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REVIEW

Ceftaroline: A New Cephalosporin with Activity Against Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Abstract: Microbial resistance has reached alarming levels, threatening to outpace the ability to counter with more potent antimicrobial agents. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA) has become a leading cause of skin and soft-tissue infections and PVL-positive strains have been associated with necrotizing pneumonia. Increasing reports of growing resistance to glycopeptides have been noted, further limiting the efficacy of standard antibiotics, such as vancomycin. Ceftaroline is a novel fifth-generation cephalosporin, which exhibits broad-spectrum activity against Gram-positive bacteria, including MRSA and extensively-resistant strains, such as vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), and vancomycin-resistant *S. aureus* (VRSA). In addition to being an exciting new agent in the anti-MRSA armamentarium, ceftaroline provides efficacy against many respiratory pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Ceftaroline (600 mg intravenously every 12 hours) has been shown effective in phase III studies in the treatment of complicated skin and soft tissue infections and community-acquired pneumonia. To date, this unique antibiotic exhibits a low propensity for inducing resistance and has a good safety profile, although further post-marketing data and clinical experience are needed. In summary, ceftaroline provides an additional option for the management of complex multidrug resistant infections, including MRSA.

Keywords: ceftaroline, antibiotic, cephalosporin, methicillin-resistant *Staphylococcus aureus*, MRSA, multidrug resistant organisms

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Introduction

Microbial pathogens have an extraordinary capacity to develop resistance to antimicrobial agents. Within the last two decades, resistance has escalated, occasionally at seemingly exponential rates, threatening to outpace the ability to counter with more potent antimicrobial agents. Methicillin-resistant *Staphylococcus aureus* (MRSA), first isolated in the 1960s, became a prominent nosocomial pathogen over the past three decades. The advent of community-associated MRSA (CA-MRSA), which arose de novo outside the healthcare environment, has dramatically heightened the importance of MRSA. Today, MRSA is the leading cause of community-acquired skin and soft tissue infections (SSTI) and a cause of necrotizing pneumonia.[1,2] The dramatic escalation in MRSA, which is now globally ubiquitous, coupled to intrinsic resistance to many of the existing antimicrobial agents, renders this an enormous public health issue. MRSA has also recently exhibited an inexorable creep in minimum inhibitory concentrations (MIC) to the standard intravenous antibiotic (vancomycin) utilized in its management. In addition, *S. aureus* strains with vancomycin-intermediate resistance (VISA), heteroresistance (hVISA), and vancomycin resistance (VRSA) have been described.[3] These resistant strains are associated with increased morbidity and mortality above that of methicillin-sensitive *Staphylococcus aureus* (MSSA), and often require surgical intervention coupled to a sparse selection of suitable antimicrobial therapy.[4]

Fortunately, alternatives to vancomycin have been developed in the past decade for the treatment of multidrug resistant (MDR) Gram-positive bacterial infections including an oxazolidinone (linezolid), a lipopeptide (daptomycin), a streptogramin (quinupristin-dalfopristin), and a glycylcycline (tigecycline).[5,6] Telavancin is a recent addition to the Gram-positive arsenal, and is a lipoglycopeptide which inhibits both bacterial cell wall synthesis and cell-membrane function.[7]

Despite these novel agents, resistance continues to evolve, and strains resistant to linezolid, quinupristin/dalfopristin and daptomycin have been described.[5,6,8] Moreover, there are disadvantages associated with these contemporary antibiotic classes. For example, linezolid has minimal Gram-negative activity (due to efflux pumps), although it does have some activity against anaerobes and *Mycobacteria spp*.[9] Furthermore, linezolid is bacteriostatic and its long-term use (eg, >2 weeks) has been associated with the development of peripheral neuropathy, lactic acidosis, and thrombocytopenia (as well as the potential for trilineage bone marrow suppression).[10] Daptomycin lacks pulmonary activity, and may cause a pulmonary hypersensitivity reaction and myopathy.[11,12] Additionally, daptomycin resistance has been noted in the setting of prior vancomycin therapy, especially with suboptimal dosing and sequestered infections including osteomyelitis, endocarditis, and device related infections.[13–16] Daptomycin resistance had been linked to its inactivity in the setting of thickened cell walls in VISA and hVISA isolates, with reduced access to binding sites on the cell membrane, and to point mutations leading to amino acid substitutions in the MprF and YycG proteins.[16] Quinupristin-dalfopristin is limited by its administration via central venous access, its only modest activity against MRSA pneumonia, and a host of adverse side-effects including myalgias.[6] Tigecycline is active against a range of both Gram-positive and -negative organisms (notably excluding *P. aeruginosa*), and approved for the treatment of SSTI and complicated intra-abdominal infections.[17] However, it exhibits low serum concentrations, accumulates in bone (contraindicated in children and pregnancy), and is often associated with significant nausea.[18] Furthermore in a recent multicenter trial, tigecycline (+/– ceftazidime +/– aminoglycoside) versus imipenem (+/– vancomycin +/– aminoglycoside) had significantly lower cure rates for ventilator-associated pneumonia (VAP),[19] and the FDA has issued a warning that tigecycline may be associated with an increased mortality risk compared to other drugs for treatment of a variety of serious infections including VAP. Telavancin may also cause nausea and vomiting, and it has been associated with infusion-related reactions (ie, red-person syndrome).[7] Finally, many of these unique agents (ie, linezolid, daptomycin, and telavancin) are only active against Gram-positive bacteria.

Ceftaroline fosamil (brand name Teflaro, previously referred to as PPI-0903M, T-91825, TAK-599) is a novel fifth-generation parental oxyimino cephalosporin with bactericidal activity against MRSA (Fig. 1).[20,21] In contrast to most of the aforementioned MRSA antimicrobials, ceftaroline fosamil (hereafter,

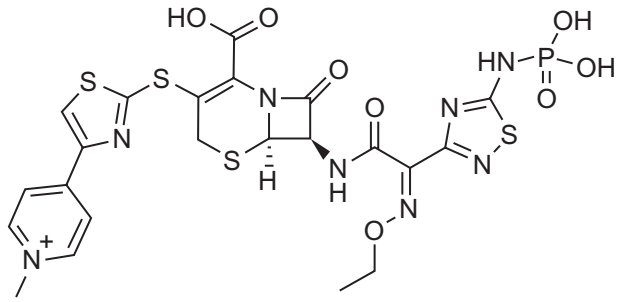

Figure 1. Chemical structure of ceftaroline fosamil acetate.

ceftaroline) exhibits broad-spectrum activity against many of the important community-acquired Gram-positive and Gram-negative pathogens,[20–22] similar to the sole other fifth-generation cephalosporin (ceftobiprole) in development.

Importantly, it has activity against MDR Gram-positive bacteria, including MRSA, VISA, hVISA, and VRSA.[23,24] It also has efficacy against respiratory bacterial pathogens such as *Streptococcus pneumoniae* (including multidrug-resistant strains), *Haemophilus influenzae*, and *Moraxella catarrhalis*. Mirroring other broad-spectrum cephalosporins, ceftaroline does not possess activity against extensively-resistant Gram-negative bacteria and exhibits limited activity against most non-fermentative Gram-negative bacilli (eg, *Pseudomonas aeruginosa, Acinetobacter spp.*) and many anaerobic species.[20–23]

A new drug application for ceftaroline (Forest Laboratories Inc., New York, NY) was submitted in December 2009, with the specific indications for the treatment of complicated SSTI and community-acquired pneumonia (CAP). This novel drug gained FDA approval in September 2010 and is expected to be available for use in early 2011.

