Ceftolozane/Tazobactam Probability of Target Attainment in Patients With Hospital-Acquired Pneumonia/ Ventilator-Associated Pneumonia

Zufei Zhang,[1] Yogesh T. Patel,[2] Wei Gao,[1] Matthew G. Johnson,[1] Jill Fiedler-Kelly,[2] Christopher J. Bruno,[1] Elizabeth Rhee,[1] Carisa De Anda,[1] Hwa-Ping Feng[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Cognigen Corporation, a Simulations Plus Company, Buffalo, NY, USA

BACKGROUND

- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are common hospital-acquired infections that are associated with mortality rates as high as 50%[1-3]
- Ceftolozane/tazobactam (C/T), a combination of a potent antipseudomonal cephalosporin (ceftolozane) with a beta-lactamase inhibitor (tazobactam), is primarily renally excreted, and requires dose adjustment based on renal function[4,5]
- C/T is approved in the European Union and United States for the treatment of adults with complicated urinary tract infections (cUTI; including pyelonephritis), complicated intra-abdominal infections (cIAI; to be used in combination with metronidazole in the United States), and HAP/VAP[4,5]
- A C/T 3 g (ceftolozane 2 g/tazobactam 1 g) dose, or C/T dose adjusted based on renal function, administered as a 1-hour infusion every 8 hours was evaluated in patients with ventilated HAP or VAP in the phase 3, randomized, controlled, double-blind ASPECT-NP study[6]
- The objective of this analysis was to apply probability of target attainment (PTA) analyses to data from the ASPECT-NP study to support the recommended C/T dosing regimen in patients with HAP/VAP

METHODS

Population Pharmacokinetic (PopPK) Modeling

- PopPK models describing plasma concentrations of ceftolozane and tazobactam in patients with HAP/VAP were developed based on a previously established 2-compartment model with first-order elimination[7,8]
- The plasma C/T concentration data from 16 clinical studies, including ASPECT-NP, informed the plasma components of the popPK models
- Pulmonary epithelial lining fluid (ELF) C/T concentration data from two phase 1 studies informed the ELF component of the popPK models; disposition of ceftolozane and tazobactam in ELF was described by a hypothetical link model with influx and elimination from the ELF compartment[9,10]
- Among the covariates identified in the developed popPK models in patients with HAP/VAP, baseline creatinine clearance (CrCl) was a significant covariate on ceftolozane and tazobactam clearance; weight and pneumonia were covariates on ceftolozane and tazobactam volumes of distribution; pneumonia was a covariate on the influx and elimination rate constants for the ELF compartment

