IDweek2022
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Population Pharmacokinetics of Ceftazidime-Avibactam in Combination with Aztreonam in a Phase I, Open-Label Study in Healthy Adult Subjects

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ABSTRACT

Background: Scant PK data are available with ceftazidime-avibactam (CZA) with aztreonam (ATM) in combination. Occurrence of asymptomatic ALT/AST elevations are common with ATM, and it is unknown if it is exacerbated by use of CZA-ATM. This analysis of COMBINE sought to describe the popPK of CZA-ATM and to assess the association between ATM exposures and ALT/AST elevations.

Methods: COMBINE was a Phase I study of 48 healthy subjects aged 18-45 years (NCT03978091). Subjects were enrolled into 1 of 6 Cohorts (Table 1). Drug(s) were administered for 7 D and intensive plasma and urine PK sampling was performed. Population PK (PopPK) models were developed for ceftazidime (CAZ), avibactam (AVI), and ATM. Empirical Bayesian estimates from the ATM PopPK model were used to simulate ATM day 1 (D1) exposures. Associations between D1 ATM exposures and highest observed ALT/AST were assessed with curvilinear regression (CR) and generalized linear models (GLM).

Results: Of enrolled 48 subjects, 19 subjects (40%) had ALT and/or AST elevations; 17 of 19 (89%) ALT/AST elevations occurred in ATM/CZA-ATM Cohorts. Two severe study product related ALT/AST AEs were observed with in the continuous infusion (CI) ATM Cohort, resulting in a study halt. All subjects with ALT/AST elevations were asymptomatic with no other signs of liver injury. In the ATM PopPK model, CZA-ATM administration reduced ATM non-renal clearance (CL_{NR}) by 1 L/hr (16% of total CL) (**Table 2**). Administration of CAZ-ATM had a negligible effect on total CAZ CL in the CAZ PopPK model and CZA-ATM was not a covariate in final AVI PopPK model. In the CR, no ATM exposure-ALT/AST associations were identified in overall analyses. Modest associations between Day 1 (D1) $C_{max,ss}$, AUC_{0-24h} and ALT/AST were observed in CR analyses restricted to the intermittent infusion (II) ATM Cohorts (**Figures 1 and 2**). In GLM, D1 $C_{max,ss}$ and AUC_{0-24h} were significantly associated with ALT/AST in the ATM II Cohort analyses. Administration of CZA-ATM was not associated with ALT/AST elevations in the GLM analyses.

Conclusions: Administration of CZA-ATM was found to reduce ATM CL, resulting in higher daily ATM AUC_{0-24h}, but did not exacerbate AST/ALT elevations relative to ATM alone. The observed associations between ATM Day 1 $C_{max,ss}$, AUC_{0-24h} and ALT/AST elevations in subjects who received II ATM suggest the risks vs benefits of using II of ATM 8 g/daily with CZA should be considered. Use of CI ATM should be used with caution given the 2 severe ALT/AST AEs in the CI ATM Cohort.

BACKGROUND

- Metallo-β-lactamases (MBLs) are an emerging resistance determinant in many Gram-negative bacteria (PMID: 27593176).
- Aztreonam (ATM) is one of the two commercially available β-lactams that are not hydrolyzed by MBLs but many MBL-producing Gram-negative bacteria express β-lactamases that inactivate ATM (PMID: 28167541).
- To circumvent this clinical conundrum, clinicians co-administered ATM with ceftazidime-avibactam (CZA) to treat patients with MBL-producing Gram-negative infections with reported success (PMID: 32427286).
- Despite its increasing use, there are currently scant published PK data when CZA-ATM are administered concurrently.
- Patients who receive ATM are at risk for serum aminotransferase elevations (https://livertox.nlm.nih.gov/Aztreonam.htm), and it is unclear if CZA-ATM exacerbates the association between ATM and occurrence of liver enzyme elevations relative to ATM alone.

OBJECTIVES

- This phase 1 study evaluated the PK profile of CZA combined with ATM relative to its standalone counterparts and assess for the presence of an ATM exposure-ALT/AST elevation association when ATM is administered alone and in combination with CZA.

