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The Strange Story Of Remdesivir, A Covid Drug That Doesn't Work

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Remdesivir in a syringe. GETTY

While clinical trials suggest remdesivir isn't very effective in treating Covid-19, recent studies have shown that it does block

Coronavirus activity.

That apparent contradiction makes the antiviral drug even more controversial.

Remdesivir is an experimental drug developed by biotech company Gilead Sciences (under the brand name Veklury) in collaboration with the US Centers for Disease Control and Army Medical Research Institute of Infectious Diseases.

It's one of many drug candidates that were originally designed in response to the threat from emerging diseases caused by RNA viruses — germs like the one behind the 2002 SARS outbreak — that have potential to cause global pandemics.

Such 'broad-spectrum' drugs target features shared by a wide range of disease-causing germs. In remdesivir's case, that's the virus' genetic material, RNA. The drug proved ineffective against the Ebola virus, however, yet was still subsequently repurposed for SARS-CoV-2 coronavirus.

Remdesivir is not effective for Covid

News media prematurely reported that patients were responding to treatment.

But the published data lated showed that "remdesivir was not associated with statistically significant clinical benefits [and]

the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies."

The controversy surrounding remdesivir therefore revolves around whether the drug is actually an effective treatment.

Early studies produced conflicting evidence on remdesivir's effectiveness. Some found that Covid patients who received the drug recovered faster and fewer people died, but other studies showed that it didn't reduce the length of hospitalization or death rate.

What's weird about remdesivir is that it hasn't been held to the same standards as other drug candidates.

Covid-19 vaccines have been developed 10 times faster than traditional drugs, but they've passed the phase-3 clinical trials that test whether a potential medicine is both safe and effective in thousands of people.

Normally, a drug is only approved for use by a regulatory body like the US Food and Drug Administration if it meets the two criteria for safety and efficacy. Nonetheless, in October 2020, remdesivir was granted approval by FDA based on promising

data from relatively small trials with about 1000 participants.

A large-scale analysis by the World Health Organization's Solidarity trial consortium has cleared-up the confusion. Based on interim results from studying more than 5000 participants, the international study concluded that remdesivir "had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay."

As a consequence of being mostly ineffective, WHO recommends against the use of remdesivir in Covid-19 patients.

Remdesivir is an expensive drug

The drug is administered over 5 or 10 days. A five-day course of treatment costs around $2600 per person.

So for a hospital with hundreds of Covid patients, that would amount to millions of dollars for one antiviral.

That price could be cost-effective if remdesivir saved lives and its use was limited to moderate or severe disease, but it's also being made available for milder cases and WHO found that it isn't a lifesaving drug.

What next for remdesivir? Following WHO's finding, an article in the *British Medical Journal* highlighted another antiviral as a cautionary tale: oseltamivir or 'Tamiflu' — a drug that aims to block the influenza virus.

During the early 2000s, governments started stockpiling Tamiflu, paying billions to its manufacturer, pharmaceutical firm Roche. Then in 2013, independent researchers gained access to Roche's

unpublished data, revealing that the drug caused many side effects and only shortened the duration of flu symptoms by a few hours.

Tamiflu only cost $75 per treatment and yet was still a massive waste of money.

The *BMJ* article implies that the story of remdesivir is another scandal waiting to happen.

Given that remdesivir is expensive and doesn't seem to save lives, does it have any value? Maybe — but not as a medicine itself. Recent research suggests scientists should at least keep studying how it works in order to develop better drugs.

Remdesivir does block Coronavirus

Remdesivir doesn't prevent people from being infected by the SARS-CoV-2 virus.

Whereas a vaccine is designed prompt your immune system to recognize the spike protein that allows Coronavirus to invade cells — and protect people from infection — antivirals such as remdesivir aim to disrupt the virus' ability to replicate, to slow its spread and give your body extra time to develop immunity.

Coronaviruses use RNA for their genetic material — not the DNA used by cells — which means that they need a special molecular machine to copy their genes when producing new virus particles. That machine, 'RNA polymerase', is what's targeted by remdesivir.

Two studies have now revealed how remdesivir blocks SARS-CoV-2 at the molecular level.

First, chemical engineers at the University of Chicago found that remdesivir is better at reducing virus replication than two similar antivirals, ribavirin and favilavir. Their computer models suggest that remdesivir beats the other drugs because it's the best at binding and destabilizing the RNA polymerase.

In the second new study, researchers at the University of Texas at Austin used 'cryogenic-electron microscopy' (cryo-EM) to take snapshots of the structure of the molecules involved in replication as they would interact in a Covid patient.

After adding remdesivir to RNA polymerase, cryo-EM images showed that the drug acts like a blockage in a photocopier, getting stuck in the RNA polymerase. When four molecules of remdesivir get between the gears of the polymerase machine, its copies of RNA 'paper' can no longer pass through, stalling the virus-copying process.

That leads us to why it's worth studying remdesivir. As structural biologist David Taylor explains, "We were able to identify the point where that paper jam happens [...] If we want to make the blockage even worse, we could do so."

One of remdesivir's flaws is its (possibly toxic) high dosage over a short timeframe, which contributes to adverse side effects. By tweaking the drug molecule's structure, scientists may be able to make it block the RNA polymerase machine with fewer molecules, which would then allow the drug to be delivered in a smaller dose.

In fact, Gilead Sciences has already isolated a compound similar to remdesivir, GS-441524, which costs less and is easier to manufacture. It's also simpler to administer: while remdesivir

must be injected, GS-441524 could be ingested in pill form. More of the molecule reaches the lungs — the main site of infection — too, which led researchers to state that "GS-441524 is superior to remdesivir for Covid-19 treatment."

As SARS-CoV-2's genetic material mutates to create new strains of the virus — and variants of Covid-19 — we may need antivirals to buy us time if those new strains end-up evading our current vaccines.

So despite being expensive and ineffective at treating Covid, remdesivir's true value could be to help researchers create more effective medicines.

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