Title

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Journal

Clinical Pharmacology & Therapeutics, 108(2)

ISSN

0009-9236

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Publication Date

2020-08-01

DOI

10.1002/cpt.1873

Peer reviewed

RESPONSE LETTER TO THE EDITOR

Response to "Quantitative Clinical Pharmacology INPUT to SARS-CoV-2 Therapeutics Should be Based on Robust Data"

Data-Driven Dosing Recommendations are Urgently Needed for Hydroxychloroquine in COVID-19 Patients: Response to Letter to the Editor

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We appreciate the response to our timely analysis and would like to address Dr. Standing's comments. As of today, there are more than 110 clinical trials registered on clinicaltrials.gov evaluating hydroxychloroquine (HCQ) efficacy for coronavirus disease 2019 (COVID-19). The common problem for all these studies is what is the optimal dosing regimen and what is the safety associated with said regimen in COVID-19 patients. Our goal was to synthesize all emerging data in real time using state-of-the-art model-based tools and to provide the community with a quantitative assessment of various HCQ regimens. As in any model-based analysis, assumptions are inevitable, and all the major ones are listed in our paper. Here we address the comments from Dr. Standing.

As opposed to using actual polymerase chain reaction cycle threshold, we modeled a transformed value, more representative of viral load. While the function we used is indeed nonlinear, the relationship over our studied range appears to be linear (R^2 = 0.97). Data transformations using various functions are commonly employed in statistical analysis, do not alter the raw data, should not affect the parameter estimates, and improve the interpretability of our results.[1]

We agree with Dr. Standing: We currently do not have sufficient data to estimate a separate treatment and immune effect on viral load. However, this is true for many other infectious diseases.[2] The world is still learning the natural history of COVID-19, including the immune response and viral-shedding dynamics. We observed that the drug effect alone is not sufficient to clear the virus. Additional (most likely) immune-dependent killing occurs, which we described by a separate function. Our sensitivity analysis illustrates how these assumptions might affect viral load trajectories and treatment efficacy (**Figure 7**).

Literature reports a 24-fold difference in *in vitro* concentration of drug producing 50% of maximum effect (EC50).[3-5] Our main question was whether better viral control could be achieved with higher doses (**Figure 2**). During this process, we identified the 48-hour EC50 from Yao *et al.* as an outlier (**Figure 4**) and elected to base our dosing simulations on the predicted clinical EC50, which aligned with the majority of EC50s reported.

Only randomized controlled trials can offer definitive answers on the use of HCQ for treatment of COVID-19. We predict a lack of clinical efficacy at the currently studied/used doses due to insufficient drug exposure. While higher HCQ doses may be needed to achieve therapeutic benefit, significant safety concerns exist, indicating that HCQ's therapeutic margin is likely very narrow.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
All authors declared no competing interests for this work.

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Received April 24, 2020; accepted April 25, 2020. doi:10.1002/cpt.1873