METHODS

Study Design and PK Population

- COMBINE (ClinicalTrials.gov Identifier: NCT03978091) was Phase I, open-label, single center study that investigated the safety and PK of 7 days of CZA-ATM, CZA alone, and ATM alone in 48 healthy adult male and female volunteers aged 18-45 years.
- Eligible subjects were sequentially assigned to 1 of 6 dosing Cohort (**Table 1**)
- Eligible subjects were admitted to the phase 1 study unit for 7 days to receive study product(s) and the final outpatient follow-up visit was Study Day 11 +3 days.
- Study safety was monitored using daily assessments of AEs, vital signs, and symptom-directed physical examinations from Day 1 through the Final Study Visit (Day 11 +3).
- Intensive plasma PK sampling was conducted in each Cohort on Day 1 after 1st dose and Day 7, and pre-dose sampling in Days 3 and 5.
- Urine PK samples were collected in each Cohort at the following intervals: >0 to 4, >4 to 8, >8 to 12, and >12 to 24 hours after the start of the morning dose on Day 1 and Day 6.

Table 1. Investigational Study Drug Cohorts (8 Subjects/Cohort)

Cohort	Investigational Study Drugs
1	CZA 2.5 g intravenously (IV) as 2-hour (hour) infusion Q8H
2	CZA 2.5 g IV as 2-hr infusion x 1, then 0.32 g per hr IV daily as a continuous infusion (CI) (7.5 g/day)
3	ATM 2 g IV as 2-hr infusion Q6H
4	ATM 2 g IV as a 2-hr infusion x 1, then 0.33 g per hr IV daily as a CI (8 g/day)
5*	CZA 2.5 g IV as 2-hr infusion Q8H and ATM 1.5 g IV as 2-hr infusion Q6H
6*	CZA 2.5 g IV as 2-hr infusion Q8H and ATM 2 g IV as 2-hr infusion Q6H

*Cohorts 5 and 6 reflect modified dosing regimens. Initial regimen for Cohort 5 was CZA 2.5 g IV as 2-hour infusion Q8H and ATM 2 g IV as 2-hour infusion Q6H. Initial regimen for Cohort 6: CZA 2.5 g IV as a 2-hour infusion x 1, then 0.32 g per hour IV daily as CI (7.5 g/day) and ATM 2 g IV as 2-hour infusion x 1, then 0.33 g per hour IV daily as CI (8 g/day). A halting rule was observed in Cohort 4 (2 subjects experienced Grade 3 related ALT/AST elevations). Due to study halt, the dosing in the Cohorts 5 and 6 were changed.

PK Evaluable Population

- PK evaluable population included subjects who received CZA, ATM alone, or CZA-ATM and had ≥ 1 quantifiable plasma or urine concentration of CAZ, AVI, or ATM.

Population PK (PopPK) Analyses

- The PopPK analyses were conducted using the first-order conditional estimation method of NONMEM (Version 7.4, Icon Solutions, Ellicott City, MD, USA).
- Population PK (PopPK) models were developed separately for CAZ, AVI, and ATM.
- 1- and 2-compartment base PopPK models were evaluated for each study product.
  - The best model structure for plasma PK for each study product was then linked to a separate compartment for urine PK via renal clearance (CL_R).
- A forward inclusion (p <~0.05 and Δ objective function value (OFV) >3.84) and backward elimination (p <~0.01 and ΔOFV >6.64) with 1 degree of freedom was used to identify significant baseline covariates for inclusion in each of the final PopPK models.
- Successful minimization, diagnostic plots, plausibility and precision of parameter estimates, objective function and shrinkage values, and prediction corrected visual predictive checks were used to assess the appropriateness of each final PopPK model.

ATM Exposure-Highest Observed ALT/AST Exposure Response Analyses

- Day 1 ATM exposure variables ($C_{max,ss}$, $C_{min,ss}$, and AUC_{0-24h}) were estimated for each subject who received ATM from the final ATM PopPK model, empirical Bayesian estimates, and individual dosing histories.
- The relationships between Day 1 ATM exposures and highest observed ALT/AST values were evaluated graphically using (Locally Weighted Scatterplot Smoothing (LOWESS) curves.
- Associations between Day 1 ATM exposures and highest observed ALT/AST were assessed with curvilinear regression (CR) and generalized linear models (GLM).

RESULTS

PK Evaluable Population (N=48 subjects)

- Median (range) age was 32 (22–45) years and median (range) weight was 74.3 (53.3-104.6) kg.
- Half were female and median (range) baseline creatinine clearance was 118.34 mL/min (75.7-209.6) mL/min.
- The subjects contributed a total of 3,475 PK samples (2,733 plasma and 742 urine).
- Nineteen subjects (40%) experienced an asymptomatic ALT and/or AST elevation of any relatedness.
  - Seventeen of the 19 subjects (89%) with ALT/AST elevations received ATM or CZA-ATM.
  - Two patients in the ATM CI Cohort had severe ALT/AST elevations, which halted the study.

