Ceftaroline fosamil therapy in patients with acute bacterial skin and skin-structure infections with systemic inflammatory signs: A retrospective dose comparison across three pivotal trials

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ABSTRACT

This post-hoc analysis compared the pharmacokinetics and clinical outcomes of ceftaroline fosamil 600 mg every 12 (q12h) versus every 8 hours (q8h) in patients with acute bacterial skin and skin-structure infection (ABSSSI) and signs of sepsis. Clinical outcomes at test-of-cure in patients with ABSSSI and systemic inflammatory signs/systemic inflammatory response syndrome (SIRS) as well as ceftaroline minimum inhibitory concentrations (MICs) against baseline pathogens were compared between the COVERS trial (ceftaroline fosamil 600 mg q8h, 2-h infusion) and the CANVAS 1 and 2 trials (ceftaroline fosamil 600 mg q12h, 1-h infusion). Ceftaroline exposure among patients in COVERS with or without markers of sepsis was compared using population pharmacokinetic modelling. In COVERS, 62% (312/506) and 41% (208/506) of ceftaroline fosamil-treated patients had ≥1 systemic inflammatory sign or SIRS, respectively, compared with 55% (378/693) and 22% (155/693), respectively, in the CANVAS trials. Clinical cure rates for the modified intent-to-treat population in COVERS and CANVAS were similar for ceftaroline fosamil-treated patients with ≥1 sign of sepsis [82% (255/312) and 85% (335/394)] and for those with SIRS [84% (168/199) and 85% (131/155)]. Ceftaroline MIC distributions were similar across trials. Sepsis did not affect predicted individual steady-state ceftaroline exposure. Clinical cure rates in patients with ≥1 systemic inflammatory sign or SIRS were comparable for both ceftaroline fosamil dosage regimens. Pathogen susceptibilities to ceftaroline were similar across trials. Ceftaroline exposure was not affected by disease severity. Ceftaroline fosamil 600 mg q12h is a robust dosage regimen for most ABSSSI patients with sepsis [ClinicalTrials.gov ID: NCT01499277, NCT00424190, NCT00423657].

1. Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs) and complicated skin and soft-tissue infections (cSSTIs) include cellulitis/erysipelas, wound infection and major cutaneous abscess [1,2], imposing a substantial burden on healthcare systems. Between 2005 and 2010, the incidence of SSTI in the USA was ca. 48 per 1000 person-years [3]; currently, up to 300 000 surgical site infections occur each year, including those of the skin and subcutaneous tissue [4]. SSTIs can be serious, requiring hospitalisation and surgical procedures, and occasionally can cause bacteraemia and death [5]. Factors associated with ABSSSI onset and clinical

failure of ABSSSI treatment include obesity and low antibiotic dosage at discharge [6,7].

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin antibiotic with in vitro activity against many of the common bacteria associated with ABSSSI, including *Staphylococcus aureus* [both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)], *Streptococcus pyogenes*, *Streptococcus agalactiae*, and non-extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* [8,9]. In the pivotal phase III CANVAS 1 and 2 trials, ceftaroline fosamil 600 mg given as a 1-h intravenous (i.v.) infusion every 12 h (q12h) was shown to be non-inferior to vancomycin plus aztreonam for the treatment of ABSSSI [10–12]. These results supported the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of ceftaroline fosamil 600 mg q12h (adjusted for renal function) for the treatment of adults with ABSSSI and cSSTI, respectively [8,9].

The presence of sepsis can impact the pharmacokinetics of some antibiotics and thus potentially affect antibiotic efficacy in patients with ABSSSI. Septic patients in the intensive care unit have shown an increased volume of distribution (V_d) and increased clearance. An increase in V_d in these patients has been shown to be due to capillary leakage and endothelial damage, which can result in subtherapeutic dosing following administration of antibiotics. Clearance is variable and is dependent on the individual's disease state. Variable exposure to drug as a result of changes in V_d and clearance can, in turn, result in variable responsiveness to treatment both in terms of efficacy and toxicity, and this can impact mortality rates in these patients [13–15].

The phase III COVERS trial was conducted to assess a ceftaroline fosamil dosage regimen of 600 mg as a 2-h infusion every 8 h (q8h) in patients with ABSSSI with systemic inflammatory response syndrome (SIRS) or underlying co-morbidities and, on average, a greater lesion size [12]. Results from COVERS showed that ceftaroline fosamil 600 mg q8h was non-inferior to vancomycin plus aztreonam in these patients [12].

The objective of this post-hoc analysis was to compare ceftaroline fosamil 600 mg q12h versus 600 mg q8h for the treatment of ABSSSI in patients with signs of sepsis, first by comparing clinical outcomes and pathogen susceptibilities in the COVERS trial with the previously published CANVAS trials, and second by using population pharmacokinetic (PK) modelling to compare ceftaroline exposure in patients with or without markers of sepsis.

