Poster 1088

A Whole-Body Quantitative System Pharmacology Physiologically Based Pharmacokinetic 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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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]
- In vitro, ADG20 displays high binding affinity and potent neutralization against all SARS-CoV-2 variants tested, including variants of concern (B.1.1.7/Alpha, B.1.351/Beta, P.1/Gamma, B.1.617.2/Delta)[2,3]
- ADG20 can be administered intramuscularly (IM) and is currently in clinical development for the treatment and prevention of COVID-19
- The quantitative systems pharmacology whole-body physiologically based pharmacokinetic (QSP/PBPK) modeling and simulation analyses herein were used to support an ADG20 dose regimen decision for a Phase 2/3 COVID-19 treatment study (STAMP: NCT04805671)

METHODS

Objectives

- To modify a previously developed QSP/PBPK model[4] to allow for the prediction of ADG20 concentrations in upper and lower respiratory epithelial lining fluid (ELF)
- To link the modified QSP/PBPK model to a COVID-19 viral dynamic model[5] to enable the prediction of the natural time course of viral load, the effect of ADG20 on viral clearance and infectivity rates, and the calculation of SARS-CoV-2 target receptor occupancy (RO)
- To perform QSP/PBPK model–based simulations to discriminate between candidate ADG20 dose regimens for a Phase 2/3 COVID-19 treatment study

QSP whole-body PBPK model

- The QSP/PBPK model comprised 15 specific tissues and one representing the rest of the body; each tissue was connected through blood and lymph flow to the systemic circulation
- In tissue endothelial spaces, mAbs enter by pinocytosis (CL_{up}) and via the interaction with neonatal Fc receptor (FcRn), FcRn-bound mAb is recycled, and unbound drug is eliminated (K_{deg})
- The QSP/PBPK model was modified such that the lung compartment was subdivided into alveoli and upper (naso-/oropharyngeal) and lower lung airway compartments (bronchi; **Figure 1A**)
  - It was assumed that the upper, lower, and alveoli sub-compartments contribute 8.5%, 8.5%, and 83.0% toward lung volume and 2.5%, 5.0%, and 92.5% toward lung blood flow, respectively
  - It was assumed that FcRn concentrations in each lung sub-compartment were the same, mAbs recycle back to ELF and interstitial compartments, CL_{up} in lung epithelium was 10-times slower than vascular endothelial cells, and the endosomal space was 0.5% of cellular space for pulmonary epithelial cells
  - mAbs were also allowed to cross epithelial cells by transcytosis (k_{trans}) and, upon entering the interstitial space, to either exit the lung via lymph flow or re-enter the vascular space via FcRn-mediated recycling
  - k_{trans} was calibrated using serum PK data along with ELF and nasopharyngeal swab PK data from reference mAbs MHAA4549A,[6] VIS-410,[7] ASN-1, and ASN-2[8]
- It was assumed that binding to SARS-CoV-2 virus does not impact the ADG20 PK at clinically relevant doses

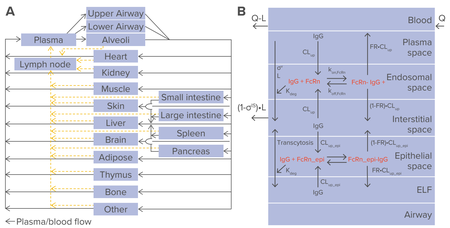
Viral dynamic model and receptor occupancy

- The QSP/PBPK-linked (**Figure 1**) viral dynamic model (**Figure 2**) was used to predict the time-course of viral load based on ADG20 concentrations in upper airway ELF, allowing for calculation of SARS-CoV-2 RO
- The viral dynamic model parameters[5,9] were calibrated to emerging viral load data from placebo and treatment groups from the REGN-COV2 program[10] ($K_{D,FcRn}$ for REGN10933 and REGN10987 was estimated to be ~51 nM to drive upper airway concentrations)
- Since dose response was not observed in the available REGN-COV2 viral load data, maximal fold change in viral clearance (S_{max}) was estimated while the drug concentration resulting in 50% of S_{max} (SC_{50}) values was fixed to in vitro values for REGN-COV2 (34 ng/mL). The S_{max} appeared to be dependent on timing of therapy relative to start of infection
- RO was calculated using
  - In vitro ADG20 antigen-binding fragment (Fab)–SARS-CoV-2 spike Biacore assay binding kinetics; association rate constant (k_{on}): 1.52E+06 M^{-1}•s^{-1}, dissociation rate constant (k_{off}): 2.81E-04 s^{-1}
  - Time course of QSP/PBPK model–forecasted ADG20 concentrations in upper airway ELF of lung
  - Time course of viral load was based upon ADG20 dosing at peak viral load (eg, log 10^7 to log 10^9 copies/mL for all patients) using the in vitro 50% half maximal concentration (IC_{50}) of 0.007 µg/mL against authentic SARS-CoV-2 (Delta variant)[11]
  - Assumption that each SARS-CoV-2 virion contains 40 spike proteins, with 3 potential binding sites per spike, when calculating total target[12]

