Pooled nephrotoxicity rates from trough-guided monitoring

Conclusion. The AUC-guided approach appeared to have lower risk of nephrotoxicity which supports the updated American Society of Health-System Pharmacists recommendations. More studies should be performed to evaluate the optimal derivation of AUC and clinical utility of repeated measurements of vancomycin AUC and trough levels.

Disclosures. **All Authors**: No reported disclosures

1098. A Phase 1 Safety and Tolerability of Single Ascending Doses of a Novel Engineered Cationic Peptide, PLG0206, in Healthy Subjects

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Session: P-62. PK/PD Studies

Background. PLG0206 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections (PJI). This abstract presents the results from the first in human study to evaluate the safety, tolerability and pharmacokinetic (PK) profile of PLG0206 when administered as an intravenous (IV) infusion.

Methods. 6 cohorts of 8 participants were planned to receive escalating single 1-hour IV infusions of PLG0206 at 0.05, 0.125, 0.25, 0.5, 1, 2 and 3 mg/kg dose or placebo. Participants were randomized to receive either PLG0206 (6 per cohort) or placebo (2 per cohort). At each dose level, there were 2 sentinel participants (1 active, 1 placebo) who were dosed at least 48 hours in advance of the other participants in their group. Serial pharmacokinetic samples were taken prior to infusion and up to 48 post infusion. Safety and tolerability was assessed throughout the study. There was at least a 7-day period after dosing at each of the dose levels before dose escalation.

Results. PLG0206 was safe and well tolerated when administered to healthy volunteers at doses ranging from 0.05 and 1 mg/kg. Therapeutic exposures were achieved at 1 mg/kg. The 2 and 3 mg/kg cohorts were not studied. The incidence of treatment emergent adverse events related to study drug administration was low and most events mild (Grade 1) in severity and was similar between the PLG0206 treatment and placebo groups. There were no SAEs, life-threatening events or deaths throughout the study. IV PLG0206 exhibited linear PK over the dose range of 0.05 to 1.0 mg/kg. The median terminal half-life (t½) ranged from 7.37 to 19.97 hours. $AUC_{0-\infty}$ increased with increasing PLG0206 dose ranging between 1581.41 and 21141.52 ng.hr/mL. Cmax ranged between 256 and 2653 ng/mL. The mean apparent volume of distribution (Vz) increased was between 25.49 and 94.2 L, mean clearance (CL) were similar across all and ranged from 2.42 to 4.18 L/hour.

Conclusion. Following single IV infusion to healthy volunteers, PLG0206 was safe and well tolerated at doses ranging from 0.05 to 1 mg/kg. IV PLG0206 exhibits linear PK over the dose range. These findings support the ongoing development of IV PLG0206 and will inform dosing regimens in future studies to investigate its utility as an antimicrobial agent.

Disclosures. **David Huang, MD, PhD**, **Peptilogics** (Employee) **Despina Dobbins, BS**, **Peptilogics** (Employee) **Parviz Ghahramani, PhD, PharmD, MSc, MBA**, **Peptilogics** (Consultant) **Jonathan Steckbeck, PhD**, **Peptilogics** (Employee)

1099. Evaluation of the Safety and Pharmacokinetics (PK) following Administration of Single and Multiple Doses of Anti-Staphylococcal Lysin, LSVT-1701, in Healthy Adult Subjects

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Session: P-62. PK/PD Studies

Background. LSVT-1701 is an anti-staphylococcal phage lysin being developed for treatment of MRSA infections in combination with SoC antibiotics. The safety and PK of single ascending doses of LSVT-1701 0.1 to 10 mg/kg in healthy adult volunteers were previously described (Jun, et.al, AAC 2017;61:e02629-16). We further evaluated the safety and PK of multiple ascending doses of LSVT-1701 in healthy adult subjects.

Methods. Study ITB-101-1b was a Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study. 8 subjects were randomized 3:1 to active:placebo in each cohort. LSVT-1701 was administered as a 6 mg/kg single dose and twice daily (BID) doses of 1.5, 3.0, and 4.5 mg/kg for 4 days (24h between Doses 1-2, 12h between Doses 2-6). Study drugs were administered as a 1-hour IV infusion. Serial serum samples were collected over 24 hours following the first and last doses for measurement of LSVT-1701 concentrations by a validated ELISA method. PK analysis of LSVT-1701 concentration-time data was done using noncompartmental methods. Safety was assessed by AEs, clinical labs, vital signs, and ECG.

Results. 30/32 (94%) subjects completed the study. No subjects withdrew due to AEs, and there were no severe AEs, no serious AEs, and no deaths. AEs were of mild (97%) to moderate (3%) intensity and were reported by all subjects in the LSVT-1701 6 mg/kg single dose group and 1-3 (17-50%) of subjects receiving 1.5 to 4.5 mg/kg BID or placebo. The most common AEs of headache, chills, rigors, and fever generally lasted for ≤2 days with or without acetaminophen treatment, and no clinically significant changes in blood pressure, heart rate, ECG, or clinical labs (other than transient increases in CRP) were observed. Infusion site reactions (erythema, pain, induration, warmth) were observed with BID administration of LSVT-1701, but not with the single 6 mg/kg dose or placebo. LSVT-1701 exposure increased greater than in proportion to dose and $t_{1/2}$ was concentration-dependent, increasing with higher doses. No accumulation in LSVT-1701 exposure was observed.

