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New antimicrobial alternatives in the treatment of pneumonia

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Ceftolozane-tazobactam in nosocomial pneumonia

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ABSTRACT

Ceftolozane is a potent antimicrobial against *Pseudomonas aeruginosa*, including carbapenem-resistant and multidrug-resistant strains, and is also active against *Enterobacteriaceae*. It MIC (minimal inhibitory concentration) and MPC (mutant preventive concentration) are close together, allowing to avoid the mutant selection window specifically in the treatment of *Pseudomonas aeruginosa* infection. The molecule is time-dependent and stable when reconstituted at room temperature, facilitating safe and effective dosage optimization in frail and critically ill patients. It has been shown to be non-inferior to meropenem in the treatment of nosocomial infection in the ASPECT-NP study but superior in post-hoc studies in the subgroup of patients with ventilator-associated pneumonia, without the emergence of resistance during treatment. It is FDA approved at a dose of 3 g every 8 hours in the treatment of nosocomial pneumonia (HABP/VABP) in adults.

Keywords: Ceftolozane-tazobactam, molecular structure, in vitro activity, pharmacokinetic-Pharmacodynamic profile, nosocomial pneumonia.

MOLECULAR STRUCTURE AND *IN VITRO* ACTIVITY

Ceftolozane-tazobactam (CT) is the fusion of two molecules. A modified cephalosporin and a beta-lactamase inhibitor. Ceftolozane has an aminothiadiazole ring in the side chain, which, like that of ceftazidime and other extended-spectrum cephalosporins, confers activity against Gram-negatives. Its oxime group confers stability against beta-lactamases and dimethylacetic acid gives it enhanced anti-pseudomonal activity. The difference between ceftolozane and ceftazidime lies in position 3 of the side chain: ceftolozane has a pyrazole (heavier) instead of the pyridinium (lighter) found in ceftazidime. The pyrazole ring confers a steric hindrance between the ceftolozane and the gateway to the binding pocket in the active site of beta-lactamase, thus preventing hydrolysis and ensuring stability against *ampC* (figure 1 and 2) [1,2]. The result of these structural changes is its potent inhibition of *PBP3* with high affinity for *PBP1b* and *PBP1c* of *Pseudomonas aeruginosa*, while maintaining stability against ampC-type beta-lactamases. In addition, it is less affected than other antipseudomonal drugs by changes in permeability, Gram-negative outer membrane efflux pumps, reduced uptake through porins or modification of PBPs. Ceftolozane has activity against Gram-negative bacilli carrying classical class A beta-lactamases (TEM-1 and SHV-1), but like ceftazidime or ceftriaxone, it is hydrolyzed by extended-spectrum beta-lactamases (ESBLs) or carbapenemases. The addition of tazobactam extends the activity of ceftolozane against ESBL-producing bacteria, especially *Escherichia coli* and some anaerobic species.

Data collected in the United States between 2011 and 2014 reported up to 97% susceptibility to CT in *P. aeruginosa*, including multidrug-resistant and carbapenemase-insusceptible strains [3]. Equivalent data were reported in the USA between 2015 and 2017, showing 97.5% susceptibility in *P. aeruginosa* ($MIC_{50/90}$, 0.5/2 mg/L), including multirresistant (82.8% susceptible to CT) and extensively resistant (82.9% susceptibility) isolates [4]. Sader *et al.* reported slightly reduced overall susceptibility rates in *P. aeruginosa* isolates from Europe, 86.3% (at 8 mg/L) and 84.5% (4 mg/L), respectively [5]. In two Spanish studies with more than 1400 *P. aeruginosa* isolates, CT activity exceeded 94% sensitivity, the most frequently expressed resistance mechanism was oprD + ampC (80%) and the clone, in more than 68%, was ST175 [6,7]. The antipseudomonal activity of CT remains stable (MIC ≤ 2 mg/L) even when the MIC of ceftazidime, cefepime or piperacillin-tazobactam rises above 32 and 128 mg/l in carbapenem-resistant strains [8].

