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## Is Hydroxychloroquine a Possible Postexposure Prophylaxis Drug to Limit the Transmission to Healthcare Workers Exposed to Coronavirus Disease 2019?

TO THE EDITOR—We read with great interest the study by Yao et al [1] reporting that hydroxychloroquine has better antiviral activity than chloroquine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is associated

with a high lung-to-plasma concentration ratio and immunomodulatory effects. Moreover, the authors highlighted that hydroxychloroquine half maximal effective concentration values “tended to decrease with longer incubation times” and that, in the simulation model, the lung trough concentrations were still above the target concentration on day 10 after a 5-day course of hydroxychloroquine.

Besides household contacts, SARS-CoV-2 can be acquired in hospital settings, with healthcare workers (HCWs) attending at invasive procedures on the respiratory tract (ie, intubation, endotracheal tube aspiration, or bronchoscopy) at the highest risk. Accidentally infected HCWs represent an important source of infection during the period that they are asymptomatic or presymptomatic, as they can transmit the virus to household contacts and to patients seeking medical care for reasons unrelated to SARS-CoV-2 infection. For these reasons, we suggest preventive strategies for those accidentally exposed to SARS-CoV-2 such as preexposure or postexposure prophylaxis to avoid viral transmission, as largely accepted for those exposed to other viral agents such as human immunodeficiency virus (HIV) [2].

Chloroquine and hydroxychloroquine are able to inhibit replication at early stages of viral infection, increasing endosomal pH at the time of virus/cell fusion, as well as impairing the glycosylation of cellular receptors of many viruses including coronavirus [3]. In contrast, no similar effect on early phases of coronavirus infection has been reported for other drugs proposed for SARS-CoV-2 treatment, which are able to interfere only after cell infection, affecting protease cleavage (protease inhibitors) or viral genome replication (remdesivir or ribavirin). These effects of chloroquine on early phases of viral replication permit the attenuation of vertical transmission in an animal model of Zika virus infection, significantly reducing brain viral load, and make cells refractory to SARS-CoV infection in an in vitro model [4, 5].

Hydroxychloroquine, the HIV protease inhibitors (particularly lopinavir), ribavirin, and remdesivir are the most promising drugs proposed for coronavirus disease 2019 (COVID-19) treatment, but currently no drug has been proposed for postexposure or preexposure prophylaxis for those accidentally exposed to SARS-CoV-2 [6].

On the basis of these investigations, we believe that hydroxychloroquine can be effective in preventing respiratory tract invasion in HCWs exposed to SARS-CoV-2 and that hydroxychloroquine administration as a prophylactic agent could be particularly useful for HCWs attending to high-risk procedures on the respiratory tract in COVID-19 patients. Hydroxychloroquine's effectiveness profile, its ability to inhibit lung viral replication for a 10-day period after only a 5-day cycle of therapy, and the large amounts of knowledge in term of safety deriving from its use for malaria prophylaxis and rheumatologic diseases lead us to recommend its preexposure or postexposure use for those performing procedures at high risk of viral diffusion in patients with COVID-19 pneumonia.

## Note

**Potential conflicts of interest.** The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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## Could Chloroquine / Hydroxychloroquine Be Harmful in Coronavirus Disease 2019 (COVID-19) Treatment?

TO THE EDITOR—We read with great interest the article by Yao et al [1] reporting in vitro activity of hydroxychloroquine (HCQ) in inhibiting severe acute respiratory syndrome coronavirus (SARS-CoV)-2. The authors suggest, on an in vitro experiment results basis, an alternative HCQ dose regimen for future clinical trials while several clinical trials on chloroquine (CQ)- and HCQ-based regimens for coronavirus disease 2019 (COVID-19) are still ongoing [1].

Taking into account the antiviral in vitro effect, CQ has been considered to be a valuable candidate, alone or in combination with lopinavir, for further testing in animal models or direct off-label use for coronavirus-related diseases [2]. Unfortunately, CQ did not show efficacy in inhibiting viral replication in a mouse SARS-CoV model [3]. Nevertheless, by considering its anti-inflammatory properties, it has been postulated that CQ/HCQ may have some effect on SARS [3, 4]—in particular, by inhibiting the production of proinflammatory cytokines (tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ], interleukin [IL] 6) and consequently blocking the subsequent cascade of events which

leads to acute respiratory distress syndrome (ARDS) [4].

Due to the aforementioned evidence, the negligible cost, its large worldwide use, and the known safety profile, CQ/HCQ has been considered as a potentially useful drug in patients affected by SARS-CoV-2 [1, 5, 6].

Despite in vitro activity in inhibiting the growth of several viruses, to date no acute virus infection has been successfully treated by CQ/HCQ [7]. Moreover, CQ showed a paradoxical effect when administered in treating Chikungunya virus infection: in a prophylactic study in a nonhuman primate model the infection was enhanced by CQ treatment; in a curative study in a human cohort, CQ did not affect the acute phase of the disease, in term of symptoms and viral clearance, but the chronic complications of Chikungunya were more frequent in the treated group compared with the control group. This paradoxical effect has been explained by a delay in immune adaptive response to the virus provoked by CQ administration that could nullify the antiviral activity shown in vitro [8].

The pathogenesis of SARS-CoV-2 is still unknown; however, preliminary studies have shown differences with respect to SARS pathogenesis. In particular, an initial increase in the secretion of T helper (Th)-2 cytokines (IL-4, IL-10), which suppress inflammation [9], has been shown and which could balance the Th-1 cell hyper-response that is supposed to lead to ARDS in patients affected by SARS [4].

It has been demonstrated that CQ inhibits T-cell proliferation by reducing IL-2 production and IL-2 responsiveness [10], and it seems that IL-2 plays a crucial role in “priming” T cells for Th-2 cell differentiation [11]. Therefore, if Th-2 cell response could play a role in suppressing inflammation in SARS-CoV-2 infection [9], it cannot be excluded that CQ/HCQ negatively impacts the immune response to the virus.

In conclusion:

- Despite the in vivo antiviral activity, no acute virus infection has been successfully treated by CQ/HCQ in humans [7];
- CQ/HCQ did not show any anti-SARS-CoV effect in an in vivo model [3]; and
- The pathogenesis of COVID-19 is still unknown; therefore, the immune effect provoked by CQ/HCQ administration in patients with COVID-19 is unpredictable.

For the aforementioned points, CQ/HCQ not only could be useless in treating patients with COVID-19 but may even be harmful, as it was for Chikungunya virus infection. Hence, despite the proven in vitro efficacy, before publication of clinical trial results and/or further clarification about COVID-19 pathogenesis clinicians should use CQ/HCQ cautiously.

## Note

**Potential conflicts of interest.** The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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