Review Article

Repurposing of chloroquine and hydroxychloroquine for the management of COVID-19

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ABSTRACT

The Coronavirus Disease-19 (COVID-19) pandemic has impacted adversely on the global health and socio-economic activities. There is currently no evidence-based anti-SARS-CoV-2 drug for COVID-19 therapy. This review highlights some pharmacological properties of chloroquine and hydroxychloroquine and prospects of repurposing them for the treatment of COVID-19. Google scholar was employed in searching relevant published journal articles (n=118) in English. The search was later narrowed down to SARS-CoV-2, pathophysiology of COVID-19, available drugs for the management of COVID-19, clinical trials on repurposing drugs for COVID-19 therapy, and the role of chloroquine and hydroxychloroquine in the treatment of COVID-19. Documented evidence revealed that chloroquine and hydroxychloroquine have antiviral and immune-modulatory properties. Their antiviral effect is due to inhibition of the spike proteins of SARS-CoV-2 from binding to the cellular transmembrane receptors, angiotensin converting enzyme-2 thereby preventing viral infections. Also, sequestration of these drugs into the lysosomes elevates lysosomal pH thus inhibiting lysosomal enzymatic functions vital for viral replication in those cells. Whereas, their immune-modulatory activity averts the inflammatory complications of COVID-19, particularly acute respiratory syndrome, by preventing cytokine storm through suppression of the production and putative release of pro-inflammatory cytokines. The adverse effects from these drugs, notably irreversible retinopathy and cardiac arrhythmia are rare but become life-threatening when they occur. These are minimal with hydroxychloroquine compared to chloroquine. Chloroquine and hydroxychloroquine could be repurposed for managing COVID-19 cases because they are already extensively used for treating acute nonresistant malaria and auto-immune diseases. Also, a viable vaccine cannot be available in the near future while there is a pressing need for treatments to lower the daily rise in morbidity and mortality associated with the disease. Nevertheless, we suggest that emphasis should be on hydroxychloroquine because of its superior antiviral effect and clinical safety.

Keywords: Angiotensin converting enzyme, 2, 4-aminoquinolines, Pandemic, SARS-CoV-2, Cytokine storm

INTRODUCTION

An outbreak of acute respiratory illness (pneumonia) of unknown etiology emerged in December 2019, in three patients from the city of Wuhan, Hubei Province, China. Subsequently, in January 2020, a novel coronavirus, later named "Severe Acute Respiratory Syndrome-Coronavirus-2" (SARS-CoV-2) was identified as the cause of this disease; now referred to as "Coronavirus Disease-2019" (COVID-19). At present, the spread of COVID-19 is out of proportion and is officially declared by the World Health Organization (WHO) as a pandemic since more

than 100 countries have been affected with very high and increasing morbidity and mortality rates within a few months.[1] This pandemic has not only impacted adversely on the global health, but also on socio-economic activities.

At present, there is no clinically validated and officially approved or recommended anti-SARS-CoV-2 drug. Supportive management protocol such as fluid and electrolytes therapy, oxygen supplementation, improved ventilation, and broad-spectrum antibacterial therapy against inevitable secondary bacterial infections is fundamental in managing COVID-19.[2] During disease outbreaks of either epidemic or pandemic proportion, including COVID-19, time is usually a limitation to embark on new drug discovery and development; consequently physicians often try the existing drugs or drugs already into clinical trial but against a different condition peradventure they could effectively give the desired therapeutic outcome aside their originally validated and approved or intended clinical use, a practice referred to as drug "repurposing" or "repositioning". The aims of managing any epidemic or pandemic infectious disease are to successfully treat patients with confirmed cases, devise measures to circumvent or curtail the spread of the disease, and to protect the non-infected persons using vaccines. Since treatment of those infected is one of the key strategies for limiting the spread of infectious diseases, several treatment protocols have been proposed or adopted as off-label or on compassionate ground for the management and/or treatment of COVID-19 globally. One of these drugs is the use of chloroquine (CQ) or its analogue, hydroxychloroquine (HCQ) both with proven clinical efficacy against non-resistant malaria parasites and auto-immune diseases, including rheumatoid arthritis.[3]

The available reports on the use of CQ or HCQ for the treatment of COVID-19 has not been officially recommended/approved for now because such clinical trials had no control for comparison, and/or the sample size of the patients were too small, hence it would be irrational and premature to correlate the reported therapeutic outcomes (success or failures) with these drugs based on these studies.[4,5] In addition, the in vitro inhibition of the SARS-CoV-2 by HCQ and the recommended dose regimen may not be translated into clinical efficacy until a controlled clinical trial is conducted on a required population of patients.[6,7] Therefore, it is not plausible at the moment to establish the therapeutic effectiveness or otherwise of CQ and HCQ against SARS-CoV-2 infected patients as well as their clinical safety in patients based on anecdotal evidence. However, there are several ongoing well designed, controlled, randomized, and open-label clinical trials on the clinical efficacy and safety of CQ and HCQ in COVID-19 patients.

