A Polyclonal Antibody Dosing Strategy to Reduce the Viral Load of Multiple Coronavirus Mutants in COVID-19 Patients with Pneumonia

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Research Article

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A Polyclonal Antibody Dosing Strategy to Reduce the Viral Load of Multiple Coronavirus Mutants in COVID-19 Patients with Pneumonia

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Short Title: Polyclonal Antibody Dosing Strategy for COVID-19 Patients with Pneumonia

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Abstract

Purpose

Monoclonal antibodies target a single epitope or region in an antigen for therapeutic purposes. Given the highly mutant nature of SARS-COV-2 or coronavirus, it is likely that a cocktail of antibodies or a polyclonal antibody targeting multiple regions of the virus might be more beneficial in treating COVID-19. The purpose of this project, based on the reported clinical evaluation of XAV-19 polyclonal antibody in pneumonia patients, is to develop a pharmacokinetic-pharmacodynamic (PK-PD) model to explain the relationship between drug concentrations and reduction in the nasopharyngeal viral load.

Methods:

The concentration of the drug in a time course was related to the effect at each time point to determine the PK-PD relationship. Using Berkeley-Madonna, a PK-PD mathematical model including a central serum compartment, a peripheral effect compartment, and an Emax model for drug effects was developed to explain the observed drug concentrations and effects. Using published EC50 concentrations for XAV-19 and various variants of SARS-CoV-2, the time course of drug effect was predicted for the virus variants including D614G, alpha, beta, gamma, and delta.

Results:

The results indicated a counter-clockwise hysteresis loop for the PK-PD relationship, suggesting lower effects at the same concentration initially, followed by greater effects at the same concentration later. This is consistent with separation of the effect compartment from the serum compartment, where concentrations are measured. The model explained the observed data well.

Conclusion:

The PK-PD model is useful in predicting dose-response relationships for the new polyclonal antibody. Further, it can be extended to other emerging variants of the coronavirus.

Key Words: SARS-COV-2, COVID-19, XAV-19, Polyclonal antibody, PK-PD model, and Humans Subjects

1. Introduction

COVID-19 disease led to 4.8M deaths in the world since December 2019 (https://www.worldometers.info/coronavirus/; accessed 10/2/2021). SARS-CoV-2 or severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) is the pathogen responsible for the disease. The main complication of COVID-19 is pneumonia and failure of lung function, with 15-20% of patients being admitted to the intensive care unit (ICU) due to respiratory failure [4]. The pathology includes diminished oxygen supply to the blood, brain, and the rest of the body, ultimately resulting in multiple organ failure and death. Since 2019, the virus mutated into several new forms including alpha, beta, delta, gamma, and most recently mu [5]. Currently, the delta variant accounts for most of the COVID-19 cases in the USA. The vaccines developed to date, including those based on mRNA or live viruses, are losing their effectiveness against the new variants [5]. The number of cases as well as deaths are still high, and the new variants may continue to cause more loss of life. Vaccines only prevent the disease. They are not useful in patients with existing COVID-19. To treat existing disease, reducing virus content or load in the body is critical. This can be achieved using antiviral drugs including those that kill the virus and antibodies that bind and eliminate the virus. Currently there is no effective antiviral agent to kill the virus. Monoclonal antibodies targeted against a single epitope of the spike protein antigen received emergency use authorization (e.g., tocilizumab, casirivimab and imdevimab). However, they are limited in their effectiveness and may not be effective against variants with mutations in spike protein [5]. There is an urgent need to develop new antibodies that target multiple parts of the virus antigen. Such antibodies are called polyclonal antibodies. They contain a mixture of antibodies to neutralize the virus more effectively. Key coronavirus mutants responsible for evading vaccine/therapeutic efficacy include alpha (B.1.1.7), beta (B.1.35), gamma (P.1), delta (B.1.617.2), and most recently, omicron (1.1.529, BA.1, BA 1.1 to BA 1.5) (Table 1) [5,6].

Gaborit et al. (2021) reported the pharmacokinetics and safety of XAV-19, a swine glyco-humanized polyclonal anti-SARS-CoV-2 antibody, in patients with COVID-19-related moderate pneumonia [7]. The authors determined the intravenous infusion dose of XAV-19 that is effective and safe in these patients. The team did not observe any infusion-related reactions or hypersensitivity events during the treatment. Further, no medication discontinuations occurred due to adverse events. Additionally, no serious adverse events could be related to the study drug. The study observed that XAV-19 at a single intravenous dose of 2 mg/kg had good tolerability and high serum concentrations. The concentrations achieved were deemed to be potent and durable in neutralizing viral load. This

research explains how the XAV-19 in certain doses was effective and safe in treating COVID-19. In addition to serum concentrations, this article reported the nasal viral load of coronavirus, which declined in response to the drug. Based on this prior publication, the overall hypothesis of this study was that a pharmacokinetic-pharmacodynamic (PK-PD) model can be developed to relate serum concentrations of XAV-19 to nasal viral load in pneumonia patients. The benefits of the model include prediction of drug concentration and responses simultaneously in the human subjects after repeated doses. The model allows dose selection of XAV-19 for treating coronavirus and its mutants.

