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REVIEW ARTICLE

Ceftolozane/Tazobactam: A Novel Cephalosporin/β-Lactamase Inhibitor Combination with Activity Against Multidrug-Resistant Gram-Negative Bacilli

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Abstract Ceftolozane is a novel cephalosporin currently being developed with the β-lactamase inhibitor tazobactam for the treatment of complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), and ventilator-associated bacterial pneumonia (VABP). The chemical structure of ceftolozane is similar to that of ceftazidime, with the exception of a modified side-chain at the 3-position of the cephem nucleus, which confers potent antipseudomonal activity. As a β-lactam, its mechanism of action is the inhibition of penicillin-binding proteins (PBPs). Ceftolozane displays increased activity against Gram-negative bacilli, including those that harbor classical β-lactamases (e.g., TEM-1 and SHV-1), but, similar to other oxyimino-cephalosporins such as ceftazidime and ceftriaxone, it is compromised by extended-spectrum β-lactamases (ESBLs) and carbapenemases. The addition of tazobactam extends the activity of ceftolozane to include most ESBL producers as well as some anaerobic species. Ceftolozane is distinguished from other cephalosporins by its potent activity versus *Pseudomonas aeruginosa,* including various drug-resistant phenotypes such as carbapenem, piperacillin/tazobactam, and ceftazidime-resistant isolates, as well as those strains that are multidrug-resistant (MDR). Its antipseudomonal activity is attributed to its ability to evade the multitude of resistance mechanisms employed by *P. aeruginosa*, including efflux pumps, reduced uptake through porins and modification of PBPs. Ceftolozane demonstrates linear pharmacokinetics unaffected by the coadministration of tazobactam; specifically, it follows a two-compartmental model with linear elimination. Following single doses, ranging from 250 to 2,000 mg, over a 1-h intravenous infusion, ceftolozane displays a mean plasma half-life of 2.3 h (range 1.9–2.6 h), a steady-state volume of distribution that ranges from 13.1 to 17.6 L, and a mean clearance of 102.4 mL/min. It demonstrates low plasma protein binding (20 %), is primarily eliminated via urinary excretion (≥92 %), and may require dose adjustments in patients with a creatinine

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clearance <50 mL/min. Time-kill experiments and animal infection models have demonstrated that the pharmacokinetic–pharmacodynamic index that is best correlated with ceftolozane's in vivo efficacy is the percentage of time in which free plasma drug concentrations exceed the minimum inhibitory concentration of a given pathogen ($\%fT_{>\mathrm{MIC}}$), as expected of β-lactams. Two phase II clinical trials have been conducted to evaluate ceftolozane ± tazobactam in the settings of cUTIs and cIAIs. One trial compared ceftolozane 1,000 mg every 8 h (q8h) versus ceftazidime 1,000 mg q8h in the treatment of cUTI, including pyelonephritis, and demonstrated similar microbiologic and clinical outcomes, as well as a similar incidence of adverse effects after 7–10 days of treatment, respectively. A second trial has been conducted comparing ceftolozane/tazobactam 1,000/500 mg and metronidazole 500 mg q8h versus meropenem 1,000 mg q8h in the treatment of cIAI. A number of phase I and phase II studies have reported ceftolozane to possess a good safety and tolerability profile, one that is consistent with that of other cephalosporins. In conclusion, ceftolozane is a new cephalosporin with activity versus MDR organisms including *P. aeruginosa*. Tazobactam allows the broadening of the spectrum of ceftolozane versus β-lactamase-producing Gram-negative bacilli including ESBLs. Potential roles for ceftolozane/tazobactam include empiric therapy where infection by a resistant Gram-negative organism (e.g., ESBL) is suspected, or as part of combination therapy (e.g., with metronidazole) where a polymicrobial infection is suspected. In addition, ceftolozane/tazobactam may represent alternative therapy to the third-generation cephalosporins after treatment failure or for documented infections due to Gram-negative bacilli producing ESBLs. Finally, the increased activity of ceftolozane/tazobactam versus *P. aeruginosa,* including MDR strains, may lead to the treatment of suspected and documented *P. aeruginosa* infections with this agent. Currently, ceftolozane/tazobactam is being evaluated in three phase III trials for the treatment of cUTI, cIAI, and VABP.

1 Introduction

Antimicrobial resistance continues to be a growing threat to public health as we face increasing global resistance rates in many bacterial species implicated in life-threatening infections [1]. A significant proportion of healthcare-associated infections has been attributed to the "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), aptly named for their ability to escape the effects of most or all currently available antimicrobials [2]. The rapid increase in multidrug-resistant (MDR), Gram-negative ESKAPE pathogens is of particular concern due to the dearth of novel antimicrobials able to combat them, so much so that concerted efforts have been initiated to address this resistance pandemic. The "10 × '20 Initiative" is one such undertaking that was launched in 2010 by the Infectious Diseases Society of America. This initiative calls for a global commitment to creating a sustainable antimicrobial research and development enterprise that will support the short-term goal of developing ten novel, systemic antimicrobials by 2020 [3, 4].

P. aeruginosa is a nosocomial pathogen frequently isolated in many life-threatening infections, including healthcare-associated bacteremia and pneumonia; intra-abdominal, urogenital, wound and burn infections; and chronic respiratory infections (CRIs) in cystic fibrosis patients [5–7]. The treatment of pseudomonal infections has become clinically challenging owing to the organism's inherent propensity towards antimicrobial resistance due to increased expression of β-lactamases and multiple efflux pumps, decreased expression of porins, and alterations of its antimicrobial targets [7–9]. The constitutive expression of AmpC along with the acquisition of extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) (class B carbapenemases) by means of horizontal gene transfer result in the organism's frequent MDR phenotype [7–9]. These resistance mechanisms have resulted in strains resistant to available antipseudomonal agents, including β-lactams, fluoroquinolones and aminoglycosides, and have greatly compromised the clinical efficacy of these agents [5, 10].

Ceftolozane (previously CXA-101and FR264205) is a novel, broad-spectrum cephalosporin with potent antipseudomonal activity that extends to include isolates highly resistant to other β-lactams, fluoroquinolones and aminoglycosides, as well as MDR isolates [10–13]. It demonstrates remarkable stability against the numerous resistance mechanisms employed by *P. aeruginosa,* including overexpression of AmpC, a lack of cross-resistance with other antipseudomonal agents and a low propensity for inducing resistance in this organism [13–15]. Ceftolozane also demonstrates good activity against members of the Enterobacteriaceae, but similar to other established oxyimino-cephalosporins (e.g., ceftazidime, ceftriaxone, and cefotaxime), it is compromised in Enterobacteriaceae by the production of ESBLs and carbapenamses and some strains harboring stably derepressed AmpC β-lactamases [16]. The addition of tazobactam, a well-established β-lactamase inhibitor, broadens the spectrum of ceftolozane to include many ESBL-producing organisms as well as some anaerobes, such as *Bacteroides* spp. [16].

Ceftolozane/tazobactam is therefore being developed for the treatment of serious Gram-negative infections. Cubist Pharmaceuticals, Inc. has completed phase III clinical trials evaluating ceftolozane/tazobactam for the treatment of complicated urinary tract infections (cUTIs; http://clinicaltrials.gov, identifiers NCT01345955, NCT01345929) and complicated intra-abdominal infections (cIAIs) (NCT01445665, NCT01445678). A program to evaluate ceftolozane/tazobactam for the treatment of ventilator-associated bacterial pneumonia (VABP) is ongoing (NCT01853982).

This article reviews existing published data on ceftolozane/tazobactam, including relevant chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, and efficacy and safety data from animal and clinical trials. A comprehensive literature search was conducted using MEDLINE, SCOPUS, and databases of scientific meetings from 2005 to June 2013 for all materials containing the name "Ceftolozane" and any of "CXA-201", "CXA-101", or "FR264205". These results were supplemented by bibliographies obtained from Cubist Pharmaceuticals, Inc. (http://www.cubist.com/products/cxa_201).

2 Chemistry

Cephalosporins are characterized by a cephem core, a bicyclic ring system composed of a four-membered β-lactam ring fused with a six-membered dihydrothiazine ring, with a carboxyl group located at position 4. The diversity of cephalosporins is attributed to the variations observed in the side-chains at positions 3 and 7 of this ring system [17].

Ceftolozane is structurally similar to ceftazidime (Fig. 1). The structure–activity relationships of ceftolozane described below are summarized in Fig. 2. The aminothiadiazole ring on ceftolozane's 7-position side-chain provides enhanced activity against Gram-negative bacilli and is analogous to the aminothiazole rings found in ceftazidime and other extended-spectrum cephalosporins (Figs. 1, 2) [5, 18, 19]. The oxime group confers stability against β-lactamases and the attached dimethylacetic acid moiety provides improved antipseudomonal activity (Fig. 2) [5, 19, 20].

The distinction between ceftolozane and ceftazidime lies in the 3-position side-chain: a heavier, substituted pyrazole is present in ceftolozane in place of the lighter pyridinium substituent found in ceftazidime (Fig. 1). The pyrazole ring confers steric hindrance between ceftolozane and the entry gate to the 3-position side-chain binding pocket at the β-lactamase active site, thereby preventing hydrolysis and granting stability against AmpC β-lactamase-overproducing *P. aeruginosa*, against which ceftazidime has low activity [21].

The particular choices of substituents found on ceftolozane's pyrazole ring stems from early studies that examined the impact on antipseudomonal activity from modifying the pyrazole ring of FK518, a synthetic predecessor of ceftolozane [20]. Firstly, out of four FK518 derivatives synthesized, a 2-methylpyrazole group was noted to have the best antipseudomonal activity, demonstrated by a mean minimum inhibitory concentration (MIC) of 1.24 mg/L against 54 clinical *P. aeruginosa* isolates, and was chosen for subsequent modifications. Secondly, the basicity of the 3-position side-chain was positively correlated with improved outer membrane permeability, but with the caveat of having an increased convulsion-inducing potential. For example, a guanidino FK518 derivative [acid dissociation constant (pK_a) = 10.66] demonstrated potent antipseudomonal activity (mean MIC = 0.66 μg/mL) but with a very strong convulsion-inducing effect in mice, evidenced by an ED_{50} (the effective dose, dose required to achieve a pharmacological effect in 50 % of a population exposed to the drug) of 4.69 μg/head via intracerebroventricular injections. By introducing side-chains of varying basicity to position 4 of the pyrazole ring, ceftolozane (pKa = 7.95) was discovered to have the best balance of activity against AmpC β-lactamase-producing *P. aeruginosa* [MIC required to inhibit 50 % of isolates (MIC_{50}) = 0.5 mg/L; 196 clinical isolates] and the weakest convulsing-inducing effect (ED_{50}; 428 μg/head) in mice, weaker than that of ceftazidime and cefepime.