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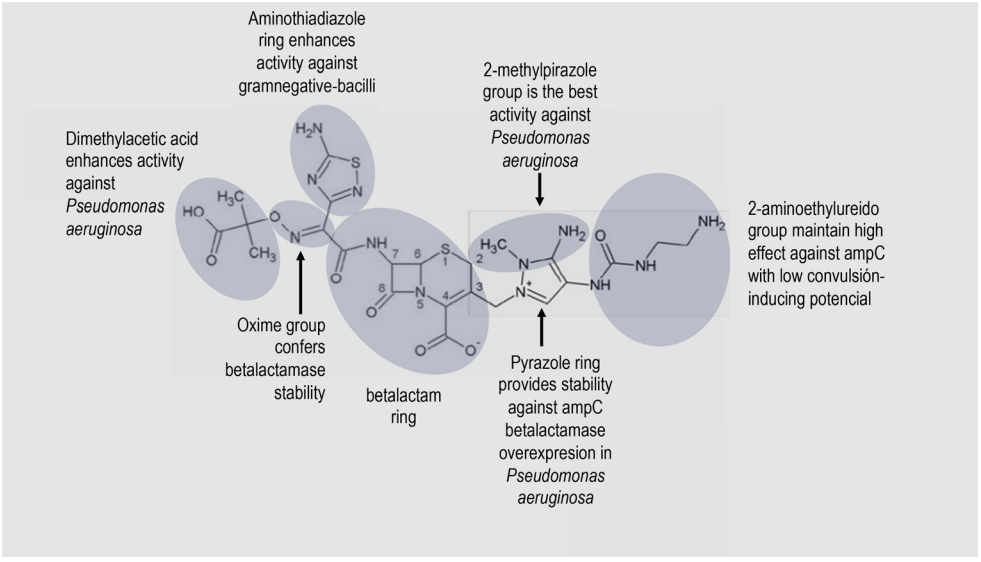

Figure 1 | **Structure–activity relationships for ceftolozane**

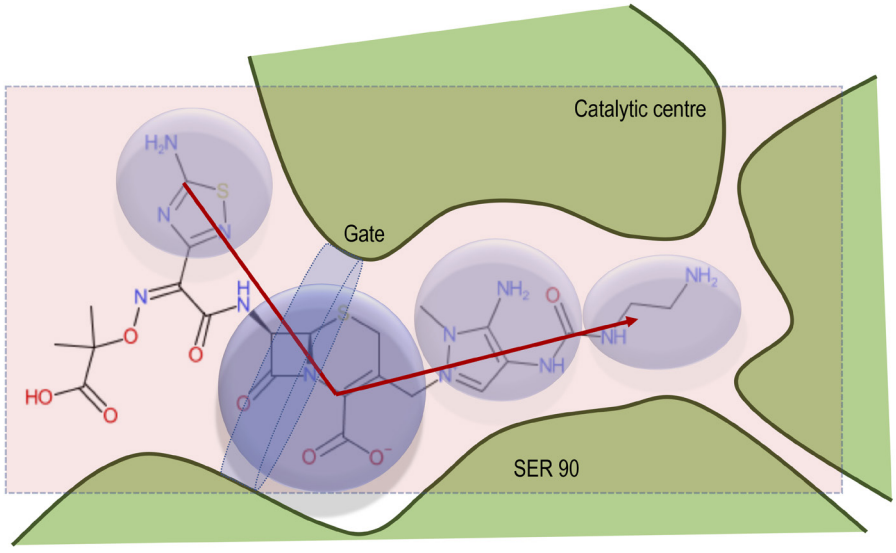

Figure 2 | **The gate of the 3-side chain binding pocket of AmpC b-lactamase and the chain of ceftolozane approaching (modified from reference 2)**

Analyzing activity against enterobacteria, Pazzini *et al* reported that CT was active against 85% of ESBL-producing *E. coli* isolates, in contrast to 57.5% of ESBL-producing *K. pneumoniae*. The CENIT study conducted on isolates from Spanish hospitals showed that CT was highly active not only against multidrug-resistant *P. aeruginosa*, but also against *E. coli*, including wild-type, *ampC* phenotype and ESBL-producing isolates. Activity decreased against the ESBL-producing strains *Klebsiella* spp. ($MIC_{50/90}$, 4/16 mg/L) and the combination was not active against carbapenemase-producing bacteria (MIC 64 mg/L) [9].

Results obtained from the follow-up study of respiratory samples conducted in American hospitals between 2013 and 2015 with more than 1,500 isolates of *P. aeruginosa* and more than 2,360 strains of *Enterobacteriaceae*, in which CT was shown to be the most active antibiotic against *P. aeruginosa*

and with activity against ESBL-producing *Enterobacteriaceae* isolates, detected in 13.4% of *E coli* and *K. pneumoniae* isolates. CT was active against $bla_{CTX\text{-}M\text{-}14}$-like and $bla_{CTX\text{-}M\text{-}15}$-like isolates. However, it was less active against $bla_{CTX\text{-}M}$ and had low activity against *Proteus* spp [10]. Taking clinical isolates from patients in the ASPECT-NP study, CT was active against more than 75% of *Enterobacteriaceae* isolates that did not carry carbapenemases and together with amikacin showed the highest activity against *P. aeruginosa* isolates [11].

