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Feature

Hydroxychloroquine for covid-19: the end of the line?

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Controversies and disappointing trial results have dampened excitement about an established drug touted as a “game changer” for th… coronavirus. **Elisabeth Mahase** asks what the future now holds for hydroxychloroquine

Before the covid-19 pandemic hydroxychloroquine was known chiefly as a drug to prevent and treat malaria and also as a treatment for rheumatoid arthritis and lupus. It has been around for decades, but as the coronavirus spread rapidly across the world it quickly became one of the potential treatment frontrunners. So much so that in March the drug company Teva donated millions of doses of hydroxychloroquine sulfate to hospitals across the US, after a request from the government. This was despite experts warning that the drug’s effectiveness was unproved.

At the time the US president, Donald Trump, said the drug had shown “very, very encouraging early results.”[1] A week later the US Food and Drug Administration issued an emergency use authorisation, enabling clinicians to prescribe hydroxychloroquine for patients admitted to hospital with covid-19. The agency said the approval was based on “limited in-vitro and anecdotal clinical data.”[2]

Around this time, a number of large international trials were launched to assess the effectiveness of hydroxychloroquine, as well as other potential covid-19 treatments. The WHO Solidarity trial, comparing four treatments against the standard care for patients with such symptoms, began in March and has since recruited over 3500 patients in 35 countries, with more than 400 hospitals taking part.[3] A team at the University of Oxford began a similar study, the RECOVERY trial, to assess six different treatments, including hydroxychloroquine. The trial has so far enrolled more than 11 000 patients from 175 NHS hospitals in the UK.

As these trials continued, the medical community waited for any indication that a treatment would be effective against the disease. Then, in the space of two weeks, confusion and controversy hit.

Retraction scandal

On 22 May the *Lancet* published a study claiming that patients with covid-19 treated with chloroquine or hydroxychloroquine (with or without a

In the following days serious concerns were raised about the data used in the studies and the legitimacy of Surgisphere after it refused to transfer the full dataset and associated information. The company argued that doing this would violate confidentiality requirements and agreements with clients. Both the *Lancet* and *NEJM* studies were retracted,[4] with the authors not linked to Surgisphere saying they could "no longer vouch for the veracity of the primary data sources."[5] WHO then restarted its trial on 4 June.

Ineffective in hospital patients

Just as it seemed that hydroxychloroquine had been given a second chance, it took another blow. The day after WHO's trial restarted, the team leading the RECOVERY trial announced that it would be ending its hydroxychloroquine arm. It had concluded that the drug had no clinical benefit for patients in hospital with covid-19.[6]

So what happens next? WHO told *The BMJ* that the RECOVERY trial team had shared the preliminary results but that it was awaiting the final analysis. Its statement said, "Our Data Safety and Monitoring Committee will certainly consider the final results and evidence coming from other randomised trials and we will continue to inform the public as new evidence will be made available."

Other studies are also reviewing the situation. Anthony Gordon, UK chief investigator for REMAP-CAP,[7] an international trial looking at hydroxychloroquine for critically ill patients, told *The BMJ* that his team has suspended recruitment to its hydroxychloroquine arm. The trial involves 392 critically ill patients with covid-19 in 124 UK intensive care units.

Not the end

While it seems that hydroxychloroquine is not effective for patients being treated in hospital, it is still being investigated for prevention. The PRINCIPLE trial at the University of Oxford, started on 12 May, is investigating whether a seven day course of hydroxychloroquine can reduce the severity of symptoms in vulnerable groups and help prevent admission to hospital. The team has enrolled over 500 general practices from across the country to recruit patients aged 50 and over with underlying health conditions, or people aged over 65.[8]

A similar question is being looked at in the US, where the National Institute of Allergy and Infectious Diseases is assessing whether hydroxychloroquine, given with azithromycin, can prevent admission to hospital or death from covid-19 in people who have tested positive. The trial, announced on 14 May, is set to enrol 2000 adults across the US who are experiencing symptoms such as fever, cough, or shortness of breath. They will be randomly assigned to receive either a short term treatment of hydroxychloroquine and azithromycin, supplied by Teva, or a placebo.[9]

But there is concern that hydroxychloroquine prophylaxis is being prematurely promoted outside clinical trials. In India doctors have criticised the Indian Council of Medical Research after it recommended that healthcare workers and the police take the drug to prevent covid-19.[10] Meanwhile Trump has publicly spoken about taking the drug as a prevention method. Speaking at a press conference in May, he claimed that many frontline workers were taking it.[11]

Bradley Connor, medical director of the New York Center for Travel and Tropical Medicine, told *The BMJ* that hydroxychloroquine had been "politicised" and promoted irresponsibly in spite of the lack of evidence from randomised controlled trials. Yet he still holds out hope for the drug.

Connor is leading the HERO trial looking at whether taking hydroxychloroquine once daily before exposure could reduce both symptomatic and asymptomatic covid-19 disease in healthcare workers. HERO, which has just started recruiting participants, is double blinded, randomised, and placebo controlled, and it aims to recruit 374 healthcare workers who will be randomised between the intervention and placebo arms and followed for 90 days.[12]

As this article was being written, yet another *NEJM* study of 821 participants reported that hydroxychloroquine was ineffective as postexposure prophylaxis.[13] Connor says the *NEJM* study was "very different" from what his team is looking at, citing study design and HERO's focus on taking the drug pre-exposure.

"We hope our trial will show a benefit in terms of prevention," he says. "We are staying the course. This is not the end of the line for this drug."

https://bmj.com/coronavirus/usage

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