PERSPECTIVE

A Real-World Evidence Framework for Optimizing Dosing in All Patients With COVID-19

Richard W. Peck[1,*], Daniel Weiner[2], Jack Cook[3] and J. Robert Powell[4]

Potential treatments for coronavirus disease 2019 (COVID-19) are being investigated at unprecedented speed, and successful treatments will rapidly be used in tens or hundreds of thousands of patients. To ensure safe and effective use in all those patents it is essential also to develop, at unprecedented speed, a means to provide frequently updated, optimal dosing information for all patient subgroups. Success will require immediate collaboration between drug developers, academics, and regulators.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and associated coronavirus disease 2019 (COVID-19) disease are straining healthcare systems around the world with large numbers of patients becoming ill in a very short period of time, overwhelming healthcare systems in many countries. Several drugs are being repurposed into clinical trials in COVID-19 patients, ranging from drugs already well established in other diseases, such as chloroquine/hydroxychloroquine, lopinavir + ritonavir, azithromycin, and tocilizumab/sarilumab, to those such as remdesivir, still in development for their initial indication.[1] The opportunities for clinical pharmacology to contribute to the development of new treatments have already been described by others in *Clinical Pharmacology & Therapeutics*.[2]

It is clear that the first drugs demonstrated to be effective will rapidly gain widespread clinical use. This has already been seen with the US Food and Drug Administration (FDA) emergency use authorization for chloroquine/hydroxychloroquine and reports of hospitals exhausting available supplies of tocilizumab even before the results of well-designed randomized controlled trials are available. When the results of the ongoing randomized controlled trials are published, the effective drugs will immediately start being used in large numbers of COVID-19 patients, many of whom will be outside the range of patients included in the trials. The gap between clinical trial participants and real-world-use patients is well known; real-world patients are often older or younger, larger or smaller, pregnant, have worse organ dysfunction, are taking

other drugs, have multiple comorbidities, have more or less severe disease for longer or shorter periods of time, or are otherwise different from those in the clinical trials. The speed at which this gap is closed for effective treatments for COVID-19 must be unprecedented. The risk of not doing so is that many patients or subgroups of patients may still die through not being treated with their optimal drug regimen. A general approach to adjusting the drug development and approval process to manage this for other diseases has been described by us in a companion paper of *Clinical Pharmacology & Therapeutics*.[3] Here we consider the specific needs, challenges, and opportunities presented by COVID-19.

The specific needs for optimal drug use and dose selection in COVID-19 are fourfold. First, typically the repurposed drugs are studied at the same doses for which they currently have approval. This may not be the optimal dose for COVID-19. Comparisons of expected plasma exposures to *in vitro* effective concentrations for antiviral activity may provide some dose justification, but there is currently little clinical assessment of dose response for repurposed drugs. Furthermore, pharmacokinetics and exposure–response could be very different in COVID-19 patients, a population that may have differences in demographics and important covariates from those currently treated. Second, there is an obvious need to avoid underdosing patients who will then be at risk of dying from avoidable lack of efficacy. Third, some of the drugs already under investigation and in clinical use have narrow therapeutic windows and potentially fatal adverse effects. For example, viral kinetic modeling suggests that hydroxychloroquine may need to be dosed above 800 mg daily in a typical patient to have much chance of efficacy while doses above 1,200 mg daily may

[1]Clinical Pharmacology, Pharma Research & Early Development, Roche Innovation Center, Basel, Switzerland; [2]Pharmacometrics Consultant, Chapel Hill, North Carolina, USA; [3]Clinical Pharmacology, Pfizer Inc, Groton, Connecticut, USA; [4]Clinical Pharmacology Consultant, Chapel Hill, North Carolina, USA. *Correspondence: Richard W. Peck (richard.peck@roche.com)

have an unacceptable risk of QTc prolongation, a surrogate for fatal arrhythmias.[4] Thus failing to adjust dosing for subjects at risk of higher-than-usual concentrations may carry a risk of significant adverse effects. Fourth, even for drugs with a wide therapeutic index, a policy of using a large dose in everyone, to mitigate the risk of treatment failure, may lead to drug shortages and an inability to treat all patients who might benefit.

Additional challenges for COVID-19 patients include the impact of the disease on the therapy. COVID-19 patients often have obesity, diabetes, renal or hepatic impairment, and other comorbidities.[5] Some have elevated levels of interleukin (IL)-6, which can suppress hepatic cytochromes, including cytochrome P450 (CYP) 3A4, with elevation of exposures for its many substrates.[6] The natural history of the disease may impact efficacy; direct antivirals may be more effective in the early stages of the disease,[7] whereas treatment intended to modify the host immune response may need to be used only in late disease. The impact of disease appears to vary between populations, for example, men appear to be at greater risk of dying from COVID-19 than women;[8] might there be differences in exposure–response to therapies due to gender or other factors? Disease

progression and the effect of treatment will produce intrapatient variability with changes in clearance as the patient deteriorates or recovers. Inclusion criteria limit the impact of all this variation in clinical trials; therefore understanding and correcting for it in subsequent real-world use will be essential for optimal treatment of many patients.

