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Pharmacodynamics of Ceftaroline against *Staphylococcus aureus* Studied in an *In Vitro* Pharmacokinetic Model of Infection

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An *in vitro* single-compartment dilutional pharmacokinetic model was used to study the pharmacodynamics of ceftaroline against *Staphylococcus aureus* (both methicillin-susceptible *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]). Mean serum free concentrations of ceftaroline (the active metabolite of the prodrug ceftaroline fosamil) dosed in humans at 600 mg every 12 h (q12h) were simulated, and activities against 12 *S. aureus* strains (3 MSSA strains and 9 MRSA strains, 3 of which had a vancomycin-intermediate phenotype) were determined. Ceftaroline produced 2.5- to 4.0-$\log_{10}$-unit reductions in viable counts by 24 h with all strains and a 0.5- to 4.0-log-unit drop in counts at 96 h. The antibacterial effect could not be related to the strain MIC across the ceftaroline MIC range from 0.12 to 2.0 μg/ml. In dose-ranging studies, the cumulative percentage of a 24-h period that the free drug concentration exceeded the MIC under steady-state pharmacokinetic conditions (fT_{MIC}) of 24.5% ± 8.9% was associated with a 24-h bacteriostatic effect, one of 27.8% ± 9.5% was associated with a −1-log-unit drop, and one of 32.1% ± 8.1% was associated with a −2-log-unit drop. The MSSA and MRSA strains had similar fT_{MIC} values. fT_{MIC} values increased with increasing duration of exposure up to 96 h. Changes in ceftaroline population analysis profiles were related to fT_{MIC}. fT_{MIC}s of <50% were associated with growth on 4× MIC recovery plates at 96 h of drug exposure. These data support the use of ceftaroline fosamil at doses of 600 mg q12h to treat *S. aureus* strains with MICs of ≤2 μg/ml. An fT_{MIC} of 25 to 30% would make a suitable pharmacodynamic index target, but fT_{MIC} values of ≥50% are needed to suppress the emergence of resistance and require clinical evaluation.

Ceftaroline fosamil (CPT) has been approved by the U.S. FDA for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia: market authorization in the European Union (EU) for complicated skin and soft tissue infections and community-acquired pneumonia is pending.

Ceftaroline fosamil (previously PP1-0903, T-91825, and TAK-599) is the prodrug of ceftaroline and is the first β-lactam with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) marketed for clinical use in the United States. International surveillance studies conducted on MRSA strains in North America and the EU indicate that in the United States, the ceftaroline MIC_{50} and MIC_{90} are 1 and 1 μg/ml, respectively, with 5.2% of strains having MICs of >1 μg/ml. In contrast, in Europe the MIC_{50} and MIC_{90} are 1 and 2 μg/ml, respectively, with 17.3% of strains having MICs of >1 μg/ml. The FDA clinical breakpoint for susceptibility among *S. aureus* isolates is ≤1 μg/ml (1, 2). The proposed European (EUCAST) clinical breakpoint has not yet been published, but a breakpoint similar to that used in the United States will present significant problems in laboratory testing of ceftaroline, as it will cut through the MRSA MIC distribution.

Ceftaroline is approximately 2-fold more potent *in vitro* than ceftobiprole against *S. aureus*, the only other anti-MRSA β-lactam so far evaluated in phase III clinical trials (3). Ceftaroline has MICs of ≤1 μg/ml against community-associated MRSA, vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus*, heteroresistant VISA (hVISA), and daptomycin-nonsusceptible *S. aureus* strains isolated in the United States (4). The improved *in vitro* potency of ceftaroline against MRSA correlates with the drug's high affinity for MRSA PBP 2a (5).

Pharmacodynamic analysis of ceftaroline fosamil for the treatment of complicated skin and skin structure infections has indicated high target attainment rates for *S. aureus* strains when it is used at concentrations of up to 2 μg/ml (6). However, targets for the cumulative percentage of a 24-h period that the free drug concentration exceeds the MIC under steady-state pharmacokinetic conditions (fT_{MIC}) for *S. aureus* were based on only four *S. aureus* strains, and the antibacterial effects (ABEs) of prolonged ceftaroline dosing plus the risks of emergence of resistance were not assessed.