2. Materials and Methods

2.1. Literature review: Published literature was reviewed using PubMed database. Articles reporting XAV-19 data in animal (preclinical) and human (clinical) models were identified and obtained. Additionally, literature was reviewed for any PK-PD reports related to XAV-19.

2.2. Plotdigitizer: Plotdigitizer software (SourceForge) was used to extract the drug concentration-time profile and nasal viral load-time profiles from Gaborit et al. [1] (Figures 1 and 2).

2.3. PK-PD model development and verification: Berkeley Madonna software (version 10.1.3) was used to generate a PK-PD model and solve differential equations. Within Berkeley Madonna, a flow chart-based PK-PD model was created. The model included a central compartment to represent serum concentration and a peripheral effect compartment representing the nasopharyngeal region for viral load lowering effect. The model used the sigmoidal Emax model to relate the drug concentrations to percent reduction in viral load. The model was used to predict drug concentration and response time-courses.

2.4. Data analysis: Data was modeled using Berkeley Madonna and plotted using Berkeley-Madonna or Microsoft Excel Spreadsheet.

Results

2.5. Relationship between serum concentration and effect: Gaborit et al. (2021) reported Log units of viral load as a function of time. Change in viral load was calculated using Excel and plotted. The drop in viral load vs. serum concentration of antibody showed an anti-clockwise profile as the concentrations are followed as per increasing time (Figure 3). This indicates a delay between the peak concentrations in the serum and drug effects. This is consistent with a delay in delivery of the drug to the remote effect compartment. Therefore, an effect compartment is to be included in the model.

2.6. PK-PD model: PK-PD model for the antibody is shown in Figure 4. The model included an effect compartment representing the nasopharyngeal region. The serum concentrations and viral load drop could be simultaneously fit using the model. The parameters used to explain the data are shown in Table 2. Based on the parameters used, the best fit obtained using Berkeley-Madonna is shown in Figure 5.

2.7. Prediction of drug effects on key coronavirus variants: Using the PK-PD model in Figure 4 and the EC50 values shown in Table 3, the effect of XAV-19 on nasopharyngeal load of various virus mutants was predicted. The results are shown in Figure 6.

3. Discussion

A PK-PD model was developed to explain the serum concentrations and nasal viral load reduction byXAV-19, a novel polyclonal antibody against SARS-CoV-2. The model predicted the serum concentrations of the drug as well as the reduction in the number of virus copies in the nasopharyngeal region of infected patients. Further, based on half-maximal effect concentrations determined in vitro, the model predicted the effect time-course of the antibody in reducing various novel coronavirus mutants.

XAV-19 is a polyclonal antibody unlike the currently approved antibodies directed against SARS-CoV-2. The antibody is raised against the receptor-binding domain of the spike protein in the virus. Due to its polyclonal nature, it can bind multiple regions or epitopes in the target antigen unlike monoclonal antibodies developed against a single epitope. Since spike protein exhibits high mutation potential, prior monoclonal antibodies are losing their activity against new spike mutants of the virus. For instance, bamlanivimab, an antibody against a spike protein epitope is ineffective against the beta variant of SARS-CoV-2 [3]. On the other hand, XAV-19 has potent activity against the beta variant. Thus, XAV-19 will likely be more beneficial in addressing emerging variants. XAV-19 is a humanized antibody raised in knockout pigs and it does not induce adverse allergic reactions that are common with foreign antibodies [3].

Dosing of XAV-19 or any other drug requires an understanding how the drug is disposed in the human body and the relationship between drug concentrations and effects [8]. To this end, a clinical study was conducted in human subjects for XAV-19. Specifically, the concentration vs. time and effect vs. time profiles were reported for the drug in COVID-19 patients with moderate pneumonia [1]. In this study, an intravenous dose of 2 mg/kg was deemed safe, and it showed beneficial effect. The current study developed a PK-PD model to predict this previously published drug concentration and effect data. A PK-PD model can include multiple compartments for the body or relevant organs [8]. The model can further include properties of different organs as desired to predict drug performance based on organ function or property. The model designed in this study included dosing elements for infusion or continuous drug dosing at a fixed rate over a specified duration (in this case, 1 hour), a compartment to represent the serum concentrations, and another compartment to represent the effect compartment (Figure 4). The use of an effect compartment is justified on the basis that there is a delay between peak drug concentrations in the serum and the effect. While drug levels were analyzed in the serum derived from blood samples, viral load was analyzed using a swab

applied to the nasopharyngeal region. This region is distant from the serum compartment. Antibodies, being large, may experience a delay in reaching the target tissue from serum [9]. Based on their large size, they are not filtered readily by the kidney. Therefore, they persist for longer periods in the blood, resulting in long half-life, as observed in the current study. Specifically, XAV-19 has a half-life of 11.2 days, which allows maintenance of effective concentrations for a few weeks. This value, estimated by Gaborit et al. [1] was used to determine the elimination rate constant for XAV-19 (Table 2). Table 2 shows the other parameters used to fit the pharmacokinetic and pharmacodynamic data.

