Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Chloroquine paradox may cause more damage than help fight COVID-19

A B S T R A C T

Novel coronavirus disease 2019 (COVID-19) pandemic is the most recent health care crisis without specific prophylactic or therapeutic drugs. Antimalarial drug chloroquine (CHL) and its safer derivative hydroxychloroquine (HCHL) have been proposed to be repurposed to treat SARS coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19. CHL/HCHL have anti-inflammatory activity and are used to treat rheumatoid arthritis, osteoarthritis and lupus. Although, CHL/HCHL have an anti-viral activity against several viruses in cell-cultures, the anti-viral activity *in-vivo* is questionable. Repurposing of CHL/HCHL to treat SARS-CoV-2 infection is appealing. However, there is empirical evidence from animal studies with other viruses suggesting that CHL/HCHL may have an untoward paradoxical effect. One thus cannot exclude the possibility that CHL may increase the severity of the disease and prove deleterious both for the patients and public health efforts to contain the highly contagious and explosive spread of SARS-CoV-2.

1. Main text

As the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak reaches pandemic proportions, there is a frantic search for effective anti-SARS-CoV-2 drug. Recently, among others, chloroquine (CHL) and its safer derivative hydroxychloroquine (HCHL) [1] have been propelled as anti-SARS-CoV-2 drugs as CHL inhibited the virus in cell cultures [2] and appear to reduce virus load in patients in an open label non-randomized trial [3]. The U.S. Food and Drug Administration has given an emergency use authorization for use of HCHL for treatment of novel coronavirus disease 2019 (COVID-19). CHL/HCHL are excellent anti-viral drugs *in-vitro*, as they increase endosomal and lysosomal pH [4] and interfere with the glycosylation of the proteins [5]. Acidic pH of endosomes and lysosomes aids in virus fusion to cells as well as release of their genetic material in the cells to initiate active virus replication [4]. Modification of the protein glycosylation including that of the viral envelop proteins interferes with virus assembly and release of mature virus particles. By inhibiting these two crucial steps, it's not surprising that CHL/HCHL have indeed been found to be effective anti-viral agents *in-vitro,* including that of the SARS-CoV [6]. In fact there is no report of CHL/HCHL being not effective as an anti-viral agent when tested against any virus in cell cultures (*in vitro*).

However, *in-vivo*, CHL/HCHL have been shown to either have no effect on virus replication or have increased the viral replication and disease severity such as that of influenza [7], dengue [8,9], Semliki forest virus (SFV) [10,11], encephalomyocarditis virus (EMCV) [10], Nipah and Hendra viruses [12], chikungunya virus [13] and Ebola virus [14]. In clinical trials, CHL treatment failed to prevent influenza and chikungunya virus infections in human subjects and was suggested to increase the risk of infection as well as symptom severity [7,15]. In children treated with CHL following malarial infection, the incidence of Herpes zoster virus (HZV) was markedly enhanced, which otherwise is not common in children [16]. Similar association was later reported in adults suggesting high incidences of HZV in dermatomyositis/polymyosistis patients treated with chloroquine [17]. For treatment of plasmodium infection, CHL/HCHL blocks the intra-erythrocytic stage of the plasmodium but, has no activity against the hepatic stage of plasmodium life cycle [18]. The hepatic stage (sporozoite) of plasmodium, which can cause relapsing malaria, is treated by other quinolone drugs such as mefloquine and primaquine [19]. Treatment with gamma-interferon (IFN-γ) alone is effective against exo-erythritic stage of the *Plasmodium cynomolgi* infection in monkeys and prevented relapse of parasitemia [20]. However, when combined with CHL, the anti-sporozoite activity of IFN-γ was abolished resulting in parasitemia relapse. More importantly, CHL was shown to abolish the anti-viral activity of IFN in mice against Semliki forest virus [11]. Note that IFN is the earliest defense response presented to virus infections and such immunomodulatory activity of CHL may help virus infections [21]. In context of coronaviruses (CoV) that causes milder disease in humans, protection of the newborn mice from human CoV-OC43 induced death after treatment of mother mice with CHL have been shown [22]. However, newborns were presumed to acquire CHL transplacentally or via mother's milk which, limits the extrapolation of results to anti-CoV activity by direct treatment of animals with CHL/HCHL. Against SARS-CoV, which causes severe respiratory syndrome involving lower respiratory tract, CHL did not show anti-viral activity in mice [23].

