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PATIENTS WITH ACUTE PANCREATITIS (AP) AND ACCOMPANYING SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS) HAVE A LARGER VOLUME OF DISTRIBUTION COMPARED TO HEALTHY VOLUNTEERS

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INTRODUCTION

It has been demonstrated that critically ill patients may develop increased volumes of distribution for therapeutic agents necessitating higher doses to ensure desired clinical effects. CARPO (NCT04681066) was a global blinded RCT that assessed the dose response and efficacy of zegocractin, a calcium release-activated calcium channel inhibitor, in 214 patients with AP and SIRS. A population pharmacokinetic (popPK) analysis was conducted using plasma concentration-time data.

AIM

The aim of the study was to characterize the concentration time profile of zegocractin in patients with AP and SIRS to help determine the optimal dose for future studies, especially for patients with clinical parameters, such as an elevated hematocrit, signifying hyperinflammation.

METHODS

- Patients were randomized 1:1:1:1 to a low dose (0.3125 mL/kg), a middle dose (0.625 mL/kg), or a high dose (1.25 mL/kg) of zegocractin intravenous emulsion (Auxora) or a matching volume of placebo.
- Study drug was infused over 4 hours every 24 hours for three consecutive days. For the popPK analysis, sparse sampling of plasma was performed at the following 4 time points: 1) within 2 hours following the first dose, 2) at 24 hours (30 min prior to the 2nd dose), 3) at 72 hours (24 hours after the 3rd dose), and 4) on day 30.
- The combined PK data set from CARPO consisted of 310 PK samples from 90 paitents receiving zegocractin. The popPK analysis was based on a 3-compartment model with first-order elimination from the central compartment, using NONMEM® 7.4.4 (ICON Development) for parameter estimation.

RESULTS

- PK samples were collected from 90 patients receiving zegocractin. Because the pharmacokinetic data from CARPO was sparse, the 3-compartment popPK model developed from the single ascending dose and multiple ascending dose studies in healthy volunteers was used as the prior for the data analysis from CARPO.
- Lower plasma concentrations of zegocractin were observed in patients with AP and SIRS compared to other subjects/patients receiving the drug (Figure 1).
- The concentration-time profile of zegocractin in patients with AP and SIRS could be characterized by the 3-compartment model, consistent with the model developed in healthy volunteers (Table 1).
- Based on the popPK model, the volume of distribution in patients with AP and SIRS was substantially higher, two- to three-fold, than in healthy volunteers, explaining the lower plasma concentrations in this group of patients (Table 1)
- In addition, an elevated hematocrit (≥44% in men and ≥40% in women) was associated with lower plasma concentrations at the 24-hour time point (Figure 2), consistent with the idea that hyperinflammation-induced third spacing contributed to the increased volume of distribution.

Figure 1: Comparison Across Studies

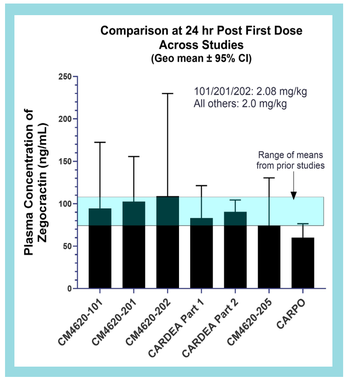

Figure 1 shows the range of geometric mean plasma concentrations of zegocractin (± 95% CI) from prior studies compared to CARPO. For comparison, data were taken from time points collected 24 hours after the first infusion of either 2.0 or 2.08 mg/kg zegocractin.

CM4620-101: SAD in healthy volunteers
CM4620-201: 6 patients with AP and SIRS
CM4620-202: 7 patients with AP alone
CARDEA: Patients with COVID-19 pneumonia
CM4620-205: Patients with COVID-19 pneumonia
CARPO: 29 patients with AP and SIRS

Figure 2: Low vs High Hematocrit

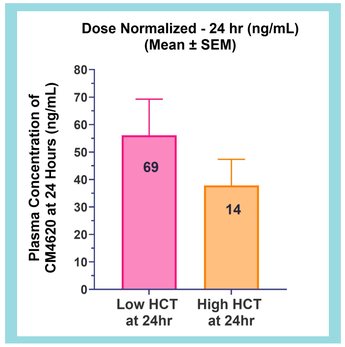

Figure 2 compares the dose-normalized mean plasma concentrations of zegocractin in patients with AP and SIRS who had either low or high hematocrit (HCT) at randomization. Data were taken from the time point collected 24 hours after the first infusion of zegocractin.

Table 1: PopPK Parameter Estimates in Patients with AP and SIRS Compared to Healthy Volunteers

Parameter	Healthy Volunteers	Patients from CARPO	Unit	Description
CL	0.298	0.32	L/h	Clearance from compartment 1
Vd1	57.6	198	L	Volume of distribution of compartment 1
Vd2	189	584	L	Volume of distribution of compartment 2
Vd3	1290	2748	L	Volume of distribution of compartment 3
Q1	12.5	12.2	L/h	Intercompartment clearance: comp 1 & 2
Q2	14.8	49.9	L/h	Intercompartment clearance: comp 1 & 3

Table 1 shows the popPK parameter estimates in patients with AP and SIRS (from CARPO) compared to estimates from healthy volunteers (from both SAD and MAD phase 1 studies). The popPK model identified 3 compartments, as follows: central (1) , shallow peripheral (2), and deep peripheral (3). In patients from the CARPO study, the volume of distribution (Vd) in all 3 compartments was increased relative to those determined in healthy volunteers. In addition, intercompartmental clearance between compartments 1 and 3 was increased. No change in clearance (CL) was observed.

CONCLUSIONS

1. Lower plasma concentrations of zegocractin were observed in patients from CARPO with AP and SIRS, compared to previous studies in subjects/patients with the drug. The one previous study in patients with AP and SIRS (CM4620-201) had very low patient numbers (6) and high variability, likely explaining the inconsistency with the current CARPO data.
2. The lower plasma concentrations in CARPO could be explained by increased Vd in all compartments, as determined from popPK modeling.
3. The cause of the increased Vd is likely related to increased third spacing and intraperitoneal inflammation in patients with AP and SIRS. A previous study in patients with severe AP came to the same conclusion to explain an increased Vd with vancomycin (He et al, 2016). Consistent with this idea, plasma levels were lower in patients with high HCT compared to those with low HCT. High HCT may identify patients in a hyperinflammatory state.
4. Higher doses of therapeutic agents may be required in treating patients with severe and predicted severe AP.

REFERENCES

He, J., Mao, E. Q., Feng, J., Jiang, H. T., Yang, W. H., & Chen, E. Z. (2016). The pharmacokinetics of vancomycin in patients with severe acute pancreatitis. *European journal of clinical pharmacology*, 72, 697-702.

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