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# Hydroxychloroquine in patients with rheumatic diseases during the COVID-19 pandemic: a letter to clinicians

In the initial phase of the COVID-19 pandemic, the immune modulator hydroxychloroquine received substantial international scientific and media attention. We wish to express our concerns about the continuing implications of this increased attention for our patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome.

Hydroxychloroquine is licensed for the treatment of rheumatoid arthritis, SLE, and juvenile idiopathic arthritis. In 2018, the drug gained an orphan designation for the treatment of patients with antiphospholipid syndrome. From February, 2020, hydroxychloroquine attracted attention for its potential antiviral and immunomodulatory effects in the treatment of COVID-19 and was suggested as a potential therapeutic agent for the treatment of COVID-19-associated pneumonia. This led to emergency US Food and Drug Adminstration approval for use of hydroxychloroquine in patients with COVID-19.[1]

In June, 2020, WHO published interim results from the SOLIDARITY trial, which showed no benefit (or harm) associated with hydroxychloroquine use in the treatment of COVID-19. Other studies suggested a potential cardiac risk associated with high-dose hydroxychloroquine (800 mg daily) in patients with COVID-19, especially when given with the pro-arrhythmogenic drug azithromycin.[2] A systematic review of the effect of hydroxychloroquine in the treatment of COVID-19 showed highly variable outcomes of observational studies,[3] leading the authors to conclude that the evidence was weak and conflicting with regard to the benefits and harms of using hydroxychloroquine to treat COVID-19.

To achieve the immunomodulatory effects of hydroxychloroquine, the prescribed dose usually varies between 200–400 mg daily, although recommendations from the American Academy of Ophthalmology suggest a maximum dose of 5 mg/kg to avoid any retinal changes after 5 years of treatment. It is important to highlight and inform patients that the doses of hydroxychloroquine used in the acute settings of COVID-19 studies that reported cardiotoxicity were much higher (ie, exceeding 800 mg daily) than the doses used in rheumatological practice.

Our concerns go beyond the conflicting publicity that hydroxychloroquine has received during the COVID-19 pandemic. Hydroxychloroquine is clearly efficacious for many patients with SLE. It reduces organ damage accrual and disease flare rate and severity, is protective against SLE renal damage, and improves overall survival. The British Society for Rheumatology (BSR) and the American College of Rheumatology (ACR) recommend use of hydroxychloroquine in patients with SLE, including during pregnancy (unlike other disease-modifying antirheumatic drugs). Ongoing studies are evaluating the role of hydroxychloroquine in patients with antiphospholipid antibodies.

In our experience, patients taking hydroxychloroquine have an increased awareness of the drug, and as rheumatologists we are often confronted with questions around its safety. It is clear that patients feel confused as to whether hydroxychloroquine is effective, harmful, or has no effect in COVID-19. Accumulating evidence suggests that patients with rheumatic diseases who are treated with hydroxychloroquine long-term are not more likely to be infected with severe acute respiratory syndrome coronavirus 2 and do not have a more severe disease course or increased mortality. These patients are also unlikely to be protected from infection.[4]

Initially, the publicity around a potential beneficial effect of hydroxychloroquine in patients with COVID-19 threatened the availably of the drug for patients with rheumatic diseases, while the publicity around potential harmful effects of the drug in patients with COVID-19 has led some patients with SLE and antiphospholipid syndrome to stop taking it. Both publicity effects have had ongoing, potentially harmful effects on patients.

Randomised controlled trials, such as the RECOVERY trial, have seen no benefit of hydroxychloroquine in hospitalised patients with COVID-19.[5] We encourage clinicians to advise patients with SLE or antiphospholipid syndrome to adhere to any hydroxychloroquine medication prescribed for long-term disease control, in keeping with the current BSR, European League Against Rheumatism, and ACR guidance. We recommend that physicians actively inform and guide patients on how to find relevant information from reliable sources to avoid misleading information on the use and safety of hydroxychloroquine.

IG reports an unrestricted educational grant from UCB, speaker and travels fees from UCB, and speaker fees from Lupus Academy. HC reports institutional research support to attend scientific meetings from Bayer Healthcare, honoraria from Bayer Healthcare, and consultancy fees from UCB paid to University College London Hospital Charity. SM reports grants and personal fees from Aspen, Daiichi Sankyo, and Bayer, and personal fees from Bristol Myers Squibb-Pfizer, Boehringer-Ingelheim, Portola, and AbbVie, outside the submitted work. All other authors declare no competing interests.

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*Lancet Rheumatol* 2020
Published **Online** October 29, 2020 https://doi.org/10.1016/S2665-9913(20)30382-9

For **European League Against Rheumatism guidance for patients during COVID-19** see https://www.eular.org/eular_guidance_for_patients_covid19_outbreak.cfm

For **American College of Rheumatology guidance for patients during COVID-19** see *Arthritis Rheumatol* 2020; published online April 29. https://doi.org/10.1002/art.41301

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1 US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalised patients. June 15, 2020. https://www.fda.gov/media/136537/download (accessed Oct 10, 2020).

2 Tleyjeh I, Kashour Z, AlDosary O, et al. The cardiac toxicity of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-regression analysis. *medRxiv* 2020; published online June 18. https://doi.org/10.1101/2020.06.16.20132878 (preprint).

3 Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Update alert: hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. *Ann Intern Med* 2020; **173:** W78–79.

4 Gentry CA, Humphrey MB, Thind SK, Hendrickson SC, Kurdgelashvili G, Williams RJ II. Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** e689–97.

5 The RECOVERY Collborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020; published online Oct 8. https://doi.org/10.1056/NEJMoa2022926.