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Opinion Article

Plausible Pharmacological Interpretation of Hydroxychloroquine Ineffectiveness for Treatment of COVID-19 in Hospitalized Patients

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Abstract

The COVID-19 pandemic is an ongoing global pandemic of coronavirus disease 2019 as an atypical type of viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2). Many potential treatments and preventive options are currently being investigated against this disease. Hydroxychloroquine (HCQ) and its related parent compound; chloroquine (CQ), were among the monotherapies that were investigated early during this pandemic. Recently, the COVID-19 Treatment Guidelines Panel of the NIH recommended against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 in hospitalized patients based on the results of the many relevant clinical trials conducted. This article provides plausible interpretation of their ineffectiveness from a pharmacological point of view, based on the pharmacodynamics and pharmacokinetic profile of these drugs

Keywords: Chloroquine; COVID-19; Hydroxychloroquine; Perspective; Pharmacokinetics; Pharmacodynamics.

Introduction

Two structurally similar antimalarial drugs; chloroquine (CQ) and hydroxychloroquine (HCQ), are 4-aminoquinolines that were found to inhibit infection of cells by SARS-CoV-2 in vitro [1-4]. Early on during the course of COVID-19 pandemic, these drugs were believed to have potential therapeutic and/or preventive value in COVID-19. Preliminary clinical data showed that CQ was superior to placebo in reducing COVID-19 pneumonia exacerbation, duration of illness, and duration of viral clearance [5]. HCQ was also suggested to be equally effective as CQ in managing COVID-19 pneumonia [6]. Several months ago, there was insufficient and often conflicting evidence on the benefits of using HCQ or CQ to treat COVID-19 disease [7-9]. Then, the COVID-19 Treatment Guidelines Panel of the NIH recommended against the use of CQ or HCQ for the treatment of COVID-19 in hospitalized patients based on the results of the many relevant clinical trials conducted [10]. In non-hospitalized patients, the Panel recommends against the use of CQ or HCQ for the treatment of COVID-19, except in a clinical trial. This article provides a plausible interpretation for the ineffectiveness of HCQ and CQ as monotherapies in treatment of hospitalized COVID-19 patients from a pharmacological point of view which could scientifically explain and justify the recommendation of the COVID-19 Treatment Guidelines Panel of the NIH against the use of CQ or HCQ for the treatment of COVID-19 in hospitalized patients.

Pharmacokinetics of HCQ and CQ:

The pharmacokinetics and the safety-related aspects of both HQ and CQ are complex and yet to be completely understood. The unknown dose-response relationships of these drugs and the lack of definitions of the minimum dose needed for clinical efficacy

and what doses are toxic pose challenges to clinical practice [11]. Nevertheless, both drugs were reported to have a slow onset of action [12,13]. It was also reported that it might take weeks to reach the maximal activity of both HCQ and CQ with prolonged efficacy even after drug discontinuation which could be explained by the extensive volume of distribution and long/variable plasma elimination half-lives of both drugs and their dealkylated metabolites [14,15]. Such long elimination half-life of these drugs was reported by the CDC to be 30–45 days which justifies their weekly dosing when used in the prevention of malaria, and a short 48-hour treatment course when used to treat malaria [16]. Regarding the slow onset of these drugs, it was hypothesized that dose-loading over a short time may quickly increase concentrations to effective levels in the tissues, and thereby shorten the time to onset of effect [17]. Nevertheless, such pharmacokinetic profile of these drugs may partially explain their ineffectiveness in treating hospitalized patients with COVID-19 disease reported to have a rapid progression rate.

Although there are some potentially favorable pharmacodynamic effects of HCQ and CQ in COVID-19 disease, there are other potentially unfavorable pharmacodynamic effects of these drugs that could also partially explain their ineffectiveness for treatment of COVID-19 patients. These pharmacodynamics effects are summarized as follow:

Potentially Favorable Pharmacodynamic Effects of HCQ and CQ in COVID-19 Disease.

