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ORIGINAL ARTICLE

Model informed dosing of hydroxycholoroquine in COVID-19 patients: Learnings from the recent experience, remaining uncertainties and gaps

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Aims: In the absence of a commonly agreed dosing protocol based on pharmacokinetic (PK) considerations, the dose and treatment duration for hydroxychloroquine (HCQ) in COVID-19 disease currently vary across national guidelines and clinical study protocols. We have used a model-based approach to explore the relative impact of alternative dosing regimens proposed in different dosing protocols for hydroxychloroquine in COVID-19.

Methods: We compared different PK exposures using Monte Carlo simulations based on a previously published population pharmacokinetic model in patients with rheumatoid arthritis, externally validated using both independent data in lupus erythematous patients and recent data in French COVID-19 patients. Clinical efficacy and safety information from COVID-19 patients treated with HCQ were used to contextualize and assess the actual clinical value of the model predictions.

Results: Literature and observed clinical data confirm the variability in clinical responses in COVID-19 when treated with the same fixed doses. Confounding factors were identified that should be taken into account for dose recommendation. For 80% of patients, doses higher than 800 mg day on day 1 followed by 600 mg daily on following days might not be needed for being cured. Limited adverse drug reactions have been reported so far for this dosing regimen, most often confounded by co-medications, comorbidities or underlying COVID-19 disease effects.

Conclusion: Our results were clear, indicating the unmet need for characterization of target PK exposures to inform HCQ dosing optimization in COVID-19. Dosing optimization for HCQ in COVID-19 is still an unmet need. Efforts in this sense are a prerequisite for best benefit/risk balance.

KEYWORDS

dosing optimization, dosing rationale, hydroxychloroquine, modelling and simulations, pharmacokinetics

The authors confirm that there is no principal investigator in this study because this study only includes observational data from standard clinical practice data.

1 | BACKGROUND

SARS Coronavirus disease 2019 is the most severe pandemic for almost a century with more than 1,000,000 infections and 60,000 deaths all over the world within less than 6 months,[1] creating an unprecedented urgent need for an effective and safe drug to stop its spread and protect populations less skilled to manage the crisis.

Standard drug and vaccine development approaches are lengthy and expensive: they require years/decades of research and development: they are therefore not the optimal response for the current outbreak in view of the rapid spread of the disease. It is therefore commonly agreed that there is a more pressing need for alternative solutions, including drug repurposing and modelling and simulations.

Drug repurposing consists in this context of using already marketed drugs or therapeutics under development for other indications based on their potential pharmacological interest or the available non-clinical or clinical data with SARS coronavirus. It can be combined with alternative evidence generation approaches including modelling and simulation to address some important questions such as determining the acceptable dose for the different drugs to be either tested in clinical trials or implemented in compassionate/off-label use during the outbreak.

Hydroxychloroquine (HCQ), a 4-aminoquinolein drug approved and used for decades in the treatment of malaria,[2] rheumatoid arthritis[3] and cutaneous lupus erythematosus (CLE),[4] is being considered as a potential therapeutic option in COVID-19. Recent in vitro studies demonstrated the antiviral activity of **chloroquine** (CQ) and HCQ on SARS-CoV-2 (see, e.g., Refs. 5, 6 and references therein) with results showing higher potency (lower in vitro EC_{50}) for HCQ as compared to CQ, so that lower doses (than in approved indications) could be used in COVID-19.

HCQ has been used in clinical trials for COVID-19 treatment with different outcomes/results,[7–13] it is currently investigated in a series of additional ongoing/planned clinical trials,[14] and is included in some national guidelines for management of COVID-19. However, in the absence of a clear dosing protocol based on drug exposure in plasma/blood and at the site of infection, dosage and duration of treatment currently vary across national and clinical study protocols. Inappropriate dosing regimen can lead to an increase risk of either therapeutic failure or adverse events such as cardiotoxicity (QT prolongation) and retinopathies.

Modelling and simulation have the potential to optimize the dose based on the pharmacokinetics (PK) behaviour of the drug, provided that exposure–response is understood and target concentrations are characterized for both efficacy and safety. It is therefore considered timely to explore how the evidence gathered with the clinical use of HCQ could feed the understanding of its PK and PD and inform the dosing in COVID-19 patients. In March 2020, a physiologically based pharmacokinetic (PBPK) model was published by Yao et al. to simulate/predict the HCQ concentrations in blood, plasma and lung fluid of Chinese patients.[5] Based on the PBPK model results, the authors recommend an oral loading dose of 400 mg twice daily of hydroxychloroquine sulfate, followed by a maintenance dose of 200 mg given twice daily for 4 days However, no PK data in COVID-19 patients were available to clinically validate the model. A different and much higher dosing regimen (at least 800 mg daily over 10 days) has recently been recommended by Garcia-Cremades et al. based on PK/PD simulation of HCQ effects on SARS COV-2 viral load on the one hand, and on QT prolonging effects of chloroquine (CQ) (a similar drug), on the other.[15]

The first aim of this work is to assess and compare different dosing regimens using Monte Carlo simulations based on a previously published population pharmacokinetic (popPK) model in patients with rheumatoid arthritis (RA),[3] externally validated using both independent data in patients with cutaneous lupus erythematosus (CLE)[4] and recent data in COVID-19 patients.[5] Moreover, clinical efficacy and safety information from COVID-19 patients treated with HCQ at Saint-Pierre hospital (Brussels, Belgium) and as included in the recently published studies are used to assess the clinical value of the model predictions.

