Poster 1132

Integrated quantitative systems pharmacology characterizing viral dynamics after intramuscular adintrevimab administration in participants with mild to moderate coronavirus disease (COVID-19)

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INTRODUCTION

- Adintrevimab is a fully human immunoglobulin G1 monoclonal antibody engineered to have an extended half-life with high potency and broad neutralization against SARS-CoV-2 and other SARS-like coronaviruses[1,2]
- Safety and pharmacokinetic (PK) data from a first-in-human, phase 1, single-ascending dose study in healthy adults[3] supported the evaluation of a single 300 mg intramuscular (IM) dose of adintrevimab in 2 ongoing phase 2/3 studies: EVADE (prevention) and STAMP (treatment) for COVID-19[4–6]
- We previously developed a modified quantitative systems pharmacology whole-body physiologically based PK (QSP/PBPK) model, which adequately a priori predicted the observed adintrevimab PK in humans[7,8]
- Here, we describe further modification of the QSP model in which adintrevimab concentrations in upper airway (UA), epithelial lining fluid (ELF), and saliva were linked to a viral dynamic model in order to describe the impact of adintrevimab on SARS-CoV-2 viral load relative to placebo

METHODS

QSP/PBPK Modeling

- The previously described QSP/PBPK model was modified by splitting the lung compartment into 3 distinct sub-compartments: UA (esophagus, trachea, bronchi), lower airway (bronchioles), and alveoli[7]
- The current model was fit in NONMEM Version 7.4 using PK data collected from participants in the phase 1 study (N=24, intravenous [IV] and IM)[5] and the phase 2/3 EVADE (N=659, IM)[4] and STAMP (N=189, IM)[5,6] clinical studies
  - Participants in phase 1 received a single dose of adintrevimab 300 mg IM, 500 mg IV, or 600 mg IM
  - Participants in the phase 2/3 EVADE and STAMP studies received a single dose of adintrevimab 300 mg IM. Enrollment began in mid-2021 and was paused in January 2022 because of the emergence of the Omicron variant, against which adintrevimab had decreased in vitro neutralization activity[2]
- The QSP/PBPK model was optimized using the PK data and body weight distribution from participants in all 3 studies to better reflect the observed variability. The final parameter estimates are shown in **Table 1**

Table 1. Final parameter estimates for the QSP/PBPK model[a]

Parameter	Final estimate	%RSE
V_{plasma} (L) for a 71 kg human	1.41	Fixed
K_a (hr^{-1})	0.0687	6.4
$K_{clf,FcRn}$ (hr^{-1})	2.26	5.3
ω^2 for V_{plasma}	1.40 (175% CV)	6.7
ω^2 for K_a	0.681 (98.8% CV)	27.8
ω^2 for $K_{clf,FcRn}$	0.598 (90.5% CV)	18.2
Residual variability (σ^2)	0.0286 (17.0% CV)	9.8

[a]Fitting was performed with NONMEM Version 7.4. The SAEM and IMP estimation routines were utilized. The Beal M3 method was used to handle BLQ data during the IM absorption phase and potentially in the elimination phase. BLQ, below limit of quantification; CV, coefficient of variation; IMP, importance sampling expectation-maximization; RSE, relative standard error; SAEM, stochastic approximation expectation-maximization. Other definitions can be found in Table 2.

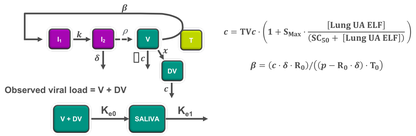
Survival Analysis

- A survival analysis was completed to associate findings from the viral dynamic model to clinical efficacy
- Time to hospitalization and death for each subject in the STAMP study was analyzed using Kaplan-Meier survival analysis and log-rank test, stratifying the data based on treatment group
- Right censoring was used if hospitalization or death was not directly observed by day 29