Tazobactam is a sulfone derivative of penicillanic acid [17]. Like other early β-lactamase inhibitors (e.g., clavulanic acid, sulbactam), the moiety at position 1 (a sulfone group in tazobactam) acts as a leaving group that promotes secondary ring opening at the β-lactamase active site, thereby facilitating covalent bond formation between tazobactam and the enzyme, and subsequently leading to irreversible inhibition [22, 23]. The presence of the triazole ring leads to improved 50 % inhibitory concentrations (IC_{50} values) against β-lactamases and lowered MICs against organisms producing class A and C β-lactamases as defined under the Ambler classification scheme [22].

3 Mechanism of Action

β-Lactams bear structural resemblance to a natural substrate of penicillin-binding proteins (PBPs), i.e., the dipeptide D-alanyl-D-alanine, allowing them to effectively bind these enzymes [24, 25]. At the PBP active site, a serine residue attacks the carbonyl carbon of the β-lactam, resulting in the formation of a covalent acyl-enzyme

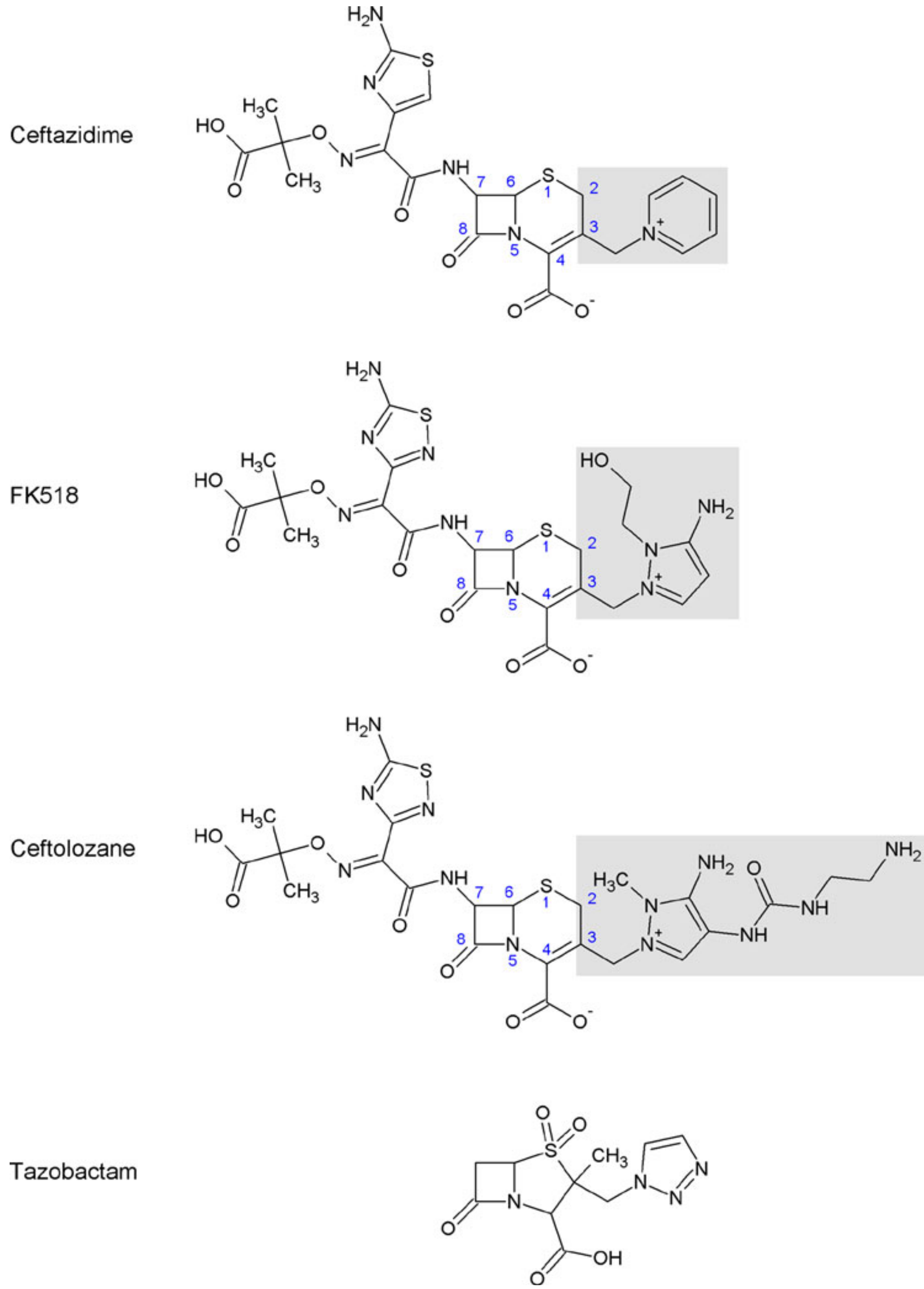

Fig. 1 Chemical structures of ceftazidime, FK518, ceftolozane, and tazobactam

complex that is slowly hydrolyzed [26]. PBP inhibition impairs peptidoglycan cross-linking, thereby leading to deregulation of bacterial cell wall synthesis and activation of cell lysis [24, 25].

A given bacterium possesses a variable number of PBPs, for which differences in binding affinities can arise among the β-lactams [17, 25]. The determination of PBP inhibition profiles is therefore important for establishing β-lactam activity against a given species. In the case of *P. aeruginosa*, the targets of β-lactams are the PBPs essential for cell viability, namely PBP1b, PBP1c, PBP2, and PBP3 [27]. Also noteworthy is the non-essential PBP, PBP4, whose inhibition triggers a highly efficient and complex β-lactam resistance response and hence serves as a trap target for β-lactams [27, 28].

Few studies have been conducted to evaluate the PBP inhibition profile of ceftolozane against common pathogens. Moya et al. [27] determined the binding affinity of ceftolozane to various PBPs of *P. aeruginosa* PAO1 by measuring IC_{50} values for each PBP and comparing them with those of ceftazidime and imipenem. Among the essential PBPs, ceftolozane was the most potent PBP1b and

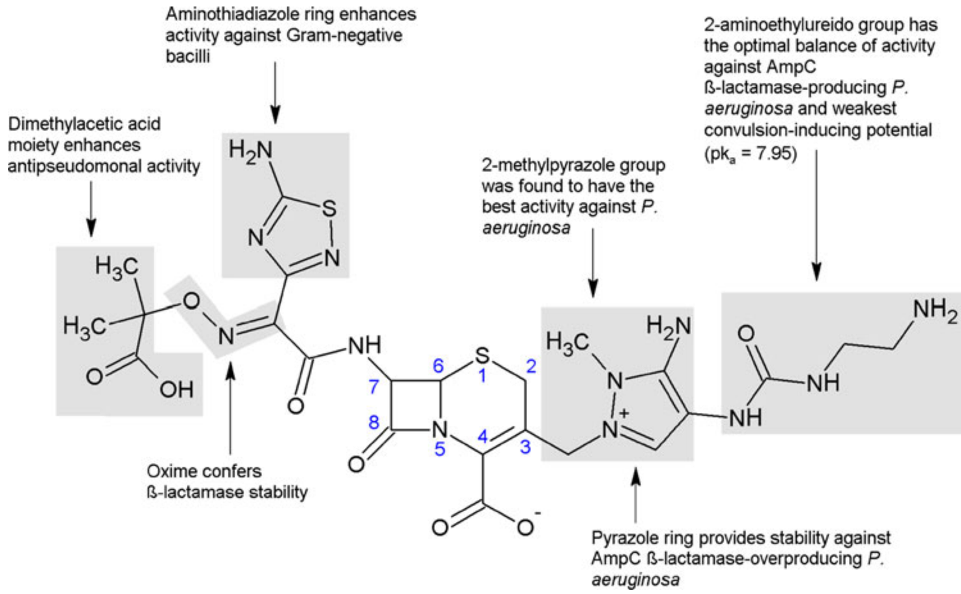

Fig. 2 Structure–activity relationships for ceftolozane (adapted from Toda et al. [20]). pK_a acid dissociation constant

PBP3 inhibitor (mean PBP1b $IC_{50} = 0.07 \pm 0.01$ mg/L; mean PBP3 $IC_{50} = 0.02 \pm 0.007$ mg/L) and demonstrated ≥2-fold higher affinities for all essential PBPs than ceftazidime. Imipenem was the most potent PBP1c and PBP2 inhibitor (mean PBP1c $IC_{50} = 0.08 \pm 0.005$ mg/L; mean PBP2 $IC_{50} = 0.08 \pm 0.01$ mg/L). Regarding PBP4 affinities, ceftolozane (mean $IC_{50} = 0.29 \pm 0.05$ mg/L) demonstrated a 15-fold lower and a fourfold higher affinity than those of imipenem (mean PBP4 $IC_{50} = 0.02 \pm 0.01$ mg/L) and ceftazidime (mean PBP4 $IC_{50} = 1.23 \pm 0.49$ mg/L), respectively. Data from the study's induction experiments suggests that ceftolozane's affinity for PBP4 is not significant enough to induce AmpC β-lactamase expression.

Tazobactam is an inhibitor of most class A β-lactamases (including many ESBLs) and some class C β-lactamases (cephalosporinases) under the Ambler classification scheme; its mechanism of inhibition is well-described [17, 22, 23, 29]. At the β-lactamase active site, tazobactam forms a stable imine acyl-enzyme complex that undergoes hydrolysis much more slowly than the complex formed by β-lactams to eventually free the enzyme (transient inhibition) [17]. Often referred to as an irreversible or "suicide" β-lactamase inhibitor, tazobactam actually undergoes multiple fates after the formation of this complex: (1) deacylation of the complex to regenerate the active enzyme and an inactive product; (2) tautomerization of the imine to form an enamine, also a reversibly inhibited enzyme; and (3) the formation of an irreversibly inactivated enzyme after a series of degradation reactions [23]. The functional inhibition of the enzyme is determined by the relative rates of each of these pathways [22].

