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REVIEW

Clinical evaluation of the role of ceftaroline in the management of community acquired bacterial pneumonia

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Abstract: Ceftaroline fosamil (ceftaroline) was recently approved for the treatment of community-acquired pneumonia (CAP) and complicated skin infections. This newly developed cephalosporin possesses a broad spectrum of activity against gram-positive and gram-negative bacteria. Most importantly, ceftaroline demonstrates potent in vitro antimicrobial activity against multi-drug resistant *Streptococcus pneumoniae* and methicillin-resistant strains of *Staphylococcus aureus*. In two Phase III, double-blinded, randomized, prospective trials (FOCUS 1 and FOCUS 2), ceftaroline was shown to be non-inferior to ceftriaxone for the treatment of CAP in hospitalized patients. Ceftaroline exhibits low resistance rates and a safety profile similar to that of other cephalosporins. In this review, we will evaluate the pharmacological characteristics, safety, antimicrobial properties, and efficacy of ceftaroline and its applications in the treatment of CAP.

Keywords: *s. pneumoniae, s. aureus,* cephalosporins, pneumonia, ceftaroline, community acquired pneumonia

Introduction

The ideal antibiotic for the treatment of community-acquired pneumonia (CAP) should have the following characteristics: (a) a spectrum of activity that covers the majority of pathogens associated with this infection; (b) documented clinical efficacy and safety in a variety of patient populations; and (c) cost-effectiveness. Current guidelines recommend stratifying patients into groups depending on the presence of specific risk factors and evaluating health care utilization history to select appropriate empirical antimicrobial therapy.[1] The implementation of these guidelines has greatly increased the rate of treatment success for CAP.[2,3] Despite this, treatment failures continue to exist and the need for more effective therapies is a consequence of two main issues: the emergence of antimicrobial resistance and newly emerging pathogens causing CAP.

The rise in the detection of multi-drug resistant *Streptococcus pneumoniae* (*S. pneumoniae*) (MDRSP) has caused significant concern.[4,5] This pathogen displays elevated minimum inhibitory concentrations (MIC) for penicillin and cephalosporins, and often demonstrates cross resistance with other classes, including macrolides, tetracycline and trimethoprim/sulfamethoxazole; although the fluoroquinolone class is relatively spared.[6] There is controversy regarding how in vitro resistance translates into clinical outcomes. Studies evaluating the mortality of patients affected by MDRSP compared to more susceptible strains of *S. pneumoniae* have shown conflicting results.[7–10] However, some of these studies were limited by confounding factors including age, comorbidities, and severity of illness.[8] Nevertheless, there are reports that patients with MDRSP

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may have more complications, longer hospital lengths of stay, and greater therapeutic failures.[6,11,12]

Staphylococcus aureus (*S. aureus*) is a dynamic pathogen that continues to pose a great challenge to clinicians treating patients with CAP and other infections. Methicillin-resistant strains of *S. aureus* (MRSA) infections cause significant mortality and contribute to increased health care costs.[13–15] Most worrisome are data demonstrating a rise in CAP due to MRSA.[16–19] Community-associated MRSA characteristically belongs to the USA-300 pulse-field electrophoresis type, containing the Panton-Valentine leukocidin gene, and is an important cause of necrotizing CAP.[20,21] Compared to other sites of infection, CAP caused by MRSA of the USA-300 type is associated with worse clinical outcomes.[22] Due to these emerging trends of resistance and the need to treat a wider range of patient populations, newer therapies should be explored for the treatment of MRSA, and other resistant gram-positive bacteria.[23]

The USA Federal Drug Administration (FDA) has recently approved ceftaroline fosamil (TEFLARO™, Forest Pharmaceuticals Inc, St Louis, MO) for the treatment of CAP and complicated skin infections. This antibiotic possesses a broad spectrum of activity against gram-positive and gram-negative bacteria. Most importantly, ceftaroline has antimicrobial activity against MDRSP and MRSA. We will review the pharmacological characteristics, safety, antimicrobial properties, and effectiveness of ceftaroline and its applications in the treatment of CAP patients.