Mechanism of Action

Like other β-lactams, ceftaroline's mechanism of action is mediated by binding to the penicillin-binding protein (PBP), the enzyme mediating the cross-linking transpeptidation of the peptidoglycan which are the terminal steps in completing formation of the bacterial cell wall. MRSA strains have a mutated PBP2a (coded by the *mecA* gene residing on the staphylococcal chromosomal cassette), which prohibits β-lactam antibiotics from accessing its active site that mediates the transpeptidation reaction (Fig. 2). The interaction of PBP2a at an allosteric site within peptidoglycan triggers conformational changes potentiating access to the active state. When not actively involved in transpeptidation, the active site is closed, effectively "shielded" from potential β-lactam antibiotics.[25] Ceftaroline possesses an ethoxyimino side-chain mimicking a portion of a cell wall structure, which acts as a "Trojan horse", allosterically opening and facilitating access to the active site of the PBP2a (Fig. 2).[25,26]

More specifically, β-lactam antibiotics form a non-covalent complex with the transpeptidase enzymatic domain of the PBP. This is characterized by an equilibrium dissociation constant, K_D, which is converted to the covalent acyl-enzyme form with a rate constant, k_2. The acyl-enzyme complex prevents transpeptidation, and as free enzyme regeneration

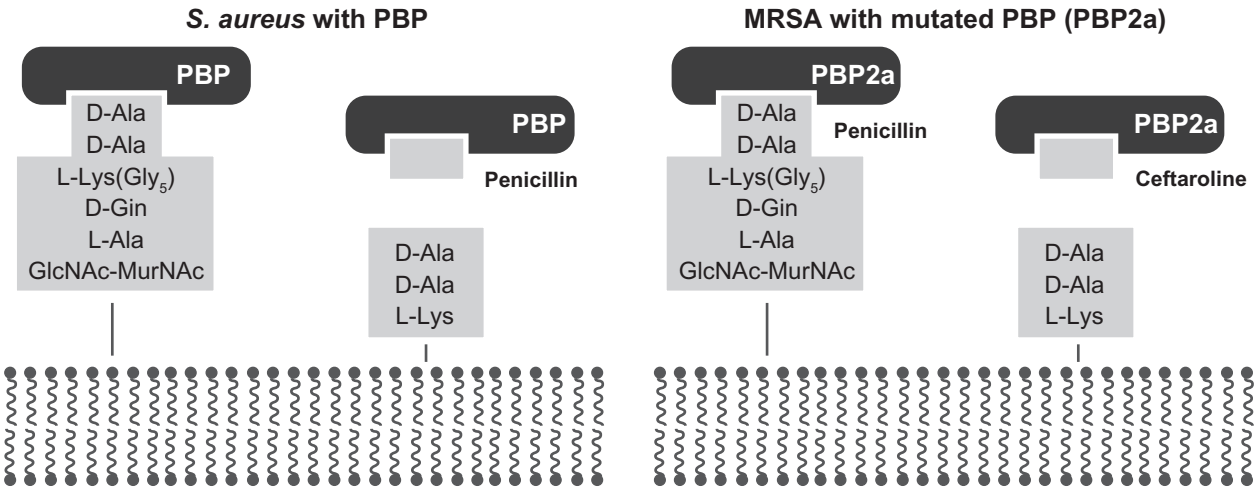

Figure 2. The penicillin binding protein (PBP) of S. aureus is blocked by penicillin-like drugs. The mutated PBP (PBP2a) of MRSA is not blocked by penicillin and most beta-lactam drugs; however, the novel drug, ceftaroline, is able to block PBP2a and inhibit cell wall synthesis of MRSA.

via hydrolytic deacylation characterized by the rate constant (k_3) is slow (eclipsing duration of cell viability) the bacteria undergoes lysis. Now the dissociation constant for the non-covalent interaction of the transpeptidase enzymatic region of PBP2a with the β-lactam is very high due to structural inaccessibility of the β-lactam due to the presence of a peptide loop shielding the active site of PBP2a. Binding of muropeptide of peptidoglycan to an allosteric site of the PBP2a potentiates a conformation change displacing the peptide loop enabling access of substrate for wall synthesis. Ceftaroline possesses a side chain mimetic of the muropeptide which can interact with the allosteric site of PBP2a duplicating the conformational change necessary to displace the peptide loop shielding access, allowing formation of the initial non-covalent interaction of the transpeptidase enzymatic region of PBP2a with the β-lactam.[27]

Hence, ceftaroline's anti-MRSA efficacy stems from high affinity for the MRSA-associated PBP2a (perhaps ≥256-fold over other β-lactams). For example, the MIC_{50} for the PBP2a for ceftaroline is 0.90 μg/ml compared with 408 μg/ml for oxacillin, 677 μg/ml for ceftriaxone, and 57 μg/ml for imipenem. The inhibition of PBP by ceftaroline results in cell wall irregularities and eventual bacterial cell death.[28] Ceftaroline also demonstrates superior affinity for all the prominent PBPs utilized within both sensitive (PBP 1–3) and resistant strains of *S. aureus*. Furthermore, it has activity to the mutable PBPs of *S. pneumoniae* including multiple drug-resistant *S. pneumoniae* (MDRSP) (PBP1a, PBP2a, PBP2b, PBP2x, PBP3) and the PBP3 of Gram-negative bacteria.[28,29] Finally, ceftaroline remains effective in the setting of the cell wall changes which mediate resistance within VISA, hVISA, VRSA, and daptomycin-resistant isolates.[22,24,30]

Pharmacokinetics

Ceftaroline is the bioactive metabolite of ceftaroline fosamil, an *N*-phosphonoamino water-soluble cephalosporin prodrug, which is rapidly converted in vivo upon the hydrolysis of the phosphonate group by plasma phosphatises.[23] Ceftaroline's chemical stability and water solubility is attributed in part from improved crystallization and hygroscopicity imparted by innovated chemical modifications, necessitating administration as a prodrug via intravenous or intramuscular routes.

Following single 500 mg and 750 mg intravenous doses, ceftaroline reaches peak serum concentration (Cmax) of 16.5 and 23 μg/ml, respectively, and steady state AUC values of 44.7 and 56.9 μg/hour/ml, respectively. Escalating single doses of ceftaroline fosamil (50 to 1000 mg) administered intravenously as one-hour infusions to healthy male individuals (n = 48) yielded ceftaroline concentrations ranging from 1.5 to 30.2 μg/ml; mean half-lives of ceftaroline fosamil, ceftaroline, and the major metabolite (ceftaroline-M-1) were 0.4, 2.4, and 4.5 hours, respectively.[31]

Multiple escalating doses of ceftaroline fosamil were administered intravenously in healthy male subjects as 300 and 600 mg, respectively, every 12 hours for 14 days, and 800 mg every 24 hours for 7 days. Ceftaroline again formed rapidly after dosing, exhibiting a half-life of 2.6 (range 2.3–2.9) hours. The values of Cmax, AUC and clearance for the three respective groups were: Cmax: 8.4, 21, and 31 μg/ml; AUC: 24, 56, and 73 μg/hour/ml; clearance: 183, 159, and 161 ml/min, respectively. For multiple intravenous doses of 600 mg given over one hour every 12 hours for 14 days, the maximum plasma concentration was 19.0 μg/ml and 21.0 μg/ml for first and last doses, respectively, without evidencing drug accumulation with multiple dosing.[31,32]

