

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 α [TNF- α], 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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