The aim of this study was to describe the antibacterial effect of ceftaroline against *S. aureus* strains with a range of ceftaroline MICs in 96-h experiments with doses simulating those in humans. In addition, the relationship between fT_{MIC} and antibacterial effect and the risk of changes in population profiles were established for both methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA strains.

MATERIALS AND METHODS

***In vitro* pharmacokinetic model.** A FerMac 310 fermentation system (ElectroLab, Tewkesbury, England) *in vitro* pharmacokinetic model was used to simulate serum free ceftaroline concentrations associated with intravenous (i.v.) dosing at 600 mg every 12 h (q12h) in humans. The apparatus, which has been described before (7), consists of a single central chamber connected to a reservoir containing broth. The central chamber

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TABLE 1 Measured and target serum free ceftaroline concentrations for simulations with a dose of 600 mg q12h

Parameter	Concn (mg/liter) at:				$t_{1/2}$ (h)	AUC_{0-12}[a] (mg·h/liter)
	1 h	4 h	7 h	12 h		
Target	23	10.4	4.6	1.1	2.8	63.9
Measured	21.1 ± 4.9	7.6 ± 2.3	3.4 ± 1.3	1.6 ± 0.9	2.0 ± 0.7	68.4 ± 8.2

[a] AUC_{0-12}, area under the concentration-time curve from time zero to 12 h.

(360 ml) is connected to a collecting vessel for overflow (7). The contents of the central chamber were diluted with broth using a peristaltic pump (Ismatec; Cole, Parmer, Hanwell, London, United Kingdom) at a flow rate of 96 ml/h. The temperature was maintained at 37°C, and the broth in the central chamber was agitated by a magnetic stirrer.

Media. Cation-supplemented Mueller-Hinton broth (MHB; 100%) was used in all experiments. Nutrient agar plates (Oxoid, Basingstoke, England) were used to recover *S. aureus* strains from the model. Five microliters β-lactamase (kindly supplied by the University of Bristol) was used to neutralize ceftaroline. The β-lactamase-neutralized ceftaroline was added to nutrient agar plates up to a concentration of 75 μg/ml for recovery of total bacterial counts. No β-lactamase was added to the 1×, 2×, 4×, and 8× MIC plates used to assess changes in population structure.

Strains. Twelve strains of *S. aureus* were used in the simulations of an i.v. dose of 600 mg q12h. Three strains were MSSA: clinical strain SMD 44099 (CPT MIC, 0.12 μg/ml/liter), clinical strain SMD 44100 (CPT MIC, 0.12 μg/ml), and JMI Laboratories (North Liberty, IA) strain SMD 43448 (CPT MIC, 1.0 μg/ml). Six strains were vancomycin-susceptible MRSA: clinical strain SMD 42690 (CPT MIC, 0.25 μg/ml), JMI Laboratories strain SMD 43450 (CPT MIC, 0.25 μg/ml), clinical strain SMD 42689 (CPT MIC, 0.5 μg/ml), JMI Laboratories strain SMD 43454 (CPT MIC, 1.0 μg/ml), clinical strain SMD 33815 (CPT MIC, 1.5 μg/ml), and JMI Laboratories strain SMD 43456 (CPT MIC, 2.0 μg/ml). Three strains of MRSA with a heteroresistant vancomycin-intermediate or vancomycin-intermediate phenotype were also tested: the VISA SMD 19898 Michigan strain (CPT MIC, 1.0 μg/ml), the VISA SMD 20201 Glasgow strain (CPT MIC, 1.0 μg/ml), and hVISA SMD 21286 LIM3 strain France (CPT MIC, 0.5 μg/ml).

Antibiotic. Ceftaroline was supplied by AstraZeneca, Waltham, MA. Fresh solutions were prepared according to British Society for Antimicrobial Chemotherapy Guidelines (8).

MICs. Ceftaroline MICs were determined by the standard broth dilution method according to CLSI guidelines (9). MICs were performed in 100% MHB and at nondoubling dilutions to more accurately determine MICs.