Summary of LSVT-1701 PK Parameters

LSVT-1701 Dose (mg/kg) BID [N=6/cohort]	Day	Mean (SD)		
		AUC[a] (µg.h/mL)	Cmax (µg/mL)	t/1/2 (h)
1.5 single dose (N=6)	1	1.14 (0.519)	1.24 (0.509)	0.39 (0.08)
3.0 single dose (N=6)	1	5.70 (1.35)	4.93 (1.08)	0.73 (0.21)
4.5 single dose (N=6)	1	11.8 (1.15)	10.8 (1.53)	1.16 (0.29)
6.0 single dose (N=6)	1	24.8 (7.05)	21.4 (3.91)	3.38 (3.40)
1.5 BID (N=6)	4	1.23 (0.657)	1.30 (0.696)	0.45 (0.16)
3.0 BID (N=6)	4	5.70 (1.34)	5.01 (1.21)	2.02 (0.78)
4.5 BID (N=6)	4	10.3 (1.56)	10.2 (1.43)	3.72 (2.85)

[a]AUC = AUCinf for single doses (Day 1) and AUCτ for multiple dose (Day 4)

Summary of LSVT-1701 PK Parameters

Conclusion. The safety and PK profile of LSVT-1701 is favorable for evaluation in patients with

S. aureus infections, including bacteremia and infective endocarditis, for which new treatments are needed.

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1100. A Prospective Evaluation of Neurotoxicity Among Patients Receiving Dose-Optimized Cefepime or Meropenem With Concomitant Therapeutic Drug Monitoring

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Session: P-62. PK/PD Studies

Background. Cefepime (FEP) induced neurotoxicity (NT) may have serious implications for patients (pts). Retrospective studies have employed variable definitions of NT, finding renal impairment and FEP trough concentrations (Cmin) > 20 mg/L as risk factors. Prospective studies comparing antibiotics have not been performed.

Methods. We conducted a prospective study of pts receiving FEP or meropenem (MEM) with neurologic evaluation and therapeutic drug monitoring (TDM). A NT advisory board (NTAB) was established to develop standardized definitions of possible, probable and definitive NT (Fig 1). Cases of potential NT were adjudicated by the NTAB who were blinded to study treatment. FEP and MEM midpoint and Cmin concentrations were measured at steady-state by validated methods.

Figure 1. Neurotoxicity Definitions

Beta-lactam Neurotoxicity	Onset of Symptoms	Alternative Diagnosis	EEG Findings	Neuroimaging findings	Clinical Improvement
Unlikely	Prior to beta-lactam initiation or after beta-lactam discontinuation	Alternative diagnosis **more likely** to have caused clinical syndrome	EEG normal or changes **consistent** with alternative explanation	Neuroimaging **absent or inconclusive** for etiology of neurotoxicity.	No clinical improvement after discontinuation of beta-lactam
Possible	During beta-lactam therapy	Alternative diagnosis **as likely** to have caused clinical presentation	EEG changes **equally consistent** with beta-lactam neurotoxicity or alternative explanation	Neuroimaging **absent or inconclusive** for etiology of neurotoxicity.	No clinical improvement or unclear clinical improvement after discontinuation of beta-lactam
Probable	≤ 5 days from ≥ 1 of the following: Beta-lactam initiation or Dose increase or Worsening renal function	Alternative diagnosis **less likely** than beta-lactam to have caused symptoms	EEG changes **consistent** with beta-lactam neurotoxicity and alternative explanation **less likely**	Neuroimaging **less likely** to support alternative etiology of neurotoxicity	Clinical improvement after discontinuation of beta-lactam
Definitive	≤ 5 days from ≥ 1 of the following: Beta-lactam initiation or Dose increase or Worsening renal function	Alternative diagnosis **much less** likely to have cause symptoms	EEG changes **consistent** with beta-lactam neurotoxicity **without** alternative explanation **and** improvement in EEG **off** of beta-lactam	Neuroimaging **not supportive** of alternative etiologies for neurotoxicity	Clinical improvement after discontinuation of beta-lactam

Objective Neurotoxicity	Subjective Neurotoxicity	Neurologic Adverse Reactions
Ataxia	Altered mental status	Headache
Encephalopathy	Cognitive disturbances	Dizziness
Myoclonus	Paresthesia	Blurry vision
Seizures	Somnolence	Other
Non-epileptiform EEG changes (See separate chart)	Difficulty awakening from sedation	

Neurotoxicity Advisory Board (NTAB)	
ID Physician	ID Pharmacist
Intensivist	Neuro Intensivist
Epileptologist x2	

Results. 127 patients were included (70 FEP, 57 MEM). Demographics and treatment characteristics were similar between groups (Fig 2); 63% were in the ICU. FEP and MEM Cmin varied from 1.9 – 140.5 and 0.6 – 31.3 mg/L, respectively. Median FEP Cmin and total exposures (AUC) were 23.1 mg/L and 347.6 hr*mg/L, respectively. Corresponding MEM values were 5.9 mg/L and 124.8 hr*mg/L, respectively. Cmin values were inversely correlated with renal function for both FEP and MEM (P< 0.001). Rates of possible, probable, or definitive NT were 10% and 5% for FEP and MEM, respectively (P=0.51; Fig 3). 16% and 3% of pts with FEP Cmin > or < 20 mg/L had NT, respectively (P=0.11; Fig 4). Median MEM Cmin were 12.3 and 5.4 mg/L among pts with and without NT, respectively (P=0.09; Fig 4). Rates of NT did not vary by infusion length or dose. FEP and MEM exposures were similar between patients with (17%) or without (83%) microbiologic recurrence due to the same pathogen. FEP was discontinued in 4 pts due to NT; no pts stopped MEM due to NT.