Model-Informed Drug Development Approaches to Assist New Drug Development in the COVID-19 Pandemic

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Leveraging limited clinical and nonclinical data through modeling approaches facilitates new drug development and regulatory decision making amid the coronavirus disease 2019 (COVID-19) pandemic. Model-informed drug development (MIDD) is an essential tool to integrate those data and generate evidence to (i) provide support for effectiveness in repurposed or new compounds to combat COVID-19 and dose selection when clinical data are lacking; (ii) assess efficacy under practical situations such as dose reduction to overcome supply issues or emergence of resistant variant strains; (iii) demonstrate applicability of MIDD for full extrapolation to adolescents and sometimes to young pediatric patients; and (iv) evaluate the appropriateness for prolonging a dosing interval to reduce the frequency of hospital visits during the pandemic. Ongoing research activities of MIDD reflect our continuous effort and commitment in bridging knowledge gaps that leads to the availability of effective treatments through innovation. Case examples are presented to illustrate how MIDD has been used in various stages of drug development and has the potential to inform regulatory decision making.

Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic, causing more than 613,000 deaths in the United States alone as of August 2021. Scientists from industry, academia, and regulatory agencies have been working collaboratively to fight against this disease and improve patient care for other diseases during the pandemic. The mutual goal is to shorten the drug development cycle to make promising therapies that meet regulatory requirement available as soon as possible and save people's lives. Several key questions have been raised that remain critical to the development of safe and effective treatments of COVID-19. The first question is how to identify promising candidate compounds, especially from the existing compound pool, for treating COVID-19. The second question is how to fill in knowledge gaps in clinical development programs for new treatments, knowing that the clinical development programs may be more abbreviated as compared with routine programs due to time constraints and limited resources. The third question is how to safely provide sufficient treatments for patients with diseases other than COVID-19 who require long-term medical care where there is a shortage of medical resources and treatment at facilities may increase the risk of viral infections in patients.

Model-informed drug development (MIDD) is well suited to tackle these critical questions. MIDD represents the application of a broad range of quantitative models to facilitate new drug development and regulatory decision making. It allows an integration of the current knowledge of disease, pharmacology, and patient characteristics. In a nutshell, MIDD provides a unique platform to leverage findings from different sources to address critical questions in drug development. During the COVID-19 pandemic, emergency use authorization (EUA) is a unique pathway to make promising therapeutic interventions available to the public when evidence suggests that it is "reasonable to believe" that the product "may be effective" in treating the disease or condition identified in an emergency declaration by the Secretary of the Department of Health and Human Services. MIDD is playing an important role in the review process when clinical trials do not have a full coverage for proposed doses, indications, or populations for EUA. In the following sections, recent experiences utilizing MIDD to address the aforementioned key questions are outlined. In sharing these cases, it is the authors' intention to inform and illustrate tools that have been and will continue to be useful for informing therapeutic interventions of COVID-19.

UNDERSTANDING THE POTENTIAL EFFECT FOR CANDIDATE COMPOUNDS FOR TREATING COVID-19

COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a single-strand RNA virus and highly contagious in humans. When the pandemic started, no molecule was known to have an antiviral effect against SARS-CoV-2. A first response from the scientific and pharmaceutical community was to identify potential candidates from the existing compound pool. Some development programs that applied MIDD approaches are presented below to highlight the key evidence and considerations in curating prior knowledge to assess the potential antiviral effect of the candidate compounds.

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Hydroxychloroquine

Hydroxychloroquine sulfate is approved by the US Food and Drug Administration (FDA) for prophylaxis and treatment of malaria, treatment of lupus erythematosus, and rheumatoid arthritis. The FDA authorized hydroxychloroquine sulfate for EUA to treat certain patients hospitalized with COVID-19 in March 2020; based on additional data, including MIDD analyses, the FDA revoked the authorization in June 2020.[1]