Pharmacokinetics. The maximum concentration of drug in plasma (C_{max}) was 19.0 mg/liter after a 1-h infusion, with a half-life ($t_{1/2}$) of 2.5 h, and dosing was q12h for 96 h for human dosing simulations. In addition, between 7 and 16 doses were simulated per strain in dose-ranging experiments designed to achieve an fT_{MIC} range of 0 to 100% for each strain to define the fT_{MIC}-antibacterial effect relationship. In these experiments, the dose frequency was fixed at 12 h and various amounts of drug were added to achieve the targeted fT_{MIC}. The concentrations of ceftaroline were determined by high-pressure liquid chromatography. Chromatography was performed on a Gemini-NXNM C_{18} 110A column (Phenomenex, Macclesfield, England) using a mobile phase of 0.1 M sodium acetate–0.1 M glacial acetic acid–acetonitrile (86:2.8:11.2, vol/vol) at 254 nm. The flow rate was 1.8 ml/min. Detection was by UV absorbance. Intra- and interday accuracy and precision were assessed by use of quality control standards, with limits for accuracy of 10% and a coefficient of variation for precision of 5%.

ABEs. Experiments to determine ABEs were performed at an initial inoculum of 10^6 CFU/ml prepared as previously described (10). Samples were taken throughout the simulation period for detection of viable counts. Bacteria were quantified by use of a spiral plater (Don Whitley Spiral Systems, Shipley, West Yorkshire, England). The minimum level of detection was 10^2 CFU/ml. Aliquots were stored at −70°C for ceftaroline measurement.

Emergence of resistance. Ceftaroline resistance was assessed using population analysis profiles (7) at time zero (preexposure) and every 24 h postexposure. Samples were plated onto agar containing no antibiotic and antibiotic at 1×, 2×, 4×, and 8× MIC to quantify any resistant subpopulations. The limit of detection was 10^2 CFU/ml. The frequency of mutation of the strains in response to ceftaroline was not assessed.

All pharmacokinetic simulations of human doses to determine ABEs or changes in population profiles were performed at least in triplicate.

Pharmacodynamics and measurement of ABEs. The ABE of ceftaroline was calculated by determining the log change in viable counts at 24 h (d24), 48 h (d48), 72 h (d72), and 96 h (d96). The area under the bacterial kill curve (AUBKC; log number of CFU/ml·h) was calculated using the log linear-trapezoidal rule four times from 0 to 24 h (AUBKC 24), 0 to 48 h (AUBKC 48) 0 to 72 h (AUBKC 72), and 0 to 96 h (AUBKC 96). The relationship between fT_{MIC} and ABE was delineated using a Boltzmann sigmoid maximum effect model (Prism software; GraphPad Software, San Diego, CA).

RESULTS

Pharmacokinetic curves and pharmacodynamic index sizes. The measured pharmacokinetic values for the serum free ceftaroline concentrations for simulation of an i.v. dose of 600 mg q12h are shown in Table 1. The fT_{MIC}s for ceftaroline given at 600 mg q12h by a 1-h infusion for the 12 strains tested are shown in Table 2.

Antibacterial effect of ceftaroline over 96 h. The activity of human serum free CPT concentrations associated with dosing at 600 mg q12h i.v. over 48 h (4 strains) or 96 h (8 strains) against 12 *S. aureus* strains with CPT MICs over the range of 0.12 to 2.0 μg/ml was tested (Table 2; Fig. 1). CPT produced a >2-log_{10}-unit drop in the staphylococcal viable count at 24 h with all strains and a ≥4-log_{10}-unit drop with six strains. The MIC was not related to the log drop in viable count. At 48 h, drops were >3 log_{10} units with 11 strains, and drops were >2 log_{10} units with six of eight strains at 96 h. The log change in the viable count AUBKC was not related to the CPT MIC. There was no emergence of resistance with any simulation, as indicated by the growth of *S. aureus* on media containing ceftaroline at 2× MIC or 4× MIC over 96 h; however, regrowth after 24 h was apparent with strain SMD 44100 (Fig. 1a), strain SMD 33815 (Fig. 1d), and strain SMD 43456 (Fig. 1e).