We propose several actions to address these challenges and turn them into opportunities to enable optimal dosing of all COVID-19 patients (**Figure 1**).

Include biomarkers of disease and drug activity in all trials to characterize baseline disease severity and response to treatment. Required biomarkers include serial measures of viral shedding and acute response markers such as high-sensitivity C-reactive protein (CRP) and treatment-specific markers such as soluble IL-6 receptor levels for studies of anti-IL6 therapies.

Include sparse sampling for drug concentrations to support development of population pharmacokinetic/pharmacodynamic (PKPD) models in COVID-19 patients with identification of potential therapeutic ranges for drug exposures and an understanding of the impact of COVID-19 related covariates on drug exposures and efficacy. It would also be useful to have

plasma concentration data from patients developing adverse events or significant changes in symptoms. The additional burden of collecting these samples is recognized, but they are essential to ensuring safe and effective use in all patients.

Publish or otherwise make available all population PKPD models, and, whenever possible, deidentified data, for the treatments under investigation to provide a basis for development of disease specific models. This would allow immediate exploration of the COVID-19 patient covariates, singly or in combination, predicted to be associated with lower or higher-than-desired drug exposures, potential toxicity or lack of efficacy or that provide an opportunity to use lower doses and allow scarce drug supplies to be used for more patients.

Develop and make available drug-disease models including viral kinetic time-course models; models linking viral time-course to inflammation, coagulation, and other pathophysiological systems; and physiologically-based pharmacokinetic models to predict the impact of COVID-19 on pharmacokinetic parameters.

Identify a trusted third-party repository and partner, possibly the World Health Organization (WHO), Gates
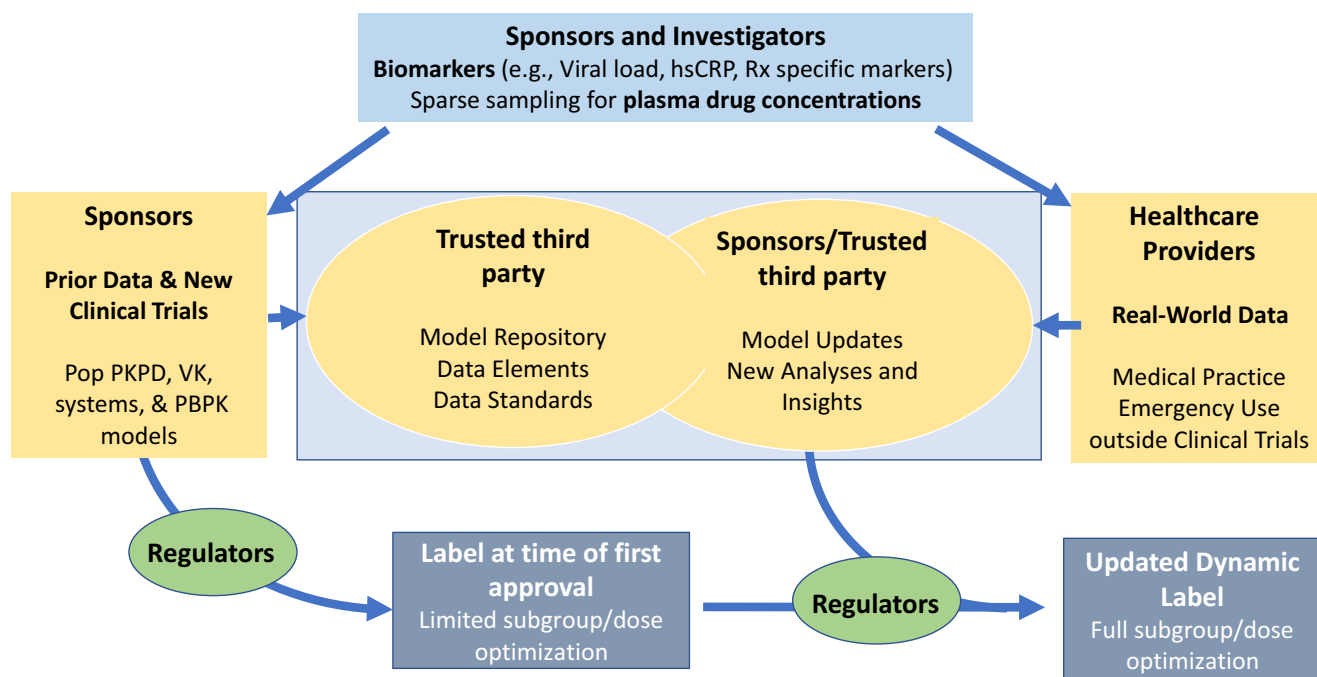

Figure 1 A model-based and real-world data–based framework for continuous updating of dosing recommendations and labeling of treatments for COVID-19 patients. hsCRP, high-sensitivity C-reactive protein; PBPK, physiologically-based pharmacokinetic; Rx, treatment; PKPD, pharmacokinetic/pharmacodynamic; VK, viral kinetic.

