus, the reason for targeting this parameter when determining a human simulated ceftaroline dosing regimen. Similar $fT > \text{MIC}$ values were achieved between the human simulated murine regimen and healthy volunteers up to MIC values of 32 $\mu\text{g/ml}$. Although the concentration-time curves for mice and humans do not need to be interchangeable and only the pertinent exposures (i.e., $fT > \text{MIC}$ for ceftaroline) need to be in concordance, comparable peak concentrations and areas under the concentration-time curve between species were achieved in addition to the $fT > \text{MIC}$. Of note is that the CV (reported at the peak concentration) was 20% for healthy volunteers (7); however, larger variability is often observed in patients. While we simulated the mean concentration-time profile obtained from healthy volunteers in the current study, we have included an

TABLE 2. The $fT > \text{MIC}$ achieved with the human simulated regimen of ceftaroline at 600 mg every 12 h in mice and the corresponding targets in humans

Regimen designation	$fT > \text{MIC}$ achieved at indicated MIC ($\mu\text{g/ml}$)							
	≤ 0.13	0.25	0.5	1	2	4	8	32
Mouse	100	94.2	81.7	60.8	44.2	27.5	15.8	5.0
Human	100	95.8	78.3	60.8	44.2	28.3	15.0	0.8

FIG. 2. (A) Change in $\log_{10}$ CFU/ml for human simulated ceftaroline at 24 h relative to 0-h controls for 26 *Staphylococcus aureus* isolates with a MIC range of 0.125 to 4 μ g/ml in the neutropenic thigh infection model. (B) Change in $\log_{10}$ CFU/ml for human simulated ceftaroline at 24 h relative to 24-h controls for 13 *Staphylococcus aureus* isolates with a MIC range of 0.5 to 4 μ g/ml in immunocompetent thigh infection model.

anticipated patient variability of 40% in Fig. 1. By utilizing the multiple-descending-dose methodology in mice to mimic the pharmacokinetic profile in man, the mean murine profile was within the reported healthy volunteer CV (i.e., 20%) for 57% of the dosing interval. Moreover, the observed murine concentrations had deviation around this mean, which may more accurately reflect patient pharmacokinetic variability and thus the anticipated pharmacodynamic profile of infected patients.

In both models of infection, efficacy was noted when the $fT > MIC$ was 27.5%, which correlates to a MIC of 4 μ g/ml and an $fT > MIC$ of 19.3% resulted in a 1 $\log_{10}$ CFU/ml reduction

FIG. 3. Ceftaroline activity versus $fT > MIC$ against 26 *Staphylococcus aureus* isolates in the neutropenic murine thigh infection model.

in bacterial density. This is in concordance with the results observed for ceftobiprole, another cephalosporin with MRSA activity, in the murine lung infection model in which a $fT > MIC$ target of 20 to 30% was needed for maximal efficacy against *S. aureus* (12). In another study (2) which analyzed ceftaroline against 4 *S. aureus* isolates, the mean $fT > MIC$ was 33% for a 1 $\log_{10}$ CFU/ml reduction in bacterial density; however, when utilizing only their MRSA data ($n = 2$), the $fT > MIC$ was lower with 26%. These data in conjunction with ours seem to indicate that a $fT > MIC$ of approximately 20 to 30% is needed for a 1 $\log_{10}$ CFU/ml reduction in bacterial density.

While including isolates with higher MICs would have better defined both the pharmacodynamic breakpoint for efficacy and E_{max} curve, the ceftaroline MIC_{90} for *S. aureus* in both the United States ($n = 3,965$) and Europe ($n = 2,700$) was 1 μ g/ml, whereas for only the MRSA isolates, the MIC_{90} values were 1 μ g/ml and 2 μ g/ml in the United States ($n = 2,254$) and Europe ($n = 734$), respectively (9). In this surveillance study, only four isolates with MIC values greater than 2 μ g/ml were identified. All four of these isolates had a MIC of 4 μ g/ml, were collected in a single medical center in Greece, and were included in our pharmacodynamic analyses. Our cohort of isolates represents the ceftaroline MIC_{90} and includes the highest MIC that has been encountered: 4 μ g/ml. Furthermore, the FDA-defined MIC susceptibility breakpoint against *S. aureus* is 1 μ g/ml, and our study demonstrated a substantial reduction in bacterial density beyond this MIC breakpoint (i.e., up to and including 4 μ g/ml).

Although the utilization of the neutropenic murine host has been considered a conservative estimate of antimicrobial efficacy, the humanized ceftaroline exposures appeared to maximize the efficacy per isolate, and therefore the added benefit of the intact host was not recognized. Thus, the regimen of ceftaroline at 600 mg every 12 h appears to provide adequate exposures regardless of immune competency. Additionally, this regimen had similar efficacies irrespective of the genotypes considered (i.e., MSSA, community-acquired MRSA, and hospital-acquired MRSA), as the phenotype profile appeared to be a more important driver when considering the antibacterial effects of the compound.

Ceftaroline fosamil is a novel cephalosporin and has been shown to have *in vitro* potency against MRSA and positive clinical outcomes when utilized for acute bacterial skin and skin structure infections (5). In the murine thigh infection model, regardless of immune status, human simulated exposures of ceftaroline at 600 mg every 12 h provided predictable efficacy against all tested *S. aureus* isolates across a range of MIC values. These data support the clinical utility and durability of ceftaroline against *S. aureus*, including MRSA, with MICs up to and including 4 µg/ml for the treatment of complicated skin and skin structure infections.

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