Dose-ranging studies with *S. aureus*. A range of dosing simulations (n = 9 to 11) per strain was used to provide an fT_{MIC} range of 0 to 100% for each of eight *S. aureus* strains (four MSSA and four MRSA strains). The antibacterial effect was measured from d24, d48, d72, and d96 (only data for d24, d48, and d96 are shown). Using d24 as the primary outcome measure, the fT_{MIC} for a 24-h static effect for all *S. aureus* strains was 24.5% ± 8.9% (mean ± standard deviation); that for a −1-log-unit reduction was 27.8% ± 9.5%, increasing to 32.1% ± 8.1% for a −3-log-unit

TABLE 2 ABE of ceftaroline at 600 mg q12h against 12 *S. aureus* strains with MICs in the range of 0.12 to 2 μg/ml in human simulations

Strain	Phenotype	Ceftaroline MIC (μg/ml)	fT_{MIC} (%)	Change in viable count (log no. of CFU/ml) at:				AUBKC (log no. of CFU/ml) at:			
				24 h	48 h	72 h	96 h	24 h	48 h	72 h	96 h
SMD 44099	MSSA	0.12	100	−4.0 ± 0.5	−33 ± 1.0	−2.3 ± 1.9	−1.9 ± 2.1	20 ± 2	29 ± 4	63 ± 32	116 ± 72
SMD 44100	MSSA	0.12	100	−4.2 ± 0.3	−3.3 ± 1.2	−2.2 ± 2.2	−0.7 ± 1.1	23 ± 4	33 ± 6	69 ± 39	125 ± 83
SMD 42690	MRSA	0.25	100	−3.2 ± 0.8	−3.0 ± 0.9	−4.1 ± 0.4	−4.1 ± 0.3	20 ± 2	35 ± 10	39 ± 10	44 ± 18
SMD 43450	MRSA	0.25	100	−4.0 ± 0.3	−3.8 ± 0.5	−3.6 ± 0.6	−4.3 ± 0.1	18 ± 1	25 ± 3	33 ± 1	40 ± 2
SMD 42689	MRSA	0.5	100	−2.2 ± 1.1	−2.5 ± 0.7	ND[a]	ND	29 ± 6	43 ± 6	ND	ND
SMD 21286	hVISA	0.5	100	−3.2 ± 0.8	−3.6 ± 0.4	ND	ND	27 ± 18	35 ± 25	ND	ND
SMD 43448	MSSA	1.0	100	−4.1 ± 0.3	−4.0 ± 0.5	−3.9 ± 0.4	−3.9 ± 0.7	15 ± 3	22 ± 5	29 ± 6	34 ± 6
SMD 19898	VISA	1.0	100	−3.7 ± 0.4	−3.7 ± 0.3	ND	ND	20 ± 5	26 ± 10	ND	ND
SMD 20201	VISA	1.0	100	−3.8 ± 0.6	−3.9 ± 0.4	ND	ND	21 ± 1	25 ± 4	ND	ND
SMD 4345 4	MRSA	1.0	100	−4.3 ± 0.1	−3.8 ± 0.5	−4.0 ± 0.5	−3.7 ± 0.6	13 ± 2	20 ± 1	28 ± 4	35 ± 6
SMD 33815	MRSA	1.5	90	−2.4 ± 0.9	−3.7 ± 0.3	−3.3 ± 1.1	−2.6 ± 1.5	36 ± 11	45 ± 13	48 ± 19	76 ± 45
SMD 43456	MRSA	2.0	82	−4.3 ± 0.2	−3.5 ± 1.0	−2.6 ± 0.8	−2.0	33 ± 4	40 ± 8	61 ± 12	89 ± 27

[a] ND, not done.

reduction in count (Table 3). The relationship of fT_{MIC} to the antibacterial effect for ceftaroline at 48 h is shown in Table 4. The fT_{MIC}s were increased for static and bactericidal effects at 96 h: the fT_{MIC} for a static effect at 96 h was 42.9% ± 13.5%, that for a −1-log-unit reduction in count was 46.1% ± 15.0%, and that for a −3-log-unit reduction in count was 53.7% ± 20.4% for all *S. aureus* strains (Table 5).