The intramuscular route of delivery is attractive, given its potential convenience of administration. In animal models, intramuscular administration exhibited similar pharmacokinetics to that of intravascular administration with almost 100% bioavailability.[26,33] The AUCs for the intramuscular route was comparable to that achieved with intravenous dosing in both rabbits (mean AUC 7.3% greater) and monkeys (12.7% greater), indicating excellent bioavailability via this route.[33] In addition, the half-lives of the two routes were comparable. The time to achieve Cmax was slightly longer, with intramuscular administration and initial peak levels slightly lower, perhaps due to the slower release of the pro-drug from the intramuscular site. Data showing near equivalence regarding intramuscular and intravenous routes have also been noted in human studies.[34]

Ceftaroline's volume of distribution is an estimated 0.37 L/kg, corresponding to the extracellular fluid volume of about 16–17 liters with plasma protein binding of <20%.[23,35,36] Establishing pulmonary tissue

penetration was imperative in seeking approval for an indication to treat CAP. The mean pulmonary penetration in a rabbit model was 42% (+/−11.2%) relative to plasma levels over two hours; intravenous dosing was administered at 20 mg/kg for 30 minutes, with plasma and lung tissue concentrations of 41.0 mg/L and 18.7 mg/kg, respectively. Further, the pulmonary concentrations exceeded the MICs of most respiratory pathogens.[37] Assessment of pulmonary penetration in human studies is pending. Furthermore, pharmacokinetic studies await evaluation of cerebrospinal fluid penetration. If ceftaroline provides adequate CSF penetration, coupled to its impressive anti-MDRSP activity,[38] ceftaroline would offer a promising option against bacterial meningitis.

Elimination (drug clearance) occurs primarily through renal excretion, exhibiting classical two-compartmental linear pharmacokinetics with upwards of 75% of drug recovered in urine (52 +/− 33%). After conversion from the prodrug ceftaroline fosamil to ceftaroline, a small fraction of the latter is converted to an inactive metabolite, ceftaroline-M-1. Approximately 50% of ceftaroline (clearance ranging from 90.0 to 129.2 ml/min) and 7% of ceftaroline-M-1 are excreted in the urine.[31,32,35]

In a small study (n = 18, 6 per group), individuals with normal renal function (creatinine clearance (CrCl) >80 ml/min), mild renal impairment (CrCl of 51–80 ml/min), or moderate renal impairment (CrCl of 31–50 ml/min) received ceftaroline fosamil (600 mg) as an one-hour intravenous infusion, with subsequent plasma and urine collections for up to 48 hours. Ceftaroline exhibited an increasing plasma half-life with increased renal impairment from 2.8, 3.6, to 4.5 hours, respectively. The Cmax of ceftaroline was unaffected by renal function, ranging from 27 to 31 μg/ml, while AUC values increased with worsening renal function: 68 to 120 μg/hour/ml, with a commensurate reduction in the clearance from 126 to 74 ml/min. The renal clearance of ceftaroline and ceftaroline-M-1 was decreased significantly by 65% and 84%, respectively.[35]

Based on Monte Carlo simulations, dosage adjustment is recommended for patients with moderate renal impairment (creatinine clearance 31–50 ml/min) at 400 mg intravenously (infused over one hour) every 12 hours. No dosage adjustment is necessary for mild renal impairment (CrCl >50 ml/min).[35,39] There are no recommendations for dosing in severe renal dysfunction (CrCl <30 ml/min) or hemodialysis available at this time, but some pharmacokinetic data suggest that a dose reduction of at least 50%, or doubling of the dosing interval will be warranted among these patients.[40,41]

Ceftaroline lacks a p450-dependent mechanism of metabolism and is unlikely to interfere with drugs metabolized through cytochromes in the liver.[42] Minimal ceftaroline was recovered in the bile or intestines after administration, further confirming that most of the drug is excreted renally and suggesting minimal hepatic influence on pharmacokinetics.[43] In addition, hepatic impairment will likely have minimal influence on ceftaroline dosing.

Pharmacodynamics

The %T > MIC is the most important pharmokinetic/pharmacodynamic parameter, predicting ceftaroline's clinical efficacy consistent with the β-lactam antibiotic class. Target attainment studies performed with cephalosporins reported that bacteriostatic and bactericidal effects are achieved for staphylococci when free drug concentrations exceed the MIC for 30% or 50% of the dosing interval, respectively. As true for the cephalosporin class, superior pharmacokinetic/pharmacodynamic efficacy correlates with the duration (and not the peak concentrations) eclipsing the MIC.[23,26,44] The %T > MIC necessary to produce 1 log killing were 43 ± 9% (*S. pneumoniae*), 33 ± 9% (*S. aureus*), and 41 ± 11% (Gram-negative bacilli). The data for 2 log killing were 50 ± 10% (*S. pneumoniae*), 45 ± 13% (*S. aureus*), and 54 ± 3% (Gram-negative *Enterobacteriaceae* bacilli), respectively, in a murine model.

A population pharmacokinetic analysis of data from phase I and II trials for ceftaroline found that the probability of target attainment for %T > MIC of 50% for a 1-μg/ml target was 96% and 50% for a 2-μg/ml target, assuming subjects with normal renal function and administered 600 mg ceftaroline over a one-hour infusion every 12 hours. The ceftaroline MIC distribution for susceptible bacteria is narrow, with only 4.5% of the strains displaying a MIC of ≤0.25 μg/ml and 1.5% with a MIC of ≥2 μg/ml. The MIC_{50} and MIC_{90} rarely deviate significantly, as minimum bactericidal concentration (MBC) values are consistently equal to, or within a single dilution

higher than, their respective MICs for 86% of tested organisms, while 90% of strains had an ideal MBC/MIC ratio of ≤4.[38] Kill-curve kinetic studies corroborated MBC determinations for ceftaroline, as bactericidal (≥3 $\log_{10}$ CFU/ml reductions) action could be demonstrated in the majority of strains at up to eight times the reference MIC tested.[45]

Ceftaroline breakpoints have been proposed, but not confirmed, since the final MIC values and disc diffusion breakpoints await analyses of the results from Phase III clinical trials.[22,26] Susceptible Gram-positive quality control strains all had zone diameters exceeding >20 mm for the 10–100 µg disc concentrations and a corresponding MIC ≤0.5 µg/ml. The maximum zone diameter differences of approximately 10 mm were achieved between susceptible and possibly resistant strains utilizing the 10 or 30 µg disc. Therefore, the 10 or 30 µg disc content may be a reasonable choice for potential correlation of MIC breakpoints of ≤1–4 µg/ml.[22,45,46]

As PBP affinity correlates with the MIC, predictably, ceftaroline enjoys superior efficacy (ie, reduced MICs) to that of contemporary β-lactams.[28] This is best illustrated with high binding affinity of ceftaroline to PBP2a associated with superior MICs against MRSA (0.05–2 µg/ml).[24] An apparent relatively lengthy post antibiotic effect (PAE) has been noted in treatment of Gram-positive organisms, especially *S. aureus*, which could prevent bacterial re-growth when ceftaroline levels in serum fall below the MIC.[47] Predictably and consistent with the cephalosporin class, ceftaroline fails to achieve a significant PAE against most other types of bacteria.[26] Bacterial re-growth has been uncorrelated to resistance, drug instability, or tolerance, thus far. Preliminary data suggest that the in vivo activity of ceftaroline parallels the in vitro MICs.[48]

Microbiology

Ceftaroline, in contradistinction to other drugs within the cephalosporin class, has good efficacy against MRSA, VISA, hVISA, and VRSA; linezolid- and daptomycin-resistant *S. aureus*; and MDRSP, while retaining efficacy against numerous Gram-negative pathogens including respiratory and non-extended-spectrum β-lactamases (ESBL) producing *Enterobacteriaceae* (Table 1).[20,21,23,38]

Table 1. Ceftraroline's Mean Inhibitory Concentrations (MICs) for selected organisms.

