Poster 1086

A Whole-Body Quantitative System Pharmacology Physiologically Based Pharmacokinetic Model That a Priori Predicts Pharmacokinetics of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Treatment and Prevention of COVID-19

Scott A. Van Wart,[1] Evan D. Tarbell,[1] Donald E. Mager,[1,2] Dhaval K. Shah,[2] Lynn E. Connolly,[3] Paul G. Ambrose[3,4]

[1]Enhanced Pharmacodynamics, LLC, Buffalo, NY, USA; [2]University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY, USA; [3]Adagio Therapeutics, Inc., Waltham, MA, USA; [4]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY, USA

Dr Scott A. Van Wart
Enhanced Pharmacodynamics, LLC
701 Ellicott Street
Buffalo, NY, 14203
Email: svanwart@epd-llc.com
Phone: (888) 714-6624

INTRODUCTION

- ADG20 is a fully human IgG1 monoclonal antibody (mAb) engineered to have high potency and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential by binding to a highly conserved epitope in the receptor-binding domain of the spike protein[1]
- The Fc region of ADG20 has been modified to provide an extended half-life[1]
- Innovative approaches are needed to support early dose regimen decisions in the face of limited experimental data
- One way to increase certainty around dose and reduce risk is by utilizing a quantitative systems pharmacology (QSP) whole-body physiologically based pharmacokinetic (PBPK) modeling and simulation strategy
- Here, we describe modification of an existing QSP whole-body PBPK model constructed to a priori predict and subsequently confirm non-human primate (NHP) and human ADG20 pharmacokinetics (PK)

METHODS

Objectives

- To construct a QSP whole-body PBPK model and forecast ADG20 concentration-time profiles for NHPs and humans prior to the availability of measured ADG20 concentrations from any species
- Compare forecasted and observed ADG20 concentration-time profiles from NHPs, recalibrate the QSP whole-body PBPK, and update initial human forecasts
- Compare updated forecasted and observed human ADG20 data from a first-in-human, Phase 1, single ascending-dose study in healthy adults[2]

QSP whole-body PBPK model

- QSP modeling involved reconstructing a platform whole-body PBPK model developed for wild-type IgG1 and engineered mAbs[3]
- The model comprised 15 specific tissues and one representing the rest of the body (**Figure 1A**); each tissue was connected through blood and lymph flow to the systemic circulation
- In the endothelial space of each tissue, mAbs enter by pinocytosis (CL_{up}) where they can interact with neonatal Fc receptor (FcRn). The FcRn-bound mAb is recycled and the unbound antibody is eliminated (k_{deg}; **Figure 1B**)

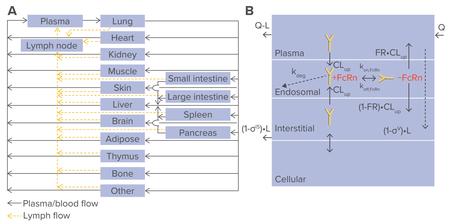
QSP whole-body PBPK model modifications

- The platform whole-body PBPK model[3] was primarily modified in two ways
  - NHP and human apparent dissociation rate-constant (K_D) for mAb to FcRn ($K_{D,FcRn}$) was replaced by values estimated for up to 7 other extended half-life mAbs
    - Each selected mAb displayed no inherent target-mediated drug disposition
  - Patches of positive charge (PPC) was used as a covariate on the rate of pinocytosis into the endosomal space (CL_{up})

Initial QSP whole-body PBPK model projections

- The modified QSP whole-body PBPK model, estimated NHP and human apparent-$K_{D,FcRn}$ distributions, and a reference US Centers for Disease Control body weight distribution[4] were used to provide initial simulation (1000 iterations) forecasts of NHP and human ADG20 serum concentration-time profiles
- When measured NHP ADG20 serum concentrations became available, the raw data were later overlaid on the initial median and 90% prediction interval (PI) forecast for NHPs[5]

Figure 1. QSP whole-body PBPK model at the tissue level (A) and cellular level (B)



σ', vascular reflection coefficient; σ^L, interstitial fluid reflection coefficient; CL_{up}, rate of pinocytosis of antibody entry and exit from the epithelial space; FR, fraction of FcRn bound antibody that recycles to the vascular space; k_{deg}, degradation rate constant; $k_{off,FcRn}$, first-order dissociation rate constant of antibody from FcRn; $k_{on,FcRn}$, second-order association rate constant for binding of antibody to FcRn; L, lymphatic flow rate; Q, blood flow rate.

Optimized QSP whole-body model projections

- The modified QSP whole-body PBPK model was optimized by estimating NHP intramuscular (IM) bioavailability and ADG20 $K_{D,FcRn}$ and applying an NHP:human $K_{D,FcRn}$ ratio to the NHP $K_{D,FcRn}$ values estimated for ADG20 to better forecast human ADG20 concentration-time profiles
- When measured human ADG20 serum concentrations became available, the raw data were overlaid on the forecasted median and 90% PI forecast for humans[2]
- The QSP whole-body PBPK model was then optimized by estimating $K_{D,FcRn}$ and IM bioavailability using the interim human PK data, along with estimating inter-individual variability for some key parameters to better reflect observed variability

