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NEWS

Covid-19: what treatments are being investigated?

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With no current specific treatment for covid-19, the race is on to develop or repurpose drugs to help end the epidemic. The World Health Organization has now launched the SOLIDARITY trial to investigate four potential treatments: remdesivir, chloroquine/hydroxychloroquine; lopinavir and ritonavir; and lopinavir and ritonavir plus interferon-β.[1] The trial will not be double blind, as WHO said it needed to find a balance between gold standard research practice and speed, but it will include thousands of patients from several countries.

These are not, however, the only treatments being considered for covid-19. Here is a breakdown of the drugs that have been suggested so far.

Chloroquine

This is the drug that US president Donald Trump has declared "very powerful" with "very, very encouraging early results." After a request from the US government, pharmaceutical company Teva has agreed to donate more than six million doses of hydroxychloroquine sulfate tablets—a less toxic metabolite of chloroquine—to hospitals across the country.[2]

Chloroquine is approved to treat malaria and rheumatoid arthritis. While it has previously been tested in vitro against a number of viruses, including SARS, and found to inhibit growth, no benefit has been seen in animal models.[3] In a limited way, the drug has been tested against SARS-CoV-2—the cause of covid-19—and has reportedly been found "highly effective," although the evidence is still limited, with much of the data unpublished.[4 5]

Andrew Preston, reader in microbial pathogenesis at the University of Bath, said that while the early results are "promising" they have "yet to be fully scrutinised, and, of course, it is essential to conduct other, larger controlled trials to determine accurately the effectiveness of chloroquine as a treatment for covid-19. But in among the oppressive darkness of the current situation, any glimmer of hope is very welcome."

Robin May, professor of infectious disease at the University of Birmingham, said while the mode of action against covid-19 has not been established, there are three different ways chloroquine—which acts to neutralise acids—could potentially work.

"Many viruses enter host cells through a process called endocytosis. This means that the virus is initially taken up into an intracellular 'compartment' which is typically acidic. Chloroquine would alter the acidity of this compartment, which can interfere with the ability of viruses to escape into the host cell and start replicating.

"Another possibility is that chloroquine may alter the ability of the virus to bind to the outside of a host cell in the first place, which is an essential first step for entry. Lastly, chloroquine has subtle effects on a wide variety of immune cells. For this reason, the drug is sometimes used in autoimmune conditions like lupus or rheumatoid arthritis. It may be that one of these effects helps stimulate the body's ability to fight off covid-19."

May added that as chloroquine has a "long history of clinical use, the safety profile is well established, and it is cheap and relatively easy to manufacture, so it would—theoretically—be fairly easy to accelerate into clinical trials and, if successful, eventually into treatment."

However, co-ordinating editor of the Cochrane Infectious Diseases Group, Paul Garner, from the Liverpool School of Tropical Medicine, warned that there is currently "absolutely no evidence that chloroquine is effective in people infected with coronavirus" and said it should "not be given outside the context of a randomised controlled trial."

"This is a new infection; chloroquine could even do harm. We have to have the trials to assess this," Garner said.

Lopinavir and ritonavir (Kaletra)

Kaletra is a combination of two antiviral drugs—lopinavir and ritonavir—normally used to treat HIV. Lopinavir was identified after the 2003 SARS outbreak as a potential treatment. Convincing evidence of its effect, however, was lacking. Recently, researchers from China tested the efficacy and safety of oral lopinavir-ritonavir for SARS-CoV-2 infection through a randomised controlled trial but found "no benefit" beyond standard care.[6]

"Whether combining lopinavir-ritonavir with other antiviral agents, as has been done in SARS and is being studied in MERS-CoV, might enhance antiviral effects and improve clinical outcomes remains to be determined," the researchers concluded.

A new trial looking at the effectiveness of lopinavir-ritonavir, as well as low dose dexamethasone (a steroid used to reduce inflammation), has just started at the University of Oxford. The trial team has said it will continuously review information on new drugs and will include promising ones in the trial.

If Kaletra is found to be effective as a covid-19 treatment, countries will be able to buy generic forms of it after pharmaceutical company AbbVie announced that it will not enforce its global patent rights on the drug.[7]

Interferon β 1a (SNG001)

SNG001 is an inhaled formulation of a drug called interferon β—a molecule that forms part of the lung's own defence mechanism to fight off viruses. It has been tested in phase two trials for asthma patients and was found to lead to improvements in lung function. In covid-19, the theory has been raised that SNG001 could work by increasing the production of INF-β—thought to be suppressed by coronaviruses—to prevent or decrease symptoms of severe respiratory illness, such as pneumonia.

In the UK, pharmaceutical company Synairgen has been given expedited approval from the Medicines and Healthcare Products Regulatory Agency and Health Research Authority to test the drug for patients with covid-19 in a clinical trial.

Ian Hall, professor of molecular medicine at the University of Nottingham, said, "The idea behind the trial is that by giving more of this molecule to the lung it could help reduce the severity of infection with covid-19, especially in those people who have reduced immune responses to the virus. If the trial shows that interferon beta is a useful treatment for covid-19, it would provide a way to reduce the severity of disease and potentially reduce death rates."

Remdesivir

It gives the company several perks including stopping generic versions becoming available for several years and significant tax incentives. But just days after the designation, the FDA removed it at the request of the pharmaceutical company Gilead. This came after criticism from experts who said treating covid-19 as a rare disease was "disingenuous."

Remdesivir, which works to inhibit viral replication, is a drug currently being investigated as a potential covid-19 treatment through several clinical trials. It has caused controversy, however, as the US Food and Drug Administration (FDA) initially designated it as an orphan drug. Orphan status is a mechanism designed to promote the development of drugs for rare diseases, where there is only a small number of people (less than 200 000 people in the US) that could be treated. It gives the company several perks including stopping generic versions becoming available for several years and significant tax incentives.[8] But just days after the designation, the FDA removed it at the request of pharmaceutical company Gilead.

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Tocilizumab (Actemra)

Tocilizumab is a monoclonal antibody which blocks the IL-6 signalling pathway and is used to treat rheumatoid arthritis. Currently, there is limited evidence on the safety or efficacy of the drug in clinical treatment of covid-19, however it is currently being investigated by the FDA through a double blind, randomised phase III clinical trial as a treatment for severe covid-19 pneumonia, in combination with standard of care.

Favipiravir (Avigan)

This antiviral drug, manufactured by Japanese pharmaceutical company Fujifilm Toyama Chemical, gained a lot of media attention after a Chinese official told reporters that studies had found it to be "clearly effective" in treating covid-19. In reality, researchers from Wuhan, China, reported that the drug was "preferred" over the antiviral Arbidol for patients with covid-19 pneumonia, but not the most severe cases.[9] This was because they found that the "time of fever reduction and cough relief in favipiravir group was significantly shorter than that in Arbidol group (both $P < 0.001$), but there was no statistical difference observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both $P > 0.05$)."

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