4 Mechanism of Resistance

Early studies by Takeda et al. [13] evaluated the in vitro activities of ceftolozane and various comparators, providing insight on the activity of ceftolozane in strains with specific β-lactam resistance mechanisms as well as assessing the likelihood of ceftolozane inducing resistance.

The effects of classical β-lactamases and ESBLs on the activity of ceftolozane were examined by exposing a series of *Escherichia coli* strains bearing specific enzymes to ceftolozane, ceftazidime, and imipenem; MICs for each of these three agents against the host strain *E. coli* (strain C600) were 0.25 mg/L. The narrow-spectrum β-lactamases (TEM-1, TEM-2, SHV-1, OXA-1) had minimal effects on the activities of the three agents, while ESBLs (TEM-3, -4, -5, -6, -7, -8, -9; SHV-2, -3, -4; OXA-2; CTX-M-3, -18) reduced the activity of ceftolozane (MICs ranged from 1 to 32 mg/L) and, to a greater extent, ceftazidime (MICs ranged from 4 to >128 mg/L). The activity of imipenem was expectedly not affected by either narrow-spectrum β-lactamases or ESBLs. Against MBL-producing *P. aeruginosa*, neither ceftolozane nor its comparators were active (MIC ≥128 mg/L). Against the mutant *P. aeruginosa* strain PAO1456 (MIC = 1 mg/L), an overproducer of AmpC β-lactamases, a twofold reduction in the activity of ceftolozane was observed (MIC = 0.5 mg/L) with respect to the parent strain PAO4069, whereas a 16-fold reduction in activity was observed for ceftazidime (MIC = 32 vs. 2 mg/L), suggesting that ceftolozane demonstrates relatively high stability against AmpC β-lactamases.

A subsequent study [14] characterized this stability by subjecting AmpD-deficient strains of *P. aeruginosa*

(PAO1ΔAmpD) to ceftolozane and ceftazidime, operating under the principle that *ampD* inactivation leads to AmpC β-lactamase overproduction. Inactivation of the *ampD* gene had little effect on the activity of ceftolozane (MIC_{PAO1} = 0.5 mg/L vs. $MIC_{PAO1\Delta AmpD}$ = 1 mg/L) but significantly reduced that of ceftazidime (MIC_{PAO1} = 2 mg/L vs. $MIC_{PAO1\Delta AmpD}$ = 32 mg/L). Kinetic parameters of the AmpC β-lactamase were also measured to compare the hydrolysis efficiencies [catalytic rate constant (k_{cat})/Michaelis-Menten constant (K_m)] towards both agents. The catalytic constants against both cephalosporins were the same and notably low ($k_{cat} = 2.0 \times 10^{-3}\ s^{-1}$) but the K_m against ceftolozane (120 μmol/L) was substantially greater than that against ceftazidime (6 μmol/L), indicative of ceftolozane's poorer binding affinity for AmpC β-lactamases. Thus, the hydrolysis efficiency towards ceftolozane ($k_{cat}/K_m = 1.6 \times 10^{-5}$ μmol/L^{-1} s^{-1}) was significantly lower than that towards ceftazidime ($k_{cat}/K_m = 3.3 \times 10^{-4}$ μmol/L^{-1} s^{-1}).

The effects of increased expression of efflux pumps (MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY) and reduced expression of carbapenem-specific porins (OprD) on the activity of ceftolozane have also been examined in various studies, all of which concluded that ceftolozane remained unaffected by either of these resistance mechanisms [8, 13, 30, 31].

The modification of essential PBPs has been evaluated as a potential resistance mechanism in pan-β-lactam-resistant (PBLR) *P. aeruginosa* [8]. In this study, Moya et al. determined the PBP expression profiles of six clonally related pairs of susceptible and PBLR *P. aeruginosa* isolates and analyzed IC_{50} values of ceftolozane, ceftazidime, and imipenem in three of them. No differences in gene expression of PBPs were observed within susceptible–PBLR pairs, but PBP IC_{50} values revealed variations in binding affinities. The PBP3 IC_{50} values, for instance, were increased in PBLR isolates relative to their susceptible counterparts within their respective pairs for ceftolozane (0.07 ± 0.02 vs. 0.18 ± 0.13 mg/L), ceftazidime (0.12 ± 0.02 vs. 0.19 ± 0.02 mg/L), and imipenem (0.34 ± 0.06 vs. 0.69 ± 0.12 mg/L). Despite the increases in IC_{50} values, susceptibility testing revealed that ceftolozane maintained activity against all PBLR isolates (MICs ≤4 mg/L), in contrast to its comparators (tobramycin, ciprofloxacin, piperacillin/tazobactam, imipenem, ceftazidime, cefepime, aztreonam, meropenem) whose MICs were compromised several-fold.

The propensity of ceftolozane to select for resistant *P. aeruginosa* strains was examined by Takeda et al. [13]. In the first experiment, spontaneous mutational frequencies of ceftolozane and its comparators were calculated following the inoculation of agar plates with these agents at concentrations 4-, 8-, and 16-times their MICs against *P. aeruginosa* PAO1. No resistant mutants were selected on the agar plates containing ceftolozane, evidenced by mutational frequencies $<6.1 \times 10^{-9}$ at all tested concentrations. These values were less than those of ceftazidime and were less than or equal to those of imipenem and ciprofloxacin. In the second experiment, the development of antimicrobial resistance was assessed by subjecting PAO1 to a serial passage experiment. After five serial passages, ceftolozane demonstrated a fourfold reduction in susceptibility with a final MIC of 2 mg/L, while 16- to 32-fold reductions were observed for ceftazidime, imipenem, and ciprofloxacin. In the case of ceftazidime and imipenem, 8- to 16-fold reductions were observed following a single passage of the *P. aeruginosa* strain.

P. aeruginosa, in the context of CRIs, exhibits additional mechanisms that confer to it an extraordinary capacity to develop resistance to almost all available antimicrobials [15]. Noteworthy is its ability to reside within the lungs as biofilm structures and the selection of adaptive mutations that lead to its long-term persistence in CRIs, which include alginate hyperproduction, mediated by *mucA* inactivation, and defective DNA mismatch repair systems due to alterations in *mutS* or *mutL* genes [6, 32]. Riera et al. [6] evaluated the activity of ceftolozane and its comparators against biofilms of wild-type *P. aeruginosa* PAO1 and its mucoid (*mucA*), hypermutable (*mutS*), and mucoid-hypermutable mutant variants. Susceptibility testing revealed that neither the MICs nor minimum bactericidal concentrations of ceftolozane were significantly affected, in contrast to ceftazidime, meropenem and ciprofloxacin, which generated high numbers of resistant mutants. The spontaneous mutational frequencies of these agents at four and 16 times their MICs were also determined in the wild-type strain PAO1 and its hypermutable variant PAOMS. The mutational frequencies of ceftolozane's comparators were high, at four times their MICs for both strains (in the order of 10^{-7} for PAO1 and 10^{-4} to 10^{-5} for PAOMS). At 16 times their MICs, the mutational frequencies of ceftazidime were still high for both strains; that of meropenem was below the detection limit for PAO1 ($<5 \times 10^{-11}$) but high for PAOMS (1.3×10^{-7}); and that of ciprofloxacin was below the detection limit for PAO1 ($<5 \times 10^{-11}$) and was low for PAOMS (7.4×10^{-11}). In sharp contrast, the mutational frequencies of ceftolozane were below the detection limit ($<5 \times 10^{-11}$) at all concentrations tested for both strains, which suggests that resistance to ceftolozane cannot be driven by single-step mutations. These resistance data suggest that traditional β-lactam resistance mechanisms employed by *P. aeruginosa* do not result in resistance with ceftolozane/tazobactam. Further studies are required to understand what resistance mechanism(s) will be employed by *P. aeruginosa* to confer reduced susceptibility or resistance to ceftolozane/tazobactam.

5 Microbiology

The in vitro activities of ceftolozane/tazobactam and its comparators against various aerobes, anaerobes, drug-resistant *P. aeruginosa* phenotypes, and specific β-lactamase-producing *E. coli* and *K. pneumoniae* isolates are presented in Tables 1, 2, 3, and 4. The MIC values presented therein are derived from available in vitro studies conducted on ceftolozane and ceftolozane/tazobactam, whose data representing thousands of isolates were pooled and reviewed [10–13, 15, 16, 31, 33–57]. Comparator data were pooled from these same studies and are included in the tables when such data were available.

Table 1 shows the activities of ceftolozane/tazobactam and its comparators against common Gram-negative and Gram-positive aerobes [10, 12, 13, 15, 16, 31, 33–52]. The activity of ceftolozane against Gram-negative bacteria is either retained or enhanced upon the addition of tazobactam, with notable increases in activity observed against ceftazidime-resistant and ESBL-harboring Enterobacteriaceae. Against Gram-positive bacteria, ceftolozane is active versus *Streptococcus* spp., but has only limited activity versus *Staphylococcus* spp. The addition of tazobactam has little impact on the activity of ceftolozane against Gram-positive cocci.

Table 2 shows the activities of ceftolozane/tazobactam and ceftolozane alone against various anaerobes [16, 40, 53]. The addition of tazobactam produced lower MICs (mg/L) to inhibit 90 % of isolates (MIC_{90}) in most Gram-negative anaerobes, with the greatest reductions observed in some *Bacteroides* spp. and *Prevotella* spp. Among the Gram-positive anaerobes, ceftolozane/tazobactam demonstrated limited activity against *Clostridium* spp.

Table 3 shows the activities of ceftolozane/tazobactam and its comparators against *P. aeruginosa* and its various drug-resistant phenotypes [10, 11, 13, 15, 16, 31, 33, 34, 36, 38–40, 42, 46–48, 52, 54]. Tazobactam does not confer additional activity to the already potent antipseudomonal properties of ceftolozane. The extent to which resistance mechanisms expressed by *P. aeruginosa* reduce the activity of ceftolozane is limited (refer to Sect. 4 regarding the impact of specific resistance mechanisms on the activity of ceftolozane). These data show that ceftolozane/tazobactam is very active against *P. aeruginosa* strains, including a variety of drug-resistant phenotypes, including MDR. It should be noted that in *P. aeruginosa,* ceftolozane alone is active against AmpC-derepressed strains [58].

