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Letter to Editors

Use of hydroxychloroquine and interferon alpha-2b for the prophylaxis of COVID-19

A B S T R A C T

The ongoing pandemic of COVID-19 infection demands efforts to reduce spread. In order to eradicate an infectious disease, a method of prevention with low social cost is the most effective way. While we wait for new therapies and a vaccine, we are proposing a solution based on the existing knowledge in biomedical sciences. Here we propose to use low doses of hydroxychloroquine (50–100 mg daily orally) and intranasal interferon alpha-2b (IFN α-2b) spray (0.5×10^6 IU twice daily) for the prophylaxis of COVID-19. Although there are ongoing clinical trials to test the efficacy of hydroxychloroquine for prophylaxis, there has not been any proposal to test the efficacy of IFN α-2b together with hydroxychloroquine to increase protection against COVID-19. Since the two act on two different mechanisms, we strongly believe that the two could have additive effects in prophylaxis against COVID-19. We recommend using a randomized control study to prove efficacy and safety.

Dear Editor:

Background

SARS-CoV-2 is an enveloped positive stranded RNA coronavirus and is genetically related to SARS-CoV, which was responsible for the SARS outbreak in 2002–3. The receptor-binding domain of the S1 subunit has high affinity for angiotensin-converting enzyme 2 (ACE-2) receptor [2]. ACE2 protein is primarily expressed in the epithelia of human lung and small intestine but is also expressed in heart, kidneys, and brain [3].

SARS-CoV2 enters the host cell through the endocytosis [2]. Both SARS-CoV and SARS-CoV2 have been implicated to hijack the endocytic pathway to gain entry into host cells [4]. After receptor binding and endocytosis of the virus, in the acidic environment of the endocytic vesicle, proteolytic cleavage of S allows the virus to fuse with the membrane of the endosome, dumping viral nucleocapsid into the cytosol of the cell [4,5]. Taken together, targeting the endocytic-lysosomal pathway could be beneficial in the prevention of SARS-CoV2 from entry into the host cell.

Chloroquine is a well-known drug that has been used for the prevention or treatment of malaria and treatment of rheumatoid arthritis and lupus. In addition, the drug has been known to have anti-viral properties against viruses such as HIV [7] and SARS-CoV [8]. The mechanism of chloroquine is well-known: it inhibits the acidification of endosome, thus inhibiting the entry of the virus into the cytosol. It is also reported that chloroquine can inhibit the glycosylation of S1 protein preventing the entry into the host cell [8].

Interferon alpha-2b (IFN α-2b) is an antiviral cytokine produced from leukocytes and other cells that are infected by a virus and is currently used to treat viral hepatitis C and hepatitis B. While the antiviral mechanisms of IFN α-2b are incompletely known, IFN α inhibits viral replication through prevention of protein translation [9]. Since chloroquine and IFN α have two different mechanisms of action, we predict that the two therapies would have additive effects in the prophylaxis of COVID-19.

Studies involving chloroquine and IFN α

In vitro, chloroquine is reported to have antiviral activity against many types of RNA viruses as reviewed by Devaux [6]. Chloroquine has been studied in vitro using cell lines and found to be effective in preventing the entry of the virus into the cells [11].

The prophylactic properties of IFN α-2b have been tested against a variety of viruses including coronavirus [1] in human. In the study involving cold caused by coronavirus, volunteers used nasal spray of IFN α-2b or placebo before inoculation of coronavirus 229E. Nasal spray of IFN α reduced cold symptoms significantly compared to placebo, although the rate of viral infection was the same [1].

Proposed use of chloroquine and IFN α as prophylactic treatment

Given the effectiveness of prophylactic chloroquine in vitro and demonstrated ability of IFN α-2b to reduce symptoms of coronavirus in human, we are proposing to use chloroquine together with IFN α-2b as a prophylactic measure in human, most likely first line hospital workers and high-risk patients in the hospital and nursing home. The efficacy of this method can be tested in a randomized controlled study clinically. In the high risk group of patients, individuals with the prophylaxis can be compared with the individuals without prophylaxis. Ideally there would be three experimental groups: placebo, hydroxychloroquine alone, and hydroxychloroquine with IFN α-2b. Rate of infection and severity of symptoms can be compared between all three groups. Due to the low side effect profile of chloroquine and IFN α-2b, the benefit to risk ratio of using chloroquine and IFN α-2b to prevent the spread of SARS-CoV2 and COVID-19 could be enormous.

Chloroquine has a long half-life of 150–290 h [12]. For this reason, in the prevention of malaria, the patient is asked to take the drug once a week for the period of traveling to malaria-infected region. Chloroquine has a large volume of distribution and can penetrate almost all tissues including the liver, spleen, brain, kidney, lungs, and spleen [10]. Due to the long half-life and large volume of distribution of chloroquine, chloroquine can potentially prevent SARS-CoV2 from entry into host cell in all different organs.

Perhaps the most appealing aspect of using chloroquine as a prophylactic treatment is the low side effect profile. There have been few reports of severe side effect for the long-term use of chloroquine, but there are some reports on cardiomyopathy as a severe adverse effect caused by chloroquine [13]. Bernstein analyzed all published cases and

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Food and Drug Administration reports of retinopathy induced by hydroxychloroquine. He concluded that there is no evidence of permanent visual-field scotomas occurring when the daily dose did not exceed 6.5 mg/kg body weight for maintenance therapy [14]. The dosage we are proposing is 12.5% to 25% of the dosage used in the long term treatment. Thus, the rate of side effects should be significantly lower, especially in short period of use.

Intranasal IFN α given as prophylaxis intranasally also had a mild side effect profile. Side effects mainly were nose bleeds [1].

We propose to test 50–100 mg of chloroquine daily for the prophylaxis of COVID-19**.** At this lower concentration, the side effect of chloroquine will be minimized so that the general public can use for a period of time until COVID-19 is under control. The concentration in plasma would be expected to be 0.16–0.8 μM, well below the threshold for side effects at 1.25 μM. Whole blood concentrations of chloroquine are 5–10 times higher than plasma [10], and tissue concentrations are 200–700 times higher than plasma [15]. Thus, at a dose of 50–100 mg daily, the concentrations of chloroquine in tissue should be high enough to have prophylactic effect, according to the concentrations of chloroquine used in vitro without minimal risk of adverse events [8].

Several forms of chloroquine have been approved for use in the clinic. Hydroxychloroquine is an analog of chloroquine with less drug-drug interactions and has been found to be more potent [16]. Thus, hydroxychloroquine may be the most appropriate form of chloroquine to give for prophylaxis.

In the study involving prophylaxis of cold caused by coronavirus in healthy individuals, dose of 0.5×10^6 IU twice a day of intranasal IFN α-2b decreased symptoms of cold caused by coronavirus [1]. Since we hypothesize that the prophylactic effects of IFN α-2b and chloroquine would be additive, we recommend using a low intranasal dose of 0.5×10^6 IU twice a day to minimize adverse effects of IFN α-2b treatment.

Note: After the submission of the manuscript, Dr. Jinping Xu and Dr. Youcheng Liu of Wayne State University School of Medicine decided to collaborate with the authors to initiate a clinical trial to test the hypothesis.

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Author contributions

B.Y. and C.Y. conceived of the presented idea. All authors contributed to the writing and editing of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109802.

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