1531. A Twenty 3-Year Retrospective Study of Secondary Hemophagocytic Syndrome in a Pediatric Third-Level Referral Center in Mexico City

Napoleon Gonzalez Saldaña, MD; Francisco Javier Otero Mendoza, MD; Ana Jocelyn. Carmona Vargas, MD; Izveidy Zuyino Mondragon Salinas, Medical Doctor; Instituto Nacional de Pediatria, Mexico City, Distrito Federal, Mexico

Session: 161. Pediatric ParaInfectious Syndromes

Friday, October 4, 2019: 12:15 PM

Background. Secondary hemophagocytic syndrome (SHS) may develop as a result of excessive immune activation, with proliferation of T cells and macrophages. It is often fatal and remains ill-recognized in children, leading to false or delayed diagnosis and suboptimal management. This condition has been described more often in association with virus, but it can be secondary to bacteria, fungi, and parasites.

Methods. Retrospective, descriptive, and observational study. We systematically reviewed the clinical files of patients diagnosed with SHS at the Instituto Nacional de Pediatría between January 1995 and December 2018; age, gender, clinical features, laboratory results, management, and final outcome were registered.

Results. 49 cases of SHS were diagnosed, 26 (53%) were male, mean age at diagnosis was 67.5 months (newborn–15.5 years), 47 (96%) presented with fever, 46 (94%) hepatomegaly, 37 (76%) splenomegaly, 28 (57%) lymphadenopathy, 18 (37%) jaundice, and 4 (8%) bleeding. The most common laboratory findings were anemia in 29 (59%) patients, thrombocytopenia in 39 (80%), hypertriglyceridemia in 39 (80%), with isolation of Epstein Barr Virus in 18 (35%), followed by Cytomegalovirus in 2 (4%), *Escherichia coli* in 2 (4%), *Salmonella enterica* in 2 (4%), and *Leptospira*, *Brucella abortus*, *Shigella sonnei*, *Enterococcus faecium*, Enterovirus and congenital Rubella in 1 case each (2%). Intravenous Gamma-globulin therapy was administered to 38 (78%) patients, antimicrobials to 26 (53%), systemic steroids to 46 (94%) and VP16 to 32 (65%). 22 (45%) had full recovery, 6 (12%) patients presented with a recurrent episode of SHS, and 21 (43%) died.

Conclusion. Due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings, the diagnosis of SHS is often delayed. EBV remains an important etiologic agent of this syndrome, identified in 35% of our cases. The mortality rate around the world is reported approximately around 45%, confirmed in our study in 43% of the cases, remarking the importance of prompt diagnosis and treatment to increase the survival in our population.

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

1532. Population Pharmacokinetic (PPK) Modeling and Simulation of Long-Acting (LA) Cabotegravir (CAB) to Inform Strategies Following Dosing Interruptions in HIV-1-Infected Subjects

Kelong Han, PhD[1]; Mark Baker, PhD[2]; Parul Patel, PharmD[2]; David Margolis, MD, MPH[2]; William Spreen, PharmD[2]; Katy P. Moore, PharmD, RPh[2]; Susan L. Ford, PharmD[1]; [1]GlaxoSmithKline, Collegeville, Pennsylvania; [2]ViiV Healthcare, Nyon, Vaud, Switzerland

Session: 162. PK/PD and Susceptibility Testing

Friday, October 4, 2019: 12:15 PM

Background. CAB is an integrase strand transfer inhibitor under investigation as an injectable LA formulation for the treatment and prevention of HIV, and as a tablet formulation as an oral lead-in (OLI) and bridging treatment for dose interruptions. The monthly injection regimen of CAB LA and rilpivirine (RPV) LA was noninferior to standard oral therapy in maintaining HIV-1 suppression in Phase 3 trials. PPK modeling and simulation was used to inform strategies for managing dosing interruptions.

Methods. A 2-compartment model with first-order oral and LA absorption and elimination adequately described the data from 1,647 healthy (28%) and HIV-infected (72%) adult subjects in 16 studies. Gender was a significant covariate on LA absorption; therefore, simulations of 5,000 virtual subjects were performed using a 4:1 male:female ratio to ensure 1,000 representative females and covariate sampling with replacement from the analysis dataset. One- to 12-week delays in dosing of the second, third, and fourth injection were simulated, and predicted troughs were compared with the 5th percentile (0.65 µg/mL) of trough concentrations following the first injection in Phase 3. Simulations of 1–2 months of oral bridging with CAB 30 mg once daily from time of a missed injection until CAB LA dosing resumed were performed, with the median Cmax (13.1 µg/mL) observed following oral CAB 60mg once daily in Phase 2b as an upper reference.

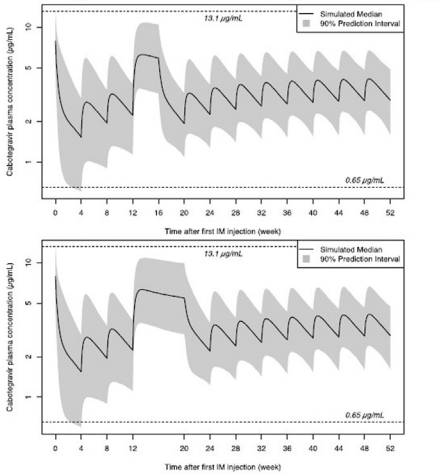
Results. Proportions of subjects predicted to achieve target plasma CAB trough concentrations are shown by length of delay and injection visit in Table 1. Oral bridging with CAB 30mg once daily starting at the time of a planned missed injection is predicted to provide exposures within ranges observed in clinical studies (Figure 1).

