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 35%.

Ceftolozane-tazobactam (CTZ-TAZ) is a combination of a potent anti-pseudomonal beta-lactamase inhibitor and, tazobactam, a beta-lactamase inhibitor, approved for the treatment of complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), including pyelonephritis, and HAP, and IVP in the European Union and United States.

Both ceftolozane and tazobactam are eliminated renally; therefore dose adjustment is necessary based on renal function.

The efficacy and safety of CT for the treatment of HAP/VAP are well described. In a phase 2, placebo-controlled, randomized clinical trial, 1 g dose by 1-hour infusion every 8 hours during 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.

Background

Objective

Methods

Population Pharmacokinetic (PopPK) Modeling

The plasma concentration-time profiles for ceftolozane and tazobactam in patients with HAP/VAP were developed based on previously established models for cIAI/cUTI.

The model consists of 2-compartment with first-order elimination, and were informed by data from 10 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 (CLCR) was a significant covariate on ceftolozane and tazobactam body weight and pharmacokinetic parameters.

Based on concentration data from patients with ESRD in ASPECT-NP (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 to plasma PK reported previously.

The pulmonary epithelial lining fluid (ELF) concentration of the models were informed by ELF concentration data from 2 phase 1 studies.

The ELF disposition models were the plasma models with a hypothetical ELF compartment linked to the plasma compartment.

Ceftolozane was a covariate on the influx and elimination rate constants for the ELF compartment.

The popPK models for ceftolozane and tazobactam in HAP/VAP patients were used to simulate daily plasma and ELF concentrations.

The plasma components of the popPK models for ceftolozane and tazobactam in patients with HAP/VAP were informed by data from 16 clinical studies.

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).

RESULTS

- For ceftolozane, when evaluated at a target of 300 μg/1 mL (MIC<4 μg/mL), both plasma and ELF PTA values were >95% for all 3 dosing regimen (Table 1).
- When evaluated at target of 500 μg/1 mL (MIC<4 μg/mL), ceftolozane plasma and ELF PTA for the 3X CTZ-TAZ ESID dosing regimen was >90% for the entire 14-day dosing duration, including on HD days.
- For tazobactam, when evaluated at a target of 20 μg/1 mL (MIC<1 μg/mL), plasma PTA values were >90%, for 3 dosing regimens and ELF PTA values were >95% for the 3X and 4X CTZ-TAZ ESID dosing regimens; however, ELF PTA values were <80% on dialysis days for the 2X CTZ-TAZ ESID dosing regimen.

When evaluated at a target of 300 μg/1 mL (MIC<1 μg/mL), tazobactam plasma PTA for the entire 14-day dosing duration, including HD days, whereas tazobactam ELF PTA for the 3X CTZ-TAZ dosing regimen was >90% for non-HD days and was >88% on HD day for the 2X and 3X dosing regimens.

Table 1. Simulated Daily PTA for Ceftolozane (300 μg/1 mL-C/T MIC<4 μg/mL) and Tazobactam (20 μg/1 mL-C/T MIC<1 μg/mL) in Plasma and ELF Over the 14-Day Treatment Duration for Each of the 3 ESID Dosing Regimens

Figure 1. (A) Ceftolozane and (B) Tazobactam Plasma AUC(0-24h) and Cmax values for HAP/VAP 4Q, 3Q, 2Q, and 1Q dosing regimens.

The simulated daily plasma ceftolozane AUC(0-24h) values for the 4X CTZ-TAZ ESID dosing regimen (median AUC(0-24h) range over days 1-14: 1,500–3,057 μg·h/mL) were much higher than those for the 2X CTZ-TAZ ESID dosing regimen and extended outside of the clinical experience in ASPECT-NP.

Figure 1A was plotted within the phase 3 clinical experience for the 2X and 3X CTZ-TAZ ESID dosing regimen.

The plasma exposure to CTZ-TAZ 1 g dose was >90% for non-HD days, whereas tazobactam ELF PTA for the 3X CTZ-TAZ dosing regimen was >97% for the entire 14-day dosing duration, including HD days.

CONCLUSIONS

- The 3X CTZ-TAZ ESID dosing [2.25 g CTZ loading dose (1.5 g ceftolozane and 0.75 g tazobactam) and 0.45 g CT maintenance dose (0.3 g ceftolozane and 0.15 g tazobactam)] administered every 8 hours provides an acceptable safety profile and is the recommended dosing regimen for ESRD patients with HAP/VAP with intermittent HD.

REFERENCES


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