The PK-PD model was successful in simultaneously predicting the time courses for drug concentration and effect (Figure 5). The predicted lines fit the observed data well, based on visual inspection and low values for the root mean square error between the predicted and observed values. The model was further extended to predict the effect time courses for various coronavirus variants. Within a few days after 2 mg/kg infusion dose, the antibody is predicted to eliminate the virus variants almost completely, with the rank order for effects being: Gamma < Beta < Delta < D614G < Alpha < Wuhan.

There are several limitations to this study. Drug concentrations reported in the source article [1] as mean values and drug effects reported as median values were used in this study. The model was fit to these mean/median concentrations and did not account for the variability in the data. It is anticipated that there is variation in drug concentrations as well as effects in the patient population, which should be considered while dosing. However, in general practice, the same dose is given to all COVID-19 patients. Another limitation of the study is based on a data extraction approach. Since the actual data for concentration and effect were in graphs, the data was extracted using PlotDigitizer software. This approach, while giving numbers close to actual observed values, is error prone. This may have affected the outcomes to an extent. Yet another limitation is that one data point at the peak concentration was not fit by the predictions (Figure 5). This data point may fall on the fitted line if another compartment or two phases of drug concentration decline are considered [8]. The observed effect data showed a sigmoidal pattern. The model can be improved by considering a modified Emax model with an exponent for the effect compartment concentration in the equation.

4. Conclusion

The PK-PD model developed in this study can be used to predict the effects on other mutants of the coronavirus, once the EC50 concentrations are known based on in vitro studies. The model is useful in predicting the doses, either single or repeated, to reduce coronavirus load in infected patients.

Statements and Declarations

Conflict of Interest: Author Rohini Kompella and Madhoosudan Patil declare that they have no conflict of interest.

Competing Interests and Funding

The authors did not receive support from any organization for the submitted work. The authors have no relevant financial or non-financial interests to disclose.

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Figures:

Fig. 1 Serum concentrations of XAV-19 polyclonal antibody following single intravenous infusion at a dose of 2 mg/kg. Based on Gaborit et al. [1].

Fig. 2 Nasopharyngeal viral load over time in the XAV-19 2-mg/kg group. Based on Gaborit et al. [1].

Fig. 3 Relationship between nasopharyngeal viral load vs. serum antibody concentration in the XAV-19 2-mg/kg group. A counterclockwise hysteresis loop was observed.

Fig. 4 PK-PD model developed for XAV-19. Berkeley-Madonna was used to create the PK-PD model.

Fig. 5 Simultaneous PK-PD model fit to reported serum concentration and drop in nasopharyngeal viral load drop in patients with moderate pneumonia. The PK-PD model shown in Figure 2 and parameters reported in Table 2 were used. Circles represent actual data. Solid lines represent model predictions. Actual data is based on Gaborit et al. [1].

Fig. 6 Prediction of the effect of XAV-19 (2 mg/kg, 1-hour intravenous infusion) on the nasopharyngeal load of various coronavirus mutants in patients with moderate pneumonia. The PK-PD model in Figure 4 and data in Tables 2 and 3 were used. The sensitivity of variants was in the order: Gamma < Beta < Delta < D614G < Alpha < Wuhan.

Tables

Mutant responsible for evading vaccine/therapeutic efficacy	**Other names**
Alpha	B.1.1.7
Beta	B.1.351
Gamma	P.1
Delta	B.1.617.2
Omicron	1.1.529, BA.1, BA.1.1, BA.2, BA.3, etc.

Table 1. Key mutants of SARS-CoV-2.

Parameter Name	**Value**	**Unit**
STARTTIME	0	*days*
STOPTIME	30	*days*
DT	0.02	
DTOUT	0	
INIT Aserum	0	*mcg*
INIT Dose_amount	0	*mcg*
INIT Aeffect	0	*mcg*
Ks0	0.11	*1/day*
Vserum	3200	*ml*
T	0.0417	*days*
Dose	140000	*mcg*
Dosing_interval	5	*days*
Start_time	0	
Number_of_doses	1	
Emax	4.82	*Log(Viral Load/Count)*
EC50/IC50	5	*mcg/ml*
Veffect	4500	*ml*
Kse	0.007	*1/day*
X	8.5717	

Table 2. Parameters and values used for curve fitting XAV-19 antibody's serum concentration and effect data using Berkeley-Madonna. Key: mcg – micrograms; A_{serum} – amount in central compartment, that is, serum; A_{effect} – amount in effect compartment; K_{s0}- first-order rate constant for drug loss from serum; K_{ce}- first-order rate constant for drug transfer from central to effect compartment; V represents volume; T- duration of infusion; EC_{50} – concentration for half maximal effect (same as inhibitory concentration for 50% of the maximum effect or IC_{50}); E_{max} – maximum effect; Single dose was simulated in this study and the dosing interval can be selected as needed.

