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Case report

SARS-CoV-2 infection in a patient on chronic hydroxychloroquine therapy: Implications for prophylaxis

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ABSTRACT

People exposed to COVID-19 have a risk of developing disease, and health care workers are at risk at a time when they are badly needed during a health care crisis. Hydroxychloroquine and chloroquine have been used as treatment and are being considered as prophylaxis. Our patient developed COVID-19 while on hydroxychloroquine and although more work is needed, this calls into question the role of these medications as preventive therapy.

Introduction

A pandemic of a novel coronavirus called SARS-CoV-2 causing Coronavirus Disease-2019 (COVID-19) emerged, spread from China, and to date is affecting more than 197 countries and territories around the world since December 2019 [1,2]. SARS-CoV-2 infection transmits from human to human through droplets and through contact with infected surfaces. Efforts to discover potential treatments for COVID-19 are accelerating with a focus on repositioning previously tested *in vitro* compounds. Hydroxychloroquine and chloroquine are antimalarial agents with both immunomodulatory and anti-inflammatory activities that have been proposed as possible treatments for COVID-19 disease [3]. There has also been interest in their use as prophylaxis for people with high-risk exposure to COVID-19 who have not yet become infected, although there are currently no data to support the use of these medications as preventive therapy [4].

Case presentation

A 39-year-old female with medical history of mitral valve repair, cardiomyopathy with ejection fraction of 40–45 %, and rheumatoid arthritis on oral hydroxychloroquine 200 mg per day developed new onset fever as well as mild sore throat and rhinorrhea following exposure to a coworker who tested positive for SARS-CoV-2. The day following onset of symptoms, she received a RT-PCR test that resulted as positive. She was sent home where she continued to have fever and developed symptoms of mild productive cough, exertional shortness of breathing, generalized body pain, diffuse headache, myalgia, fatigue, nausea and diarrhea. One week after the onset of symptoms, she was admitted to our hospital for further management.

Upon presentation, the patient was febrile, normotensive, and in no distress with a normal chest examination. Radiograph of the chest showed no infiltrates. Laboratory values were pertinent for white blood cells of 5.1 [normal 3.6–11 $\times$ 10^9 cells/L], lymphocytopenia to 0.64 [normal 0.90–2.90 $\times$ 10^9 cells/L], neutrophil-lymphocyte ratio 6.1, platelets of 164 [normal 150–400 $\times$ 10^9 cells per liter], creatinine clearance >60 mL/min, normal hepatic transaminases and bilirubin, C-reactive protein of 1.06 [normal <3.0 mg/L] and mildly elevated prothrombin time and international normalized ratio of 1.2. Over the next two days of hospitalization, her home hydroxychloroquine was continued at 200 mg daily, and no other treatments intended to specifically target SARS-CoV-2 or the inflammatory cascade were added. She developed no additional fevers and her symptoms resolved. At that

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point, it was determined that she had mild disease and was deemed appropriate for discharge to continue self-quarantine at home.

Discussion

Chloroquine and hydroxychloroquine are agents which have generated significant interest for treatment in persons with COVID-19 infection. They appear to have an antiviral effect mediated through increasing the endosomal pH thereby impeding virus to cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2 [5,6]. Both drugs are known for their long elimination half-life of at least one month and high accumulation rate in cells [7].

Rationale for the use of these antimalarial compounds emerged from experiments in Vero E6 cells. In a recent letter published by Wang and colleagues, the *in vitro* activity of chloroquine against SARS-CoV-2 showed an effective concentration (EC50) at 48 h of 1.13 μM, indicating potency [8]. Similar studies of chloroquine were previously done on SARS-CoV and MERS-CoV showing an EC50 in a comparable range [9]. A recently published comparison study of their *in vitro* activity demonstrated higher potency of hydroxychloroquine over chloroquine, with EC50 values similar to prior data [10]. The authors utilized physiologically-based pharmacokinetic modeling and simulation techniques and provided a rationale for the optimal dosing regimen for hydroxychloroquine (400 mg twice on day 1 followed by 200 mg twice daily) based on their *in silico* experiment.

In terms of *in vivo* data, at least 15 clinical trials have been conducted on chloroquine and hydroxychloroquine in China [11], the results of which have not yet been formally published. However, a preliminary report was released in a letter by Gao and colleagues from one hundred patients which demonstrated that chloroquine is superior to standard of care treatment in preventing exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course [11].

There have been several proposed dosages for chloroquine and hydroxychloroquine as treatment options for COVID-19. One study referring to Korean guidelines recommended 500 mg of chloroquine twice daily or 400 mg of hydroxychloroquine daily [12]. A panel in China recommended chloroquine at a dose of 500 mg twice a day for 10 days for patients with any severity of pneumonia [13]. The Dutch Centers for Disease Control (CDC) suggested a treatment regimen in adults consisting of an initial 600 mg dose of chloroquine followed by 300 mg 1 h later on day 1, then 300 mg twice a day on days 2–5 days. Another guideline document by the Italian Society of Infectious and Tropical Diseases (Lombardy section) recommended the use of chloroquine 500 mg twice a day or hydroxychloroquine 200 mg twice daily for 10 days. A meta-analysis of 6 published articles and 23 ongoing trials primarily in China listed a variety of different regimens being studied [14]. Most recently, an open-label non-randomized trial by Gautret et al. suggested hydroxychloroquine 200 mg three times daily for 10 days, with the addition of azithromycin depending on severity of illness [15]. These proposed dosages for COVID- 19 are greater than the hydroxychloroquine dose suggested for rheumatoid arthritis, which is 200–400 mg daily as a single oral daily dose or in 2 divided doses [16].

People exposed to SARS-CoV-2 have a high risk of developing COVID-19, and health care workers are at particularly elevated risk being at the forefront of this public health crisis. As such, there is significant interest in finding effective prophylaxis, for which hydroxychloroquine and chloroquine have been considered [17]. In a preprint non-peer reviewed retrospective cohort, veterans who received hydroxychloroquine as treatment for COVID-19 either with or without azithromycin had no reduction in risk of mechanical ventilation [18]. Currently in the US, a randomized clinical trial of post exposure prophylaxis for SARS-CoV-2 at the University of Minnesota is actively recruiting (NCT04308668). Another trial assessing chloroquine prevention of SARS-CoV-2 infection in the health care setting at the University of Oxford is being planned (NCT04303507).

Our patient developed COVID-19 infection despite long-term use of hydroxychloroquine. Her hydroxychloroquine dose was lower compared to any of the proposed dose regimens for COVID-19 treatment or prophylaxis; however, the chronicity of her treatment (3 years) would be expected to mitigate this difference. Considering the long elimination half-life of the drug (30 days) in addition to its known intracellular accumulation, we would expect the intracellular and extracellular levels of hydroxychloroquine in a patient such as ours taking the medication chronically to be relatively comparable to the minimum desired dose for treating COVID-19.

The fact that our patient developed the disease in this context raises questions about the effectiveness of hydroxychloroquine, both as a therapeutic as well as a prophylactic agent [19,20]. Were hydroxychloroquine effective as prophylaxis, one might expect only mild asymptomatic infection not requiring hospitalization. A critical need exists for further investigation of hydroxychloroquine and other chloroquine derivatives, not only as treatment for COVID-19 disease but also as preventive therapy. Further, the effects of potential confounding factors like age, comorbidities, underlying autoimmune disease, and clinical stage of COVID-19 disease are yet to be determined. More data from larger randomized clinical trials is necessary in order to elucidate these questions.

Author statement

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