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Letter to the Editor

Can we use hydroxychloroquine to treat COVID-19 now?

Dear Editor,

We read with great interest the manuscript by Gautret, et al which showed the antiviral activity of hydroxychloroquine (HCQ) in treating coronavirus disease 2019 (COVID-19), especially when coadministrated with azithromycin [1].

In Feb, 2020, we conducted the first single-center, randomized, open-label clinical trial to evaluate the antiviral activity and safety of HCQ in treating mild COVID-19 cases in Shanghai, China (NCT04261517) [2]. Participants were given HCQ 400mg per day for 5 days. The participants also received the standard of care as recommend by the guideline in China (interferon alpha inhaling plus Lopinavir/ritonavir or arbidol). The two study groups were well balanced in terms of age, gender, comorbidity, duration from onset of symptoms to randomization, as well as the clinical and laboratory characteristics. Unfortunately, in this pilot study with 30 participants (15 patients in each group), we failed to find any trend of benefit of HCQ either in virologic clearance rate (86.7% in HCQ group vs. 93.3% in the control group) or in clinical improvement at day 7 after randomization [2].

Both the two studies were limited by the small sample size. However, the different results between our study and the study conducted by Gautret, et al needs further investigation. There were many difference including the study design and study population. Compared to the 200 mg TID dose used in their study, we used 400 mg QD, a regimen that used routinely in clinic to treat autoimmune diseases. We then suspected if that dose was not enough to archive the desired concentration to inhibit SARS-CoV-2 replication. We determined the plasma concentration of HCQ using liquid chromatography–mass spectrometry in another 4 patients that received the same regimens. The through concentration of HCQ was 0.34 ± 0.07 uM, which was close to the EC50 of HCQ (0.72 uM) showed in vitro. In addition, animal models showed that the HCQ concentrations in the lung could reach levels of 10 to 700 times higher than those in the plasma [3]. Therefore, lacking of antiviral activity of HCQ in our study could not been explained by the low HCQ concentration. Another difference is the comedication. Our patients also receive other treatment drugs with potential antiviral effects which might cover up the antiviral effects of HCQ in our study. This was partially evidenced as the control groups showed very good response when compared with that in the Gautret, et al.

The most interesting part of the study by Gautret, et al was that in all the 6 patients who received HCQ in combination with azithromycin, PCR tests all turned negative at day 3. In our pilot study, the median time to PCR negative after randomization was 4 (1-9) days in HCQ group and 2(1-4) days in the control group. As the viral clearance rate was closely associated with the severity of the diseases, it is possible that the positive finding in Gautret, et al was made by chance. Concerning that both drugs could lead to prolonged QT interval, the safety of this combination warrants close monitoring.

Although the antiviral effects of hydroxychloroquine/chloroquine against several different virus were proved in vitro, their antiviral activities have not been confirmed in any of the viral diseases in human. In randomized controlled study, chloroquine does not reduce the durations of viraemia and antigenaemia in dengue patients. It is also ineffective in prevention of influenza illness. Chloroquine treatment during the acute phase of chikungunya virus infections also fails to show suppressive effect on peripheral viral load, while it delays immune response [4]. More importantly, in HIV-infected patients without antiretroviral therapy, use of HCQ compared with placebo results in a greater decline in CD4 cell count and increased viral replication [5]. Despite in vitro antiviral effects against SARS-CoV-2, HCQ also has an immunomodulatory role which suppress immune response, and therefore may theoretically delay viral clearance. Therefore, it is important to validate the effects of HCQ in large sample size, randomized, control studies before it be broadly used to treat and prevent COVID-19.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Ethical Approval

Not required

Reference

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