This work also aims to present and discuss the strength of evidence and the uncertainties for a model-informed approach based on the currently available data as well as the current gaps in information for HCQ dose optimization in COVID-19.

What is already known

- Inconsistent doses of hydroxychloroquine are included in national guidelines and clinical study protocols for management of COVID-19 disease.
- Modelling and simulation approaches have recently been proposed for dose selection but (external) clinical validation was either lacking or carrying important limitations and unverified assumptions.

Wha this study adds

- We propose a model-based approach for hydroxychloroquine dose rationale with clinical validation using literature pharmacokinetic data in autoimmune disease and COVID-19.
- Clinical efficacy and safety data in COVID-19 patients are used for contextualization.
- Uncertainties and gaps are identified as well as data needed to address them.

2 | METHODS

2.1 | Population pharmacokinetic modelling and simulation

Two previous published population pharmacokinetic models have been published for hydroxychloroquine (HCQ) in patients with RA[3]

and lupus erythematosus[4] using whole-blood HCQ concentrations. Four additional models describe plasma concentrations or merged blood and plasma concentrations.[16–19] Blood concentrations are known to be more reproducible (because higher, with lesser analytical sensitivity issues). We therefore used the model by Carmichael et al.[3] for subsequent simulation after independent validation. The authors developed a one-compartment model with first-order elimination and absorption and an absorption lag time. Nine of the patients received oral dose and intravenous infusion for the bioavailability study. Patients received Plaquenil® tablets, each tablet having 200 mg of racemic HCQ sulfate equivalent to 155 mg of racemic HCQ base. The only covariate retained in the model is the methotrexate, a drug most commonly used in RA.

This model was externally validated using digitized blood concentrations obtained from the Morita et al. paper. In this study, HCQ was used to treat patients with cutaneous lupus erythematosus.[4] The 90 patients received one of these three dosing regimens of HCQ sulfate, depending on their ideal body weight: 200 mg daily (n = 20), 200 mg and 400 mg every other day (n = 55), or 400 mg daily (n = 15). The steady-state blood concentration data (three samples per patient) were digitized from figure 1 in the paper by Morita et al.,[4] using MATLAB R2016b software (The MathWorks Inc., Natick City, MA). Monte Carlo simulations were performed using NONMEM software, version 7.3 (Icon Development Solutions, Ellicott City, MD).

This model was also used for simulations of the serum concentrations serum PK data including data from 20 patients from the Gautret et al. study[6] with a serum/whole blood correction ratio of 0.53.[20] The patients in the Gautret et al. study were confirmed COVID-19 and received 200 mg every 8 hours for 10 days. It is assumed that they were trough concentrations, measured before the first dose of the indicated day. NONMEM software was used for this purpose.

Subsequently, we used this model to perform simulations of blood concentrations of HCQ base for different dosing protocols for treatment of COVID-19. Table 1 includes the relevant information on the simulations performed. The figures were generated using MATLAB software.

2.2 | Additional clinical data

In addition to data used for model validation, additional data were used to get some insight on dose–exposure–response as regards clinically relevant beneficial and toxic effects of HCQ in COVID-19. Even though these data could not permit a formal exposure–response analysis, they were used to describe the doses and PK exposure distributions in COVID-19 patients either with favourable responses (discharge from the hospital based on criteria described below) or experiencing adverse drug reactions after treatment with HCQ. Summary-level and patient-level data were used for this purpose.

i. Summary-level data

These include data from three previously published clinical data in COVID-19 patients treated either with HCQ monotherapy[8,9] or with HCQ combined with azithromycin (AZM).[7,10]

ii. Patient-level data

Clinical data were obtained from 172 COVID-19 in-patients hospitalized at Saint-Pierre Hospital in Brussels (Belgium) from 1 March to 6 April 2020 and treated with HCQ monotherapy. Summary of patient characteristics as well as relevant information available on their disease stage and response to HCQ monotherapy are included in Table 2. Statistical analysis was performed using SAS JMP v.10 soft-

TABLE 1 Hydroxychloroquine sulfate dosing regimens assessed by Monte Carlo simulations