2. Materials and methods

2.1. Study design

COVERS (NCT01499277) and CANVAS 1 and 2 (NCT00424190 and NCT00423657) were phase III, multicentre, randomised, double-blind, comparative safety and efficacy trials of i.v. ceftaroline fosamil versus vancomycin plus aztreonam for the treatment of ABSSSI [10–12]. Patients were randomised to receive ceftaroline fosamil or vancomycin plus aztreonam at a ratio of 2:1 in COVERS and 1:1 in CANVAS 1 and 2. In COVERS, ceftaroline fosamil was administered at 600 mg q8h and vancomycin was administered at 15 mg/kg q12h with aztreonam at 1 g q8h. In CANVAS 1 and 2, ceftaroline fosamil was administered at 600 mg q12h and vancomycin plus aztreonam were each administered at 1 g q12h. Ceftaroline fosamil dosages were adjusted for patients with baseline creatinine clearance (CL_{Cr}) $\leq$50 mL/min, and vancomycin plus aztreonam dosages were adjusted according to the respective product labelling and institutional practice guidelines. Treatments were given for 5–14 days in all trials. The primary outcome measure for all three trials was the clinical cure rate at test-of-cure (TOC)

in the modified intent-to-treat (MITT) and clinically evaluable (CE) patient populations.

2.2. Patients and disease characteristics

The COVERS and CANVAS trials enrolled adult patients with cSSTI. The entire COVERS patient population, and a proportion of those in the CANVAS trials, met the FDA definition of ABSSSI [1]. Inclusion and exclusion criteria for the CANVAS trials have been described previously [10,11]. In brief, patients had a diagnosis of cSSTI (defined as deep extensive cellulitis, major cutaneous abscess requiring surgical drainage, or infected wound, ulcer or burn) of sufficient severity to warrant hospitalisation and $\geq$5 days of parenteral antibacterial therapy. Inclusion and exclusion criteria for COVERS were similar to the CANVAS trials, with an additional requirement of ABSSSI with surrounding area of erythema, oedema and/or induration with surface area $\geq$75 cm^2, reflecting regulatory guidance at the time the study was initiated [1,12]; of note, COVERS (but not CANVAS) excluded patients with diabetic foot infections. Disease characteristics assessed at baseline included systemic signs of infection, presence of SIRS [defined as the presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or on blood gas, a PaCO$_2$ <32 mmHg (4.3 kPa); white blood cell (WBC) count <4000 cells/mm^3 or >12 000 cells/mm^3, or >10% band forms (immature WBCs)] and an elevated C-reactive protein (CRP) level. Patients were required to give informed consent prior to enrolment in the trials.

2.3. Microbiology

Baseline pathogen susceptibilities to ceftaroline [minimum inhibitory concentrations (MICs)] were determined using Clinical and Laboratory Standards Institute (CLSI) methodology [16] by a central reference laboratory.

2.4. Clinical outcomes

Clinical cure was defined as total resolution of all signs and symptoms of the baseline infection or improvement such that no further antimicrobial therapy was necessary. Outcome was determined at the TOC time point (8–15 days after the last dose of study drug) in the MITT population (all randomised patients who received any study medication) and CE population, a subset of the MITT population who had a diagnosis of ABSSSI, had no non-eligible infections, received a prespecified minimum of study drug, had an evaluation at the TOC (or were determined to be a clinical failure at end of therapy) and did not receive any systemically active antibacterial agents that may have affected the infection under study [12,17]. Clinical cure rates were summarised for the MITT and CE populations overall and for patient subgroups with at least one systemic sign of inflammation, or sepsis [fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/mm^3 or bands >10%)], at least two severe signs or symptoms (erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator) or SIRS. As body weight and renal function have also been shown to impact ceftaroline pharmacokinetics [18,19], clinical cure rates were summarised by body mass index (BMI) and CL_{Cr} to compare outcomes across BMI and CL_{Cr} subgroups. Finally, clinical cure rates were also summarised by baseline pathogen. Safety was assessed in all randomised patients who received at least one dose of study therapy.

2.5. Population pharmacokinetic modelling

The ceftaroline population PK model used in this analysis was developed using a large patient PK data set that included data

Table 1
Patient demographics and baseline characteristics of the modified intent-to-treat (MITT) population[a]

Characteristic	COVERS		CANVAS 1 and 2	
	Ceftaroline fosamil ($n = 506$)	Vancomycin + aztreonam ($n = 255$)	Ceftaroline fosamil ($n = 693$)	Vancomycin + aztreonam ($n = 685$)
Age (years) (mean ± S.D.)	52.6 ± 16.5	53.6 ± 16.3	47.5 ± 17.0	48.4 ± 16.6
Sex				
Female	196 (38.7)	107 (42.0)	249 (35.9)	266 (38.8)
Male	310 (61.3)	148 (58.0)	444 (64.1)	419 (61.2)
Race				
White	341 (67.4)	160 (62.7)	506 (73.0)	512 (74.7)
Black or African–American	13 (2.6)	13 (5.1)	48 (6.9)	41 (6.0)
Asian	126 (24.9)	64 (25.1)	6 (0.9)	5 (0.7)
American Indian or Alaska Native	1 (0.2)	0	6 (0.9)	4 (0.6)
Native Hawaiian or other Pacific Islander	–	–	2 (0.3)	2 (0.3)
Multiracial/other/unknown	25 (4.9)	18 (7.1)	125 (18.0)	121 (17.7)
BMI (kg/m^2) [median (range)]	26.6 (15.0–50.0)	26.6 (14.0–50.0)	26.9 (14.1–74.1)	27.4 (16.6–66.5)
Baseline CL$_{Cr}$ (mL/min)[b]				
>30 to ≤50	31 (6.1)	17 (6.7)	23 (3.3)	26 (3.8)
>50 to ≤80	91 (18.0)	46 (18.0)	99 (14.3)	98 (14.3)
>80	362 (71.5)	183 (71.8)	569 (82.1)	559 (81.6)
Baseline CRP (mg/L)[c]				
≤50	178 (35.2)	100 (39.2)	396 (57.1)	387 (56.5)
>50 to ≤150	178 (35.2)	80 (31.4)	177 (25.5)	166 (24.2)
>150	139 (27.5)	68 (26.7)	98 (14.1)	111 (16.2)
Primary diagnosis of cellulitis	300 (59.3)	136 (53.3)	249 (35.9)	273 (39.9)
Co-morbid conditions				
Diabetes mellitus	84 (16.6)	38 (14.9)	122 (17.6)	120 (17.5)
Peripheral vascular disease	27 (5.3)	11 (4.3)	93 (13.4)	93 (13.6)
Infection area (cm^2) [median (range)]	400 (75–5040)	400 (77–6048)	156 (1–3150)	150 (0.04–4950)
Prior antibiotic therapy	240 (47.4)	116 (45.5)	276 (39.8)	260 (38.0)
≥1 systemic inflammatory sign[d]	312 (61.7)	166 (65.1)	378 (54.5)	363 (53.0)
≥2 severe signs and/or symptoms[e]	329 (65.0)	165 (64.7)	372 (53.7)	379 (55.3)
SIRS[f]	199 (39.3)	105 (41.2)	155 (22.4)	163 (23.8)