Conclusion. Dosing delays of up to one week appear to have minimal impact, but the effect is more likely to become problematic with longer delays, particularly in the first few months of dosing. Oral bridging provides therapeutic and safe exposures for planned interruptions in LA dosing. Regardless of use of oral bridging, simulations support resuming CAB LA dosing for interruptions <1 month (<2 months between injections) and reinitiating CAB LA with a loading dose and subsequent monthly injections for interruptions ≥ 1 month (≥ 2 months between injections).

Table 1. Proportion of Subjects (%) with Predicted Plasma CAB Trough Concentrations >0.65 µg/mL

Delayed Injection	Length of Delay (Weeks)							
	None	1	2	3	4	6	8	12
2nd	93.3	92.3	90.1	87.6	81.2	61.2	37.9	10.2
3rd	98.1	97.8	97.2	94.0	91.3	79.4	64.9	35.3
4th	99.2	99.0	98.2	96.1	92.9	85.3	72.5	48.4

Figure 1 **Simulated CAB Plasma Concentration-Time Profiles of Planned Injection Delays with Oral Bridging for 1 month (Resuming with 400 mg IM Dose (upper panel)) and 2 months (Resuming with 600 mg IM Dose (lower panel))**



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

1533. Is Cation-Adjusted Mueller–Hinton Broth (CAMHB) Appropriate for Metallo-β-lactamase (MBL) Susceptibility Testing? Novel Insights in *In Vitro–In Vivo* Discordance Among MBL-Producing Enterobacteriaceae

Tomefa E. Asempa, PharmD; Kamilia Abdelraouf, PhD; David P. Nicolau, PharmD; Hartford Hospital, Hartford, Connecticut

Session: 162. PK/PD and Susceptibility Testing

Friday, October 4, 2019: 12:15 PM

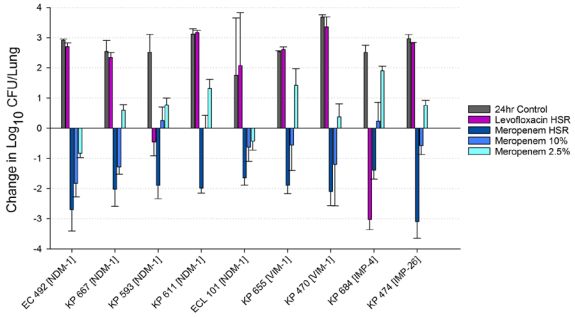
Background. MBLs, which require Zn for catalytic activity, are a major contributor to high-level β-lactam resistance when tested using conventional CAMHB. We have previously reported marked reductions in meropenem (MEM) MICs in Zn-depleted media (Chelex-CAMHB and EDTA-CAMHB; Zn [C] <0.002 mg/L) compared with conventional CAMHB (Zn [C] 0.959 mg/L) against a variety of MBL-producing isolates, whereas Zn-depletion had no impact on levofloxacin (LVX) MICs (ASM Microbe 2019, San Francisco. Abstract P508). To explore in vivo implications, we evaluated the efficacy of MEM human simulated regimen (HSR) against MBL-producing isolates in a murine pneumonia model. In addition, LVX HSR was examined for model validation.

Methods. Nine MBL-producing isolates (NDM, *n* = 5; VIM, *n* = 2; IMP, *n* = 2) were utilized. CAMHB, Chelex-CAMHB, and EDTA-CAMHB MEM MICs ranged from 16 to > 64, ≤0.0625 to 0.5, and ≤ 0.0625 to 0.5 mg/L, respectively. LVX MICs ranged from ≤ 0.0625 – > 64 mg/L. Neutropenic lung-infected ICR mice received a MEM HSR of 2g q8h [1.5 hours infusion], 2 lower MEM exposures or LVX 750 mg q24h HSR. Zn [C] were determined in the epithelial lining fluid (ELF) of infected mice.

Results. LVX displayed predictable in vivo efficacy consistent with its phenotypic profile irrespective of the media utilized for MIC testing (figure). Despite attaining zero %T> MIC using values generated in CAMHB, MEM HSR produced marked bacterial reductions against all MBL-producing isolates (figure). Reductions in MEM exposures produced bacterial killing concordant with its pharmacodynamic profile using Zn-depleted CAMHB MIC values. Zn [C] in infected murine ELF were undetectable, i.e., <0.002 mg/L.

Conclusion. Our results indicate that MEM in vivo efficacy is best represented by the pharmacodynamic profile generated using MICs determined in Zn-depleted media for MBL-producing Enterobacteriaceae. These observations are consistent with the case reports describing positive outcomes in MBL-infected patients following treatment with carbapenems (Infection 2018;46:1–13). Our translational data suggest that the use of conventional CAMHB for MBL susceptibility testing is inappropriate in distinguishing meaningful in vivo resistance given that Zn [C] are supraphysiologic in conventional CAMHB and negligible at infection sites.

Figure. Mean change in $\log_{10}$CFU/lung ± SD at 24hr relative to 0hr controls with levofloxacin HSR, meropenem HSR, meropenem 10%, and meropenem 2.5% against MBL-producing Enterobacteriaceae



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