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Comment on: Rationale of a loading dose initiation for hydroxychloroquine treatment in COVID-19 infection in the DisCoVeRy trial

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Sir,

We read the article by Lê *et al.*[1] explaining how a hydroxychloroquine dose regimen of 400 mg twice daily at Day 1 followed by 400 mg once daily from Day 2 to Day 10 was determined to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients in the DisCoVeRy trial (NCT04315948). The authors calculated the hydroxychloroquine loading dose, taking into account its bioavailability (∼75%), volume of distribution (5522 L) and desired target concentration based on Yao's *in vitro* concentration producing 50% of maximum effect (EC_{50}; 242 ng/mL).[2] To choose the maintenance regimen, they relied on Yao's physiologically based pharmacokinetic (PBPK) model predicting hydroxychloroquine concentrations in lung fluid *in silico* by optimizing the free lung tissue trough concentration-to-EC_{50} ratio.[2] We believe that several pitfalls preclude the achievement of hydroxychloroquine-related antiviral and immunomodulatory activity using the regimen of Lê *et al.*[1]

Firstly, no validated *in vitro* model can predict anti-SARS-CoV-2 drug effects in the lung. As a substitute, monkey kidney epithelial cell cultures were used to determine EC_{50},[2] questioning the relevance of Yao's model to predict hydroxychloroquine-related effects in the lung. A 24-fold difference has been reported between hydroxychloroquine EC_{50} values against SARS-CoV-2.[2,3] While EC_{50} is not a time-dependent parameter, Yao's values[2] varied depending on how long the experiment was run, questioning the estimate reliability obtained in non-steady-state conditions.[4] Undoubtedly, EC_{90} would have been the optimal anti-SARS-CoV-2 activity marker to consider,[5] as EC_{50} depends on the concentration–response curve slope being expected to be smooth for *in vitro* SARS-CoV-2 models, thus underestimating the required concentration allowing for almost 100% viral suppression.

Secondly, Yao's PBPK model[2] incorporated no intracellular compartment, while hydroxychloroquine PK, characterized by hydroxychloroquine's extensive volume of distribution (intracellular concentrations up to 1000-fold the extracellular concentrations), are driven by the lysosomotropic mechanism of its main anti-SARS-CoV-2 activity consisting of acidotic intra-organelle pH modulation (e.g. the endosomes, lysosomes and Golgi apparatus). No correlation between blood exposure to hydroxychloroquine and the resulting autophagy inhibition is expected with such incomplete PBPK models.[4]

Thirdly, using *in vitro* anti-SARS-CoV-2 activity and drug exposure at the putative target site of action to determine the effective regimen *in vivo* is misleading.[6] Antiviral EC_{50} determined in culture media should be compared with *in vivo* free drug plasma concentrations, likely to be equal to free extracellular tissue concentrations. If assuming that cell accumulation is equivalent *in vivo* to *in vitro* studies, free lung concentrations that would result from the proposed regimen would be far below the *in vitro* EC_{50} values, questioning its clinical effectiveness. Given its complex tissue distribution, attempts to simulate lung hydroxychloroquine levels should be cautiously considered.[4]

Interestingly, one mechanistic PK/virological/QTc model developed to predict SARS-CoV-2 decline rate and QTc prolongation suggested that only elevated hydroxychloroquine regimens (>400 mg twice daily for ≥5 days) are predicted to rapidly decrease viral loads, reduce the infected patient proportion and shorten the treatment course, compared with routine regimens (≤400 mg daily).[7] Suboptimal regimens such as that of Lê *et al.*[1] have been predicted to be non-efficient, resulting in wasted time and resources.

In a randomized trial, hydroxychloroquine did not increase the probability of negating SARS-CoV-2 conversion, despite a higher-dose regimen (loading dose of 1200 mg daily for 3 days followed by maintenance dose of 800 mg daily for 2 weeks in mild-to-moderate patients and 3 weeks in severe patients).[8] The Recovery trial (NCT04381936) data monitoring committee recommended stopping enrolling patients to the hydroxychloroquine arm due to the absence of benefit based on the primary endpoint of 28 day mortality. Yet, the hydroxychloroquine regimen (loading dose of 2400 mg including initial 800 mg followed by 800, 400 and 400 mg administered 6, 12 and 24 h later, respectively, and maintenance dose of 400 mg/12 h for 9 days) was much higher than that recommended by Lê *et al.*[1] Therefore, consistent with the models and negative results from the released trials, studies investigating higher doses up to 600 mg twice daily have been launched such as the PATCH trial (NCT04329923). However, safety hazards have become likely when reinforcing hydroxychloroquine regimens, given SARS-CoV-2-infected patient conditions with advanced age, comorbidities, possible myocarditis and kidney injuries and drug–drug interactions.[9] Models suggested that doses >600 mg twice daily may prolong QTc intervals with consequences warranting safety considerations.[7] With a 400 mg loading dose followed by a 10 day 200 mg thrice daily course, toxic blood concentrations were reached despite normal renal function.[10] Unsurprisingly, side effects were also observed at therapeutic concentrations.

Since no safe and suitable regimen is expected, the synergistic azithromycin/hydroxychloroquine co-administration should be

rationally considered, allowing reduction of the minimum hydroxychloroquine concentration to negate SARS-CoV-2 load by 29-fold.[10] Lastly, the time at which hydroxychloroquine is initiated in the disease course is also another issue as highlighted by the difficulties in reaching intracellular steady-state in the predictive models.

To conclude, prediction of the effective hydroxychloroquine regimen to treat the SARS-CoV-2-infected patient is doomed due to uncertainties related to the lack of *in vitro* model reliability and EC_{50} pertinence and to the weakness of used PBPK models that did not mirror hydroxychloroquine PK complexity at the intracellular target level.

Transparency declarations

None to declare.

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