1114. Effectiveness and Safety of Beta-lactam Antibiotics with and without Therapeutic Drug Monitoring in Patients with Pseudomonas aeruginosa Pneumonia or Bloodstream Infection

Ashlan J. Kunz Coyne, Pharm.D.; Mohammad H. Al-Shaer, PharmD; Anthony M. Casapao, PharmD, MPh1; Jason Ferreira, PharmD; BCPs, BCCCP, FCCM; Carmen Isache, M.D.;1 Christopher Jankowski, Pharm.D., BCPS,1 UF Health Jacksonville, Jacksonville, Florida;2 University of Florida, Gainesville, Fl;3University of Florida College of Pharmacy, Jacksonville, Florida

Session: P-62. PK/PD Studies

Background. Pseudomonas aeruginosa (PSAR) is challenging to treat due to its multiple resistance mechanisms, limited anti-PSAR agents, and population pharmacokinetic (PK) variances. Beta-lactam antibiotics (BLA) are commonly used to treat PSAR infections and although they have a wide therapeutic index, suboptimal exposures may lead to treatment failure and antimicrobial resistance while high exposure may result in adverse effects. Certain patient populations may benefit from BLA therapeutic drug monitoring (TDM) due to their significant PK variability. The purpose of this study was to compare clinical outcomes in patients with PSAR pneumonia (PNA) or bloodstream infection (BSI) receiving BLA with and without the guidance of TDM.

Methods. Retrospective, parallel cohort study conducted at UF Shands Gainesville and UF Health Jacksonville evaluating five years of patients with PSAR PNA or BSI. TDM group was defined for routine BLA TDM compared to nonroutine BLA TDM service (non-TDM). Patients were excluded if they died before a culture or bloodstream infection (BSI) was obtained. PNA was defined as pneumonia due to PSAR in patients with another underlying condition. PNA due to PSAR in immunocompromised patients with primary hematology malignancies or solid tumors was also included. BSI was defined as bacteremia or fungemia due to PSAR. PSAR is considered to be resistant if it is resistant to 3 or more of the following classes of antibiotics: beta-lactams, aminoglycosides, fluoroquinolones, and carbapenems.

Results. Two-hundred patients were included (TDM n=95; non-TDM n=105). The overall primary composite outcome of presumed clinical cure occurred in 73% of patients (82% and 75% of the TDM and non-TDM cohorts, respectively; p=0.301). A post-hoc multivariate analysis was conducted to assess predictors of not attaining clinical cure.

Conclusion. While there was no difference in the primary composite outcome of presumed clinical cure, future studies can use these data to assess TDM patient selection and whether a bundled care approach of BLA regimens with known clinical benefit, early TDM-guided dose optimization, and continued clinical assessment improves outcomes in patients with PSAR PNA or BSI compared to use of each modality individually.

Figure 1. Boxplot of f_{cryst}/MIC ratios for BLA administered

Disclosures. All Authors: No reported disclosures

1115. Evaluation of Gepotidacin (GSK2140944) Pharmacokinetics and Food Effect in Japanese Subjects

Mohammad Hossain, PhD2; Courtney Tiffany, BSc1; Aline Barth, MSc,PhD; Aparna Raychaudhuri, Ph.D.2; Ettiene F. Dumont, MD;3 GlaxoSmithKline plc., Collegeville, PA, USA, Collegeville, Pennsylvania;1 GSK

Session: P-62. PK/PD Studies

Background. Gepotidacin, a novel, first-in-class triazaacenaphthylene antibiotic, inhibits bacterial replication and has in vitro and in vivo activity against key pathogens, including drug-resistant strains, associated with a range of infections. Gepotidacin is currently in Phase 3 clinical studies for the treatment of uncomplicated urinary tract infections and gonorrhea. This study (NCT02853435) was designed to assess gepotidacin pharmacokinetics (PK) in Japanese subjects (fasted and fed).

Methods. A tablet formulation of 1500 mg gepotidacin free base was used in the study, which was conducted in two parts: Part 1, gepotidacin PK was assessed following 1500 and 3000 mg single oral doses in the fasted state; and Part 2, gepotidacin PK was assessed following 1500, 2250, and 3000 mg single oral doses in the fed state. Serial blood and urine samples were collected in both study parts.

Results. The same formulation. Following gepotidacin dosing in the fasted state, the 1500 mg dose was tolerated, while the 3000 mg dose was poorly tolerated with mild or moderate gastro-intestinal adverse effects (GI AEs) reported by most subjects shortly
after being dosed. Part 2: PK was linear with doses in the range of 1500–3000 mg. Administration of gepotidacin 3000 mg tablets in the fasted state slightly reduced C_{max} and significantly increased AUC at the 3000 mg dose level. The 1500 and 2250 mg doses were tolerated while the 3000 mg dose was better tolerated compared to the fasted state with fewer and shorter-lived GI AEs, mostly mild in intensity. After oral administration of 1500–3000 mg, high urine drug concentrations were detected, remaining above the minimum inhibitory concentration of 4 μg/mL for up to 24 hours.