Mechanisms of action

Ceftaroline is a fifth-generation cephalosporin with a mechanism of action similar to that of other commercially available β-lactams.[24–26] It binds to penicillin binding proteins (PBPs) and prevents the synthesis of peptidoglycan, an essential component in bacterial cell walls.[24–26] The drug's activity against *S. aureus* and MRSA is due to its high affinity for PBP1–3 and PBP2a.[24–26] Additionally, ceftaroline binds to PBP3, PBP1A, PBP2X, PBP1B, and PBP2A/B, which are primary targets for *S. pneumoniae*, including resistant strains.[24–26]

Microbiologic activity

Ceftaroline has demonstrated activity against a broad spectrum of gram-positive pathogens (Table 1). Several studies evaluating the in vitro activity of ceftaroline have been carried out (Table 2).[27–33] A surveillance study of 6,496 CAP pathogens compared ceftaroline to comparator agents.[32] Ceftaroline was found to be eight-fold more active against 1,340 *S. pneumoniae* strains than ceftriaxone. Furthermore, ceftaroline exhibited excellent activity against MDRSP.[32,34,35] Another group found ceftaroline to be the most active agent against 120 strains of cefotaxime-resistant *S. pneumoniae*.[36] Additionally, ceftaroline was noted to have potent activity against strains with defined PBPs and *murM* mutations known to confer resistance to β-lactams.[36] Similar results were evidenced in a susceptibility study of 891strains of *S. pneumoniae* isolated in the United States, which compared ceftaroline with current available antibiotic therapies. Again, ceftaroline was the most effective agent tested and displayed a high level of activity against the subset of strains considered to be resistant to penicillin, macrolides, lincosamides, trimethoprim-sulfamethoxazole, and quinolones.[31] Likewise, in another study, ceftaroline demonstrated very high potency against 584 strains of *Haemophilus influenzae* and 377 strains of *Moraxella catarrhalis* – a degree of activity comparable to ceftriaxone.[32] The characteristics of ceftaroline were tested in vivo in an experimental pneumonia rabbit model where subjects were inoculated with different strains of *S. pneumoniae*. Ceftaroline was similar to ceftriaxone in eradicating the infection in subjects infected with penicillin susceptible *S. pneumoniae* strains; but more importantly, ceftaroline was superior in the treatment of MDRSP strains.[37]

Ceftaroline is the first cephalosporin approved to have in vitro activity against methicillin-resistant *S. aureus* (MRSA), a characteristic that may prove to be particularly useful if this pathogen continues to increase in frequency. Large series of isolates have demonstrated bactericidal activity against coagulase-negative staphylococci as well as methicillin-susceptible and methicillin-resistant *S. aureus*.[29,32] Furthermore, ceftaroline has exhibited potent activity against vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA), linezolid-resistant

Table 1 Spectrum of microbiological coverage

Gram-positive bacteria	Gram-negative bacteria
• *Staphylococcus aureus* (MSSA and MRSA)	• *Klebsiella pneumoniae*
• *Streptococcus pyogenes*	• *Klebsiella oxytoca*
• *Streptococcus agalactiae*	• *Escherichia coli*
• *Streptococcus pneumoniae*	• *Citrobacter koseri*
• *Streptococcus dysgalactiae*	• *Citrobacter freundii*
	• *Enterobacter cloacae*
	• *Enterobacter aerogenes*
	• *Haemophilus influenzae*
	• *Haemophilus parainfluenzae*
	• *Proteus mirabilis*
	• *Moraxella catarrhalis*

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Table 2 Susceptibility for ceftaroline in in vitro studies

