Title: Optimizing COVID-19 candidate therapeutics: Thinking Without Borders

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Introduction

This commentary seeks to share some key insights relevant to optimizing COVID-19 candidate therapeutics that were learned from attempts to optimize anti-infective posology in settings where quality and timely availability of data is challenging, with particular focus on influenza, including experiences from H5N1 and pH1N1 outbreaks.

As of March 18, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the COVID-19 disease, has infected more than 190,000 people globally and caused >7,800 deaths, with >90, 000 confirmed infections in Western Pacific Region and >3300 deaths and >74,000 confirmed cases in European region with >3300 deaths. Estimates of case fatality rate and infectivity place SARS-CoV-2 and COVID-19 as a significant global threat with WHO risk assessment of Very High at a Global Level and on March 11 was a declaration of a pandemic.[1] It is very likely that the actual number of infections and cases are higher, perhaps significantly, as a result of reporting practices and lack of test availability in many countries.

Emerging infectious pathogens are incredibly efficient at evolving rapidly, with infectivity and virulence optimized for their own promulgation, governed by laws of Darwinism. Juxtaposed on top of the nimbleness of an emerging pandemic pathogen, is the sluggish human response for martialing a public health response to such a crisis. In an effort to find therapeutics where none currently exist, the current response to COVID-19 largely centers around the execution of product development plans developed for non-crisis times.

It doesn't seem like a fair fight!

With COVID-19 vaccine availability likely 12-18 months away, there is an immediate need to examine COVID-19 therapeutic candidate options, which could arrive on the scene more rapidly. In the race to move forward with urgency, it is essential to ensure optimal posology of these drugs in this new indication. It is imperative to consider a drug's activity against the pathogen of interest, as it is critical that the concentrations obtained at the site(s) of action are sufficient to result in viral inhibition. If the antiviral activity (eg, IC_{50}) of a drug approved for use against another virus differs against SARS-CoV-2, the standard dosing regimen may not be sufficient. Beyond this, it is important to consider differences in pharmacokinetics (PK), which may impact dosing for different patient populations including treatment of infected patients as well as prophylaxis of healthcare workers and contacts and of course for different patient subpopulations including children, elderly, and those with renal and hepatic impairment and on concomitant medications. It is not uncommon for young healthy individuals (such as first responders) to have more rapid drug clearance and lower exposures of a drug compared to the approved patient population. In such cases there may be a risk of under dosing, depending on the drug. On the other hand, antiretroviral drugs being considered for use against this pathogen have been largely dosed to younger patients rather than the older population who are at greater risk for severe disease. Their physiological differences also must be considered in developing effective treatment regimens.

Beyond PK, it is also important to consider intrinsic and extrinsic factors which may impact pharmacodynamics (PD), including patients who are immunocompromised who may require longer durations of therapy.

In pandemic situations, drug supply is often compromised. In the setting of limited stockpiles, optimal posology is critical, as every milligram above optimal means a potential patient or healthcare worker may go untreated. From a public health perspective, this equates to resources that could have been deployed to other interventions and may be considered wasted. Every milligram below optimal may potentially result in the emergence of resistance, reduced susceptibility, and reduced efficacy to therapeutic interventions.

This commentary seeks to share some key insights relevant to optimizing posology of COVID-19 candidate therapeutics that were learned from attempts to optimize anti-infective posology in settings where quality and timely availability of data is challenging, with particular focus on influenza, including experiences from H5N1 and pH1N1 outbreaks.

