Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkaa193

COVID-19 infection also occurs in patients taking hydroxychloroquine

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Sir,

Hydroxychloroquine is a synthetic antimalarial drug that has also been used for its immunomodulatory activity in lupus erythematosus, rheumatoid arthritis and other inflammatory diseases for years.

Two *in vitro* studies in China have demonstrated the inhibitory activity of hydroxychloroquine against SARS-CoV-2[1,2] with a greater potency compared with chloroquine, in addition to its immunomodulatory activity.

Clinical data from case series and non-randomized controlled studies suggest hydroxychloroquine may have a positive impact on the outcome of COVID-19 infection and hydroxychloroquine has been largely introduced as a standard of care in many guidelines without formal proof of efficacy. Many ongoing trials are evaluating its efficacy versus standard of care and antivirals. It has also been suggested that hydroxychloroquine could prevent COVID-19 infection and other trials are evaluating hydroxychloroquine alone or in combination in a prevention strategy.[3]

Here we report on two severe cases of COVID-19 in patients already using hydroxychloroquine for a long time to treat inflammatory disease.

Observation 1

A 64-year-old woman was admitted to hospital for fever. She had a long-term history of treatment by hydroxychloroquine 400 mg once daily for mixed connectivitis. She had been experiencing major headaches, myalgias, fever and nausea for 10 days. Family members had been previously hospitalized for confirmed COVID-19. On admission, physical examination revealed a 38.5°C fever with a respiratory rate of 25 breaths/min and oxygen saturation of 85% while breathing ambient air. C-reactive protein (CRP) was raised (21 mg/L). A nasopharyngeal swab was collected and the COVID-19 RT–PCR performed on the same day was positive. Despite stopping hydroxychloroquine treatment one day prior to hospitalization because of nausea, plasma concentration of hydroxychloroquine measured on admission, 36 h after the last dose, was 222 ng/mL. Her oxygen saturation was 97% on the next day and she was discharged in the absence of clinical severity criteria.

Observation 2

A 58-year-old woman was admitted to the emergency department with complaints of fever and asthenia for one week. She was on a long-term regimen of hydroxychloroquine 400 mg once daily and prednisone 8 mg once daily for rheumatoid arthritis, with a good adherence to treatment. Two days prior to hospitalization she was prescribed azithromycin by her family doctor. On admission her body temperature was 39°C and oxygen saturation was 91% while breathing ambient air, which led to the initiation of oxygen therapy. CRP level was 185 mg/L. CT of the chest showed ground-glass opacities at a moderate stage.

COVID-19 was confirmed by RT–PCR performed on a nasopharyngeal swab. During hospitalization, hydroxychloroquine was continued and prednisone was stopped. At Day 1, the hydroxychloroquine plasma level was 407 ng/mL, indicating a massive impregnation of the drug before hospitalization. Clinical improvement was finally noted and supplemental oxygen could progressively be withdrawn.

These two observations, along with three additional cases in the series by Monti *et al.*,[4] are describing COVID-19 infection in patients already on a long-term hydroxychloroquine regimen. High plasma levels of hydroxychloroquine collected on admission in our cases confirm chronic exposure and adherence to hydroxychloroquine. These values are close to or higher than the EC_{50} described by Yao *et al.*,[2] not taking into account lung diffusion. Patients actually taking long-term hydroxychloroquine are potentially immunosuppressed patients since they are living with chronic inflammatory diseases and thus do not represent the general population exposed to COVID-19. However, these observational data are not in favour of a universal protective effect of hydroxychloroquine. Moreover, it is suggested that the immunomodulation generated by hydroxychloroquine may increase the risk of COVID-19 acquisition owing to the anti-inflammatory activity of hydroxychloroquine. Chloroquine and hydroxychloroquine inhibit IL-2 production and then T cell proliferation and differentiation.[5,6] Thereafter, if the type 2 T-helper (TH-2) response could play a role in suppressing early inflammation in SARS-CoV-2 infection, it cannot be excluded that chloroquine and hydroxychloroquine negatively impact the early inflammatory response to the virus and the risk of acquisition of infection.[7,8]

So, if hydroxychloroquine may have favourable effects thanks to its antiviral and anti-inflammatory properties to prevent the cytokine storm occurring during COVID-19 infection, we believe that clinicians should use it carefully, awaiting the results of clinical trials, particularly in the context of prevention.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

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