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Covid-19: What now for remdesivir?

The spectre of past pandemics looms large over remdesivir, one of the first drug treatments for covid-19. With a WHO trial finding little benefit, Jeremy Hsu asks if the expensive drug is just Tamiflu redux?

Jeremy Hsu

It's a cautionary tale worth remembering amid the coronavirus pandemic.

Starting in the early 2000s, governments spent billions of dollars stockpiling the antiviral drug oseltamivir (Tamiflu) in anticipation of flu pandemics. Years later, independent researchers gained access to unpublished clinical studies that showed the drug had only a modest effect on reducing the duration of symptoms, had many side effects, and displayed insufficient data to conclude whether it could prevent influenza's most serious complications.[1 2]

Fast forward to 2020 and we have remdesivir, an expensive, experimental antiviral and one of the first, and hence hyped, treatments to emerge for covid-19.

It comes from a collaboration between Gilead Sciences, the US Centers for Disease Control and Prevention (CDC), and the US Army Medical Research Institute of Infectious Diseases that sought to find treatments for RNA based viruses with the potential to spark pandemics.[3 4] After disappointing results treating Ebola in 2014, remdesivir was tested in the early stages of the covid-19 pandemic. Initial trial evidence suggested that it can shorten recovery times for severely ill hospitalised patients,[5] giving it global attention.

The results were lauded by the National Institutes of Health (NIH) and an emergency use authorisation (EUA) was swiftly made by the US Food and Drug Administration (FDA) in May.[6] It is soon to be more widely available in the UK and Europe.[7]

None of the randomised controlled trials published so far, however, have shown that remdesivir saves significantly more lives than standard medical care. There is conflicting evidence about whether a five or 10 day treatment cycle leads to any clinical improvement. And the World Health Organization's Solidarity trial—a huge international study involving thousands of patients—has published interim results showing that the drug has no significant impact on mortality, length of hospital stay, or need for ventilation among hospitalised patients.[8] This represents some of the strongest evidence yet that remdesivir is unlikely to be the lifesaving drug for the masses that many have hoped for.

Instead, researchers are now focusing on moderately ill patients who could still benefit from the drug if it's given early. But considering the high price, limited stocks, and now arguably limited benefits, what now for remdesivir and doctors considering using it?

A high price to pay

"Paying a high price for remdesivir without good evidence of mortality benefit is a gamble," says Robin Ferner, a physician and professor of clinical pharmacology at the University of Birmingham.

Even before the Solidarity trial results came out, many doctors questioned remdesivir's effectiveness, particularly considering its cost can quickly add up to millions for a single hospital dealing with hundreds of covid-19 patients.

A treatment cycle may take 5-10 days.[9] A five day course of treatment for one patient costs around $2340 (£1773; €1976) for government programmes and $3120 for private insurers, although Gilead has reached agreements to make cheaper generic versions of the drug available in low and middle income countries. For comparison, Tamiflu costs less than $75 per course of treatment to shorten symptom duration for patients with influenza (generic versions of the drug can cost even less).

Many hospitals have also faced difficult decisions about which patients would benefit from taking remdesivir—a challenge further complicated by supply problems, changing regulatory advice, and lingering questions about clinical effectiveness and safety.

Steven Pearson, a physician and president of the Institute for Clinical and Economic Review, a Boston based non-profit organisation focused on cost effectiveness analyses of medical treatments and tests, has said that Gilead's pricing of remdesivir is cost effective only if two key assumptions hold true. "The current price would meet a key cost effectiveness threshold only if it were used solely to treat patients hospitalised with moderate-to-severe disease and—importantly—only if one still assumes that remdesivir saves lives," Pearson said in a statement in November.[10]

The first assumption is undermined by the fact that US regulators have expanded possible use of remdesivir to patients with milder cases of the disease. The second assumption also remains unproved given that the Solidarity trial and other clinical trials have shown no significant mortality benefit. As a result, the Institute for Clinical and Economic Review's pricing model "suggests that remdesivir's current US price is too high to align reasonably with its demonstrated benefits to patients," Pearson said.

Compounding matters, none of the preclinical studies that tested remdesivir on animals infected with

SARS-CoV-2 have yet established a record of robust safety and efficacy, according to Rokuro Hama, a physician and director of the non-profit Japan Institute of Pharmacovigilance in Osaka, who has also extensively studied Tamiflu. The FDA's prescribing information for remdesivir currently includes cautionary notes about the need to monitor kidney and liver function in human patients.[11]

Unlike some researchers who are pushing for more human clinical trials, Hama prefers to first see evidence that remdesivir can reduce mortality among infected animals when administered after covid-19 symptoms begin. He notes drug toxicity concerns that surfaced in prior animal studies. "Clinical dose of remdesivir for covid-19 is equivalent to double the toxic dose in rats and monkeys which showed renal damage," Hama says.

Even in humans, the ideal way to study any drug is to compare its treatment outcomes in one group with the outcomes from a control group receiving a placebo. An early placebo controlled trial in China found no evidence of benefit from remdesivir. Instead, the FDA's drug approval announcement cites just one placebo controlled trial: ACTT-1 which was sponsored by the NIH. ACTT-1 showed a five day course of remdesivir improved patients' time to clinical improvement, but this study also made the controversial decision to end the placebo treatment arm early.[12] That limited the capability to collect more data on the effects of remdesivir and possibly see if the drug can reduce mortality rates.