**Conclusion.** The PK of gepotidacin following administration of a single oral dose to Japanese subjects was linear from 1500–3000 mg and food decreased C_{max} without impact on exposure. Administration of gepotidacin resulted in an improved GI tolerability profile at the higher dose tested in Japanese subjects.

**Disclosures.** Mohammad Hossain, PhD, GlaxoSmithKline plc. (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) GlaxoSmithKline plc. (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) Etienne F. Dumont, MD, GlaxoSmithKline plc. (Employee, Shareholder, Former employee of and shareholder in GlaxoSmithKline plc.)

1117. Taxobactam Pharmacokinetic/Pharmacodynamic Target Attainment in Healthy Volunteers and Critically-Ill Hospitalized Patients

Shamir N. Kalaria, PharmD, PhD; Jason M Pogue, PharmD, BCPS, BCIDP; Emily Heil, PharmD, MS, BCIDP; Emily Heil, PharmD, MS, BCIDP; University of Maryland School of Pharmacy, University of Michigan, Ann Arbor, Michigan; University of Michigan School of Pharmacy, University of Maryland Medical Center, Baltimore, MD

**Session:** P-62. PK/PD Studies

**Background.** Pharmacokinetic/pharmacodynamic (PK/PD) targets and attainment are well described for beta-lactams; however, they are rarely considered for beta-lactamase inhibitors. Recent evidence suggests that taxobactam (TAZ) target exposures to restore piperacillin bacteriostatic activity and 1 log 10 bactericidal activity against Enterobacteriales are fT> the piperacillin/tazobactam (TZP) MIC of 16 mg/L and was 0.25 mg/L for bactericidal activity. These were only achieved with extended infusion administration where ~90% PTA was achieved for bacteriostasis was 1 mg/L and was 0.25 mg/L.

**Methods.** PK exposures in 1,000 patients with varying degrees of renal function were simulated using a previously described TAZ PK model developed with data from critically ill infected patients. An identical one-compartment structural model describing TAZ PK using mean population parameters observed in phase 1 PK studies was also used to simulate exposures in healthy volunteers. All simulated patients received 500 mg of TAZ as an intravenous infusion over 30 minutes or as a 3-hour extended-infusion.

**Results.** The table displays PTA results for patients with an estimated creatinine clearance of 60 mL/min. Based on healthy volunteer data, the highest TAZ MIC where ~90% PTA was achieved for bacteriostasis was 1 mg/L and was 0.25 mg/L for bactericidal activity. These were only achieved with extended infusion administration of TAZ. In the cohort of hospitalized patients, ~90% PTA of TAZ exposures associated with bacteriostasis and 1 log 10 bactericidal activity were achieved up to a MIC of 2 for intermittent infusion and up to 4 mg/L for extended infusion, due to decreased TAZ clearance in hospitalized patients. These values are significantly lower than the CLSI TAZ susceptible breakpoint of 16 mg/L, and PTA rates were lower at increased creatinine clearances.

| MIC (mg/L) | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 |
|-----------|------|-----|---|---|---|---|----|
| fT> | 90% | 90% | 90% | 90% | 90% | 90% | 90% |

**Conclusion.** fT-TZP MIC target attainment is poor with maximal package insert tazobactam doses given with piperacillin, even when administered as an extended infusion. These findings have serious implications for the role of TAZ in beta-lactamase producing Enterobacteriales, including ESBLs, and suggest the current susceptibility breakpoints for bacteriostasis and bactericidal activity (AUC_{0-24h}/MIC) are ~32 fold higher than those suggested by PK/PD data.

**Disclosures.** Jason M Pogue, PharmD, BCPS, BCIDP. Merck (Consultant); QPex (Consultant); Shionogi (Consultant); Utility Therapeutics (Consultant); VenatoRX (Consultant); Emily Heil, PharmD, MS, BCIDP. Nothing to disclose

1118. Population Pharmacokinetics of Contezolid Acosofamil and Contezolid – Rationale for a Safe and Effective Loading Dose Regimen

Jürgen B. Bulitta, PhD; Barry HAFKIN, MD, Edward Fang, MD; Florida University, Orlando, Florida; MicuRx Pharmaceuticals / Consultant, Austin, Texas; MicuRx Pharmaceuticals, San Carlos, California

**Session:** P-62. PK/PD Studies

**Background.** Contezolid (CZD) is a novel oral oxazolidinone with comparable activity and potentially improved safety compared to current oxazolidinones. The intravenous (IV) formulation of contezolid acosofamil (CZDa) is converted via MRX-1352 to active CZD. CZDa paired with CZD holds promise as a safe and effective treatment for serious Gram-positive infections such as those caused by methicillin-resistant Staphylococcus aureus. Sequential therapy with CZD IV followed by CZD oral (PO) offers flexible treatment options in hospital and outpatient settings for conditions such as diabetic foot infections. We aimed to design a CZD/CZDa dosage regimen leveraging population pharmacokinetic modeling (PopPK).

