Review Article:

Prophylactic Effect of Chloroquine and Hydroxychloroquine on COVID-19 Treatment

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease, named 'coronavirus disease 2019' (COVID-19), which has threatened human health and public safety.

Objectives: Hydroxychloroquine (HCQ) is an anti-malaria drug with controversial antiviral properties. Some in vitro studies have approved its antiviral effects. Many efforts have been made to prevent and treat COVID-19, but effective drugs for complete eradication of COVID-19 have not been found yet and all available drugs are supportive.

Methods: We tried to review some new aspects of HCQ efficacy in the prevention and treatment of COVID-19 infection. Also, some data from recent clinical trials were studied. It has been shown that HCQ may improve some symptoms of patients, but in severe or critical stages, it did not have significant therapeutic effects and did not reduce the rate of mortality.

Results: In this review article, we explained some results of recent studies, including clinical trials on the effects of HCQ on the prevention and treatment of COVID-19 infection. Some studies have revealed HCQ's beneficial effects in outpatients, and some data showed its hazardous impacts on the heart. The available evidence suggests that CQ or HCQ does not improve clinical outcomes in COVID-19. Well-designed randomized trials are required for assessing the efficacy and safety of HCQ and CQ for COVID.

Conclusion: It was suggested that the dose of HCQ administration must be adjusted and monitored correctly; furthermore, the levels of some myocardial biomarkers, such as troponin must be measured in mild to moderate, severe, and critical infection. Also, combination therapy with other drugs, such as azithromycin may have better anti-inflammatory and antiviral effects.

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Introduction

Coronavirus disease in 2019 (COVID-19) is a pandemic that has affected most countries leading to morbidity and mortality worldwide. Many strategies for the prevention and treatment of the disease have been developed. Some efforts for the discovery of vaccines and eradication of the COVID-19 have been made. Several drugs, such as favipiravir, remdesivir, tocilizumab, lopinavir, ritonavir, oseltamivir, ivermectin, Hrs-ACE2, dexamethasone, etc. have been used for the treatment of COVID-19 and some vaccines have been produced by some companies and have been investigated in some clinical trials. Nevertheless, COVID-19's complete eradication has not been successful yet, and many scientists have been trying to find a way for the successful treatment of COVID-19. The virus shows mild to moderate, severe, and critical infection. Acute respiratory failure may be observed in the severe phase of COVID19, and mortality rates in all cases are about 2-3% in the world [1]. Chloroquine (CQ) is an anti-malaria drug and is effective in the treatment of influenza A (H5N1) [2]. CQ increases the intracellular pH, which prevents the diffusion and uncoating of the virus, and has inhibitory effects on viral replication [3]. Besides, HCQ interacts with ACE2 terminal glycosylation, the membrane protein for adhesion and entrance of the virus into the tissue [3]. CQ and HCQ have a similar structure, while HCQ has lower toxicity [4]. The significant toxicities of HCQ are retinopathy and cardiomyopathy in long time usage. On the other hand, HCQ is an immune modulator that reduces cytokine release from macrophages and decreases the levels of inflammatory cytokines [5]. Another study on 100 patients indicated that HCQ reduced lung injury and shortened hospitalization with no pronounced adverse effects [6]. In a study on 62 patients, HCQ shortened the recovery time of COVID-19 [7]. Another study in France displayed that HCQ with azithromycin (AZM) could reduce patients' viral load [8]. It was recommended that HCQ could be used for chemoprophylaxis of asymptomatic treatment [7].

Azithromycin

HCQ alone or in combination with AZM in a nonrandomized study reduced the severe acute respiratory syndrome [8, 9]. On the other hand, when HCQ and AZM were used, QT interval prolongation occurred, and the Torsade de Pointes (TdP) phenomenon may be increased, and then sudden cardiac death may happen [10]. This phenomenon was reported in 84 patients that received HCQ/AZM. Furthermore, the relation between HCQ/AZM administration and the cardiac arrhythmia risk has been observed [11]. Therefore, HCQ/AZM treatment prolongs the QT interval and increases the risk of TdP, and the risk/benefit ratio should be considered in all patients [11]. This problem is increased with hospitalization. Also, myocarditis and increasing the level of troponin may be related to this problem. On the other hand, this risk is increased with CRP elevation in patients. It was hypothesized that myocarditis and increasing troponin levels are related to HCQ arrhythmia [11]. Although in non-COVID-19 patients, such as in systemic lupus erythematosus (SLE) patients, HCQ rarely induces fatal arrhythmia and the use of HCQ in autoimmune diseases has no dangerous side effects. It was shown that the prolonged usage of HCQ may cause cardiomyopathy in some individuals [12].