In view of the importance of translating *in vitro* antiviral activity to *in vivo* efficacy in informing drug development and clinical management for COVID-19, in May 2020, the FDA's Office of Clinical Pharmacology published a scientific article discussing the key aspects in translating *in vitro* antiviral activity to appropriate clinical dosing regimens using hydroxychloroquine sulfate as a case example.[2] The discussion was based on a thorough literature review and evaluation of the reported mechanism of action, clinical pharmacology, *in vitro* antiviral and prophylactic activity testing, animal tissue data, modeling and simulation, and proposed dosing regimens which were believed to be safe and effective. It is important to note that the *in vitro* half maximal effective concentration (EC_{50}) values used in the literature reports were based on the drug concentrations in the cell culture media (extracellular concentration). Thus, the rationale of significantly higher total lung concentrations relative to the *in vitro* EC_{50} value, which several publications relied on to support hydroxychloroquine sulfate as potentially efficacious against SARS-CoV-2 at the proposed dosage, was not substantiated. Rather, the free extracellular lung concentration (the level of which is close to the free plasma hydroxychloroquine sulfate concentration) should be used to compare with the *in vitro* EC_{50}/EC_{90} (90% maximal effective concentration) values. The misuse of concentrations for comparison could lead to the wrong conclusion regarding *in vivo* efficacy because there is a considerable difference between total lung concentrations and free extracellular lung concentrations resulting from a substantial intracellular accumulation. In our article, translating the *in vitro* antiviral activity to the *in vivo* setting for hydroxychloroquine sulfate was detailed. Schematically, the developed hydroxychloroquine sulfate physiologically-based pharmacokinetics (PBPK) model was used to first simulate the free plasma exposure of hydroxychloroquine sulfate, then to estimate the free lung extracellular concentration achieved with the proposed hydroxychloroquine sulfate dosing regimens. Under the assumption that *in vitro* accumulation is similar to *in vivo*, the calculated free lung concentrations that resulted from the proposed dosing regimens were well below the *in vitro* EC_{50} values. Therefore, it was concluded the antiviral effect of hydroxychloroquine sulfate against SARS-CoV-2 could not be achieved with a safe oral dosing regimen. Randomized clinical trials evaluating hydroxychloroquine sulfate as a treatment for COVID-19 failed to confirm that the drug is effective for this use, which is consistent with our analysis.[3,4] This effort highlights the essential contribution of MIDD to COVID-19 drug repurposing.

Remdesivir

Remdesivir, a phosphoramidate ester of a C-adenosine analog, is a prodrug which was developed for the treatment of human Ebola virus. It is the first drug approved by the FDA for the treatment of COVID-19 in hospitalized patients. Before the outbreak of COVID-19, remdesivir was being evaluated for the treatment of other human coronavirus diseases caused by SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Antiviral activities against these coronaviruses were anticipated based on *in vitro* to *in vivo* translation in that human plasma concentrations after a 100-mg daily dose were above the *in vitro* IC_{50}.[5] In animals infected with the coronaviruses, prophylactic or treatment doses of 25 mg/g twice daily (in mice) and 5 or 10 mg/kg/day (in rhesus macaque) prevented the disease and the reduced lung viral load after lethal SARS-CoV and MERS-CoV inoculations.[6,7] Consequently, after the COVID-19 outbreak, remdesivir was a logical choice against SARS-CoV-2 and underwent preclinical anti–SARS-CoV-2 tests and treatment trials for COVID-19. However, uncertainty still existed as to whether the *in vitro* activity could translate to effective antiviral activities in human lungs. Pharmacokinetic (PK) bridging from the effective animal dose to the human dose for COVID-19 was based on rhesus macaque infection models and PK studies in healthy subjects. It was observed that plasma and peripheral blood mononuclear cell concentrations of remdesivir and GS-443902 (the active nucleotide triphosphate metabolite), respectively, in rhesus macaques after a 5-mg/kg/day dose were comparable to the corresponding concentrations in humans after a 100-mg/day dose. Additionally, the plasma concentration of GS-441524, the main circulating metabolite, was comparable between humans (20- mg first dose followed by 10- mg/day dose) and macaques (10-mg/kg/day dose) for 28 days.[6] Based on the PK bridging analysis and safety profiles from the Ebola trial, the remdesivir dosages of 200 mg on Day 1 followed by 100 mg/day intravenous (i.v.) for 5 to 10 days were considered appropriate for the treatment of COVID-19 and showed clinical effectiveness in hospitalized adults in the Adaptive COVID-19 Treatment Trial (ACTT)-1, which supported the EUA and subsequent full approval.[5]

DOSE DETERMINATION FOR NEUTRALIZING ANTIBODIES TARGETING SARS-COV-2

Neutralizing antibodies (nAbs) are designed to reduce viral entry of SARS-CoV-2 into host cells, thereby reducing the severity of COVID-19 and risk of hospitalization. While vaccinations are considered to be the cornerstone in the arsenal to combat COVID-19, protection largely relies on the capacity and magnitude of the host immune response to inoculation. For people who are not fully vaccinated, not expected to mount an adequate immune response to vaccination (e.g., immunosuppressed individuals), or not willing/able/eligible to be vaccinated, nAbs offer potential for treatment, and in one case, prophylaxis. To address urgent needs, MIDD approaches were used to provide timely support for a reduced dose of nAbs with pending clinical outcomes, allowing for more people to have access when the supply is limited and assess efficacy periodically for variant strains in this emerging, rapidly evolving pandemic.