Viral Load Modeling

- Saliva and nasopharynx (NP) samples were collected from 392 participants in the STAMP study who received adintrevimab or placebo and were infected with the Delta or Omicron (BA.1, BA 1.1, BA.3) SARS-CoV-2 variants
- Viral load (log_{10} copies/mL) was assessed by reverse transcription-quantitative polymerase chain reaction
- A mathematical viral dynamic model was used to analyze data on the impact of adintrevimab on SARS-CoV-2 viral loads
  - To compare within-host viral dynamics for infected participants
  - To assess the impact of adintrevimab on SARS-CoV-2 viral load and the risk of hospitalization or death relative to placebo
  - To allow for rapid dose identification in response to emerging variants
- The viral dynamic model was based on the published QSP model[7,8] and was modified to include both active (V) and deactivated (DV) virus (**Figure 1**)
- The model was fit in NONMEM Version 7.4 to the NP swab viral load data (2 samples per participant) standardized to time since infection, based on recorded symptom onset (assumed to be 5 days for patients infected with the Delta variant and 3 days for patients infected with the Omicron variant)
- Saliva data (7–8 samples per participant) were fit sequentially using a biophase compartment given that the peak viral load was modestly lower and later relative to NP swab data
- The impact of adintrevimab was estimated using the model-based simulated median and 90% prediction interval (PI) forecast for viral load reduction

Figure 1. Modified viral dynamic model



$$c = TVc \cdot \left(1 + S_{Max} \cdot \frac{[\text{Lung UA ELF}]}{(SC_{50} + [\text{Lung UA ELF}])}\right)$$

$$\beta = (c \cdot \delta \cdot R_0)/((p - R_0 \cdot \delta) \cdot T_0)$$

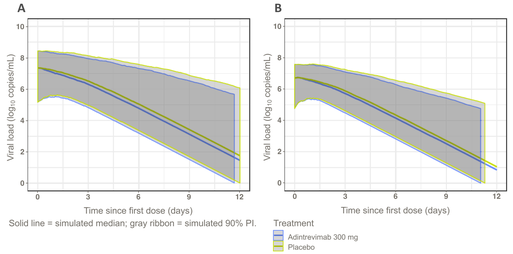
I_1, infected cell 1; I_2, infected cell 2; TVc, time to viral clearance. Other definitions can be found in **Table 2**.

RESULTS

Baseline Characteristics

- The QSP model provided an excellent fit to serum adintrevimab concentration-time data after estimation of a transit rate to account for IM absorption, plasma volume, and the adintrevimab-neonatal Fc receptor dissociation rate constant
- Adintrevimab concentration in UA and ELF resulting in 50% of S_{max} (SC_{50}) was estimated to be 0.086 mg/L for Delta and 1.05 mg/L for Omicron
- Model-based simulated median (90% PI) viral load reduction in adintrevimab-treated and placebo-treated patients for the Delta and Omicron variants are shown in **Figure 2**

Figure 2. NP viral dynamic simulations of placebo vs adintrevimab in patients infected with the (A) Delta and (B) Omicron variants

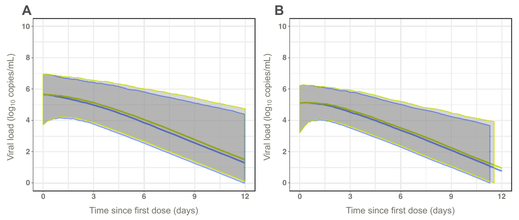


Solid line = simulated median; gray ribbon = simulated 90% PI.

Viral Load Modeling of Saliva Data

- The linked viral dynamic model captured the saliva viral load data after estimating differences in transit rate from viral UA to saliva compartment (Ke0) and removal rate from saliva (Ke1; **Table 2**)
- Model-based simulated median (90% PI) viral load reduction in adintrevimab-treated or placebo-treated patients for the Delta and Omicron variants are shown in **Figure 3**

Figure 3. Saliva viral dynamic simulations of placebo vs adintrevimab in patients infected with the (A) Delta and (B) Omicron variants



Solid line = simulated median; gray ribbon = simulated 90% PI.

- Logistic regression modelling of hospitalization and death data showed that an NP viral load of ~7.91 log_{10} copies/mL or lower at 7 days after COVID-19 exposure was associated with a 70% reduction in hospitalization risk

Table 2. Final parameter estimates for the modified viral dynamic QSP model – saliva data[a]