In Enterobacteriaceae, the addition of tazobactam to ceftolozane extends the activity of ceftolozane alone to include many ESBL producers and some AmpC-derepressed *Enterobacter* spp., while pathogens harboring carbapenemases, such as *K. pneumoniae* carbapenemases (KPCs) and MBLs, remain resistant [10, 12, 13, 43, 55, 58]. Livermore et al. [58] prepared MIC checkerboards with varying concentrations of ceftolozane and tazobactam against a panel of Enterobacteriaceae isolates that produced ESBLs (CTX-M, SHV, TEM, and PER-1), derepressed AmpC β-lactamases, KPC carbapenemases, and K1 enzymes. The addition of tazobactam to ceftolozane resulted in concentration-dependent reductions in MICs against ESBL-producing and AmpC-derepressed isolates: ceftolozane 8 mg/L and tazobactam 4 mg/L yielded susceptibilities of 76 % against ESBL-producing isolates and 70 % against AmpC-derepressed isolates, while ceftolozane 8 mg/L and tazobactam 8 mg/L yielded susceptibilities of 93 and 95 %, respectively. KPC producers remained resistant to the combination even at very high concentrations of tazobactam (>16 mg/L). Against K1-hyperproducing *Klebsiella oxytoca*, MICs were reduced from 4 to 2 mg/L by the addition of tazobactam. Table 4 shows the activities of ceftolozane/tazobactam and its comparators against *E. coli-* and *K. pneumoniae*-expressing specific β-lactamases [13, 43, 44, 55–57]. Because of the small number of individually tested strains expressing a given β-lactamase, with the exception of CTX-M-14 and CTX-M-15, the reader is cautioned that the MIC values presented are subject to variation. Regarding CTX-M-14 and CTX-M-15, the MIC values against these enzymes stem from a study [43] that evaluated the in vitro activity of ceftolozane with and without tazobactam against ESBL-producing *E. coli* and *K. pneumoniae*, most of which expressed the aforementioned β-lactamases. Against 108 *E. coli* isolates harboring CTX-M-15, only 2 % of the isolates were susceptible to ceftolozane (using a susceptibility breakpoint of ≤1 mg/L), while 95 % of the isolates were susceptible (using a susceptibility breakpoint of ≤1 mg/L) to ceftolozane/tazobactam. From the published data thus far, ceftolozane/tazobactam appears to be very active versus most ESBLs, including the common enzymes CTX-M-14 and CTX-M-15, but may be less active versus SHV ESBLs.

6 Pharmacokinetics

The results of three phase I pharmacokinetic studies are summarized in Table 5. They describe the pharmacokinetic parameters of ceftolozane upon intravenous administration alone and in combination with tazobactam in healthy adults [59–61].

Ge et al. [59] evaluated the pharmacokinetics of ceftolozane when administered alone in single doses, ranging from 250 to 2,000 mg, and when administered in multiple-dose regimens, consisting of 10-day courses of 500 mg every 8 h (q8h), 1,000 mg q8h, and 1,500 mg every 12 h (q12h). Ceftolozane demonstrated linear pharmacokinetics over the studied dosing range. The mean plasma half-life

Table 1 In vitro activities of ceftolozane/tazobactam[a] and comparators against Gram-negative and Gram-positive aerobes

Organism	Ceftolozane			Ceftolozane/tazobactam[a]			Ceftazidime		Cefepime		Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Gram-negative aerobes												
Acinetobacter baumannii	–[b]	–	–	0.5	2	≤0.12 to 16	8	16	–	–	–	–
Acinetobacter spp.	8	>32	≤0.12 to ≥32	8	>32	≤0.12 to ≥32	32	>32	16	16	–	–
Burkholderia cepacia	4	32	≤0.25 to >256	–	–	–	4	32	32	>32	–	–
Citrobacter spp. (all)	0.5	16	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32	0.25	64	≤0.5	1	0.12	>8
Ceftazidime-resistant[c]	32	>32	1 to >32	16	>16	0.25 to >16	>64	>64	1	16	32	>32
Enterobacter cloacae	0.25	32	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32	0.25	≥32	0.06	4	–	–
Enterobacter spp.	0.5	16	–	0.25	8	≤0.03 to ≥32	0.25	>32	≤0.5	4	0.25	>8
Ceftazidime-resistant[c]/non-susceptible	>32	>32	4 to >32	8	32	0.25 to >32	>32	>32	2	>16	>32	>32
Escherichia coli (all)	0.12	0.5	0.12 to >64	0.12	0.5	≤0.12 to >32	0.25	8	≤0.5	4	≤0.06	>8
Ceftazidime resistant[c]	>32	>32	1 to >32	1	16	≤0.12 to >16	64	>64	>16	>16	>32	>32
ESBL producers	64	>64	0.25 to >64	0.5	4	≤0.12 to >32	16	>32	>16	>16	>8	>8
Haemophilus influenzae	0.12	0.25	≤0.12 to 1	≤0.12	0.25	≤0.12 to 1	≤0.06	0.12	0.06	0.25	–	–
Klebsiella oxytoca	–	–	–	≤0.12	0.5	≤0.12 to 2	≤0.25	0.5	–	–	–	–
Klebsiella pneumoniae (all)	0.25	16	≤0.12 to >64	0.25	8	≤0.12 to ≥32	0.25	64	≤0.06	8	–	–
Ceftazidime-resistant[c]	>32	>32	4 to >32	4	>16	≤0.12 to >16	>64	>64	8	>16	>32	>32
ESBL producers	32	>64	2 to >64	0.5	64	≤0.12 to >64	32	–	–	–	–	–
KPC producers	>32	>32	32 to >32	>16	>16	16 to >16	>64	>64	>16	>16	>32	>32
Klebsiella spp. (all)	0.25	>32	–	0.25	4	0.12 to >32	0.12	32	≤0.5	>16	≤0.06	>8
ESBL producers	>32	>32	–	2	>32	0.12 to >32	32	>32	>16	>16	>8	>8
Moraxella catarrhalis	≤0.12	0.5	–	–	–	–	≤0.06	0.12	0.25	1	–	–
Proteus mirabilis (all)	0.25	0.5	≤0.12 to 16	0.25	0.5	≤0.12 to 16	0.06	0.25	≤0.06	0.12	≤0.06	2
ESBL producers	8	>32	≤0.25 to >32	1	8	0.25 to >16	≤4	>64	4	>16	8	>32
Proteus spp., indole-positive	–	–	–	0.25	1	0.12 to ≥32	0.12	16	≤0.5	≤0.5	≤0.06	4
Ceftazidime-resistant[c]	>32	>32	4 to >32	2	>16	0.25 to >16	64	>64	0.5	16	8	>32
Pseudomonas aeruginosa (all)	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128	2	32	4	32	–	–
Serratia marcescens	0.5	1	0.25 to ≥32	0.5	1	≤0.12 to ≥32	0.25	0.5	0.06	0.25	–	–
Serratia spp.	0.5	1	–	0.5	1	0.12 to ≥32	0.12	0.5	≤0.5	≤0.5	0.25	1
Stenotrophomonas maltophilia	–	–	–	16	>64	0.5 to >64	32	>32	>16	>16	–	–
Gram-positive aerobes												
Enterococcus faecalis	64	>64	–	–	–	–	>64	>64	>32	>32	–	–
Enterococcus faecium	64	>64	–	–	–	–	>64	>64	>32	>32	–	–
Staphylococcus aureus	32	32	16 to 64	32	64	4 to 128	8	32	2	16	–	–
Streptococcus agalactiae	0.5	0.5	≤0.12 to 0.25	0.5	0.5	≤0.12 to 0.5	0.5	0.5	0.12	0.12	–	–

Table 1 continued

Organism	Ceftolozane			Ceftolozane/tazobactam[a]			Ceftazidime		Cefepime		Ceftriaxone	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Streptococcus pneumoniae	≤0.12	4	≤0.12 to 16	≤0.12	8	≤0.12 to 16	0.25	8	≤0.06	1	–	–
Streptococcus pyogenes	≤0.12	≤0.12	≤0.12 to 0.25	≤0.12	≤0.12	≤0.12 to 2	0.12	0.12	≤0.06	≤0.06	–	–

Adapted from references [10, 12, 13, 15, 16, 31, 33–52]

ESBL extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemases, *MIC_{50}* minimum concentration (mg/L) to inhibit growth of 50 % of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90 % of isolates

[a] Fixed tazobactam concentration of 4 mg/L

[b] No data available. MIC_{90} not calculated when there were less than ten isolates

[c] Ceftazidime MIC ≥32 mg/L

($t_{½}$) was 2.3 h (range 1.9–2.6 h). The mean steady-state volume of distribution (V_{ss}) ranged from 13.1 to 17.6 L, which approximates human extracellular fluid volume [60]. The plasma protein binding of ceftolozane was 20 %. Clearance (CL) averaged 102.4 and 112.2 mL/min following single- and multiple-dose administration, respectively, and was primarily eliminated via urinary excretion (≥92 %). Minimal changes in the area under the plasma concentration–time curve (AUC) values and lack of drug accumulation were observed between days 1 and 10 of all multiple-dosing regimens.

Miller et al. [60] conducted a study to evaluate the pharmacokinetics of ceftolozane and tazobactam administered alone or in combination as a 2:1 ratio. In single-dose studies, ceftolozane and tazobactam were administered in doses from 500 to 2,000 mg and 250 to 1,000 mg, respectively. In multiple-dosing studies, 10-day regimens of ceftolozane 1,000 mg q8h, ceftolozane 1,500 mg q12h, tazobactam 500 mg q8h, tazobactam 750 mg q12h, ceftolozane/tazobactam 1,000/500 mg q8h, and ceftolozane/tazobactam 1,500/750 mg q12h were evaluated. In single-dose studies, ceftolozane had a mean plasma $t_{½}$ of 2.6 h (range 2.43–2.64 h), V_{ss} of 12.3 L (range 11.0–14.0 L), and CL of 5.1 L/h (range 4.35–5.81 L/h) with 100 % urinary excretion of unchanged drug. The pharmacokinetic profile of ceftolozane when coadministered with tazobactam was similar to that of ceftolozane when administered alone. Similarly, the pharmacokinetic profile of tazobactam when administered alone was unaffected when administered in combination with ceftolozane. The lack of an interaction is likely attributed to the fact that ceftolozane does not undergo significant renal tubular secretion, unlike piperacillin, and therefore inhibits tazobactam excretion [62]. Miller et al. [61] conducted a second phase I study in 16 healthy subjects assessing the pharmacokinetics, safety, and tolerability of ceftolozane/tazobactam at a higher dose of 2,000/1,000 mg q8h for 10 days compared to the 1,000/500 mg q8h regimen. The authors concluded that ceftolozane/tazobactam demonstrated linear pharmacokinetics and was safe and well-tolerated across the studied doses.