Bamlanivimab and etesevimab

Bamlanivimab and etesevimab are both recombinant human immunoglobulin G1 kappa monoclonal nAbs that can bind to the spike protein on SARS-CoV-2 and block viral entry into host cells

to reduce the extent of host infection. Bamlanivimab monotherapy of 700 mg i.v. for the treatment of COVID-19 was granted an EUA in December 2020 based on the totality of the scientific evidence available, including evidence from virology, symptomology, and hospitalization. In February 2021, the FDA issued an EUA for bamlanivimab and etesevimab administered together based on data that demonstrated significance in clinical end points, formation of fewer treatment-emergent variants, and additional viral load reduction compared with bamlanivimab alone.[8] However, at the time of the February 2021 EUA, a lower dose in the treatment regimen (700 mg bamlanivimab and 1,400 mg etesevimab i.v.) with pending clinical results was proposed instead of the substantive dose (2,800 mg of each nAb) to expand the utility given the limited supply. Notably, dose selection for each nAb in the regimen is based on individual receptor-binding characteristics, considering the two nAbs cover different but overlapping epitopes on receptor binding domain of viral S-protein. A pharmacokinetic/pharmacodynamic (PK/PD) model was developed to describe the relationship between plasma concentrations of the two nAbs and changes in viral load collected from nasal swab over time. Due to the lack of clinical data for different doses of etesevimab, the *in vivo* plasma EC_{50} values were estimated under the assumption of threefold antiviral potency of bamlanivimab relative to etesevimab derived from *in vitro* studies. Simulations using the PK/PD model suggested a comparable antiviral efficacy with the proposed dose. In efforts to address the concern for the relative antiviral potency assumption as the ratio varied among viral isolates (twofold for Washington isolate to sevenfold for Italy isolate), we performed a sensitivity analysis to independently estimate the EC_{50} of etesevimab without such an assumption. Despite uncertainties arising from the single-dose data, the EC_{50} estimate of etesevimab converged within a reasonable range. The proposed dose of bamlanivimab and etesevimab is expected to provide sufficient coverage for 28 days based on concentrations over the highest EC_{90} value. This conservative margin provided further support for the antiviral efficacy of the reduced dose, which was later confirmed with the virology data in the Blaze-4 (NCT04634409) study.[9,10]

With the increasing prevalence of emerging variants, efficacy was reevaluated in view of potential resistance to treatment regimens of bamlanivimab alone and two nAbs used together. The exposure margin over the EC_{90} of the prevalent variants with reduced susceptibility can provide qualitative assessment based on various extrapolation approaches, such as scaling up the estimated *in vivo* EC_{90} by fold shift of the *in vitro* EC_{50}/EC_{90} of the variant relative to the wild type for comparison with serum concentrations and/or estimating lung concentrations by an expected percentage of lung penetration for comparison with the *in vitro* EC_{90}. Clinical data for the variants, though limited, were also evaluated if available. Bamlanivimab alone is not favorable due to an increased frequency of resistant variants, and thus the EUA for this regimen was revoked in April 2021.[11]

PEDIATRIC EXTRAPOLATION OF DRUGS APPROVED/AUTHORIZED TO TREAT COVID-19

Traditionally, the approval of a pediatric indication is supported by clinical trials conducted in pediatric patients to characterize the PK/PD profiles and/or to demonstrate effectiveness and safety. There can be a significant delay between the approval in adults and labeling in pediatric patients.[12] MIDD in recent years has been commonly applied for dose selection and optimization to facilitate pediatric drug development based on the exposure matching principle.[13] Given the urgent need for effective treatments of COVID-19 and limited time for pediatric development, MIDD approaches with limited PK data were used to best leverage the knowledge from various sources to support the use of approved or authorized COVID-19 therapies in pediatric patients. Pathogenesis, the course of the disease, and the effect of the drug product were assumed to be similar between pediatric patients and adults for efficacy extrapolation, and safety data from adult clinical studies were used as supportive information in pediatric assessment.[14,15]

