Received: 12 June 2020 | Accepted: 13 June 2020

DOI: 10.1111/dth.13857

DERMATOLOGIC THERAPY WILEY

LETTER

Hydroxychloroquine for COVID-19: Myths vs facts

Dear Editor,

Hydroxychloroquine is the β-hydroxylated analogue of chloroquine which has garnered unprecedented attention as a potential drug for COVID-19, following preliminary reports on its in vitro activity against the virus.

Hydroxychloroquine (half-maximal effective concentration [EC50] = 0.72 μM) was found to be more potent than chloroquine (EC50 = 5.47 μM) in vitro against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] By contrast, Liu et al found a lower EC50 for hydroxychloroquine with a similar 50% cytotoxic concentration for both the drugs.[2]

A randomized controlled trial from China evaluating hydroxychloroquine 400 mg/day (200 mg BD) from day 1 to 5 for mild COVID-19, reported faster resolution of cough and fever in the hydroxychloroquine arm.[3] The largest observational study of Million et al, with a sample size of 1061 patients, demonstrated good virological and clinical outcomes with hydroxychloroquine therapy.[4] An observational prospective study in 334 health care workers at AIIMS New Delhi, out of which 248 took hydroxychloroquine prophylaxis (median 6 weeks of follow-up) also showed lower incidence of SARS-CoV-2 infection in those taking it.[5]

Based on the EC50 values, therapeutic dose of hydroxychloroquine can be calculated. A physiologically based pharmacokinetic modeling study recommended a loading dose of hydroxychloroquine 400 mg PO BD, followed by 200 mg BD for 4 days for the treatment of COVID-19.[1] Nonetheless, this dosing regimen should be interpreted with caution since a 95% confidence interval for the estimate of the EC50 was not provided. The Indian Council of Medical Research has recommended chemoprophylaxis with hydroxychloroquine (400 mg twice on day 1, and then 400 mg once a week thereafter) for asymptomatic frontline workers and household contacts of confirmed cases.[5] The dosing recommendations in the special population, such as pregnant women, obese patients, pediatric population or patients with systemic comorbidities diagnosed with COVID-19 are unavailable.

A recent study by Tang et al reported that hydroxychloroquine did not lead to higher negative conversion rates, but had reduced clinical symptoms through its anti-inflammatory properties and recovery of lymphopenia.[6] Similarly, Molina et al,[7] Mahevas et al[8] have shown negative results with hydroxychloroquine treatment.

In a cross-sectional study carried out among 140 doctors taking hydroxychloroquine prophylaxis for COVID-19, 44 participants (31%) reported adverse effects; most frequent symptoms being headache followed by nausea, dizziness, abdominal cramps, and diarrhea. Hypoglycemia was seen in three participants with diabetes.[9] Gastrointestinal effect appears to be dose dependent and most often occurs with loading doses ≥800 mg. Across the world, there have been several reports of overdoses in people self-medicating with hydroxychloroquine during the current pandemic.

From the safety point of view, short-term hydroxychloroquine treatment has been considered safe, even in pregnancy. World Health Organization has reinitiated the hydroxychloroquine arm of its solidarity trial which was previously suspended after a study published in the Lancet raising warnings about the drug's safety.[10] The study is now retracted.

The incidence of QTc prolongation in the setting of hydroxychloroquine use is largely limited to case reports of chronic use. It is highly dependent on baseline electrocardiogram findings; risk being exacerbated with concomitant QTc-prolonging medications. Considering that COVID-19 itself can have cardiac manifestations, periodic QT interval should be monitored in COVID-19 patients on hydroxychloroquine.

Although some of the clinical studies have shown a good effectiveness of hydroxychloroquine in achieving virological and clinical endpoints in patients with COVID-19, they have had some major limitations with high risk of bias, varied dosing protocols and short treatment periods. Hence, the factual clinical benefit of hydroxychloroquine in COVID-19 is still elusive. Finally, pharmacovigilance on its potentially serious adverse effects is also required.

ACKNOWLEDGMENTS

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

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