Organism	MIC_{90} (µg/ml)
Gram-Positive Bacteria	
Staphylococcus aureus	
MSSA	0.25 µg/ml (≤0.03–1.0)
MRSA	0.5–2.0
hVISA	0.25–4.0
Quinupristin-dalfopristin-resistant	1
Staphylococcus epidermidis	
Oxacillin-sensitive	0.12 (0.06–0.12)
Oxacillin-resistant	0.5 (0.25–2.0)
Vancomycin-intermediate (VISE)	≤0.016–2.0
Quinupristin-dalfopristin-resistant	1.0
Linezolid-resistant	0.5
Streptococcus pneumoniae	
Penicillin-susceptible	0.015
Penicillin-intermediate	0.06
Penicillin-resistant (MDRSP)	(0.12–0.25)
Ceftazidime-resistant	1.0
Ceftriaxone- and cefotaxime-resistant	0.25
Erythromycin-resistant	0.25
Levofloxacin-resistant	0.12
Streptococcus (β hemolytic)	≤0.008–0.016
Enterococcus faecalis	2.0–4.0
Enterococcus faecium	16–64
Gram-Negative Bacteria	
H. influenzae	≤0.016–0.03
Enterobacteriaceae	
No β-lactamases	0.06–4.0
ESBL positive	≥32
AmpC positive	>128
Citrobacter freundii	2.0
E. coli	
All isolates	0.12
–TEM/SHV	0.015–0.03
+TEM/SHV	0.5–2.0
Klebsiella pneumoniae	0.5
Morganella morganii	0.12
Proteus mirabilis	0.12
Serratia marcescens	2.0
Non-*Enterobacteriaceae*	
Pseudomonas spp.	>32
Acinetobacter spp.	>16–32
Stenotrophomonas maltophila	>32
Anaerobes	
Peptostreptococcus spp.	0.12
Propionibacterium spp.	0.12
Bacteroides spp.	≥32
Prevotella spp.	≥32
Pasteurella multocida	0.06
Clostridium difficile	4

Gram-positive organisms

Ceftaroline has 16-fold greater activity than ceftriaxone against MSSA isolates. For example, ceftaroline's MIC_{90} is consistently reported to be 0.25 μg/ml (≤0.03–1 μg/ml) for MSSA, compared with 4 μg/ml for ceftriaxone, 1 μg/ml for vancomycin, and ≤0.12 μg/ml for imipenem. Ceftaroline demonstrated up to four-fold greater activity than vancomycin against MRSA isolates, independent of the isolate's source (blood, skin, or respiratory tract), demonstrating MIC and MBC values ranging between 0.125 to 2 μg/ml and 0.5 to 2 μg/ml for ceftaroline and vancomycin, respectively.[20,21,49] As expected, ceftaroline was ≥8-fold more potent than cefepime and ≥16-fold more active than ceftriaxone against MRSA strains.[42] Ceftaroline MIC_{90} values against MRSA were 0.5–2 μg/ml, similar to that of linezolid and vancomycin (MIC_{90} of 1–2 μg/ml).[49] Moreover, the MBC against MRSA strains were 1, 2, and >64 μg/ml, respectively, for ceftaroline, vancomycin, and linezolid.

Ceftaroline's superiority over vancomycin was evident in hVISA, VISA, and VRSA as well as MRSA strains concomitantly resistant to linezolid and daptomycin.[50–52] The MICs and MBCs for hVISA strains (n = 100 isolates) were 2 (0.25–4 μg/ml) and 2 μg/ml, respectively, for ceftaroline. The corresponding MICs and MBCs were 4 and 8 μg/ml, respectively, for vancomycin and 1 and 16 μg/ml, respectively, for linezolid.[44] Ceftaroline yielded MICs of 1–4 μg/ml against both linezolid-sensitive and -resistant *S. aureus* isolates. Additionally, ceftaroline exhibited bactericidal effects, as opposed to the slowly bactericidal activity exhibited by vancomycin and the bacteriostatic activity of linezolid, and has synergy in combination with tobramycin.[50] Finally, ceftaroline's MIC values against quinupristin-dalfopristin-resistant strains were similar in activity to that described for MRSA (MIC_{50} and MIC_{90}, 1 μg/ml).[21]

Ceftaroline is also active against coagulase-negative *Staphylococcus epidermidis* (CoNS). Ceftaroline exhibited MIC_{90} of 0.12 (0.06–0.12) and 0.5 (0.25–2.0) μg/ml for oxacillin-susceptible and oxacillin-resistant isolates of CoNS, respectively.[20,21,49] Ceftaroline demonstrated MICs of ≤0.016 to 2 μg/ml against CoNS strains having reduced susceptibility to vancomycin (MIC of 4 μg/ml).[21] Ceftaroline was also active against 15 quinupristin-dalfopristin- and linezolid-nonsusceptible isolates (MIC_{90}, 1.0 μg/ml and 0.5 μg/ml), respectively.[21]

Consistent with other cephalosporins, the MIC_{90} value is lower against penicillin-susceptible strains of *S. pneumoniae* (MIC_{90} = 0.015 μg/ml) than against penicillin-intermediate (0.06 μg/ml) or penicillin-resistant strains (0.12–0.25 μg/ml).[38,53,54] Moreover, MICs (both MIC_{50} and MIC_{90}) varied between <0.008 and 0.5 μg/ml against 891 clinical human pneumococcal isolates collected from 22 centers in the United States in 2008.[53,54] Ceftaroline remained highly active, regardless of penicillin-susceptibility status (MIC_{90} ≤0.5 μg/ml), levofloxacin- susceptibility, and MDR strains, remaining 2–16 fold more active than other β-lactam comparators, including cefotaxime, ceftriaxone (MIC = 1 to 2 μg/ml), amoxicillin (8 μg/ml), meropenem, cefepime, and the new cephalosporin, ceftobiprole (1 μg/ml).[20,21,40,42,54,55] The MBC/MIC ratios for ceftaroline were also lower than all comparators to penicillin-susceptible and penicillin non-susceptible isolates.[55] Ceftaroline (MIC_{90} 0.03 μg/ml) was superior in isolates containing known mutations within the PBPs (ie, 1A, 2B, and 2X) exhibiting MIC_{90} values against MDRSP of 0.25 μg/ml.[42,45] Ceftaroline maintained MICs of 1.0 μg/ml against penicillin- and ceftazidime-resistant *S. pneumoniae* and MIC_{90} of 0.5 μg/ml (0.125–2.0 μg/ml) against highly cephalosporin-resistant clinical isolates of *S. pneumoniae* (cefotaxime and ceftriaxone MIC_{90} ≥4–16 μg/ml).[49] Against amoxicillin- and cefotaxime-resistant strains, the ceftaroline MIC_{90} (0.25 μg/ml) was four and 16 times lower, respectively, than that of ceftriaxone (1 and 4 μg/ml, respectively). Ceftaroline's MIC_{90} against erythromycin- and levofloxacin-resistant strains were 0.25 μg/ml and 0.12 μg/ml, respectively.[53–56]

