PERSPECTIVE

Clinical Pharmacology-Informed Development of COVID-19 Therapeutics: Regulatory Experience

Su-Young Choi[1,*], Vikram Arya[1] and Kellie Reynolds[1]

Coronavirus disease 2019 (COVID-19) is overwhelming every sector of the society. The scientific community is under pressure to identify therapeutic options at an accelerated pace. However, our understanding of the pandemic, the virus, and the clinical course of the disease is constantly and rapidly evolving. Thus, the clinical pharmacology community faces a key challenging question: how do we effectively apply core clinical pharmacology principles to facilitate drug development for COVID-19 without compromising scientific rigor?

Clinical pharmacology plays a critical role across the drug development spectrum and the core principles, and tools of clinical pharmacology have greatly contributed to facilitate rational drug development. Although the tools and applications available to the clinical pharmacology community have not changed during the pandemic, a pandemic situation necessitates urgency that significantly shortens the time available to thoroughly engage these tools. For many repurposed drugs, dosing regimens approved for other indication(s) are evaluated in patients with COVID-19 because the safety of these dosing regimen(s) has been established. Time and resource constraints often make it challenging to conduct traditional dose finding studies to identify optimal regimens for patients with COVID-19 and additional clinical pharmacology studies are sometimes viewed as a roadblock that slows down development. Optimized pharmacokinetic (PK) sample collection may not be feasible in the setting of social distancing. The standard of care and the list of potentially promising investigational drugs (including repurposed drugs) have changed multiple times over the pandemic's course. In this situation, clinical pharmacologists are asked to be adaptive and flexible while still providing scientifically justified clinical pharmacology decisions.

This perspective shares experiences and lessons learned while reviewing regulatory submissions for the prevention and treatment of COVID-19. Based on these lessons, the authors outline some key principles and considerations of successful drug development for COVID-19 products, which could also be extended to other emerging infections in the future.

Translating in vitro findings to predict an effective dose in humans

For an antiviral drug, determining the *in vitro* activities (e.g., effective concentration (EC_{50}) or EC_{90}) against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and comparing these values to the predicted or observed exposures in humans are typically the first steps to selecting an effective dose in humans. Although this is the first and critical step to determine whether an investigational agent has antiviral activity, the appropriateness of the *in vitro* system used, the quantitative translatability to *in vivo* antiviral activities, and the reproducibility is often not adequately evaluated. As outlined in the US Food and Drug Administration (FDA) communication,[1] many experimental factors can influence the estimation of antiviral potency (e.g., the EC_{50}), and it should be distinguished from maximum effects. For some drugs, a wide range of *in vitro* EC_{50} values have been reported and conflicting conclusions have been made regarding the optimal dosing regimens for COVID-19.[2] In addition, the apparent antiviral activity of an investigational product can be the result of cytotoxicity in a cell culture model, especially for drugs regulating host cell functions. In this case, toxicities may be unavoidable at a therapeutic dose.

When translating *in vitro* findings to human dose selection, distribution to the target tissues should be considered. Because only free drug can be distributed to the target tissue and exert pharmacological action, protein binding should be considered and interpreted appropriately.[3]

[1]Division of Infectious Disease Pharmacology, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. *Correspondence: Su-Young Choi (Su-Young.Choi@fda.hhs.gov)

Received November 18, 2020; accepted February 9, 2021. doi:10.1002/cpt.2210

For most small molecules, target tissue drug concentrations are not readily available or directly measurable. Information can be leveraged from preclinical tissue distribution studies and/or physiologically-based PK approaches to provide estimates of target concentrations. For monoclonal antibodies, some publications report measured or predicted concentrations in the respiratory tract or lung tissue, although a wide range of tissue distribution ratios have been reported.

In addition to comparison to *in vitro* antiviral activities, the drug's PK characteristics should be considered. For drugs with a long half-life, a loading dose may be beneficial to quickly reach and maintain the target concentrations. Some drugs, such as nucleoside analogues, exhibit intracellular PKs that are distinct from plasma PKs. Thus, intracellular kinetics of active moieties should inform dose selection.