Pathogens	In vitro studies – MIC range (μg/mL)						
	Sader[27]	Ge[28]	Brown[29]	Saravolatz[30]	Jacobs[31]	Jones[32]	Kaushik[33]
S. aureus			0.25 to 2			≤0.12 to 2	
MRSA	0.12 to 2	0.12 to 2	0.5 to 1			≤0.25 to 2	0.25 to 2
MSSA	0.03 to 0.5	≤0.03 to 1	0.25 to 0.5			≤0.1 to 0.5	≤0.008 to 1
CA-MRSA				≤0.251			
VISA/hVISA	0.25 to 4		0.25 to 2	≤0.251			0.25 to 4
VRSA			0.5 to 1	≤0.121			
Streptococcus pneumoniae			0.015 to 0.5		≤0.008 to 0.5	≤0.008 to 0.5	
Streptococcus pneumoniae PCN resistant	0.06 to 0.5	≤0.008 to 0.5	0.015 to 0.5		≤0.006 to 0.5		≤0.008 to 0.5
Streptococcus pneumoniae PCN susceptible	≤0.016 to 0.06	≤0.008 to 0.12	0.015 to 0.12				≤0.008 to 0.12
Streptococcus pyogenes Macrolide resistant		≤0.008 to 0.03	0.015 to 0.5				
Moraxella catarrhalis	≤0.016 to 012	≤0.03 to 0.5	0.015 to 1			≤0.008 to 1	≤0.008 to 0.5
Haemophilus influenzae	≤0.016 to 0.25	≤0.008 to 2	0.015 to 0.25			≤0.008 to 0.12	≤0.008 to 0.25
Klebsiella pneumoniae	0.03 to 4	≤0.03 to >16	0.03 to 1			≤0.008 to >16	≤0.03 to 165
Escherichia coli	≤0.016 to 0.025	≤0.03 to >16	0.015 to 16			≤0.015 to >16	0.5 to >16
Enterobacter cloacae	0.03 to >32	≤0.03 to >16	0.06 to 2			≤0.015 to >16	≤0.03 to >16
Pseudomonas aeruginosa	4 to >32		0.5 to 32				1 to >128

Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; CA-MRSA, community acquired methicillin-resistant *Staphylococcus aureus*; VISA/hVISA, vancomycin-intermediate *S. aureus*/hetero-resistant VISA; VRSA, vancomycin-resistant *S. aureus*; PCN, penicillin.

S. aureus (LRSA), and daptomycin-nonsusceptible *S. aureus* (DNSSA).[30,38] The activity against DNSSA was confirmed in a study that tested ceftaroline against four different strains. Ceftaroline showed sustained bactericidal activity against three of the strains and a sustained reduction in the bacterial counts with respect to the fourth.[39]

Ceftaroline has similar microbial coverage as other third-generation cephalosporins for gram-negative microorganisms (Table 1). The potency of ceftaroline is comparable with ceftriaxone, ceftazidime, and piperacillin/tazobactam for *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, and *Enterobacter cloacae*.[32] However, it is important to note that ceftaroline, in a similar fashion to third-generation cephalosporins, does not have significant in vitro activity against extended-spectrum beta-lactamase (ESBL) producing organisms, *Pseudomonas* sp., or atypical microorganisms.

Pharmacokinetics

The absorption of ceftaroline has been analyzed in healthy adults. The prodrug ceftaroline fosamil acetate (CFA) and inactivated ceftaroline metabolites displayed linear-dose kinetics.[33] Additionally, ceftaroline's concentrations were not associated to the duration of the dosing interval. The drug's pharmacokinetic analysis is compatible with a two-compartmental model with zero order input and first order elimination.[40] The volume of distribution of ceftaroline is 28.3 L (0.37 L/kg; range 0.31–0.45 L/kg) and the drug does not significantly bind to serum proteins, with less than 20% being protein-bound. CFA does not have any penetration into erythrocytes.[33]

Ceftaroline fosamil acetate is rapidly metabolized by phosphatases, which convert it to ceftaroline after intravenous administration. The active drug then undergoes further conversion by hydrolysis into the inactive ceftaroline-M-1. The average half-life of ceftaroline and ceftaroline M-1 is 2.6 hours and 4.5 hours, respectively.[41] Of the ceftaroline metabolites, ceftaroline is not detected in the urine, while approximately 50% of the dose is excreted as active drug with a small portion (average 7%) excreted as ceftaroline-M-1.[41] Ceftaroline has only minimal enteric elimination. In patients with mild renal impairment (creatinine clearance [CrCl] of 50–80 mL/min), the area under the curve (AUC) was 25% higher and the half-life 14% longer. In patients with moderate renal impairment (CrCl 30–50 mL/min), the AUC was 50% higher. Because of these characteristics, ceftaroline should be used with caution in patients with moderate to severe renal impairment, and dosing adjustments according to renal function are advised.[42]

