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Archives of Pharmacology and Therapeutics Commentary

The Use of Hydroxychloroquine and Interferons for the Prophylaxis of COVID-19

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Abstract

At the beginning of Covid-19 pandemic, we proposed to use hydroxychloroquine (HCQ) and intranasal interferon (IFN) α-2b spray to prevent SARS-CoV-2. Since then, clinical trials testing these two drugs separately for the treatment and prophylaxis have been reported. A consensus is forming that HCQ and IFNs are not effective in treating severe Covid-19. However, the pathogenesis of Covid-19 suggests that early intervention could reduce the infection and prevent the progression from mild to severe Covid-19. This commentary will focus on discussion regarding the prophylaxis and early treatment of SARS-CoV-2 infection. After review and re-analysis of the two randomized clinical trials (RCTs) using HCQ for postexposure prophylaxis, we concluded that HCQ is beneficial for the prophylaxis of SARS-CoV-2. The side effects of HCQ are mild, and severe side effects such as life-threatening arrhythmia are rare. Thus, risk-benefit ratio strongly suggests that the use of HCQ for pre-exposure prophylaxis should be available, especially among high risk population with no known cardiovascular diseases. The risk-benefit ratio for postexposure prophylaxis is even better for Covid-19 with a medium infection fatality rate of 0.27%. Clinical trials using type I IFN (IFN I) for prophylaxis are still ongoing. Clinical studies using IFN Is for early or in mild Covid-19 hospitalized patients suggest that IFN α-2b may be beneficial. Clinical trials testing the combination of HCQ and IFN Is in the prophylaxis and early treatment of SARS-CoV-2 are still needed to test if the combination improves monotherapy treatment.

Keywords: Covid-19, Hydroxychloroquine, Interferon, Prophylaxis

List of Abbreviations: COVID-19: Coronavirus disease 2019; HCQ: Hydroxychloroquine; IFN: Interferon; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; RCTs: Randomized Controlled Trials; IU: International Unit; TMPSS2: Transmembrane Serine Protease 2; FDA: Food and Drug Administration; EKG: Electrocardiograph; QTc: QT corrected; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor alpha

Prophylactic pharmacological intervention has been largely focused on vaccination development. Until a vaccine is available, it is worth considering chemoprevention with data from clinical studies given the urgent need for interventions in a pandemic. Previously, we proposed to use a low dose of hydroxychloroquine (HCQ), 50 – 100 mg daily orally and intranasal IFN α-2b spray, 0.5 X 10^6 IU twice daily, for the prophylaxis of COVID-19 and recommended using an RCT to prove the efficacy and safety of combined use of HCQ and intranasal IFN α-2b spray [1]. Although there are several clinical trials testing existing drugs for COVID-19 prophylaxis, there has not been an RCT designed to test the efficacy and safety of HCQ with intranasal IFN α-2b. Recent clinical evidence suggests the efficacy of both HCQ in prophylaxis and IFN in the early treatment of Covid-19. In this article, we will review the clinical advances for the use of HCQ and IFN in the prophylaxis and early treatment of Covid-19. More importantly, the potential side effect of HCQ will be reviewed after an extensive search of the available literature.

SARS-CoV-2 enters host cells by endocytosis via endosomal cleavage through protease cathepsin B/L and plasma membrane protease TMPSS2 cleavage [2]. HCQ

was shown to inhibit endocytosis process in vitro without affecting TMPSS2 cleavage perhaps explaining the mixed results with treatment of severe Covid-19 in hospitalized patients. However, in postexposure prophylaxis, we reviewed and re-analyzed the data from two RCTs showing beneficial effect of HCQ compared to placebo. In the clinical trial by Boulware et al., use of HCQ reduces the infection rate in a time-dependent manner [3]. Cochran-Amitage analysis of trend indicates that the trend is statistically significant (P=0.0496) [4]. Even among infected patients taking HCQ, the clinical trial by Mitja et al. suggested that there are 55% more patients with antibody against SARS-CoV-2 on day 14 after the exposure compared to placebo group. Presumably, these patients with earlier activation of adaptive immune response will have better disease outcome [5]. Yang et al. have reviewed all the clinical studies on the use of HCQ and IFN I [4]. In the review, there is a table listing all the important studies. Recently, Rajasingham et al. reported another double-blinded RCT enrolled 1483 healthcare workers using HCQ in pre-exposure prophylaxis [6]. They planned to recruit 3150 participants, however, due to the negative warning from FDA, they could not reach the planned recruitment thus decided to terminate the study early. They tested 400 mg HCQ once weekly or twice weekly for participants against placebo. The hazardous ratio for participants taking HCQ once weekly is 0.72 and 0.74 for twice weekly; both were insignificant. Overall incidence rate in HCQ group was 5.9% while the incidence rate in placebo group was 7.9%. Since the incidence rate is low, the trial may not have enough power to detect the efficacy of HCQ. It should also be noted that HCQ used in postexposure prophylaxis study carried out by Boulware et al. used much higher dosage. HCQ or placebo was provided to the participants at 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days. Risch and Hernan conducted a meta-analysis of the available RCTs and concluded that HCQ provided a significant 22-24% reduction in infection, hospitalization, and death [7].

