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Excitement around hydroxychloroquine for treating COVID-19 causes challenges for rheumatology

Excitement about a potential new treatment for the coronavirus disease 2019 (COVID-19) pandemic currently engulfing the world is causing problems for patients with arthritis and systemic lupus erythematosus (SLE), who routinely use the drug to control their symptoms.

The antimalarial drug chloroquine and its safer derivative hydroxychloroquine have been used since the 1940s to treat autoimmune disorders, says Thomas Dörner, a rheumatologist at the Charité University Hospital in Berlin. Though the drug is rarely used for rheumatoid arthritis, around two-thirds of patients with SLE in Europe use hydroxychloroquine to manage their symptoms, and it is the only known therapy so far for primary Sjögren's syndrome, he says.

But the drug has also attracted attention over the past few decades as a potential antiviral agent, currently as a possible treatment for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19. Reports from China found that chloroquine could inhibit SARS-CoV-2 in vitro, and showed apparent efficacy in treating COVID-19 in humans. A small non-randomised trial in France also found hydroxychloroquine to be a promising potential treatment.

The findings have prompted many, including US President Donald Trump, to tout hydroxychloroquine as a game-changer in the fight against COVID-19. The US Food and Drug Administration has designated hydroxychloroquine for off-label, compassionate use for treating COVID-19, and WHO added the drug to its large global SOLIDARITY trial to test a variety of potential treatments. But virologists and infectious disease experts caution that the excitement is premature.

"Whether hydroxychloroquine works in vivo is not proven for any virus, and in fact in randomised controlled trials against a number of viruses, including influenza, it doesn't work at all," says Douglas Richman, a virologist and infectious disease physician at the University of California, San Diego. "It's my personal prejudice that this is also going to be the case with coronavirus."

Hydroxychloroquine has been studied as a possible antiviral for approximately the past 40 years, says Richman. The mechanism of action is not entirely clear, but it is known to decrease the acidity in endosomes, which might prevent the endosome from releasing the virus into the cytoplasm.

Hydroxychloroquine has shown activity in vitro against many viruses, including influenza and coronaviruses, but that has largely failed to translate into success in either animals or humans. In 2005, the drug showed in vitro activity against SARS-CoV, which is closely related to the

current pandemic virus, but it failed to decrease viral load in mice, and clinical interest drifted away, says Christopher Tignanelli, a surgeon at the University of Minnesota in Minneapolis, who is involved in clinical trials of COVID-19 treatments.

"There is not a huge amount of pre-clinical data for this drug," says Tignanelli. "It's mostly test-tube and anecdote."

Despite the absence of strong evidence, some people are already attempting to self-medicate with the drug, with disastrous consequences. Hydroxychloroquine can have dangerous side-effects if the dose is not carefully controlled, and cases of chloroquine poisoning have been reported in Nigeria and the USA.

Additionally, the sudden interest in hydroxychloroquine has led to reports of shortages for patients who rely on the drug to treat their autoimmune disease. Kaiser Permanente, a major health-care network in the USA, is no longer filling routine prescriptions for chloroquine.

"It's a challenge for us and for our patients," says Dörner. "When I write a prescription now, I tell my patients that they might need to go to several pharmacies before they get it filled."

The Lupus Foundation of America has called on drug manufacturers to increase the production of hydroxychloroquine, to ensure that patients with SLE who need the medication will still be able to access it while it is being investigated for COVID-19. "For many people with lupus there are no alternatives to these medications," the Foundation said in a statement.

Although the existing evidence is thin, it is promising enough to warrant further study, says David Boulware, an infectious disease physician at the University of Minnesota in Minneapolis. "When someone is sick in hospital, we throw the kitchen sink at them, but we don't always know if it works," he says. "That's why we need clinical trials."

Boulware is leading a trial to investigate whether hydroxychloroquine could be efficacious as a post-exposure prophylactic to prevent the development of the disease, and to prevent progression of the disease to avoid admission to hospital. The trial (NCT04308668) has already enrolled around 25% of its subjects. Initial results are expected within 3–4 weeks.

Though he is skeptical of its efficacy, Richman fully supports further research to establish whether hydroxychloroquine is a good option for treating COVID-19. "It's imperative that good RCTs are implemented to get answers one way or another," he says.

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For more on **chloroquine and SARS-CoV-2 in vitro** see *Cell Research* 2020; **30**: 269–71

For more on **trials of chloroquine and hydroxychloroquine in COVID-19** see

Int J Antimicrob Agents 2020; published online March 20; <https://doi.org/10.1016/j.jantimicag.2020.105949> and *BioScience Trends* 2020; **14**: 72–73

For more on **cases of chloroquine poisoning** see <https://edition.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html> and <https://www.cnn.com/2020/03/23/health/arizona-coronavirus-chloroquine-death/index.html>

For more on **hydroxychloroquine shortages** see <https://www.reuters.com/article/us-health-coronavirus-usa-shortages-excl/exclusive-potential-coronavirus-treatment-touted-by-trump-already-in-shortage-pharmacists-idUSKBN2163JD>

For the **Lupus Foundation of America statement** see <https://www.lupus.org/news/lupus-foundation-statement-manufacturers-hydroxychloroquine-chloroquine>