S.D., standard deviation; BMI, body mass index; CL$_{Cr}$, creatinine clearance; CRP, C-reactive protein; WBC, white blood cell; SIRS, systemic inflammatory response syndrome.

[a] Data are n (%) unless otherwise stated.
[b] 9 patients had CL$_{Cr}$ >20 to <30 mL/min and 22 patients had missing CL$_{Cr}$ data in COVERS; 4 patients had CL$_{Cr}$ ≤30 mL/min in CANVAS 1 and 2.
[c] 18 patients had missing CRP data in COVERS; 43 patients had missing CRP data in CANVAS 1 and 2.
[d] Systemic inflammatory signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/mm^3) or bands >10%.
[e] Severe local signs were erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator.
[f] SIRS criteria were defined as the presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min, or on blood gas, a PaCO$_2$, <32 mmHg (4.3 kPa); WBC count <4000 cells/mm^3 or >12 000 cells/mm^3, or >10% band forms (immature WBCs).

from 14 phase I trials in healthy subjects (with normal renal function or renal impairment), 1 phase II trial in patients with cSSTI, 3 phase III trials in patients with cSSTI (CANVAS 1, CANVAS 2 and COVERS) and 3 phase III trials in patients with community-acquired pneumonia [10–12,19–28]. Patient PK data were obtained in COVERS and in a subset of 45 patients in CANVAS 1 and 2 trials by sparse PK sampling over a single dosing interval (i.e. 8 h) on Day 3, with intensive PK samples taken in a subset of patients [29]. The population PK model was derived from first-order conditional estimation with the interaction model using the software program NONMEM v.7.2.0 (ICON plc, Dublin, Ireland). Details related to the PK modelling have been previously described [30]. Ceftaroline PK profiles were estimated for individual patients in COVERS with available ceftaroline PK data. Steady-state ceftaroline exposures [maximum plasma concentration ($C_{max,ss}$) and area under the concentration–time curve (AUC_{ss})] were derived from the individual predicted ceftaroline concentration–time courses from the population PK model using non-compartmental analysis. To assess whether the presence of markers of systemic inflammation or sepsis had any impact on ceftaroline exposures, AUC_{ss} and $C_{max,ss}$ were compared for the following patient subgroups: fever ≤38°C or >38°C; WBC count ≤12 000/mm^3 or >12 000/mm^3; CRP ≤50 mg/L, >50 mg/L to ≤150 mg/L or >150 mg/L; and presence or absence of SIRS or bacteraemia at baseline [29].

2.6. Statistical analyses

Patient outcomes are presented using descriptive statistics, and between-group outcome differences (95% confidence interval) were determined using the Miettinen & Nurminen method [31]. Full details of the statistical analyses used in the COVERS and CANVAS 1 and 2 trials have previously been described [10,11].

3. Results

3.1. Patient demographics and baseline characteristics

Patient demographics and baseline characteristics are summarised in Table 1. Most patients were male and white. Overall, baseline characteristics, including BMI, co-morbidities and prior antibiotic therapy, were similar between the patient populations in COVERS and the CANVAS trials. Patients were slightly older in COVERS compared with the CANVAS trials (mean ± standard deviation age, 52.6 ± 16.5 years vs. 47.5 ± 17.0 years for ceftaroline fosamil-treated patients) and there was a greater proportion of patients with a primary cSSTI diagnosis of cellulitis in COVERS [300 (59.3%) vs. 249 (35.9%) for ceftaroline fosamil-treated patients].

As expected based on inclusion criteria, more severe ABSSSI was observed in patients in COVERS; the median (range) infection area was greater among ceftaroline fosamil-treated patients from COVERS [400 (75–5040) cm^2] compared with those from CANVAS 1 and 2 [156 (1–3150) cm^2]. A greater proportion of ceftaroline fosamil-treated patients from COVERS also had at least one systemic inflammatory sign [312/506 (61.7%) COVERS vs. 378/693 (54.5%) CANVAS 1 and 2] and SIRS [208/506 (41.1%) COVERS vs. 155/693 (22.4%) CANVAS 1 and 2] at baseline. Compared with

Table 2
Susceptibility to ceftaroline of pathogens isolated at baseline in the modified intent-to-treat (MITT) population