The dosing recommendation for intravenous dosing is as follows depending on the CrCl: (1) higher than 50 mL/min: no adjustment (600 mg every 12 hours); (2) 30–50 mL/min: 400 mg every 12 hours; (3) 15–30 mL/min:

300 mg every 12 hours; (4) for patients on dialysis: 200 mg every 12 hours.[41,43] Animal models have shown a favorable pharmacokinetic profile with intramuscular administration comparable to intravenous dosing.[44,45] The absolute bioavailability after an intramuscular dose was equivalent to an intravenous dose.[43]

Pharmacodynamics

Ceftaroline exhibits time-dependent killing. As such, the amount of time that the serum concentration remains above the minimum inhibitory concentration (MIC); (%T > MIC) represents the main pharmacodynamic predictor of efficacy. Pharmacodynamic evaluations have been performed in murine thigh and lung infection models.[46] The results from this study demonstrated a minimal post-antibiotic effect ranging from 0.33 hours to 7.2 hours for *S. pneumoniae*, *E. coli*, and *S. aureus*.[46] Additionally, ceftaroline was found to be bacteriostatic for staphylococci and gram-negative bacilli when free drug concentration exceeded the MIC for 30% and 40% of the dosing interval, respectively.[46] On the other hand, bactericidal activity for staphylococci and gram-negative bacilli with ceftaroline occurred when %T > MIC was 50% and 60%, respectively.[46]

Clinical use and efficacy in CAP

The efficacy and safety of ceftaroline for the treatment of CAP was evaluated in the FOCUS (ceFtarOline Community-acquired pneUmonia) trial against ceftriaxone in hospitalized patients with CAP. This study included two similar, Phase III, double-blinded, randomized, multinational, prospective trial designs (FOCUS 1 and FOCUS 2).[47] The primary objective of these studies was to determine non-inferiority in clinical cure rates of ceftaroline compared with ceftriaxone in the clinically evaluable and modified intent-to-treat efficacy populations. Clinical cure was defined as resolution of all signs and symptoms of pneumonia or improvement such that no further antimicrobial therapy was necessary.[47] Patients were also required to have absence of fever for 24 consecutive hours with signs and symptoms of CAP returning to baseline levels.[47]

The study design for both trials involved randomization of patients with CAP based severity using the Pneumonia Outcomes Research Team (PORT) score of III or IV (patients that required an admission to the hospital for administration of intravenous antibiotics) to receive either 600 mg intravenously of ceftaroline every 12 hours or one gram intravenously of ceftriaxone daily for 5–7 days. Importantly, the studies excluded patients who were not admitted to the hospital (PORT I and II) or directly to the intensive care unit (ICU) (PORT V). Other notable exclusion criteria were patients with severe renal impairment (CrCl ≤ 30 mL/min), risk factors for hospital-acquired infections, known or suspected infections with atypical microorganisms, risk factors or positive cultures for MRSA, and immunosuppression. The sole difference between these two studies was that the patients enrolled in FOCUS 1 received two doses of clarithromycin on day one. This additional treatment was required to enable enrollment in North America, where macrolide therapy is recommended, but to limit potential confounding of study drug treatment effect, it was only given during the first 24 hours of treatment.

