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Summary of the safety and tolerability of two treatment regimens of ceftaroline fosamil: 600 mg every 8 h versus 600 mg every 12 h

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Background: The recommended adult dose of ceftaroline fosamil is 600 mg q12h by 1 h intravenous (iv) infusion for 5–14 days in complicated skin and soft tissue infection (cSSTI) and 5–7 days in community-acquired pneumonia (CAP). A dosage of 600 mg q8h by 2 h iv infusion is approved in some regions for cSSTI patients with *Staphylococcus aureus* infection where the ceftaroline MIC is 2 or 4 mg/L. This analysis compares the safety profiles of the q8h and q12h regimens.

Methods: Safety data from six Phase III, randomized, double-blind clinical trials were collated into the q8h cSSTI pool (ceftaroline fosamil $n = 506$; NCT01499277) and the q12h pool {ceftaroline fosamil $n = 1686$; comprising five studies [two cSSTI (NCT00424190 and NCT00423657) and three CAP (NCT01371838, NCT00621504 and NCT00509106)]}.

Results: The pattern and incidence of adverse events were similar between the q8h and q12h ceftaroline fosamil pools. Most were gastrointestinal and of mild or moderate intensity. Overall, rash intensity was similar between the q8h pool and the q12h pool. For the q8h regimen, there was a higher frequency of rash in some Asian study sites, associated with longer duration of therapy ($\geq$7 days); most cases were mild and resolved following treatment discontinuation. No dose-related vital sign or ECG abnormalities were detected with either regimen.

Conclusions: The q8h regimen in cSSTI was generally well tolerated; the observed safety profile was consistent with the known safety profile of ceftaroline fosamil, reflective of the cephalosporin class and qualitatively consistent with the q12h regimen.

Introduction

Ceftaroline fosamil is indicated for treatment of community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTIs).[1] Safety and efficacy of ceftaroline fosamil for cSSTI was established in two Phase III trials (CANVAS 1 and 2), demonstrating non-inferiority of 600 mg of ceftaroline fosamil [1 h intravenous (iv) infusion] q12h to vancomycin plus aztreonam.[2,3] Another Phase III study (COVERS) assessed 600 mg of ceftaroline fosamil (2 h infusion) q8h in cSSTI patients with more serious infections.[4] COVERS demonstrated safety and efficacy of the q8h regimen, with clinical outcomes comparable with those observed in CANVAS 1 and 2, suggesting the q12h regimen is appropriate for most cSSTI patients.[2–4]

The q12h regimen achieves >90% PTA against MSSA and MRSA isolates with MICs of ceftaroline $\leq$2 mg/L.[5] Although *Staphylococcus aureus* isolates with ceftaroline MICs >2 mg/L are rare in the USA and the EU (MIC_{90}, 1 mg/L),[6,7] they are more common in Latin America and the Asia-Pacific region (MIC_{90}, 2 mg/L).[8–10] Ongoing surveillance has identified rare MRSA isolates with MICs of 4 mg/L.[11] With pharmacokinetic (PK) and pharmacodynamic (PD) modelling and simulation predicting >90% PTA for *S. aureus* with ceftaroline MICs up to 4 mg/L, the q8h regimen may be a treatment option for these difficult-to-treat pathogens.[5] The objective of the current analysis is to compare the safety of 600 mg of ceftaroline fosamil q8h with that observed from the q12h trials.[2–4,12–14]

Patients and methods

Study design and patients

All six Phase III, randomized, controlled ceftaroline fosamil studies from the clinical development programme were included: three in cSSTI (COVERS, CANVAS 1 and CANVAS 2) and three in CAP (Asia CAP, FOCUS 1 and FOCUS 2; Table S1, available as Supplementary data at *JAC* Online).[2–4,12–14] The studies in each infection generally had similar designs and inclusion criteria (Table S1). COVERS enrolled a higher proportion of patients with severe infection compared with the other two cSSTI studies.[15]

The dosage of ceftaroline fosamil in COVERS was 600 mg q8h by 2 h iv infusion for 5–14 days, whereas it was 600 mg q12h by 1 h iv infusion for 5–14 days in the other cSSTI studies and for 5–7 days in the CAP studies (Table S1).

Ethics

All studies were conducted in compliance with the Declaration of Helsinki and/or the International Conference on Harmonization Good Clinical Practice Guidelines. All study protocols (NCT01499277, NCT00424190, NCT00423657, NCT01371838, NCT00621504 and NCT00509106) were approved by relevant Institutional Review Boards and/or Independent Ethics Committees. All patients (or their representatives) provided written informed consent.

