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Comment on: COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression

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Sir,

We read with interest the paper by Zhou *et al.*[1] proposing the use of hydroxychloroquine (HCQ) for therapeutic and prophylactic purposes against SARS-CoV-2 infection.[1] Zhou *et al.*[1] pointed out that HCQ is effective in inhibiting the binding of the virus to and the entry of the virus into host cells. Zhou *et al.*[1] also highlighted that HCQ is immunomodulatory and inhibits the Th1 response, thus preventing a cytokine storm from happening in COVID-19 patients. They concluded that HCQ is an attractive candidate for therapeutic and prophylactic use given its antiviral activity, immunomodulatory function and excellent safety record. We here contend that, although HCQ may be useful as a therapeutic agent, caution should be exercised in using HCQ as a prophylactic agent.

The use of HCQ as a prophylactic agent may increase the initial viral load, should prophylaxis fail and infection occur, due to the suppression of the Th1 response by HCQ. The result from a randomized trial on the effect of HCQ in decreasing immune activation in HIV patients indicated that administration of HCQ increased HIV viral load.[2] This increase may be due to the immunomodulatory effect of HCQ. HCQ is capable of inhibiting the cytokine secretion of monocytes,[3] antigen presentation of plasmacytoid dendritic cells (pDCs)[4] and activation of CD4 T cells.[3] These functions may result in the weakening of innate immunity and a delay in the activation of T cells and B cells and thus in the mounting of an effective antiviral response. An effective immune response is crucial to virus clearance. A clinical observation made in the SARS epidemic in 2003 indicated that a high initial viral load is associated with adverse outcome.[5] The use of HCQ as a prophylactic agent for the general public may prevent infection. However, HCQ may also lead to a delay in the mounting of the initial antiviral response and an increase in the initial viral load, thus increasing the risk of an adverse clinical outcome should a healthy individual be infected.

Apart from the risk of increasing the initial viral load and subsequent adverse clinical outcome, toxicity may also be a concern in using HCQ as a prophylactic agent against SARS-CoV-2 infection. Although the common side effects of HCQ at a prophylactic dose against malaria, such as pruritus, headache and gastrointestinal upset, are generally mild, HCQ interacts with many commonly used medicines and may lead to serious side effects.[6] HCQ was reported to increase the risk of neuropsychiatric adverse events when used with the antivirals indinavir, nelfinavir and ritonavir (one of the proposed medicines against SARS-CoV-2 infection) or aminoglycoside antibiotics at doses used for treating rheumatic diseases.[7] Interaction between HCQ and a QT-prolonging agent or a QT-shortening agent (digoxin) also increases the risk of arrhythmias.[8] In addition, with long plasma half-lives [1300 h for HCQ and 900 h for chloroquine (CQ)], HCQ and CQ may accumulate in the body and be passed to babies via breast milk, although no permanent harm has been reported so far in humans.[6] With all these concerns, the safe and effective prophylactic dosage and the eligibility criteria would be the critical parameters to be determined and considered in the decision-making process of adopting HCQ for prophylaxis. It was suggested that doses below 6.5 mg/kg/day for HCQ and 3 mg/kg/day for CQ are well tolerated by patients in general.[7] A double-blinded, randomized clinical trial of CQ was launched recently to investigate the protective effect of CQ in a healthcare setting against COVID-19 infection.[9] A similar study should be conducted to determine the protective effect of HCQ.

Given that a vaccine against SARS-CoV-2 has yet to be developed, prescribing HCQ for prophylaxis may be a favourable option for protecting the healthy population from infection, slowing the pandemic and reducing the pressure put on the healthcare system. However, given the risks of worsening prognosis and the possible adverse effects on certain population groups, caution should be exercised in using HCQ for prophylaxis. Further research through clinical trials is required to identify: (i) the effect of HCQ on initial viral load; (ii) the individuals who may benefit or may be harmed; and (iii) the optimal dose and duration. The information obtained will help in the design of a prophylactic regimen with adequate protection without compromising the immune system.

Transparency declarations

None to declare.

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