Foundation, National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority (BARDA), Critical Path Institute, or FDA to facilitate integration between models and their ongoing updating and refinement as new data become available. This will help maximize the value from all the data being collected in the many trials now ongoing, will be more informative than many separate models each developed from smaller data sets, and will allow faster achievement of a consensus for how to adjust dosing of effective drugs to optimize responses in all patients. Today it can still take years to develop dosing recommendations for children, pregnant women, and other important patient groups, or it may never happen at all. This should not be acceptable for COVID-19.

Establish a system for capturing data from the real-world patients treated with effective medicines or receiving novel treatments as emergency therapy prior to completion of randomized clinical trials. Such a system is required to characterize the efficacy–effectiveness gap and help identify where dosing adjustments are needed to maximize safety and efficacy across all patients. Critical patient covariates, disease biomarkers, and clinical response data should be collected for all patients, and plasma drug concentration data should also be collected wherever possible. The minimum list of key data elements and data standards should be agreed upon as soon as possible. The FDA or another independent third party could guide this in combination with the repository of population PKPD models and a procedure for updating them with the data collected from the real-world patients.

Work with major regulators including the FDA, European Medicines Agency (EMA), National Medical Products Administration (NMPA) and Pharmaceuticals and Medical Devices Agency (PMDA), to determine how dynamic prescribing information and labeling will be approved. As the real-world patient analyses, described above, identify patient groups who require dose modifications or identify changes to existing dosing guidelines, this information must be included rapidly in approved drug labels.

What are the immediate next steps? Many pharmaceutical companies have already agreed to collaborate on meaningful ways to accelerate the discovery and development of new treatments. For example, the NIH has launched a public–private partnership to accelerate discovery and development of new treatments for COVID-19,[9] and Transcelerate consortium members have agreed to share clinical trial control group data.[10] This should also now include working together to ensure optimal use of effective treatments in all real-world patients.

1. The global heads of clinical pharmacology from the pharmaceutical companies developing potential treatments should meet together with representatives from organizations interested in becoming trusted third parties and key regulatory and academic opinion leaders to agree on the principles for model and deidentified data sharing and how to establish the necessary infrastructure.
2. Academic, industry, and regulatory authority opinion leaders should meet with healthcare providers to agree on the key real-world data that should be collected and how this can be implemented.
3. The above groups should agree on how real-world data will be analyzed, how models will be updated, and how to reach alignment on and publish new insights from the data analyses.
4. Regulatory authorities should agree on a mechanism for rapid, initial, temporary approval of a new COVID-19 treatment with a mandated, and later, more detailed safety & efficacy review and reevaluation with potential updates to the label.

The means to achieve this must be established now to reduce the risk of continued, off-label prescribing of suboptimal dosing regimens for future COVID-19 therapies. Even with effective treatments for COVID-19, there will be no second chances for patients who are treated incorrectly.

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1. Sanders, J.M., Monongue, M.L., Jodlowski, T.Z. & Cutrell, J.B. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA (2020). https://doi.org/10.1001/jama.2020.6019.
2. Venkatakrishnan, K., Yalkinoglu, O., Dong, J.Q. & Benincosa, L.J. Challenges in drug development posed by the COVID-19 pandemic: an opportunity for clinical pharmacology. *Clin. Pharmacol. Ther.* **108**, 699–702 (2020).
3. Powell, J.R., Cook, J., Wang, Y., Peck, R.W. & Weiner, D. Drug dosing recommendations for all patients: a roadmap for change. *Clin. Pharmacol. Ther.* (2020). https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1923
4. Garcia-Cremedas, M. *et al.* Optimizing hydroxychloroquine dosing for patients with COVID-19: an integrative modeling approach for effective drug repurposing. *Clin. Pharmacol. Ther.* **108**, 253–263 (2020).
5. Centers for Disease Control and Prevention (CDC). Groups at higher risk of severe illness <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html> (2020). Accessed April 23, 2020.
6. Lee, J.-I., Zhang, L., Men, A.Y., Kenna, L.A. & Huang, S.-W. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. *Clin. Pharmacokinet.* **49**, 295–310 (2010).
7. Gonçalves, A. *et al.* Timing of antiviral treatment initiation is critical to reduce SARS-CoV-2 viral load. *medRxiv* (2020). https://doi.org/10.1101/2020.04.04.20047886.
8. The gendered dimensions of COVID-19. *The Lancet* **395**, 1168 (2020).
9. NIH to launch public–private partnership to speed COVID-19 vaccine and treatment options <https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-COVID-19-vaccine-treatment-options> (2020). Accessed April 23, 2020.
10. Transcelerate. COVID-19 <https://transceleratebiopharmainc.com/COVID-19/>. Accessed April 23, 2020.