Variant	IC50 for Coronavirus Variant (µg/ml)				
	Quantitative real-time polymerase chain reaction (qRT-PCR)*	**Average of qRT-PCR**	**Cytopathic effect (CPE) assay***	**Average of CPE assay**	**Overall average**
Wuhan D614G	0.5/3.6	2.1	0.4 (Wuhan)	0.4	1.2
B.1 D614G	0.5/3.6/3.7	2.6	2.2/2.7	2.5	2.5
Alpha	1.2/3.6/3.4	2.7	0.1/2.2/2.3	1.5	2.1
Beta	6/8.9/8.0	7.6	3.2/6.5	4.9	6.2
Gamma	2.4/13.8	8.1	8.1	8.1	8.1
Delta	5.5	5.5	4.2	4.2	4.9

*Multilple values indicate data from different laboratories reported in a prior publication [2]. The paper indicated Wuhan D614G for the RT-PCR assay and Wuhan for cytopathic effect assay.

Table 3. Effect of XAV-19 on various SARS-CoV-2 mutants isolated from patients. Table is based on data summarized in a publication by Vanhove et al. [3].

Figures

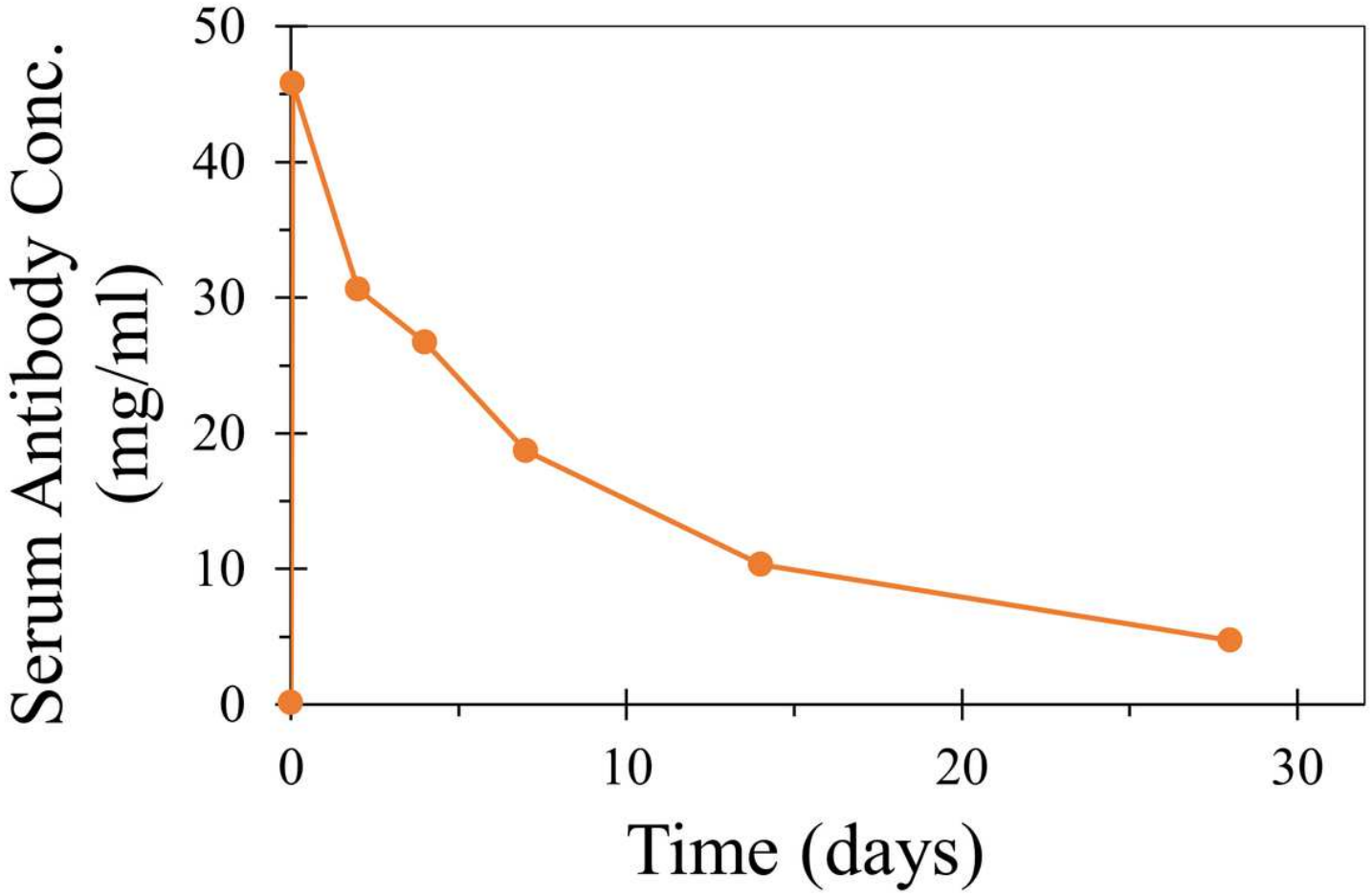

Figure 1

Serum concentrations of XAV-19 polyclonal antibody following single intravenous infusion at a dose of 2 mg/kg. Based on Gaborit et al. [1].