The influence of mild to moderate renal impairment on the pharmacokinetics of ceftolozane/tazobactam following a single 1,000/500 mg dose was investigated in a phase I study. [63]. In six subjects (mean age = 72.3 years, mean bodyweight = 65.4 kg) with mild renal impairment, defined as a creatinine clearance (CL_{CR}) of 60–89 mL/min, ceftolozane had a $t_{½}$ of 3.26 ± 0.35 h, V_{ss} of 11.9 ± 1.4 L, and CL of 3.27 ± 0.37 L/h. In seven subjects (mean age = 65.6 years, mean bodyweight = 83.9 kg) with moderate renal impairment (CL_{CR} 30–59 mL/min), ceftolozane had a $t_{½}$ of 6.31 ± 2.66 h, V_{ss} of 14.2 ± 3.1 L, and CL of 1.91 ± 0.74 L/h. The investigators observed linear

Table 2 In vitro activities of ceftolozane and ceftolozane/tazobactam[a] against anaerobes

Organism	Ceftolozane			Ceftolozane/tazobactam[a]		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Gram-negative anaerobes						
Fusobacterium spp.	≤0.12	16	≤0.12 to 16	≤0.12	0.25	≤0.12 to ≥256
Bacteroides caccae	64	>256	≤0.12 to >256	0.25	16	≤0.12 to 16
Bacteroides fragilis	>32	>32	≤0.12 to >256	1	4	≤0.12 to 256
Bacteroides ovatus	>256	>256	1 to >256	4	32	≤0.12 to >256
Bacteroides thetaiotaomicron	>256	>256	0.25 to >256	4	32	≤0.12 to >128
Bacteroides vulgatus	128	>256	0.25 to >256	4	32	<0.12 to >256
Parabacteroides distasonis	>256	>256	8 to >256	16	32	≤0.12 to 16
Other *Bacteroides* spp.[c]	8	>256	0.25 to >256	0.25	8	<0.12 to 128
Prevotella spp.	16	≥256	≤0.12 to ≥256	≤0.12	1	≤0.12 to 4
Gram-positive anaerobes						
Clostridium difficile	>256	>256	32 to >256	>256	>256	0.25 to >256
Clostridium perfringens	1	64	0.5 to 64	0.25	32	≤0.12 to 32
Clostridium spp.[d]	>256	>256	0.5 to >256	16	>256	≤0.12 to >256
Propionibacterium spp.	0.5	–[b]	≤0.12 to 16	≤0.12	–	≤0.12
Anaerobic Gram-positive cocci	4	16	≤0.12 to >256	2	8	≤0.12 to 64

Adapted from references [16, 40, 53]

MIC_{50} minimum concentration (mg/L) to inhibit growth of 50 % of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90 % of isolates

[a] Fixed tazobactam concentration of 4 mg/L

[b] MIC_{90} not calculated when there were less than ten isolates

[c] 2 *B. dorei*, 4 *P. goldsteinii*, 2 *B. intestinalis*, 1 *P. johnsonii*, 1 *P. merdae*, 1 *B. stercoris*, 1 non-speciated

[d] 3 *C. septicum*, 1 *C. subterminale*, 1 *C. tertium*, 1 *C. cadaveris*, 1 *C. clostridiforme*, 9 *Clostridium* spp.

pharmacokinetics for ceftolozane over the range of renal function studied and suggested that dose adjustments may be necessary in subjects with CL_{CR} <50 mL/min.

In population pharmacokinetic studies, ceftolozane was best described by a two-compartmental model with linear elimination [64, 65]. Inter-subject variability in central volume of distribution and systemic CL were explained by bodyweight and CL_{CR}, respectively. The presence of pyelonephritis and complicated lower urinary tract infections did not have significant effect on the pharmacokinetics of ceftolozane compared with that observed in healthy volunteers [65].

Chandorkar et al. [66] conducted a phase I study determining the extent to which ceftolozane/tazobactam penetrates into the pulmonary epithelial lining fluid (ELF). Fifty-one healthy adults received ceftolozane/tazobactam 1.5 g q8h via a 60-min infusion or piperacillin/tazobactam 4.5 g every 6 h (q6h) via a 30-min infusion for three doses. The mean maximum plasma concentration (C_{max}) and AUC over the dosing interval (AUC_{τ}) for ceftolozane were 67.2 ± 12.1 mg/L and 158.5 ± 24.1 mg·h/L, respectively, while the mean ELF C_{max} and AUC_{τ} were 21.8 mg/L and 75.1 mg·h/L, respectively. The ELF concentrations exceeded 8 mg/L for >60 % of the 8-h dosing interval. ELF penetration was measured by the calculation of ELF AUC to total plasma AUC ratios. Adjusting for the known plasma protein binding of 20 % for ceftolozane [67] and ~30 % for piperacillin, ratios of 0.59 and 0.38 were reported for ceftolozane and piperacillin, respectively.

7 Pharmacodynamics

The bactericidal activity of ceftolozane alone and in combination with tazobactam has been evaluated in various in vitro time-kill experiments. An early study by Brown et al. [68] tested ceftolozane against 65 isolates consisting of *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Streptococcus pneumoniae*, *Burkholderia cepacia*, and *Moraxella catarrhalis*. Ceftolozane demonstrated bactericidal activity against all isolates at four to eight times the MIC with 3-log_{10} reductions in bacterial counts within 6–8 h.

Jacqueline et al. [69] subjected four *E. coli* and four *K. pneumoniae* strains, including ESBL-producing isolates, and six ceftazidime- or imipenem-resistant *P. aeruginosa* strains to a fixed concentration of tazobactam (4 mg/L) with varying concentrations of ceftolozane (two to eight times the MIC) over 24 h. Bactericidal activity was

Table 3 In vitro activities of ceftolozane/tazobactam[a] and comparators against *Pseudomonas aeruginosa* and its various resistant phenotypes

P. aeruginosa phenotypes	Ceftolozane			Ceftolozane/tazobactam[a]			Ceftazidime		Cefepime	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
All	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128	2	32	4	32
Amikacin-resistant	1	32	≤0.5 to >32	2	–[b]	≤0.25 to >16	–	–	–	–
Aztreonam-resistant/non-susceptible	1	4	≤0.12 to >32	–	–	–	–	–	–	–
Cefepime-resistant/non-susceptible	1	4	≤0.12 to ≥128	4	–	2 to ≥16	–	–	–	–
Ceftazidime-resistant/non-susceptible	2	16	≤0.12 to ≥128	4	16	0.25 to >64	32	256	16	64
Ciprofloxacin-resistant	1	4	0.12 to ≥128	1	4	≤0.25 to >16	4	16	–	–
Doripenem non-susceptible	1	4	0.5 to >32	–	–	–	–	–	–	–
Gentamicin-resistant	1	4	≤0.12 to ≥128	1	4	≤0.25 to >16	–	–	–	–
Imipenem-resistant/non-susceptible	1	4	≤0.12 to ≥128	1	8	0.25 to >64	8	16	8	32
Levofloxacin-resistant/non-susceptible	1	4	0.25 to >32	–	–	–	–	–	–	–
Meropenem-resistant/non-susceptible	1	8	≤0.12 to ≥128	1	8	0.25 to >32	8	>32	8	>16
Piperacillin–tazobactam resistant/non-susceptible	2	4	≤0.12 to ≥128	2	4	0.5 to >64	32	128	16	32
Tobramycin-resistant	2	64	≤0.12 to ≥128	2	64	0.5 to >64	32	128	16	64
Ceftazidime- and imipenem non-susceptible	4	16	0.5 to >128	2	16	0.5 to >128	64	>128	16	>16
Ceftazidime- and meropenem non-susceptible	–	–	–	4	≥32	1 to ≥32	–	–	–	–
Multidrug-resistant[c]	2	16	0.12 to ≥128	1	2	0.5 to >64	64	256	16	64
Pan-β-lactam-resistant[d]	–	–	1 to 4	–	–	–	–	–	–	–

Adapted from references [10, 11, 13, 15, 16, 31, 33, 34, 36, 38–40, 42, 46–48, 52, 54]

MIC_{50} minimum concentration (mg/L) to inhibit growth of 50 % of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90 % of isolates

[a] Fixed tazobactam concentration of 4 mg/L

[b] No data available. MIC_{90} not calculated when there were less than ten isolates

[c] Resistant to ≥3 antimicrobials of different classes (ceftazidime, imipenem, piperacillin/tazobactam, ciprofloxacin/levofloxacin, tobramycin)

[d] Resistant to all of ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem

achieved against all Enterobacteriaceae strains and the majority of *P. aeruginosa* strains, with relatively moderate activity (1- to 1.3-$\log_{10}$ reduction) against the remaining *P. aeruginosa* strains.

Soon et al. [70] exposed four isogenic strains of *E. coli* with differing β-lactamase expression (none, AmpC, CMY-10, and CTX-M-15) to various combinations of ceftolozane (0–256 mg/L) and tazobactam (0–64 mg/L) over 48 h. Ceftolozane, at concentrations two to 16 times the MIC, and tazobactam demonstrated rapid, bactericidal activity against all tested strains, with increasing tazobactam concentrations enhancing the activity of ceftolozane against AmpC- and CMY-10-producing *E. coli*.

