

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

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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

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 protein¹
- The Fc region of ADG20 has been modified to provide an extended half-life²
- 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 adults²

QSP whole-body PBPK model

- QSP modeling involved reconstructing a platform whole-body PBPK model developed for wild-type IgG1 and engineered mAbs³
- 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 model³ 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 distribution⁴ were used to provide initial simulation (1000 iterations) forecasts of NHP and human ADG20 serum concentration-time profiles

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DISCLOSURES

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Acknowledgments

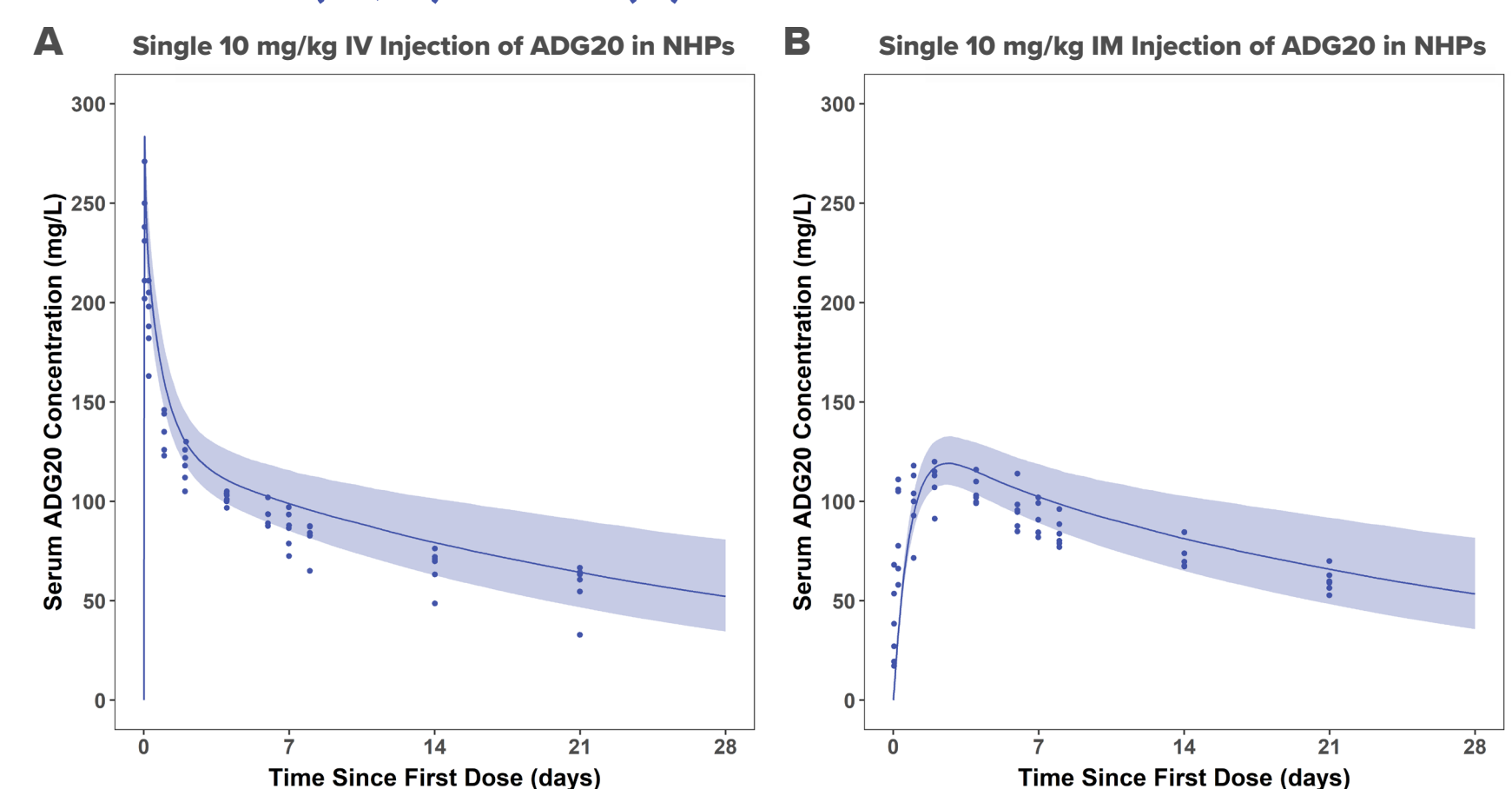
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RESULTS

QSP whole-body PBPK model modifications

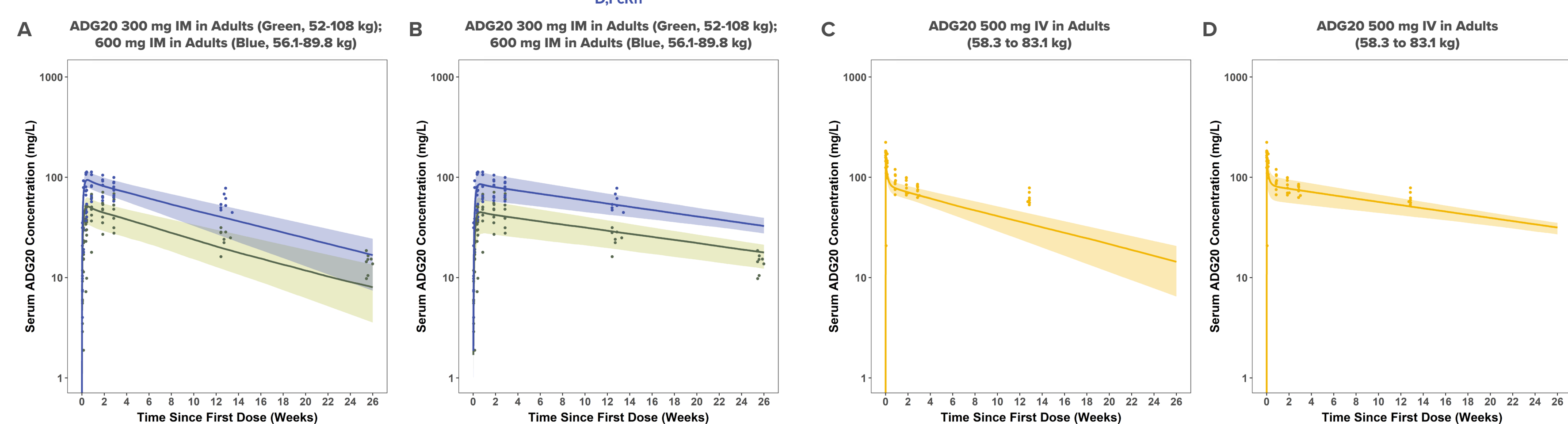
- Mean NHP and human serum PK data for 7 mAbs were extracted from the literature and digitized, and the apparent-K_{d,FcRn} was estimated for each drug while keeping all other parameters and the CL_{up}-PPC relationship constant during development of the modified QSP whole-body PBPK model
 - Human data: MEDI524,⁶ MEDI4893,⁷ MEDI8897,⁹ ravulizumab,⁹ VIR2482,¹⁰ and VRC01-LS¹¹
 - NHP data: MEDI524,¹² MEDI8897,¹³ mepolizumab,¹⁴ and VRC01-LS¹⁵
- 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 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 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.