Dosing regimen	Loading dose (Day 1)	Total loading dose	Maintenance dose	Total daily dose	Duration of treatment
Scenario 0(a)	400 mg BID	800 mg	200 mg BID	400 mg	5 days
	400 mg BID	800 mg	200 mg BID	400 mg	10 days
Alternative scenario 0	/	/	200 mg TID	600 mg	10 days
Alternative scenario 1 (b)	600 mg BID	1,200 mg	200 mg BID	400 mg	5 days
	600 mg BID	1,200 mg	200 mg BID	400 mg	10 days
Alternative scenario 2 (c)	200 mg TID	600 mg	200 mg BID	400 mg	5 days
	200 mg TID	600 mg	200 mg BID	400 mg	10 days
Alternative scenario 3 (d)	/	/	200 mg BID	400 mg	5 days
	/	/	200 mg BID	400 mg	10 days
Alternative scenario 4 (e)	400 mg BID	800 mg	400 mg daily	400 mg	5 days
	400 mg BID	800 mg	400 mg daily	400 mg	10 days
Alternative scenario 5 (f)	800 mg followed by 400 mg 6 hours later	1,200 mg	200 mg BID	400 mg	5 days
	800 mg followed by 400 mg 6 hours later	1,200 mg	200 mg BID	400 mg	10 days

ware. Criteria for hospitalization included COVID-19 suspicion based on radiological findings in patients with known severity factors (hypertension, diabetes, lung disease, age >60) and/or with one of the following criteria: oxygen desaturation <94% while breathing ambient air, respiratory rate > 22/min, heart rate >125, decrease of oxygen saturation <94% after one minute walking test, altered consciousness. The following criteria were taken into account before discharge: no requirement of oxygen supplementation, no evidence of desaturation while walking without oxygen supplementation, ability of oral medication intake, and appropriate condition for isolation at home.

Moreover, EudraVigilance (EV), a European public vigilance database including spontaneous reports of adverse events with medications, was consulted and cases related to the use of HCQ in COVID-19 extracted.

2.3 | Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.[21]

3 | RESULTS

The popPK model by Carmichael et al. was successfully replicated as shown in Figure 1. Results of external validation were satisfactory:

TABLE 2 Summary characteristics of patients treated with HCQ monotherapy at Saint Pierre hospital

Parameter	Median [range]/ frequency	Total (*n*)
Age (years)	60 [26;96]	172
Gender (males/females)	101/71	172
Time interval from start of symptoms to start of treatment (days)	8 [1; 31]	172
Treatment duration (days)	5 [3; 8]	172
Patients in intensive care unit (yes/no)	40/131	172
Time interval from start of treatment to discharge from the hospital (days)	6 [1;18]	172
Death (yes/no)	20/152	172
Diabetes (yes/no)	55/117	172
Hypertension (yes/no)	78/94	172
Cardiomyopathies (yes/no)	34/138	172
Obesity (yes/no)	49/122	172
C-reactive protein (mg/L)	146.1 [2.2; 547.6]	317[a]
Blood oxygen (%)	92 [23;100]	152[a]
Absolute lymphocytes (cells/nL)	1.03 [0.16; 8.55]	286[a]

[a]Some of the patients had more than one value measured.

the model by Carmichael was able to acceptably predict previously published data from external sources in CLE and in COVID-19 patients (see Figure 1).

This model was therefore used to simulate different dosing scenarios including in national guidelines and ongoing/planned clinical study protocols in Belgium. Results of the different simulations are shown in Figure 2.

Selected clinical response markers including time to discharge from the hospital, survival, C-reactive protein (CRP), blood oxygen levels and absolute lymphocyte counts were collected from a cohort of 172 patients treated with HCQ monotherapy at Saint Pierre Hospital in Brussels. Summary descriptive statistics are included in Table 2 together with patient age and relevant comorbidities. Most of these patients received a 5-day treatment scheme with 400 mg BID on day 1 followed by 200 mg BID from days 2 to 5. Three patients received 6 or 7 days of treatment. As regards impact of HCQ treatment on CRP, blood oxygen levels and absolute lymphocyte counts, while all the patients received the same dosing regimen for HCQ, variable responses were observed for each of the biomarkers: a subset had their levels decreasing (i.e. negative slope) after start of treatment with HCQ, while others showed an increase in the levels (positive slope). Moreover, time delay from appearance of symptoms to implementation of treatment was a significant predictor of admission to the intensive care unit ($p < 0.01$, AUC ROC curve = 0.63) and death ($p < 0.01$, AUC ROC curve = 0.61) based on logistic regression analysis, while patient age, hypertension, cardiomyopathies, cancer and obesity were significantly correlated with patient death ($p < 0.05$).

As regards clinical safety, case reports were found from literature data and public vigilance database (EV). The dosing regimens information was extracted when provided in the report and in most cases 800 mg daily or lower doses were reported for day 1 and 400–600 mg daily were reported for the following days. The time delay from start of treatment to onset of ADR was very variable (from 1 to several days). Cardiac disorders and especially QT prolongation were the most frequently reported adverse drug reactions. At least one of the following additional risk factors was reported in patients experiencing adverse drug reactions: concomitant medication with at least one drug known to carry QT prolonging drugs or cardiac toxicity, relevant comorbidities (e.g. renal impairment), cardiovascular disease, cardiomyopathies and hypokalaemia (see Table 2).