A neutropenic murine thigh infection model [71] was used to evaluate the in vivo efficacy of ceftolozane ± tazobactam. Mice were infected with various Gram-negative bacilli and were administered dosing regimens designed to simulate the percentage of time that the drug concentrations exceeded the MIC of the pathogen ($\%T_{>MIC}$) values that would be observed in humans when administered ceftolozane 1,000 mg q8h, ceftolozane/tazobactam 1.5 g q8h, and piperacillin/tazobactam 4.5 g q6h. Ceftolozane demonstrated ≥1-log reductions in bacterial density after 24 h against seven of the eight *P. aeruginosa* isolates studied, with the addition of tazobactam improving upon these reductions. Against four *K. pneumoniae* isolates, ceftolozane and ceftolozane/tazobactam produced changes ranging from >0.5-$\log_{10}$ increases to ≥1-$\log_{10}$ decreases against three ESBL producers, while ceftolozane produced significant reductions against the one non-ESBL producer in comparison with ceftolozane/tazobactam. Ceftolozane/tazobactam demonstrated the most in vivo activity against ESBL-producing *E. coli* isolates with reductions in bacterial density ranging from 1.2- to 1.5-log units. Overall, ceftolozane alone was the most effective agent against non-ESBL-producing

Table 4 In vitro activities of ceftolozane/tazobactam[a] and comparators against *Escherichia coli* and *Klebsiella pneumoniae* expressing specific β-lactamase enzymes

	β-lactamase enzyme	Number of isolates (*n*)	MIC (mg/L)		
			Ceftolozane	Ceftolozane/tazobactam[a]	Ceftazidime
E. coli					
Extended-spectrum β-lactamases	CTX-M-2	2	8 to 32	<0.25 to 4	–
	CTX-M-3	2	4 to 16	0.25	0.5 to 4
	CTX-M-14	30	<0.25 to >64	<0.25 to 4	–
	CTX-M-15	108	2 to >64	<0.25 to 64	–
	CTX-M-18	1	16	–	4
	OXA-1	2	0.25 to 0.5	0.25	0.25 to 0.5
	OXA-2	2	0.25 to 4	0.25	0.25 to 4
	OXA-3	1	0.5	0.5	1
	OXA-4	1	0.25	0.25	0.25
	OXA-5	1	32	0.5	128
	OXA-7	1	2	1	1
	SHV-1	2	0.25 to 0.5	0.5	0.25 to 1
	SHV-2	2	4 to 32	2	16 to 128
	SHV-3	1	32	–	>128
	SHV-4	2	16 to 64	16	128 to >128
	SHV-5	3	2 to 64	<0.25 to 2	>128
	SHV-12	7	2 to 16	<0.25 to 4	–
	TEM-1	2	0.12 to 0.25	0.25	0.25
	TEM-2	2	0.12 to 0.5	0.06	0.125 to 1
	TEM-3	2	0.5 to 1	0.25	8 to 32
	TEM-4	1	2	–	32
	TEM-5	1	32	–	32
	TEM-6	2	32 to 64	0.5	64 to >128
	TEM-7	1	32	–	64
	TEM-8	1	16	–	128
	TEM-9	2	32 to >128	8	32 to >128
	TEM-10	2	16 to 64	1 to 16	>128
Carbapenemases	NMC-A	1	0.25	0.12	0.25
	PER-1	1	>128	16	>128
Metallo-β-lactamases	IMP-1	2	32 to >128	32	16 to >128
K. pneumoniae					
Extended-spectrum β-lactamases	CTX-M-2	1	8	<0.25	–
	CTX-M-14	6	2 to 32	<0.25 to 1	–
	CTX-M-15	11	16 to >64	<0.25 to >64	–
	SHV-5	3	8 to >64	<0.25 to 64	–
	TEM-29	1	>64	32	–
	SHV-1, TEM-10	1	>64	8	–
	SHV-1, TEM-26	1	>64	16	–
AmpC β-lactamases	AmpC, CTX-M-3	1	32 to 64	1	–

Adapted from references [13, 43, 44, 55–57]

MIC minimum inhibitory concentration (mg/L)

[a] Fixed tazobactam concentration of 4 mg/L

[b] No data available

Table 5 Pharmacokinetic parameters of ceftolozane and ceftolozane/tazobactam from phase I studies in healthy human adults

Study	Total number of subjects	Subject demographics	*n*	Ceftolozane/tazobactam dose (mg)[a]	C_{max} (mg/L)[b]	AUC (mg·h/L)[b]	$t_{½}$ (h)[b]	CL (L/h)[b]	V_{ss} (L)[b]
Ge et al. [59]	64	30 healthy adults: 17 males, 13 females Mean age (years): 33.1 (range 19–59) Mean weight (kg): 74.1 (range 58.1–96.5)	6	250/0 × 1 dose	16.5 ± 2.6	40.1 ± 3.4	1.86 ± 0.18	6.23 ± 0.53	13.1 ± 2.0
			6	500/0 × 1 dose	32.2 ± 3.9	84.1 ± 12.1	2.34 ± 0.83	5.95 ± 0.86	14.8 ± 3.3
			6	1,000/0 × 1 dose	58.4 ± 18.4	152.1 ± 30.0	2.25 ± 0.36	6.58 ± 1.30	16.3 ± 4.2
			6	1,500/0 × 1 dose	87.4 ± 7.0	242.8 ± 20.2	2.62 ± 0.36	6.18 ± 0.51	17.6 ± 2.2
			6	2,000/0 × 1 dose	127.7 ± 15.0	344.2 ± 77.4	2.45 ± 0.55	5.81 ± 1.31	14.8 ± 1.4
		18 healthy adults: 13 males, 5 females Mean age (years): 35.2 (range 22–55) Mean weight (kg): 75.3 (range 60.2–93.5)	6	500/0 q8h × 10 days	33.3 ± 5.3	82.9 ± 17.1	2.20 ± 0.39	6.04 ± 1.24	14.0 ± 2.7
			6	1,000/0 q8h × 10 days	58.0 ± 6.0	143.3 ± 22.0	2.69 ± 0.65	6.98 ± 1.08	17.1 ± 2.3
			6	1,500/0 q12h × 10 days	82.6 ± 13.1	207.0 ± 32.9	2.34 ± 0.11	7.25 ± 1.15	18.1 ± 2.6
Miller et al. [60]	58	18 healthy adults: 10 males, 8 females Mean age (years): 38.4 (range 25–59) Mean weight (kg): 71.4 (range 59.6–95.9)	6	500/0 × 1 dose	42.6 ± 5.8	98.6 ± 16.1	2.48 ± 0.20	5.18 ± 0.79	11.8 ± 1.6
			6	500/250 × 1 dose	40.2 ± 5.1	97.3 ± 14.6	2.43 ± 0.46	5.23 ± 0.69	11.7 ± 1.6
			6	1,000/0 × 1 dose	92.3 ± 11.9	230 ± 13	2.64 ± 0.52	4.35 ± 0.26	11.0 ± 2.1
			6	1,000/500 × 1 dose	90.2 ± 9.6	209 ± 19	2.58 ± 0.48	4.82 ± 0.50	11.8 ± 1.9
			6	2,000/0 × 1 dose	153 ± 17	375 ± 62	2.62 ± 0.44	5.43 ± 0.74	13.3 ± 2.0
			6	2,000/1,000 × 1 dose	140 ± 21	353 ± 64	2.62 ± 0.48	5.81 ± 0.90	14.0 ± 2.6
		40 healthy adults: 28 males, 12 females Mean age (years): 34.2 (range 21–62) Mean weight (kg): 81.3 (range 55.9–93.7)	5	1,000/0 q8h × 10 days	73.4 ± 11.1	195 ± 30	2.73 ± 0.66	5.54 ± 0.74	13.4 ± 2.4
			10	1,000/500 q8h × 10 days	74.4 ± 10.1	197 ± 33	3.12 ± 0.68	5.58 ± 0.70	14.2 ± 2.4
			5	1,500/0 q12h × 10 days	110 ± 14	266 ± 54	2.48 ± 0.73	5.88 ± 1.02	13.0 ± 1.2
			10	1,500/750 q12h × 10 days	124 ± 14	313 ± 30	3.18 ± 0.43	4.97 ± 0.53	12.2 ± 1.4
Miller et al. [61]	16	Demographic details not provided	4	1,000/500 q8h × 10 days	60 (54–63)	144 (130–162)	2.1 (2.1–2.7)	7.0 (6.2–7.7)	17.1 (15.2–19.0)
			8	2,000/1,000 q8h × 10 days	117 (85–128)	301 (245–343)	2.7 (2.4–3.6)	6.7 (5.8–8.2)	17.6 (15.9–21.4)

AUC area under the plasma concentration–time curve, *CL* clearance, C_{max} maximum plasma concentration, *q8h* every 8 h, *q12h* every 12 h, $t_{½}$ elimination half-life, V_{ss} volume of distribution at steady-state

[a] 1-h intravenous infusion

[b] Mean ± standard deviation or median (range)

isolates, with the addition of tazobactam extending its activity to include ESBL producers.

A second murine thigh infection model study [57] was used to study the pharmacodynamics of ceftolozane and the index that was best correlated with in vivo efficacy. Mice infected with non-ESBL-producing strains of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were treated with ceftolozane in varying doses from 3.12 to 1,600 mg/kg and intervals of 3, 6, 12, and 24 h for 24 h. Antimicrobial activity, as determined by bacterial counts in the thigh at the end of treatment, was best correlated with the $\%T_{>\mathrm{MIC}}$ ($R^2 = 0.62$ for *E. coli*, $R^2 = 0.61$ for *K. pneumoniae*). Bacteriostasis and 1-$\log_{10}$ bacterial kill against wild-type Enterobacteriaceae and *P. aeruginosa* were observed at $\%T_{>\mathrm{MIC}}$ values of 25.2 ± 2.8 % and 31.5 ± 2.8 %, respectively. This study also compared the efficacy of regimens consisting of ceftolozane alone and in combination with tazobactam in 2:1, 4:1, and 8:1 ratios in mice infected with ESBL-producing Enterobacteriaceae. The 2:1 combination was the most active and the only to differ from ceftolozane alone in efficacy.

VanScoy et al. [72] found that $\%T_{>\mathrm{MIC}}$ was also most predictive of tazobactam efficacy in combination with ceftolozane. In an in vitro model, three isogenic *E. coli* strains of differing levels of CTX-M-15 expression were subjected to ceftolozane/tazobactam regimens that simulated human exposure. Tazobactam administered in 6- and 8-h dosing intervals, with a fixed 8-h dosing of ceftolozane, yielded the greatest bacterial kill (>2-$\log_{10}$ reduction at 24 h). $\%T_{>\mathrm{MIC}}$ values of 35, 50, and 70 % were associated with bacteriostasis and 1- and 2-$\log_{10}$ bacterial kill, respectively, at 24 h. A follow-up study [73] simulated six regimens of ceftolozane–tazobactam (2:1) administered q8h for 10 days in a hollow-fiber infection model and concluded that regimens of 750/375 mg q8h and higher prevented the amplification of drug resistance in *E. coli* and eradicated antimicrobial-resistant subpopulations.

