Session: P-61. Novel Agents

Background. Nontuberculous mycobacteria (NTM) are resistant to numerous antibiotics and lead to significant morbidity and mortality. Omacutacin is an aminomethylcycline antibiotic that is Food and Drug Administration-approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Furthermore, OMC has shown in vitro activity against NTM. Given that real-world evidence is lacking, our primary objective was to evaluate the clinical success and tolerability of OMC when used for a variety of NTM infections.

Methods. This was a multicenter, retrospective, observational study conducted from January 2020 to June 2021. We included all patients ≥18 years of age that received OMC of any indication for Mycobacterium spp. The primary outcome was clinical success, defined as a lack of all-cause mortality, lack of persistence or re-emergence of infection during or after therapy, and lack of alteration of OMC. Incidence of adverse effects potentially attributable to OMC and reasons for OMC utilization were also analyzed.

Results. A total of 31 patients were included from 12 geographically distinct academic health systems (median age: 57 [IQR: 45–63] years; 45% male; 81% Caucasian). The majority of isolated pathogens were Mycobacterium abscessus complex (84%) and of those with subspecies performed (54%), the majority (86%) were subsp. abscessus. The primary infections were of pulmonary origin (67%) and the median (IQR) duration of OMC therapy was 5.3 (3.2–9.4) months. Most isolates did not have OMC susceptibility conducted (87%), while the majority did for tigecycline (90%). Clinical success was reported in 81% of the population. Most patients were on combination antimicrobial therapy, and 39% of patients reported an adverse effect while on OMC (58% gastrointestinal distress). The majority of patients were prescribed OMC due to ease of administration (61%) and antimicrobial resistance to previous antibiotics (42%).

Conclusion. OMC may be a potential option for the therapy of NTM infections. Prospective, randomized clinical trials are needed to confirm our preliminary findings.

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1084. Comparative Outcomes Among Patients Receiving Varying Daptomycin Dosing Regimens During Hemodialysis. Tyler Maxwell, PharmD1; James E. Orban, III, PharmD2; Christine Babcock, B.S. Biology2; Wesley D. Kufel, PharmD3; Christopher Destache, PharmD4; Karen S. Williams, PharmD, BCPS AQ-ID5; Manasa Velagapudi, MBB5; Brandon Bookstaver, Pharm D6; Luis Tatem, MD1; James A. McCracken, PharmD1; Bethannie Carpenter, PharmD, BCPS, BCIDP1; Roolapi Sharma, BS, PharmD1; AAHIVP BCPS (AQ-ID)1, SUNY Downstate Medical Center, Brooklyn, New York; 1University of South Carolina, Columbia, South Carolina; 2Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, New York; 3Creighton University Schools of Medicine and Pharmacy, MD Stewart, Omaha, Nebraska; 4Guthrie Robert Packer Hospital, Sayre, Pennsylvania; 5CHI Health - Creighton University Medical Center - Bergan Mercy, Omaha, Nebraska; 6University of South Carolina College of Pharmacy, Columbia, SC; 7Rutgers, The State University of New Jersey, Newark Park, New Jersey; 8University of Central Florida Health System, San Jose, California; 9Touro College of Pharmacy, New York, NY

Session: P-62. PK/PD Studies

Background. Daptomycin (DAP) has become an appealing treatment option for gram-positive infections, which are common in patients receiving hemodialysis (HD), due to frequent access and manipulation. The approved DAP dosing of 4 to 6 mg/kg every 48 hours (q48h) quickly becomes desynchronized from the patient’s HD schedule and requires the burden of additional IV access. Previous pharmacokinetic studies have suggested that DAP can be dosed three-times weekly following HD, but no studies have evaluated clinical outcomes of this regimen.

Methods. This was a multi-center, retrospective cohort study across 6 hospitals in the United States. Adult, nonpregnant patients who received HD and DAP between 2015 and 2020 were screened for inclusion. Electronic medical records were reviewed for relevant study data. The primary outcome was clinical and microbiological outcomes among patients who received DAP thrice weekly versus q48h dosing. Microbiological Failure was defined as positive cultures after 7 days and further study definitions are included under Table 3.

Results. Baseline characteristics are summarized in Table 1. Length of stay was similar between both groups at a median of 25 days and patients had a median QPitt score of 0 on admission. The average DAP dose used was 7 mg/kg and 7 mg/kg on HD days in the q48h dosing and thrice weekly dosing regimens, respectively. The majority of patients had bacteremia and the most commonly isolated bacteria was methicillin-resistant Staphylococcus aureus. No differences in clinical outcomes were observed (p=0.87). Microbiological failure was higher among patients who received DAP thrice weekly compared to q48h dosing (69.2% vs 34.8%, p=0.047).