Insight 1: ***It is critical that clinical pharmacology and optimal posology need to be deeply integrated into the evaluation and determination of COVID-19 candidate therapeutic options.***

This insight is not at all obvious for many clinical investigators, public health officials, and other stakeholders who seek to establish recommendations for use of candidate therapeutics against COVID-19. As of March 1, 2020, excluding suspended, terminated, or completed trials, there were 24 interventional "drug" clinical trials to treat coronavirus disease listed on ClinicalTrials.gov. The primary focus of such trials is the comparative efficacy of single and combination-dose regimens of therapeutic interventions or standard of care (SOC). Even though the full details of the protocols is not available for many trials on the website, it is striking that none of the trials appear to examine dose ranging of the therapeutic interventions within the designs. Furthermore, it is not apparent whether PK or exposure-response is being evaluated in any of the trials, and the interventions focus on evaluating treatment interventions of infected patients rather than prophylaxis.[2] Even if an intervention appears more efficacious than another

intervention or SOC in one of the trials, it appears that the current clinical trials underway as listed on ClinicalTrials.gov provide no insight into dose-response and therefore no guidance on optimal dosing of a specific therapeutic intervention for COVID-19.

A WHO-sponsored COVID-19 master protocol evaluating investigational therapeutics for treatment of COVID-19 in hospitalized patients does include a provision for obtaining PK and performing exposure-response analyses.[3] In general, there is little known about antiviral clinical pharmacology against COVID-19. Many COVID-19 antiviral candidates have complex pharmacology ranging from nucleoside prodrug conversion to nucleotide (remdesivir) to PK enhancement (lopinavir/ritonavir, darunavir/cobicistat), and complex drug-drug interaction profiles including CYP3A4 autoinduction and inhibition. In order to mitigate the potential for incorrectly selecting a dose for further evaluation, it is recommended that clinical trials with candidate therapeutics advance the suggestions above by WHO and consider the following: include additional dose regimen arms, collect PK, conduct exposure-response analyses, and apply modeling and simulation. These recommendations are equally relevant for investigational studies evaluating prophylaxis. Ideally, the data from these multitude of small trials will be made available in a useable format to allow pooling of data and more informative analyses.

Also of note, the current clinical trials underway as listed on ClinicalTrials.gov are relatively restrictive based on their study populations, i.e., primarily adults without significant renal or hepatic impairment. It is suggested that the clinical and quantitative pharmacology community engage with COVID-19 investigators and other stakeholders to ensure trials and programs take into account clinical pharmacology fundamentals, such as dosing requirements for patient subpopulations including pediatrics, elderly, pregnancy, and those with renal or hepatic impairment, or receiving concomitant medications.

Without conscious and deep integration of clinical pharmacology into the evaluation and determination of COVID-19 candidate therapeutic options, there is a risk of repeating experiences with 2014-2015 Ebola epidemic, where none of the therapeutic trials ended with conclusive results on product efficacy, and some of the inconclusive trials may have actually set back the search for safe and effective therapeutics.[4]

Insight 2: ***Contingencies need to be built in to support decision making in the COVID-19 epidemic given that randomized controlled trials (RCTs) may not provide definitive outcomes.***

At the WHO novel coronavirus forum held on February 11-12, 2020, it was apparent that there is much still to learn about COVID-19. Fundamental information, such as the virus, its transmissibility and virulence, patients groups impacted, and clinical manifestations of the disease, might be changing. There is little known about the time-course of viral shedding in the respiratory tract, blood, and gastrointestinal tract, the relative importance for each for an antiviral regimen, or the potential treatment window when an antiviral may be effective or not effective. There is also an absence of information on the potential for COVID-19 to generate resistance to antivirals as well as agreed upon clinical trial endpoints, which are the subject of learning and refinement in the WHO master protocol. Due to the rapidly evolving nature of the information, therapeutic interventions and RCT designs will continue to be honed and lead to data quality challenges and critical assumptions underpinning comparative efficacy assessments from such trials. Thus, in parallel to the RCTs, it is essential that additional decision quality data is identified both as a risk mitigation approach but also to augment information generated from RCTs.

There is an opportunity to leverage emergency and compassionate use programs of candidate COVID-19 therapeutics to collect useful clinical pharmacology data to inform posology.

