Probability of Target Attainment Analyses to Inform Ceftolozane/Tazobactam Dosing Regimens in Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia Patients With End-Stage Renal Disease on Intermittent Hemodialysis

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BACKGROUND

- Nosocomial pneumonia, including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), is a common type of hospital-acquired infection, with mortality rates estimated to be as high as 50%[1-3]
- Ceftolozane/tazobactam (C/T)—a combination of ceftolozane, a potent antipseudomonal cephalosporin, and tazobactam, a beta-lactamase inhibitor—is approved for the treatment of complicated intra-abdominal infections (cIAI); complicated urinary tract infections (cUTI), including pyelonephritis; and HAP, including VAP, in the European Union and United States[4,5]
- Both ceftolozane and tazobactam are eliminated renally; therefore dose adjustment is necessary based on renal function[4,5]
- The efficacy and safety of C/T for the treatment of HAP/VAP was demonstrated with a C/T 3 g (ceftolozane 2 g/tazobactam 1 g) dose by 1-hour infusion every 8 hours dosing regimen in the phase 3, randomized, controlled, double-blind ASPECT-NP study; however, patients with end-stage renal disease (ESRD) requiring hemodialysis were excluded from the study[6]

OBJECTIVE

- Apply probability of target attainment (PTA) analyses to data from the ASPECT-NP study to inform the C/T-recommended dosing regimen in HAP/VAP patients with ESRD on intermittent hemodialysis (HD)

METHODS

Population Pharmacokinetic (PopPK) Modeling

- The plasma components of the popPK models for ceftolozane and tazobactam in patients with HAP/VAP were developed based on previously established models for cIAI/cUTI[7]
  - The models consist of 2-compartments with first-order elimination, and were informed by data from 16 clinical studies, including patients with HAP/VAP in ASPECT-NP and patients with ESRD without infection
  - Among the covariates identified in the developed popPK models in HAP/VAP patients, baseline creatinine clearance (CrCl) was a significant covariate on ceftolozane and tazobactam clearance; body weight and pneumonia were covariates on ceftolozane and tazobactam volumes of distribution
  - Based on concentration data from 6 patients with ESRD,[8] ESRD (as a categorical covariate) was identified as a significant predictor of ceftolozane and tazobactam plasma clearance and volume of distribution, in addition to the covariate effects described above and of ESRD and HD on plasma PK reported previously[9]
- The pulmonary epithelial lining fluid (ELF) components of the models were informed by ELF concentration data from 2 phase 1 studies[10,11]
  - The ELF disposition models were the plasma models with a hypothetical ELF compartment linked to the plasma compartment
  - Pneumonia was a covariate on the influx and elimination rate constants for the ELF compartment

Simulations

- The popPK models for ceftolozane and tazobactam in HAP/VAP patients were used to simulate daily plasma and ELF ceftolozane and tazobactam concentration-time profiles in ESRD patients with HAP/VAP (n=1000); the simulated concentration-time profiles were used to estimate exposures (area under the time-curve [AUC] and maximum concentration [C_{max}]) and calculate PTA in this population at 3 different dosing levels relative to the recommended dose used in patients with cIAI/cUTI and ESRD (at two times [2X] the dose: 1 g/0.5 g C/T loading dose + 0.2 g/0.1 g C/T maintenance dose; three times [3X] the dose: 1.5 g/0.75 g C/T loading dose + 0.3 g/0.15 g C/T maintenance dose, or four times [4X] the dose: 2 g/1 g C/T loading dose + 0.4 g/0.2 g C/T maintenance dose) by 1-hour infusion every 8 hours over a 14-day treatment duration, with HD on every other weekday
- PTA was calculated based on a target for ceftolozane of 30% of the dosing interval that the free drug concentration (fT) exceeded the minimum inhibitory concentration (MIC; 30% fT>MIC=4 µg/mL; 1-log kill) 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)
  - Sensitivity analyses were performed at ceftolozane targets up to 50% fT>MIC=4 µg/mL (2-log kill) and a tazobactam target of 35% fT>C_T=1 µg/mL

RESULTS

- For ceftolozane, when evaluated at a target of 30% fT>MIC=4 µg/mL, both plasma and ELF PTA values were ≥95% for all 3 dosing regimens (**Table 1**)
  - When evaluated at a ceftolozane target of up to 50% fT>MIC=4 µg/mL, ceftolozane plasma and ELF PTA for the 3X cIAI/cUTI ESRD dosing regimen was >97% for the entire 14-day dosing duration, including on HD days
- For tazobactam, when evaluated at a target of 20% fT>C_T=1 µg/mL, plasma PTA values were >99% for all 3 dosing regimens and ELF PTA values were >90% for the 3X and 4X cIAI/cUTI ESRD dosing regimens; however, ELF PTA values were <80% on dialysis days for the 2X cIAI/cUTI ESRD dosing regimen
  - When evaluated at a tazobactam target of 35% fT>C_T=1 µg/mL (restoring ceftolozane antibacterial activity to 1-log kill), tazobactam plasma PTA for the 3X cIAI/cUTI dosing regimen was 99% for the entire 14-day dosing duration, including HD days, whereas tazobactam ELF PTA for the 3X cIAI/cUTI dosing regimen was >90% for non-HD days and was >88% on HD days

Table 1. Simulated Daily PTA for Ceftolozane (30% fT>MIC=4 µg/mL) and Tazobactam (20% fT>C_T = 1 µg/mL) in Plasma and ELF Over the 14-day Treatment Duration for Each of the 3 ESRD Dosing Regimens[a]