An integrated analysis of both trials included a total of 1,228 patients (ceftaroline, n = 614 versus ceftriaxone, n = 614). Baseline characteristics were similar between the groups. The study groups had the following similar baseline characteristics: age distribution, race, gender, comorbid conditions, PORT scores, white-blood cell counts, bacteremia, and immature band counts. The primary outcomes demonstrated that of the clinically evaluable patients treated with ceftaroline, 84.3% achieved a clinical cure, compared with 77.7% of patients treated with ceftriaxone (95% CI, 1.6%–11.8%). In the modified intent-to-treat efficacy population, clinical cure was achieved in 82.6% of the patients treated with ceftaroline, compared to 76.6% treated with ceftriaxone (95% CI, 1.4%–10.7%). The adverse effects and tolerability of the medications were similar in both groups. There were 27 reported deaths during the study; 15 (2.4%) in the ceftaroline group and 12 (2.0%) in the ceftriaxone group (Table 3).[47]

The most frequent isolated pathogen was *S. pneumonia*e, with a combined prevalence of 33.6% (122 isolates), which is consistent with the epidemiology of CAP. The clinical cure rates for *S. pneumoniae* were 85.7% (54 of 63 patients) for ceftaroline and 69.5% (41 of 59 patients) for ceftriaxone. Even though the total number of patients treated for MDRSP CAP was low (n = 13), ceftaroline exhibited a higher rate of clinical cure (4/4, 100%) compared to ceftriaxone (2/9, 22%).

Staphylococcus aureus was the second most common pathogen isolated with an incidence of 14.3% (52 isolates). The clinical cure rates for *S. aureus* were 72.0% (18 of 25 patients) for ceftaroline and 55.6% (15 of 27 patients) for ceftriaxone. Out of the *S. aureus* isolates, only two were MRSA, and both were in the ceftriaxone study arm. The low

Table 3 Clinical cure rates comparing ceftaroline against ceftriaxone in CAP patients enrolled in the FOCUS 1 and FOCUS 2 studies

Test of cure	FOCUS 1		FOCUS 2		Integrated FOCUS 1 and 2	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
	Primary outcomes n/N (%)					
Clinical evaluable	194/224 (86.6)*	244/291 (83.8)	193/235 (82)	166/215 (77)	387/459 (84)*	349/449 (77)
Modified intent to treat efficacy	244/291 (83)	23/300 (77)	235/289 (81)	206/273 (75)	479/580 (82)*	439/573 (76)
	Secondary outcomes					
Microbiologically evaluable	62/69 (89)*	54/71 (76)	69/85 (81)	57/76 (75)	131/154 (85)*	111/147 (75)
Streptococcus pneumoniae	24/27 (88.9)	20/30 (66)	35/42 (83.3)	28/40 (70)	59/69 (85.5)	48/70 (68)
Streptococcus pneumoniae PCN resistant	2/2 (100)	0/1 (0)	2/2 (100)	2/8 (25)	4/4 (100)	2/9 (22)
Staphylococcus aureus	8/10 (80)	9/14 (64)	10/15 (66.7)	9/16 (56)	18/25 (72)	18/30 (60)
Haemophilus influenzae	4/5 (80)	7/10 (70)	13/15 (86)	13/14 (92)	17/20 (85)	20/24 (83)
Klebsiella pneumoniae	7/8 (87)	3/5 (60)	7/7 (100)	7/8 (87)	14/15 (93)	10/13 (76)
Escherichia coli	8/8 (100)	5/7 (71)	2/4 (50)	4/6 (66)	10/12 (83)	9/13 (69)
Microbiological modified intent to treat efficacy	66/75 (88)*	60/80 (75)	72/90 (80)	66/88 (75)	138/165 (83)	126/168 (75)
PORT risk class III	136/150 (90)*	113/142 (79)	113/137 (82)	104/132 (78)	249/287 (86)*	217/274 (79)
PORT risk class IV	58/74 (78)	70/92 (76)	80/98 (81)	62/83 (74)	138/172 (80)	132/175 (75)
End of therapy	**Secondary outcomes**					
Clinical evaluable	197/224 (87)*	188/234 (80)	102/235 (86)	172/215 (80)		

Note: *$P < 0.05$ when comparing ceftaroline versus ceftriax.
Abbreviations: PCN, penicillin; PORT, Pneumonia Outcomes Research Team.

prevalence of MRSA is likely due to both a relative low frequency of occurrence of this pathogen causing CAP and the exclusion criteria of the FOCUS 1 and FOCUS 2 studies.[48]