Table 1: Baseline Characteristics

| Table 1: Baseline Characteristics |
|----------------------------------|
| Every 48 Hour Dosing (n=78)      |
| 3-Times Weekly Dosing (n=88)     |
| Age, mean (SD)                  |
| Male, n (%)                     |
| Female, n (%)                   |
| Allergies                       |
| Pesticin, n (%)                 |
| Vancinomycin, n (%)             |
| Vancomycin, n (%)               |
| Sulfur Drugs, n (%)             |
| Fluorquinolones, n (%)          |
| No Known Drug Allergies, n (%)  |
| Common Co-morbidities, n (%)    |
| Coronary Artery Disease, n (%)  |
| Benign Prostatic Hypertension, n |
| Cancer, n (%)                   |
| Chronic Obstructive Pulmonary Disease, n |
| Diabetes, n (%)                 |
| Hyper-Epidemic, n (%)           |
| Hypertension, n (%)             |
| Obesity, n (%)                  |
| Charlson Comorbidity Score, n   |
| Total Length of Hospital Stay, n |
| Total Duration of Antibiotic Therapy (days), median (IQR) |

| Table 2: Hospitalization Characteristics |
|------------------------------------------|
| Every 48 Hour Dosing (n=78)              |
| 3-Times Weekly Dosing (n=88)             |
| Length of Hospital Stay, median (IQR)    |
| QPitt Criteria on Admission, median (IQR) |
| Daptomycin dosing (mg/kg)                |
| 48-hour interval, median (IQR)           |
| 72-hour interval, median (IQR)           |
| Total Duration of Antibiotic Therapy (days), median (IQR) |

| Antimicrobial Activity                           |
|-------------------------------------------------|
| Bacteremia, n (%)                               |
| Osteomyelitis, n (%)                            |
| Urgent Thrombosis                              |
| Upper Respiratory Infection, n (%)              |
| Lower Respiratory Infection, n (%)              |
| Septicemia, n (%)                               |
| Other, n (%)                                     |
| Antibiotic Source Control                        |
| No, n (%)                                       |
| Unknown, n (%)                                  |
| Culture Results                                 |
| MSSA, n (%)                                     |
| MRSA, n (%)                                     |
| vancomycin-resistant Staphylococcus, n (%)      |
| Enterococci, n (%)                              |
| Enterococci, n (%)                              |
| Not Specified, n (%)                            |

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DAP dosed thrice weekly on HD days offers similar clinical resolution compared to q48h dosing. While the thrice weekly dosing regimen did have a significantly higher rate of microbiological failure, the analysis was limited by a small sample size. As this is a retrospective analysis not accounting for confounding variables, additional prospective studies are warranted to confirm these findings.

Table 3: Relationship between Day of Treatment and Microbiological Outcomes and Clinical Resolution

| Variable                        | Level    | 48 Hours (N) | 3x Weekly (N) | p-value a |
|---------------------------------|----------|--------------|---------------|-----------|
| Clinical Resolution             | No Resolution | 18 (73.9%)   | 8 (32.1%)     | 0.87      |
| Partial Resolution              | 14 (61.4%) | 5 (25.0%)    |               |           |
| Full Resolution                 | 13 (57.1%) | 6 (28.6%)    |               |           |
| Microbiological Cure            | Yes      | 22 (96.5%)   | 11 (46.2%)    |           |
| Microbiological Failure         | Yes      | 8 (34.8%)    | 5 (23.8%)     | 0.047     |
| Microbiological Resolution      | No       | 30 (65.9%)   | 16 (66.7%)    |           |
| Lost to Follow-up               | Yes      | 23 (10.3%)   | 11 (29.7%)    | 0.954     |
| non-evaluable                   | No       | 18 (23.7%)   | 8 (10.2%)     | 0.807     |

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1085. Comparison of the Incidence of AKI in Vancomycin AUC Based Goal Trough Dosing vs. Traditional Trough Dosing in the Outpatient Setting

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Session: P-62. PK/PD Studies

Background. Recent changes to vancomycin guidelines recommend dosing by targeting an AUC of 400-600 in most patients, due to similar effectiveness and reduced rates of acute kidney injury (AKI). AKI was defined as an increase of ≥ 0.5 mg/dl, a 50% increase in serum creatinine from baseline on two consecutive readings, or a decrease in creatinine clearance from 50% from baseline on two consecutive readings. The purpose of this study was to assess the incidence of AKI in patients receiving vancomycin dosed by AUC based trough goals and vancomycin dosed by traditional trough goals (15-20 mcg/mL) in the outpatient setting.