Population PK Analyses

- A 2-compartment PopPK model with first-order elimination linked to a compartment for urine elimination best characterized the plasma and urine PK data of each study product.
- Final PopPK Models for CAZ, AVI, and ATM are shown in **Tables 2 and 3**.
  - PopPK CAZ model: CZA-ATM was a significant covariate on CL_R and non-renal clearance (CL_{NR}) but the net change of CZA-ATM administration on total CL was negligible.
  - PopPK AVI model: CZA-ATM was not a significant covariate on any PK parameters.
  - PopPK ATM model: CZA-ATM administration reduced CL_{NR} by 1 L/h (16% of overall CL), resulting in increased daily ATM exposures.

Table 2. Final Population PK Models and Parameter Estimates for CAZ, AVI, and ATM

Final Ceftazidime PopPK Model			Final Avibactam PopPK Model			Final Aztreonam PopPK Model		
Param	Estimate	RSE	Param	Estimates	RSE	Param	Estimates	RSE
CL_R (L/h)	5.69	3.8%	CL_R (L/h)	12.20	2.7%	CL_R (L/h)	4.79	3.3%
V_1 (L)	10.50	4.0%	V_1 (L)	12.40	4.5%	V_1 (L)	3.77	37.9%
Q (L/h)	6.93	10.3%	Q (L/h)	7.81	9.3%	Q (L/h)	28.7	24.3%
V_2 (L)	8.40	4.0%	V_2 (L)	9.06	4.9%	V_2 (L)	9.87	13.7%
CL_{NR} (L/h)	2.89	8.6%	CL_{NR} (L/h)	1.39	25.5%	CL_{NR} (L/h)	2.66	5.8%
$\theta_{(CLR-LBW)}$	0.0146	17.5%	$\theta_{(V1-LBW)}$	0.0194	22.9%	$\theta_{(CLR-CLcr)}$	0.622	20.4%
$\theta_{(V1-LBW)}$	0.0166	22.8%	$\theta_{(Q-LBW)}$	0.021	42.2%	$\theta_{(V1-BSA)}$	4.11	34.5%
$\theta_{(Q-LBW)}$	1.42	32.5%	$\theta_{(V2-LBW)}$	0.0214	23.0%	$\theta_{(CLNR-IND)}$	-0.391	14.0%
$\theta_{(V2-LBW)}$	0.0254	1.01%	$\theta_{(CLR-CLcr)}$	0.00453	21.0%			
$\theta_{(CLNR-ATM)}$	-0.905	6.3%	$\theta_{(Q-CI)}$	-0.407	20.3%			
$\theta_{(CLR-ATM)}$	1.39	4.9%						
$\theta_{(CLR-SCR)}$	-0.494	25.3%						
$\theta_{(Q-CI)}$	-0.396	21.8%						

Footnotes: Param: Paramter; V_1: the volume of the central compartment; Q: inter-compartmental clearance; V_2: volume of the peripheral compartment; CL_R: renal clearance; CL_{NR}: non-renal clearance; RSE: relative standard error.

Table 3. Inter-Individual Variability and Error Terms For Final Population PK Models

Final Ceftazidime PopPK Model				Final Avibactam PopPK Model				Final Aztreonam PopPK Model			
Inter-Individual Variability (%)											
IIV/BSV	CV	RSE	ETA Shrinkage	IIV/BSV	CV	RSE	ETA Shrinkage	IIV/BSV	CV	RSE	ETA Shrinkage
CL_R	8.6%	22.5%	16.7%	CL_R	8.1%	26.7%	29.6%	CL_R	10.9%	20.5%	14.5%
V_1	12.9%	20.2%	20.1%	V_1	12.9%	25.4%	27.4%	V_1	0%**		
Q	25.1%	20.5%	20.3%	Q	0%*			Q	0%*		
V_2	0%*			V_2	4.0%	96.0%	63.4%	V_2	13.0%	21.1%	12.1%
CL_{NR}	24.4%	28.2%	38.4%	CL_{NR}	83.6%	22.7%	19.8%	CL_{NR}	12.0%	5.2%	44.3%

