

*Mini-Review*

# **Host-microbe-drug triad: Role of chloroquine/hydroxychloroquine in Covid-19 treatment-focus on inflammatory cytokine inhibition**

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The threat caused by the recent coronavirus disease 2019 (COVID-19) virus pandemic has thrown everyone into a panic mode including scientists, medical practitioners and pharmaceutical firms trying to discover a drug for its treatment. This has seen many clinical studies registered within the past few months. This has called for repositioning of some drugs in order to manage the crisis with hydroxychloroquine and chloroquine being in the front line. The two have been with us over 50 years and have been demonstrated to have strong antiviral activities. Studies have shown that Covid-19 induces an inflammatory response while chloroquine and hydroxychloroquine induce an anti-inflammatory response in the body. Here, we review available information on the interaction between Covid-19 and the innate immune systems of the hosts, the type of inflammatory responses induced by Covid-19 and the anti-inflammatory response conferred by the CQ and HCQ in a bid to understand if there is a justifiable link between the two to support the latter being used as a treatment.

**Key words:** Covid-19, inflammation, cytokines, chloroquine, hydroxychloroquine, treatment.

## **INTRODUCTION**

The coronavirus disease 2019 (COVID-19) is a new global pandemic caused by the novel Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belonging to the same family of coronaviruses such as SARS (SARS-Cov) and MERS (MERS-Cov) (Chen et al., 2020; Prompetchara et al., 2020). The virus has spread to over 213 countries and territories infecting over 50 million people and leaving over 1.2 million deaths as at 9<sup>th</sup> November 2020 and over 30 million recoveries. Due to its rapid spread and severe symptoms to some patients, the virus has caused strain in health facilities and caused panic globally. There is currently no recommended

treatment for Covid-19 and researchers are working round the clock to find a cure. As the cure takes longer and the disease goes on spreading; it would also call for drug repositioning to test what has worked before as we wait for the new cure. It is in this search and the thought for repositioning the old anti-malarial drugs; chloroquine (CQ) and hydroxychloroquine (HCQ) has come into limelight.

Persons infected with Covid-19 have shown varying symptoms ranging from some being asymptomatic (Rothe et al., 2020), to others having hyper-inflammatory cytokines (Cao, 2020; Shi et al., 2020). The pathogenicity

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of covid-19 is proposed to be through production of inflammatory cytokines such as interleukin-6 (IL-6), IL-1 $\beta$ , as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1 $\alpha$  and tumor necrosis factor alpha (TNF- $\alpha$ ) among others (Cao, 2020; Chen et al., 2020; Huang et al., 2020) especially at the severe stage. Hence any drug that suppresses the production of these cytokines would be a good candidate for the management of the virus. Currently there is no drug approved for the treatment of Covid-19 (Cao, 2020) and mostly the drugs being used are all on trial or being recommended based on studies targeting other SARS-CoV viruses.

Chloroquine (CQ) and Hydroxychloroquine (HCQ) have been in the market as malaria drugs for the longest time. While they are primarily anti-malaria, the drugs have demonstrated to have anti-inflammatory effects (Vincent et al., 2005), a property that brought about the hypothesis that they could be viable option for the treatment of Covid-19 infections. Hydroxychloroquine and Chloroquine have been demonstrated to be able to reduce the production of anti-inflammatory cytokines IL-1, IL-6, TNF and IFN $\gamma$  by mononuclear cells through various signaling mechanisms (Al-Bari, 2015; Schrezenmeier and Doerner, 2020). It is against this background that we thought of reviewing available information to back this triad, where the body infected by Covid-19 produces pro-inflammatory cytokines and administration of CQ and HCQ suppresses the same cytokines restoring the body to normal. This review aims at consolidating the existing knowledge on the host-microbe-drug interactions and fills the gaps that could shed some light in support of CQ and HCQ in the treatment of Covid-19.