Comparison of the fT_{MIC} targets for static or bactericidal ef-

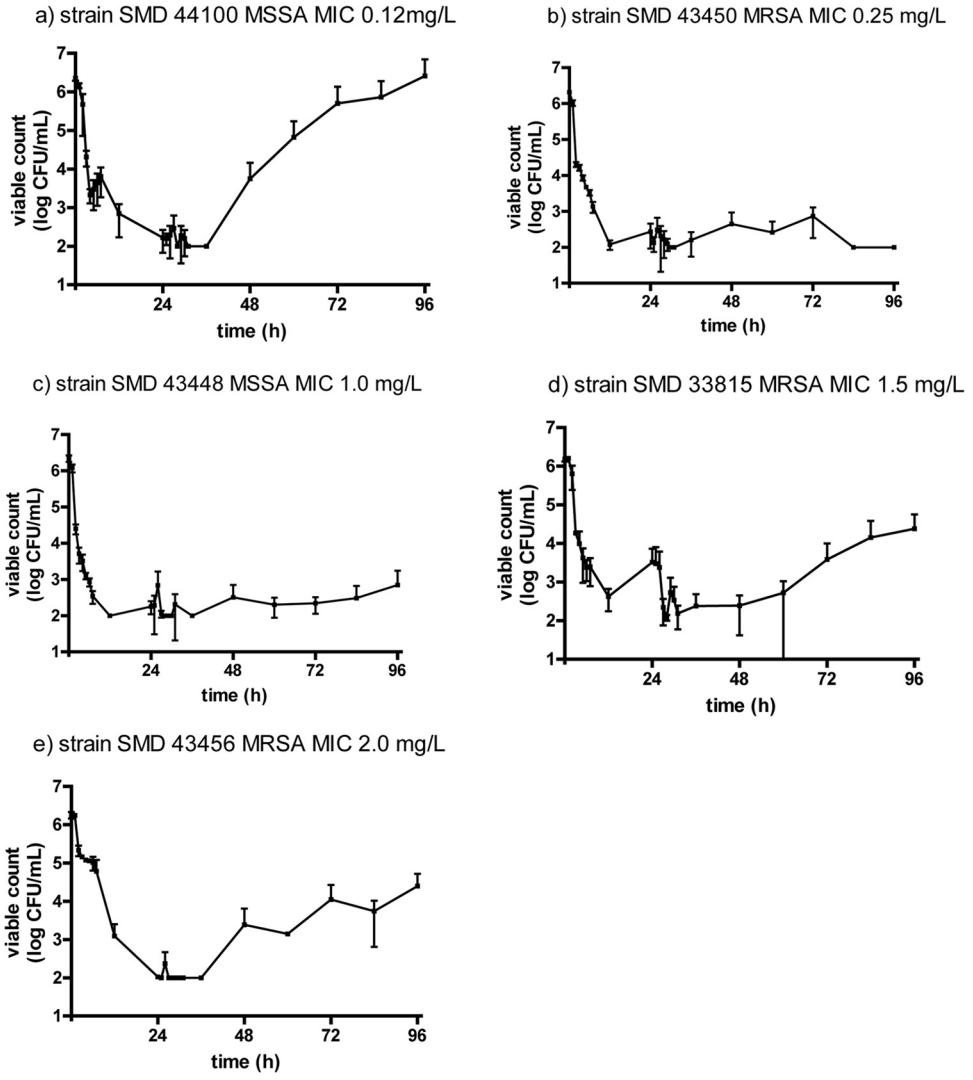

FIG 1 Antibactericidal effect of serum free ceftaroline concentrations against *S. aureus* strains.

