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1087. Imipenem-Cilastatin-Relebactam (I/R) Pharmacokinetics (PK) in Critically Ill Patients with Augmented Renal Clearance (ARC)

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Session: P-62. PK/PD Studies

Background. Imipenem (IMI) and relebactam (REL) are predominantly excreted via glomerular filtration. ARC is a common syndrome in critically ill patients with sepsis, whereby increased renal blood flow may result in enhanced solute clearance; therefore, sub-therapeutic antibiotic concentrations are of concern. Herein, we describe the PK of I/R in critically-ill patients with confirmed ARC.

Methods. Infected patients in the intensive care unit with ARC (CrCl ≥130 mL/min) received a single dose of I/R 1.25g as a 30min infusion. Blood samples were collected over 6 hours (hr) for IMI and REL concentration determination by a validated LC/MS/MS assay. Protein binding was assessed at 0.5hr by ultrafiltration (UF). An 8hr urine creatinine (UCr) collection was performed to confirm ARC. IMI and REL plasma concentrations were fitted to compartmental models in WinNonlin. Simulated concentration vs time profiles were used to assess attainment of pharmacodynamic (PD) targets for IMI (30%*f*T >MIC) and REL (*f*AUC:MIC 18) at the susceptibility breakpoint of 2 mg/L.

Results. Five patients (60% female) completed the study. Mean (SD) age, weight, and APACHE II were 43 (14) years, 90 (15) kg, and 16 (6), respectively. All patients had confirmed ARC with CrCl of 160.6 ± 47.0 mL/min (range: 135-244mL/min) based on UCr. Both IMI and REL concentrations fitted a 2-compartment better than 1-compartment model. IMI PK was: clearance, 17.9 ± 8.7 L/hr; volume of central compartment, 15.6 ± 11.2 L; volume of peripheral compartment, 10.6 ± 5.4 L; and intercompartmental clearance, 16.6 ± 14.5 L/hr. REL PK parameters were 11.9 ± 7.5 L/hr, 17.0 ± 11.3 L, 13.5 ± 9.9 L, and 13.4 ± 11.1 L/hr, respectively. Half-life was 1.5 ± 0.5 for IMI and 2.8 ± 2.2 hr for REL. Protein binding for IMI ranged from 0-10%, while REL was 0-14%. IMI *f*T >MIC ranged from 40-90%, and REL *f*AUC:MIC ranged from 22.6-59.0.

Conclusion. These are the first data to describe IMI and REL PK in critically-ill infected patients with ARC. Despite plasma clearance values greater than those reported in healthy volunteers and patients in clinical trials, I/R 1.25g as a 30 minute infusion provided optimal exposure in all patients for isolates with MICs ≤2 mg/L.

Disclosures. **David P. Nicolau, PharmD**, **Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt, Shionogi, Tetraphase** (Other Financial or Material Support, I have been a consultant, speakers bureau member, or have received research funding from the above listed companies.) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**BioMérieux** (Consultant, Research Grant or Support, Speaker's Bureau)**Contrafect** (Scientific Research Study Investigator)**GSK** (Consultant)**Merck** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Roche Diagnostics** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Summit** (Scientific Research Study Investigator)

1088. A Whole-Body Quantitative System Pharmacology Physiologically-Based Pharmacokinetic (QSP/PBPK) Model to Support Dose Selection of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Treatment of Coronavirus Disease (COVID-19)

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Session: P-62. PK/PD Studies