Ceftaroline exhibits excellent potency against β-hemolytic streptococci, including *Streptococcus pyogenes* and *Streptococcus agalactiae,* with the vast majority of strains inhibited at a MIC_{90} ≤0.008–0.016 μg/ml, irrespective of macrolide- and levofloxacin-susceptibility status.[42] Ceftaroline retained MIC_{50} and MIC_{90} of 0.03 and 0.5 μg/ml for penicillin-susceptible and penicillin-resistant viridans group streptococci strains, respectively, irrespective of levofloxacin-susceptibility status.[20,56] Quinupristin-dalfopristin-nonsusceptible *Streptococcus bovis* and

S. mitis strains were also sensitive to ceftaroline, exhibiting MICs varying widely from ≤0.016–8 μg/ml.[21]

Ceftaroline exhibits an MIC_{90} of 4 μg/ml (0.25– 8 μg/ml) for *Enterococcus faecalis,* irrespective of vancomycin-, linezolid-, quinupristin-dalfopristin-, or ampicillin-susceptibility status. Ceftaroline MICs varied from 2–4 μg/ml against vancomycin- sensitive and -resistant *E. faecalis* strains (including Van^r).[20,21,48] However, ceftaroline yielded minimal activity against vancomycin-susceptible or -resistant *Enterococcus faecium* isolates with MIC_{90} of 16–64 μg/ml.[21,42,48,49]

Gram-negative organisms

MICs against *Enterobacteriaceae* isolates without β-lactamases range from 0.06–4 μg/ml (typically with a MIC_{90} of 1 μg/ml, Table 1), exhibiting similar to modestly inferior activity compared to cefepime, ceftazidime, cefotaxime, and ceftriaxone.[20,21,42] Example MICs for non-ESBL producing *Enterobacteriaceae* isolates include *Citrobacter freundii* (MIC_{50} 0.15 μg/ml; MIC_{90}, 2 μg/ml), *E. coli* (MIC_{50} 0.06 μg/ml; MIC_{90}, 0.12 μg/ml), *Klebsiella pneumoniae* (MIC_{50} 0.06 μg/ml; MIC_{90}, 0.5 μg/ml), *Morganella morganii* (MIC_{50} 0.06 μg/ml; MIC_{90}, 0.12 μg/ml), *Proteus mirabilis* (MIC_{50} 0.06–0.5 μg/ml; MIC_{90}, 0.12 μg/ml), and *Serratia marcescens* (MIC_{50} 0.12–1 μg/ml; MIC_{90}, 2.0 μg/ml). Ceftaroline also exhibits potent activity in vitro against the respiratory pathogens, *H. influenzae* and *M. catarrhalis* regardless of β-lactamase production (including ampicillin-resistant strains). For example, the MIC_{90} is ≤0.016–0.03 μg/ml for *H. influenzae.*[20,21]

Mirroring its predecessor oxyimino cephalosporins, ceftaroline lacks activity against ceftazidime non-susceptible *Enterobacteriaceae*. In addition, ceftaroline demonstrated generally poor activity (ie, MIC_{90} of ≥32 μg/ml), similar to ceftriaxone and inferior to cefepime, ceftazidime, and imipenem against a diverse group of nonfermentative Gram-negative bacilli.

Saliently, ceftaroline does not exhibit reliable activity against *Pseudomonas spp., Acinetobacter spp.,* or *Stenotrophomonas spp*. The MIC_{50} against *Pseudomonas aeruginosa* ranges from 2–16 μg/ml, while the MIC_{90} exceeds 32 μg/ml; hence, ceftaroline is not considered active against this organism. The MICs for *Acinetobacter spp.* isolates ranges from 4–>128 μg/ml, (MIC_{90}(>16–32)), and for *Stenotrophomonas maltophilia,* the MIC_{90} is typically ≥32 μg/ml.[20,21]

Against classical β-lactamases, such as TEM-1, TEM-2, or SHV-1, MICs have a significant variability ranging from 2–16 μg/ml. Additionally, ceftaroline exhibits (rather uniquely for an oxyimino cephalosporin) mild labiality to classic TEM and SHV β-lactamases, exhibiting four-fold elevations in its MICs, with high inoculums or with isolates upregulating their expression (demonstrated in many isolates of *E. coli*, *P. mirabilis,* and *Klebsiella spp.*). For example, ceftaroline MICs varied from 0.015–0.03 μg/ml to 0.5–2.0 μg/ml in *E. coli* isolates with and without classical TEM/SHV β-lactamases.[49]

Consistent with the cephalosporin class, ceftaroline exhibits little activity and is inactivated by ESBL-producing *Enterobacteriaceae* isolates (MIC_{90} ≥32 μg/ml), particularly compromised against CTX-M ESBL (the predominant ESBL in much of Europe, Asia, and South America). Ceftaroline also exhibits high MICs (>128 μg/ml) against bacteria containing AmpC enzymes (derepressed or constitutively expressed) and carbapenemases (OXA-48, KPC, K1, and metallo-β-lactamases).[20,21,49]

Studies are underway to examine the potential protection with a β-lactamase inhibitors (clavulanic acid and tazobactam), which could markedly reduce the MICs of ceftaroline potentially restoring activity against ESBL-producing isolates, including classical- and extended-spectrum class A (TEM, SHV) and D (OXA) β-lactamases, as well as the K1 carbapenemases. Forest Laboratories is developing a combination product consisting of ceftaroline and NXL104, a novel β-lactamase inhibitor, to enhance activity against ESBLs and AmpCs; the effectiveness of this combination is under evaluation. Preliminary chequerboard analysis suggests potentiation of ceftaroline activity against *Enterobacteriaceae* producing AmpCs, KPCs (K1 enzyme), and non- metalloenzymatic β-lactamases (including OXA-48 carbapenemases), including isolates with impermeability.[57] Furthermore, NXL104 has been shown to potentiate ceftazidime activity against non-fermenting *Pseudomonas aeruginosa* (including isolates producing AmpC with MICs decreased to <8 μg/ml) and ESBLs (except those exhibiting up-regulated efflux).[58]

Anaerobic organisms

Ceftaroline possesses activity against Gram-positive anaerobes, including *Peptostreptococcus spp., Propionibacterium spp.*, and non-difficile *Clostridium spp.* similar to that of amoxicillin-clavulanate, and 4–8 fold superior to ceftriaxone (Table 1). It also has good activity against *Pasteurella multocida* with an MIC_{90} of 0.06 μg/ml.[20] It has minimal activity against *Bacteroides spp.* and *Prevotella spp.* (MIC_{90} ≥32 μg/ml). It possesses similar activity to that of ceftriaxone against Gram-negative non-β-lactamase producing anaerobes, and possesses insignificant activity against *Clostridium difficile* (MIC_{50}, 2 μg/ml; MIC_{90}, 4 μg/ml).[21,59]

Animal Studies

Animal studies on the efficacy of ceftaroline are summarized in Table 2. In a murine pyomyositis model, ceftaroline and linezolid were both superior to vancomycin ($P \leq 0.01$).[60] Ceftaroline demonstrated superior efficacy to vancomycin and linezolid in a rabbit model of joint infection due to MRSA and VISA isolates by reducing the CFU/gram tissue of MRSA in synovium by −1.98 $\log_{10}$. Finally, ceftaroline and linezolid (but not vancomycin) significantly reduced bacterial counts by means of −2.95 and −2.69 $\log_{10}$ CFU/gram in bone marrow tissue, and −2.83 and −2.25 $\log_{10}$ CFU/gram in bone, respectively. Overall, ceftaroline was the only intervention demonstrating homogeneous in vivo activity against MRSA and VISA isolates in all three tissues (ie, synovium, bone, and bone marrow).[60,61]