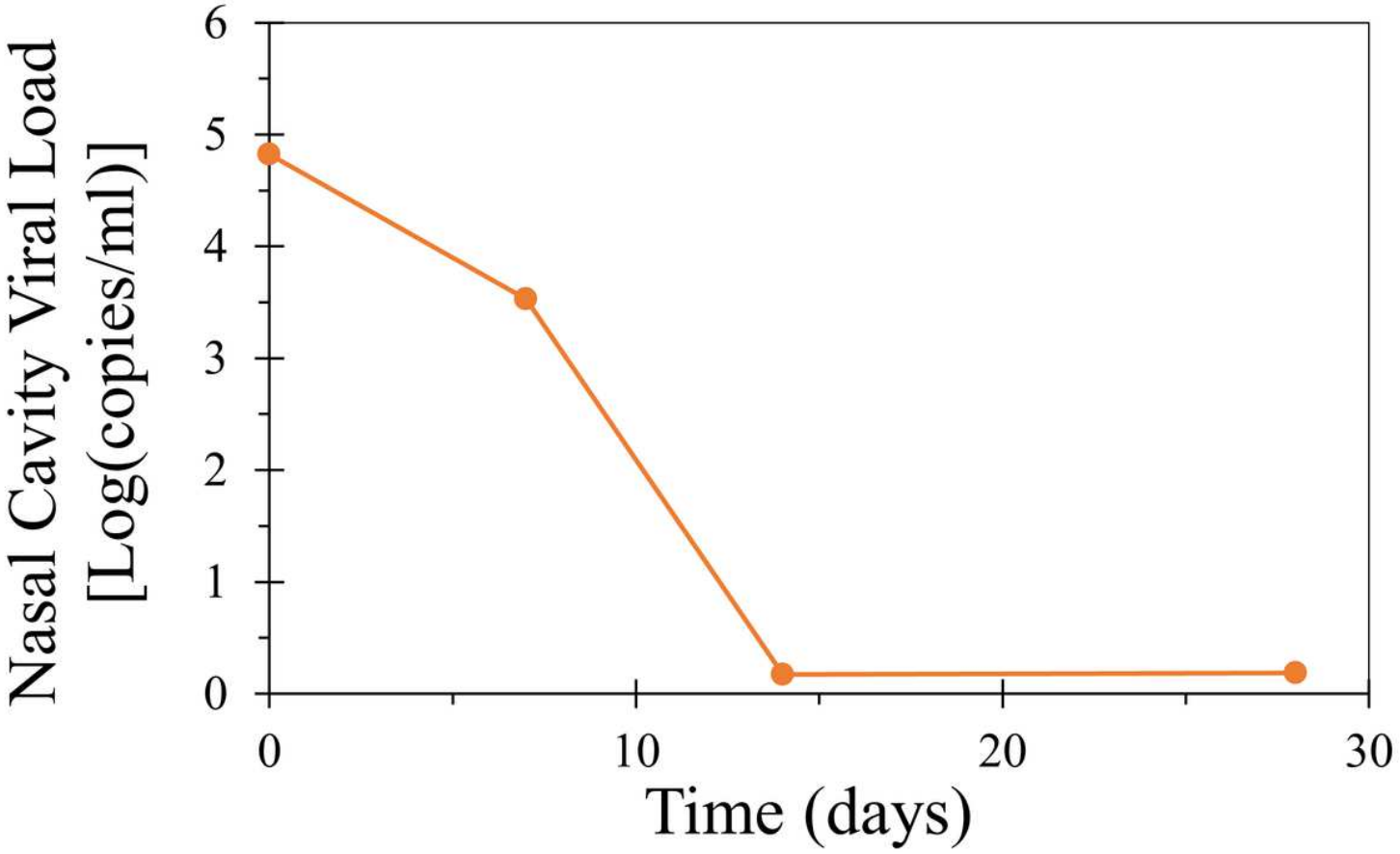

Figure 2

Nasopharyngeal viral load over time in the XAV-19 2-mg/kg group. Based on Gaborit et al. [1].

