Communication

Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19)

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SUMMARY   Drugs that are specifically efficacious against SARS-CoV-2 have yet to be established. Chloroquine and hydroxychloroquine have garnered considerable attention for their potential to treat coronavirus disease 2019 (COVID-19). Increasing evidence obtained from completed clinical studies indicates the prospects for chloroquine/hydroxychloroquine to treat COVID-19. More randomized control clinical studies are warranted to determine the feasibility of these two drugs in treating COVID-19.

Keywords   SARS-CoV-2, COVID-19, chloroquine, hydroxychloroquine

Coronavirus disease 2019 (COVID-19) has caused more than 1 million confirmed cases and approximately 70,000 deaths worldwide as of April 6, 2020 (*1*). Drugs that are specifically efficacious against SARS-CoV-2 have yet to be established. Chloroquine and hydroxychloroquine have garnered considerable attention for their potential to treat COVID-19. In China, chloroquine was added to the "Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis, and Management" issued by the National Health Commission on February 18, 2020 (*2*). The U.S. Food and Drug Administration (FDA) issued an emergency use authorization for chloroquine/hydroxychloroquine to treat COVID-19 on March 28, 2020 (*3*). The European Medicines Agency contended that the two drugs should be used in clinical trials or national emergency use programs for the treatment of COVID-19 on April 1, 2020 (*4*). The low cost and easy availability of chloroquine/hydroxychloroquine may help to curb this global public health emergency if their efficacy and safety are ultimately verified in clinical studies.

Chloroquine phosphate is the first drug reported to display efficacy against COVID-19 in early clinical studies in China (*5,6*). Based on this encouraging finding, chloroquine phosphate was added to the Sixth Edition of the Guidance for tentative treatment of COVID-19 (*2*). The Sixth Edition recommended that adult patients in whom chloroquine is not contraindicated should take chloroquine phosphate tablets, 500 mg (300 mg for chloroquine) twice a day for no more than 10 days (*7*). To reduce the risk of adverse effects of chloroquine, the Seventh Edition of the Guidance, issued on March

3, 2020, recommends a reduced dosage and shortened duration of treatment (*8*). Specifically, the dosage of chloroquine phosphate for adult patients (ages 18-65) with a body weight greater than 50 kg is 500 mg twice a day for 7 days and that for adult patients (ages 18-65) with a body weight less than 50 kg is 500 mg twice a day for the first 2 days and 500 mg once a day for the following 3-7 days (*8*). Regarding the treatment strategy, chloroquine and another antiviral favipiravir that also displayed efficacy in clinical trials are highlighted for their use in mild and moderate COVID-19 cases to prevent disease progression (*9*).

In a pilot study (*10*) aiming to evaluate the efficacy and safety of chloroquine in inpatients with COVID-19, 10 patients (3 with severe disease and 7 with moderate disease) received chloroquine phosphate 500 mg orally twice a day for 10 days, and 12 patients (5 with severe disease and 7 with moderate disease) received lopinavir/ritonavir 400/100 mg orally twice a day for 10 days. Chloroquine was slightly superior to lopinavir/ritonavir in terms of virus-negative conversion since the chloroquine group tested negative for SARS-CoV-2 at a slightly higher rate than the control group on day 7, day 10, and day 14 post-treatment (*10*). However, chloroquine was superior to lopinavir/ritonavir in improving the radiological appearance of the lungs and decreasing the duration of hospitalization. Adverse events including vomiting, abdominal pain, nausea, diarrhea, a rash or itch, a cough, and shortness of breath were observed in the chloroquine group, but chloroquine was not discontinued in any of the patients during the treatment period. The efficacy and safety of chloroquine

phosphate was also tested in an open-label, multicenter, non-randomized trial in China and the results were disclosed in an international meeting to share experiences to prevent and control COVID-19 (*11*). Chloroquine demonstrated significant efficacy in reducing the time until virus-negative conversion and returning body temperature to normal (*11*).

Hydroxychloroquine, a more tolerable derivative of chloroquine, also displayed potent activity against SARS-CoV-2 *in vitro* (*12*). A study in France by Raoult *et al.* (*13*) evaluated the efficacy of hydroxychloroquine in 26 patients with COVID-19 and found that administration of hydroxychloroquine 200 mg, three times a day led to a significant reduction in viral carriage on day 6 post-treatment compared to that in the control group, which did not receive hydroxychloroquine. That study also revealed that adding azithromycin to hydroxychloroquine appears to more efficiently clear the virus. A subsequent study by Raoult *et al.* (*14*) involving 80 patients with COVID-19 found that treatment with hydroxychloroquine and azithromycin resulted in a rapid decline in the nasopharyngeal viral load, with a virus-negative rate of 83% on day 7 and a rate of 93% on day 8. Although a control group was not included in that study, its results suggest the potential of hydroxychloroquine to treat COVID-19 given that the recorded median duration of viral shedding is 20 days in survivors (*15*). In addition to the studies cited above, a Chinese team recently released the results of a clinical study on hydroxychloroquine to treat COVID-19 (*16*). That study divided 62 patients into a hydroxychloroquine group and a control group at a ratio of 1:1. Patients in the control group received standard treatment including oxygen therapy, antivirals, antibacterials, and immunoglobulin with or without corticosteroids. Patients in the hydroxychloroquine group received hydroxychloroquine sulfate 200 mg, twice a day for 5 days in addition to the standard treatment. Results indicated that hydroxychloroquine helped reduce the time until body temperature returned to normal, it decreased the duration of cough, and it improved lung imaging findings (*16*). The above studies together favors the usefulness of hydroxychloroquine in treating COVID-19.

A point worth noting is that a pilot study (*17*) in China found that hydroxychloroquine might not help promote virus-negative conversion, reduce the time until body temperature returned to normal, or prevent disease progression. The pilot study involved 30 patients who were randomly divided into a hydroxychloroquine group and a control group at a ratio of 1:1. Patients in the control group received antivirals recommended in the Guidance including IFN-α (100% of patients), arbidol (66.7% of patients), and lopinavir/ritonavir (13.3% of patients). Patients in the hydroxychloroquine group received hydroxychloroquine 400 mg once a day for 5 days (100% of patients), IFN-α (100% of patients), and arbidol (80% of patients). Results indicated that on day 7 post-inclusion the virus-negative rate was 86.7% in the hydroxychloroquine group and 93.3% in the control group (*17*). The median time until virus-negative conversion, the time until body temperature returned to normal, and the rate of disease progression were comparable in both groups (*17*). As patients in both groups received multiple antivirals except for hydroxychloroquine and prognosis was good for all patients, distinguishing the effects of hydroxychloroquine from those of the other antivirals used is difficult. Another possibility is that the combination of antivirals had a ceiling effect since both groups had a high rate of virus-negative conversion.

In general, completed clinical studies have yielded relatively promising results regarding the efficacy and safety of chloroquine/hydroxychloroquine in the treatment of COVID-19. More randomized control clinical studies are warranted to verify the value of these two drugs. To obtain clear and strong evidence, the World Health Organization is launching multi-country clinical trials to test the feasibility of chloroquine/hydroxychloroquine in treating COVID-19, and those results are keenly awaited.

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