Study Title: A study of Avycaz (ceftazidime/avibactam) Pharmacokinetics/Pharmacodynamics (PK/PD) in Critically Ill Patients

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1 STUDY RATIONALE/BACKGROUND

Avycaz is a new cephalosporin (ceftazidine)/beta-lactamase (avibactam) inhibitor combination antibiotic which has been approved by the FDA for treatment of complicated UTI and IA infections. Ceftazidime is a third generation cephalosporin with good activity against gram-negative rods (GNR) and has been marketed in the U.S. since 1985 for a variety of bacterial infections (1). Avibactam is a new non-beta-lactam/beta-lactamase inhibitor.

The addition of avibactam improves ceftazidime's activity against *Pseudomonas aeruginosa* and many extended-spectrum beta-lactamase (ESBL)-producing gram-negative pathogens. Ceftazidime/avibactam is the first beta-lactam/beta-lactamase inhibitor combination to have activity against some carbapenem-resistant Enterobacteriaceae, including those that produce *Klebsiella pneumoniae* carbapenemase (KPC), the most common carbapenemase in the U.S.(2).

A PK/PD analysis of Avycaz in patients with medical or post-surgical infections in the ICU has not been conducted. These studies are critical to understanding appropriate dosing of beta-lactams in critically ill patients and important for comparison against other newer agents.

2 STUDY HYPOTHESIS

Failure with emerging antibiotics in critically ill patients is an ongoing challenge. Effective antibiotic therapy is crucial for improving outcomes in these patients. Compared to healthy volunteers, both the volume of distribution and clearance of antibiotics can be altered in critically ill patients (3). Moreover, altered protein binding can also occur in severely ill patients (4). These variations in PK can affect the antimicrobial activity of antibiotics in patients in the ICU (5). Several studies have shown altered PK for beta-lactams in critically ill patients (6). Most recently, the Vd of doripenem in ICU patients was found to be significantly higher (2-times) than in healthy subjects (7). This finding is similar to our study of doripenem in neutropenic patients (8).

Obtaining only PK parameters is useful for comparison to healthy subjects but does not provide documentation on microbiologic efficacy. The use of serum to analyze PD efficacy has been shown to be a better estimate of activity compared to *in vitro* studies, because one uses actual serum antibiotic levels with serum factors to determine microbiological activity (9). Monte-Carlo simulations using PK parameters are also useful to define appropriate dosing schedules in patients with altered PK (8).

2.1 PRELIMINARY DATA

A study of ceftazidime in acutely ill hospitalized elderly patients found that clearance was reduced, T ½ increased, and the volume of distribution was reduced (10). In surgical patients with IA infection, the disposition of ceftazidime was dependent on CrCl and Vd and not altered by surgery or infectious process (11). The higher dose and longer dosing administration of Avycaz may enhance its activity against MDR pathogens in critically ill patients.

3 STUDY OBJECTIVE AND ENDPOINTS

3.1 STUDY OBJECTIVE

To analyze the PK/PD of AvyCaz in critically ill patients in the *Intensive Care Unit* (12). This study will include medical and post-surgical patients who develop an infection where Avycaz can be utilized. Since these patients will have variable PK parameters, we will also analyze (time-kill) these serum concentrations (*ex vivo*) against relevant clinical isolates (e.g. GNR with ESBL or KPC) from the ICU to determine microbiologic activity of Avycaz in critically ill patients with variable characteristics. Monte-Carlo simulations will also be conducted against clinical ICU isolates (JMI labs) to help determine appropriate dosing schedules based upon these PK parameters.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT:

A pharmacokinetic analysis of Avycaz in critically ill patients.

3.2.1.1 PRIMARY ENDPOINT DEFINITION:

PK parameters such as Vd, Cl and T½.

3.2.2 SECONDARY ENDPOINT(S):

A pharmacodynamic (time-kill) analysis of Avycaz against selected organisms in critically ill patients as well as Monte-Carlo simulations using these PK parameters for dosing of MDR pathogens.

3.2.2.1 SECONDARY ENDPOINT DEFINITION(S):

Time-kill curves and Monte-Carlo simulations against selected GN bacteria using obtained sera.

4 STUDY DESIGN

4.1 CLINICAL STUDIES (INCLUDING STEWARDSHIP GRANTS)

4.1.1 SITES

This study will be conducted at Sparrow Hospital, Lansing, MI (Level 1 trauma center) by the investigators listed below, including John Kepros, MD, chief of Trauma Surgery and Daniel Havlichek MD, ID Division Chief. This hospital is affiliated with Michigan State University and the Mayo Clinics. Patients in the Medical/Surgical ICU commonly

develop infections such as skin/soft tissue infections, urinary infections, IA infections and pneumonia (including VAP). Ceftazidime has been used clinically for these infections for the past 30 years. Samples for this investigation will be obtained from medical and post-surgical infected patients in the ICU. High volumes of antibiotics are used in these patients.

