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Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and treatment?

To the Editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread all over the world. While awaiting a vaccine, we need effective drugs to treat or, even better, prevent coronavirus disease-19 (COVID-19). Two drugs classically used by dermatologists are being examined in the fight against COVID-19: hydroxychloroquine (HCQ), and, very recently, ivermectin. We hypothesize that HCQ and ivermectin may show a consequential and synergistic action if administered simultaneously both for chemoprophylaxis and treatment of COVID-19.

HCQ is an antimalarial drug, an analog of chloroquine (CQ), considered as an immunomodulator rather than immunosuppressant.[1] HCQ and CQ inhibit SARS-CoV-2 in vitro, with HCQ found to be more potent than chloroquine (CQ).[2] HCQ has shown antiviral effects at both preinfection and postinfection stages.[1] Indeed, HCQ could interfere with the glycosylation of angiotensin-converting enzyme 2, thereby reducing the binding efficiency between angiotensin-converting enzyme 2 on host cells and the SARS-CoV-2 spike protein. Moreover, HCQ could be able to block virus fusion with the host cell through the inhibition of protease activity in cleaving coronavirus surface spike proteins.[1]

Significantly, HCQ contributes to the suppression of the "cytokine storm" responsible for the disease progression to acute respiratory distress syndrome by several mechanisms, including the reduction of T-cell activation and differentiation as well as decreased production of cytokines by T cells and B cells. Several studies in vivo are underway to assess HCQ effectiveness on SARS-CoV-2 infection, with promising preliminary results.

Ivermectin is an antiparasitic drug, classically prescribed at our dermatologic clinic as first-line treatment for cutaneous larva migrans. Interestingly, it also displayed an antiviral activity. Indeed, ivermectin acts as a specific inhibitor of importin-α/β–mediated nuclear import. Thus, by impacting on importin-α/β–dependent nuclear transport of viral proteins, ivermectin suppresses the replication of several RNA viruses, including HIV, chikungunya virus, and yellow fever virus.[3]

Very recently, Caly et al[4] demonstrated antiviral action of ivermectin against the SARS-CoV-2 clinical isolate in vitro, with a single dose of the drug able to control viral replication within 24 to 48 hours. The authors hypothesized that such results were likely due to the inhibition of importin-α/β1–mediated nuclear import of viral proteins, as shown for other RNA viruses.[4] However, no study with ivermectin in vivo has been conducted.

Based on all such evidence, we hypothesize that HCQ and ivermectin could act in a consequential and synergistic manner. Indeed, HCQ would behave as a first-level barrier by inhibiting the entry of the virus into the host cell, while ivermectin could reduce viral replication if the virus did get in, strengthening HCQ antiviral effects. HCQ is cheap to produce and safe if monitored properly. Ivermectin seems to be safe and well tolerated, with no serious drug-related adverse events.[5] Moreover, the 2 drugs do not seem to have a between-drug interaction. However, no in vitro or in vivo studies have been conducted on the combined effect of HCQ and ivermectin on SARS-CoV-2 infection. Ours is only a hypothesis and a suggestion, but if not now, when should researchers share ideas?

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