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Ceftolozane-tazobactam: When, how and why using it?

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ABSTRACT

Ceftolozane-tazobactam is currently the most active antipseudomonal agent, including multidrug-resistant extensively drug-resistant strains. Tazobactam provides additional activity against many extended-spectrum beta-lactamases *Enterobacterales*. Ceftolozane-tazobactam is formally approved for complicated urinary tract infection, complicated intra-abdominal infection, and hospital-acquired and ventilator-associated bacterial pneumonia. The clinical and microbiological success is over 70-80% in many series. However, resistant mutants to ceftolozane-tazobactam have been already described. Combination therapies with colistin or meropenem could be among the strategies to avoid the resistance emergence.

Key words: Ceftolozane-tazobactam, *Pseudomonas aeruginosa*, multidrug resistant, extensively drug resistant, extended spectrum β-lactamase.

INTRODUCTION

Ceftolozane-tazobactam (TOL-TAZ) combines a new antipseudomonal cephalosporin (ceftolozane) with enhanced antipseudomonal activity with a classic β-lactamase inhibitor (tazobactam). It exhibits bactericidal properties through inhibition of bacterial cell wall biosynthesis, which is mediated through penicillin-binding proteins (PBPs). Ceftolozane is a potent PBP3 inhibitor and has a higher affinity for PBP1b and PBP1c compared with other β-lactam agents. PBP1b and PBP1c are present in *Pseudomonas aeruginosa*. Moreover, ceftolozane has high stability against amp-C type betalactamases, which are frequently present in *P. aeruginosa*, and it is significantly less affected by the changes in the porin permeability or efflux pumps of the external membrane of gram negatives. Because of this ceftolozane has higher antipseudomonal activity than other antipseudomonals. Further, due to the combination with tazobactam, TOL-TAZ inhibits class A serine-betalactamases and extended-spectrum beta-lactamases (ESBL). TOL-TAZ also acts against non-ESBL class D oxacillinases, but it lacks activity against carbapenemases [1].

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SPECTRUM OF ACTIVITY

TOL-TAZ is an effective combination against several multidrug-resistant (MDR) Gram-negative bacilli, particularly MDR or extensively drug-resistant (XDR) *P. aeruginosa*. It is also active against AmpC and ESBLs producing *Enterobacterales*, but with a limited activity against ESBL-producing *Klebsiella pneumoniae*. Further, it remains activity against *Streptococcus* spp. (excluding *Enterococcus* spp.) and some anaerobes (*Bacteroides fragilis* and non-Bacteroides Gram-negatives) [2,3].

APPROVED INDICATIONS

TOL-TAZ was first approved for the treatment of adults with complicated intra-abdominal infection (cIAI) (in combination with metronidazole 500 mg every 8 hours) and complicated urinary tract infection (cUTI), including pyelonephritis. The dosage approved for these indications was 1.5 g 3 times a day. It was lately approved for adults with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) at a dosage of 3 g every 8 h [2].

CLINICAL EXPERIENCE

The efficacy of TOL-TAZ in *P. aeruginosa* and ESBL *Enterobacterales* infections has been evaluated in several studies to the date (Table 1).

Regarding infections caused by *P. aeruginosa*, all these studies included patients treated with a dose of either 1.5 g every 8 h or 3 g every 8 h, with the high dose usually adminis-

Table 1 **Clinical studies evaluating ceftolozane-tazobactam for *P. aeruginosa* and Enterobacterales infections. Adapted from [2]**