4.1.2 INCLUSION CRITERIA

- Adult (≥18y/o) patients with a medical or post-surgical infection such as skin/soft tissue infections, urinary infections, IA infections and pneumonia (including VAP)
- Patients requiring intensive care (critically ill patients) in the med/surg ICU (APACHE II score ≥~~15)~~ 10 with a mean ≥15 for these patients)
- Patients prescribed Avycaz for their infection will receive FDA recommended dosages and times of administration
- Written informed consent

4.1.3 EXCLUSION CRITERIA

- Pregnant Patients, patients older than 90 y/o, those with CrCl < 30 mL/min, patients with a BMI > 45 Kg/m^2, patients unable to provide serum samples, and those with the risk of imminent death during the study

4.1.4 SAMPLE SIZE AND DETERMINATION

12 patients is sufficient for PK analysis [similar to other PK studies]

4.1.5 RANDOMIZATION

Prospective, open-label, non-randomized study

4.1.6 TREATMENT

Avycaz 2500 mg (1250 mg for CrCl 31-50 mL/min) IV over 120 minutes, every 8 hours [other antibiotics can also be administered as needed]. Patients will receive at least 3 doses (steady-state) of Avycaz prior to obtaining serum samples.

4.1.7 INTERVENTION

The only treatment intervention will be the use of Avycaz when empirically or directly needed to treat a medical or post-surgical infection. The duration of treatment and the use of other antibiotics, such as vancomycin, will be determined by the attending physician(s).

Blood samples (after at least 3rd dose) will be obtained at 2, 4, 6, 8 hours after starting the 2h IV infusion. These four collection times will allow for determination of serum PK and provide concentrations relevant for PD (time-kill) and Monte-Carlo determinations.

4.2 NON-CLINICAL STUDIES

4.2.1 SITES

See above (single site study)

4.2.2 PRIMARY METHODS

Patient serum at each collection time point will be used to determine time-kill curves against strains of Avycaz-susceptible GNR. These *ex vivo* PD experiments will be helpful to determine the effectiveness of Avycaz to inhibit the replication of GN bacteria in serum. These experiments have enhanced value compared to *in vitro* studies because they test actual clinical levels, including protein binding, of Avycaz against relevant pathogens. These investigations will be conducted in the ID lab at Michigan State University (Dr. Stein). Monte-Carlo simulations will be determined using the PK parameters obtained against various MDR pathogens (MIC_{90}) such as *P. aeruginosa* (MIC = 4 mg/L) and CRE (eg. KPC = 4mg/L) (Dr. Nicolau, co-investigator).

4.2.3 SAMPLE SIZE AND DETERMINATION

See above

4.2.4 TREATMENT

See above

5 DATA COLLECTION AND ANALYSIS

5.1 DATA COLLECTION

Patients

- Patient demographic data (Ht, Wt, Age, BMI) as well as renal/liver function tests will be collected for each patient. Medical co-morbidities as well as APACHE II scores will also be recorded. Serum will be collected from subjects as stated above and frozen at -70°C until analysis.
- Ceftazidime and avibactam concentrations will be determined by LC-MS/MS analysis per Dr. Nicolau (co-investigator).
- PK parameters (mean ± SD) will be calculated from serum samples per Dr. Smith (co-Investigator).
  Serum drug concentrations from study patients will be used to develop a pharmacokinetic model for critically ill patients with infections.

Ex Vivo:

- Antimicrobial activity for selected GNR (ESBL + KPC isolates) will be determined and tested against each patient serum at each collection time.
- The geometric mean changes in bacterial density at each time point (n=12 patients) will be used to construct time-kill curves of Avycaz against selected GNR pathogens. The MIC_{90} for Avycaz against selected ICU clinical isolates (eg., KPC, ESBL *E. coli*) obtained from JMI labs (National Database) will be used in these time-kill experiments:
  - CTX-M-15 MIC = 1.0 mg/L
  - ESBL E. coli MIC = 0.25 mg/L
  - ESBL K. pneumoniae MIC = 1.0 mg/L
  - KPC MIC = 4.0 mg/L

- Monte-Carlo simulations will also be conducted against these selected ICU pathogens. These simulations will be performed using the PK model derived from patient data. The MIC data for the Monte Carlo simulations will be obtained from a national database and targets for Monte Carlo simulations will be %fT>MIC for ceftazidime and %fT>threshold concentrations for avibactam.

5.2 DATA / STATISTICAL ANALYSIS

The PK analysis will be conducted with standard software (Phoenix WinNonLin Version 6.3) by Dr. Curtis Smith. The mean ± SD will be calculated for each PK parameter. Time-kill curve data will be determined as the geometric mean kill at each time point (n=12) for each tested GN isolate (Dr. Stein). Monte-Carlo analyses will be conducted using 5000-patient simulations (Crystal Ball 2000 Professional Edition) against various (see above) isolates (Dr. Nicolau).

6 PUBLICATION

- A summary report will be sent to Allergan following all data analysis.
- An abstract will be sent to a local meeting (MIDS) as well as to a National meeting such as ICAAC or ID-week.
- A paper for publication will be written and sent to a pharmacy or antibiotic journal (eg. AAC, JAC, Pharmacotherapy)
- The investigators have conducted and published several PK/PD papers on newer antibiotics as well as Monte-Carlo simulations including a study of Teflaro in neurosurgical patients (8,13,14).

7 TIMELINE

IRB/Contract Approval and Study Initiation	3 months
Patient Enrollment/Sample Procurement	6 months
Data Analysis/Study Report/Publication	3 months
Total	12 months

8 REFERENCES

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