8 Animal Studies

The efficacy of ceftolozane with or without tazobactam has been evaluated in various animal infection models.

Takeda et al. [13] evaluated the in vivo efficacy of ceftolozane using pulmonary, urinary tract, and burn wound infections in neutropenic mice caused by *P. aeruginosa.* Ceftolozane was demonstrated to be effective in all infection models and was either comparable or superior to its comparators, ceftazidime and imipenem, as measured by reductions in bacterial density following treatment. In the pulmonary infection model, anesthetized mice were intranasally inoculated with 3.30 $\log_{10}$ colony forming units (CFU) of *P. aeruginosa* strain 93 and were administered ceftolozane, ceftazidime, or imipenem subcutaneously twice daily at either 2 or 10 mg/kg/dose starting 3 h after infection for 3 days. At the end of treatment, ceftolozane was highly effective in both dosing regimens, yielding similar efficacy to that of imipenem and statistically significantly better efficacy than that of ceftazidime. Lung bacterial counts in the untreated control group increased to 6.93 $\log_{10}$ CFU/lung, while those of the 2 mg/kg/dose treatment groups decreased to ~3.4, ~4.9, and ~3.2 $\log_{10}$ CFU/lung for ceftolozane, ceftazidime, and imipenem, respectively. In the urinary tract infection model, female mice were inoculated with 4.32 $\log_{10}$ CFU of *P. aeruginosa* strain 93 and, 5 h later, received twice-daily subcutaneous injections of ceftolozane and comparators at 0.5 or 2 mg/kg/dose for 2 days. At the end of treatment, bacterial counts in the kidneys increased to ~8.0 $\log_{10}$ CFU/kidney in the untreated control group, while those of the 0.5 mg/kg/dose treatment groups decreased to ~4.5, ~5.6, and ~6.1 $\log_{10}$ CFU/kidney for ceftolozane, ceftazidime, and imipenem, respectively. In the burn wound infection model, male mice received ethanol flame burn injuries to their backs followed by inoculation with 4.60 $\log_{10}$ CFU of *P. aeruginosa* strain 93 into the burn site; 10 and 50 mg/kg of ceftolozane and its comparators were administered twice daily intravenously starting 3 h after infection for a total of 3 days. At the end of treatment, bacterial counts from the burn lesions increased to ~8.1, ~7.6, and ~6.8 $\log_{10}$ CFU/site in the untreated control group, ceftazidime, and imipenem (10 mg/kg dosing regimens) groups, respectively, while those of the ceftolozane group decreased to ~4.3 $\log_{10}$ CFU/site.

Jacqueline et al. investigated the efficacy of ceftolozane in a pulmonary infection model in two studies [74, 75]. In a murine model of acute pneumonia [74], mice inoculated transtracheally with *P. aeruginosa* were assigned to an untreated control group or one of three 2-day treatment regimens: subcutaneous ceftolozane 180 mg/kg q8h, ceftazidime 200 mg/kg q8h, or piperacillin/tazobactam 400 mg/kg q8h, each designed to achieve similar AUC values obtained in humans after typical dosing. After 48 h of treatment, ceftolozane demonstrated greater bactericidal efficacy in affected lungs (3.44 $\log_{10}$ CFU/g reduction) than ceftazidime (2.31 $\log_{10}$ CFU/g reduction) and piperacillin/tazobactam (2.01 $\log_{10}$ CFU/g reduction). The survival rate of the mice treated with ceftolozane was noted to significantly improve after 24 and 36 h of treatment in comparison with ceftazidime and piperacillin/tazobactam, although the differences in survival between the untreated control and treated mice were not statistically significant after 48 h. In the second study [75], pneumonia was induced in rabbits via endobronchial inoculation of *P. aeruginosa* and antimicrobials were initiated starting 5 h post-infection for 2 days. Treatment regimens included human equivalent doses of ceftolozane 1 g q8h, ceftolozane 2 g q8h, ceftazidime 2 g q8h, piperacillin/tazobactam 4/0.5 g q6h, and imipenem 1 g q8h. After 48 h of treatment, significant reductions in lung and spleen bacterial counts were observed all treatment groups except piperacillin/tazobactam, which failed to produce significant reductions in either.

The ED_{50} of ceftolozane with or without tazobactam was investigated as a measure of in vivo efficacy in two murine sepsis model studies [76, 77]. In the first study [76], mice were infected intraperitoneally with one of three strains of *E. coli*, two of which were ESBL-producing isolates, and were administered ceftolozane, ceftolozane/tazobactam (2:1), ceftazidime, or piperacillin/tazobactam (8:1) at concentrations ranging from 0.01 to 300 mg/kg at 2, 4, and 6 h after infection. After 5 days of observation, all tested β-lactams demonstrated similar in vivo efficacy against the one non-ESBL-producing strain (ED_{50} ranged from 0.4 to 0.9 mg/kg) except for piperacillin/tazobactam ($ED_{50} = 14.7$ mg/kg). Against the two ESBL-producing strains, ceftolozane/tazobactam was active against both (ED_{50}; 25.9 and 25.5 mg/kg) and ceftazidime was active against one (ED_{50}; 25.6 and 263.3 mg/kg), whereas ceftolozane alone (ED_{50}; 192.3 and 123.3 mg/kg) and piperacillin/tazobactam (both ED_{50} values >300 mg/kg) were much less active. In the second study [77], mice were infected intraperitoneally with one of three strains of *K. pneumoniae*, two of which were ESBL-producing isolates and one of which was ceftazidime-resistant, and were treated with the same agents used in the first study. The conclusions were similar: the in vivo efficacies among all agents, except piperacillin/tazobactam, were comparable against the non-ESBL-producing strain; and the addition of tazobactam to ceftolozane enhanced its efficacy such that this was the only treatment active against both ESBL-producing strains. Both studies noted that tazobactam exhibits a particularly short $t_{1/2}$ in mice, which suggests that the efficacy of ceftolozane/tazobactam may have been underestimated.

In conclusion, the efficacy of ceftolozane with or without tazobactam has been evaluated in various animal infection models including lung, urinary tract, burn wound, sepsis, and thigh. Ceftolozane, with or without tazobactam, has been demonstrated to provide efficacy similar to or superior to that of other β-lactams.

9 Clinical Trials

Cubist Pharmaceuticals, Inc. has completed two phase II trials that evaluated the efficacy of ceftolozane in the treatment of cUTIs and ceftolozane/tazobactam in the treatment of cIAIs (Table 6).

A prospective, multicenter, double-blind randomized (2:1) study assessed the safety and efficacy of ceftolozane 1,000 mg q8h and ceftazidime 1,000 mg q8h, both administered for 10 days, in the treatment of cUTI, including pyelonephritis (NCT00921024) (Table 6) [78]. The inclusion criteria comprised males and females aged 18–90 years who demonstrated pyuria and clinical signs and/or symptoms of either pyelonephritis or complicated lower urinary tract infection. Exclusion criteria included a history of hypersensitivity to any β-lactam; concomitant infection requiring systemic therapy at the time of randomization; complete, permanent obstruction of the urinary tract; confirmed fungal urinary tract infection; suspected or confirmed perinephric or intrarenal abscess; suspected or confirmed prostatitis; ileal loop or viscera-ureteral reflux; and pregnant or nursing women. 129 patients were initially enrolled in the study, with 86 in the ceftolozane treatment arm and 43 in the ceftazidime treatment arm. Two patients, one from each treatment arm, discontinued their respective study drug as a result of adverse effects (see Sect. 10). The primary outcome measure was the microbiological response at the test-of-cure (TOC) visit, i.e., 6–9 days after the end of treatment, in the microbiological modified intention-to-treat (mMITT)[1] and the microbiologically evaluable (ME)[2] populations. The secondary outcome measures included determining the safety of ceftolozane, the clinical response at the TOC visit and the pharmacokinetic profile of ceftolozane in subjects with cUTI. Microbiological cure rates were 83.1 % (54/65) for ceftolozane and 76.3 % (29/38) for ceftazidime in the mMITT population, and 85.5 % (47/55) for ceftolozane and 92.6 % (25/27) for ceftazidime in the ME population. The microbiological eradication[3] rates at the TOC in subjects with *E. coli*, the most common pathogen isolated, were 91.7 % for ceftolozane and 94.7 % for ceftazidime. Clinical response rates at the TOC visit were 90.8 % (59/65) for ceftolozane and 92.1 % (35/38) for ceftazidime in the mMITT population, and 92.7 % (51/55) for ceftolozane and 100 % (27/27) for ceftazidime in the ME population. A late follow-up visit 3–4 weeks post-treatment revealed sustained clinical cure rates of 98.0 % for the ceftolozane

[1] mMITT population: all randomized subjects who received any amount of study drug and had at least one acceptable causative pathogen from a study-qualifying pretreatment baseline urine specimen.

[2] ME population: subjects in the mMITT population who met the minimal disease criteria, had no protocol deviation likely to impact the microbiological outcome, received an appropriate duration of study drug therapy, had an interpretable urine culture at the TOC visit, and attended the TOC visit (or was classified as a microbiological failure before the TOC visit).

[3] Microbiological eradication: a urine culture with $\geq 10^5$ CFU/mL of the uropathogen at baseline that has been reduced to $<10^4$ CFU/mL at the TOC visit.