TABLE 3 fT_{MIC} relationship to ABE for ceftaroline at 24 h

ABE at 24 h	fT_{MIC} (%)[a]									
	MSSA					MRSA				
	Strain SMD 44100 (0.12)	Strain SMD 44099 (0.12)	Strain SMD 43450 (0.25)	Strain SMD 43448 (1.0)	All MSSA strains	Strain SMD 42690 (0.25)	Strain SMD 43454 (1.0)	Strain SMD 33815 (1.5)	Strain SMD 43456 (2.0)	All MRSA strains	All *S. aureus* strains
Static	40.0	26.2	24.0	17.0	26.8 ± 9.6	29.0	31.0	12.8	17.0	22.4 ± 8.9	24.5 ± 8.9
−1-log-unit drop	47.1	28.5	29.0	19.0	30.9 ± 11.7	29.0	32.0	20.1	18.0	24.8 ± 6.8	27.8 ± 9.5
−2-log-unit drop		31.5	32.0	21.0	28.2 ± 6.2 ($n = 3$)	30.0	33.0	28.2	18.5	27.4 ± 6.2	27.7 ± 5.7 ($n = 7$)
−3-log-unit drop		36.9	39.0	23.0	32.9 ± 8.9 ($n = 3$)	30.0	34.0	41.6	20.0	31.4 ± 9.0 ($n = 3$)	32.1 ± 8.1 ($n = 7$)
−4-log-unit drop			51.0	29.0		31.0	38.0	69.1		46.0 ± 20.3 ($n = 3$)	37.6 ± 18.6 ($n = 5$)

[a] Data in parentheses are MICs (in micrograms per milliliter).

fects at 24 h, 48 h, or 96 h indicated that there were no differences in the fT_{MIC} targets between the MSSA strains and MRSA strains tested (Tables 3 to 5).

Changes in population profiles. *S. aureus* population profiles changed as a result of the fT_{MIC} exposures in the dose-ranging experiments (Table 6). At 48 h for fT_{MIC} exposures of <50%, growth occurred on 2× MIC recovery plates but not 4× MIC plates. For experiments with fT_{MIC}s over the range of ≥15 to <30%, the majority of experiments had isolates recovered from 2× MIC plates. At 96 h, all fT_{MIC} exposures of <90% had colonies recovered from 2× MIC plates. These occurred in most experiments with fT_{MIC}s of <50%, with >5-log-unit mean counts associated with fT_{MIC} exposures of <40%. In contrast to the findings at 48 h, at 96 h colonies were also recovered from 4× MIC plates, with mean counts being >4 $\log_{10}$ units over the fT_{MIC} range of ≥20 to <40%.

DISCUSSION

The pharmacodynamics of cephalosporins, including ceftaroline, are well understood. In time-kill studies, ceftaroline is bactericidal against *S. aureus* strains at 2×, 4×, and 8× MICs (11) and has an *in vitro* postantibiotic effect (PAE) of 0.7 to 2.2 h for staphylococci (12). *In vivo* fT_{MIC} is the dominant pharmacodynamic index and the *in vivo* PAE is 0.8 to 7.2 h. fT_{MIC} magnitudes of 20% have been associated with a 24-h bacteriostatic effect for cefazolin against MSSA; a 2-log-unit kill was associated with a T_{MIC} of 40%, and a 3-log-unit drop was associated with a T_{MIC} of 50 to 60% (13). Similar observations have been made with anti-MRSA cephalosporins; for example, the fT_{MIC} for a 24-h static effect against eight strains of *S. aureus* (five MRSA and three MSSA strains) for ceftobiprole was 21.1% ± 3.9%, and the equivalent value for a 2-log-unit kill was 29.3% ± 4.6% (14). For ceftaroline, using a similar neutropenic thigh/lung infection model but only four *S. aureus* strains (two MRSA and two MSSA strains), the fT_{MIC} for a 24-h static effect was 26% ± 8% and that for a 2-log-unit kill was 45% ± 13% (15). Our data are in keeping with these findings, indicating for eight *S. aureus* strains (four MRSA and four MSSA strains) that the 24-h bacteriostatic fT_{MIC} is 24.5% ± 8.9%; our fT_{MIC} associated with a −2-log-unit kill was 27.7% ± 5.7%, which is shorter than that reported in animal experiments with ceftaroline but very similar to values from animal models with ceftobiprole (14, 15). We continued studying the fT_{MIC} required for static and bactericidal effects beyond 24 h. As may be expected, the fT_{MIC} targets increase with increasing time of drug exposure. However, the fT_{MIC} for a static effect at 96 h was only 42.9% ± 13.5% and that for a −2-log-unit kill was 49.3% ± 16.6%; similar data have also been reported with the anti-MRSA carbapenem razupenem (16).