Remdesivir

Remdesivir received FDA approval in October 2020 for the treatment of COVID-19 in adults and pediatric patients 12 years and older and weighing at least 40 kg who require hospitalization.[16] Data related to remdesivir use in pediatric patients were limited, and PK data in pediatric patients were not available at the time of approval. The same dosing regimen of remdesivir used in pediatric patients and adults was supported by PBPK modeling and population PK analyses. Applying the modeling analyses to simulate exposures, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and its metabolites in adolescents as observed in healthy adults.[5] Such analyses relied on the current understanding of enzyme maturation in adolescents and the experience of allometric relationships in PK across pediatric age groups. Remdesivir use in the approved pediatric population was based on extrapolation of pediatric efficacy from well-controlled studies in adults, and safety data available in adults weighing 40–50 kg and a limited number of pediatric subjects who received remdesivir in a compassionate use program in patients with Ebola.[16]

For pediatric patients less than 12 years of age and weighing at least 3.5 kg, remdesivir is available through an EUA. A weight-based dosing regimen (a single loading dose of 5 mg/kg followed by 2.5 mg/kg/day i.v.) was recommended by PBPK modeling to derive an expected exposure range of remdesivir and plasma metabolites in this age group within the adult steady-state exposure range. Of note, the predicted pediatric exposure would not exceed exposures observed in healthy adults who received 14 daily doses of 150-mg remdesivir. Additionally, before starting and during remdesivir administration, laboratory testing for renal and hepatic functions and prothrombin time is a measure implemented to monitor potential safety risks in patients, including this vulnerable population. The PBPK-informed dose for this age group would include uncertainties such as knowledge gaps on enzyme maturation rates in younger children.[17,18] The impact of these uncertainties on the exposure of remdesivir and plasma metabolites in younger pediatric patients needs to be verified when the clinical data become available. Nonetheless, the dosage was derived with a reasonable level of confidence to

provide access to the drug for patients less than 12 years of age during the pandemic. Confirmatory PK, supportive efficacy, and safety information are being collected in an ongoing pediatric clinical trial.

Baricitinib

The FDA originally issued an EUA for baricitinib, in combination with remdesivir, for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation in November 2020. The EUA was based on a randomized, double-blind, placebo-controlled clinical trial (ACTT-2).[19] Baricitinib is a Janus kinase inhibitor and approved for the treatment of rheumatoid arthritis (RA) in adults.[20] For COVID-19, baricitinib is expected to improve clinical outcomes through modulating inflammatory response and preventing a hyperinflammatory state, and it can now be used alone based on the revised EUA issued in July 2021.[21,22] During the EUA review, one of the key clinical pharmacology questions was the appropriateness of the dosing recommendation for pediatric patients 2 years or older. The PK of baricitinib in adult and pediatric patients with COVID-19 was unknown, and the dose in adults was recommended based on the dose used in the clinical trial ACTT-2. It was known that the baricitinib exposure in patients with RA is approximately twofold of that in healthy volunteers. Therefore, PK may vary by health status and diseases. The dose recommendation for pediatric patients with COVID-19 was established by applying the dose ratio of pediatric patients to adults rather than the pediatric dose obtained from other indications. PK in pediatric patients with juvenile idiopathic arthritis, atopic dermatitis, and type I interferonopathies have been evaluated, hence exposure comparison of baricitinib between pediatric patients and adults with the same disease was made to determine the dose ratio. PBPK modeling and simulation in healthy pediatric patients and adults, adult patients with RA, and pediatric subjects with juvenile idiopathic arthritis confirmed similar exposure using the proposed dose ratio. The effectiveness and safety of baricitinib in pediatric patients are continuously being evaluated in ongoing clinical trials.

Bamlanivimab and etesevimab

Bamlanivimab and etesevimab are authorized to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years and older weighing at least 40 kg) with positive results of direct SARS-CoV2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Dosing of these agents across the age range was informed by MIDD methodology. Applying the population PK modeling that accounts for the difference in body size with weight allometry, the mean of simulated area under the concentration-time curve (AUC) in pediatric patients is anticipated to be ~ 25% higher than that in adults.[9] Given a linear PK and available adult safety data from higher dose cohorts, the adult dose is considered appropriate for pediatric patients 12 years and older weighing at least 40 kg. The efficacy of these nAbs is determined by their neutralizing capacities to the virus; thus the effect in these pediatric patients as authorized was expected to be comparable to adults given near-maximal antiviral activity would be achieved based on a large predicted-exposure margin over *in vivo* EC_{90}.