Because of the propensity of the development of resistance by pathogenic organisms, including viruses, the practice of drug repurposing ought to be handled with caution, particularly in pathogens whose characteristics are not fully understood, including SARS-CoV-2. This would probably circumvent the unintended consequences following the use of such drugs. It has been established that

4-aminoquinoline compounds, principally CQ and HCQ could cause serious adverse effects in patients such as irreversible retinal damage and cardiomyopathy even though the incidence is rare.[9] Reports from unpublished sources, including the media have revealed that many people who are tested positive but asymptomatic, or those that are sure that they had contact with those tested positive who are either manifesting typical symptoms or not, or those that are not yet exposed have resorted to self-medication with either CQ or HCQ for the inhibition, or for prophylactic purpose.

OBJECTIVE

Considering the inherent adverse effects of the 4-aminoquinolines and the probability of the emergence of resistant strains of infectious agents following irrational self-medications, this concise review presents the therapeutic potentials and possible mechanisms of action of HCQ/CQ in ameliorating SARS-CoV-2 infection, as well as the adverse effects following the use of these drugs in patients.

EVIDENCE ACQUISITION

An extensive and synchronized review of original or review journal articles were executed between March and April, 2020. Google scholar search was conducted to obtain literatures from relevant English-published journals (n=118) exclusively. We also employed secondary and hand searches of references list as well as other studies cross-indexed by the respective authors. Some of the major items searched included Coronaviruses and diseases caused by them including, SARS-CoV-2 and COVID-19, respectively; pathophysiology of COVID-19; clinical trials of drugs and vaccines for diseases caused by Coronaviruses, including COVID-19; therapeutic management of COVID-19; drug repurposing in diseases caused by coronaviruses, including COVID-19; and physicochemical and pharmacological properties of CQ and HCQ.

Even though the search was initially broad, it was subsequently narrowed down to the structure of SARS-CoV-2; pathophysiology of COVID-19; available drugs for the management of COVID-19; concluded and ongoing clinical trials on repurposing drugs for COVID-19 therapy; and the role of CQ and HCQ in the treatment of COVID-19. The authenticity of the information contained in the respective articles obtained through the search was evaluated based on the impact factor of the journal, the methodology employed, and the references given by the authors.

DEVELOPMENT

Mechanism of action

Chloroquine and its analogues, HCQ are alkylated 4-aminoquinolines (Figure 1) which are weak bases.[9] Hydroxychloroquine is more polar and less lipophilic

compared to CQ, consequently with a lower rate and extent of absorption and volume of distribution. Chloroquine and its hydroxyl analogue, HCQ are racemic mixtures with equal amounts of R (−) and S (+) enantiomers which are traditionally used for the treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus.[10] Both CQ and HCQ are potential drugs for the treatment of emerging viral infections due to their antiviral and immunomodulatory properties.[11] Depending on the therapeutic target, potential anti-coronavirus therapies could be classified into those acting on the virus itself, and/or on the immune system or cells of the host.[12]
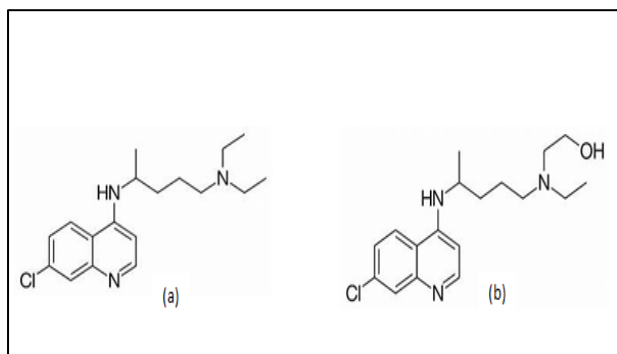
Figure 1: Chemical structures of chloroquine (a) and hydroxychloroquine (b).