Study reference	Design	No. and source of infection	Microorganism	Outcomes
Pseudomonas aeruginosa				
Miller 2016, Antimicrob Agents Chemother	Post hoc analysis of RCT: C-T vs. Meropenem	IAI (C/T: 26 vs. Meropenem 29)	MDR	Clinical cure: C-T 100% vs. meropenem 93.1%
Caston 2017, Antimicrob Agents Chemother	Case series with C-T	6 LRTI, 5 BSI, 3 IAI, 3 others	MDR	Mortality 25%, Clinical cure 75%, Microbiological cure 58.3%
Dinh 2017, Int J Antimicrob Agents	Case series with C-T	7 LRTI, 3 UTI, 2 IAI, 3 others	XDR	Mortality 27%, Clinical cure 67%, Microbiological cure 75%
Haidar 2017, Clin Infect Dis	Retrospective study	18 LRTI, 1 BSI, 1 ITU, 1 IAI	MDR/XDR	Mortality 10%, clinical cure 71,4%
Munita 2017, Clin Infect Dis	Retrospective study	18 LRTI, 6 BSI	CR	Mortality 22.3%, clinical cure 74%, Microbiological cure 100%
Diaz-Cañestro 2018, Clin Infect Dis	Prospective observational study	35 LRTI, 10 UTI, 4 IAI,3 BSI, 6 others	MDR/XDR	Mortality 27.6%, Clinical cure 63.8%, Microbiological cure 70%
Escola Verge 2018, Infection	Retrospective study	14 LRTI, 11 BSI, 6 UTI, 6 SSTI, 4 IAI, 8 others	XDR	Mortality 13.2%, Clinical cure 68.4%-86.6%, Microbiological cure 68.4%
Gallagher 2018, Open Forum Infect Dis	Retrospective study	121 LRTI, 28 UTI, 25 BSI, 20 IAI, 42 others	MDR	Mortality 19%, Clinical cure 73.7%, Microbiological cure 70.7%
Xipell 2018, J Glob Antimicrob Resist	Case series with C-T	8 LRTI, 7 UTI, 6 SSTI, 3 IAI	MDR/XDR/PDR	Mortality 22%, Clinical cure 88%, Microbiological cure 75%
Bassetti 2019, Int J Antimicrob Agents	Retrospective study	32 LRTI, 22 BSI, 21 SSTI, 14 UTI, 13 IAI, 6 others	Non-MDR/MDR/XDR/PDR	Mortality 5%, Clinical cure 83.2%
Pogue 2019, Clin Infect Dis	Retrospective study: C-T vs polymyxin or aminoglycoside	C-T: 64 LRTI, 16 UTI, 13 SSTI, 6 BSI, 7 others Comparator: 75 LRTI, 11 UTI, 6 SSTI, 6 BSI, 6 others	MDR/XDR	Mortality: C-T 20% vs. comparator 25% Clinical cure: C-T 81% vs. comparator 61%
Vena 2019, Clin Infect Dis	Case control study C-T vs polymyxin or aminoglycoside	C-T 16 vs comparator 32: 27 LRTI, 21 BSI	MDR/XDR	Mortality: C-T 18.8% vs. comparator 28.1% Clinical cure: C-T 81.3% vs. comparator 56.3%
Bosaeed 2020, Infect Dis	Retrospective study	LRTI 6, BSI 4, SSTI 3, UTI 2, IAI 3, bone 1	CR	Mortality 21%, Clinical cure 94.7%, Microbiological cure 73.7%
Coppola 2020, Microorganisms	Case series with C-T	SSTI 2, BSI 2, 1 other	MDR	Mortality 0%
Hart 2021, Open Forum Infect Dis	Retrospective study	UTI 45, SSTI 8, IAI 6, BSI 6, bone/joiont 4, brain 3.	MDR	Mortality 19%, clinical cure 68%
Enterobacterales				
Huntington 2016, J Antimicrob Chemother	Post hoc analysis of RCT: C-T vs. Levofloxacin	212 UTI, 7 BSI	186 Enterobacterales 85 ESBL	Clinical cure: C-T 90% vs. comparator 76.8% Microbiological cure: C-T 63% vs. comparator 43.8%
Popejoy 2017, J Antimicrob Chemother	Post hoc analysis of 2 RCT: C-T vs. Levofloxacin C-T vs. Meropenem	UTI: 54 C-T, 46 Levofloxacin IAI: 24 C-T, 26 Meropenem	ESBL	Clinical cure: C-T 97.4% vs. Levofloxacin 82.6% and vs Meropenem 88.5%. Microbiological cure: C-T 79.5% vs. Levofloxacin/Meropenem 62.5%
Arakawa 2019, J Infect Chemother	Nonrandomized open-label trial	90 UIT, 24 BSI	93 Enterobacterales 13 ESBL	For ESBL: Mortality 0%, Microbiological cure 38.5%
Mikamo 2019, J Infect Chemother	Nonrandomized open-label trial	130 IAI	58 Enterobacterales 5 ESBL	For ESBL: Mortality 0%, Clinical cure 100%, Microbiological cure 100%