DOSE INTERVAL PROLONGATION OF THERAPEUTIC PROTEIN DRUG AMID THE PANDEMIC

During the pandemic, it is critical to ensure patients with diseases other than COVID-19 can receive their needed treatments safely where there is a shortage of medical resources and an increased risk of viral infection in medical facilities. Frequent visits to hospitals or infusion centers for a chronic treatment may increase the risk of patients contracting SARS-CoV-2. The issue may be more prominent for oncology patients whose immune system is generally compromised due to the treatment received (e.g., radiotherapy or chemotherapy). As shown below, MIDD approaches were used to support less frequent dosing in these patients in order to minimize the risk of viral infection.

Pembrolizumab

In April 2020, FDA approved an alternative dosing regimen of 400 mg every six weeks (Q6W) for pembrolizumab, a monoclonal antibody that binds to the PD-1 receptor, under the accelerated approval pathway. Results of MIDD analyses provide the pivotal evidence in support of the approval of pembrolizumab Q6W dosing regimen. Modeling and simulation based on PK data from 4,687 subjects across multiple tumor types suggest a significant overlap in concentration-time profiles and comparable exposures between 400 mg Q6W and efficacious dosing regimen 200 mg Q3W or 2 mg/kg Q3W. The predicted trough concentration for 400 mg Q6W is 34% lower than that of 200 mg Q3W, which was suggested to have a minimal effect on the efficacy based on exposure response analyses. The three dosing regimens were expected to achieve a similar efficacy profile. The predicted peak concentration for 400 mg Q6W was substantially (~60%) lower than that of 10 mg/kg Q2W dose, which was tested to be tolerable in the clinical trial.

Other monoclonal antibodies for oncology patients

Similar MIDD approaches were also applied in the approval of less frequent dosing for nivolumab,[23] atezolizumab, cetuximab, and adalimumab, and the development of subcutaneous injection for nivolumab and pembrolizumab to offer a convenient and effective alternative dosing regimen. The availability of the alternative measures for administering these monoclonal antibodies are expected to decrease the number of clinic visits and reduce the chance of patients contracting SARS-Cov2.

RESEARCH ACTIVITIES IN CLINICAL PHARMACOLOGY FOR COVID-19–RELATED THERAPIES

In addition to supporting new drug application and EUA reviews, MIDD approaches have been widely used to address various questions relating to COVID-19 through our research projects that might be critical in different development programs. The following examples reflect our continuous efforts in assisting new drug development amid the COVID-19 pandemic.

Anti–SARS-CoV-2 repurposing drug database: Clinical pharmacology considerations

In light of the analyses we conducted for hydroxychloroquine regarding *in vitro* to *in vivo* anti–SARS-CoV-2 activity extrapolation, we expanded the analyses to a large number of molecules/repurposed drugs whose *in vitro* anti–SARS-CoV-2 activity was reported and developed an "Anti–SARS-CoV-2 Repurposing Drug Database." This database includes *in vitro* anti–SARS-CoV-2 activities, *in vivo* PK data (peak plasma concentration (C_{max})), unbound fraction in plasma (f_{up}), as well as equations comparing *in vitro* antiviral activities and *in vivo* exposures. There are more than 100 drugs/compounds with both PK and EC_{50} data available, and ~ 80 compounds with EC_{50} data only. Variability exists in both PK and EC_{50} values. Reasons that can cause difference in EC_{50} values are manifold: methods of how virus was quantified, types of cell lines used, *in vitro* experiment conditions, etc. In evaluation of the potential *in vivo* antiviral activity, both the EC_{50} range and relevance should be considered. Currently, the variability in PK (i.e., C_{max} and f_{up}) was not inquired in the database. The C_{max} of only the highest relevant dose level was provided. The value of f_{up} was collected from the labels or publications or assumed to be 1 when no data are available. The highest possible C_{max} and f_{up} were used to maximize the unbound exposure with the intent to capture as many molecules as possible for further evaluation regarding *in vivo* antiviral activity. This database highlights the clinical pharmacology considerations and can further be used by drug developers as a screening tool for evaluating an anti–SARS-CoV-2 drug.[24] The database was developed based on the *in vitro* studies published prior to November 2020. As research on COVID-19 is still evolving, the database should be actively updated and maintained, for example, to include the emerging data for the new variants. With the publication of the database, we rely on scientists in this area to keep updating the database.

