



Hydroxychloroquine is used to treat malaria and some autoimmune diseases.

CHLOROQUINE HYPE DERAILS CORONAVIRUS DRUG TRIALS

People hoping to use malaria drugs to fight COVID-19 are turning away from clinical trials of other therapies.

By Heidi Ledford

People with COVID-19 who arrive at the Salvador Zubirán National Institute of Medical Sciences and Nutrition in Mexico City to search for treatment can choose from a menu of clinical trials, carefully presented by a worker trained to offer an unbiased portrait of the potential risks and benefits.

But neurologist Sergio Iván Valdés-Ferrer already knows which trial most will choose — and it's not his. Instead, many people opt for one involving hydroxychloroquine, a malaria drug that has been touted by US President Donald Trump and other influential figures as an effective coronavirus treatment.

"There's a tremendous bias," says Valdés-Ferrer, who is studying the effects of a dementia drug on COVID-19. "Studies of any other drug that are enrolling all ages and degrees of severity are in big trouble."

Hydroxychloroquine and its close chemical cousin chloroquine have attracted disproportionate attention in the coronavirus pandemic, spurred by preliminary studies and added publicity from political leaders such as Trump and French President Emmanuel Macron. So far,

there are very few data backing the idea that hydroxychloroquine works against coronavirus infection, yet the fervour surrounding it has created drug shortages and affected enrolment in clinical trials for other potential treatments.

Early evidence

The US Food and Drug Administration (FDA) has approved chloroquine and hydroxychloroquine to treat malaria and, because of the drugs' anti-inflammatory properties, to treat some autoimmune diseases, such as rheumatoid arthritis and lupus. In February, researchers showed that chloroquine could reduce coronavirus infection of human cells grown in the laboratory (M. Wang *et al. Cell Res.* **30**, 269–271; 2020). A few days later came a report of clinical trials involving people with COVID-19 in ten hospitals in China, which suggested that chloroquine treatment might shorten the duration of the disease (J. Gao *et al. Biosci. Trends* **14**, 72–73; 2020). Since then, a handful of small studies have been reported. None has shown definitively whether or not the drug can benefit people with COVID-19.

But the initial findings were sufficient for politicians keen to offer worried voters and

suffering economies a glimmer of hope. Trump claimed that he had considered taking chloroquine as a precaution. Hospitals in Iran, New York, Spain and China turned to hydroxychloroquine and chloroquine as a standard therapy for people with COVID-19, despite guidance from the World Health Organization and several medical associations that the drugs should not be used for this purpose except in clinical trials.

The resulting race to take, or even to hoard, chloroquine led to global shortages, and there were reports of illness and deaths linked to overdoses in the United States and Nigeria.

Endangered studies

Some people don't want to participate in clinical trials that would require them to give up chloroquine treatments. This has made it difficult to enrol people in a trial of HIV drugs as potential COVID-19 treatments, says infectious-disease specialist Sung-Han Kim at the University of Ulsan College of Medicine in Seoul. Kim's story isn't unique. Psychiatrist Eric Lenze of Washington University in St. Louis, Missouri, recently launched a trial of an antidepressant that he hopes could lessen the immune response linked to some severe COVID-19 cases. The trial has so far enrolled just ten participants; three others declined to take part because they were already planning to take hydroxychloroquine.

In Iran, pathologist Alireza Ghaffarieh gave up plans to exclude chloroquine treatment from his trial of an iron-chelating medicine in people with COVID-19 at the Kermanshah University of Medical Sciences. Instead, he accepts participants who might be taking other medications, and hopes that this will not complicate interpretation of his results.

Delays in enrolment can endanger a clinical trial, particularly during a pandemic, says Prashant Malhotra, an infectious-disease specialist at North Shore University Hospital in Manhasset, New York. It's best if trials can be completed early, he says, before health-care systems become overwhelmed.

Researchers might have settled some of these issues weeks ago if there had been a rapid, international effort to develop a rigorous chloroquine clinical trial, says Ole Søgaaard, an infectious-disease physician at Aarhus University Hospital in Denmark. Now, there are more than 100 clinical trials that aim to test chloroquine or hydroxychloroquine against COVID-19. It's a worthwhile effort, Søgaaard says, despite the lack of evidence supporting the drugs. "Being able to cross something like hydroxychloroquine off the list and move on to other things would be a major achievement," he says. "Then you could shut down a lot of trials and replace them with something you believe in."

Additional reporting by Amy Maxmen.