Pathogen	COVERS			CANVAS 1 and 2		
	Isolates (n)[a]	MIC range[b]	MIC$_{90}$[b,c]	Isolates (n)[a]	MIC range[b]	MIC$_{90}$[b]
Gram-positive bacteria						
Staphylococcus aureus[d,e]	217	0.06–1.0	0.5	399	0.06–2.0	0.5
MSSA	164	0.06–0.5	0.25	235	0.06–0.5	0.25
MRSA	54	0.25–1.0	0.5	164	0.25–2.0	0.5
Streptococci						
Streptococcus pyogenes[f]	25	≤0.008	≤0.008	61	≤0.004–0.008	≤0.004
Streptococcus agalactiae[f]	16	≤0.008–0.015	0.015	22	0.008–0.015	0.015
Streptococcus dysgalactiae	12	≤0.008–0.06	0.015	13	≤0.004–0.008	0.008
Streptococcus anginosus group	21	≤0.008–0.03	0.03	14	≤0.004–0.06	0.03
Enterococcus faecalis	13	0.5–64	8	27	0.25–16	8
Gram-negative bacteria[g]						
Escherichia coli (non-ESBL-producing)	26	≤0.015–8	1.0	23	0.015 to >16	1.0
Klebsiella oxytoca	8	0.03–0.25	–	11	0.03–0.25	0.25
Klebsiella pneumoniae	12	0.06 to >32	>32	18	0.03 to >16	>16
Morganella morganii	7	0.03–0.12	–	11	0.06 to >16	>16
Proteus mirabilis	11	0.03 to >32	0.12	16	≤0.008 to >16	>16

MIC, minimum inhibitory concentration; MIC$_{90}$, MIC required to inhibit 90% of the isolates; FDA, US Food and Drug Administration; CLSI, Clinical and Laboratory Standards Institute; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; ESBL, extended-spectrum β-lactamase.
  [a] Some pathogens that were isolated were not able to be tested.
  [b] MIC range and MIC$_{90}$ expressed in mg/L.
  [c] MIC$_{90}$ not calculated when $n < 10$.
  [d] Patients with both MRSA and MSSA were counted only once.
  [e] FDA/CLSI ceftaroline susceptible/resistant breakpoints ≤1/≥4 mg/L.
  [f] FDA/CLSI ceftaroline susceptible breakpoint ≤0.5 mg/L.
  [g] FDA/CLSI ceftaroline susceptible/resistant breakpoint for Enterobacteriaceae ≤0.5/≥2 mg/L [32].

CANVAS 1 and 2, a greater proportion of patients in COVERS had elevated baseline CRP levels.

3.2. Baseline pathogens

The most common pathogens isolated and tested at baseline in the COVERS patient population were MSSA ($n = 164$; 39%), MRSA ($n = 54$; 13%), non-ESBL-producing *E. coli* ($n = 26$; 6%) and *S. pyogenes* ($n = 25$; 6%). In the CANVAS trials, MSSA ($n = 235$; 36%), MRSA ($n = 164$; 25%), *S. pyogenes* ($n = 61$; 9%) and *Enterococcus faecalis* ($n = 27$; 4%) were the most commonly isolated pathogens. The proportion of patients with no baseline pathogen identified was higher in COVERS ($n = 378$; 49.0%) compared with the CANVAS trials ($n = 324$; 23.2%), reflecting the higher proportion of patients with cellulitis in the COVERS trial.

The ceftaroline susceptibility of pathogens isolated at baseline were generally similar between the COVERS and CANVAS trials (Table 2). Both in COVERS and the CANVAS trials, the ceftaroline MIC (range) and MIC$_{90}$ (MIC required to inhibit 90% of the isolates) for MSSA isolates were 0.06–0.5 mg/L and 0.25 mg/L, respectively. Ceftaroline susceptibility among MRSA isolates was as follows: COVERS MIC range, 0.25–1.0 mg/L, MIC$_{90}$, 0.5 mg/L; and CANVAS MIC range, 0.25–2.0 mg/L, MIC$_{90}$, 0.5 mg/L. The ceftaroline MIC range and MIC$_{90}$ of *S. pyogenes* isolates from COVERS were both ≤0.008 mg/L; the ceftaroline MIC range and MIC$_{90}$ of *S. pyogenes* isolates from the CANVAS trials were <0.004–0.0008 mg/L and ≤0.004 mg/L, respectively.

3.3. Clinical outcomes (modified intent-to-treat population)

Overall clinical cure rates at TOC for ceftaroline fosamil were 78.3% (396/506) in the COVERS trial and 85.9% (595/693) in the CANVAS trials. For patients treated with vancomycin plus aztreonam, overall clinical cure rates were 79.2% (202/255) in the COVERS trial and 85.5% (586/685) in the CANVAS trials. Clinical cure rates by inflammatory sign, BMI and CL$_{Cr}$ subgroups and overall are summarised in Table 3. Clinical cure rates for ceftaroline fosamil-treated patients across all subgroups with systemic inflammatory

signs or SIRS were broadly similar in the COVERS and CANVAS trials, ranging from 79% to 85% in COVERS and from 83% to 89% in the CANVAS trials. For comparison, the clinical cure rates for vancomycin plus aztreonam ranged from 72% to 88% in the COVERS trial and from 84% to 90% in the CANVAS trials. Among ceftaroline fosamil-treated patients with at least one systemic sign of inflammation, or sepsis, clinical cure was observed in 81.7% of patients (255/312) in COVERS and 85.0% (335/394) in CANVAS 1 and 2. Among ceftaroline fosamil-treated patients with SIRS, clinical cure was observed in 84.4% (168/199) from COVERS and 84.5% (131/155) from CANVAS 1 and 2. Clinical cure rates by inflammatory sign and overall for the CE population were similar to those in the MITT population (Supplementary Table S1).