**Methods.** PopPK simultaneously fit data from 184 adult subjects. These were 1) plasma concentrations (by LC-MS/MS) of MRX-1352, CZD, and its metabolite MRX-1320 from 66 healthy subjects receiving CZD (150-2400 mg IV) for up to 10 days, 2) CZD and MRX-1320 concentrations from 44 healthy subjects receiving single CZD PO doses of 400, 800, or 1200 mg with and without food or multiple doses Q12h for up to 28 days, and 3) CZD concentrations from 74 Phase 2 patients receiving CZD 800 mg PO Q12h. PopPK and Monte Carlo simulations were used to optimize CZD exposures.

**Results.** CZDa was rapidly converted to MRX-1352, which was converted less rapidly to CZD. CZD was well absorbed and food enhanced its bioavailability. For CZD 400 mg PO with food, apparent total clearance of CZD was 13.1 L/h (22% coefficient of variation) in healthy subjects and 14.5 L/h (53% CV) in patients. The apparent volume of distribution at steady-state was 20.5 L. A loading dose of CZDa 2000 mg IV, then CZDa 1000 mg IV Q12h, and followed by CZD 800 mg PO Q12h achieved areas under the curve (AUC) between 75 and 100 mg*hour/L (medians; Figure) on all study days. Compared to CZD AUCs, the MRX-1352 AUCs during IV dosing were higher. While the median MRX-1320 AUCs were lower (18 to 48 mg*hour/L), some accumulation was predicted in ~5% of subjects.

**Figure.** Monte Carlo simulation of contezolid acosofamil 2000 mg IV at 0 h, then 1000 mg IV at 12, 24 & 36 h, followed by 800 mg oral contezolid Q12h

**Conclusion.** A loading dose of CZDa 2000 mg IV followed by either CZDa 1000 mg IV or CZD 800 mg PO Q12h was predicted to achieve efficacious CZD exposures on day 1 and maintain those exposures throughout therapy. This regimen will be evaluated in Phase 3 studies in complicated skin infections and diabetic foot infections.

**Disclosures.** Jürgen B. Bulitta, PhD, MicuRx Pharmaceuticals, Inc. (Consultant); Barry HAFKIN, MD, MicuRx Pharmaceuticals Inc. (Consultant)

1119. Assessment of Vancomycin Pharmacokinetic Parameters in Pediatric Patients After Liver Transplantation

Ronald Morales Jr., 1,2 Vanessa D. Jodoinis, n/a,3 Daniela Caro de Souza, n/a,3 Silvia Regina C. Jorge Santos, n/a,3 1 São Paulo University, São Paulo, São Paulo, Brazil; 2 Sao-Libanés Hospital, São Paulo, São Paulo, Brazil

**Session:** P-62. PK/PD Studies

**Background.** Vancomycin is largely prescribed to treat gram-positive bacterial infections in pediatric patients after liver transplantation with the same empirical doses prescribed in other critical conditions due to the absence of pharmacokinetic studies in this population. The objective of this investigation was to describe the vancomycin pharmacokinetic parameters and to assess the vancomycin percentage of target attainment with empirical regimen.

**Methods.** Prospective and longitudinal study with pediatric post-liver transplantation patients who received at least 48 hours of vancomycin between January 2020 and May 2021. Patients with acute or chronic renal failure or receiving renal replacement therapy were excluded. Vancomycin therapy started with 40–60mg/kg daily, one-hour infusion. The pharmacokinetic parameters were determined by one-compartment model with first-order kinetics using near steady-state postdistributional peak and trough within the same dosing interval. Therapeutic target was defined as vancomycin 24-hour area under the curve/minimum inhibitory concentration (AUC_{0-24}/MIC) ≥ 400 and < 600. The study protocol was approved by the local ethics committee.

**Results.** We included 18 sets of peak/trough serum concentrations obtained from 12 patients. The patients had median age of 11 (interquartile range [IQ] 8-16) months. The found vancomycin clearance, volume of distribution and half-life values were,