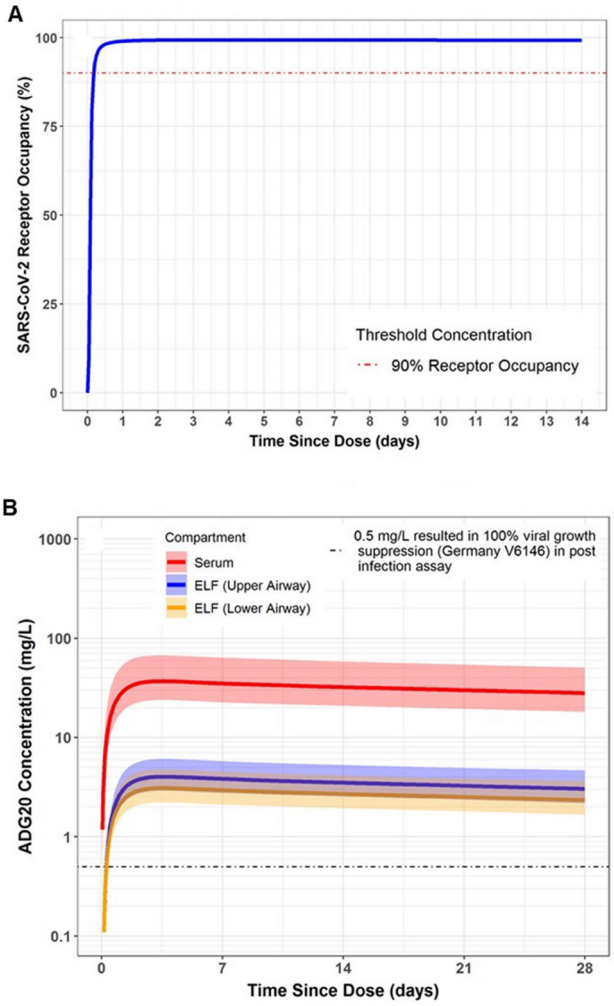
Background. ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential and an extended half-life. ADG20 is administered intramuscularly (IM). A QSP/PBPK model was constructed to support dose selection for a Phase 2/3 trial of ambulatory patients with mild to moderate COVID-19 (STAMP: NCT04805671).

Methods. A QSP/PBPK model was used to simulate receptor occupancy (RO) and drug exposure in the upper airway (nasopharyngeal/oropharyngeal epithelial lining fluid [ELF] compartment). RO was linked to an existing viral dynamic model to enable the prediction of the natural time course of viral load and the effect of ADG20 on viral clearance and infectivity rate. RO was calculated using: 1) in vitro ADG20–SARS-CoV-2 binding kinetics (association rate constant (k_{on}) of 1.52E+06 M^{-1}•s^{1} and dissociation rate constant (k_{off}) of 2.81E-04 s^{-1} from a Biacore assay; 2) time course of ADG20 concentrations in ELF; and 3) time course of viral load following ADG20 administration. Molar SARS-CoV-2 viral binding site capacity was calculated assuming 40 spike proteins per virion, 3 binding sites per spike, and an initial viral load of log 10^{7} copies/mL for all patients. The QSP/PBPK model and a 2018 CDC reference body weight distribution (45–150 kg) were used to simulate 1000 concentration-time profiles for a range of candidate ADG20 regimens. ADG20 regimens were evaluated against 2 criteria: 1) ability to attain near complete (>90%), and durable (28-day) SARS-CoV-2 RO in the ELF; and 2) ability to maintain ELF ADG20 concentrations relative to a concentration (0.5 mg/L) associated with 100% viral growth suppression in an in vitro post-infection assay.

Results. A single 300 mg IM ADG20 dose met the dose selection criteria in terms of RO (Figure A) and viral growth suppression (Figure B).

Conclusion. These data support the evaluation of an ADG20 300 mg IM dose for the treatment of mild to moderate COVID-19. ADG20 is forecasted to attain near complete (>90%) SARS-CoV-2 RO in the ELF and maintain ELF ADG20 concentrations above that associated with 100% viral growth suppression in vitro.

Figure. QSP/PBPK model forecast of ADG20 300 mg IM in adults



(A) Predicted RO expressed as percent occupancy with the dotted line representing the threshold for 90% RO. (B) Predicted median concentration of ADG20 relative to a concentration (0.5 mg/L) associated with 100% viral growth suppression as indicated by the dotted line; the shaded area represents the 90% prediction interval.

Disclosures. **Evan D. Tarbell, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Scott A. Van Wart, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Laura M. Walker, PhD**, **Adagio Therapeutics, Inc.** (Other Financial or Material Support, Laura M. Walker is an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.) **Andrew Santulli, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Lynn E. Connolly, MD, PhD**, **Adagio Therapeutics, Inc.** (Employee) **Donald E Mager, PharmD, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Paul G. Ambrose, PharmD**, **Adagio Therapeutics, Inc.** (Employee)

1089. Use of a Whole-Body Quantitative System Pharmacology Physiologically-Based Pharmacokinetic (QSP/PBPK) Model to Support Dose Selection of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Prevention of Coronavirus Disease (COVID-19)

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