



Correspondence

Hydroxychloroquine for prophylaxis in COVID-19: Need to revisit dosing regimen

Sir,

We read with interest the case-control study by Chatterjee *et al*¹ investigating the risks and protective factors against SARS-CoV-2 infection among healthcare workers (HCWs) in India and would like to put forth our comments and an important suggestion.

During a pandemic, HCWs are on the front lines delivering care to patients and playing pivotal role in limiting morbidity and mortality of the population. It is critical that these workers be protected from acquiring or transmitting infection in and outside the hospital to restrict further spread of the disease. In earlier pandemics, prophylaxis of HCWs has been suggested as an important part of public health efforts for minimizing pandemic burden and its socio-economic disruption². Approaches to protect HCWs include vaccination, drugs, use of personal protective equipment and adherence to other infection control practices. In the absence of vaccination till date, agents with antiviral activities are being aggressively evaluated for prophylactic action against SARS-CoV-2. In one *in vitro* study, hydroxychloroquine (HCQ) exhibited good anti-SARS-CoV-2 activity. Interestingly, in this study, the researchers also found that HCQ had prophylactic action against SARS-CoV-2 by adding the drug prior to the viral challenge³. It was also noted that the half-maximal effective concentration (EC_{50}) of HCQ decreased with longer incubation times, suggesting that a longer incubation period may provide more time for the drug to accumulate to higher intracellular concentrations and ultimately exhibit a better antiviral effect. This could also be the reason behind the observation in the study by Chatterjee *et al*¹, in which the number of maintenance doses taken by HCWs following the intake of a loading dose revealed a protective dose-response relationship. Consumption of ≥ 4 maintenance doses was associated with a significant decline in the risk of SARS-CoV-2 infection among

the study participants while ≥ 6 doses had a remarkably high ($>80\%$) protective effect.

Advisory by the National Task force for COVID-19 in India constituted by the Indian Council of Medical Research (ICMR released on March 23, 2020; and revised on May 22, 2020) recommends the use of HCQ as prophylaxis against SARS-CoV-2 infection in asymptomatic HCWs and frontline workers involved in COVID-19 related activities as well as asymptomatic household contacts of laboratory confirmed cases⁴. The recommended regimen is 400 mg twice a day on day one, followed by 400 mg once weekly for next three or seven weeks depending on the category. In the revised advisory, experts have taken cognisance of the safety and tolerability of HCQ, and recommended its use beyond eight weeks with strict monitoring of clinical and ECG parameters. In line with this advisory, the 7th version of the Temporary Methodical Recommendations by the Russian task force for COVID-19 released on June 3, 2020, also recommended HCQ in similar regimen for prophylaxis against COVID-19⁵.

The current study by Chatterjee *et al*¹ provided another important piece of evidence in the ongoing evaluation of HCQ as a prophylactic agent against SARS-CoV-2. In addition, investigations from government hospitals in New Delhi indicated that among HCWs involved in COVID-19 care, those on HCQ prophylaxis were less likely to develop SARS-CoV-2 infection, compared to those who were not on it⁴. Another study from a tertiary care centre at Kolkata, recently posted on a pre-print server, reported that among 106 HCWs, HCQ consumption as pre-exposure prophylaxis was associated with a significant reduction in risk of SARS-CoV-2 infection⁶. None of the HCQ users reported any serious adverse effects. A cross-sectional questionnaire-based study among 166 HCWs involved in COVID-19-related services across India reported that use of HCQ

for pre-exposure prophylaxis was associated with a relatively higher incidence of adverse effects⁷. However, majority were gastrointestinal side-effects and self-limiting, with no serious cardiovascular events. The gastrointestinal adverse effects can often be lessened by taking HCQ with food, as also mentioned in the ICMR advisory⁴.

In the context of using HCQ for short-term in COVID-19 (treatment or prophylaxis), it is critical to understand the relationship between dosing and concentration profiles. HCQ has rapid absorption after oral administration, with a large total apparent volume of distribution attributed to tissue uptake by ion trapping rather than tissue binding. Consequently, the terminal phase elimination half-life of HCQ has been estimated to be about 54 days⁸. Thus, the initial blood concentration profile of HCQ when used in acute condition is determined mainly by distribution processes and not by drug elimination. In such conditions, the treatment regimens are designed to include an initial loading dose to fill the body so that concentrations that would take weeks to achieve, are achieved as soon as safely possible. However, the loading dose will not maintain the target concentration unless an appropriate maintenance dose is also used. Probably based on this pharmacokinetic understanding, the ICMR Task Force recommended the initial loading dose of 400 mg twice on day one followed by maintenance dose of 400 mg once weekly. However, we suggest that the regimen be changed to 400 mg twice weekly (instead of once a week) taken three days apart. This will lead to a quick achievement of the 4-6 maintenance doses shown to impart protection against SARS-CoV-2 infection without adversely affecting the safety. This is critical because of the potential to protect the HCWs in 2-3 wk instead of 4-6 wk currently; and with the clinical experience and pharmacokinetic profile of HCQ, this regimen should be well-tolerated. This is also reflected in the fact that several ongoing large clinical trials evaluating HCQ for prophylaxis in HCWs such as the COPCOV study (NCT04303507) and the PATCH study (NCT04329923) are designed to dose HCQ daily as maintenance doses following the loading dose.

Confusion over cardiac safety of HCQ has hampered several ongoing clinical trials preventing and treating in COVID-19 infections. While conduction disorders are considered to be rare, but known adverse effect of HCQ; it has been suggested that HCQ being a quinidine derivative has anti-arrhythmic effects

and potential to prevent high-risk arrhythmias such as supra-ventricular and ventricular ectopies⁹. These remain under-evaluated though recognised as early as in the 1950s including a study from India^{10,11}. More recently, in a retrospective cohort of 1,646 patients with systemic lupus erythematosus, it was seen that HCQ use was associated with a substantial reduced risk of incident atrial fibrillation¹². Thus, the pro-arrhythmic and anti-arrhythmic effects of HCQ have been poorly characterized and arrhythmia risks have been inferred from QT prolongation rather than observed. Overall, majority of evidence for currently approved regimens is reassuring and for healthy people who are not taking regular medications which prolong the QT interval, there should be no concerns about cardiotoxicity¹³.

In summary, we concur that use of HCQ as a prophylactic agent in HCWs is a prudent approach considering the risk-benefit analysis¹⁴. The study by Chatterjee *et al*¹ is an important step in understanding the effects of HCQ as a prophylactic agent against COVID-19 and more such studies must be conducted. Our suggested regimen of HCQ can lead to quicker prophylactic effect in HCWs and needs to be evaluated in clinical trials.

Conflicts of Interest: The first (AP) and third (RTM) authors are employees of Ipca Laboratories Ltd., India, and are involved in clinical research on hydroxychloroquine. The second author (SB) declares no conflicts of interest.

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Received July 17, 2020

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