Analyses sets and assessments

Data were collated for the q8h pool (comprising COVERS; 506 patients received ceftaroline fosamil) and the q12h pool (comprising CANVAS 1 and 2, FOCUS 1 and 2, and Asia CAP; 1686 patients received ceftaroline fosamil). The safety analyses set included all randomized patients receiving any amount of ceftaroline fosamil.

Safety and tolerability of ceftaroline fosamil was assessed using treatment-emergent adverse events (TEAEs), laboratory results, urinalysis, ECGs and vital signs. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.0 for COVERS, 16.0 for Asia CAP and 11.1 for CANVAS and FOCUS). Severity of TEAEs was classified as: mild (awareness of sign or symptom but easily tolerated), moderate (disturbing/uncomfortable but still tolerable) or severe (intolerable/severe discomfort).

The individual Phase III studies were designed primarily to assess efficacy. They were not powered for formal comparison of safety between study treatments. Thus, safety data in the individual trials and in this pooled analysis were not subject to formal statistical analysis/hypothesis testing.[16]

Data sharing statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices: (i) for indications that have been approved in the USA and/or EU; or (ii) in programmes that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Results

Patients

Baseline characteristics were generally similar for patients in the q8h and q12h pools (Table S2). In the q8h and q12h pools, 39.3% and 22.4% of ceftaroline fosamil-treated cSSTI patients had systemic inflammatory response syndrome, respectively. Treatment discontinuations are shown in Table S3.

TEAEs

The most common TEAEs in ceftaroline fosamil-treated patients in the q8h pool were nausea, headache and hypokalaemia and in the q12h pool were diarrhoea, nausea and headache (Table 1). Incidence of rash was higher in the q8h pool than the q12h pool, with greater incidence detected in Asian versus non-Asian study sites (18.5% versus 5.5%, respectively). Most cases were mild and resolved following treatment discontinuation. In the q8h pool, 5.1% of patients receiving ceftaroline fosamil experienced serious AEs (SAEs; Table 1); all were single reports except two (0.4%) patients had cardiac failure and two (0.4%) had deep vein thrombosis. In the q12h pool, 7.7% of patients experienced at least one SAE (including death), with many reflecting CAP-associated respiratory events (Table S4).

Ceftaroline fosamil-related TEAEs and SAEs were observed in 16.0% and 1.0%, respectively, in the q8h pool and 16.8% and 0.4%, respectively, in the q12h pool.

TEAEs leading to discontinuation

TEAEs leading to discontinuation of ceftaroline fosamil were reported in 32/506 (6.3%) patients in the q8h pool and 55/1686 (3.3%) in the q12h pool (Table 2). The AEs most frequently leading to treatment discontinuation were in the system organ class of skin and subcutaneous tissue disorders (Table 2). Ceftaroline fosamil-treated patients from Asian study sites (China, Hong Kong, South Korea and Taiwan) in the q8h pool had a higher incidence of TEAEs leading to treatment discontinuation [20/124 patients (16.1%)] compared with non-Asian regions in the q8h pool [12/382 patients (3.1%)] and the total q12h pool [55/1686 (3.3%)]. Rash resulted in ceftaroline fosamil discontinuation in 10 of the 20 patients from Asian study sites.

Vital signs and other safety observations

End organ toxicities and/or reactions that are of known association with the cephalosporin drug class include allergic reactions, haematological effects, renal impairment, liver injury, antibiotic-associated diarrhoea and seizures. Consistent with studies concerning 600 mg of ceftaroline fosamil q12h, data from the q8h pool did not result in the identification of any new renal, hepatic or seizure-related adverse drug reactions (Table 1). Potential antibiotic-associated diarrhoea was reported in the q8h pool at a slightly lower incidence than in the q12h pool (Table 1).

Laboratory parameters in the q8h pool were generally similar to the q12h pool. Coombs seroconversion rate was higher in the q8h pool (Table S5), where there were two reports of mild haemolytic anaemia. Neither contained sufficient clinical and/or laboratory evidence to support this diagnosis. There were no significant trends in urinalysis, vital sign or ECG parameters in the ceftaroline fosamil q8h or q12h pools (Table S5).

Discussion

In this safety analysis, the safety profile of 600 mg of ceftaroline fosamil q8h (2 h iv infusion) was shown to be consistent with that of the 600 mg q12h regimen[1] and reflective of the cephalosporin class.[4,17]

Studies have shown that administration of high cephalosporin dosages may be associated with nephrotoxicity and neurotoxicity.[17] The incidence and pattern of renal disorder AEs in the ceftaroline fosamil q8h pool reported here were consistent with the q12h pool. There were no cases of seizures in the ceftaroline fosamil q8h pool and the three cases identified in the q12h pool (0.2%) occurred in patients who had plausible alternative explanations

Table 1. Treatment exposure and overview of TEAEs (safety population)