## LITERATURE REVIEW

A literature review was performed in PubMed, Google Scholar, EMBASE, other trial Registries for studies on the use of chloroquine in patients with COVID-19. The search words included Host-microbe interaction, Microbes and Cytokines, Covid-19, SARS-Cov-2, Pro-inflammatory Cytokines, MERSCoV, Chloroquine and Hydroxychloroquine and Covid-19 treatment. The search focused on clinical trials, review articles and case studies and this resulted in four hundred and twenty relevant articles. The article was written based on full paper and abstract reviews and 44 relevant articles were selected, independently reviewed and referenced. Only articles that focused on modulation of the immune response were considered in this review.

### The immune response and cytokine profiles in COVID-19 infections

Covid-19 infection results in monocyte, macrophage, and dendritic cell activation in two phases. The first phase is

the incubation and non-severe one where the specific adaptive immune response eliminates the virus and prevents the disease from progressing further to the critical stage (Li et al., 2020; Shi et al., 2020). At this stage, anyone with a sound immune system will fight and eliminate the infection or any immune boosting intervention will help the host to fight the infection and eliminate it (Shi et al., 2020). The patients at this stage have mild symptoms or are completely asymptomatic as the case of the Germany patient 1, who did not show any symptoms but continued to infect others (Rothe et al., 2020).

The second phase is the severe disease symptoms such as fever, coughing, respiratory distress syndrome and pneumonia leading to tissue destruction and even mortality (Guan et al., 2020; Li et al., 2020; Wang et al., 2020a; Wölfel et al., 2020; Xu et al., 2020). This stage occurs if the protective immune system is impaired enabling the virus to propagate and multiply propelling the body to produce massive pro-inflammatory cytokines (Moore and June, 2020; Wang et al., 2020a). Once this occurs the remedy would be to suppress the inflammation and manage other disease symptom that sets in at this stage (Shi et al., 2020). The second phase is characterized by cytokines release syndrome (CRS) (Wang et al., 2020a) where the body produces massive pro-inflammatory cytokines such as IL-1, IL-6 and TNF (Huang et al., 2020) which leads to excessive tissue damage.

Excessive inflammatory immune response was confirmed in separate studies by presence of elevated levels of chemokines and Interleukin-6 (IL-6) in Covid-19 patients' serum (Huang et al., 2020). This indicates that the pathogenicity of Covid-19 is through induction of inflammatory cytokines. Earlier studies have reported that most Covid-19 patients had elevated levels of IL-6 confirming these assertions (McGonagle et al., 2020). Based on these studies, one would therefore hypothesize that any drug or treatment that suppresses the cytokine storms would be a good remedy for the management of Covid-19.

### Chloroquine and hydroxychloroquine mode of action

Chloroquine (CQ) and hydroxychloroquine (HCQ) are old and very popular drugs which have been used for a long time for treatment of malaria. The drugs have long history of safe use and are readily available and affordable. Since there is no approved or recommended treatment for Covid-19, everybody is looking everywhere for any treatments that can help manage Covid-19 infections and these two drugs have been proposed as potential remedies. These two drugs have been shown to possess various immunomodulatory and immunosuppressive effects (Al-Bari, 2015); thus their role in the management of Covid-19 cannot be ignored.

Chloroquine and hydroxychloroquine have been demonstrated to contain strong antiviral effects against SARS-CoV when administered before and after infection (Chang et al., 2014; Keyaerts et al., 2004; Sun et al., 2020; Vincent et al., 2005). This means that it can serve as both a prophylactic and a treatment drug for SARS-CoV infections (Vincent et al., 2005). More studies also demonstrate that HCQ and CQ are effective against HIV, hepatitis B, HBV, influenza (Wang et al., 2015). HCQ and CQ mode of action has been proposed to be through the reduction of intracellular pH and inhibiting lysosomal activity in the antigen-presenting cells (APCs), inhibition of pro-inflammatory cytokines pathways by interfering signaling pathways and transcriptional activity and interfering with terminal glycosylation of ACE2 resulting in blocking of virus-receptor binding and subsequent cell entry (Al-Bari, 2015; Vincent et al., 2005). The overall result is blocking the viral replication and subsequent infection and also reduced IL-1, IL-6 and TNF- $\alpha$  production (Al-Bari, 2015; Schrezenmeier and Doerner, 2020). It is through these mechanisms that many researchers hypothesize that HCQ and CQ are potential candidates for treatment of Covid-19 infections.