Studies in patients with ventilator-associated pneumonia [12,13] caused by *P. aeruginosa,* showed high mortality rates if initial empirical antibiotic treatment is not appropriate. This has been replicated in other models of infection with high severity or greater inoculum effect such as bacteremia [14-16]. In these complex or severe infection models, the MIC and, if possible, the MPC (mutant preventive concentration) should be reached as soon as possible to prevent the antimicrobial from falling within the mutant selection window and to avoid intra- or post-treatment resistance. At MPC >32 mg/L for ceftazidime, cefepime, aztreonam, piperacillin-tazobactam and imipenem, the likelihood of serum concentrations of these antibiotics falling within the mutant selection window is very high, even when administered at maximal doses by prolonged or continuous infusion. The risk is moderate for meropenem (8 mg/L MPC) administered at doses of 6 g daily by prolonged infusion, and very low for CT (2 mg/L MPC) at doses of 3 g by 3-4-hour infusion every 8 h [17]. Also, cross-resistance between classical antipseudomonics may modify the emergence of resistance, so that CT could be a safe alternative in this type of infections.

Although CT has been shown to be the treatment of choice for *P. aeruginosa* infections, including multidrug-resistant and extensively resistant strains, some cases of resistance have also been reported. The most reported cause is associated with mutations in the *ampC* gene. The rate of development of this type of resistance ranged from 2-14% depending on the published series [18]. Another reason for resistance in treatment would be related to activity in the PDC-3 catalytic center of the *ampC* pocket [19]. These conformational changes in the PDC-3 loop are caused by the substitution of the amino acid E221K, which produces morphological and electrostatic modifications in the catalytic center. This facilitates the hydrolysis of ceftazidime, aztreonam, cefepime and ceftolozane. This mechanism has already been described in other species and for ceftolozane is estimated at 1.5% of isolates. Inhibitors (tazobactam, avibactam) partially restore this change. A final reason is the presence of other enzymes in the periplasmic space (OXA-17, OXA-24, MBL, GES).

PHARMACOKINETIC-PHARMACODYNAMIC PROFILE

Ceftolozane is an intravenous cephalosporin that exhibits linearity after single or multiple administrations. The mean Cmax after a 1 g dose of ceftolozane ranges from 58.4 mg/L to 92.3 mg/L and plasma half-life values range from 2.3 to 2.7 h. Protein binding of the drug is approximately 20%, and the volume of distribution is approximately 14 L [20]. It is eliminated by glomerular filtration; ceftolozane is minimally metabolized, and approximately 20% of tazobactam is metabolized by hydrolysis [21]. Ceftolozane is not a substrate of organic anion transporters organic anion transporters 1 and 3 (OAT1 and OAT3), whereas tazobactam is. Ceftolozane administration does not influence the clearance of tazobactam and increases the concentration of tazobactam [22].

CT is bactericidal, and the main pharmacodynamic parameter is time above MIC (for 40-50% of the dosing interval). In a population pharmacokinetic model to evaluate CT doses in nosocomial pneumonia through Monte Carlo simulations, a doubling of CT doses (2 g ceftolozane/1 g tazobactam) was found to substantially improve the number of patients achieving adequate time-above-MIC values. For MIC values up to 8 mg/L, the probability of target attachment (PTA) was 59-75% for doses of 1.5 g every 8 h, while for doses of 3 g every 8 hours, it was 88-96%. This manuscript justifies the dose of CT used in the clinical studies of patients with nosocomial pneumonia [23]. This dose of 3 g three times daily achieves sufficient PTA in populations with increased glomerular filtration rate ([CrCl] ≥ 130 mL/min)) [21], so common in the critically ill patient. Ceftolozane is also stable when reconstituted for more than 24 h at room temperature diluted in both saline and 5% dextrose, as demonstrated by particle degradation studies, in polyvinyl infusion systems or elastomeric pumps, as used in home hospitalization units [24].

Therefore, β-lactam antibiotics (except for imipenem) and especially CT should be administered at high doses, in prolonged or continuous infusion and after a loading dose. This recommendation is based on achieving several objectives: i) achieving time-dependent bactericidal activity, ii) the inoculum effect in foci with high bacterial load (present at the start of treatment), iii) ensuring the PK/PD ratio for high MIC against *P. aeruginosa*, iv) overcoming the changes that renal clearance may cause in drug distribution, and v) overcoming the preventive concentration of mutants in the infective focus [17]. This, as we shall see, is particularly indicated in nosocomial pneumonia.