Table 6 Clinical trials of ceftolozane alone and ceftolozane/tazobactam

Trial description	Number of patients	Treatment regimens	Primary outcome measures	Secondary outcome measures	Clinicaltrials.gov identifier number
Phase II treatment of cUTI, including pyelonephritis [78]	129	Ceftolozane 1,000 mg IV, q8h × 7–10 days Ceftazidime 1,000 mg IV, q8h × 7–10 days	Microbiological response at the TOC visit in the mMITT and ME populations *Eradication rates at TOC* / *mMITT population* / *ME population* Ceftolozane 83.1 % 85.5 % Ceftazidime 76.3 % 92.6 %	Safety and pharmacokinetics of ceftolozane, clinical response at the TOC visit *Clinical cure rates at TOC* / *mMITT population* / *ME population* Ceftolozane 90.8 % 92.7 % Ceftazidime 92.1 % 100.0 %	NCT00921024
Phase II treatment of cIAI [79]	122	Ceftolozane/tazobactam 1.5 g + metronidazole 500 mg IV, q8h × 7–14 days Meropenem 1,000 mg IV, q8h × 7–14 days	Clinical response at the TOC visit in the mMITT and ME populations *Clinical cure rates at TOC* / *mMITT population* / *ME population* Ceftolozane/tazobactam 83.6 % 88.7 % Meropenem 96.0 % 95.8 %	Safety of ceftolozane/tazobactam + metronidazole Pharmacokinetics of ceftolozane/tazobactam Microbiological response at the TOC visit in the ME population	NCT01147640
Phase III treatment of cUTI, including pyelonephritis	525	Ceftolozane/tazobactam 1.5 g IV, q8h × 7 days Levofloxacin 750 mg IV, once daily × 7 days	Microbiological outcome of eradication and clinical outcome of cure	Proportion of subjects in each treatment group reported as a clinical cure, failure, or indeterminate, and as a microbiological eradication, persistence, or indeterminate for each unique pathogen and overall Safety as evaluated by adverse events, laboratory evaluations, vital signs, and physical examinations	NCT01345955 NCT01345929
Phase III treatment of cIAI	~500	Ceftolozane/tazobactam 1.5 g + metronidazole 500 mg IV, q8h × 4–14 days Meropenem 1,000 mg IV, q8h × 4–14 days	Clinical outcome of cure	Proportion of subjects with the microbiological outcome of success; clinical outcome of cure, failure, or indeterminate, and microbiological outcome of success at the end of therapy and late follow-up Safety as evaluated by adverse events, laboratory evaluations, vital signs, and physical examinations	NCT01445665 NCT01445678
Phase III treatment of ventilator-associated pneumonia	~300	Ceftolozane/tazobactam 3 g IV, q8h Piperacillin–tazobactam 4.5 g IV, q6h	Clinical response at the end of therapy visit in the mITT population	None provided	NCT01853982

cIAI complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *IV* intravenous, *ME* microbiologically evaluable, *mITT* modified intention-to-treat, *mMITT* microbiological modified-intention-to-treat, *q6h* every 6 h, *q8h* every 8 h, *TOC* test-of-cure group and 92.6 % for the ceftazidime group. Neither microbiological cure rates nor clinical rates were significantly different between therapies. Adverse effects occurred in 47.1 % (40/85) of subjects receiving ceftolozane and 38.1 % (16/42) of subjects receiving ceftazidime ($p > 0.5$).

A second phase II, prospective, multicenter, double-blind randomized (2:1) study compared ceftolozane/tazobactam 1.5 g q8h and metronidazole 500 mg q8h with meropenem 1 g q8h in the treatment of cIAI in adult subjects (NCT01147640) (Table 6). The inclusion criteria comprised males and females aged 18–90 years who had cIAI requiring surgical intervention, and a diagnosis of cholecystitis (including gangrenous) with rupture or perforation, diverticular disease with perforation or abscess, appendiceal perforation or peri-appendiceal abscess, acute gastric or duodenal perforation (only if operated on >24 h after the occurrence), traumatic perforation of the intestine (only if operated on >12 h after the occurrence), peritonitis due to a perforated viscus, intra-abdominal infection following a prior operative procedure, postoperative peritonitis, or intra-abdominal abscess. Exclusion criteria included simple cholecystitis, simple appendicitis, or small bowel obstruction without perforation or rupture; abscesses of the abdominal wall; acute suppurative cholangitis; infected, necrotizing pancreatitis or pancreatic abscess; the need for concomitant systemic antimicrobials; previous use of carbapenems or cefepime for the current cIAI; any rapidly progressing diseases or life-threatening illnesses; impaired renal function (CL_{CR} <50 mL/min); and pregnant or nursing women. The primary outcome measure was to determine the clinical response of both treatment regimens at the TOC visit, i.e., 7–14 days following treatment, in the mMITT and ME populations. Secondary outcome measures included determining the microbiological response of both treatments, describing the safety profile of ceftolozane/tazobactam and metronidazole, and evaluating the pharmacokinetics of ceftolozane/tazobactam. In this study of patients with cIAI, clinical cure rates were 83.6 % (51/61) for ceftolozane/tazobactam and 96.0 % (24/25) for meropenem in the mMITT population and 88.7 %, (47/53) and 95.8 %, (23/24), respectively, for the ME population. Against *E. coli*, the most common pathogen, microbiological success was observed for 89.5 % (34/38) of patients in the ceftolozane/tazobactam group and 94.7 % (18/19) of patients in the meropenem group (ME population).

Ceftolozane/tazobactam is currently being studied in three phase III trials, one of which has been completed as of July 2013; however, results are not yet available (Table 6). In the first study, 525 subjects were randomized to one of two treatment arms, ceftolozane/tazobactam 1.5 g q8h or levofloxacin 750 mg once daily, for the treatment of cUTI including pyelonephritis (NCT01345955, NCT01345929). Another study compared ceftolozane/tazobactam 1.5 g q8h and metronidazole 500 mg q8h versus meropenem 1 g q8h for the treatment of cIAI (NCT01445665, NCT01445678). In the third study, ceftolozane/tazobactam 3 g q8h was compared with piperacillin/tazobactam 4.5 g q6h for the treatment of VABP (NCT01853982); in addition, a fourth trial comparing ceftolozane/tazobactam 3 g q8h versus imipenem/cilastatin 1 g q8h is being planned in this setting. Thus, currently ceftolozane/tazobactam is being dosed at 1.5 g q8h for cUTI and cIAI, and 3 g q8h in VABP.

10 Adverse Effects

The safety and tolerability of ceftolozane/tazobactam from phase I and phase II studies were reviewed. Drug-related adverse events were infrequent and considered mild in severity across 189 healthy subjects in four phase I pharmacokinetic studies. Following single doses of ceftolozane (250–2,000 mg) alone or ceftolozane/tazobactam (500/250–2,000/1,000 mg), 23 adverse events were reported as mild and included abdominal pain, nausea, headache, paresthesia, somnolence, vulvovaginal pruritus, and constipation [59, 60]. Three episodes of clinically significant asymptomatic hypoglycemia were documented but were attributed to variation in blood glucose normally seen in healthy subjects at different stages of fasting. One occurrence of generalized body aches was reported as moderate [60]. Following 10-day multiple-dose regimens of ceftolozane with or without tazobactam up to 3,000/1,500 mg/day, adverse events included nausea, vomiting, hypoesthesia, paresthesia, flushing, menstrual cramps, and intravenous infusion-related events (pruritus, erythema). A single occurrence of menstrual cramps was reported as moderate in severity while the remaining events were all reported as mild, of which infusion site-related events were the most common [59, 60]. In the trial by Miller et al. assessing ceftolozane/tazobactam 2,000/1,000 mg q8h for 10 days, one subject withdrew from the study as a result of treatment-related mild intermittent vomiting, nausea, flushing, and leg aches [61]. In the trial that compared the intrapulmonary penetration of ceftolozane/tazobactam and piperacillin/tazobactam, the incidence of adverse events was similar between both treatment groups [66]. In the ceftolozane/tazobactam treatment arm, all adverse events were mild in severity and included single occurrences of diarrhea, viral upper respiratory tract infection, musculoskeletal chest pain, somnolence, hematuria, and cough [66]. The nature and incidence of the adverse events reported in these phase I studies did not appear to be dose dependent nor were dose-limiting toxicities identified. No serious adverse events or deaths were reported.

In a phase II clinical trial comparing the efficacy of ceftolozane versus ceftazidime in adults with cUTIs, at least one treatment-emergent adverse event (TEAE) was reported by 47.1 % (40/85) and 38.1 % (16/42) of subjects receiving ceftolozane and ceftazidime, respectively ($p > 0.5$) [78]. TEAEs occurring in $\geq$3 % of subjects who received ceftolozane included constipation, diarrhea, headache, infusion site irritation, insomnia, nausea, pyrexia, and sleep disorder. The incidence and patterns of adverse events were generally similar between both treatment groups. TEAEs assessed as serious or severe in the ceftolozane treatment arm included single occurrences of recurrent pyelonephritis, abdominal pain, and worsening anemia, all of which were deemed unrelated to study treatment. Two subjects, one in each treatment arm, discontinued their respective study drug as a result of adverse events: the subject who received ceftolozane had a decreasing CL_{CR} to <50 mL/min by the third day of treatment, while the subject who received ceftazidime experienced vomiting and diarrhea. In a phase II clinical trial comparing the efficacy and safety of ceftolozane/tazobactam and meropenem in adults with cIAI, the incidence of adverse events was similar between treatment groups (50 vs. 48.8 %) and, overall, ceftolozane/tazobactam was well-tolerated in these patients [79].

Based on limited phase I and II data, the adverse effect profile of ceftolozane/tazobactam does not appear to be different to other β-lactams. Ongoing clinical trials are required to fully elucidate the adverse effect profile of ceftolozane/tazobactam, including whether it is associated with *Clostridium difficile* infection.

11 Place of Ceftolozane/Tazobactam in Therapy

Ceftolozane/tazobactam demonstrates in vitro activity that extends beyond that of currently marketed cephalosporins to include ESBL-producing Enterobacteriaceae and drug-resistant *P. aeruginosa*, all the while possessing a safety and tolerability profile with which clinicians are familiar, based on their experience with other β-lactams. These attributes make ceftolozane/tazobactam a suitable contender as one of the hoped for "10 × '20" antimicrobials in combating the growing threat of resistant ESKAPE pathogens. Ceftolozane/tazobactam provides clinicians with an alternative option for the empiric treatment of serious infections caused by Gram-negative bacilli, although the lack of activity versus isolates harboring KPC or MBL enzymes remains a limitation. Against *P. aeruginosa*, an organism known to be intrinsically resistant to many antimicrobial classes and capable of acquiring resistance during therapy, ceftolozane/tazobactam possesses particularly potent activity relative to currently available antipseudomonal agents. The excellent ELF penetration combined with potent activity against *P. aeruginosa* makes ceftolozane/tazobactam a potentially extremely important compound for treatment of hospital- and ventilator-acquired pneumonia. Even in the context of CRIs in cystic fibrosis patients, in which *P. aeruginosa* possesses further capacity to develop antimicrobial resistance, ceftolozane retains its in vitro activity, thus providing a potential avenue for future clinical investigation. Phase III trials are currently underway in the settings of cIAIs, cUTIs, and ventilator-associated pneumonia. These studies will help to further define the safety and efficacy of ceftolozane/tazobactam, and the role of this novel antibacterial.

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