Long-Term Care Updates

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Hydroxychloroquine, Chloroquine, and COVID-19

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Introduction

A novel coronavirus, SARS-CoV-2, has led to the outbreak of a respiratory disease named coronavirus disease 2019 (COVID-19). Currently, the only form of treatment is supportive care, as there is no known pharmacological treatment FDA-approved to be safe and effective for COVID-19. On March 29th, the FDA issued an emergency use authorization for donated hydroxychloroquine sulfate and chloroquine phosphate to be donated to the Strategic National Stockpile.[1] While in-vitro studies have suggested that these aminoquinoline drugs, which are typically used for malaria, rheumatoid arthritis, and lupus, are effective in reducing the viral efficacy of SARS-associated coronavirus, the safety and efficacy of their use for treating COVID-19 remains unclear.[2]

Chloroquine and hydroxychloroquine are the two drugs in the aminoquinoline class that have an off-label indication for the treatment of COVID-19.[2,3] A dose of 500 mg of chloroquine by mouth twice daily for 10 days and a dose of hydroxychloroquine 400 mg by mouth twice daily on day 1, followed by 200 mg by mouth twice daily for 4 days are being evaluated for their use in shortening the disease course.[3,4]

In this newsletter, we will discuss the efficacy of using quinine-related drugs in decreasing the longevity or severity of symptoms associated with COVID-19.

Chloroquine

Cortegiani et al. performed a systematic review on the safety and efficacy of chloroquine for the treatment of COVID-19. The authors found six relevant articles and twenty-three registered clinical trials.[5]

The efficacy of chloroquine in vitro was studied in China. Vero E6 cells were infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05. Researchers found chloroquine had an effective concentration (EC_{90}) of 6.90 µM, showing it was very effective in lowering viral replication. They suggested that given the drug's favorable tissue penetration, such EC_{90} would be possible with standard dosing. Additionally, they stated that chloroquine's antiviral effect comes from its ability to restrict glycosylation of viral cellular receptors and increase the endosomal pH that is necessary for virus-cell fusion, and chloroquine's immune modulating effect may also increase its in vivo antiviral efficacy.[4,5]

None of the articles the researchers evaluated were randomized control trials. Five of the six articles recommended the use of chloroquine in humans but did not provide any statistically or clinically significant evidence in support of such a proposal. The first and third articles suggest chloroquine be tested in COVID-19 patients given its efficacy in vitro and its historical viral efficacy and safety. Twenty-three different clinical trials in human subjects are ongoing with hope that chloroquine will prove to be a safe and effective treatment option.[5] However, until results from such clinical trials are completed and released, chloroquine has not yet been proven to be safe and effective for treating COVID-19.

Hydroxychloroquine

A derivative of chloroquine, hydroxychloroquine, is thought to be less toxic than chloroquine due to the extra hydroxyl group. Because chloroquine and hydroxychloroquine have similar chemical structures and mechanisms of action, hydroxychloroquine may also be a potential treatment option for COVID-19. However, as clinical trials are ongoing, there is a lack of evidence that hydroxychloroquine is effective for COVID-19.[6]

Yao et al. conducted an in vitro study comparing the pharmacological activity of chloroquine and hydroxychloroquine in treating and preventing COVID-19. In the treatment study, Vero E6 cells were infected at a MOI of 0.01 for 2 hours and treated with either chloroquine or hydroxychloroquine. In the pretreatment study, Vero cells were pretreated with chloroquine or hydroxychloroquine for 2 hours, then added to the virus-containing medium. Both chloroquine and hydroxychloroquine were found to decrease the viral replication in a concentration-dependent manner. The effective concentration (EC_{50}) of chloroquine was 23.90 μM and 5.47 μM at 24 and 48 hours, while the EC_{50} for hydroxychloroquine 6.14 μM and 0.72 μM at 24 and 48 hours in the treatment study group. In the pretreatment study, hydroxychloroquine was shown to have superior in vitro antiviral effects in comparison to chloroquine. The EC_{50} values for chloroquine were greater than 100 μM and 18.01 μM at 24 and 48 hours, respectively. EC_{50} values for hydroxychloroquine were 6.25 μM and 5.85 μM at 24 and 48 hours. When comparing chloroquine and hydroxychloroquine in both treatment and pretreatment groups, hydroxychloroquine was found to have a more potent antiviral efficacy and a more favorable safety profile.[6]

The authors suggested that both chloroquine and hydroxychloroquine have immunomodulatory effects that can suppress the increase of immune factors associated with COVID-19. It is possible that early treatment with either drug may prevent the progression of a life-threatening disease state. Several clinical trials assessing the use of hydroxychloroquine are currently under investigation; thus, its safety and efficacy in treating COVID-19 is unknown.[6]

A recent small randomized controlled trial evaluated hydroxychloroquine in 30 mild cases of confirmed COVID-19 in treatment naïve patients in China. Patients were given hydroxychloroquine 400 mg daily for 5 days or conventional therapies only. The primary endpoint was clearance of the virus measured by throat swab, sputum, or lower respiratory tract secretion at day 7 or death within 2 weeks. In this trial, one patient in the intervention group became severe and the test was discontinued on day 4. A total of 13 patients receiving hydroxychloroquine and 14 patients receiving placebo tested negative for COVID-19 on the seventh day after enrollment. There was no statistically significant difference in time to clearance of the virus, and all patients survived at the end of follow-up. This study found no benefit with hydroxychloroquine but was too small and thus underpowered to effectively evaluate treatment.[7]

Conclusion

In vitro studies using chloroquine and hydroxychloroquine suggest that these agents may be effective in treating patients with COVID-19. Clinical trials in humans are still ongoing, so until the results of those studies are released, the safety and efficacy of chloroquine for treating patients with COVID-19 cannot be confirmed. Current doses under investigation include chloroquine 500 mg by mouth twice daily for 10 days and a loading dose of hydroxychloroquine 400 mg by mouth twice daily on day 1, then 200 mg by mouth twice daily for 4 days thereafter. At this time, these medications should be used judiciously. Ideally, patients receiving these medications should be enrolled in clinical trials or under state- or institution-specific monitoring programs.

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