Antiviral effect of HCQ

HCQ may have antiviral properties [13]. Some researchers have studied the effect of HCQ on COVID-19 treatment [13]. On the other hand, randomized clinical trials have indicated little to no impact on the COVID-19 treatment [13]. A more extensive randomized study on 62 patients revealed that HCQ significantly decreased the duration and incidence of pneumonia [14]. These data do not have significant statistical outcomes to approve HCQ effects against COVID-19. Furthermore, other drug availability and the risk of sudden cardiac death due to QT prolongation restrict HCQ usage in patients with COVID-19 [15]. In a clinical trial on 20 patients who received daily 600 mg HCQ, after testing viral load in nasopharyngeal swabs, AZM was added to the treatment. The results showed that viral loads were reduced, and AZM reinforced its effects [16]. HCQ is known to block virus infection by increasing the endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of COVID-19.

HCQ functioned at both entrances, and at post-entry stages of the COVID-19 infection in Vero E6 cells. Besides its antiviral activity, HCQ has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. HCQ has been investigated to reduce the replication of the virus in vitro [17]. HCQ inhibited the production of IL-1-alpha and IL-6. In contrast, IL-2, IL-4, TNF-alpha, and IFN-gamma production were not affected. Preferential inhibition of IL-1-alpha production by monocytes and IL-6 production by T cells and monocytes may contribute to its anti-inflammatory effect in autoimmune diseases. HCQ inhibits virus replication at low micromolar concentra-

tion. HCQ was more potent than CQ for inhibition of virus replication [16]. HCQ does not reduce the mortality rate of hospitalized COVID-19 patients significantly [15]. COVID-19 prognosis via HCQ was better than the control group and in outpatients, it increased the rate of improvement. The virus budding is done in the Golgi organelles that cause the envelope to mutate into the virus [18]. Spike glycoprotein facilitates viral adhesion to the cellular membrane superficial receptor and infection initiation. Also, ACE2 is a receptor for virus infusion and antibody transfer [19, 20]. DNA vaccines or parainfluenza virus express the spike protein and interferon, and monoclonal antibody to the S1-subunit inhibits receptor binding [21]. HCQ is an alkaloid that increases the pH of lysosomes, endosomes, and Golgi apparatus. HCQ can decrease infection and inhibit virus diffusion from endosomes. HCQ effectively treats amoebiosis, malaria, HIV, and autoimmune diseases, without dangerous adverse effects [22]. It inhibits virus proliferation in cell culture by the same doses in patients' treatment process; these findings suggest that effective anti-viral agents can prevent or treat the disease [22].

A pilot study on HCQ for the treatment of patients with moderate COVID-19 showed that the prognosis of COVID-19 moderate patients was good. Studies with larger sample sizes are needed to investigate the effects of HCQ in the treatment of COVID-19.

Anti-inflammatory effect of HCQ

HCQ is used for SLE. HCQ can effectively treat disease manifestations, such as joint pain and rashes, reduce thrombotic events, and prolong survival [15]. HCQ has been approved for autoimmune disease treatment. It plays a role in interaction with lysosomal acidification and antigen presentation [23], phospholipase A2 interaction, prevention of UV light coetaneous reactions [23], DNA stabilizing and binding to DNA [24], toll-like receptor signaling inhibition [24], inhibition of T and B cell receptors, and diminishing the cytokine release [23, 24]. These functions inhibit autoimmunity without immune suppressing [25]. The inhibition of cytokines in immune cells and TNF-alpha inhibition by HCQ also were reported [25]. These effects are significant because many viruses express IL-1, IL-6, and TNF-alpha [25]. HCQ and CQ would be efficient in COVID-19 treatment because endocytosis of the virus to the cell is inhibited, an important response that causes the severity of infection mediated by TNF-alpha and IL-6 [26].

Weak bases increase the pH of lysosomal and trans-golgi network (TGN) vesicles and inhibit acid hydrolases and post-translational modification of newly synthesized proteins. The HCQ -mediated rise in endosome pH modulates iron metabolism and decreases the intracellular concentration of iron and affects the function of many enzymes involved in pathways leading to replication of cellular DNA and expression of different genes [26-32]. The mechanism of HCQ is an increase in the intracytoplasmic pH and preventing acidification and maturation of endosomes. IFN-a in SLE patients can be produced by plasmacytoid dendritic cells (pDCs) in response to immune complexes that are internalized by CD32 (FcgRIIA), with subsequent detection of DNA and RNA by endosomal TLR-9 and TLR-7 in pDCs. HCQ would inhibit