In their study, Sperber et al. (1993) demonstrated that CQ and HCQ acted by inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 by T cells. This was also demonstrated by later studies which all came into conclusion that IL-6 inhibition was a key mode of action of both CQ and HCQ (Chen et al., 2020; Dijkmans and Verweij, 1997; Ornstein and Sperber, 1996). Several recent studies concluded that HCQ treatment did not only significantly prolong life but also significantly reduce fatality of critically ill patients with COVID-19 and greatly lowered the levels of IL-6, one of the most inflammatory cytokines. The studies also demonstrated that when administration of HCQ was discontinued, levels of IL-6 went up significantly. This study is consistent with earlier studies both *in-vitro* and *in-vivo* (Wang et al., 2020b). Hjorton et al. (2018) also demonstrated that HCQ and CQ were able to inhibit cytokines production in patients with SLE and their results were consistent earlier observations where HCQ was able to inhibit the production of IFN $\alpha$  in patients with SLE (Willis et al., 2012). There are however very few clinical studies on application of HCQ and CQ on Covid-19 patients, although the few that exist indicate that treatment of patients with HCQ and CQ shows promising results (Gautret et al., 2020; Liu et al., 2020; Wang et al., 2020b). A study in France where patients with Covid-19 were treated with HCQ showed a complete elimination of virus although the treatment was reinforced with Azithromycin and had a small sample size (36) (Gautret et al., 2020). A few studies showed no effect on the treatment of Covid-19 patients with HCQ (Molina et al., 2020) although the cases in this study were severe unlike the other studies. Although there seems to be limited data on the efficacy of HCQ and CQ in terms of clinical applications, many countries have started to apply HCQ and CQ treatment as they await the results of a well-

designed clinical trial. Since the drugs have a safe history of use and are very affordable they would form a cheaper option for the treatment of Covid-19. Their effects on the immune system has been studied extensively both *in-vivo* and *in-vitro* and all studies arriving at a conclusion that CQ and HCQ are effective anti-inflammatory and antivirals (Sperber et al., 1993; Vincent et al., 2005).

## CONCLUSIONS

One way of combating disease is by understanding the host-microbe interaction. Understanding host-microbe interaction allows us to understand how the body reacts to certain infections. In this understanding we can then design drugs or administer drugs that target the reversal of the immune reaction causing the inflammation; hence controlling the disease. This is the case of Covid-19. Evidence exists supporting that the Covid-19 infection induces the excessive pro-inflammatory cytokines and that administration of CQ and HCQ reduces the production of pro-inflammatory cytokines. HCQ and CQ are likely to control infections as well as deter the progression of Covid-19 infections through the inhibition of cytokine storm which is a major characteristic of Covid-19 progression by modulating the T-cells. Since we are alive that it will take months if not years to get a recommended drug to treat Covid-19 while infections and deaths are increasing day by day; it would make sense to re-look at the existing drugs with history of safe use and screen them for Covid-19 treatment. In conclusion, from the reviewed literature; Chloroquine seems to be effective in limiting the replication of SARS-CoV-2 (virus causing COVID-19) *in vitro*. The rationale for use may be justified by their long time use. There is a wide existing knowledge supporting use of CQ and HCQ in treatment of Covid-19 although the evidence is supported by few studies involving very limited sample sizes that are not well controlled. We therefore recommend a further, well designed and randomized clinical trials on the efficacy of CQ and HCQ on Covid-19 as a treatment option.

## CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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