Antiviral effects

Both CQ and HCQ exert direct antiviral effects as well as inhibit the pH-dependent steps in the replication of several viruses, including members of the coronaviruses.[11] Direct antiviral effects of CQ and HCQ are due to their inhibition of the endosome-mediated viral entry by blocking the virus from binding to transmembrane receptors of the cells, and inhibition of virus replication by acting on its critical enzymes. It has been reported that SARS-CoV-2 has four structural proteins, namely spike protein, envelope protein, membrane protein, and nucleocapsid protein.[13,14]

Spike proteins (SP) are the main proteins that interact and bind with the host cells receptor to mediate virus invasion of the target tissue or organ, consequently determining viral tissue or host tropism during infection.[15] Therefore, it is suggestive that SP could determine host range of the virus.

Both CQ and HCQ are known to interfere with terminal glycosylation of the Angiotensin Converting Enzyme-2 (ACE-2), a cellular transmembrane receptor (therapeutic target) for the SP on the SARS-CoV-2 expressed on the epithelial surface of the lungs, kidneys, gastrointestinal tract, and blood vessels. It is worthy of note that priming of the SP by the transmembrane protease serine 2 (TMPRSS2) from the virus-target host cell is a crucial step for the fusion between the SP and the ACE-2 on the targeted host cell membrane and entry into the cell.[16,17]

Just like SARS-CoV which is the etiologic agent of Severe Acute Respiratory Syndrome (SARS), SARS-CoV-2 binds with ACE-2 for intracellular invasion. A protein-protein docking during a computational study revealed that the SP of SARS-CoV-2 has a high binding affinity to the human ACE-2 receptor.[18] Binding of the virus with this receptor reduces the production of heptapeptide angiotensin (AT1-7) that is known to mediate anti-inflammatory, anti-apoptosis, and anti-fibrosis, particularly in the lungs.[19] Conversely, this interference elevates amounts of angiotensin 2 (AT-2), increases activation of type 1 angiotensin 2 receptor (AT1R), consequent development of acute respiratory syndrome due to the enhanced pro-inflammatory, pro-apoptosis, and pro-fibrosis effects consistent with the activation of AT1R by AT-2.[20-22] Compounds, including CQ and HCQ that have a significant binding affinity with SP may block the binding of SARS-CoV-2 to ACE-2, which could result in the prevention of the infection. Also, elevation of the pH at the surface of the effector cell membrane by CQ or HCQ could prevent fusion between the virus and the cell membrane with subsequent prevention of the infection.

A recently conducted in silico study earlier referred to in this review showed that some compounds were able to bind to the ACE-2 target using virtual screening. Also, the same study revealed that none of the docked compounds could bind with or interrupt the ACE-2–SP complex, suggesting that these compounds might only inhibit ACE-2 without interfering with an already on-going infection following the formation of ACE-2-SP complex.[13] However, these potential ACE-2 inhibitors, including CQ and HCQ may not be suitable for use as drugs in treating SARS-CoV-2 infection based solely on this mechanism of action since this (inhibition of ACE-2) could nullify the protective anti-inflammatory effect of ACE-2 through the AT1-7, a protective factor of lung injury as explained in the preceding statement.

The non-protonated (uncharged) form of CQ or HCQ diffuses freely and quickly across cell membranes into the acidic lysosomes, consequently increasing their pH.[23] The accumulation of these drugs in the lysosomes due to protonation and sequestration is referred to as "lysosomotropism". Once the non-protonated drug diffuses into the lysosome, it is protonated (charged), hence unable to diffuse out (ion trapping). This elevates the lysosomal pH with the resultant inhibition of lysosomal enzymatic functions vital for viral replication.[24] The consequence is, therefore, the inhibition of nucleic acid replication, glycosylation of viral SP, virus assembly, new virus particle transport, virus release and other processes to achieve its antiviral effects. An in vitro study suggested that the anti-SARS-CoV-2 potency of HCQ is superior to CQ with the former having an EC50 value well below the later.[11,25]

Immune-modulatory effects

The major cause of death from COVID-19 is acute respiratory distress syndrome which is a consistent immune-mediated pathologic event associated with SARS-CoV-2 infection in human.[18] The SARS-CoV-2-induced pneumonia is marked by hyper-activation of effector T cells and excessive production of large amount of pro-inflammatory cytokines, particularly Tumor Necrosis Factor (TNFα) and interleukins (IL-6, IL-10), a scenario described as "cytokine storm".[2,26,27] These facilitate increased vascular permeability and plasma leakage culminating to pulmonary edema, multiple organ failure, and sometimes death.[28-30,18] The immune-modulatory effect of CQ and HCQ involves suppression of the production and release of these cytokines and to some extent the chemokines that are known to mediate the inflammatory complications of several viral diseases, including COVID-19.