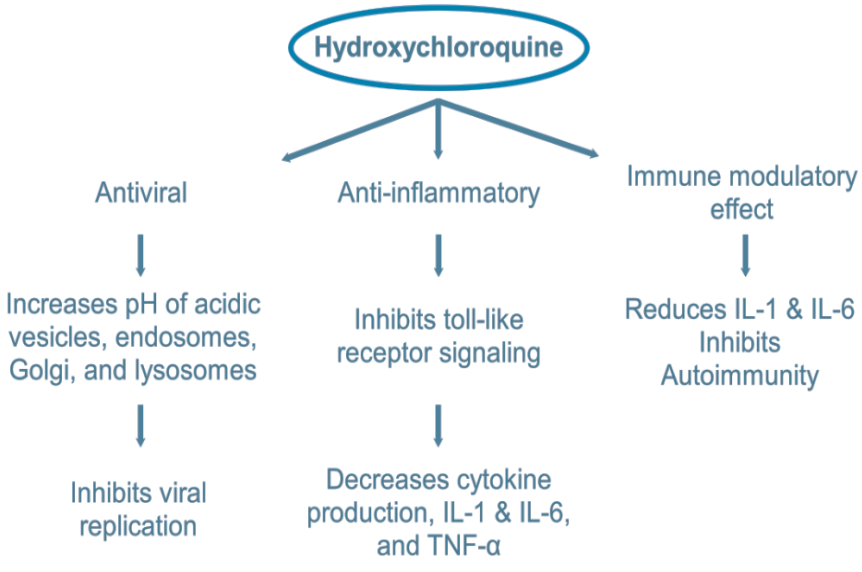

Figure 1. Diagram representing the possible effects of Hydroxychloroquine on COVID-19 treatment

TLR-9/7 stimulation. Importantly, HCQ has been shown to inhibit the production of IFN-a in pDCs in vitro, either after induction by DNA-containing immune complexes or upon stimulation with TLR-9 agonists [33-37].

HCQ adverse effects

HCQ has been used to treat rheumatic diseases and SLE [12]. Retinal toxicity, myopathy, and cardiac toxicity are its toxic side effects following its use for a long time [12]. Cardiomyopathy is rare but severe toxicity may be reversible with drug withdrawal [12]. However, the mechanism of its toxic effect is unknown and heredity may be responsible for this detrimental effect [21]. Anti-malaria-related cardio toxicities are clinically related to thickening restrictive cardiomyopathy diffusely or with conduction system impairment, such as atria ventricular and bundle branch block [21]. The cardiotoxicity mechanism has remained unknown yet [27]. It was indicated that HCQ is less toxic than HCQ; thus, the HCQ prescription has been increased [28]. Retinal toxicity is the most common disorder of long-term use of these drugs [26] and less cardiotoxicity or neurotoxicity has been reported. Furthermore, several reports of cardiomyopathy induced by HCQ have been recorded [29, 30]. HCQ with chronic usage shows cardiac toxicity with myocardial thickening, conduction disorders, restrictive cardiomyopathy, and heart failure by large myocardiocytes containing intracytoplasmic vacuoles, which in ultra-structural examination consist of myelin figures and curvilinear bodies [14, 31]. Antimalarial drugs induce ventricular arrhythmias and QT prolongation, which are more observed in critically ill patients [15].

Discussion

HCQ, an anti-malaria drug, has been used for the treatment of prophylaxis or confirmed cases of COVID-19 and asymptomatic patients. Because of cardiotoxicity and some lethal arrhythmia, its use has been restricted, and dose adjustment and heart monitoring must be applied in high-risk patients. It seems that a low dose of HCQ in outpatients may be a benefit in the prevention of infection, and also, its immune-modulatory effect may be a benefit for prevention of cytokine storm and reducing heart and lung inflammation. The combination therapy of HCQ with AZM may increase the risk of heart arrhythmia and an interval must be considered between HCQ and AZM administration. It is suggested to add a beta-blocker, such as propranolol to the HCQ prescription (Figure 1).

HCQ has antiviral, anti-inflammatory, and immune-modulatory effects. It inhibits Toll-like receptor signaling and decreases cytokine production, such as IL-1 and IL-6, and also decreases TNF-α production. Also, HCQ reduces autoimmunity and cytokine storm. It was suggested to use a very low dose of HCQ in separate doses and the level of troponin must be determined in COVID-19 patients. HCQ is contraindicated in patients with high troponin levels and myocarditis because of lethal arrhythmia. The available evidence suggests that CQ or HCQ does not improve clinical outcomes in COVID-19. Well-designed randomized trials are required for assessing the efficacy and safety of HCQ and CQ for COVID-19. It was suggested that the dose of HCQ administration must be adjusted and monitored correctly; furthermore, the levels of some myocardial biomarkers, such as troponin must be measured in moderate to severe COVID-19. Also, combination therapy with other drugs, such as AZM may have better anti-inflammatory and antiviral effects. A pilot study on HCQ for the treatment of patients with moderate COVID-19 showed that the prognosis of COVID-19 moderate patients was good. Studies with larger sample sizes are needed to investigate the effects of HCQ on the treatment of COVID-19 [14].

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Writing – original draft: Amin Ataie; Writing – review & editing: Ramin Ataee; Methodology, Data collection, and Data analysis: All authors.

Conflict of interest

The authors declared no conflicts of interests.

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