Model-based simulations and dose regimen discrimination

- Using the QSP/PBPK model and a US Centers for Disease Control reference body weight distribution[13] truncated to 45 to 150 kg, PK-pharmacodynamics data were simulated for 1000 patients for a range of candidate single-dose IM ADG20 dosing regimens
- ADG20 regimens were evaluated against two criteria
  - Ability to maintain ELF ADG20 concentrations >0.27 mg/L, which was associated with 95% viral growth suppression in an in vitro post-infection assay against the Beta variant
  - Ability to attain near complete (>90%) and durable (28-day) SARS-CoV-2 RO in the ELF against the Delta variant

Figure 1. QSP whole-body PBPK model in (A) tissues and (B) cells



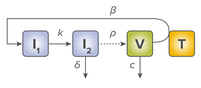
σ, vascular reflection coefficient; σ^{ls}, interstitial fluid reflection coefficient; $CL_{up,epi}$, rate of pinocytosis of antibody entry and exit from the epithelial space; FR, fraction of FcRn-bound antibody that recycles to the vascular space; L, lymphatic flow rate; k_{deg}, degradation rate constant;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

RESULTS

Viral dynamic modeling

- The final viral dynamic model diagram and equations are shown in **Figure 2** and **Table 1**, respectively
- **Figure 3** shows the model predictions for the placebo and REGN-COV2 treatment groups by baseline viral titer groupings

Figure 2. Viral dynamic model diagram and equations



$$\beta = (c \cdot \delta \cdot R_0)/([\rho - R_0 \cdot \delta] \cdot T_0) \quad (1)$$

$$c = c \cdot \left(1 + S_{max} \cdot \frac{[UA\ ELF]}{(100 \cdot IC_{50} + [UA\ ELF])}\right) \quad (2)$$

$$\beta = \beta \cdot \left(1 - \frac{[UA\ ELF]}{(100 \cdot IC_{50} + [UA\ ELF])}\right) \quad (3)$$

Abbreviations are defined in Table 1.

Table 1. Viral dynamic model parameter estimates

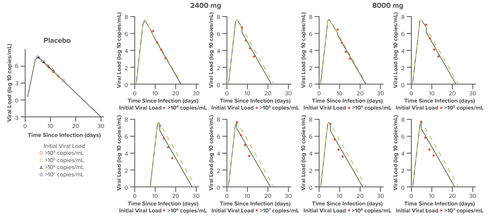
Parameter	Description	Units	Value from Goncalves et al. 2020	Value from Ke et al. 2020	Final estimate from viral dynamic model (95% CI)
R_0	Within-host replication factor	None	8.2	74.2	25.8 (3.20-208)
k	Eclipse rate from IC1 to IC2	1/day	3[a]	4[a]	3[a]
β	Derived infectivity rate				
δ	Loss rate of infected cells	1/day	0.6	1.9	0.99 (0.94-1.04)
ρ	Viral production rate	1/day	21.4	NA	5890 (3471-9996)
c	Viral clearance rate	1/day	10^a	10^a	10^a
V_0	Initial viral load	Copies/mL	0.1[a]	NA	0.1[a]
T_0	Initial target cell number	Cells/mL	4e8 / 30 mL / 100[a]	4.00E+06	4e8 / 30 mL / 100[a]
offset1	Days since time of infection for 10^4 to 10^5 copies/mL[b]	Days	NA	NA	14.6 (10.2-20.9)
offset2	Days since time of infection for 10^5 to 10^6 copies/mL[b]	Days	NA	NA	11.1 (7.02-20.9)
offset3	Days since time of infection for 10^6 to 10^7 copies/mL[b]	Days	NA	NA	7.3 (3.6-15.0)
offset4	Days since time of infection for $>10^7$ copies/mL[b]	Days	NA	NA	4.7 (1.61-13.9)
SC_{50}	Drug concentration resulting in 50% of S_{max}	ng/mL	NA	NA	34[a,c]
S_{max1}	Maximal fold change in viral clearance for baseline titer of 10^4 to 10^5 copies/mL[c]	-	NA	NA	0.43 (0.04-4.85)
S_{max2}	Maximal fold change in viral clearance for baseline titer of 10^5 to 10^6 copies/mL[c]	-	NA	NA	2.28 (0.86-6.00)
$S_{max3,4}$	Maximal fold change in viral clearance for baseline titer of $>10^6$ copies/mL[c]	-	NA	NA	4.79 (2.83-8.10)