Furthermore, increased lysosomes pH inhibits immune cell functioning by decreasing chemotaxis, phagocytosis, and superoxide production by the neutrophils.[31] Sequestration of CQ or HCQ into acidic cellular organelles and elevation of the pH distorts the normal activities of enzymes, particularly the production of several cytokines, chemokines, or mediators where excessive appearance contributes to the severity of viral infections generally. Thus, by these, CQ or HCQ could be said to have therapeutic potential for treating viral diseases, particularly by ameliorating the associated pathologies like pneumonia caused by the cytokine storm. Again, the suppressing effect observed following treatment of cell culture with CQ pre- or post- exposure to the virus suggests that these agents have prophylactic as well as therapeutic potentials.[32,33] Consequently, early administration of these proposed-repurposed drugs at clinically relevant doses could avert the progression of COVID-19 pathophysiology to a critical and life-threatening stage.

ADVERSE EFFECTS OF CHLOROQUINE AND HYDROXYCHLOROQUINE

Incidence of adverse effects following therapeutic use of CQ and HCQ are rare, nevertheless could be potentially life-threatening. Although the prolonged use of CQ and HCQ in malaria therapy revealed the safety of these drugs in humans, the rare risk of irreversible retinopathy and cardiac arrhythmia cannot be overemphasized.[34,35] The adverse effects following treatment of patients with CQ or HCQ are due to some of their physicochemical and pharmacokinetic profiles. Ion trapping of these drugs within the lysosomes increasing the lysosomal pH, high lipophilic property, large volume of distribution to tissues (about 65,000 L), high dose-dependent plasma concentrations, long terminal half-life (about 41 days), slow rate of excretion, and long duration of therapy are factors that could contribute to the toxicity associated with CQ and HCQ.[36] In addition, doses above 2.3mg/kg body weight/day for CQ and 5.0 mg/kg body weight/day for HCQ are reported to be associated with toxicity.[37]

The most serious but uncommon adverse effect of CQ and HCQ is irreversible retinopathy, which depends on the cumulative rather than on the daily dose.[38] Both CQ and HCQ bind strongly to melanin on the melanin-containing tissues, particularly the retina pigment epithelium and the iris of the eye. The functions of melanin here are absorption of light, prevention of scatter, and protection against free radicals. This melanotrophilic characteristic of these drugs impacts significantly on the susceptibility of patients treated with these drugs to retinopathy. Also, CQ- or HCQ- related cardiac disorder is rare but is a severe adverse event that could lead to death. However, the adverse effects of CQ and HCQ could be reduced because the coronaviruses are reported to respond to lower doses compared to that used for treatment of malaria.[33] A commonly reported cardiac complication is cardiac arrhythmias.[39] In all these, the clinical safety profile of HCQ is superior to CQ as well as having lower incidence of drug-drug interactions.[37,40] This is largely due to its less lipophilicity, smaller volume of distribution, and shorter terminal half-life as compared with CQ.

CONCLUSION

Chloroquine and hydroxychloroquine could be repurposed for managing COVID-19 cases because they are already extensively used for treating acute non-resistant malaria and auto-immune diseases. Also, a viable vaccine cannot be available in the near future while there is daily rise in morbidity and mortality associated with the disease. Nevertheless, considering the rare but life-threatening concentration-dependent adverse effects of these drugs, and the propensity of emergence of resistant virus strains, it is more appropriate to pause till the final report from several ongoing controlled, randomized, and open-label clinical trials which are aimed at establishing the repurposing claims of these drugs for the treatment of COVID-19. This would circumvent therapeutic errors from the non-judicious use of these drugs and subsequent therapeutic failures as well as adverse effects on patients. This does not discount the prospect of chloroquine and its analogue, hydroxychloroquine bouncing back again to play a prominent role in fighting the pandemic 2019-Coronavirus disease which has brought the whole world to a virtual standstill.

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