EDITORIAL

Initiation of Antiviral Treatment in SARS-CoV2: Modeling Viral Dynamics and Drug Properties

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As the coronavirus disease 2019 (COVID-19) pandemic has evolved, the search for vaccines and treatments continues in earnest. This pandemic is causing sharp increases in morbidity and mortality and an urgency to make therapies widely available. The COVID-19 pandemic reveals the limited preparedness of health systems worldwide, and healthcare workers have very few options to combat this emergent disease and save patients' lives. This search for new vaccines and treatments is a test of our collective ability to assess medications, presenting both an opportunity and a challenge to drug research, development, and approval apparatus. Well-conducted randomized, controlled trials in acutely ill patients will be needed to evaluate survival, hospitalization, number of days spent in intensive care, and need for a ventilator. Current strategies generally use one of two approaches: novel treatments targeted against the virus and repurposed drugs with well-characterized clinical safety and pharmacokinetics.

Prior to large clinical trials, assessing the therapeutic potential of repurposed drugs based only on very early efficacy data—including *in vitro* studies or preliminary clinical experiences—is a major challenge.[1,2] Quantitative modeling and simulation approaches can tackle this challenge by integrating the available data to provide optimal dosing recommendations, either within a clinical trial or in an emergency setting. Given the number of drugs under investigation for use in COVID-19, fundamental questions related to clinical pharmacology are more critical than ever. What is an appropriate dose(s)? When should a treatment be initiated? How long should we treat a patient?

In this issue of *CPT:PSP*, Goncalves *et al*.[3] developed a viral dynamic model to predict the outcomes of COVID-19 treatment. The work uses a well-characterized model for predicting the dynamics of virus infections based on studies of the dynamics of influenza virus infections in humans.[4,5] After fitting the model to data from 13 hospitalized patients in Singapore to understand viral replication in the absence of treatment, they then simulated outcomes for a range of therapies considering both antiviral potency and the timing of treatment initiation. They concluded that a modestly effective antiviral agent (i.e., blocking 60% of viral production) could dramatically reduce viral loads if administered at the time of infection. However, if treatment does not start until symptoms emerge, then 90% efficacy would be required for the same outcome. Conceptually, their work is illustrated in **Figure 1**. In their assessment, a treatment that reduces peak viral load 100-fold is assumed to achieve desired clinical outcomes. Both the potency and timing of treatment determine outcomes (red and light blue curves). The basic model fits the data well and utilizes a mixed-effects modeling approach. The authors highlighted areas that require future work to address limitations in the model, which include the fixing of certain parameters and simplification of immune effects. In particular, the influenza model upon which this work is based considers only short-term dynamics and does not include adaptive immunity. Indeed, COVID-19 infections are of longer duration, particularly among those with severe symptoms, and both cellular and humoral immune responses are likely important to understanding resolution of the infection. In addition, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) may combat innate immune control by blocking interferon expression,[6] causing viral dynamics to diverge even further from a model based on influenza.

Two key assumptions in this work are ripe for further exploration in studies of viral dynamics. The first assumption is the selection of an efficacy target of a 100-fold reduction in viral load, 5 days after onset of symptoms. According to their data, this timing was chosen as it corresponded to typical peak viral load in the absence of treatment. A relationship between increasing viral load and disease severity has been observed in other viral infections, such as hepatitis B, HIV, H1N1 influenza, and respiratory syncytial virus,[7,8] but establishing such a relationship for SARS-CoV-2 may be a complex task.