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Due to the anti-inflammatory activity of CHL/HCHL these drugs are used to treat variety of disease where inflammation is central to disease pathogenesis such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and osteoarthritis [24]. As SARS-CoV-2 causes an acute inflammation in the lungs, a condition central to the pathology of COVID-19, a potential beneficial effect of CHL/HCHL due to an anti-inflammatory activity is postulated. Although encouraging, the difference of treating inflammation of COVID-19 vs SLE or RA is the presence of an infectious agent *i.e.*, SARS-CoV-2. In animal studies, CHL enhanced severity of the inflammatory viral disease such as that of SFV and EMCV, and increased arthritic symptoms in CHIKV infected patients [10,25]. Therefore, beneficial anti-inflammatory effect of CHL may not translate as it is, into SARS-CoV-2 infected patients. Only a carefully planned animal study and/or clinical trials will be able to answer this important question.

Preliminary findings of a non-randomized open-label trial showed reduction in SARS-CoV-2 viral RNA load in HCHL and HCHL combined with azithromycin treatment [3]. However, HCHL treatment was started in 26 patients of which, six were not included in the final analysis as the drug treatment was not completed in these patients. Of these six, four (15.3% of the total patients) patients experienced severe COVID-19 including one death, additionally another patient experienced adverse effects and did not complete the trial. Control patients did not experience severe form of COVID-19 [3]. Adverse effect of HCHL treatment in patients and virus titer data from patients which progressed into more severe disease after treatment with HCHL was not available, limiting the ability to conclude with certainty the beneficial effect of HCHL and the potential exacerbation of the disease by HCHL treatment in four patients cannot be ruled out. Contradictory results on the protective efficacy of CHL/HCHL in COVID-19 patients have been reported in other recent clinical reports and trials [26–29]. In a separate study, treatment of COVID-19 patients with HCHL in combination with azithromycin was found to be beneficial. However, no direct comparison with non-drug treated COVID-19 patients was made. Although most patients recovered, three HCHL treated COVID-19 patients progressed to severe disease including one death [26]. A randomized clinical study in with 62 COVID-19 patients reported beneficial effect of HCHL treatment compared to standard clinical care of COVID-19 [29]. In contrast, a small cohort study with 11 patients found no protective efficacy of HCHL and azithromycin in COVID-19 patients and reported one death and one adverse effect (18.1%) after initiation of HCHL treatment [27]. Progression of disease severity in HCHL treated COVID-19 patient was also observed in another study, which otherwise showed no beneficial effect of HCHL treatment on prognosis of COVID-19 patients [28].

The paradoxical studies on the effect of CHL/HCHL on virus replication are of particular importance from a public health perspective. Animal studies indicate that CHL/HCHL can increase the severity of some viruses including those where inflammation is at the core of disease pathology. Although controversial, some clinical reports have indicated beneficial effect of HCHL against COVID-19, but progression of disease severity in HCHL treated COVID-19 pateints over that of non-drug treated COVID19 patients have also been observed in these studies. A cautious and thorough review of antiviral activity of CHL/HCHL before widespread use of the drugs to treat COVID19 is needed [30,31]. Hasty application of CHL/HCHL to treat COVID19 may end up in exacerbating the disease and increasing morbidity. Drawbacks of self-administration of CHL/HCHL are highlighted by the overdose toxicity and fatal outcome of self-administration of CHL [32,33]. Therefore, extreme caution is needed while extrapolating the anti-viral activity of CHL/HCHL to SARS-CoV-2 in these testing times.

Opinions expressed herewith are those of the author and are not necessarily representative of those of the USUHS, DoD, or the United States Army, Navy or Air Force.

Declaration of Competing Interest

Author declare no conflict of interest.

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