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LETTER TO THE EDITOR

# Hydroxychloroquine: is there a role in long COVID?

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Dear Editor,

Post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID is a potential public health problem due to a large number of patients affected [1]. The definition of long COVID still remains contested due to the challenges of defining the illness and its non-specific symptoms [2]. Furthermore, the symptoms of long COVID are debilitating and appear to be prolonged with limited choices of treatment available [1]. Long COVID exerts stress on a healthcare system that is recovering from the COVID-19 pandemic [1]. Effective treatment for long COVID is an urgent unmet need.

Hydroxychloroquine (HCQ) was initially investigated to treat acute COVID-19 infection at the beginning of the pandemic but was subsequently proven to be ineffective [3]. However, its role in long COVID should not be dismissed because of its ineffectiveness in acute COVID-19, given the different underlying pathophysiology [4]. HCQ could be explored as a potential therapeutic agent in long COVID for a few reasons.

First, a persistent residual virus may drive the unremitting inflammatory response in long COVID [5]. HCQ is an immunomodulatory drug by inhibits toll-like receptor (TLR) 7/9 sensing virus [6]. HCQ inhibits TLR signaling by altering the pH of endosomes involved in TLR processing and/or preventing TLR7/9 from binding to their respective ligands (RNA and DNA) [7]. HCQ can also exert its immunomodulatory effects through the inhibition of nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) by interfering with cGAS binding to cytosolic DNA. cGAS stimulator of IFN genes (STING) pathway is a major source of the type I interferon (IFN) response, and through inhibition of this pathway, it can reduce the production of pro-inflammatory cytokines, including type I IFN [7]. HCQ is able to inhibit cytokine production in various immune cells, for example, the production of IL-1, IL-6, TNF, and IFNγ by mononuclear cells and the production of TNF, IFNα, and IL-6 by plasmacytoid dendritic cells and natural killer cells [7]. Therefore, HCQ may dampen the unremitting hyperinflammatory response seen in long COVID by suppressing TLR 7/9 activation, pro-inflammatory cytokine release, and also subsequent immune activation.

Second, long COVID has been associated with autoantibodies [5]. HCQ might address this problem through the prevention of MHC class II-mediated autoantigen presentation through inhibition of lysosomal activity [7]. HCQ inhibits the degradation of cargo derived externally (via endocytosis or phagocytosis) or internally (via the autophagy pathway) in autolysosomes by increasing the pH of endosomal compartments, impairing the maturation of lysosomes and autophagosomes, and inhibit auto-antigen presentation along the lysosomal pathway [7].

Another postulated mechanism of long COVID is a sustained endotheliopathy due to microthrombi; it was noted that in patients with long COVID, their plasma vWF antigen and propeptide levels correlated inversely with exercise capacity [8]. HCQ is well-proven to reduce thromboembolic events in SLE and improve endothelial dysfunction [9]. Assuming that the ongoing endotheliopathy is associated with immune-mediated microthromboses, HCQ could

**Key Point**

• *Long COVID may have a chronic autoimmune/inflammatory process for which hydroxychloroquine might be effective.*

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**Table 1** Table showing the postulated pathophysiological mechanisms of long COVID and potential mechanisms of action for HCQ to address long COVID

| Potential mechanisms of action for HCQ | Postulated pathophysiological mechanisms of long COVID |
|---|---|
| (a) Immunomodulation through inhibition of toll-like receptor (TLR) 7/9. (6)<br>(b) Preventing MHC class II-mediated autoantigen presentation through lysosomal inhibition. (7)<br>(c) Inhibit the cGAS–stimulator of the IFN genes (STING) pathway, which can reduce the production of pro-inflammatory cytokines. (7) | Chronic autoimmune hyperinflammatory process. (5) |
| HCQ is well-proven to reduce thromboembolic events in auto-immune conditions like SLE. Immunomodulatory effects of HCQ may result in less immune-mediated microthromboses. (9) | Sustained endotheliopathy secondary to microthrombi. (8) |

potentially improve endothelial dysfunction that is also found in the pathogenesis of long COVID.

Lastly, HCQ is safe and widely used in rheumatology for patients with SLE, and rheumatoid arthritis, which are prototypes of chronic inflammatory/autoimmune disease.

Hence, should long COVID be defined as a disease of a prolonged and dysregulated inflammatory state HCQ might be a suitable immunomodulatory agent to dampen and alter the hyperinflammatory response, given the above mechanisms of HCQ and the current understanding of the pathophysiology of long COVID.

It may be worthwhile to consider exploring treatment options/trials to evaluate the effectiveness and mechanisms of action of HCQ in long COVID patients. Ideally, a double-blind, randomized placebo-controlled trial should be carried out in patients with long COVID treated with HCQ and placebo. The outcome measures could be patient-reported outcomes, inflammatory markers, and endothelial function. This should be the future research agenda, and we are looking forward to it (Table 1).

**Author contribution** All authors had access to the data and a role in writing the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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