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Correspondence

SARS-CoV-2 infection among healthcare workers in India: Limitations of the case-control investigation

Sir,

We read with interest the article by Chatterjee *et al*[1]. This is a commendable effort from the authors in very difficult times. The main argument for the efficacy of hydroxychloroquine (HCQ) was based on a multivariate analysis that demonstrated that intake of 4-5 maintenance doses independently imparted a protective effect [adjusted odds ratio (AOR): 0.44; confidence interval (CI): 0.22-0.88][1]. No other adjustments (*e.g*., propensity scoring, inverse probability of weighting) have been applied for the potential biases (*e.g*., limited matching) and thus the quoted treatment effects may be unreliable[2]. The authors consider this protective effect as a sign of efficacy. Paradoxically, healthcare workers exposed to 2-3 maintenance doses of HCQ have an increased risk for SARS-CoV-2 infection - AOR of 2.34 (CI: 1.23-4.83). The authors ascribe this detrimental effect to 'risk homoeostasis'[1].

In both new drug development and repurposing, a dose-response relationship is considered a significant proof of concept[3]. Visual inspection of the dose-response figure in the study suggests that a parabolic relationship may be appropriate[1]. The authors demonstrated a relationship by fitting a linear trend line to the HCQ data.

In the context of the study, the dose-response relationship may be related to the increasing number of maintenance doses (≥4-5 doses) or increasing number of weeks (≥4-5 wk with weekly dosing). The increasing number of maintenance doses may be related to an improved response if it is associated with an increase in a pharmacokinetic (PK) parameter that correlates with efficacy [such as area under the curve (AUC), concentration maximum, concentration minimum, steady state, time above threshold, *etc*.). This can happen when the drug accumulates with repeated dosing (*i.e.,* follows non-linear kinetics). A dose-response relationship with increased duration may happen when there is a delayed pharmacodynamic (PD) or chronopharmacologic effect (*e.g*., need for downstream transcription and remodelling) before clinical response[3]. No evidence is provided either for HCQ accumulation with a weekly dosing regimen or for a delayed PD effect. The efficacy with 4-5 doses appears to be an incidental finding with no scientific or biologic basis.

In this study, safety is assessed by comparing adverse drug reactions between cases and controls (not between HCQ and no HCQ). Based on the findings, there does not appear to be a drug-disease interaction, *i.e.,* no difference in reactions between cases and controls. In the light of the risk homoeostasis, should the ICMR revisit its advisory[1] of three maintenance doses for household contacts (who are likely not using any personal protective equipment) of a laboratory-confirmed case in the post-exposure prophylaxis setting? Given all the limitations of a case-control study, it would be wise to await the outcome of randomized clinical trials and other data before making any changes to their advisory.

The lack of a drug-disease interaction remains a meaningful conclusion from the study.

***Conflicts of Interest*:** The second author (NK) owns equity in F. Hoffmann-La Roche, a pharmaceutical company developing drugs for the treatment of COVID-19.

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