[a]Fixed parameter in model; [b]The composite time since start of infection was a weighted average of the proportion of patients in each titer bin and was calculated to be 4.73 days for titers $>10^4$ copies/mL, 5.35 days for titers $>10^5$ copies/mL, 7.15 days for titers $>10^6$ copies/mL, and 8.86 days for titers $>10^7$ copies/mL; [c]Simulated lung upper airway ELF data for either 1200 mg or 4000 mg of REGN 10987 were assumed to be the principal driver of the viral load effect for the 2400 mg or 8000 mg combination dose; [d]An in vitro IC_{50} (0.007 µg/mL) was used as the SC_{50} in simulations for ADG20. CI, confidence interval; IC1/2, inhibitory concentration 1/2; NA, not available.

Table 2. ADG20 potency against SARS-CoV-2 variants of concern[11]

Lineage	WHO Designation	IC_{50}, µg/mL	10 × IC_{50}, µg/mL
Victoria	–	0.015	0.15
B.1.1.7	Alpha	0.023	0.23
B.1.351	Beta	0.095	0.95
P.1	Gamma	0.034	0.34
B.1.617.2	Delta	0.04	0.4

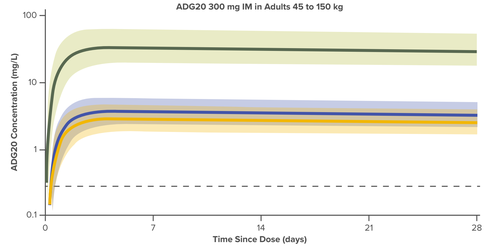
Figure 3. Viral dynamic model fittings to placebo (left), 2400 mg (middle), or 8000 mg (right) REGN-COV2 treated patients



QSP/PBPK/viral dynamic model–based simulations

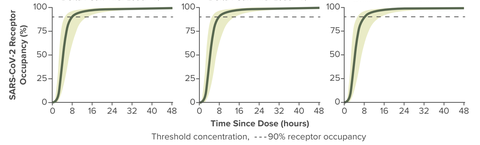
- **Figure 4** shows the QSP model–predicted median (90% prediction interval; PI) ADG20 PK profiles associated with viral growth suppression.[14] Times to attaining relevant target concentrations are provided in the table
- **Table 2** shows ADG20 potency against SARS-CoV-2 variants of concern
  - As shown in **Figure 4** and **Table 2**, ADG20 attains ELF concentrations above 10 × the IC_{50} of other variants of concern
- **Figure 5** shows ADG20 RO at various Delta variant virion densities after a single 300 mg IM injection of ADG20

Figure 4. QSP model-predicted median (90% PI) ADG20 PK profiles following a single 300 mg IM injection in different compartments overlaid by the threshold associated with 95% viral growth suppression for the SARS-CoV-2 Beta variant in a post-infection assay[14]



Concentration (mg/L)	Matrix	Median Time to Concentration, hours
0.04	Upper/Lower ELF	5
0.27	Upper/Lower ELF	10
0.4	Upper/Lower ELF	11

Figure 5. ADG20 RO at various Delta variant virion densities (10^7 left, 10^8 middle, 10^9 right) after a single 300 mg IM injection



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DISCLOSURES

LEC, LMW, and PGA are employees of Adagio Therapeutics, Inc. EDT, DKS, DEM, ARS, and SAVW received funding from Adagio Therapeutics, Inc. for the conduct of this work. LMW is an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.

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KEY FINDINGS

A QSP whole-body PBPK modeling and simulation approach was integrated with a viral dynamic model and used to evaluate candidate ADG20 dose regimens for a Phase 2/3 COVID-19 treatment study (STAMP)

A QSP/PBPK model, which was developed to forecast extended half-life mAb serum concentrations, was modified such that ADG20 concentrations in upper and lower ELF could be predicted at relevant drug-effect sites

The QSP/PBPK model was linked to a viral dynamic model and used in conjunction with in vitro binding kinetics for SARS-CoV-2 spike and ADG20 Fab to predict ADG20 effect on viral clearance and calculate RO

This innovative QSP/PBPK and viral dynamic modeling approach was used to support dose selection for ADG20 for the treatment of COVID-19

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CONCLUSIONS

- These data provide support for the evaluation of a single 300 mg IM injection of ADG20 for the treatment of COVID-19
- With high binding affinity in vitro and potent neutralization against all SARS-CoV-2 variants tested to date,[2] ADG20 might be especially useful in addressing future emerging SARS-CoV-2 variants in the rapidly evolving COVID-19 pandemic
- Using a single IM injection, ADG20 has the potential to be a readily accessible therapeutic that can provide rapid and durable protection