- Increasing the pH of the intracellular endosome in host cells: HCQ and CQ have similar mechanisms of action. As other antimalarial drugs, they are lipophilic weak bases that easily pass plasma membranes to increase the pH of the intracellular endosome in host cells [18]. Increasing evidence suggests that the entry, replication and infection processes of several viruses are highly dependent on endosomal-lysosomal acidification. The change in the pH of the endosome caused by HCQ and CQ is believed to prevent viral entry, transport and post-entry events inhibiting autophagosome-lysosome fusion and inactivating enzymes that viruses require for replication [19]. The immunomodulatory activity of both HCQ and CQ was suggested to occur as a result of inhibiting the acidification of endosomes which is required for toll-like receptor (TLR) activation and/or a result of direct interaction with nucleic acids and consequently causing structural modifications of the TLR ligand preventing TLR7 and TLR9 from binding their ligands (RNA and DNA, respectively) leads to inhibition of autophagy and immune activation of different cell types, which inhibits cytokine production and modulates CD154 expression on T cells [20-23]. So, preventing TLR9 from binding to its ligand by HCQ and CQ is a favorable effect and is mainly responsible for their immunomodulatory effects against the cytokine storm/ autoimmune-like reaction. Similar to the effect of TLR9 on DNA-containing immune complexes in the blood, TLR7 receptors; as another intracellular receptors expressed in the endosome, may also sense self-derived RNA-containing immune complexes in the blood, which activate plasmacytoid dendritic cells (pDCs) leading to breaking the tolerance to self-nucleic acids, inducing proinflammatory cytokine production, and leading to autoimmune disease development [24,25]. HCQ and CQ can inhibit cytokine storm through inhibition of TLR7 and TLR7 signalling pathway activation in plasmacytoid dendritic cells (pDCs) and other immune antigen-presenting cells (APCs) triggered by cell debris during autoimmunity [11]. Therefore, the inhibitory effect of HCQ and CQ on TLR7 receptor function is also considered a favourable immunomodulatory effect.

- Interference of lysosomal activity: HCQ and CQ accumulate in lysosomes where they are suggested to increase the pH to prevent the activity of lysosomal enzymes.

- Changing of lysosomal pH by HCQ and CQ may inhibit cathepsins proteases causing the spike protein of SARS-COV-2 to be cleaved into the autophagosome and prevents viral fusion and release of the viral RNA genome into the host cytoplasm to occur [6,26]. Interference of lysosomal activity can prevent major histocompatibility complex (MHC) class II-mediated autoantigen presentation, inhibit the function of lymphocytes, and have immunomodulatory or even anti-inflammatory effects [11].

- Affecting glycosylation of ACE-2 and binding to sialic Acids.

HCQ and CQ may affect glycosylation of ACE-2, the receptor that SARS-CoV-2 uses to enter cells [27,28] and bind readily to sialic acids that may be required for cell surface binding of SARS-CoV-229. Human coronavirus HCoV-O43 use sialic acids as receptors [30].

- Reduction of cellular mitogen-activated protein kinase (MAPK) activation.

CQ was hypothesised to inhibit virus replication through reduction of cellular mitogen-activated protein (MAPK) activation and alter M protein maturation and hence interfere with virion assembly and budding [27]. In the model of HCoV-229, CQ inhibition of this coronavirus was suggested to occur through this mechanism [31].

- Antithrombotic and vascular protective effect.

One final pharmacological activity of HCQ, which may be of value in treatment of covid-19 pneumonia considering the clinical data related to the pathophysiology of the disease, is the antithrombotic and vascular protective effect that is reported to be most relevant for patients with a secondary coagulopathy owing to systemic inflammation and in patients with primary antiphospholipid syndrome as an autoimmune disorder [32,33,34]. The mechanism that leads to the thromboprotective properties of antimalarial drugs remains unknown, some studies suggest that they may affect platelet aggregation or reduce the formation of antiphospholipid–

β2-glycoprotein I complexes to phospholipid bilayers and cells [35.36].

Potentially Unfavourable Pharmacodynamic Effects of HCQ and CQ in COVID-19 Disease.

Preventing TLR9 from binding to its ligand.

Although preventing TLR9 from binding to its ligand by HCQ and CQ is a favourable effect and is mainly responsible for their immunomodulatory effects against the cytokine storm/ autoimmune-like reaction, TLR9 activation plays an important role in the innate immune response. These receptors constitute the first line of defence against pathogens where they recognizes microbial DNA [37].

Preventing TLR7 from binding to its ligand.

Although preventing TLR7 from binding to its ligand by HCQ and CQ is a favourable effect and is partly responsible for their immunomodulatory effects against the cytokine storm/ autoimmune-like reaction, TLR7 receptors recognize ssRNA of viruses and play an important role in detection of infection and hence activation of the appropriate innate immune response [38-40]. Therefore, preventing TLR7 from binding to its ligand by HCQ and CQ may partly be considered an unfavourable pharmacodynamic effect of these drugs since it may not help effective viral clearance of SARS-CoV-2 as a ssRNA virus.