Based on the above findings, the authors concluded that ceftaroline was clinically non-inferior to ceftriaxone. Furthermore, the integrated analysis demonstrated a favorable trend towards ceftaroline improving clinical cure rates reaching statistical significance. These outcomes strongly support the efficacy and safety of ceftaroline treatment in hospitalized, non-ICU patients with CAP, but leave unanswered questions regarding efficacy in other populations. Given the exclusion criteria of these studies, data are lacking regarding the efficacy of ceftaroline for CAP treatment in patients that are immunosuppressed, require ICU admission, or have risk factors for MRSA and other hospital-acquired infections. Importantly, ceftaroline showed clinical efficacy for the treatment of MDRSP, but larger studies are needed to confirm these findings. Currently, the USA Federal Drug Administration (FDA) has approved ceftaroline as an option for the treatment of CAP.

Safety

The frequency of diarrhea, nausea, vomiting, constipation, transaminitis, hypokalemia, rash, and phlebitis was similar in patients that received ceftaroline compared to treatment regimens with vancomycin plus aztreonam (skin and skin structure studies) or ceftriaxone.[47,49] Developmental toxicity studies performed in rats that received ceftaroline at a dose eight times greater than the human dose did not demonstrate maternal toxicity or effects on the fetus. Currently, there are no adequate trials evaluating the use of ceftaroline in pregnant women, and so it should be used with caution and then only when the potential benefits outweigh potential risks to the fetus. It has not been determined if ceftaroline is excreted in the human milk and caution should be exercised when administering this medication to a nursing woman. Long-term studies evaluating carcinogenesis, mutagenesis, and effects on fertility have not been performed on ceftaroline.

The ecological impact of ceftaroline in human intestinal microflora has been evaluated after healthy subjects received 600 mg intravenously (IV) every 12 hours for 7 days.[50] In this study, there was no significant impact on the numbers of resistant *E. coli*, *Bacteroides* sp., *Enterococcus* sp., or *Candida albicans* strains. More importantly, no new colonizing aerobic or anaerobic bacteria resistant to ceftaroline (MIC > 4 mg/L) were detected. Additionally, the incidence of *Clostridium difficile* infection with ceftaroline was similar to other cephalosporins.

Comparative advantages

As compared to other clinically available agents, ceftaroline exhibits low resistance rates and possesses a broader

spectrum activity against common pathogens implicated in CAP. Furthermore, ceftaroline's safety profile is similar to that of current antimicrobials utilized to treat these infections. The most common adverse effects reported with ceftaroline were diarrhea, nausea and vomiting, but serious adverse effects, such as anaphylaxis and respiratory failure, were similar between the ceftaroline and comparators.[47,51] The propensity and in vitro frequency of ceftaroline to develop resistance with major pathogens is low.[42] This was evidenced by multistep resistance studies.[52,53] Serial passage studies were carried out to determine the probability of developing resistance to ceftaroline in isolates of *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, MRSA, MSSA, and *S. pyogenes*. These studies demonstrated low ceftaroline MICs without the devolvement of clones with increased MICs.[42,52,53] Spontaneous resistance development with vancomycin-resistant *E. faecalis* and vancomycin-susceptible *E. faecalis* has been demonstrated.[33,42] Although, not inferior to ceftriaxone in the treatment of CAP patients, ceftaroline has potent activity against community-acquired MRSA as well as difficult to treat bacterial isolates including VISA, VRSA, LRSA, and DNSSA.[30] Since ceftaroline treats the most common CAP pathogens (including resistant isolates) and possesses an uncomplicated dosing and administration scheme, with a low propensity for drugs interactions, it is a good alternative agent for patients who do not tolerate or respond to other antibacterial therapies.[33,42,54]