Traditionally, emergency and compassionate use programs collect crude information that is not rigorous enough to gather insights or support decision making, e.g., emergency and compassionate use of intravenous oseltamivir phosphate during pH1N1 influenza pandemic.[5] In contrast, an innovative open-label compassionate use program was conducted for linezolid, an antibacterial with activity against multi-drug-resistant gram-positive pathogens, with the rigors of an open-label clinical trial and incorporated PK, PK/PD, and modeling and simulation. The PK/PD trial was able to demonstrate drug effect and optimal dosing via PK/PD associations from fewer than 288 patients who received a single 600 mg BID dose of linezolid.[6] The broader program was able to provide many other important insights on PK and response to difficult-to-treat infection sites and pathogens, safety, and emergence of resistance that are featured in the product label. The intrinsic PK/PD variability in this trial, along with the quantitative analyses applied, were powerful features in being able to uncover important insights for linezolid dosing. Such an approach could be very relevant to support optimal dosing of COVID-19 therapeutic candidates, augmenting RCT efforts.

The utility of translational PK/PD models extends, of course, far beyond finding drug effect from variable data environments, to strategically providing efficiencies in overarching development programs and clinical trial design. For example, a Bayesian clinical study design informed by priors from translational PK/PD models could minimize the number of patients that will need to be tested in a clinical trial, and the totality of data can then be analyzed using an integrated exposure-response model to substantiate evidence of efficacy. Akin to the animal rule, in situations of disparate and emerging data such as in the COVID-19 pandemic, there also exists significant opportunity for “model-informed totality of evidence” approach in supporting regulatory decision making for accelerating access to COVID-19 therapeutics.

Another opportunity is to develop a precompetitive *in silico* workbench to aggregate existing and emerging information on COVID-19 candidate therapeutics from in vitro, preclinical, and clinical data sources.

Such an *in silico* workbench making use of intuitive data visualization software, such as R-Shiny, could be made available to investigators and experts as a tool to integrate and share state of the art information to guide decision-making on incorporating candidate therapeutics into clinical trial evaluations and guidance's for use during the COVID-19 outbreak.

An additional contingency opportunity to help inform COVID-19 optimal posology should be a work stream focused on aggregating emerging real-world evidence and clinical trials data. Specifically, the application of meta-analytic methodologies like model-based meta-analyses provides an opportunity to mine insights on interventions (and their posology) from across pooled trials, which in of themselves may not have adequate information content to definitively address specific hypotheses.

In a rapidly emerging situation, much can be learned from prior experience with similar molecules. For example, knowing the pattern of viral kinetics for the new pathogen can provide critical insights for therapeutic intervention, including determination of the window of opportunity to initiate therapy (antivirals for respiratory diseases are ineffective if administered after the time of peak viral load), potential utility of loading doses to rapidly achieve therapeutic levels, and to inform the necessary duration of treatment to maximize antiviral response.[7]

The application of quantitative and clinical pharmacology principles described above to distill information content from "gray" and emerging information remains highly relevant to accelerate

COVID-19 therapeutics across a range of treatment modalities including monoclonal antibodies, plasma derived therapeutics, small molecules and complex biologics.

Insight 3: ***Emerging data and potential solutions must be examined and presented from the perspective of different stakeholders.***

It is essential to recognize that therapeutic intervention goals for an individual patient can diverge significantly from public health goals and differ to that from procurers. This means, the concept of optimal posology of a COVID-19 candidate therapeutic can take on many different personas depending upon the stakeholder. A treating physician may be interested in how to improve the clinical outcome of the infected patient and exposed individuals; a public health professional may be interested in minimizing viral shedding to reduce spread of COVID-19, and a procurer may be focused on where to invest health care dollars in order to maximize impact of the entire healthcare system. This subject has been exhaustively explored for pandemic planning scenarios for oseltamivir posology against a range of potential influenza virus strains, differing by infectivity and virulence (Table 1)[8] The interdisciplinary linkage of PK/PD, epidemiological and health economic models into a single quantitative framework offers an objective way for stakeholders to engage earlier in cross-sector dialogue on dosing, procurement and deployment strategies. This should have particular relevance for COVID-19 candidate therapeutics where PK/PD information may exist, but clinical evidence is sparse or lagging.