Abbreviations: RCT, randomized controlled trial; C-T, ceftolozane-tazobactam; IAI, intra-abdominal infection; LRTI, lower respiratory tract infection; BSI, bloodstream infection; ITU, urinary tract infection; SSTI, skin and soft tissue infection; MDR, multidrug resistant; XDR, extensively drug resistant; CR, carbapenem resistant; PDR, pandrug resistant; ESBL, extended spectrum β-lactamase.

tered for high inoculum sources such as pneumonia, osteomyelitis, and abscesses. However, not only the source of infection should be considered to make the decision about the dosage but also the TOL-TAZ minimum inhibitory concentration (MIC). In a study aimed to evaluate the efficacy of different TOL-TAZ doses in patients with lower respiratory infection due to MDR- or XDR-*P. aeruginosa*, *Rodríguez Núñez* et al. found that mortality was significantly lower in patients with *P. aeruginosa* strains with MIC ≤2 mg/L and receiving high dose of TOL-TAZ compared with the group with higher MIC and standard dosage (16.2% vs 35.8%; P = .041). However, in the multivariate analysis only TOL-TAZ MIC >2 mg/L was identified as an independent predictor of mortality [4].

In case of third generation cephalosporin resistant *Enterobacterales*, the results of MERINO-3 (multicentre, parallel group open-label non-inferiority trial design comparing TOL-TAZ vs. meropenem in adult patients with bloodstream infection caused by ESBL or AmpC-producing *Enterobacterales*) will provide a better comprehension about the efficacy of TOL-TAZ in such infections [5].

RESISTANCE MECHANISMS

In vitro and *in vivo* data indicate that *P. aeruginosa* resistance to TOL-TAZ is due to several mechanisms. The most important seems to be a combination of mutations leading to hyperproduction and structural modified AmpC enzymes. It has been also suggested that specific PBP3 mutations may reduce its susceptibility. Finally, although to a minor extent, the overexpression of different efflux pumps could also affect to TOL-TAZ. With respect to acquired β-lactamases, TOL-TAZ shows no activity against metallo-beta-lactamases (MBL) -producing strains. Finally, extended-spectrum mutations in horizontally acquired OXA-type β-lactamases may lead to the emergence of resistance to TOL-TAZ [3].

Regarding *Enterobacterales*, tazobactam has no activity against serine carbapenemases or MBL, and has limited activity against AmpC and some ESBL [6].

COMBINATION THERAPY AGAINST MDR/XDR P. AERUGINOSA STRAINS

In order to avoid the selection of resistance, some studies have addressed the efficacy of combination antibiotic therapy with TOL-TAZ for treating MDR/XDR *P. aeruginosa* strains**.**

In an *in vitro* study aimed to evaluate the antibacterial activity of TOL-TAZ and colistin alone and in combination against a collection of 24 clinical XDR *P. aeruginosa*, *Montero* et al. demonstrated synergistic or additive effect for TOL-TAZ plus colistin (21/24), including TOL-TAZ-resistant strains [7]. The same group also evaluated the efficacy of TOL-TAZ in combination with meropenem against XDR strains in a hollow-fiber model. This approach showed that when TOL-TAZ was administered in combination with meropenem, there was a >4 log10 CFU/ml bacterial density reduction, without resistance emergence. This result suggests that a double beta-lactam strategy based on TOL-TAZ plus meropenem may be a useful combination for treating XDR *P. aeruginosa* [8].

CONFLICTS OF INTEREST

JPH has received honoraria as speaker or for advisory activities from Pfizer, MSD, Menarini, Angelini, Zambon. All other authors declare no conflicts of interest.

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