4 | DISCUSSION

HCQ is approved and used worldwide for treatment of malaria and RA (SLE and CLE). The approved doses are higher in magnitude and of shorter duration in malaria (1,200 mg on day 1 followed by 400 mg daily over 10 days) as compared to RA (loading dose of 400–800 mg BID followed by maintenance dose of 200 mg BID chronically with sometimes therapeutic drug monitoring targeting trough plasma concentrations of 0.6-1 mg/L[4]). Several PK models are available in the literature for HCQ in these indications.[1,2,9] Our choice to use the PK model by Carmichael et al. was motivated by the fact that it was

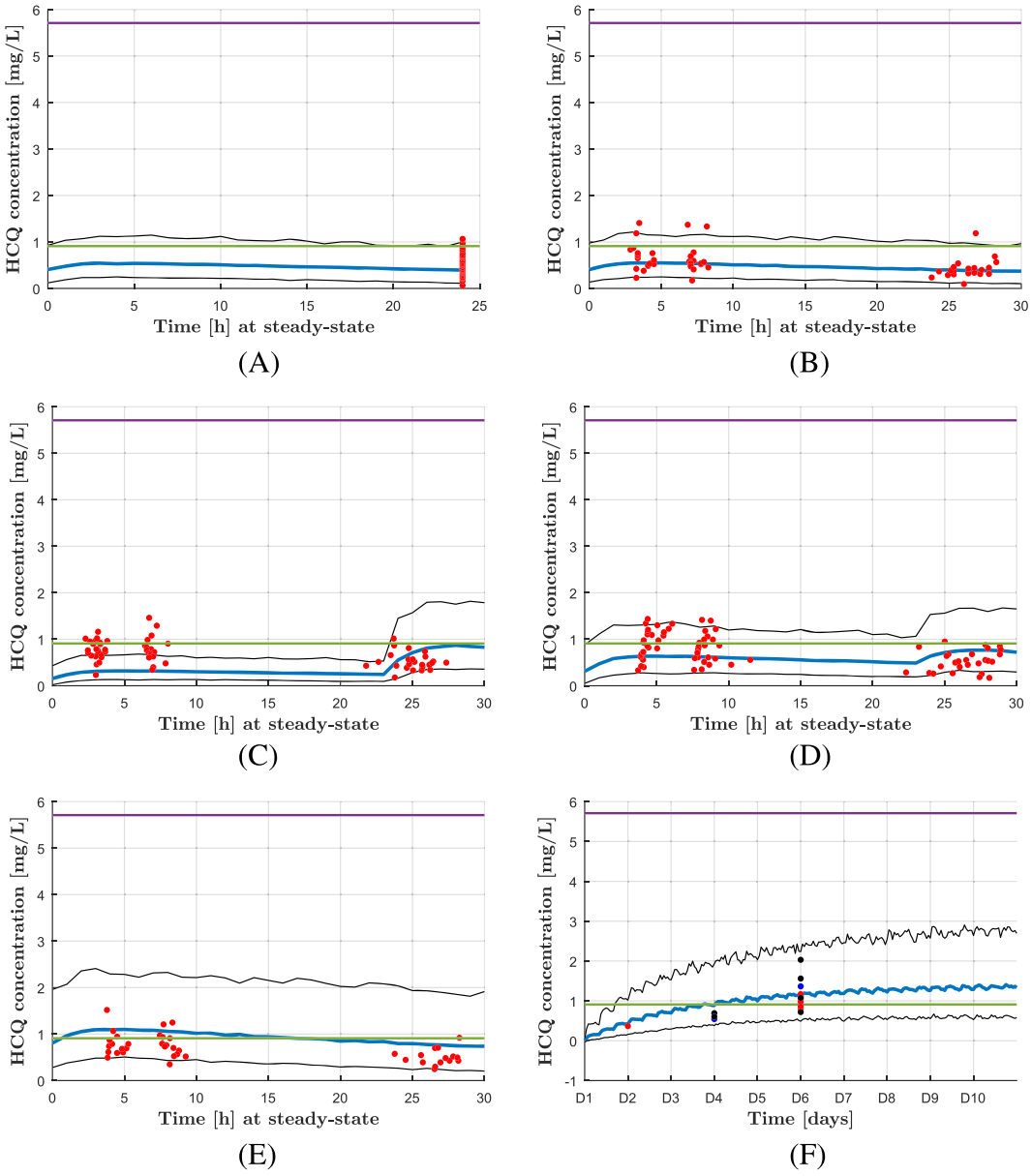

FIGURE 1 Model validation. (A) Prediction of Carmichael et al. PK data (200 mg daily). Blue line: Median. Black lines: 2.5 and 97.5 percentiles (95% prediction interval). Red circles: Observed (blood) concentrations in RA patients digitized from Carmichael et al. publication.[3] (B-E) Prediction of Morita et al. PK data for different dosing regimens: (b) 200 mg daily, (c) 200 or 400 mg every other day, when the last dosing just before blood sampling is 200 mg, (d) 200 or 400 mg every other day, when the last dosing just before blood sampling is 400 mg, (e) 400 mg daily. Blue line: Medians. Black lines: 2.5 and 97.5 percentiles (95% prediction intervals). Red circles: Observed (blood) concentrations in CLE patients digitized from Morita et al. publication.[4] (F) Prediction of Gautret et al. PK data (200 mg TID for 10 days). Blue line: Median. Black lines: 2.5 and 97.5 percentiles (95% prediction interval). Circles: Observed corrected serum concentrations in COVID-19 patients from Gautret et al. publication[6] (blue/black refers to PCR-negative patients on day 6, red refers to PCR-positive patients on day 6, black refers to patients with azithromycin added to HCQ treatment)

developed to describe a relatively large cohort of blood concentrations (known to be less variable). The estimated apparent clearance values were quite consistent across previously published popPK models: 10–11 L/h when whole blood concentrations were analysed[3,4] vs 51–68 L/h when plasma concentrations were analysed.[16–19] The predictive performance of the Carmichael et al. model was confirmed on external data including data in CLE patients and in COVID-19 patients with overall satisfactory fitting of digitized concentrations. It is therefore judged adequate to be used for exploring the differential/relative impact of alternative dosing regimens in COVID-19 patients in the absence of a refined popPK model developed using COVID-19 patient data. It should, however, be noted that this model still carries an high unexplained variability component on the volume of distribution and clearance parameters: there is therefore a need for refinement of this model and better characterization of PK in COVID-19 patients, including by adequate description of