	Phase III q8h cSSTI pool[a] (one study[b]), ceftaroline fosamil ($n = 506$)	Phase III q12h pool[a] (five studies[b]), ceftaroline fosamil ($n = 1686$)
Treatment exposure (days)		
mean	8.2	7.2
median	7.6	7.0
range	0.07–13.79	1–22
Patients with, *n* (%)		
any TEAE	232 (45.8)	769 (45.6)
any TEAE leading to discontinuation	32 (6.3)	55 (3.3)
any SAE	26 (5.1)	125 (7.4)
AEs with fatal outcome	3 (0.6)	21 (1.2)
Most common AEs according to system organ class (≥2.0% in any group)		
blood and lymphatic system disorders	19 (3.8)	31 (1.8)
anaemia	10 (2.0)	14 (0.8)
metabolism and nutrition disorders	32 (6.3)	96 (5.7)
hypokalaemia	15 (3.0)	29 (1.7)
psychiatric disorders	18 (3.6)	64 (3.8)
insomnia	7 (1.4)	38 (2.3)
nervous system disorders	33 (6.5)	117 (6.9)
headache	17 (3.4)	63 (3.7)
dizziness	10 (2.0)	31 (1.8)
vascular disorders	17 (3.4)	81 (4.8)
respiratory, thoracic and mediastinal disorders	22 (4.3)	84 (5.0)
gastrointestinal disorders	61 (12.1)	238 (14.1)
nausea	20 (4.0)	63 (3.7)
vomiting	13 (2.6)	42 (2.5)
diarrhoea	12 (2.4)	84 (5.0)
constipation	9 (1.8)	45 (2.7)
skin and subcutaneous tissue disorders	63 (12.5)	103 (6.1)
general disorders and administration site conditions	41 (8.1)	111 (6.6)
investigations	28 (5.5)	109 (6.5)
TEAE categories of special interest (associated with the cephalosporin class or other β-lactams)		
renal disorders	4 (0.8)	21 (1.2)
liver disorders	16 (3.2)	47 (2.8)
rash	44 (8.7)	42 (2.5)
hypersensitivity	10 (2.0)	17 (1.0)
pruritus[c]	4 (0.8)	39 (2.3)
diarrhoea	13 (2.6)	83 (4.9)
Clostridioides (*Clostridium*) *difficile* colitis	1 (0.2)	2 (0.1)
WBC disorders[d]	3 (0.6)	8 (0.5)
anaemia	17 (3.4)	19 (1.1)
thrombocytopenia	3 (0.6)	8 (0.5)
seizures	0	3 (0.2)[e]

In some system organ classes, none of the individual TEAEs occurred in two or more patients.
[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b]Phase III q8h cSSTI study: COVERS (NCT01499277). Phase III total q12h cSSTI and CAP pool: CANVAS 1 and CANVAS 2 (cSSTI); and FOCUS 1 (NCT00621504), FOCUS 2 (NCT00509106) and Asia CAP (NCT01371838) (CAP).
[c]Includes the following preferred terms: pruritus and pruritus generalized.
[d]Includes the following preferred terms: neutrophil count decreased, WBC count decreased, leukopenia, lymphocyte count decreased, granulocytopenia and agranulocytosis.
[e]One patient had a history of blackouts attributed to cardiac arrhythmias, cerebrovascular accident and hyponatraemia, and was diagnosed with seizures 9 days after discontinuation of ceftaroline fosamil, one patient had tonic-clonic convulsions 3 days after discontinuation of ceftaroline fosamil and associated hyperglycaemia (fasting plasma glucose 318.2 mg/dL) and the third patient had a non-serious mild AE of convulsion, which was considered unrelated by the investigator and did not result in discontinuation of ceftaroline fosamil.

Table 2. TEAEs leading to discontinuation of study drug (safety population)