Fortunately, we have several modeling approaches at our disposal to navigate obstacles that may arise in investigating this assumption. One obstacle is that in an acute care setting, the timing and availability of specimens are likely to depend on a patient's current disease state, as viral load sampling may be delayed until a patient is stabilized. This issue presents the challenge of informative censoring that can bias estimates of the relationship between viral load and clinical outcome. Joint modeling approaches have been devised to correct for these biases.[9,10] These methods have recently come to prominence in studies relating tumor burden to survival in the area of oncology, another setting in which the availability of biomarkers changes following disease
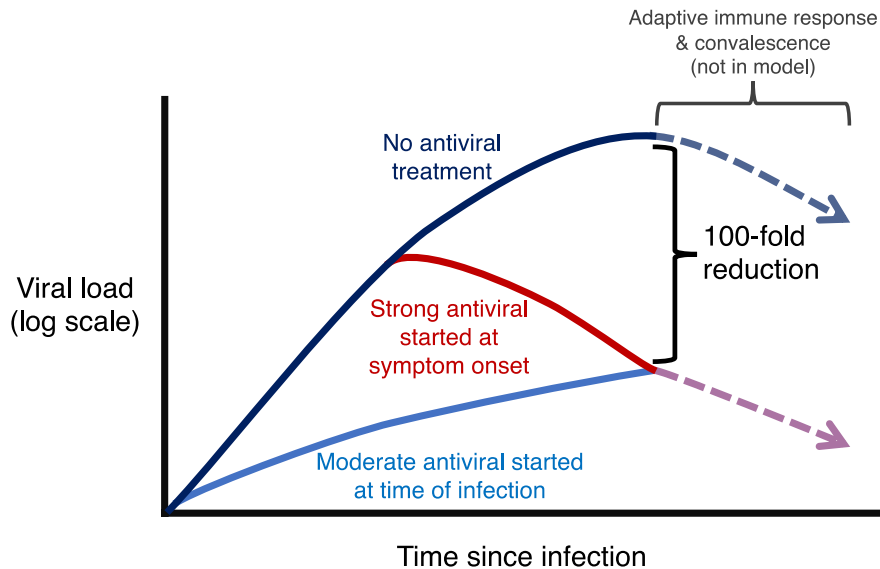
Figure 1 A conceptual illustration of model presented by Goncalves *et al.*[3]

progression. A second obstacle is that the trajectory of the disease can change following emergence of adaptive immunity. Although the adaptive immune response may occur too late to reduce peak viral load, it could still affect disease duration and severity of symptoms. As the authors note, accounting for this response would require more complex models and immunological data. The literature on immune control of HIV infection may provide a useful example for researchers interested in tackling this problem. Quantitative and experimental approaches that couple immunologic and viral dynamics have been developed to explain this complex relationship,[11] and similar models may be appropriate to describe widely varying outcomes of SARS-CoV-2 infection. Frequent and longitudinal collection of both virus and immune biomarkers would be essential to inform such immune/viral dynamic models.

A second assumption in the authors' model is that the infection is limited by a fixed number of infectable target cells, which do not recover over the course of the infection. This assumption is consistent with a short-term infection. Because nearly all of the target cell pool rapidly becomes infected in the model, the authors find that putative treatments blocking an early stage of the viral lifecycle (e.g., hydroxychloroquine) must be delivered at or before symptom onset to provide benefit. Treatments that block infected cells from producing virus (e.g., remdesivir and protease inhibitors, such as lopinavir/ritonavir), however, have a window of a few more days. The strength of this conclusion is less clear if SARS-CoV-2 persists long enough for target cells to recover—in which case, later delivery of a potent inhibitor of viral entry might still attenuate viral load. Recent reports continue to inform us about the potential of experimental treatments and the importance of treatment timing. Mathematical models of long-persisting infections, such as those used to compare different classes of anti-HIV drugs,[12,13] may be of use to investigate this question.

Models characterizing the natural history of viral load and incorporating putative treatments for COVID infections will allow researchers to assess important questions regarding drug efficacy. They will allow a realistic assessment of likelihood of success of new treatments and inform important aspects of clinical trial design; specially incorporating aspects of antiviral initiation in early clinical trials. The authors have provided an important first step on this path, enabling researchers to predict the best timing of a potential drug treatment.

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