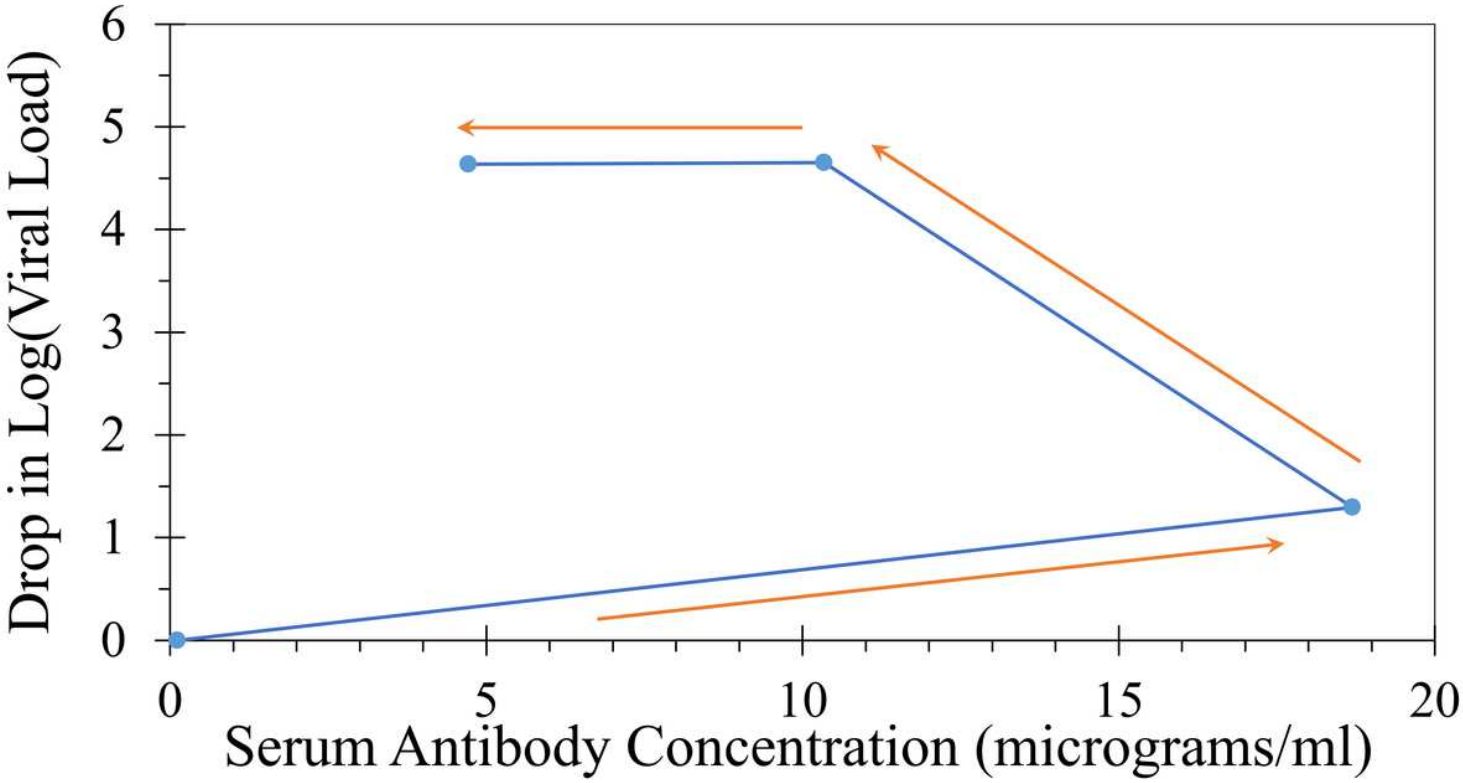

Figure 3

Relationship between nasopharyngeal viral load vs. serum antibody concentration in the XAV-19 2-mg/kg group. A counterclockwise hysteresis loop was observed.

