Response to Jia and Wang

Xu Liu¹,²#, Qi Liu¹,³#, Xueling Yao¹, Miao Zhang¹, Cheng Cui¹, Haiyan Li¹, Dongyang Liu¹*

1. Drug Clinical Trial Center, Peking University Third Hospital, Beijing, 100191, China.
2. Savaid Medical School, University of Chinese Academy of Sciences, Beijing, 101408, China.
3. Department of Orthopedics, Peking University Third Hospital, Beijing, 100191, China.

#: Xu Liu and Qi Liu contributed equally to the correspondence

*: Correspondence: Dongyang Liu, Drug Clinical Trial Center, Peking University Third Hospital, Beijing, China. (liudongyang@vip.sina.com)
Dear Editor,

Thank you for the opportunity to respond to the letter by Jia and Wang regarding our earlier publication[1].

We appreciate comments made by Jia and Wang, especially for recognizing our novel strategy of integrating in vitro activity and lung concentration of hydroxychloroquine (HCQ) using physiologically-based pharmacokinetic (PBPK) model to optimize dose regimen. The time between the determination of anti-SARS-Cov-2 activity of HCQ in vitro to the recommendation of dose regimens of HCQ and chloroquine (CQ) using PBPK simulations were less than one week, and our clinicians almost immediately used these recommended human doses to evaluate its efficacy and safety in COVID-19 patients in China (ChiCTR2000029899). This would be extremely difficult without PBPK models.

We agree with Jia and Wang that “application of PBPK…must rely on rigorous pharmacokinetic mechanism and reasonable assumption”. We declared assumptions and limitations of the model, and indicated that future studies are underway to update the models[1].

The comment “The target tissue (lung) concentration of HCQ was overestimated and mismatched the in vitro activity (EC$_{50}$)” suggests that Jia and Wang may not carefully read or understand our approach and assumptions presented in Yao paper. We described HCQ dose regimen optimization in method section as “In a recent clinical trial 500 mg of chloroquine phosphate given twice daily was shown to be effective on study day 5 ($R_{LTEC}$, day5). This dosing regimen for chloroquine was used as the target for dose optimization for hydroxychloroquine”. That means although we calculated $R_{LTEC}$ for each compound (CQ and HCQ), we ultimately used relative potency between the two compounds to facilitate HCQ’s dosing recommendations rather than to judge if HCQ is effective or not. Different from conventional method that predicts clinical efficacy based on in vitro and in vivo data of the same compound, our approach heavily relied on emerging clinical antiviral effect by CQ (CQ was reported to be effective in 22 COVID-19 patients, which was released in clinical trial website and published later) [2-4]. Even for conventional method, “mismatching” in vivo with in vitro data has been widely applied in drug development to understand uncertainty of predicting in vivo efficacy/safety. Same concept has long been employed by industry and global regulators to predict clinical drug-drug interactions by using different in vivo exposure measures for different interaction mechanisms. A recent analysis by Jansson-Löfmark et al[5] demonstrated a wide range of the ratios of unbound trough concentration in plasma to in vivo
vitro potency for 164 marketed drugs across different indications. As such, we suspect anyone can confidently claim a drug’s in vivo efficacy based on in vitro data BEFORE drug efficacy is determined clinically (Otherwise, we would either skip or significantly shorten Phase 2 clinical trials in today’s drug development).

We agree with Jia and Wang that “in vitro activity was significantly affected by experimental factors”. Unfortunately, our group was one of the first reporting EC₅₀ of HCQ against SARS-Cov-2[1]. Had we known other groups’ findings at the time we did our analyses, we would have considered them in our analyses, e.g., by conducting sensitivity analyses or using average data.

Finally, we would like to reiterate our response to an earlier letter to the editor: “Although one can employ modeling and pharmacology concepts to predict the likelihood of clinical efficacy from in vitro data, given the inherent limitations of ANY modeling approach and assumptions being made, in vitro efficacy can only be ultimately confirmed through clinical trials. To this end, any modeling analysis has to fit-for-purpose.”[6].
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Conflict of Interest

Dongyang Liu has a patent Anti-microbial infection pharmaceutical composition and its application pending. All other authors have no conflict of interest to disclose.
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