PBPK modeling for remdesivir

As a nucleoside analog prodrug, remdesivir undergoes intracellular multistep activation to form its pharmacologically active species, GS-443902, which is not detectable in the plasma. A question arises whether and which of the observed plasma exposures of remdesivir and its metabolites (GS-704277, GS-441524) would correlate with or be informative of the exposure of GS-443902 in tissues. In this study, we focused on the exposure prediction in two organs: lung and liver. Lung, as the main organ involved in the SARS-CoV-2 infection, is considered to be one of the target sites of remdesivir's action, while the active metabolite generated in the liver is generally regarded as the attribute of the liver-related adverse events in patients and healthy subjects who receive remdesivir. A whole-body PBPK modeling and simulation approach was utilized to elucidate the disposition mechanism of remdesivir and its metabolites in the lung and liver and explore the relationship between plasma and tissue PK of remdesivir and its metabolites in healthy subjects. In addition, the potential alteration of plasma and tissue PK of remdesivir and its metabolites in patients with organ dysfunction was explored. The global sensitivity analysis results indicated that (i) no correlation is expected between the plasma exposure of GS-704277 and the lung or liver exposure of GS-443902 because metabolic activation of remdesivir in other tissues instead of the liver and lung may be the major contributor to the plasma exposure of GS-704277; (ii) the plasma exposure of GS-441524 is highly correlated with the liver exposure of GS-443902, which could contribute to the liver-related adverse events; (iii) remdesivir levels in the plasma are expected to be correlated with the liver or lung exposure of GS-443902, under assumptions that the relative lung/liver enzyme expression levels and lung physiology and anatomy remain unaltered by COVID. In addition, our simulation results indicated that the intracellular exposure of GS-443902 was decreased in the liver and increased in the lung in subjects with hepatic impairment relative to the subjects with normal liver function. In subjects with severe renal impairment, the exposure of GS-443902 in the liver was slightly increased, whereas the lung exposure of GS-443902 was not impacted.[25] These predictions along with the organ impairment study results may be used to support decision making regarding the remdesivir dosage adjustment in these patient subgroups. The modeling exercise illustrated the potential of whole-body PBPK modeling to aid decision making for nucleoside analog prodrugs, particularly when the active metabolite exposure in the target tissues is not available.

Evaluation of the QT prolongation potential of hydroxychloroquine

It is important to understand the mechanism and the extent of a QT prolongation effect of COVID-19 treatments in order to apply appropriate safety monitoring procedures in patients. Both chloroquine and hydroxychloroquine sulfate were once considered potential treatments for COVID-19. The effect of chloroquine on the corrected QT (QTc) interval has been evaluated in a QT study submitted to the FDA, and the relationship between QTc interval changes and chloroquine concentrations was estimated via modeling approach.[26] Given the structural similarity, we applied a relative potency between chloroquine and hydroxychloroquine sulfate on the concentration-QT relationship of chloroquine to predict QT effect by hydroxychloroquine sulfate treatment. This relative potency was obtained from an *in vivo* experiment using isolated rabbit ventricular wedge system, the method of which was previously described by Liu *et al*.[27] Hydroxychloroquine sulfate concentrations at different clinically evaluated doses were predicted with a population PK model developed using PK data submitted to the FDA. This approach enables us to evaluate the QT effect of hydroxychloroquine sulfate in patients with COVID-19. The analysis suggested a significant, concentration-dependent QT prolongation effect driven by the accumulation of hydroxychloroquine sulfate in patients with COVID-19 and supported close electrocardiographic monitoring in this patient population (unpublished data).

CONCLUSIONS

Successful applications of different MIDD approaches have improved the efficiency of drug development and informed regulatory decision making, thus expanding the toolbox in the fight against the COVID-19 pandemic. The multiple MIDD

approaches/examples highlighted herein have been shown to be efficient tools that integrate various sources of information to streamline new drug development, especially under urgent situations such as the COVID-19 pandemic. MIDD approaches can be applied to identify potential compounds during drug discovery and early development, allowing the community to target promising candidates. In late clinical development, MIDD approaches may be used to fill in knowledge gaps, such as the potential loss of efficacy against variant strains when clinical data are limited, and the landscape of emergent variants is rapidly changing. Under various situations, such as efficacy against variants of concern and dose interval change for well-studied therapeutic proteins, MIDD approaches may alleviate the need for additional clinical trials, which is extremely valuable when the development time is restricted, and there is a high unmet medical need.

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