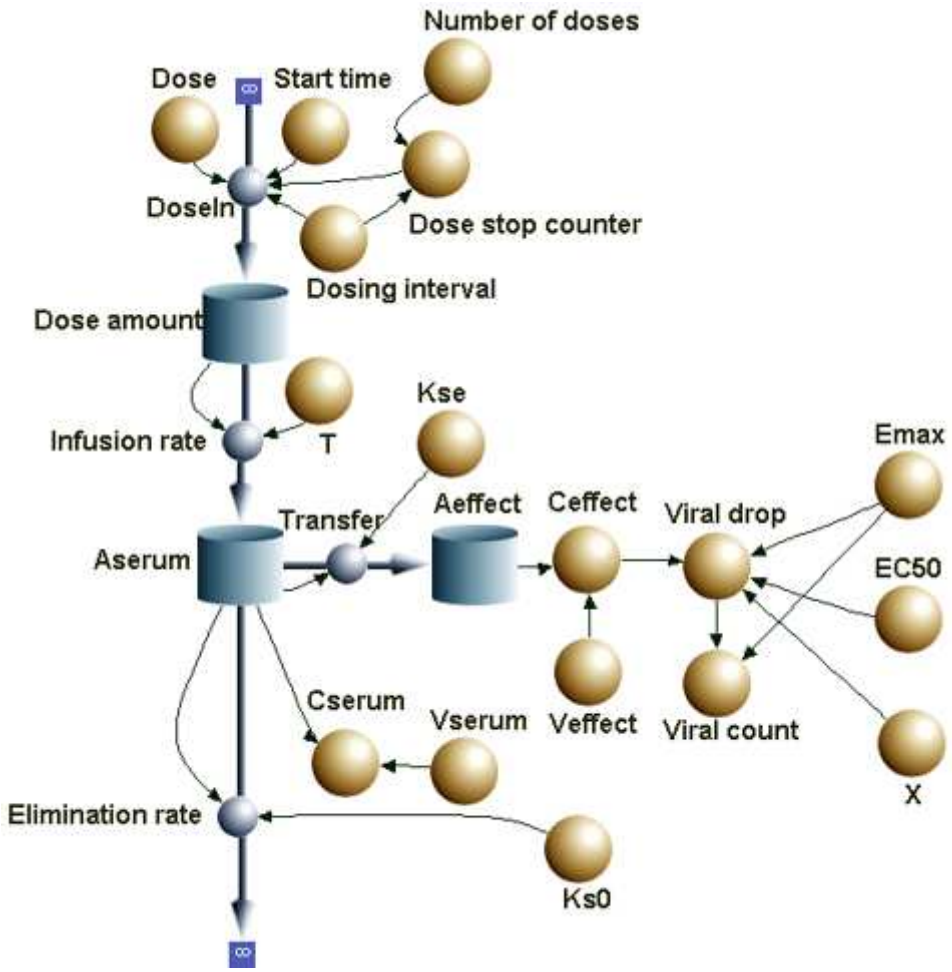

Figure 4

PK-PD model developed for XAV-19. Berkeley-Madonna was used to create the PK-PD model.