Optimizing dosing regimens

For typical drug development programs, dose optimization relies significantly on dose-ranging trials and exposure-response analyses using PK data collected from efficacy trials. However, for many trials evaluating COVID-19 therapeutics, especially those of repurposed drugs, the importance of these steps has generally been overlooked. Many investigators choose a single dosing regimen and move forward hoping to get an answer related to the efficacy of the drug as early as possible. In some cases, for repurposed drugs, not conducting a dose-ranging study may be justified if exploring higher doses is not feasible due to safety concerns or if no antiviral activity is expected at lower doses. However, a thorough justification of dose, based on COVID-19 patient specific risk-benefit assessments, should still be provided. For example, cancer drugs are being evaluated for COVID-19 and safety profiles that are deemed acceptable for advanced cancer patients with no alternative therapy may not be acceptable for outpatients or prophylaxis. In addition, certain adverse events, may exacerbate complications of COVID-19 such as gastrointestinal or cardiovascular manifestations. Needless to say, collecting PK samples is challenging during a pandemic, especially for trials conducted in an outpatient setting as minimal site visits are planned due to social distancing and infection control requirements. Consequently, limited exposure-response analyses are conducted, especially for repurposed drugs. This situation potentially limits the confidence in the appropriateness of dosing regimen(s) selected for the general population, therapeutic individualization, or specific populations. A recent lesson from the PALM trial for the treatment of Ebola viral disease highlights the importance of collecting PK data. Researchers were able to determine that certain products were superior to the standard of care, but the adequacy of the selected dose, especially for subgroups with lower efficacy (e.g., subgroup with high baseline viral load), remains unanswered.[4]

Combination treatment for COVID-19

COVID-19 can cause respiratory, thromboembolic, cardiovascular, and/or inflammatory symptoms and complications, and it is reasonable to consider combination therapies to maximize the clinical benefit of treatment (e.g., combination of an antiviral drug and an immunomodulator). For any combination therapy, the choice of drugs should be based on a clear justification taking into consideration the pathophysiology of the disease and the known PK, safety, and efficacy of the individual agents. It is important to collaborate across disciplines and experts in different therapeutic areas in order to identify the most appropriate combination treatments for COVID-19.

Once a potentially beneficial combination therapy is identified, the potential for drug interactions should be assessed prior to studying a combination treatment. For repurposed drugs approved decades ago, comprehensive information on the potential for drug interactions may not always be available. Therefore, additional assessments to fill these knowledge gaps should be considered. Drug interactions through mechanisms other than CYP-based metabolism or major drug transporters should be considered. Drug interactions by inhibiting the formation of the intracellular metabolites (e.g., hydroxychloroquine and remdesivir) or additive effects on QT prolongation (e.g., hydroxychloroquine and other drugs with QT prolongation) are good examples.

Need for safe and effective COVID-19 treatments for all populations

For conventional drug development, specific populations (especially pediatric and pregnant patients) are often excluded from clinical trials, and therapeutic optimization for these specific populations are only considered after optimizing dosing regimens for the general population. The knowledge gaps in determining the safe and effective dose for these populations due to exclusion from clinical trials may not be filled for several years after the initial trials, if at all.[5] It appears that most of the COVID-19 trials follow the same paradigm, excluding specific populations during clinical trials despite the urgent need for effective treatments in these populations. Prior experience with viral infections and with emergency investigational new drugs for COVID-19 indicate that promising drugs will likely be used in these populations despite the lack of safety, efficacy, and PK data. As such, once drugs are identified as promising agents for COVID-19 and pertinent nonclinical and clinical data are available, all stakeholders should make the best attempt to enroll these specific populations in the clinical trials. Clinical pharmacologists should also be prepared to address questions related to appropriate dosing regimens for these specific populations based on available information and plan for dose modifications (if needed) based on emerging safety, efficacy, and PK data. For example, one of the key issues addressed by clinical pharmacologists is the determination of pediatric doses based on an extrapolation approach (i.e., identifying doses producing drug exposures comparable to those associated with the optimal efficacy in adults).

To determine a safe and effective dose for all populations, the importance of determining PKs in clinical trials should be stressed. Without such data, dosing regimens for specific populations are derived solely based on the PK data from populations other than COVID-19 patients (e.g., healthy subjects or patients with different diseases), which inherently adds uncertainty in the decision.