The appropriate fT_{MIC} target for mathematical modeling of clinical breakpoints is an ongoing topic for debate. For ceftaroline and *S. aureus*, our data would suggest an fT_{MIC} target of 25 to 30%

TABLE 4 fT_{MIC} relationship to ABE for ceftaroline at 48 h

ABE at 48 h	fT_{MIC} (%)[a]									
	MSSA					MRSA				
	Strain SMD 44100 (0.12)	Strain SMD 44099 (0.12)	Strain SMD 43450 (0.25)	Strain SMD 43448 (1.0)	All MSSA strains	Strain SMD 42690 (0.25)	Strain SMD 43454 (1.0)	Strain SMD 33815 (1.5)	Strain SMD 42456 (2.0)	All MRSA strains	All *S. aureus* strains
Static	44.3	36.2	34.0	28.0	35.6 ± 6.7	38.0	31.0	34.9	19.0	30.7 ± 8.3	33.2 ± 7.5
−1-log-unit drop	52.3	41.6	36.0	29.0	39.7 ± 9.8	39.0	31.0	44.3	19.5	33.4 ± 10.8	36.6 ± 10.1
−2-log-unit drop	67.1	48.3	38.0	30.0	45.9 ± 16.0	40.0	31.0	53.0	20.0	36.0 ± 14.0	40.9 ± 14.9
−3-log-unit drop		59.1	42.0	31.0	44.0 ± 14.2 ($n = 3$)	42.0	31.0	63.1	20.5	39.1 ± 18.2	41.2 ± 14.9 ($n = 7$)
−4-log-unit drop							32.0	79.2			

[a] Data in parentheses are MICs (in micrograms per milliliter).

TABLE 5 fT_{MIC} relationship to ABE for ceftaroline at 96 h

ABE at 96 h	fT_{MIC} (%)[a]										
	MSSA					MRSA					
	Strain SMD 44100 (0.12)	Strain SMD 44099 (0.12)	Strain SMD 43450 (0.25)	Strain SMD 43448 (1.0)	All MSSA strains	Strain SMD 42690 (0.25)	Strain SMD 43454 (1.0)	Strain SMD 33815 (1.5)	Strain SMD 43456 (2.0)	All MRSA strains	All *S. aureus* strains
Static	71.1	38.9	43.0	38.0	47.8 ± 15.8	38.0	36.0	52.3	26.2	38.1 ± 10.8	42.9 ± 13.5
−1-log-unit drop	76.6	48.3	45.0	39.0	52.2 ± 16.7	39.0	37.0	56.4	27.5	40.0 ± 12.0	46.1 ± 15.0
−2-log-unit drop	81.2	58.4	48.0	41.0	57.2 ± 17.6	40.0	38.0	59.7	28.5	41.6 ± 13.1	49.3 ± 16.6
−3-log-unit drop	91.3	71.1	51.0	42.0	63.8 ± 22.0	41.0	39.0	64.4	30.2	43.7 ± 14.6	53.7 ± 20.4
−4-log-unit drop			62.0	46.0				86.6	34.9		57.3 ± 22.4 (n = 4)

[a] Data in parentheses are MICs (in micrograms per milliliter).

for a −2-log-unit kill at 24 h; this is somewhat less than the animal data for ceftaroline but in keeping with the animal data for ceftobiprole. Target attainment modeling using an fT_{MIC} target of 26% or 33% indicated that for MIC values of ≤2 μg/ml, target attainment rates were >90% for ceftaroline administered at 600 mg q12h (6). Animal modeling of average human serum concentrations of ceftaroline administered at 600 mg q12h indicated a similar response with *S. aureus* strains with MICs over the range of 0.125 to 4 μg/ml, whatever the MIC (17). Our data obtained using an *in vitro* model and longer dose exposures are similar, indicating that for *S. aureus* strains with MICs of 0.12 to 2 μg/ml and 96-h dose exposures, there was no difference in antibacterial effect, as MICs increased up to 2 μg/ml, probably in relation to the high (>80%) fT_{MIC}s in all these simulations. Although regrowth occurred with some strains, this was not related to the ceftaroline MIC or detectable changes in population analysis profiles. Like others, the *S. aureus* strains with the hVISA and VISA phenotypes that we tested responded well to ceftaroline (18, 19). These *in vitro* data indicate, with other pharmacodynamic experiments, that ceftaroline fosamil at 600 mg q12h should be adequate therapy for *S. aureus* strains with MICs up to ≤2 μg/ml; indeed, comparison of the activity of ceftaroline administered at 600 mg q12h to that of ceftaroline administered at 600 mg every 8 h against *S. aureus* in an *in vitro* model indicated no advantage to the higher dose (18).