	Phase III q8h cSSTI pool (one study[a]), ceftaroline fosamil ($n = 506$)	Phase III q12h pool (five studies[a]), ceftaroline fosamil ($n = 1686$)
Total number of subjects with TEAEs leading to discontinuation of study drug (or withdrawal from study)[b], *n* (%)	32 (6.3)	55 (3.3)
MedDRA preferred term, *n* (%)		
drug eruption	5 (1.0)	0
cardiac failure	2 (0.4)	0
nausea	2 (0.4)	0
rash	2 (0.4)	3 (0.2)
rash generalized	2 (0.4)	2 (0.1)
rash maculo-papular	2 (0.4)	2 (0.1)
urticaria	2 (0.4)	1 (0.1)
abdominal infection	1 (0.2)	0
acne	1 (0.2)	0
ALT increased	1 (0.2)	0
application site erythema	1 (0.2)	0
ascites	1 (0.2)	0
AST increased	1 (0.2)	0
blood alkaline phosphatase increased	1 (0.2)	0
cough	1 (0.2)	0
dermatitis allergic	1 (0.2)	1 (0.1)
diarrhoea	1 (0.2)	1 (0.1)
drug hypersensitivity	1 (0.2)	0
dyspnoea	1 (0.2)	0
generalized oedema	1 (0.2)	0
hepatic enzyme increased	1 (0.2)	0
hyperhidrosis	1 (0.2)	0
hypokalaemia	1 (0.2)	0
necrotizing fasciitis	1 (0.2)	0
osteomyelitis	1 (0.2)	0
osteomyelitis acute	1 (0.2)	0
palpitations	1 (0.2)	0
pleural effusion	1 (0.2)	1 (0.1)
pneumonia	1 (0.2)	2 (0.1)
pyrexia	1 (0.2)	0
rash papular	1 (0.2)	0
rash pruritic	1 (0.2)	0
toxic epidermal necrolysis	1 (0.2)	0
vomiting	1 (0.2)	0
anaemia	0	0
cardiac failure congestive	0	0
confusional state	0	0
erythema	0	0
nephropathy toxic	0	0
prothrombin time prolonged	0	0
pruritus generalized	0	2 (0.1)
upper gastrointestinal haemorrhage	0	0
blood creatinine increased	0	2 (0.1)
cardio-respiratory arrest	0	0
hypersensitivity	0	4 (0.2)
lung abscess	0	0
myocardial infarction	0	0
pruritus	0	0

Continued

Table 2. *Continued*

	Phase III q8h cSSTI pool (one study[a]), ceftaroline fosamil ($n = 506$)	Phase III q12h pool (five studies[a]), ceftaroline fosamil ($n = 1686$)
pulmonary embolism	0	2 (0.1)
renal failure	0	2 (0.1)
respiratory failure	0	2 (0.1)
septic shock	0	2 (0.1)
sudden death	0	2 (0.1)
urinary tract infection	0	2 (0.1)

[a]See Table 1 footnote b for full details of the studies that were included.
[b]This table shows TEAEs leading to discontinuation of study drug in study NCT01499277 and TEAEs leading to discontinuation of study drug or withdrawal from the study in the Phase III q12h pool. All events are shown for NCT01499277. For the Phase III q12h pool, events occurring in more than one patient in any treatment group are shown.

(Table 1). These results suggest that the increased ceftaroline fosamil dosing frequency is not associated with nephrotoxicity or neurotoxicity. Although post-marketing surveillance has provided some information regarding ceftaroline fosamil usage in patients with pre-existing seizure disorders and no new neurological toxicities have been identified here, ceftaroline fosamil should be used with caution in these patients.

Rash is a known AE associated with β-lactams.[17] The higher incidence of rash and subsequent discontinuations in the q8h pool compared with the q12h pool is likely explained by the longer duration of therapy in the q8h pool (Table 1). Incidence of rash in the q8h pool was highest among patients in Asian regions, where the median duration of ceftaroline fosamil exposure was longer compared with non-Asian regions (8.6 versus 6.8 days).[4] In these patients, most cases of rash emerged following ≥7 days of therapy. Rash was also noted in a retrospective cohort study of outpatients treated with ceftaroline fosamil for osteoarticular infection, where the average duration of treatment was 39 days.[18] Overall, occurrence of rash in the q8h and q12h pools was consistent with the cephalosporin class.[7]

The incidence of Coombs seroconversion was higher with the q8h compared with the q12h regimen (32.3% versus 11.2%, respectively); however, there were no confirmed diagnoses of haemolytic anaemia. Coombs seroconversion is a well-characterized side effect of the cephalosporin class.[17] Given that the overall trend in the incidence of anaemia was mirrored between the ceftaroline fosamil and comparator arms of both the q8h and q12h studies,[2,3,12–14] the higher incidence in the q8h pool might be explained by the difference in baseline disease severity of patients enrolled in COVERS.[4]

One possible limitation of this study is the size of the available patient pools, which are not large enough to detect subtle differences in the safety profile between treatment regimens. Moreover, since the comparators used in the individual trials comprise different dosage regimens and classes of antibiotic, comparator data have not been included here.

In conclusion, 600 mg of ceftaroline fosamil q8h was well tolerated. Incidence and severity of AEs were similar to those observed with 600 mg of ceftaroline fosamil q12h. The safety profile of the q8h regimen was consistent with the known safety profile of ceftaroline fosamil[1] and the cephalosporin class.

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Transparency declarations

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Author contributions

All authors were involved in data interpretation and drafting the manuscript for important intellectual content.

Supplementary data

Tables S1 to S5 are available as Supplementary data at *JAC* Online.

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