In a murine MRSA pneumonia model, ceftaroline had similar efficacy in decreasing MRSA bacteria counts than that of vancomycin and linezolid when the drugs were begun within two hours of infection. However, ceftaroline started one day after infection demonstrated more than 99.9% reduction in bacterial counts by day 3 in a murine MRSA neutropenic pneumonia model, whereby linezolid and vancomycin had no effect.[60]

Regarding the treatment of endocarditis, ceftaroline demonstrated bactericidal activity in a rabbit model by showing a 6 $\log_{10}$ decrease in MRSA and VISA isolates after four days of treatment.[52] Ceftaroline was superior to linezolid and comparable to vancomycin in an aortic endocarditis rabbit model with MRSA (10^8 CFU), decreasing counts to 2.5 +/− 0.3 $\log_{10}$ CFU/gram vegetation compared to 7.1+/− 0.6 $\log_{10}$ CFU/gram in linezolid, 2.7 +/− 0.8 $\log_{10}$ CFU/gram in vancomycin, and 8.9 +/− 0.5 $\log_{10}$ CFU/gram vegetation in controls.[52] Ceftaroline was the only bactericidal agent against VISA isolates (wherein both vancomycin and linezolid proved to be bacteriostatic). Regarding sterilization rates (no bacterial growth after 48 hours of incubation), ceftaroline achieved sterilization in 90% (9/10) of MRSA and 60% (6/10) of VISA compared to vancomycin, which achieved 67% (4/6) and 0% (0/5), respectively, and linezolid achieving 0% (0/7 and 0/8) against both isolates.[52]

In the same rabbit endocarditis model, ceftaroline was superior in decreasing bacterial vegetations (5.68 $\log_{10}$ CFU/gram) induced by vancomycin-susceptible *E. faecalis* strains compared to linezolid (6.88 $\log_{10}$ CFU/gram, $P < 0.05$), vancomycin (6.70 $\log_{10}$ CFU/gram, $P < 0.05$), and the control group (vs. 8.56 $\log_{10}$ CFU/gram, $P < 0.001$). Results were more impressive evaluating results against a vancomycin-resistant *E. faecalis* strain: ceftaroline vs. linezolid (3.98 vs. 6.88 $\log_{10}$ CFU/gram, $P < 0.001$), ceftaroline vs. vancomycin (vs. 8.01 $\log_{10}$ CFU/gram, $P < 0.001$), and the control group (vs. 8.60 $\log_{10}$ CFU/gram, $P < 0.001$). In a rat endocarditis model, ceftaroline at 20 mg/kg IV twice daily was compared to control, vancomycin 120 mg/kg subcutaneously twice/daily, and daptomycin 10 mg/kg subcutaneously, daily administered for three days. Ceftaroline decreased bacterial densities significantly compared with controls in the vegetation (4.88 vs. 9.87 $\log_{10}$ CFU/gram, $P < 0.0005$), kidney (4.09 vs. 7.28 $\log_{10}$ CFU/gram, $P < 0.0005$), and spleen (3.63 vs. 6.53 $\log_{10}$ CFU/gram, $P < 0.0005$). Vancomycin and daptomycin decreased bacterial densities in the vegetation, liver, and spleen to 6.76 and 7.64 $\log_{10}$ CFU/gram, 4.15 and 5.53 $\log_{10}$ CFU/gram, and 4.28 and 5.49 $\log_{10}$ CFU/gram, respectively.[48]

Clinical Efficacy

To date, phase III trials have been completed evaluating the efficacy of ceftaroline for the treatment of SSTI and CAP (Table 3). Regarding the treatment of SSTI, ceftaroline (600 mg intravenously every 12 hours) was noninferior to vancomycin (1 gram intravenously every 12 hours) plus aztreonam (1 gram intravenously every 8 hours) administered for 5–14 days. Two phase III trials, named CANVAS I and II (Ceftaroline versus Vancomy-

Table 2. Summary of animal studies evaluating the efficacy of ceftaroline.

Study reference	Study type/methods	Infection	Sample size	Antibiotics	Results
Iizawa[60]	Murine Antibiotic administered at 2, 20, and 26 hours after infection Thigh muscle infected removed day 7 and homogenized in trypticase soy broth and bacterial counts estimated	Pyomyositis	10 mice per group	Ceftaroline Linezolid Vancomycin *All dosed at 20 mg/kg	All three drugs reduced bacterial counts compared to placebo Ceftaroline and linezolid reduced counts to ≤0.1% and were superior to vancomycin
Jacqueline[61]	Rabbit Knee injected with bacteria (MRSA) Antibiotic administered 3-days later following I&D for duration 4 days Comparison of bacterial load prior to antibiotics and at day 7 in the synovial fluid	Septic Arthritis	Controls (8), ceftaroline (10), linezolid (8), and vancomycin (10)	Ceftaroline dosed to mimic 10 mg/kg or 600 mg bid Vancomycin continuous infusion to achieve 20× the MIC Linezolid mimic 10 mg/kg or 600 mg bid	Bacterial load in joint fluid: Mean +/– SD $\Delta\log_{10}$ CFU/g (D7-D3) Ceftaroline*: –1.98 +/– 1.00 Vancomcyin –0.19 +/– 1.19 Linezolid –0.77 +/– 1.39 Control 0.09 +/– 0.59 *$P < 0.05$ vs. all comparisons
Izawa[60]	Murine Antibiotic administered one day after neutropenic pneumonia Bacterial counts detection at day 3	Pneumonia	10 mice per group	Ceftaroline Vancomycin Linezolid All dosed at 20 mg/kg tid subcutaneously	Ceftaroline decreased counts 99.9% from control ($P < 0.01$) and was superior to both comparators ($P < 0.01$)
Jacqueline[52]	Rabbit Antibiotic administered 24 hours after infection of aortic valve with **MRSA** and continued 4 days Valves then excised and homogenized for culture	Endocarditis	Control (6), ceftaroline (10), linezolid (7), and vancomycin (6)	Ceftaroline 58 mg/kg over 12 hours to mimic human dose of 600 mg bid Vancomycin continuous infusion to achieve 20× the MIC Linezolid 10 mg/kg to mimic human dose of 600 mg bid	Bacterial CFU/g Mean $\log_{10}$ +/– SD (number with sterile vegetation) [a,b]Ceftaroline: 2.5 +/– 0.3 (9/10) [a,b]Vancomycin 2.7 +/– 0.8 (4/6) [a]Linezolid 7.1 +/– 0.6 (0/7) Control 8.9 +/– 0.5 (0/6) [a]$P < 0.001$ vs. controls [b]$P < 0.001$ vs. linezolid

