Disclosures. All authors: No reported disclosures.

1558. A Population Pharmacokinetic Model for Posaconazole Intravenous Solution and Oral Powder for Suspension Formulations in Pediatric Patients With Neutropenia

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Background. Posaconazole is approved in adults for prophylaxis and treatment of invasive fungal disease. Two formulations that offer weight-based dosing—intravenous (IV) and oral powder for suspension (PFS)—are being evaluated in children. A population pharmacokinetic (popPK) approach was used to characterize and predict the PK exposure of posaconazole PFS and IV formulations in children to identify dosages associated with achieving a target PK of 1200 ng/mL as the mean C_{avg} and individual C_{avg} \geq 500 ng/mL and <2500 ng/mL in ~90% of patients.

Methods. A popPK model was developed through nonlinear mixed-effects modeling using data obtained from a trial in children with neutropenia (ClinicalTrials.gov, NCT02452034; Merck protocol, MK-5592-007). Three dose cohorts (3.5, 4.5, and 6 mg/kg/day [\leq 300 mg/day]) were studied in two age groups (2–<7 years and 7–17 years). Posaconazole IV was administered twice on day 1 then once daily through at least day 10, followed by PFS once daily through day 28 at clinician discretion. A compartmental model, including both formulations, was fit to the data. Model selection was based on the Log-Likelihood Criterion, goodness-of-fit plots, and scientific plausibility. Significance of the covariates was assessed in a stepwise forward inclusion/backward procedure. An additional assessment characterized the impact of different food covariates on bioavailability.

Conclusion. This popPK-based analysis demonstrated that the 6-mg/kg/dose was well tolerated and generally met PK targets. Model-predicted C_{avg} \geq 500 ng/mL and <2500 ng/mL in ~90% of patients.

Table 1. Average Baseline log_{10}(CFU/mL) Standard Deviation (SD)

Antibiotics        24 Hours 48 Hours  
Ertapenem Alone    7.10 ± 0.46 7.21 ± 0.6  
Ceftriaxone Alone  6.67 ± 0.18 7.46 ± 0.03  
Ceftriaxone + Cefepine 4.89 ± 0.67 5.97 ± 0.28  
Ertapenem + Ceftriaxone 1.79 ± 0.51* 4.72 ± 0.52  
Ertapenem + Cefepine 2.29 ± 1.09* 5.05 ± 0.25  

Disclosures. All authors: No reported disclosures.

1560. Pharmacokinetics–Pharmacodynamics (PK-PD) of Pefitocidin (GEP) Against Enterococcus faecalis and Thigh Infection Models

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Background. GEP, a first in class novel triazaacenaphthylene bacterial topoisomerase inhibitor, inhibits bacterial replication and has in vitro activity against key pathogens implicated in a range of infections, including drug resistant strains of E. coli associated with acute cystitis.

Methods. PK and PD studies were conducted in murine (male CD-1 mice) thigh and kidney infections. The administered doses ranged from 1 to 200 mg/kg SC every 6 hours starting 1 hour post-infection. Infected tissues were evaluated for bacterial burden at 24-hour post-infection (baseline controls at 1-hour post-infection). Plasma and tissue samples (kidney or thigh homogenates) were collected at 15, 30, 60, 120, 240 and 360 minutes. A population PK (NONMEM) model was built in NONMEM using plasma exposures. Efficacy was determined against E. coli ALL, 99757, ATCC25922, IRS and NCCT13441 (MICs of 1 to 4 μg/mL) in thigh-infected neutropenic (I-) mice and against E. coli ALL in kidney-infected immune competent (I+) and 1- mice. The PK-PK model was used to determine GEP exposures associated with efficacy. PK-PD analyses were conducted using Phoenix WinNonlin 6.3 (Pharsight). The change in log_{10}–forming units (CFU) from baseline were correlated with free drug (I) AUC/MIC using an inhibitory model from the Phoenix library, and model parameter values for each isolate were used to calculate the plasma GEP/MIC associated with stasis, 1- or 2-log reductions in CFU.

Results. Plasma PK data were best fit by a 1-compartment IV model with first-order elimination and were similar in I+ vs. I- and thigh vs. kidney-infected mice. The AUC_{0-4} of GEP in kidney was approximately 4- to 5-fold higher than in plasma while the AUC_{0-4} in thigh was approximately half of plasma. In the I+ thigh model, median plasma GEP/MIC ratios for stasis, 1- or 2-log, reductions in CFU were 11, 16 and 25 (ranges 3–17, 4–25 and 7–40), respectively. Efficacy vs. E. coli ALL was similar in I- mice infected in thigh or kidney. In I+ mice, the PK-PD target was reduced by half.

Conclusion. Median plasma GEP/MIC targets ranged from 11 to 25. Higher drug levels in kidney vs. plasma or thigh did not translate into improved efficacy in pyelonephritis vs. thigh-infection models.

Disclosures. All authors: No reported disclosures.

1561. Omadacycline Pharmacokinetics: Influence of Mortality Risk Score Among Patients with Community-Acquired Bacterial Pneumonia

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