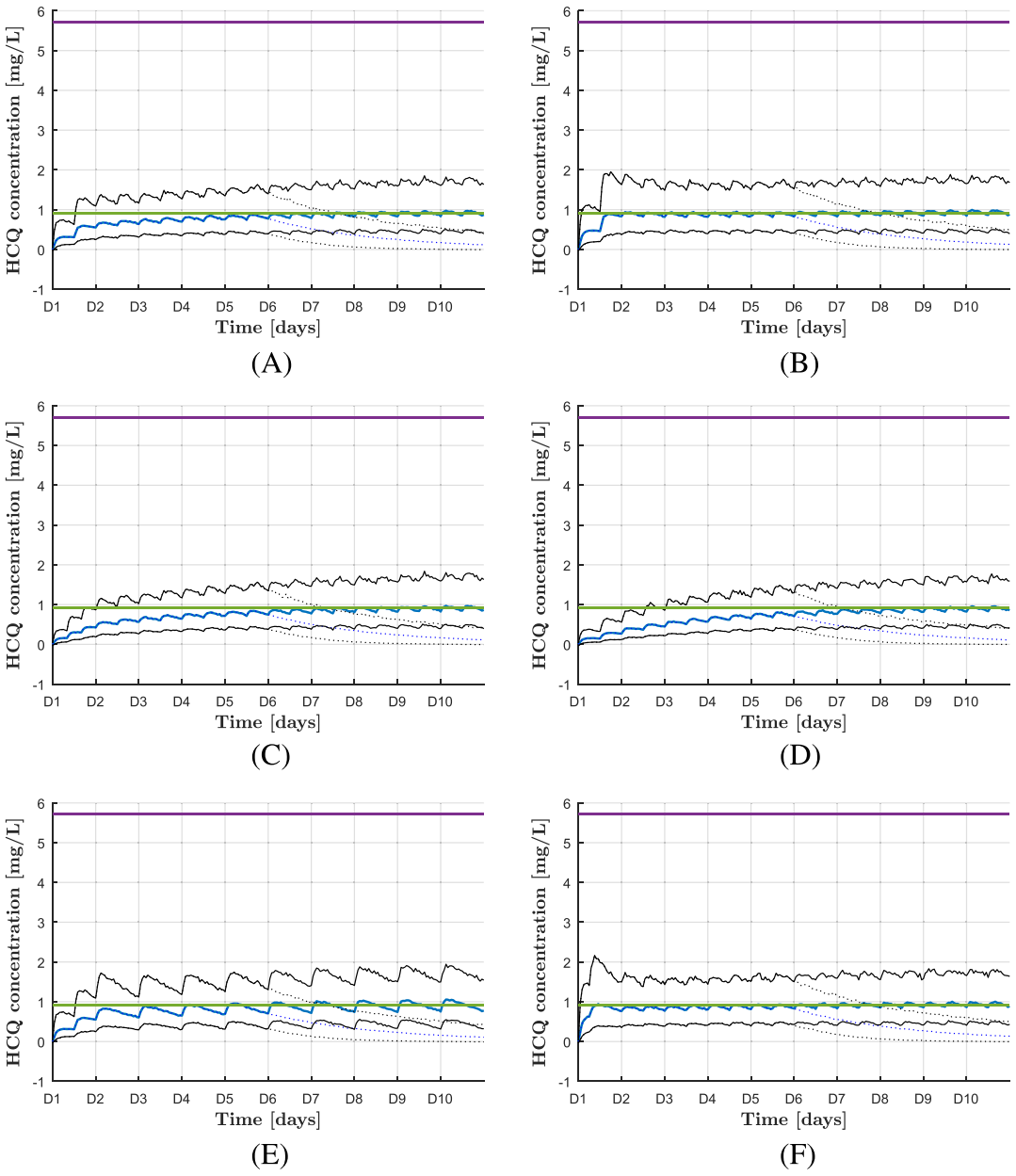

FIGURE 2 Simulated blood PK profiles for different dosing regimens: (A) 400 mg BID on day 1 followed by 200 mg BID (**Belgian protocol**), (B) 600 mg BID on day 1 followed by 200 mg BID, (C) 200 mg TID on day 1 followed by 200 mg BID, (D) no loading dose, 200 mg BID, (E) 400 mg BID on day 1 followed by 400 mg daily, (F) 800 mg and 400 mg 6 hours later on day 1, followed by 200 mg BID. Blue lines: Medians. Black lines: 5th and 95th percentiles (90% prediction intervals). Solid lines: Treatment for 10 days. Dotted lines: Treatment for 5 days. The green and purple horizontal lines represent the projected target total whole blood concentrations based on EC_{50} values from Yao et al. [ref] and Liu et al. [red], respectively

covariate effects. Potential covariates include bodyweight, CYP2D6 modulators and underlying renal impairment.

In the absence of a high loading dose, the results of the dosing simulation scenarios show that the drug progressively accumulates over the dosing periods of 5 or 10 days: safety monitoring can therefore be needed throughout the dosing period and even after. This is confirmed by case reports of patients experiencing adverse drug reactions such as QT prolongation even after drug withdrawal. The appropriate characterization of the loading and maintenance doses needed is therefore important not only for drug efficacy but also for drug safety. The use of high loading doses needs to be justified in view of the hazard for serious adverse events. There is still uncertainty on the target/relevant systemic concentrations for drug efficacy and safety. This is an important gap to be filled in the current situation because systemic concentrations are more accessible for monitoring than could be lung concentrations. There is an unmet need for adequately conducted clinical PK and exposure–response studies.

The antiviral action of HCQ is possibly the result of its cationic amphiphilic properties.[22] Hydroxychloroquine is metabolized to

