Could chloroquine /hydroxychloroquine be harmful in Coronavirus Disease 2019 (COVID-19) treatment?

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TO THE EDITOR-

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

Taking into account the antiviral in vitro effect, CQ has been considered as 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 pro-inflammatory cytokines (TNFα, IL6) and consequently blocking the subsequent cascade of events which lead to ARDS [4].

Due to the aforementioned evidences, the negligible cost, the large worldwide use and the know safety profile, CQ/HCQ has been considered as a potential 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 non-human primate model the infection was enhanced by CQ treatment; in a curative study on 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 with respect to 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 showed in vitro [8].

As a matter of fact the pathogenesis of SARS-CoV-2 is still unknown, however preliminary studies show differences with respect to SARS pathogenesis: in particular, it has been detected an initial increased secretion of T helper (TH)-2 cytokines (IL4, IL10) which suppress inflammation [9] and that could balance the TH-1 cell iper-response which is supposed to lead to ARDS in patients affected by SARS [4].

It has been demonstrated that CQ inhibits T cells proliferation by reducing IL2 production and IL2 responsiveness [10] and it seems that IL2 plays a crucial role in “priming” T cells for TH-2 differentiation [11]. Thereafter if TH-2 response could play a role in suppressing inflammation in SARS-CoV-2 infection [9], it cannot be excluded that CQ/HCQ negatively impact on 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 human [7]

- CQ/HCQ did not show any anti SARS-CoV effect on in-vivo model [3]

- The pathogenesis of COVID-19 is still unknown; therefore the immune effect provoked by CQ/HCQ administration in COVID-19 patients is unpredictable.

For the aforementioned points, CQ/HCQ not only could be useless in treating COVID-19 patients but even harmful, as it was for Chikungunya Virus infection. Hence, nevertheless the proved in vitro efficacy, before clinical trials results publication and/or further clarification about COVID-19 pathogenesis, clinicians should use it cautionally.

Conflict of interest: None

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