Clinical cure rates were generally comparable between ceftaroline fosamil-treated BMI subgroups in the COVERS and CANVAS trials, with the exception of a small number of patients with BMI <18.5 kg/m^2 [clinical cure rate 8/15 (53.3%) in COVERS compared with 11/15 (73.3%) in CANVAS]. Clinical cure rates for ceftaroline fosamil-treated patient subgroups with BMI ≥18.5 to <25, ≥25 to <30 and ≥30 kg/m^2 ranged from 75.2% to 84.5% in COVERS and from 84.5% to 91.2% in the CANVAS trials. A small proportion of ceftaroline fosamil-treated patients had moderate renal impairment (CL$_{Cr}$ >30 to ≤50 mL/min) at baseline in the COVERS and CANVAS trials [31 (6.1%) and 23 (3.3%), respectively]. Clinical cure rates for ceftaroline fosamil-treated patients with moderate renal impairment were 23/31 (74.2%) in COVERS and 19/23 (82.6%) in the CANVAS trials. Clinical cure rates for BMI and CL$_{Cr}$ subgroups in the CE population were similar to those in the MITT population (Supplementary Table S1).

Clinical cure rates by baseline pathogen (medically evaluable population) are summarised in Table 4. Among ceftaroline fosamil-treated patients with infections caused by MSSA, clinical cure rates were 93.6% (88/94) and 93.0% (212/228) in COVERS and CANVAS 1 and 2, respectively. Clinical cure was observed 84.0% (21/25) and 93.4% (142/152) of ceftaroline fosamil-treated patients with infections caused by MRSA from COVERS and CANVAS 1 and 2, respectively; all MRSA isolates from COVERS and CANVAS 1 and 2 had a ceftaroline MIC of ≤1 mg/L and ≤2 mg/L, respectively.

Table 3

Clinical cure rates at test-of-cure overall and among subgroups of patients with systemic signs of infection, systemic inflammatory response syndrome (SIRS), and body mass index (BMI) and baseline creatinine clearance (CL_Cr) categories in the modified intent-to-treat (MITT) population

Patient population	COVERS			CANVAS 1 and 2		
	Ceftaroline fosamil [n/N (%)]	Vancomycin + aztreonam [n/N (%)]	Between-group difference (95% CI)	Ceftaroline fosamil [n/N (%)]	Vancomycin + aztreonam [n/N (%)]	Between-group difference (95% CI)
Overall	396/506 (78.3)	202/255 (79.2)	−1.0 (−6.9 to 5.4)	595/693 (85.9)	586/685 (85.5)	0.3 (−3.4 to 4.0)
≥1 systemic inflammatory sign[a]	255/312 (81.7)	137/166 (82.5)	−0.8 (−7.7 to 6.8)	335/378 (88.6)	326/363 (89.8)	−1.0 (−6.0 to 4.0)
≥2 severe signs and/or symptoms[b]	259/329 (78.7)	137/165 (83.0)	−4.3 (−11.3 to 3.3)	330/372 (88.7)	332/379 (87.6)	1.1 (−3.6 to 5.8)
Fever	179/211 (84.8)	104/118 (88.1)	−3.3 (−10.6 to 4.9)	185/211 (87.7)	181/201 (90.0)	−2.4 (−8.6 to 3.8)
Elevated WBC count[c]	177/224 (79.0)	75/104 (72.1)	6.9 (−2.8 to 17.5)	205/246 (83.3)	213/254 (83.9)	−0.5 (−7.1 to 6.0)
SIRS[d]	168/199 (84.4)	83/105 (79.0)	5.4 (−3.5 to 15.2)	131/155 (84.5)	140/163 (85.9)	−1.4 (−9.4 to 6.5)
Baseline CRP (mg/L)						
≤50	149/178 (83.7)	83/100 (83.0)	0.7 (−8.0 to 10.5)	346/396 (87.4)	333/387 (86.0)	1.3 (−3.5 to 6.1)
>50 to ≤150	136/178 (76.4)	67/80 (83.8)	−7.4 (−16.9 to 3.8)	156/177 (88.1)	138/166 (83.1)	5.0 (−2.5 to 12.7)
>150	105/139 (75.5)	49/68 (72.1)	3.5 (−8.8 to 16.9)	76/98 (77.6)	95/111 (85.6)	−8.0 (−18.9 to 2.5)
BMI (kg/m²)[e,f]						
<18.5	8/15 (53.3)	6/9 (66.7)	−13.3 (−48.2 to 27.4)	11/15 (73.3)	5/7 (71.4)	1.9
≥18.5 to <25	145/185 (78.4)	67/87 (77.0)	1.4 (−8.7 to 12.7)	201/238 (84.5)	182/223 (81.6)	2.8 (−4.0 to 9.8)
≥25 to <30	115/153 (75.2)	71/86 (82.6)	−7.4 (−17.5 to 3.8)	197/216 (91.2)	210/227 (92.5)	−1.3 (−6.7 to 3.9)
≥30	125/148 (84.5)	58/73 (79.5)	5.0 (−5.3 to 16.9)	186/222 (83.8)	188/227 (82.8)	1.0 (−6.0 to 7.9)
CL_Cr (mL/min)[g]						
>30 to ≤50	23/31 (74.2)	10/17 (58.8)	15.4 (−11.6 to 42.6)	19/23 (82.6)	21/26 (80.8)	1.8 (−21.5 to 24.2)
>50 to ≤80	71/91 (78.0)	38/46 (82.6)	−4.6 (−17.6 to 10.7)	83/99 (83.8)	88/98 (89.8)	−6.0 (−15.8 to 3.7)
>80	288/362 (79.6)	149/183 (81.4)	−1.9 (−8.6 to 5.5)	492/569 (86.5)	475/559 (85.0)	1.5 (−2.6 to 5.6)

CI, confidence interval; WBC, white blood cell.

