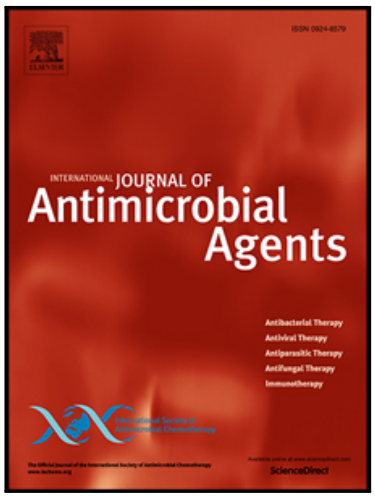

Aminoquinolines Against Coronavirus Disease 2019 (COVID-19): Chloroquine or Hydroxychloroquine

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Dear Sir,

Coronavirus disease 2019 (COVID-19) continues to spread rapidly across China. As of March 7, 2020, the infection was reported from 97 countries globally. To date, 103,882 patients have been confirmed to have COVID-19, and 3,522 of them have died [1]. Recently, many trials have been designed to determine an effective therapeutic regimen for COVID-19. Of the target regimens, chloroquine therapy is also being considered [2]. Few clinical trials in China have shown chloroquine phosphate, an aminoquinoline used in malaria treatment, to be effective against COVID-19 at a dose of 500 mg/d [3]. Chloroquine phosphate also played a promising role in the management of the Zika virus and SARS virus outbreaks. Chloroquine acts by increasing the pH of intracellular vacuoles and altering protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational protein modification in the Golgi apparatus. In macrophages and other antigen-presenting cells, chloroquine interferes with the antigen processing, thereby achieving an antirheumatic response [4]. Studies have demonstrated that chloroquine also confers its considerable broad-spectrum antiviral effects via interfering with the fusion process of these viruses by decreasing the pH. Additionally, it alters the glycosylation of the cellular receptors of coronaviruses [5]. Hydroxychloroquine (**Figure 1**), a less toxic aminoquinoline, has an N-hydroxy-ethyl side chain in place of the N-diethyl group of chloroquine.

Figure 1. Chemical structure of hydroxychloroquine (a) and chloroquine (b)

This modification makes hydroxychloroquine more soluble than chloroquine. Similar to chloroquine, hydroxychloroquine decreases the pH and confers antiviral effects. In addition, hydroxychloroquine has a modulating effect on activated immune cells, downregulates the expression of Toll-like receptors (TLRs) and TLR-mediated signal transduction, and

decreases the production of interleukin-6 [6]. Although the antimalarial activity of hydroxychloroquine is equivalent to that of chloroquine, hydroxychloroquine is preferred over chloroquine for its lower ocular toxicity [7]. Retinopathy is a dose-limiting adverse effect of hydroxychloroquine, but a safe daily dose seems to correspond to 6.5 mg/kg of the ideal body weight and 5.0 mg/kg of the actual body weight [8]. Although there are more clinical data about chloroquine's anti-coronaviral activity than those about hydroxychloroquine's, both these agents are theoretically similar in their antiviral activity [9]. Moreover, chloroquine is not as widely available as hydroxychloroquine in some countries. In addition, chloroquine is associated with greater adverse effects than hydroxychloroquine. For example, in patients with COVID-19, chloroquine can interact with lopinavir/ritonavir, resulting in prolongation of the QT interval. Hence, it is necessary to consider hydroxychloroquine instead of chloroquine when the latter is not available for treating patients with COVID-19. For example, in Iran, chloroquine availability is limited, and hydroxychloroquine can be recommended instead. Other therapeutic agents for COVID-19, such as antiviral agents (Oseltamivir, Lopinavir/Ritonavir, Ribavirin, etc.), interferons, and intravenous immunoglobulins that do not interfere with hydroxychloroquine, are currently under investigation.

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Competing Interests

None

Ethical Approval

Not required

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