Every experiment represents an opportunity to gather information content in clinical and quantitative pharmacology, clinical efficacy and safety, as well as insights in epidemiology and health economics. For immediate application to COVID-19 candidate therapeutics, the

recommendation is to apply considerable fungibility in thinking and look for opportunities to collect information that will strengthen the evidence base to support insights for multiple audiences.

Insight 4: ***Multi-sectoral collaboration and co-ordination is critical to gather the right information for the right stakeholder at the right time.***

Front-line physicians and clinical investigators, academic and scientific experts, epidemiology and public health practitioners, government procurers, not for profit and access stakeholders, patient advocates, and industry experienced drug developers all have essential, unique, and complementary competencies and perspectives to provide in the development and implementation of candidate therapeutics for COVID-19.

Currently, there is an urgent need for global leadership that recognizes how to assemble and coordinate the requisite competencies in an appropriate governance framework in order to focus on evaluation and determination of candidate therapeutics for COVID-19 and to establish a framework for responding to future pathogens beyond COVID-19. Some high level considerations for an effective global coalition to accelerate therapeutics for COVID-19 include the importance of hyper-transparent data sharing as well as applying FAIR (findability, accessibility, interoperability and reusability) guiding principles for scientific data management and stewardship[9]. In addition, it is essential that drug development principles apply advanced data science and contemporary development methods including model informed drug development methods, not to cut corners in drug development, but to increase parallel processing and making most of the available information content, to cut time and accelerate the development and access of critical medicines.

Let's not repeat this exercise in a few years' time.

"The future depends on what we do in the present." (Mahatma Gandhi)

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Table Legend:

Table 1. Integration of PK/PD, epidemiology and health economics to support pandemic planning decisions for multiple stakeholders; reprinted with permission; Kamal M.A. et al. *Br J Clin Pharmacol*. 83, 1580-1594 (2017)[8].

Comparators (Treatment *vs.* baseline)	Costs (A) (payer)	Costs (B) (payer – Baseline)	Costs (A) (societal)	Costs (B) (societal - Baseline)	Death (A)	Death (B)	Δ Death (A–B)	Δ LYs (A–B)	Δ QALYs (A–B)	Payer perspective		Societal perspective	
										Cost per LY gained	Cost per QALY gained	Cost per LY gained	Cost per QALY gained
Low transmissibility and low severity													
75 mg (A) *vs.* no treatment (B)	9 225 251	42 578 018	12 998 947	106 995 703	27	439	–412	399	430	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 (B) mg	14 835 713	9 225 251	17 109 649	12 998 947	16	27	–11	10	11	546 753	515 260	400 598	377 524
High transmissibility and high severity													
75 mg (A) *vs.* no treatment (B)	94 961 869	144 271 547	171 053 550	272 957 742	974	1591	–617	598	629	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg(B)	81 019 150	94 961 869	139 379 855	171 053 550	747	974	–227	220	227	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Low transmissibility and high severity													
75 mg (A) *vs.* no treatment (B)	11 450 971	79 213 439	15 596 974	149 869 617	53	874	–821	795	828	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg (B)	16 176 877	11 450 971	18 675 157	15 596 974	32	53	–21	20	21	231 280	223 797	150 642	145 768
High transmissibility and low severity													
75 mg (A) *vs.* no treatment (B)	54 113 197	77 547 403	123 371 900	194 871 423	489	799	–310	300	330	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg (B)	49 689 085	54 113 197	102 809 041	123 371 900	375	489	–114	110	117	Cost-saving	Cost-saving	Cost-saving	Cost-saving

All costs are expressed in 2013 USD.
A, the alternative intervention; B, the baseline intervention.