[a] Systemic signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/mm³) or bands >10%.

[b] Severe local signs were erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator.

[c] >10 000 cells/mm³.

[d] SIRS criteria were defined as presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min, or on blood gas, a PaCO₂, <32 mmHg (4.3 kPa); WBC count <4000 cells/mm³ or >12 000 cells/mm³, or >10% band forms (immature WBCs).

[e] BMI data were missing from 5 patients in COVERS and from 3 patients in CANVAS 1 and 2.

[f] CIs were calculated when the sample size for a pathogen was ≥10 patients in each treatment group using the Miettinen & Nurminen method for stratified designs (stratified by study) [31].

[g] Ceftaroline fosamil dosage regimens were adjusted for patients with CL_Cr >30 to ≤50 mL/min. Clinical cure rates for patients with CL_Cr >20 to <30 mL/min (n = 8) and patients with missing CL_Cr data (n = 22) in COVERS are not shown.

Table 4

Clinical cure rate by baseline pathogen in the medically evaluable population

Pathogen	COVERS			CANVAS 1 and 2		
	Ceftaroline fosamil [n/N (%)]	Vancomycin + aztreonam [n/N (%)]	Between-group difference (95% CI)	Ceftaroline fosamil [n/N (%)]	Vancomycin + aztreonam [n/N (%)]	Weighted[a] between-group difference (95% CI)
Gram-positive bacteria						
Staphylococcus aureus[b]	109/119 (91.6)	61/71 (85.9)	5.7 (−3.3 to 16.5)	352/378 (93.1)	336/356 (94.4)	−1.3 (−4.9 to 2.4)
MSSA	88/94 (93.6)	49/57 (86.0)	7.7 (−1.9 to 19.7)	212/228 (93.0)	225/238 (94.5)	−1.6 (−6.3 to 2.9)
MRSA	21/25 (84.0)	12/15 (80.0)	4.0 (−19.8 to 32.2)	142/152 (93.4)	115/122 (94.3)	−0.9 (−7.0 to 5.5)
Streptococci						
Streptococcus pyogenes	14/15 (93.3)	7/7 (100.0)	−6.7 (−30.5 to 30.8)	56/56 (100.0)	56/58 (96.6)	3.9 (−2.3 to 12.6)
Streptococcus agalactiae	5/6 (83.3)	7/9 (77.8)	5.6 (−41.2 to 44.9)	21/22 (95.5)	18/18 (100.0)	N/A[c]
Streptococcus dysgalactiae	9/9 (100.0)	0/0 (0)	N/A	13/13 (100.0)	15/16 (93.8)	N/A[c]
Streptococcus anginosus group	16/18 (88.9)	4/4 (100.0)	−11.1 (−33.4 to 40.6)	12/13 (92.3)	15/16 (93.8)	N/A[c]
Enterococcus faecalis	4/6 (66.7)	4/5 (80.0)	−13.3 (−59.6 to 41.6)	20/25 (80.0)	22/24 (91.7)	−12.6 (−34.1 to 8.0)
Gram-negative bacteria						
Escherichia coli	11/12 (91.7)	9/10 (90.0)	1.7 (−28.5 to 34.7)	20/21 (95.2)	19/21 (90.5)	N/A[c]
Klebsiella oxytoca	4/4 (100.0)	1/1 (100.0)	N/A	10/12 (83.3)	6/6 (100.0)	N/A[c]
Klebsiella pneumoniae	5/7 (71.4)	3/4 (75.0)	−3.6 (−51.1 to 52.1)	17/18 (94.4)	13/14 (92.9)	N/A[c]
Morganella morganii	4/4 (100.0)	2/2 (100.0)	N/A	11/12 (91.7)	5/6 (83.3)	N/A[c]
Proteus mirabilis	6/7 (85.7)	2/2 (100.0)	−14.3 (−53.5 to 58.4)	10/15 (66.7)	20/21 (95.2)	N/A[c]

CI, confidence interval; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; N/A, not applicable.

[a] Weighted difference in clinical cure rates stratified by study.

[b] Patients with MRSA and MSSA were counted only once.

[c] CIs were calculated when the sample size for a pathogen was ≥10 patients in each treatment group using the Miettinen & Nurminen method for stratified designs (stratified by study) [31].