CLINICAL EVIDENCE ON CEFTOLOZANE-TAZOBACTAM IN NOSOCOMIAL PNEUMONIA

In 2015-2016, after CT was approved at a dose of 1.5 g every 8 h in both complicated urinary tract infection and intra-abdominal infection, a pharmacokinetic model was used to justify dosing regimens in nosocomial pneumonia in phase 3 studies through Monte Carlo simulations. These showed that a 3 g dose of CT for nosocomial pneumonia patients with normal renal function is needed to achieve a PTA > 90% (98% actual) for the 1 log clearance target against pathogens with an MIC of ≤ 8 mg/L in ELF, compared to the approved 1.5 g dose for cIAIs and cUTIs [23].

With this approach, a randomized, controlled, dou-

ble-blind, non-inferiority trial was conducted in 263 hospitals in 34 countries to compare the activity of CT against meropenem in nosocomial pneumonia (ASPECT-NP study). Patients were randomly assigned to receive either 3 g of CT or 1 g of meropenem intravenously every 8 h for 8-14 days [25]. Seventy-one per cent of patients had ventilator-associated pneumonia, 33% had APACHE II scores equal or over 20, and 92% were in the intensive care unit. At 28 days, a quarter of patients in both groups had died (87 (24-0%) patients in the CT group and 92 (25-3%) in the meropenem group (weighted treatment difference 1-1% [95% CI -5-1 to 7-4]). At the test-of-cure visit 197 (54%) patients in the CT group and 194 (53%) in the meropenem group were clinically cured (weighted treatment difference 1-1% [95% CI -6-2 to 8-3]). Thus, CT was not inferior to meropenem in terms of either all-cause mortality at 28 days or clinical cure. In this study, 18% of patients enrolled in the CT group were bacteraemic vs. 11% in the meropenem group and 15% were from previous treatment failure vs. 11% in the meropenem group. These results led to U.S. Food and Drug Administration approval of CT for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in patients 18 years and older in June 2019 [26].

Clinical trials prior to ASPECT-NP on nosocomial pneumonia had generally shown a higher 28-day mortality in patients with ventilated hospital-acquired pneumonia than in those with ventilator-associated pneumonia [27]. In ASPECT-NP, a difference in mortality between the two conditions was observed only in the meropenem group. As a result, 28-day mortality in patients with ventilated hospital-acquired pneumonia was lower in the CT group than in the meropenem group. However, although the 95% CI for this treatment difference excluded zero, significance could not be inferred because analyses were not performed prospectively for both subgroups. In a *post-hoc* study, looking specifically at this group with ventilated HABP (vHABP), 99 participants in the CT arm and 108 in the meropenem arm, the odds of dying at day 28 from any cause were 2.3 times higher when participants treated with meropenem compared to those treated with CT [28].

The *post-hoc* study correlating prognosis in ASPECT-NP patients by each type of pathogen was performed. Pathogens isolated from lower respiratory tract samples were *K. pneumoniae* (34.6%), *P. aeruginosa* (25.0%) and *E. coli* (18.2%). Among the baseline *Enterobacteriaceae* isolates, 171/456 (37.5%) were ESBL positive. Susceptibility rates were 87.0% for CT and 93.3% for meropenem. 28-day all-cause mortality rates, clinical cure rate and microbiological eradication were comparable in both groups [29].

Johnson MG et al analyzed the emergence of resistance during treatment in *P. aeruginosa* isolates included in the ASPCT-NP study. Among the 59 isolates in the CT treatment arm, three (5.1%) had corresponding non-susceptible isolate pairs at baseline. Molecular analysis of these three isolates together with their reference pairs determined that two pairs had different sequence types and one pair had the same sequence type, thus only one could demonstrate the emergence of resistance during treatment. Among the 58 isolates in the meropenem treatment arm, 15 (25.9%) had corresponding pairs of non-susceptible isolates at the start of treatment. Molecular typing of these 15 isolates, together with their reference pair, determined that two pairs (3.4%) had different sequence types and that the other 13 pairs of isolates had the same sequence type. The most common molecular mechanisms of resistance found in the meropenem arm were *oprD* deficiency (n = 12 of 13; 92.3%) and overexpression of the protein and overexpression of the *MexXY* efflux system (n = 3 of 13; 23.1%) [30]. This study highlights the need to reach the MIC as soon as possible and if possible, the MPC to avoid falling into the resistance selection window. The risk is moderate for meropenem (MIC of 8 mg/L) administered at a dose of 6 g daily by prolonged infusion. However, the selection risk is very low for CT (2 mg/L MPC) at a dose of 3 g by 3–4-hour infusion every 8 h. We will observe over time whether the impact of the unavailability of CT during the COVID-19 pandemic might have generated more resistance in hospital-acquired ventilated *P. aeruginosa* pneumonia.

In conclusion, CT was clinically and microbiologically effective drug in the treatment of nosocomial pneumonia, stable at room temperature and safe at its approved dosage of 3g every 8 hours, which allows optimizing treatment in the frail or critically ill patient.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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