desethylhydroxychloroquine, which is also a cationic amphiphilic molecule, and might also carry some antiviral effects, even if this effect has not been tested/reported so far. An additive effect due to desethylhydroxyquine remains theoretically possible. Interestingly, Munster et al.[23] reported PK of hydroxychloroquine and desethylhydroxychloroquine with concentrations measured in the same patients: the PK curves were shown to be parallel with similar time to maximum concentrations and elimination half-life for HCQ and desethylhydroxychloroquine and much higher parent drug concentrations (ratios around 1.75:1). The strong correlation could therefore justify that hydroxychloroquine concentrations are also informative for desethylhydroxychloroquine concentrations in the same patient. Our results are therefore informative for drug effects even in the absence of analysis of potential metabolite effects.

Yao et al.[5] have shown in their recent publication that in vitro EC50 for prophylactic and treatment antiviral effects on SARS COV-2 were 0.72 and 5.85 μM, respectively, while higher EC_{50} values have also been reported for HCQ by other research groups (e.g. 4.51 μM for MOI 0.01 by Liu et al.[24]). For graphical comparative purposes, EC_{50} values by Yao et al.[5] and Liu et al.,[24] scaled to whole blood concentrations (assuming no protein binding in the in vitro setting and 50% protein binding in patients), are included in Figure 2. It should be noted that, for most of the dosing regimen proposed, the simulated concentrations are below the concentrations needed for relevant antiviral effects of HCQ. It should also be noted that the immunomodulatory effects of hydroxychloroquine could also contribute to the overall clinical effects in addition to the potential antiviral effects. Characterizing the PK/PD and exposure–response is beyond the scope of our paper. However, it is believed that these different effects are linked to HCQ concentrations.