Neutralizing the acidic pH and/or causing structural changes in the Golgi apparatus.

As a result of neutralizing the acidic pH and/or structural changes in the Golgi apparatus, HCQ and CQ can deactivate several enzymes, like the glycosylating enzymes; glycosyl-transferases, which in turn inhibit glycosylation. Such inhibition of glycosylation results in the host developing adaptive immune response against the infection [41] while in COVID-19 disease suppressing the adaptive immune response temporarily and avoiding its interference with the innate immune response was recently reported to allow the innate immunity to more efficiently clear the virus [42].This is of particular importance since the adaptive immune response in COVID-19 patients was suggested to emerge before the peak viral load which causes delayed depletion of vulnerable pulmonary epithelial cells [42] and that the overlap between adaptive and innate immunity leads to incomplete clearance of the exposed cells, thereby providing a source of uninfected target cells for continued infection which can induce hyperactive immune responses or secondary complications with fatal outcomes [42,43].

Preventing the Sensing of Cytosolic DNA by Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes (cGAS-STING) Pathway.

HCQ and CQ were also suggested to prevent the sensing of cytosolic DNA by cyclic GMP-AMP Synthase-Stimulator of Interferon Genes (cGAS-STING) pathway which is a component of the innate immune system that favourably senses cytosolic DNA associated with tumorigenesis, viral infection, and invasion by some intracellular bacteria [44]. Therefore, the effect of HCQ and CQ on cGAS–STING pathway may also raise some concern as possible unfavourable pharmacodynamic effect of these medications.

The hypothesis of unfavourable pharmacodynamic actions of these drugs could be supported by the findings of a systematic review and meta-analysis of the results of completed RCTs which investigated the therapeutic value of HCQ in patients with COVID-19 disease. This study concluded that no benefit on viral clearance but a significant increase in mortality was observed with HCQ use compared to controls in patients with COVID-19 disease [45].

Finally, it is suggested that combined administration of HCO, having a more favourable dose-related toxicity profile than CQ, with an appropriate antiviral and antibacterial medications together with zinc may be of value in moderate disease (COVID-19 pneumonia), rather than severe COVID-19 pneumonia or critical cases of the disease, at a loading dose followed by intermediate maintenance doses for intermediate duration of administration. Zinc was demonstrated to inhibit coronavirus RdRp activity in vitro [46]. Also zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes. In light of the demonstrated antiviral activity of zinc and that HCQ was suggested to act as zinc ionophore blocking coronavirus replication [47], the combination of HCQ with an appropriate antiviral and antibacterial medications together with zinc could be promising to achieve additive or synergistic antiviral effects.

Conclusion

Given the witnessed rapid progression of the course of COVID-19 disease, the variable pharmacokinetic profiles of both HCQ and CQ, their reported slow onset of action, the pharmacological mechanisms of their immunomodulatory activity that is only effective during autoimmunity, and the possible unfavourable pharmacodynamic effects of these drugs on both TLR7, TLR9 and cGAS-STING pathway, all could explain the ineffectiveness of these drugs as individual interventions in hospitalized COVID-19 patients.

The potential therapeutic value of both HCQ and CQ as individual interventions in mild COVID-19 disease may also be questionable given the unfavourable pharmacodynamic effect of these drugs mediated through inhibition of TLR7 receptor function critical for activation of the appropriate innate immune response against ssRNA viruses that is utterly needed early in the course of the disease.

Combined administration of HCQ or CQ with appropriate antibacterial drug against respiratory diseases and antiviral drug against ssRNA viruses are suggested to counterbalance the possible unfavourable pharmacodynamic effects of these drugs on both TLR7 and cGAS-STING pathway. When combined with an appropriate antiviral and antibacterial medications and zinc, HCO,

with a more favourable dose-related toxicity profile than CQ, may be of value in moderate disease (COVID-19 pneumonia), rather than severe COVID-19 pneumonia or critical cases of the disease, at a loading dose followed by intermediate maintenance doses for intermediate duration of administration. Zinc was demonstrated to inhibit coronavirus RdRp activity in vitro.46 Also zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes. In light of the demonstrated antiviral activity of zinc and that CQ/HCQ was suggested to act as zinc ionophore blocking coronavirus replication,47 the combination of HCQ with an appropriate antiviral and antibacterial medications together with zinc could be promising to achieve additive or synergistic antiviral effects.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors Contribution

The authors contributed to preparing this opinion article.

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