RESULTS

QSP whole-body PBPK model modifications

- Mean NHP and human serum PK data for 7 mAbs were extracted from the literature and digitized, and the apparent-$K_{D,FcRn}$ was estimated for each drug while keeping all other parameters and the CL_{up}-PPC relationship constant during development of the modified QSP whole-body PBPK model
  - Human data: MEDI524,[6] MEDI4893,[7] MEDI8897,[8] ravulizumab,[9] VIR-2482,[10] and VRC01-LS[11]
  - NHP data: MEDI524,[12] MEDI8897,[13] mepolizumab,[14] and VRC01-LS[15]
- Histograms of simulated human body weight and $K_{D,FcRn}$ distributions in humans and NHPs are shown in **Figure 2**
- **Figure 3** shows the initial QSP/PBPK model–forecasted NHP median (90% PI) serum ADG20 concentration-time profile with measured concentration data overlaid
- **Figure 4** shows the optimized QSP/PBPK model–forecasted NHP median (90% PI) serum ADG20 concentration-time profile with measured concentration data overlaid
  - The QSP whole-body PBPK model was optimized by estimating $K_{D,FcRn}$ (4.27 nM) and IM bioavailability (92.2%) using the interim human PK data, along with estimating inter-individual variability for some key parameters to better reflect observed variability
- **Figure 5** shows the observed and optimized QSP/PBPK model–forecasted human median (90% PI) serum ADG20 concentration-time profile with measured concentration data overlaid

Figure 2. Simulated human body weight (A) and distribution of estimated $K_{D,FcRn}$ values for other extended half-life mAbs in healthy human adults (log-normal, B) and NHPs (normal, C)

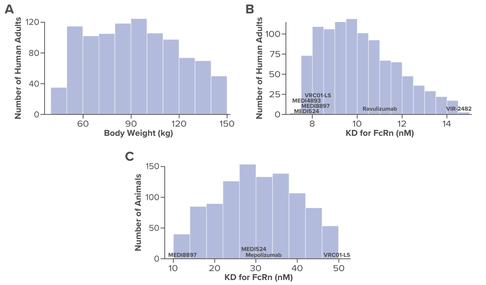
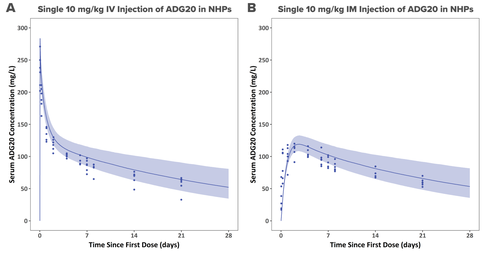
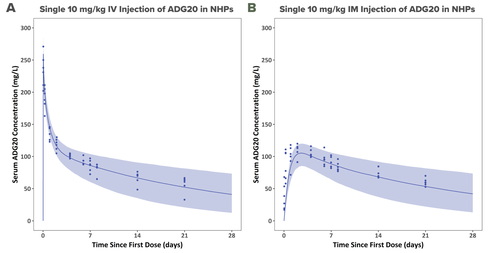


Figure 3. Observed (blue dots) and model-forecasted NHP median (90% PI) serum ADG20 PK profiles based on distribution of NHP $K_{D,FcRn}$ values for other extended half-life mAbs following intravenous (IV; A) and IM (B) administration



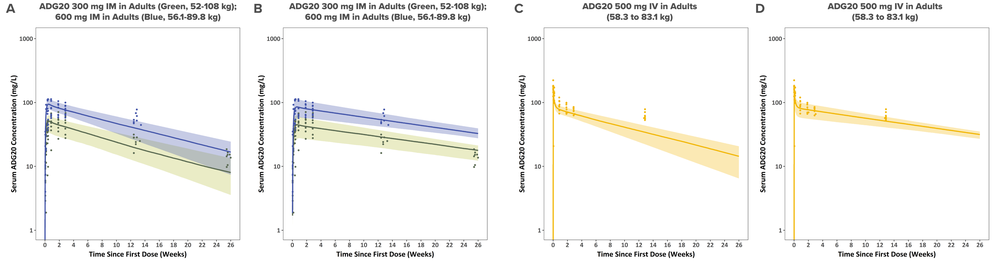
Blue dots = raw observed data; solid blue line = simulated median; blue ribbon = simulated 90% PI. SD, standard deviation.

Figure 4. Observed (blue dots) versus optimized QSP model–predicted NHP median (90% PI) serum ADG20 concentration-time profiles in NHPs following IV (A) and IM (B) administration



Blue dots = raw observed data; solid blue line = simulated median; blue ribbon = simulated 90% PI.

Figure 5. Observed data (dots) versus QSP model–predicted median (90% PI) serum ADG20 PK profiles in healthy adult participants predicted a priori based on distribution of human $K_{D,FcRn}$ values for other extended half-life mAbs (A, C) and after optimization (B, D)



Dots = raw observed data; solid line = simulated median; ribbon = simulated 90% PI.

KEY FINDINGS

The modified QSP whole-body PBPK model accounted for altered binding affinity to FcRn, adequately a priori predicted the observed ADG20 PK in NHPs and humans, and was used to support dose selection

The modeling strategy involved the modification of a platform whole-body PBPK model designed for wild-type IgG1 mAbs to forecast the PK of an extended half-life mAb

The modified QSP whole-body PBPK model accounted for altered binding affinity to FcRn and adequately a priori predicted the observed ADG20 PK in NHPs and humans, thus supporting the selected dose

This innovative modeling approach was a key element in the rapid advancement of the ADG20 program into clinical development during the COVID-19 pandemic

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CONCLUSIONS

- This novel QSP whole-body PBPK model, which was designed to forecast serum concentration-time profiles for extended half-life mAbs, predicted systemic drug exposure with high fidelity
- Before deciding to advance a mAb drug candidate into clinical development, this model platform can be used to discriminate among competing candidates based on forecasted PK differences
- This QSP model platform can be used to support the rapid advancement of potential new mAb medicines

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DISCLOSURES

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