3.4. Safety

In COVERS, 45.8% (232/506) of patients treated with ceftaroline fosamil experienced at least one adverse event (AE) compared with 45.5% (116/255) of patients treated with vancomycin plus aztreonam; and 44.7% (309/692) of patients treated with ceftaroline fosamil and 47.5% (326/686) of patients treated with vancomycin plus aztreonam experienced at least one AE in the CANVAS trials. The most common AEs among ceftaroline fosamil-treated patients in COVERS (occurring in ≥3% of patients) were nausea (4.0%), headache (3.4%) and hypokalaemia (3.0%). The most common AEs among ceftaroline fosamil-treated patients in CANVAS 1 and 2
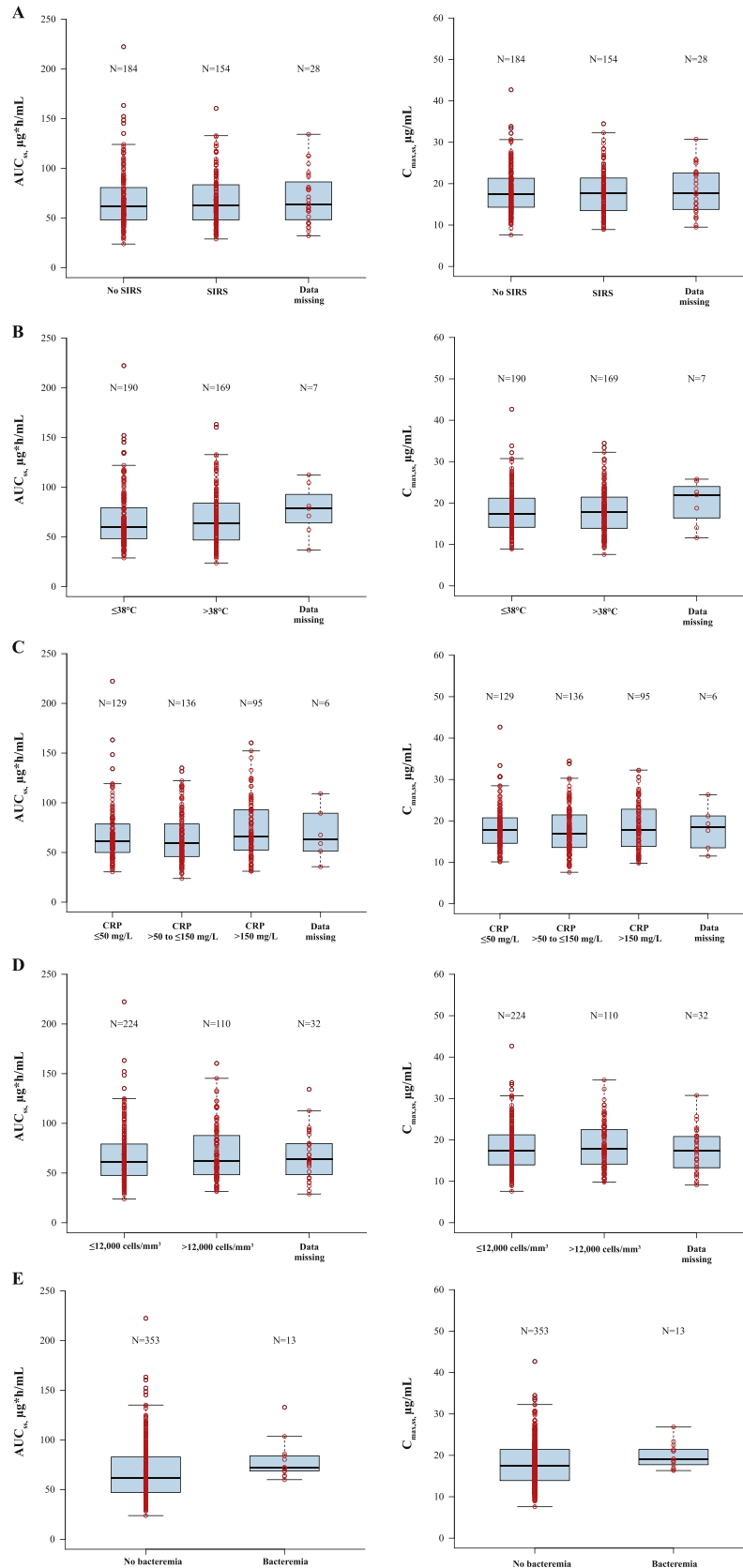
Fig. 1. Comparison of predicted steady-state ceftaroline fosamil exposures (AUC_{ss} and $C_{max,ss}$) in individual acute bacterial skin and skin-structure infection (ABSSSI) patients from COVERS (A) with and without systemic inflammatory response syndrome (SIRS), (B) with and without fever, (C) with and without high C-reactive protein (CRP), (D) with and without high white blood cell count and (E) with and without bacteraemia. AUC_{ss}, area under the concentration–time curve at steady-state; $C_{max,ss}$, maximum plasma concentration at steady-state.

(occurring in ≥3% of patients) were nausea (5.9%), headache (5.2%), diarrhoea (4.9%), pruritus (3.5%) and rash (3.2%).

3.5. Population pharmacokinetic modelling of ceftaroline exposure

Overall, the population PK modelling data set included data from 951 subjects, of which 463 were patients with cSSTI. The model described the observed ceftaroline concentration data well and was considered suitable to calculate exposure parameters for individual patients in COVERS. PK data were available from 371 patients in COVERS for whom a full ceftaroline plasma concentration time course could be calculated. Individual predictions of AUC_{ss} and $C_{max,ss}$ for these patients are summarised by the presence or absence of fever, SIRS or bacteraemia, high WBC count and CRP levels in Fig. 1. The individual, median and range AUC_{ss} and $C_{max,ss}$ values demonstrated clear evidence of overlap in patients within the respective disease severity parameters, indicating that these parameters had little effect on ceftaroline exposure.