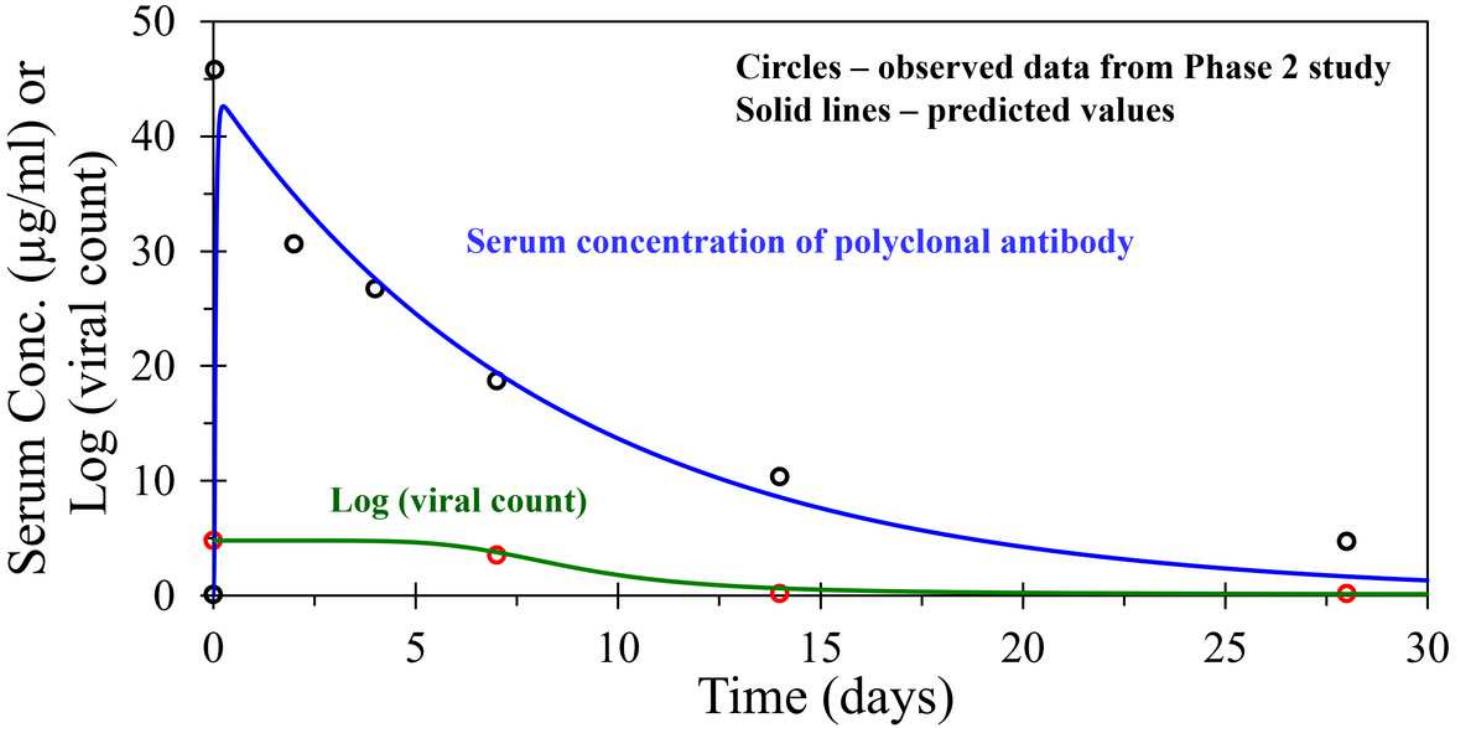

Figure 5

Simultaneous PK-PD model fit to reported serum concentration and drop in nasopharyngeal viral load drop in patients with moderate pneumonia. The PK-PD model shown in Figure 2 and parameters reported in Table 2 were used. Circles represent actual data. Solid lines represent model predictions. Actual data is based on Gaborit et al. [1].

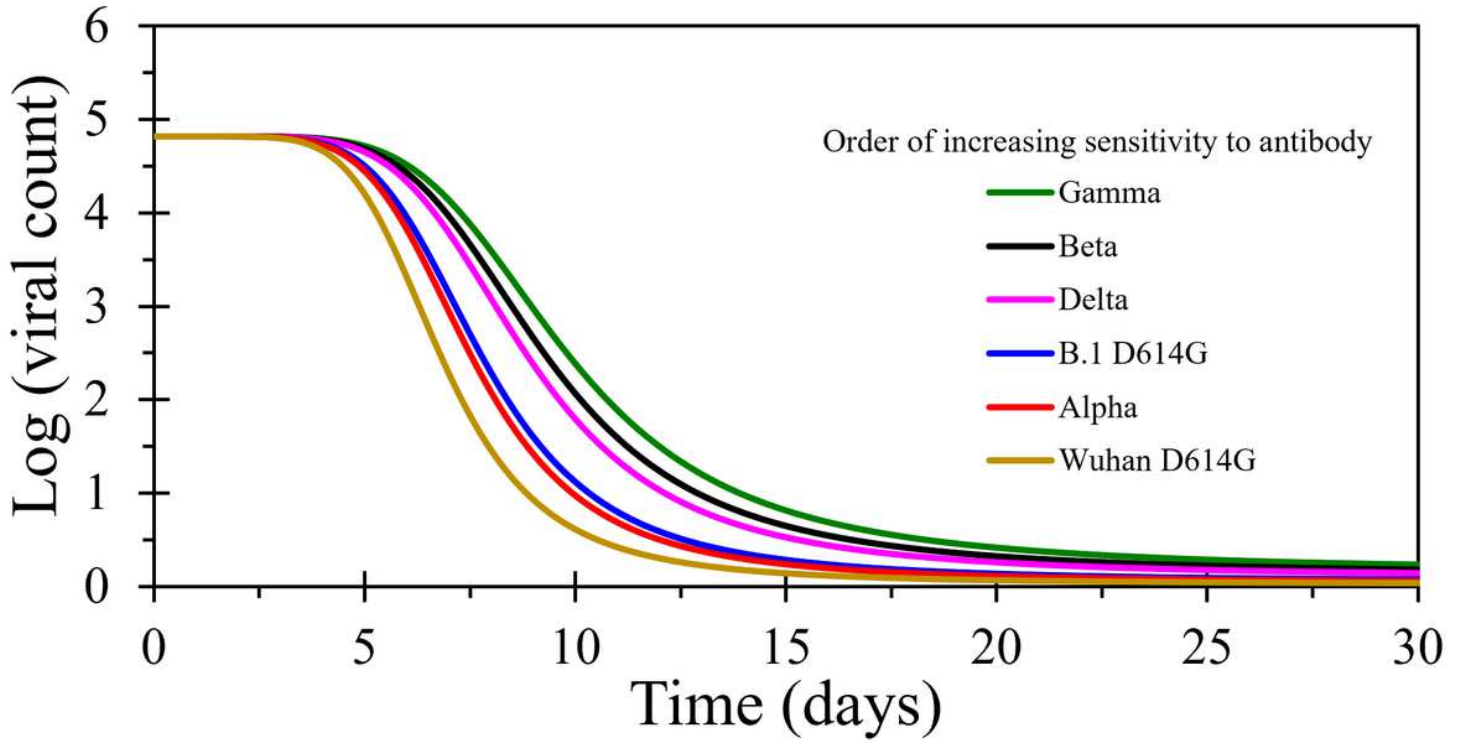

Figure 6

Prediction of the effect of XAV-19 (2 mg/kg, 1-hour intravenous infusion) on the nasopharyngeal load of various coronavirus mutants in patients with moderate pneumonia. The PK-PD model in Figure 4 and data in Tables 2 and 3 were used. The sensitivity of variants was in the order: Gamma < Beta < Delta < D614G < Alpha < Wuhan.