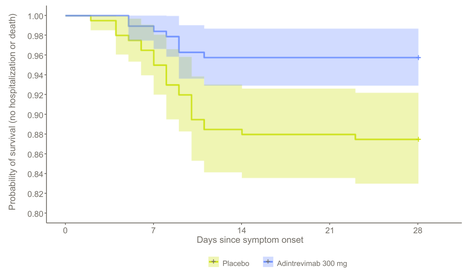
Parameter	Description	Units	REGN-fitted values[b]	Adintrevimab-fitted values (Delta)	Adintrevimab-fitted values (Omicron)
R_0	Within-host replication factor	NA	25.8	55	121
k	Eclipse rate from IC1 to IC2	day^{-1}	3	3	3
delta	Loss rate of infected cells	day^{-1}	0.99	1.29	1.29
p	Viral production rate	day^{-1}	5890	9940	1070
c	Viral clearance rate	day^{-1}	10	3.47	3.47
V_0	Initial viral load	copies/mL	0.1	0.1	0.1
T_0	Initial target cell number	cells/mL	133,333	133,333	133,333
x	Viral death rate	day^{-1}	NA	0.0987	0.0987
S_{max}	Maximum stimulatory effect	NA	0.43	0.43	0.43
SC_{50}	UA and ELF adintrevimab concentration resulting in 50% of maximal stimulation of viral clearance	mg/L	0.007 (in vitro)	0.094	1.26
K_{e0}	Transit rate from viral UA to saliva compartment	day^{-1}	NA	2.84	2.84
K_{e1}	Removal rate from saliva compartment	day^{-1}	NA	3.63	3.63
ω^2 for k	Inter-subject variability for k	–	NA	1.150	1.150
ω^2 for c	Inter-subject variability for c	–	NA	0.855	0.855
ω^2 for T_0	Inter-subject variability for T_0	–	NA	0.292	0.292
ω^2 for p	Inter-subject variability for p	–	NA	0.723	0.615
ω^2 for K_{e0}	Inter-subject variability for K_{e0}	–	NA	0.001	0.001
ω^2 for K_{e1}	Inter-subject variability for K_{e1}	–	NA	0.009	0.009
σ^2	CCV component of residual variability Additive component of residual variability		NA	0.766 0.00002	0.766 0.00002

[a]Fitting performed with NONMEM Version 7.4 (Laplacian estimation routine). Beal M3 method was used to handle BLQ viral load data. In vitro IC_{50} for adintrevimab was 0.007 mg/L for the Delta variant and 1.1 mg/L for the Omicron variant. [b]The viral dynamic model parameters were initially calibrated to emerging viral load data from the REGN-COV-2 program.[9] CCV, constant coefficient of variation; IC1 and IC2, inhibitory concentrations 1 and 2.

Survival Analysis

- An exploratory Kaplan-Meier analysis showed a higher probability of survival (no hospitalization or death) with adintrevimab at 300 mg IM vs placebo (**Figure 4**)

Figure 4. Kaplan-Meier survival plot by treatment group



KEY FINDINGS

A QSP/PBPK modeling and simulation approach was linked to a viral dynamic model to show that a single dose of adintrevimab could effectively reduce SARS-CoV-2 viral load and the risk of hospitalization or death relative to placebo in patients who were infected with the Delta or Omicron (BA.1, BA 1.1, BA.3) variants

The linked viral dynamic model accurately captured the NP swab viral load data after estimating differences in within-host replication factor (R_0) and viral production rate (p) by variant

The linked viral dynamic model accurately captured the saliva viral load data after estimating differences in transit rate from UA to saliva compartment (K_{e0}) and removal rate from saliva (K_{e1})

QSP/PBPK and viral dynamic modeling was used to describe the impact of adintrevimab on viral dynamics and hospitalization or death relative to placebo

CONCLUSIONS

- The updated QSP model, in conjunction with information on new variants available early in outbreaks (IC_{50}, infectivity [R_0], viral production rate [each a model parameter]), could allow for rapid dose identification in response to emerging variants
- Model simulations predicted that adintrevimab 300 mg IM effectively reduces SARS-CoV-2 viral load in NP and saliva, and results in a lower risk of hospitalization or death relative to placebo

REFERENCES

1. Rappazzo CG, et al. *Science*. 2021;371:823-829.
2. Kaku CI, et al. Presented at ECCMID; April 23–26, 2022. Poster P2161.
3. Schmidt P, et al. Presented at ISIRV-WHO; October 19–21, 2021. Poster 131.
4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04859517. Accessed August 24, 2022.
5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04805671. Accessed August 24, 2022.
6. Popejoy M, et al. Presented at ASM Microbe; June 9–13, 2022. Poster 5692.
7. Van Wart SA, et al. Presented at IDWeek; September 29–October 3, 2021. Poster 1086.
8. Tarbell E, et al. Presented at IDWeek; September 29–October 3, 2021. Poster 1088.
9. Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

DISCLOSURES

MP, KN, EH, XP, and JG are employees of Invivyd, Inc. (formerly Adagio Therapeutics, Inc.) and may own stock or shares of Invivyd, Inc.

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