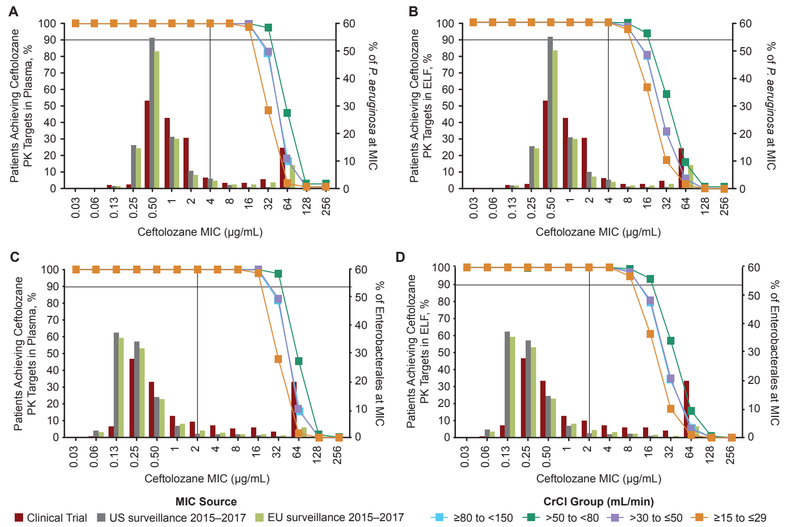
Simulations

- Virtual patients with paired weight and CrCl were randomly drawn from a large virtual population database constructed based on MSD's clinical trials in the infectious disease area for each of the following renal function categories (n=1000 each): normal (CrCl ≥80 to <150 mL/min) and mild, moderate, and severe renal impairment (CrCl >50 to <80 mL/min, CrCl ≥30 to ≤50 mL/min, and CrCl ≥15 to ≤29 mL/min, respectively)
- Ceftolozane and tazobactam concentration-time profiles in plasma and ELF were simulated using the popPK models in patients with HAP/VAP at 3 different dosing regimens, adjusted based on CrCl, administered via 1-hour infusion every 8 hours over a 14-day treatment duration:
  - Dosing regimen 1: 0.5 g/0.25 g C/T for patients with CrCl of ≥15 to ≤29 mL/min
  - Dosing regimen 2: 1 g/0.5 g C/T for patients with CrCl of ≥30 to ≤50 mL/min
  - Dosing regimen 3: 2 g/1 g C/T for patients with CrCl of >50 mL/min
- PTA was assessed based on a target for ceftolozane of 30% of the dosing interval during which the free drug concentration (fT) exceeds the minimum inhibitory concentration (MIC; 30% fT>MIC=4 µg/mL; 1-log kill in a mouse infection model) and for tazobactam of 20% fT greater than the threshold concentration (C_T) of 1 µg/mL (20% fT>C_T), restoring ceftolozane antibacterial activity to stasis in a mouse infection model[11]
  - Additional ceftolozane ELF and plasma PTA assessments were conducted for ceftolozane at PK/pharmacodynamic targets of up to 50% fT>MIC=4 µg/mL, which corresponds to a 2-log kill, and 35% fT>C_T=1 µg/mL for tazobactam, which corresponds to restoring ceftolozane antibacterial activity to 1-log kill[11]

RESULTS

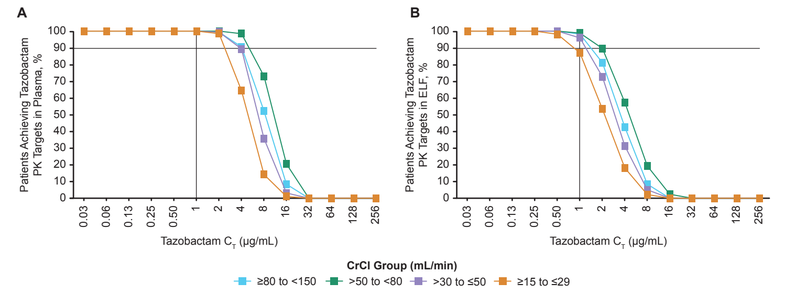
- Steady-state plasma and ELF PTA was 100% and >99%, respectively, for ceftolozane at 30% fT>MIC=4 µg/mL across renal categories with CrCl up to 150 mL/min (**Figures 1A and 1B**, overlaid with MIC distributions for *P. aeruginosa*; **Figures 1C and 1D**, overlaid with MIC distributions for Enterobacterales)
- Steady-state plasma and ELF PTA were >99% and >87%, respectively, for tazobactam at 20% fT>C_T=1 µg/mL across renal categories at CrCl up to 150 mL/min (**Figures 2A and 2B**)

Figure 1. PTA at Steady State in Plasma and ELF for Ceftolozane at a Target of 30% fT>MIC for Virtual Patients with HAP/VAP, by CrCl Category[a], with *P. aeruginosa* (Panels A and B) and Enterobacterales (Panels C and D) MIC Distributions Among Isolates



Solid horizontal line on plots represents 90% PTA; vertical line in panels A and B represents MIC=4 µg/mL; vertical line in panels C and D represents MIC=2 µg/mL.
[a]CrCl for all patients was calculated using the Cockcroft and Gault formula.[12]
CrCl, creatinine clearance; ELF, epithelial lining fluid; fT, free drug concentration during the dosing interval; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment.

Figure 2. PTA at Steady State in Plasma and ELF for Tazobactam at a Target of 20% fT>C_T for Virtual Patients with HAP/VAP, by CrCl Category[a]



Solid horizontal line on plots represents 90% PTA; vertical line represents C_T=1 µg/mL.
[a]CrCl for all patients was calculated using the Cockcroft and Gault formula.[12]
CrCl, creatinine clearance; C_T, threshold concentration; ELF, epithelial lining fluid; fT, free drug concentration during the dosing interval; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment.