Assessing the effects of intrinsic and extrinsic factors by conducting dedicated trials prior to approval may not be feasible for drugs for COVID-19 due to the expedited

drug development timelines in the setting of a public health emergency. In this setting, studies can be conducted post-approval through either a postmarketing requirement or postmarketing commitment mechanism, which is the approach used for remdesivir[6].

Utilizing quantitative modeling and simulation approach to make critical decisions

Recently advances in the area of model informed drug development, therapeutic individualization, and use of novel quantitative tools have created an unprecedented opportunity for our discipline to promote rational drug development and protect public health.[7] Quantitative modeling and simulation approaches have been utilized extensively for the development of COVID-19 treatments. Examples include prioritizing the drugs to be developed, rationalizing therapeutic combinations, selecting initial doses for early phase trials, changing doses and the route of administration during development, and determining dosing regimens for specific populations.[8,9] The strength and value of model informed drug development has been well-recognized in the clinical pharmacology community and it is even more valuable in the setting of a pandemic where we need to be quick and adaptive. For example, for assessing the dosing regimen of remdesivir for adolescent patients, various quantitative approaches such as PBPK and Pop PK were leveraged to demonstrate similarity in systemic exposure of remdesivir and its metabolites and thereby, enable extrapolation of efficacy from adults to adolescent patients[6]. However, modeling assumptions and limitations must be clearly communicated in a transparent manner to instill confidence in stakeholders with limited experience with these methodologies and knowledge of their potential. In the setting of an evolving pandemic, it is also imperative to update and refine models and simulations as data are accrued to strengthen recommendations.

CONCLUSION

The COVID-19 pandemic has posed challenges and opportunities for drug development. In the race to provide therapeutic options, core clinical pharmacology principles are often overlooked. However, the use of appropriate clinical pharmacology tools is essential to maximize the likelihood of success in drug development for COVID-19. We hope our perspective can help readers to understand how core clinical pharmacology principles can be applied in an adaptive and flexible manner to facilitate and optimize drug development for COVID-19 and other emerging infectious diseases.

ACKNOWLEDGMENTS

The authors thank Drs. Kimberly Bergman and Shiew-Mei Huang for helpful suggestions on the article.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

All authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this paper are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

1. <https://www.fda.gov/drugs/news-events-human-drugs/translating-vitro-antiviral-activity-vivo-setting-crucial-step-fighting-covid-19>. Accessed September 24, 2020.
2. Eloy, P. *et al*. Dose rationale for favipiravir use in patients infected with SARS-CoV-2. *Clin. Pharmacol. Ther.* **108**, 188 (2020).
3. Boffito, M. *et al*. Toward consensus on correct interpretation of protein binding in plasma and other biological matrices for COVID-19 therapeutic development. *Clin. Pharmacol. Ther.* (2021) https://doi.org/10.1002/cpt.2099
4. Mulangu, S. *et al*. A randomized, controlled trial of Ebola virus disease therapeutics. *N. Engl. J. Med.* **381**, 2293–2303 (2019).
5. Hwang, T.J., Orenstein, L., Kesselheim, A.S. & Bourgeois, F.T. Completion rate and reporting of mandatory pediatric postmarketing studies under the US Pediatric Research Equity Act. *JAMA Pediatr.* **173**, 68–74 (2019).
6. <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000ClinpharmR.pdf> Accessed February 8, 2021.
7. Zhu, H., Huang, S.M., Madabushi, R., Strauss, D.G., Wang, Y. & Zineh, I. Model-informed drug development: a regulatory perspective on progress. *Clin. Pharmacol. Ther.* **106**, 91–93 (2019).
8. Rosenbloom, D.S., Zhao, P. & Sinha, V. Initiation of antiviral treatment in SARS-CoV2: modeling viral dynamics and drug properties. *CPT Pharmacometrics Syst. Pharmacol.* **9**, 481–483 (2020).
9. Wallach, J.D., Egilman, A.C., Ross, J.S., Woloshin, S. & Schwartz, L.M. Timeliness of postmarket studies for new pharmaceuticals approved between 2009 and 2012: a cross-sectional analysis. *J. Gen. Intern. Med.* **34**, 492–495 (2019).