4. Discussion

The COVERS and CANVAS 1 and 2 trials included all patients with systemic signs of inflammation, or sepsis, and SIRS, allowing for an informative comparison of the clinical outcomes associated with ceftaroline fosamil 600 mg as a 1-h infusion q8h versus 600 mg as a 2-h infusion q12h in patients with severe ABSSSI. Because the pathogens isolated and their associated ceftaroline susceptibilities in the COVERS trial were similar to the CANVAS trials, the clinical outcomes and pathogen susceptibilities were compared. This provides further rationale for the comparison of clinical outcomes between the trials. Moreover, a patient-rich population ceftaroline PK model, which included data from over 900 subjects, allowed evaluation of predicted ceftaroline exposures for patients with and without sepsis, complementing the clinical data comparisons between the trials.

Although the ceftaroline fosamil q8h dosage regimen was efficacious in COVERS, clinical outcomes among ceftaroline fosamil-treated patient subgroups with more severe disease (i.e. more than one systemic sign of inflammation, or sepsis, fever, elevated WBC count or SIRS) were comparable with patients receiving ceftaroline fosamil q12h in the CANVAS trials. Clinical cure rates were also generally comparable for BMI and CL_{Cr} patient subgroups in the COVERS and CANVAS trials. Differences in clinical cure rates for ceftaroline fosamil versus vancomycin plus aztreonam were broadly similar across the trials; for both treatment groups, clinical cure rates were generally numerically lower in COVERS compared with the CANVAS trials. This is likely due to patients generally having more severe infection and co-morbidities that are not captured in a single subgroup category. Ceftaroline fosamil was well tolerated in both trials, with AEs representative of the cephalosporin class. Hence, the q12h regimen appears robust for the majority of patients with ABSSSI, regardless of the presence of systemic inflammatory signs.

These clinical data are aligned with population PK modelling of individual patients within the COVERS trial, which showed that steady-state exposures of ceftaroline were comparable across patients with and without signs of sepsis. The pharmacokinetics of ceftaroline in COVERS was similar to results previously reported for subjects treated with ceftaroline fosamil q12h [18,33], with a dose-proportional increase in exposure from the q8h dosing used in COVERS [30,33,34]. Ceftaroline pharmacokinetics therefore does not appear to be affected by disease severity, suggesting that the ceftaroline fosamil q12h regimen provides adequate exposure in ABSSSI patients with severe disease. Pathogen susceptibilities to ceftaroline were similar between the COVERS and CANVAS trials,

with both dosage regimens providing broad coverage against commonly isolated ABSSSI pathogens. The MICs of >95% of baseline isolates across the three trials were at or below respective CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints for ceftaroline fosamil 600 mg q12h [16,35]. Clinical response rates were generally comparable across the COVERS and CANVAS trials for key ABSSSI pathogens, including *S. aureus*. MRSA isolated from COVERS and CANVAS 1 and 2 had ceftaroline MICs of ≤1 mg/L and ≤2 mg/L, respectively. Probability of target attainment (PTA) analyses using the ceftaroline population PK model described above have shown that >95% PTA is predicted with the 600 mg q12h dose regimen for *S. aureus* isolates with MICs up to 2 mg/L [30]. With the 600 mg q8h dosage regimen, >95% PTA is predicted for *S. aureus* isolates with MICs up to 4 mg/L [30]. In 2017, the EMA label was updated to recommend the use of ceftaroline fosamil 600 mg q8h for cSSTI patients where the causative pathogen is *S. aureus* with a ceftaroline MIC of 2 mg/L or 4 mg/L [8]; such isolates are very rare in the USA and Europe [36,37].

Because individual study patient PK data were not analysed in this retrospective analysis and individual patients may have different disease states, this was not described in the CANVAS and COVERS trials. We believe that confounders that do exist in this particular patient population are valid but, given the positive findings in this study, do not appear to play a substantial role in the efficacy or toxicity of ceftaroline treatment. In addition, because this analysis is a retrospective cross-trial comparison, it is limited by the inability to completely control for population differences between trials. Similarly, as enrolment for COVERS and the CANVAS trials occurred in different geographic locations, regional differences in care may have affected the results. However, given that the population PK analyses support the conclusions from the cross-trial comparison, the data overall support that ceftaroline fosamil 600 mg q12h is a robust dosage regimen for the great majority of patients with ABSSSI, including those with sepsis and SIRS.

5. Conclusions

On the basis of the clinical, microbiological and population PK modelling comparisons presented here, sepsis did not affect predicted individual steady-state ceftaroline exposure. Ceftaroline fosamil 600 mg q12h is a well-tolerated, efficacious dosage regimen for the majority of patients with severe ABSSSI, regardless of the extent of sepsis.

Competing interests

MHW has received consulting fees from AiCuris, AstraZeneca, Bayer, Cerexa, Durata, The Medicines Company, Menarini, Motif Bio, Nabriva, Paratek and Pfizer, lecture fees from Allergan, AstraZeneca and Pfizer, and grant support from Motif Biosciences, Nabriva, Paratek and Pfizer; JG, DJW, SD and JI were employees of AstraZeneca at the time of study conduct and analysis; DJW, SD and JI are shareholders in AstraZeneca; AJ and HDF were employees of Cerexa (now a subsidiary of Allergan) at the time of study conduct and analysis; MD has received honoraria from and attended advisory boards for Bayer, AstraZeneca, Motif Bio, Pfizer, Matoke and MSD. GRC declares no competing interests.

Ethical approval

For each trial, the clinical study protocol was approved before enrolment of any patient into the trial, including approved by or notification to the national regulatory authority, as required by local regulations. Ethical approval was obtained from the local ethical committee at each study centre.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.01.016.

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