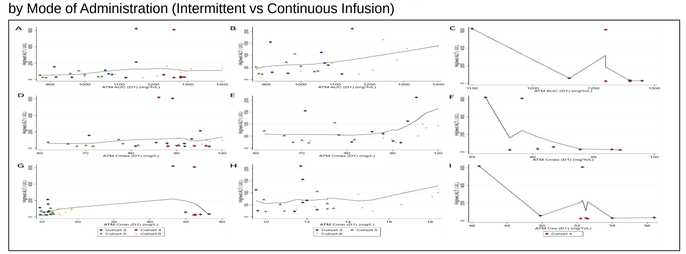
Residual Error											
Error term	Estimate	RSE	Epsilon Shrinkage	Error term	Estimate	RSE	Epsilon Shrinkage	Error term	Estimate	RSE	Epsilon Shrinkage
Pro error-plasma	16.1%	2.7%	3.8%	Pro error-plasma	19.8%	2.8%	2.6%	Pro error-plasma	15.6%	2.8%	3.4%
Add error-plasma	0.0046	39.6%		Add error-plasma	0.0005	27.0%		Pro error-urine	37.0%	5.2%	0.9%
Add error-urine	0.148	9.2%	0.9%	Pro error-urine	21.3%	12.5%	1.0%				
				Add error-urine	0.0073	17.0%					

Footnotes: Param: Paramter; V_1: the volume of the central compartment; Q: inter-compartmental clearance; V_2: volume of the peripheral compartment; CL_R: renal clearance; CL_{NR}: non-renal clearance; RSE: relative standard error; IIV/BSV: inter-individual variability/ between subject variability; CV: coefficient of variation (%)/ Pro: proportional; Add: additive. *IIV/BSV V2 was fixed to 0 in final model; the parameter estimate was near its boundary with high shrinkage of 99%.
**IIV/BSV V1 was fixed to 0 in final model, as the parameter estimate was near its boundary (shrinkage 99%).

ATM Exposure-Highest Observed ALT/AST Exposure Response Analyses

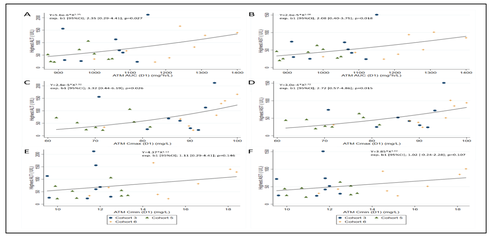
- Relationships between Day 1 ATM exposures and highest observed ALT values are graphically displayed in **Figure 1**.
  - No notable associations were identified in the overall LOWESS analyses.
  - Among subjects who received ATM as 2-hour intermittent infusions, the LOWESS curves suggested that there were potential ATM exposure-ALT/AST associations for $C_{max,SS}$ and AUC_{0-24h}.
- In the curvilinear regression analyses of the ATM 2-hour intermittent infusion Cohorts, modest associations were observed between ATM Day 1 $C_{max,SS}$ and AUC_{0-24h}, expressed as power functions, and highest observed ALT/AST (**Figure 2**).
- In the GLM analyses of the ATM 2-hour intermittent infusion Cohorts, significant associations were observed between ATM Day 1 $C_{max,SS}$ and AUC_{0-24h} and highest observed ALT/AST.
- Administration of CZA-ATM was not found to increase ALT/AST elevations relative to ATM alone in the GLM analyses.

Figure 1. Scatterplots of ATM Day 1 Exposure Parameters and Highest Observed ALT Value Overall and by Mode of Administration (Intermittent vs Continuous Infusion)



(A) All Cohorts AUC_{0-24} vs. ALT, (B) intermittent infusion Cohorts AUC_{0-24} vs. ALT, (C) CI Cohort AUC_{0-24} vs. ALT, (D) All Cohorts C_{max} vs. ALT, (E) intermittent infusion Cohorts C_{max} vs. ALT, (F) CI Cohort C_{max} vs. ALT, (G) All Cohorts C_{min} vs. ALT*, (H) intermittent infusion Cohorts C_{min} vs. ALT, (I) CI Cohort C_{ss} vs. ALT

Figure 2. Curvilinear Associations between Day 1 ATM Exposures, Expressed as Power Functions, and Highest Observed ALT/AST Among Subject Who Received Two-hour Intermittent Infusions of ATM



(A) ALT vs. AUC_{0-24h}, (B) AST vs. AUC_{0-24h}, (C) ALT vs. C_{max}, (D) AST vs. C_{max}, (E) ALT vs. C_{min}, (F) AST vs. C_{min}

CONCLUSIONS

- The PK profiles of CAZ, AVI, and ATM in this Phase 1 study were highly consistent with previous reports.
- Administration of CZA-ATM was found to reduce ATM CL, resulting in higher daily ATM AUCs, but did not exacerbate AST/ALT elevations relative to ATM alone.
- Use of continuous infusion ATM at 8 g/daily should be used with some caution given the 2 severe ALT/AST AEs in the continuous infusion ATM Cohort.

Research reported herein was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1AI104681