IFN I is able to inhibit viral replication and induce adaptive immune response. Delayed activation of IFN I response has been indicated in progression of mild to severe form of Covid-19 [8]. In severe form of Covid-19, over 10% of the patients have autoantibodies against IFN I [9]. Exogenous IFN I prior to viral entry shows promise in protecting against SARS-CoV-1 [8]. We have recently reviewed the potential use of IFN I in the prophylaxis and early treatment [4,10]. From the studies of using IFN I in mild Covid-19 and from the pathogenesis of Covid-19, IFN I has potential against Covid-19. More recently, in an observational study, Wang et al. found that subcutaneous injection of IFN α-2b shortened the hospitalization stay and accelerated the viral clearance [11]. Like HCQ, IFN α-2b effect on pathogenesis of Covid-19 seems to be time-dependent; the earlier the use the more efficacious IFN α-2b is [11]. However, in the SOLIDARITY study, IFN-β was not found to be efficacious in hospitalized patients [12]. These conflicting results may be due to the differences in the time of use and the severity of Covid-19. Compared to SARS-CoV-1, SARS-CoV-2 was found to be much more sensitive to IFN-α *in vitro* [13]. A later *in vitro* study showed that IFN-β is more efficacious than INF-α [14]. This has prompted further study for the efficacy of using IFN as part of regimen for prophylaxis and treatment of COVID-19. There are currently 99 clinical trials using IFN for Covid-19 registered on clinicaltrial.gov, and more clinical data should be available soon. HCQ and IFN I inhibit the viral replication through different mechanisms. Combination of both drugs may have additive or synergetic effect in inhibiting viral replication. Past success in treatment of human immunodeficiency virus, hepatitis C virus and hepatitis B virus also suggests that combination therapy has higher chance of success.

The side effects of IFN α and β are well understood and manageable. When given intravenously, they are known to have significant side effects such as fever, myalgia, headache, fatigue, and gastrointestinal symptoms. Since inhaled IFN does not enter systemic circulation, only mild side effects such as nose bleed have been noted [15,16]. One study by Halme showed that except for slight elevated temperature and an 18% decrease in expiratory peak flow in one patient, all other patients did not experience any major side effects when treated with inhaled IFN β [17].

The debate concerned the side effects of HCQ is cited widely since the suggested use in Covid-19. HCQ was widely tolerated for malarial prophylaxis and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. EKG monitoring was not a standard of care for those patients to be treated by HCQ pre-COVID. Therefore, we conducted careful literature review on this subject. We found that HCQ is well tolerated with <10% reporting side effects, most of whom reported noncardiac symptoms [18]. Though rare, a concerning potential side effect was QTc prolongation, which can cause life-threatening arrhythmia. However, prior and current studies found that life-threatening arrhythmia is rarely seen in healthy, and in COVID-19 population. Lofgren et al. conducted three randomized, double-blind trials using HCQ as pre-exposure, post-exposure and early treatment for COVID-19 [19]. 2,795 participants were enrolled; two individuals were hospitalized with atrial arrhythmias, one on placebo and one on HCQ. No sudden death was observed in both cohorts. The most common side effect reported was nausea and diarrhea [19]. In a meta-analysis of a total of 177 clinical trials and 35,448 participants who received quinoline, 18,436 participants underwent evaluation. There has been no report of death or syncope attributable to cardiovascular causes including Torsade de Pointes [20]. In a retrospective study of 201 hospitalized

COVID-19 patients on HCQ, 59% of which also received azithromycin (an agent that was known to prolong QTc), though QTc prolongation was reported in HCQ group, no instance of life-threatening arrhythmia was reported [21]. In recent clinical studies, the side effects from HCQ were reported to be more common than the placebo group, but no severe adverse reactions were noted [3,5]. In Mitja's study, the most frequent treatment-related adverse reactions were gastrointestinal (diarrhea, nausea, and abdominal pain) and nervous system (drowsiness, headache, metallic taste), and only 5 out of 1197 patients experienced a cardiac side effect (palpitation) [5].

In patients with COVID-19 pneumonitis, some confounding factors may also contribute to QTc prolongation as well. For example, cytokine storm with elevated IL-1, IL-6, TNF-α in COVID patients may prolong the action potential and QTc interval [22]. Low oxygen saturation was noted to be associated with prolonged QTc in human [23] and mice [24] model as well. Decreased tissue perfusion and cell oxygenation can cause aberrant gap junction phosphorylation, and misexpression of iron channels in cardiac tissue, which in turn prolongs QTc interval on electrocardiogram [25]. It is thus likely that QT prolongation observed in hospitalized patient may be due to the additive effect of the symptoms from the late stage of Covid-19 and the use of HCQ.

Given the evidence, it is reasonable to conclude that HCQ is a relatively safe medication to be prescribed. In addition, though rare, given the clinically dismal outcome of arrhythmia, the American College of Cardiology has published detailed guidelines with instructions on inpatient and outpatient use and monitoring patients with a high risk for arrhythmia [26], but overall, HCQ poses as a low cost and well-tolerated medication.

Currently, mask has been practiced in society as an effective measure to prevent the spread of the virus. Use of drugs for prevention along with mask wearing could help contain the spread of the virus.

Conclusions

Vaccine is always the first choice for infectious diseases. Prior to the availability of a vaccine of Covid-19, protecting the healthy population is still of paramount importance. Given the available evidence and careful consideration of risks and benefits of medication, we strongly suggest that HCQ be available for the pre-exposure prophylaxis of Covid-19 for patients with no known cardiovascular diseases at the discretion of primary physician and patients. The risk and benefit profile is even better for post-exposure prophylaxis thus the use of HCQ should become a general practice. We continue to propose conducting clinical trials to verify the efficacy of the dual use of HCQ and intranasal IFN I spray as prophylaxis and early treatment for patients with no known cardiovascular diseases, especially for high risk patients with no known cardiovascular diseases.

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Conflict of Interests

The authors have no actual or potential conflict of interest with this study.

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