Methods. This study was performed by retrospective chart review using the electronic health record. Patients receiving vancomycin outpatient as continuation of therapy after discharge from December 1, 2018 through March 24, 2021 were reviewed. The primary objective was incidence of AKI in patients receiving vancomycin outpatient with trough goals derived from patient specific AUC calculations compared to patients receiving vancomycin by traditional goal troughs. Secondary objectives included rate of treatment failure, average AUC estimated trough range, and number of regimen changes required.

Results. There were a total of 65 patients in the traditional trough dosing group and 53 patients in the AUC trough dosing group. The incidence of AKI was higher in the traditional trough dosing group compared to the AUC trough dosing group (23.1% vs. 5.7%; p = 0.01). There were no differences in incidence of treatment failure. The mean AUC estimated trough range was 11.4-16.9 mcg/mL. There were significantly less average regimen changes required in the AUC dosing group (1.64 vs. 1.13; p = 0.006). Patients receiving AUC trough dosing were 78% less likely to develop AKI as patients receiving traditional trough dosing (HR 0.221, 95%CI 0.051 - 0.968).

Conclusion. There was a significantly lower incidence of AKI in patients receiving vancomycin dosed by AUC based troughs compared to traditional trough dosing. Continuing AUC trough based dosing for vancomycin in the outpatient setting is convenient and may lead to reduced rates of AKI.

Disclosures. Dustin R. Carr, PharmD, BCPS, BCIDP, AAHIVP, Merck (Speaker’s Bureau).

1086. A Whole Body Quantitative System Pharmacology Physiologically-Based Pharmacokinetic (QSP/PBPK) Model that a priori Predicts Intramuscular (IM) Pharmacokinetics of ADG20: an Extended Half-life Monoclonal Antibody Being Developed for the Treatment and Prevention of Coronavirus Disease (COVID-19)

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Session: P-62. PK/PD Studies

Background. ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and additional SARS-CoV-like CoVs with pandemic potential and an extended half-life. A QSP/PBPK model was constructed using ADG20-specific physicochemical properties and published non-human primate (NHP) and human PK data for other antibodies; it was used to a priori predict and confirm NHP and human PK.

Methods. An existing QSP/PBPK model was modified to include 3 distinct lung sub-compartments: upper airway, lower airway, and alveolar tissue (Figure A). Each sub-compartment (Figure B) contained an epithelial lining fluid (ELF) space (Figure B). The model was fit separately to digitized NHP and human serum PK data for 7 extended half-life antibodies to estimate the apparent neonatal Fc receptor (FcRn) binding affinity (Kd,FcRn) and bioavailability by drug. Nasopharyngeal swab (upper airway) and lung (lower airway) ELF PK data from 4 additional antibodies were used to optimize a single rate constant for transcytosis in lung. Patches of positive charge was a covariate on the rate of pinocytosis of antibody entry and exit from the endosomal space (Figure B). Observed NHP (ADG20 10 mg/kg) and human (ADG20 300 mg IM) PK data collected over the initial 21 days post dose were compared with model forecasts from a 1000-iteration simulation.

Results. The distribution of fitted NHP Kd,FcRn provided accurate predictions of NHP serum PK data (Figure C). NHP ADG20 Kid,FcRn was optimized to be 35.7 nM and human ADG20 Kd,FcRn (9.55 nM) was derived using a mean NHP human Kd,FcRn ratio of 3.74 across antibodies. Model-based simulated human serum PK data using inter-subject variability from NHP and actual weight distribution from an ongoing Phase 1 study aligned with initial 21-day data (Figure D). Using an adult CDC weight distribution (45–150 kg), the simulated median exceeded 74 days.

Conclusion. The QSP/PBPK model a priori predicted NHP and human ADG20 PK. This innovative QSP-based modeling and simulation approach enabled the evaluation of candidate dose regimens prior to the availability of PK data, supporting the rapid advancement of the ADG20 clinical program during the COVID-19 pandemic.

Figure. Overview of the QSP/PBPK model.