Jacqueline[52]	Rabbit Antibiotic administered 24 hours after infection of aortic valve with **VISA** and continued 4 days Valves then excised and homogenized for culture	Endocarditis	Control (6), ceftaroline (10), linezolid (8), and vancomycin (5)	Ceftaroline 58 mg/kg over 12 hours to mimic human dose of 600 mg bid Vancomycin continuous infusion to achieve 20× the MIC Linezolid at 10 mg/kg to mimic human dose of 600 mg bid	[a,b]Ceftaroline: 3.0 +/– 0.9 (6/10) [b]Vancomycin 6.7 +/– 0.4 (0/5) [b]Linezolid 6.9 +/– 0.4 (0/8) Control 9.4 +/– 0.3 (0/6) [a]$P < 0.001$ vs. control [b]$P < 0.001$ vs. linezolid and vancomycin
Jacqueline[48]	Rabbit Vancomycin- sensitive *E. faecalis* Antibiotic administered 24 hours after infection of aortic valve and continued 4 days Valves then excised and homogenized for culture	Endocarditis	Control (8), ceftaroline (7), linezolid (7), and vancomycin (8)	Ceftaroline to mimic human dose of 10 mg/kg/12 hr Vancomycin continuous infusion to achieve 20× the MIC Linezolid to mimic dose of 10 mg/kg/12 hr	Bacterial CFU/g Mean $\log_{10}$ +/– SD [a,b]Ceftaroline: 5.68 +/– 0.49 Vancomcyin 6.70 +/– 0.25 Linezolid 6.88 +/– 0.7 Control 8.56 +/– 0.74 [a]$P < 0.001$ vs. control [b]$P < 0.05$ vs. linezolid and vancomycin
Jacqueline[48]	Rabbit Vancomycin- resistant *E. faecalis* Antibiotic administered 24 hours after infection of aortic valve and continued 4 days Valves then excised and homogenized for culture	Endocarditis	Control (9), ceftaroline (9), linezolid (9), and Vancomycin (8)	Ceftaroline to mimic human dose of 10 mg/kg/12 hour Vancomycin continuous infusion to achieve 20× the MIC Linezolid to mimic dose of 10 mg/kg/12 hour	[a,]Ceftaroline: 3.98 +/– 0.85 Vancomycin 8.01 +/– 0.76 Linezolid 6.88 +/– 0.77 Control 8.60 +/– 0.54 [a]$P < 0.001$ vs. all comparators

cin in Skin and Skin-Structure Infection), investigated complicated SSTI (most commonly extensive cellulitis, major abscess, and infected wounds) among 1,378 subjects comparing ceftaroline to vancomycin +/– aztreonam.[62] CANVAS I and II were randomized, double-blind, multinational phase III trials. Fifty-five study sites in 10 countries participated in CANVAS I from February to November 2007[63] and 56 study sites in 12 countries participated in CANVAS II from March to December 2007.[64] Eligibility requirements included age ≥18 years and SSTI requiring ≥5 days IV antibiotics. Four percent had concurrent bacteremia, and the most common cause of the SSTI was *S. aureus*. The clinical cure rates were 92% and 93% (non-significant difference), and microbiological eradication rates were 92% and 94% for ceftaroline vs. the comparator. Response rates for MRSA infections were also similar. Ceftaroline was inferior to the comparator in Gram-negative SSTI, particularly for *P. aeruginosa*. Results from an earlier phase II trial (n = 100, randomized 2:1) showed similar results—ceftaroline achieved clinical cure rates of 97% versus 89% for the comparator. In addition, the microbiological cure rates were comparable: 95% for ceftaroline (including all MRSA isolates identified) versus 86% for the comparator.[65]

Clinical trials have demonstrated efficacy utilizing ceftaroline for treating CAP (FOCUS 1 and 2: Ceftaroline Community Acquired Pneumonia Trial vs. Ceftriaxone in Hospitalized Patients).[66,67] In these two phase III randomized double-blind multicenter trials, 1,228 hospitalized (but not admitted to the ICU) adults with moderate to severe (PORT risk class III or IV) CAP were randomized to ceftaroline (600 mg intravenously every 12 hours) or ceftriaxone (1 gram intravenously daily) for 5–7 days (Table 3). The overall clinical cure rates were similar (84% in the ceftaroline group and 78% in the ceftriaxone group), as well as the overall microbiological response rate (87% for ceftaroline and 81% for ceftriaxone). The response rates were 86% and 69% against *S. pneumoniae* isolates and 100% (4/4) and 22% (2/9) against MDRSP for ceftaroline and ceftriaxone, respectively. Both drugs exhibited similar clinical cure rates against MSSA and Gram-negative respiratory pathogens, such as *H. influenzae* and *K. pneumoniae*.[66,67] Therefore, individual and pooled analyses of the FOCUS trials demonstrate ceftaroline to be efficacious, well tolerated, and comparable in efficacy and adverse effects to ceftriaxone in the treatment of CAP.

Although the number of cases were small, ceftaroline appears to be superior to ceftriaxone in the treatment of MDRSP as predicted by its superior affinity to the PBP2x (implicated in β-lactam resistance).[67] As expected, ceftaroline is not targeted for hospital-acquired or aspiration pneumonia, as it lacks activity against many Gram-negative pathogens including those expressing AmpC- or ESBL, *Pseudomonas*, and *Acinetobacter spp*., as well as many anaerobes. Finally, given the paucity of MRSA cases in the FOCUS studies, further data on the efficacy of ceftaroline for MRSA pneumonia are needed.

Safety

Based on clinical trial data to date, ceftaroline appears to be safe and well-tolerated. Since ceftaroline is a cephalosporin, it has caused serious hypersensitivity reactions in patients who are allergic to cephalosporins and among some patients with penicillin allergies. Hence, a careful history of prior antibiotic allergies should be obtained prior to the use of ceftaroline.

Side effects and drug discontinuation rates were similar to the comparator arm in the CANVAS studies. Among those receiving ceftaroline, the most common side effects were 6% with nausea, 5% headache, 5% diarrhea, 4% pruritis, and 3% rash. Forty-five percent had at least one adverse event (most were mild), but only 3% had to discontinue the drug, most commonly ascribed to a possible allergic reaction.[62] All adverse events were similar to that of vancomycin/aztreonam, except the latter group had a higher incidence of pruritis. No cases of neutropenia, thrombocytopenia, hemolytic anemia, or significant liver dysfunction were identified during these trials.[62] Elevations in laboratory parameters occurred infrequently for blood creatine kinase (8%), alanine aminotransferase (6%), and aspartate aminotransferase (6%) levels, but were typically asymptomatic.[63] Development of a positive direct Coombs' test has been noted, but no known cases of hemolytic anemia have been documented, thus far. Furthermore, EKG data have not noted QT interval prolongation.[63] In summary, ceftaroline has had an excellent safety profile to date; further post-marketing assessments are needed to ensure the safety of this new drug.

Ceftaroline is excreted renally, thus studies have shown minimal impact on the fecal microflora after seven days administration in healthy young adults. For example, in one study, minimal disruption was noted

Table 3. Human clinical studies on the efficacy of ceftaroline.