Comparative disadvantages

Currently, ceftaroline has been tested only on specific populations of patients (CAP in patients that require hospitalization, but not ICU care, and complicated skin and skin structure infections). This significantly limits its use, not only for other types of infections, but also for use in patients with pneumonia with different characteristics or risk factors (ie, patients admitted to the ICU or on dialysis). Other disadvantages are that ceftaroline can only be used intravenously. Although intramuscular administration has been studied, it is currently not approved. In addition, there is no oral preparation of ceftaroline that could facilitate transitioning of care. Compared to ceftriaxone, ceftaroline has to be given twice daily instead of once a day. There have been also some reports of the limited stability of ceftaroline after mixing the compound before administration.[55] Furthermore, there are currently no cost-benefit studies evaluating the use of ceftaroline in the treatment of CAP, but the current cost of this medication is higher than other comparable agents. The cost of ceftaroline is about $41 per vial, which corresponds to about >$80/day. This cost is higher than the comparators available to treat CAP which include intravenous formulations of cephalosporins and respiratory fluoroquinolones. However, if further studies show a benefit in MRSA pneumonia patients, ceftaroline might be a comparable or less expensive alternative compared to vancomycin or linezolid. Caution should be undertaken when using a newly developed medication, but current safety date does not preclude its use as it has a similar safety profile as other cephalosporins.

Even though ceftaroline has exhibited high in vitro potency against MDRSP, MRSA, VISA, VRSA, and DNSSA, and was clinically effective in treating complicated skin-structure and skin infections with theses pathogens, studies on the efficacy in CAP caused by staphylococcal species are lacking.[51] Until studies are done evaluating other applications of ceftaroline, its use should be limited to the populations where it has shown clinical efficacy.

Future investigations

The emergence of antimicrobial resistance remains a concern and requires the continued development of novel agents. Given ceftaroline's in vitro success in treating MRSA and other resistant strains of *S. aureus*, future studies should focus on the drug's clinical impact on pneumonias and other infections caused by these pathogens. Additionally, the use of ceftaroline for the treatment of pneumonia should be explored in other populations, including patients admitted to the ICU, as well as those with septic shock, infected with disseminated infections or infections affecting other organs, and requiring renal replacement therapy.

Ceftaroline, similar to other β-lactam agents, lacks the ability to combat ESBL pathogens. Given ceftaroline's wide coverage of gram-negative and gram-pathogens, there is interest in combining this antibiotic with other agents to provide additional pathogen coverage. Currently, there is an ongoing trail evaluating the combination of ceftaroline with NXL104, an inhibitor of β-lactamase. Preliminary murine models on NXL104 are promising.[56] The clinical implications of this drug combination are encouraging in an era of increasing multi-resistant pathogen induced infections.

Conclusion

Ceftaroline, a novel fifth-generation cephalosporin, is a safe and effective alternative for the treatment of CAP in non-ICU hospitalized patients. The drug's in vitro activity has

exhibited high potency activity against MDRSP, MRSA, VISA, VRSA, and DNSSA; but studies evaluating the clinical outcomes of these effects in CAP are lacking. Although other agents have been recently FDA approved or are under development, further research should continue to evaluate the possible applications of ceftaroline in patients with CAP that require ICU admission and/or have risk factors for MRSA and other resistant gram-positive pathogens that can cause pneumonia. Recent ceftaroline research is focused on evaluating the drug's clinical applications for the treatment of infections due to other pathogens. Studies evaluating the combination of ceftaroline plus NXL104 have demonstrated activity against pathogens, such as multi-resistant gram-negative bacteria. In a time of increasing multi-drug resistant infections, this research may provide additional treatment alternatives to the current antibiotic armamentarium.

Disclosure

No conflicts of interest were reported by DM, JF, CW, KE, and AN. AA is a consultant and speaker for Forest Laboratories, Bayer Pharma, GlaxoSmithKline, Boehringer-Ingleheim, and Asta-Zeneca. MR participated in advisory boards for Ortho-McNeil-Janssen, Theravan, Forest Laboratories, Johnson and Johnson, and Novartis and has been a speaker for Covidien, BARD Inc, Johnson and Johnson (Ortho-McNeil-Janssen), and Pfizer as well as a consultant for Theravan and Pfizer (Wyeth). MR's time is partially protected by award number K23HL096054 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health. The funding agencies had no role in the preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, nor the University of Texas Health Science Center at San Antonio.

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