Based on a PBPK modelling approach Yao et al. have proposed dosing regimens that allow reaching empirically determined ratios between free lung concentrations and the in vitro EC_{50}. However, in addition to the fact that this model was not validated using clinical data in COVID-19 patients, the recommended doses should still be cautiously considered because the relevant target ratios between lung or systemic concentrations and in vitro active levels are still to be established as well as the ranges for effective whole blood and plasma total concentrations. A more recent paper[15] was published in this sense using a model-based approach and PK/PD modelling of viral load and QT prolongation. However, it should be noted that this was a retrospective analysis of either aggregated or limited previously published data generated in different settings and for different purposes. Several unverified assumptions were therefore needed for the PK/viral load and the PK/QT modelling. Of note, the assumed/modelled QT prolonging effects were those of choloroquine and not hydroxychloroquine. Moreover, the overall unexplained variability was very high and covariate modelling was not implemented. Research is still needed to determine target HCQ level for in vivo (human) antiviral effect in COVID-19 and the link with clinically relevant outcomes such as patient cure and survival for the different disease stages. Given the known multiphasic features of the COVID-19 disease and the importance of the inflammatory component of the disease, it is still unclear how relevant viral load clearance by antiviral drugs are for the patient clinical outcomes in early *vs* later stages of the disease.

While it is not possible to identify the optimal dose in the absence of properly conducted dose–exposure–response analyses using relevant data in the target indication, the currently available clinical efficacy and safety data in different doses used in COVID-19 patients can already provide some useful information on the dose requirement when interpreted together with the related PK information. High rates of positive clinical outcomes have been reported with doses of 600–800 mg daily on day 1 followed by 400–600 mg daily for a total treatment duration of 5–10 days,[6–10] also confirmed in the cohort of 172 patients treated at Saint Pierre hospital (see Table 2 and Figure 3). While these studies were all either single arm (no placebo arm), uncontrolled or of limited size, and therefore precluding the robust identification of the actual drug effect size, the important learning from these data is that higher doses might not be needed for an important proportion of patients. The determinants of positive patient outcomes are still to be identified, and HCQ dose optimization can certainly be one of them. Additionally, as extensively discussed in the recent literature, disease stage, patient age and comorbidities might also play key roles.[25–27]

As regards safety, the overall safety profile seems quite good when the drug is given at a dose of 400–800 mg on day 1 followed by 400–600 mg daily for 5 to 10 days, under close clinical monitoring. Available concerning cases reported in EV or in the literature are consistent with the known safety concerns with HCQ. Aggravation of the toxicity due to comorbidities or underlying renal or liver diseases related to COVID-19 pathophysiology cannot be excluded either[25–27] (see also Table 3). It is therefore essential that patients treated with HCQ are closely monitored for these risk factors, and that appropriate risk minimization measures are implemented as needed.

It should, however, be noted that the clinical safety data from EV should be interpreted cautiously due to the potential bias related to spontaneous underreporting.

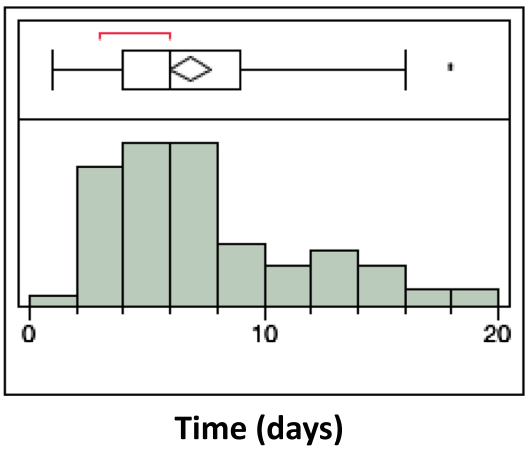

FIGURE 3 Histogram of times to discharge for patients of Saint Pierre hospital

TABLE 3 Summary of reported cases of adverse drug reactions retrieved in EV, for HCQ indicated for COVID-19, as of 6 April 2020

System organ classes/preferred term	Number of patients	Dose of HCQ sulfate	Confounders
Gastrointestinal disorders	5	400 mg/day (when stated)	Concomitant lopinavir-ritonavir (3 cases) or amoxicillin-clavulanate (1 case)
Skin disorders	3	200 mg/day	Concomitant amoxicillin-clavulanate (in one case)
Investigations/ECG QT prolonged	28/24[a]	200–800 mg/day One case reported the dose of 600 mg 2 times a day (one day prior QT prolongation)	Concomitant QT prolonging drugs (azithromycin, levofloxacin, escitalopram), hypokalaemia, renal failure, pre-existing drug-induced QT prolongation
Eye disorders	3	600 mg/day	Cataract operation 3 weeks prior (1 case)

[a]Two cases with sudden death, one case of fatal cardiac arrest, one case of fatal QT prolongation. Patient ages varied between 62 and 88 years old. Three patients had serious co-morbidities. The fourth patient for which no co-morbidity was reported had received co-suspected azithromycin, levofloxacin and lopinavir-ritonavir.

5 | CONCLUSION

We have successfully used a model-based approach to explore the relative impact of alternative dosing regimens proposed in different dosing protocols for HCQ.