Study reference	Study type	Infection	Sample size	Antibiotics	Clinical response	Microbiologic response	Miscellaneous
CANVAS I[63]	Phase III Randomized Double-blind Multicenter Multinational noninferior	SSTI	702	Ceftaroline (600 mg IV bid) Versus Vancomycin 1g IV bid +/– Aztreonam 1 g IV bid (5–14 days)	91.1%, (288/316) Versus 93.3%, (280/300) 95% CI: –2.2 (–6.6, 2.1)	92.2% (225/244) Versus 94.7% (215/227) 95% CI –2.5 (–7.2, 2.1)	MRSA 95.1% (78/82) for Ceftaroline 95.2% (59/62) for Vancomycin plus Aztreonam
CANVAS II[64]	Phase III Randomized Double-blind Multicenter noninferior	SSTI	694	Ceftaroline (600 mg IV bid) Versus Vancomycin 1 g IV bid +/– Aztreonam 1g IV bid (5–14 days)	92.2%, (271/294) Versus 92.1%, (269/292); 95% CI: 0.1% (–4.4, 4.5)	93.9% (170/181) Versus 94.4% (168/178) 95% CI –2.1% (–6.9, 2.5)	MRSA 96.6% (56/58) for Ceftaroline 94.2% (49/52) for Vancomycin plus Aztreonam
Pooled CANVAS[62]	Phase III Randomized Double-blind Multicenter noninferior	SSTI	1378	Ceftaroline (600 mg IV bid) Versus Vancomycin 1g IV bid +/– Aztreonam 1g IV bid (5–14 days)	91.6% 92.7%	92.3% 93.7%	Ceftaroline inferior to comparator for Gram-negative organisms such as *Pseudomonas spp.*
FOCUS 1[66,67]	Phase III Randomized Double-blind Multicenter	CAP PORT III/IV Hospitalized No ICU	606	Ceftaroline (600 mg IV q12) Versus Ceftriaxone (1g IV daily) 5–7 days	86.6% (194/224) Versus 78.2% (183/234) Difference: 8.4%, 95% CI (1.4%–15.4%)	89.9% (62/69) Versus 76.1% (54/71) Difference 13.8%, 95% CI (1.3%–26.4%)	
FOCUS 2[66,67]	Phase III Randomized Double-blind Multicenter	CAP PORT III/IV Hospitalized No ICU	562	Ceftaroline (600 mg IV q12) Versus Ceftriaxone (1g IV daily) 5–7 days	82.1% (193/235) Versus 77.2% (166/215) Difference: 4.9%, 95% CI (–2.5%–12.5%)	81.2% (69/85) Versus 75% (57/76) Difference: 6.2%, 95% CI (–6.7%–19.2%)	
Pooled FOCUS[66,67]	Phase III Randomized Double-blind Multicenter	CAP PORT III/IV Hospitalized No ICU	1228	Ceftaroline (600 mg IV q12) Versus Ceftriaxone (1g IV daily) 5–7 days	84.3% 77.7% Difference: 6.7%, 95% CI (1.6%–11.8%)	87.0% 81.0% Difference: 6.1%, 95% CI (–2.3% to 14.6%)	Clinical response rates were 86% vs. 69% for all *S. pneumoniae* and 100% vs. 22% for MDRSP favouring ceftaroline

in the stool ecologic flora, with modest decreases observed in *E. coli*, *Bifidobacteria,* and *Lactobacillus* isolates, and no changes were found within *Candida, Bacterioides,* or *Enterococcus spp.*[43] However, like all antibiotics, *C. difficile* infection may occur with ceftaroline—in the CANVAS I and II trials, two patients (of 693) developed a *C. difficile* infection (compared to one in the comparator group).[62]

Regarding drug-drug interactions, no formal studies have been conducted with ceftaroline, to date. Given its metabolism through the kidneys, ceftaroline likely exhibits minimal inhibition of the P450 system, suggesting limited propensity for drug interactions among medications metabolized via this system. It has no known antagonism with other antibiotics and has possible synergy with diverse antibiotic classes, to include aminoglycosides (tobramycin), piperacillin/tazobactam, aztreonam, and meropenem.[42,50] Up to now, there are no specific data on the use of ceftaroline in paediatrics or pregnant/breastfeeding women, hence, the safety of this novel antibiotic in these settings is currently unknown.

Resistance Barrier

The barrier to resistance appears sizable for Gram-positive bacteria with resistance rarely reported to date. It has a comparable profile to other oxyimino cephalosporins for Gram-negative bacteria based on investigations of the spontaneous mutation frequency and change in MIC in single-step mutant selection and serial passage studies.[23] For example, ceftaroline did not select for resistant variants of *S. aureus* in vivo.[52] In vitro passage studies have demonstrated low rates of acquired resistance of *Staphylococcus spp.* to ceftaroline.[51] Ceftaroline at concentrations of four times the MIC failed to select mutants at detectable frequencies from tested MRSA, VISA, and MDRSP isolates.[49] Ceftaroline also appeared immune to multi-step mutational induction attempts.[49] In synopsis, ceftaroline has demonstrated minimal changes in MIC in serial passage studies in Gram-positive isolates, but demonstrates similar potential to resistance development as cefotaxime to Gram-negative organisms.[23] Although these data are promising, information regarding the evolution of resistance to this novel antibiotic in clinical practice are needed. Furthermore, as previously noted, ceftaroline exhibits poor activity against ESBL and AmpC producing strains.

Ceftobiprole

There is an additional novel fifth-generation cephalosporin with activity against MRSA, ceftobiprole, currently under investigation. Ceftobiprole medocaril, the pro-drug of ceftobiprole (formerly BAL9141), is a parental investigational cephalosporin (pyrrolidinone-3-ylidene-methyl cephalosporin) evaluated for the treatment of SSTI at a dose of 500 mg every 8 hours for 7–14 days.[68,69] Ceftobiprole exhibits activity against a wide-range of Gram-positive organisms including (MRSA) and Gram-negative organisms mirroring cefepime and ceftazidime.[70–71] Per time-kill studies, ceftobiprole exhibits primarily bactericidal activity with an MBC/MIC < 4 for the majority of tested isolates. As with ceftaroline, ceftobiprole's activity against MRSA hinges upon its affinity and interaction with PBP2a. It acylates PBP2a rapidly forming a more stable acyl-enzyme complex than other cephalosporins leading to 100% inhibition.[68] It also exhibits strong affinity for PBP2x providing activity against MDRSP, PBP2, PBP3 (*E. coli*), PBP1a-b, PBP2, PBP3, PBP4 (*P. aeruginosa*). Interestingly, ceftobiprole has no activity against *Enterococcus faecium* due to a lack of activity against PBP5.[69] Ceftobiprole exhibits an MIC_{90} <2 μg/mL against MRSA and *E. faecalis*; and 0.25 μg/mL for sensitive *S. pneumoniae* and <0.5 μg/mL against penicillin-resistant *S. pneumoniae*.[68,70,71] Similar to ceftaroline, ceftobiprole exhibits vulnerability to many β-lactamases resulting in a wide range of MICs for the *Enterobacteriaceae.*[71,72] Ceftobiprole is resistant to the TEM-1 and SHV-1 β-lactamases, but similar to ceftaroline, is susceptible to a host of higher order β-lactamases including AmpC β-lactamase; CTX-M-15 ESBL; and the KPC-2 carbapenemase.

Similar to ceftaroline, ceftobiprole has demonstrated noninferiority to vancomycin with or without ceftazidime in two large-scale studies with both interventions achieving clinical cure rates of $>90\%$.[73,74] In the first phase III clinical trial, overall clinical cure rates for SSTI were 93% and 94% in the ceftobiprole and vancomycin groups, respectively (95% CI, –4.4% to 3.9%).[73] A second phase III clinical trial noted overall cure rates of 91% versus

90% compared to vancomycin plus ceftazidime without significant differences in adverse events.[74] Ceftobiprole is approved for the treatment of SSTI in Switzerland and Canada (Zevtera). However, the drug has not been approved by the FDA and is pending further evaluation.[75]

Conclusions

Ceftaroline is a novel, broad-spectrum cephalosporin, which exhibits bactericidal activity against Gram-positive bacteria, including MRSA and MDRSP. Ceftaroline offers an exciting addition to the anti-MRSA armamentarium, including activity against VISA, hVISA, VRSA, and daptomycin- and linezolid-resistant strains. Unique among many anti-MRSA agents, ceftaroline additionally provides activity against Gram-negative respiratory pathogens including *H. influenzae* and *M. catarrhalis*. Since ceftaroline is not effective against organisms with AmpC- or ESBLs, research investigating combination with β-lactamase inhibitors to provide potential activity against these Gram-negative organisms are underway. To date, ceftaroline has demonstrated an excellent safety profile comparable to contemporary cephalosporins and exhibits an inherently low propensity to inducing resistance, especially among Gram-positive organisms; however, long-term data and clinical experience with this novel agent are needed. Ceftaroline is currently FDA approved for the treatment of both STTI and CAP.

Disclosure

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