- At the recommended dosing regimens, using ceftolozane targets of 50% fT>MIC, plasma and ELF PTA was >99% at an MIC of 4 µg/mL across renal categories at CrCl up to 150 mL/min (**Table 1**)
- Using a tazobactam target of 35% fT>C_T, plasma and ELF PTA was >84% at C_T of 1 µg/mL across renal categories up to CrCl of 150 mL/min (**Table 1**)

Table 1. Percentage of HAP/VAP Patients Achieving a Ceftolozane Target of 50% fT>MIC at an MIC=4 µg/mL or Tazobactam Target of 35% fT>C_T at 1 µg/mL

	Ceftolozane Target of 50% fT>MIC=4 µg/mL		Tazobactam Target of 35% fT>C_T at 1 µg/mL	
	Plasma	ELF	Plasma	ELF
CrCl ≥15 to ≤29 mL/min	100	99.7	98.7	84.7
CrCl ≥30 to ≤50 mL/min	100	100	98.1	94.4
CrCl >50 to <80 mL/min	100	100	99.2	98.1
CrCl ≥80 to <150 mL/min	100	100	94.1	95.6

CrCl, creatinine clearance; ELF, epithelial lining fluid; fT>C_T, percent of the dosing interval during which the free drug concentration exceeds the threshold concentration; fT>MIC, percent of the dosing interval during which the free drug concentration exceeds the minimum inhibitory concentration; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MIC, minimum inhibitory concentration.

CONCLUSIONS

- At the dosing regimens evaluated in ASPECT-NP, high PTA was achieved for ceftolozane and tazobactam in both plasma and ELF for patients with HAP/VAP across renal function categories
- Together with demonstrated safety and efficacy in the ASPECT-NP clinical trial, the PTA assessment supports the appropriateness of the C/T dosing regimens, adjusted based on renal function, for patients with HAP/VAP

References

1. Kalil AC, et al. *Clin Infect Dis.* 2016;63(5):e61-e111.
2. Magill SS, et al. *N Engl J Med.* 2014;370(13):1198-1208.
3. Peleg AY, Hooper DC. *N Engl J Med.* 2010;362(19):1804-1813.
4. ZERBAXA® (ceftolozane and tazobactam): Summary of product characteristics. MSD Laboratories Chibret; Riom, France; 2019.
5. ZERBAXA® (ceftolozane and tazobactam): Prescribing information. Merck Sharp & Dohme Corp.; Whitehouse Station, NJ, USA; 2019.
6. Kollef MH, et al. *Lancet Infect Dis.* 2019;19(12):1299-1311.
7. Zhang Z, et al. *J Clin Pharmacol*; in preparation.
8. Chandorkar G, et al. *J Clin Pharmacol.* 2015;55(2):230-239.
9. Caro L, et al. *J Antimicrob Chemother.* 2020; Mar 24: doi: 10.1093/jac/dkaa049.
10. Chandorkar G, et al. *J Antimicrob Chemother.* 2012;67(10):2463-2469.
11. Craig WA, Andes DR. *Antimicrob Agents Chemother.* 2013;57(4):1577-1582.
12. Cockcroft DW, Gault MH. *Nephron.* 1976;16(1):31-41.

Acknowledgements

We thank the study participants, investigators, and trial site personnel for their contributions to the study. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD). Medical writing assistance was provided by Jessica Deckman, PhD, CMPP, of The Lockwood Group, Stamford, CT, USA. This assistance was funded by MSD.

Disclosures

ZZ, WG, MGJ, CJB, ER, CDA, and HPF are employees of MSD. YTP and JFK are employees of Cognigen Corporation, a Simulations Plus Company, which provides consulting services to MSD.

This poster was originally intended for presentation at the 30th ECCMID (Paris, France; April 18–21, 2020). This meeting was canceled due to the COVID-19 pandemic. The corresponding accepted abstract can be found in the 30th ECCMID abstract book (Abstract 1213).

Abstract accepted at the 30th ECCMID; Paris, France; April 18–21, 2020.