It was clear from our results that there is an unmet need for adequate characterization of target PK exposures in COVID-19 patients to inform the dosing optimization. Literature data and clinical data from a Belgian hospital confirm the variability in clinical responses when the same fixed doses are given to all patients. Some confounding factors were identified that should be taken into account for dose recommendation. For 80% of patients in the Saint Pierre cohort, doses higher than 600–800 mg daily on day 1 followed by 400–600 mg daily on following days might not be needed for positive outcome. Very limited ADRs have been reported so far for this dosing regimen; moreover, they were most often confounded by co-medications, comorbidities or underlying disease effects.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

P.T. performed the analysis and wrote the manuscript. N.D., L.S., F.L., M.D., R.N., A.L., M.-C.P. and D.K. treated the patients, collected the data and wrote the manuscript. F.W., C.L., V.V., J.-M.D. and J.H. collected the data and wrote the manuscript. F.T.M. designed the study, performed the analysis and wrote the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. https://coronavirus.jhu.edu/map.html
2. Lim HS, Im JS, Cho JY, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by Plasmodium vivax. *Antimicrob Agents Chemother*. 2009;53(4):1468-1475. https://doi.org/10.1128/AAC.00339-08
3. Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. *Ther Drug Monit*. 2003;25(6):671-681. PubMed PMID: 14639053
4. Morita S, Takahashi T, Yoshida Y, Yokota N. Population pharmacokinetics of hydroxychloroquine in Japanese patients with cutaneous or systemic lupus erythematosus. *Ther Drug Monit*. 2016;38(2):259-267.
5. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing Design of Hydroxychloroquine for the treatment of severe acute respiratory syndrome. *Clin Infect Dis*. 2020;2:1-25.
6. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105949
7. Gautret P, Lagier JP, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. *Travel Med Infect Dis*. 2020;34(101663). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151271/pdf/main.pdf
8. Chen J, Liu D, Lui L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *J Zhejiang Univ*. 2020;49(2):215-219.
9. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.22.20040758
10. Molina JM, Delaugerre C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384. https://doi.org/10.1016/j.medmal.2020.03.006
11. Singh AK, Singh A, Singh R, Misra A. Hydroxychloroquine in patients with COVID-19: a systematic review and meta-analysis. *Diab Metab Syndrome: Clin Res Rev*. 2020;14(4):589-596.
12. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020. https://doi.org/10.1001/jamacardio.2020.1834
13. Mehra MR, Desai SS, Ruschitzka F, Patel AN, et al. Hydroxychloroquine or chloroquine with or without a macrolide for

treatment of COVID-19: a multinational registry analysis. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)31180-6
14. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
15. Garcia-Cremades M, Solans BP, Hughes E, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: an integrative modeling approach for effective drug repurposing. *Clin Pharmacol Ther*. 2020;108(187). https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1856
16. Lim H-S, Im J-S, Cho J-Y, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in hemoprophylaxis against malaria caused by *Plasmodium vivax*. *Antimicrob Agents Chemother*. 2009;53(4):1468-1475.
17. Abdulaziz N, Shah AR, McCune WJ. Hydroxychloroquine: balancing the need to maintain therapeutic levels with ocular safety: an update. *Curr Opin Rheumatol*. 2018;30(3):249-255. https://doi.org/10.1097/BOR.0000000000000500
18. Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol*. 1989;27(6):771-779.
19. Balevic SJ, Green TP, Clowse MEB, Eudy AM, Schanberg LE, Cohen-Wolkowiez M. Pharmacokinetics of hydroxychloroquine in pregnancies with rheumatic diseases. *Clin Pharmacokinet*. 2019;58(4):525-533.
20. Blanchet B, Moez J, Allard M, et al. Hydroxychloroquine levels in patients with systemic lupus erythematosus: comparison of whole blood and serum levels [abstract]. *Arthritis Rheumatol*. 2019;71(suppl 10). https://acrabstracts.org/abstract/hydroxychloroquine-levels-in-patients-with-systemic-lupus-erythematosus-comparison-of-whole-blood-and-serum-levels/
21. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acids Res*. 2018;46(D1):D1091-D1106.
22. Salata C, Calistri A, Parolin C, Baritussio A, Palù G. Antiviral activity of cationic amphiphilic drugs. *Exp Rev Anti-Infect Ther*. 2017;15(5):483-492. https://doi.org/10.1080/14787210.2017.1305888
23. Munster T, Gibbs JP, Shen D, et al. Hydroxychloroquine concentration–response relationships in patients with rheumatoid arthritis. *Arthritis Rheum*. 2002;46:1460-1469. https://doi.org/10.1002/art.10307
24. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6(16). https://www.nature.com/articles/s41421-020-0156-0.pdf
25. Wang F-S, Zhang C. What to do next to control the 2019-nCoV epidemic. *Lancet*. 2020;395(10222):391-393.
26. Zheng Y, Ma Y, Zhang J, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259-260. https://doi.org/10.1038/s41569-020-0360-5
27. Wu C-I, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. *Heart Rhythm*. 2020; in press. https://doi.org/10.1016/j.hrthm.2020.03.024

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