TABLE 6 Changes in ceftaroline population profiles in *S. aureus* at 48 h and 96 h of drug exposure

Time of drug exposure and T_{MIC} (%)	No. of expts	No. of expts with growth on 2× MIC plates	Count on 2× MIC plates (log CFU/ml)	No. of expts with growth on 4× MIC plates	Count on 4× MIC plates (log CFU/ml)
At 48 h					
≥80	15	0	<2	0	<2
70–79	6	0	<2	0	<2
50–69	8	0	<2	0	<2
40–49	5	1	2.7	1	2.1
30–39	8	2	3.9	0	<2
25–29	8	4	4.4 ± 2.0	0	<2
20–24	8	5	4.3 ± 1.8	0	<2
15–19	7	4	5.2 ± 2.1	0	<2
10–14	7	2	4.7	0	<2
At 96 h					
≥80	15	0	<2	0	<2
70–79	6	1	2.5	0	<2
50–69	8	1	2.5	0	<2
40–49	5	3	3.4 ± 1.6	1	2.1
30–39	8	5	7.1 ± 1.0	4	4.8 ± 2.3
25–29	8	6	5.5 ± 1.4	4	4.6 ± 2.3
20–24	8	6	6.1 ± 1.7	4	4.3 ± 1.6
15–19	7	5	5.6 ± 2.6	3	3.9 ± 1.7
10–14	7	5	6.4 ± 2.3	4	3.7 ± 1.4

Unlike other investigators, we were able to perform long-term experiments to 96 h and study changes in ceftaroline population analysis profiles. With simulations with a dose of 600 mg q12h, there were no changes over 96 h. In contrast, in dose-ranging experiments, isolates able to grow on 4× MIC plates at fT_{MIC} exposures of <50% emerged by 96 h.

Preclinical-clinical pharmacokinetics-pharmacodynamics correlates so far are poor for the use of cephalosporins to treat *S. aureus* infection; however, Kimko et al. (20) reported that a ceftobiprole fT_{MIC} of ≥30% was associated with clinical cure in skin and skin structure infections. Such data are in reasonable agreement with the proposed fT_{MIC} target of ≥25 to 30% based on our data. Ceftaroline fosamil has been shown to be noninferior to vancomycin plus aztreonam in two phase III randomized, double-blind studies (NCT00424190 and NCT00423657) in patients with complicated skin and skin structure infections (21, 22). The MIC_{90}s for ceftaroline in these studies were 1 μg/ml and 0.5 μg/ml (for all strains with MICs of ≤0.5 μg/ml), respectively; hence, as yet, strains with MICs of 2 μg/ml are rare in clinical studies.

Therefore, the predicted good responses for *S. aureus* strains with a ceftaroline MIC of 2 μg/ml, based on preclinical data, have not yet been validated in clinical studies. This is an important issue, as 5.2% of the MRSA strains in the United States and 17.3% of the MRSA strains in Europe have MICs of >1 μg/ml.

In conclusion, these data from an *in vitro* pharmacokinetic model validate the use of ceftaroline fosamil at 600 mg q12h i.v. to treat *S. aureus* strains with MICs of ≤2 μg/ml. A suitable fT_{MIC} target for clinical breakpoint setting is 25 to 30%, corresponding to a 1- to 2-log-unit kill in *S. aureus* after 24 h. In long-term experiments, fT_{MIC}s of ≤50% were associated with changes in ceftaroline population profiles in *S. aureus*.

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