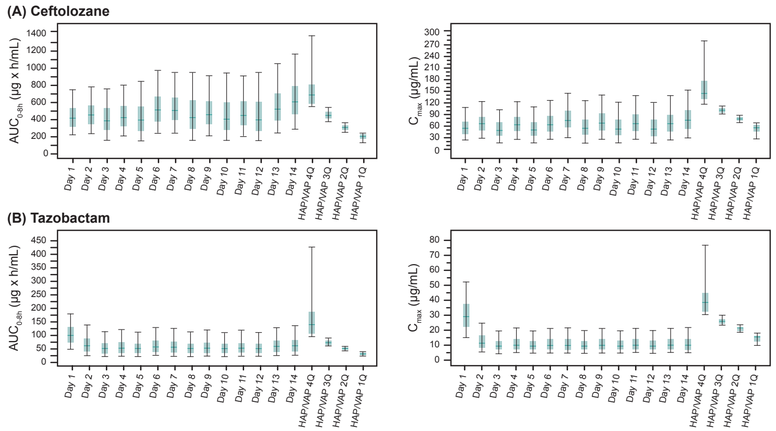
	Ceftolozane			Tazobactam		
	2X cIAI/cUTI ESRD Dose	3X cIAI/cUTI ESRD Dose	4X cIAI/cUTI ESRD Dose	2X cIAI/cUTI ESRD Dose	3X cIAI/cUTI ESRD Dose	4X cIAI/cUTI ESRD Dose
Plasma						
Day 1[b]	100	100	100	100	100	100
Day 2	100	100	100	99.9	100	100
Day 3[b]	100	100	100	99.8	100	100
Day 4	100	100	100	99.9	100	100
Day 5[b]	100	100	100	99.8	100	100
Day 6	100	100	100	99.9	100	100
Day 7	100	100	100	99.9	100	100
Day 8[b]	100	100	100	99.8	100	100
Day 9	100	100	100	99.9	100	100
Day 10[b]	100	100	100	99.8	100	100
Day 11	100	100	100	99.9	100	100
Day 12[b]	100	100	100	99.8	100	100
Day 13	100	100	100	99.9	100	100
Day 14	100	100	100	99.9	100	100
ELF						
Day 1[b]	95.0	99.1	99.9	98.1	99.9	100
Day 2	99.7	99.9	100	85.7	94.2	98.0
Day 3[b]	99.7	100	100	77.3	90.8	96.1
Day 4	99.6	100	100	82.2	92.7	97.4
Day 5[b]	99.4	100	100	77.0	90.6	96.0
Day 6	99.7	100	100	82.3	92.7	97.4
Day 7	100	100	100	83.1	93.0	97.6
Day 8[b]	99.7	100	100	77.0	90.6	96.0
Day 9	99.7	100	100	82.2	92.6	97.4
Day 10[b]	99.4	100	100	77.0	90.6	96.0
Day 11	99.6	100	100	82.2	92.6	97.4
Day 12[b]	99.3	100	100	77.0	90.6	96.0
Day 13	99.7	100	100	82.3	92.7	97.4
Day 14	100	100	100	83.1	93.0	97.6

C_T, concentration threshold; ELF, epithelial lining fluid; ESRD, end-stage renal disease; fT, free drug concentration during the dosing interval; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

[a]2X cIAI/cUTI ESRD dose: 1 g/0.5 g C/T loading dose + 0.2 g/0.1 g C/T maintenance dose; 3X cIAI/cUTI ESRD dose: 1.5 g/0.75 g C/T loading dose + 0.3 g/0.15 g C/T maintenance dose; 4X cIAI/cUTI ESRD dose: 2 g/1 g C/T loading dose + 0.4 g/0.2 g C/T maintenance dose; [b]Dialysis day; first dose administered immediately after dialysis on day 1.

- The simulated daily plasma ceftolozane AUC distributions for the 4X cIAI/cUTI ESRD dosing regimen (median $AUC_{0\text{-}8h}$ range over days 1-14: 503–797 µg·h/mL) were much higher than those for the 3X cIAI/cUTI ESRD dosing regimen and extended outside of the clinical experience in ASPECT-NP; AUC distributions for the 3X cIAI/cUTI ESRD dosing regimen (1.5 g/0.75 g C/T loading + 0.3 g/0.15 g C/T maintenance; **Figure 1A**) were contained within the phase 3 clinical experience
- Tazobactam plasma exposure distributions for both the 3X (**Figure 1B**) and 4X (data not shown) cIAI/cUTI ESRD dosing regimens were within the clinical experience of ASPECT-NP

Figure 1. (A) Ceftolozane and (B) Tazobactam Plasma $AUC_{0\text{-}8h}$ and C_{max} by Treatment Day in Patients with ESRD and HAP/VAP Receiving the 3X cIAI/cUTI ESRD Dosing Regimen[a]



$AUC_{0\text{-}8h}$, area under the concentration-time curve from time 0 to 8 hours after start of infusion; C_{max}, maximum drug concentration; ESRD, end-stage renal disease; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; Q, quartiles.

[a]3X cIAI/cUTI ESRD dose: 1.5 g/0.75 g C/T loading dose + 0.3 g/0.15 g C/T maintenance dose.

Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles; HAP/VAP 1Q to HAP/VAP 4Q represent quartiles of exposure observed in patients with HAP/VAP (n=305).

CONCLUSIONS

- The 3X cIAI/cUTI ESRD dose (2.25 g C/T loading dose [1.5 g ceftolozane and 0.75 g tazobactam] and 0.45 g C/T maintenance dose [0.3 g ceftolozane and 0.15 g tazobactam]) administered every 8 hours provides an acceptable balance between efficacy and safety considerations and is the recommended dosing regimen for ESRD patients with HAP/VAP with intermittent HD

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Disclosures

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