1555. Risk of Developing Acute Kidney Injury in Patients Receiving Piperacillin–Tazobactam and Vancomycin Compared with Those on Piperacillin–Tazobactam and Telavancin

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. The combination of piperacillin–tazobactam (PIP-TAZO) and vancomycin is associated with an increased frequency of acute kidney injury (AKI) in patients when compared with either agent alone. Like vancomycin, telavancin is also used for gram-positive infections and has been reported to cause AKI, but there is a paucity of data regarding the development of AKI with the combination of PIP-TAZO and telavancin. The purpose of this study was to compare the incidence of AKI in patients receiving PIP-TAZO with concomitant vancomycin or telavancin.

Methods. This retrospective cohort study included patients admitted between November 2016 and March 2019 who received at least 2 days of either vancomycin or telavancin in combination with PIP-TAZO. Patients were excluded if they had a baseline calculated creatinine clearance of less than 20 milliliters per minute or were receiving renal replacement therapy. Any cases of AKI were defined as a serum creatinine increase of 0.3 milligrams per deciliter (mg/dL) or an increase in creatinine of 1.5 times baseline when observed within 7 days of the studied antibiotic combinations. Statistical analysis was performed to compare baseline characteristics and the development of AKI between the two groups.

Results. Ninety-four patients with an average age of 55 years met the inclusion criteria. Forty-seven patients were included in both treatment arms. There were no statistically significant differences observed between study group baseline characteristics. All patients received PIP-TAZO 3.375 grams every 8 hours as a 4-hour infusion and the average telavancin dose was 7.5 mg/kg. Seventeen of 94 (18%) patients developed AKI, 8(17%) in the vancomycin and PIP-TAZO group and 9 (19%) in the telavancin and PIP-TAZO group ($P = 1.0$). No patients required dialysis.

Conclusion. The development of AKI appears to be similar when comparing vancomycin and PIP-TAZO to telavancin and PIP-TAZO in our population. It is noteworthy that PIP-TAZO was given as an extended infusion and telavancin dosing was lower than the manufacturer recommendations in this evaluation. Additional studies are warranted to further examine the occurrence of AKI with these antibiotic combinations.

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1556. Assessment of Translational *In Vitro* and Animal Pharmacokinetic–Pharmacodynamic Data Used to Support Drug Development of Recent Tetracycline Derivatives

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Background. Nonclinical (animal and *in vitro*) models are commonly used during the development of antibacterial drugs. Pharmacokinetic (PK) and pharmacodynamic (PD) data obtained from these nonclinical models are used to generate a PK-PD target, which can then be bridged to humans in a probability of PK-PD target attainment (PTA) analysis to support selection of the dose regimen for phase 3 trials and in vitro susceptibility testing criteria (breakpoints) to guide clinical usage.

Methods. Two recently approved tetracycline antibacterial drugs, eravacycline (ERV) and omadacycline (OMD), were evaluated. PK-PD data from nonclinical models and clinical microbiological response were collected from each of the respective clinical pharmacology reviews and assessments published by FDA and EMA, respectively. The highest MICs (minimum inhibitory concentrations) reflecting 80% success in the ability of the drug to inhibit growth in the target bacteria were identified from clinical and nonclinical data and termed the MIC cutoff. The nonclinical MIC cutoff was obtained from the PTA analysis using the PK-PD targets from animal studies. The clinical MIC cutoff was obtained from microbiological response (microbiological intent-to-treat population) data from clinical trial experience. The ratios of the clinical and nonclinical MIC cutoffs were calculated and used to evaluate potential discrepancies between the animal model prediction and clinical trial experience.

Results. The drug development programs for ERV and OMD included murine infection models and in vitro models to characterize PK-PD. The clinical to nonclinical MIC cutoff ratios ranged from 4 to 32. Higher values of the MIC cutoff signify that the drug can treat larger proportions of the bacterial population; therefore, high clinical to nonclinical MIC cutoff ratios signify that the drugs had more activity in reducing the bacterial population in clinical than in nonclinical studies.

Conclusion. Thus, the nonclinical models for ERV and OMD under-predicted microbiological response and breakpoints. While nonclinical models are generally useful, more characterization of translational factors may be needed to allow nonclinical models to be more predictive of clinical trial outcomes.

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1557. Population Pharmacokinetics of Suvratoxumab (MEDI4893), an Extended Half-life *Staphylococcus aureus* Alpha Toxin-Neutralizing Human Monoclonal Antibody, in Healthy Adults and Patients on Mechanical Ventilation in Intensive Care Units

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Suvratoxumab (suvra), an extended half-life (~80 days), *Staphylococcus aureus* (SA) alpha toxin-neutralizing IgG monoclonal antibody, is under investigation for prevention of SA pneumonia in patients on mechanical ventilation (MV). We characterized the serum PK of suvra using population pharmacokinetics (popPK) in both healthy volunteers and MV patients and quantified the proportion of patients reaching the serum target of 211 µg/mL at 30 days post-dose.

Methods. The popPK analysis included 1,368 serum samples from two early phase studies (NCT02296320; EudraCT 2014-001097-34): (1) Phase 1 study in 26 healthy adults receiving single IV suvra doses ranging from 0.225g to 5g, with PK sampled up to 360 days; and (2) Phase 2 study in MV patients with PCR-confirmed SA colonization of lower respiratory tract receiving one suvra IV dose of 2g ($n = 15$) or 5g ($n = 96$), with PK sampled up to 100 days.

Results. A two-compartment linear model with weight-based scaling of the PK parameters adequately described the serum PK data (Figure 1). MV status, number of days on MV, and age impacted the PK of suvra. A moderate between-subject variability (<45% CV) was estimated for key PK parameters. An estimated two-fold increase in MV patients' volume of distribution parameters compared with healthy volunteers explained the observed C_{max} differences between the two groups (1145±369 µg/mL vs. 1783±396 µg/mL) (Figures 2 and 3). Although age, MV status and days on MV post-dose appeared to be associated with higher systemic clearance (CL) in the model, this estimate could be biased due to limited PK data available for only one half-life (~90 days) of the drug in MV patients (Figure 2). More patients achieved suvra levels above the PK target following the 5 g (73.5%; 50/68) vs. 2 g dose (7.6%; 1/13) at 30 days post-dose.

Conclusion. MV status, post-dose duration on MV, body weight, and age were identified as statistically significant covariates influencing the PK of suvra. Serum PK and popPK analyses support the 5g dose for future studies with suvra in MV patients.