Solidarity

WHO's Solidarity trial is an open label study that does not include a control group receiving placebo. A Gilead statement attempted to cast doubt on the Solidarity trial because of its open label design that allows physicians and patients to know who is taking remdesivir, despite the fact that the pharmaceutical company has touted results from other open label studies that it sponsored.[13 14]

Solidarity was designed to look at harder, more objective health endpoints that open label clinical trials would be unlikely to influence, such as mortality, ventilation requirements, and length of hospitalisation.

Srinivas Murthy, an intensive care and infectious diseases physician at the British Columbia Children's Hospital in Vancouver and principal investigator for the Canadian portion of Solidarity, says, "Mortality should not be affected by whether a study is open label or closed or placebo blinded for obvious reasons: you or your doctors can't will yourself into staying alive by knowing you had the drug."

What Solidarity does to an impressive extent is to evaluate remdesivir's impact in a patient population on a far bigger scale than any previously published studies—2750 patients who received a 10 day course of remdesivir came from a total study population of 11 266 hospitalised adult patients. The number of Solidarity study participants dwarfs the number involved in the ACTT-1 study that has been touted by Gilead and US regulators. "The number of participants in the Solidarity trial is almost 10 times that of ACTT-1," Hama says.

The Solidarity trial also draws upon a diverse group of patients in 405 hospitals spread across 30 countries. Gilead questioned the Solidarity results because the study "prioritised broad access, resulting in significant heterogeneity in trial adoption, implementation, controls, and patient populations." But both the Solidarity team and independent experts say that this actually represents the strength of the study—a global test of how remdesivir performs in complex real world environments beyond the controlled settings of the smaller clinical trials that came before.

"With a disease that has infected over 45 million people in nearly 200 countries and caused over one million deaths, we need trials with heterogeneous populations," says Erin McCreary, an infectious diseases clinical pharmacist at the University of Pittsburgh Medical Center, who was not involved in the WHO study. "Solidarity was an impressively massive trial that is pretty much as good as it gets in a global pandemic to determine which therapies are effective and which populations optimally benefit."

Before the Solidarity results were announced, McCreary had co-authored an editorial for *JAMA* summarising the conflicting evidence from the remdesivir studies and detailing the study design differences, including the recruitment of patients with varying severities of illness.[15] Earlier studies had already consistently shown that certain subgroups of patients did not derive benefit from remdesivir: the more severely ill patients who require high flow supplemental oxygen through nose tubes, non-invasive ventilation through face masks, or invasive ventilation through a tube down the throat. "And we now have over 5000 patients in the remdesivir arm of the Solidarity trial that still show no benefit," McCreary told *The BMJ*.

That leaves clinicians to conclude that remdesivir only benefits a small subset of moderately ill patients. McCreary says the drug needs to be studied in randomised trials in this subset of patients who may benefit. "We don't have conclusive evidence to say what the ideal patient population is for this drug, and it's still a globally scarce resource (see box)."

The Solidarity trial is continuing to study if remdesivir can help such moderately ill patients who seem the most likely to benefit from the drug (those requiring low flow oxygen but who are not on ventilators). There may still be a chance of remdesivir delivering a mortality benefit for such patients. "If there is an effect, it's an exceedingly small one," Murthy says, "But any effect on mortality is something to note, and then policy makers and clinicians can make a decision as to whether or not the drug needs to be rolled out in targeted populations."

Regulation and revelations

The public health emergency compelled regulators to speed up regulatory processes and allow hospitals to make some conditional uses of remdesivir before completion of the usual approval process.

The EUA enabled the drug to skip all that and be used in clinics for emergencies. Remdesivir has also sometimes been provided on a "compassionate use" basis at cost price under FDA rules that permit the use of experimental drugs outside of clinical trials if a doctor applies.[16] But there are no restrictions on how much a pharmaceutical company can charge once it receives either an EUA or gets formal approval for a new drug application. Gilead stated the compassionate use programme in the US was winding down following the EUA.[17]

"There is always a tension between withholding a drug from general use when it is beneficial, and protecting the public from a drug that doesn't work or is unacceptably harmful," Ferner says.

One controversial regulatory decision came on 28 August, when the FDA expanded the EUA to allow use of remdesivir in all patients hospitalised with covid-19, not just severe cases. For some physicians and medical researchers, that was a step beyond what the available clinical trial evidence can support. Alyssa Letourneau, an infectious disease physician and director of the antimicrobial stewardship programme at Massachusetts General Hospital in Boston, told *The BMJ* on 6 October, "At this price point it's more

difficult to give it to patients who newly qualify under the updated EUA when the data aren't clear that they will benefit."

Similar concerns were raised in an open letter by Eric Topol, director and founder of the Scripps Research Translational Center in La Jolla, California, which questioned the credibility of the FDA commissioner, citing the expanded remdesivir EUA among other decisions.[18] "There are insufficient data to support this approval, as it is based on small, open label studies with subjective endpoints," Topol wrote. "Remdesivir is an expensive drug, costing around $3000 per treatment, in short supply, and even its approval for severe covid-19 was based on time to recovery in a relatively small trial of just over 1000 patients."

The European Medicines Agency had already granted conditional approval similar to the FDA's EUA for remdesivir back in July.[19] On 8 October, the European Commission followed up by signing a joint procurement framework contract with Gilead for a six month supply of up to 500 000 treatment courses of remdesivir worth $1.2bn.[20 21] But what the European Commission didn't know was that Gilead had already received a draft manuscript of the Solidarity findings in September.[22] The commission only learnt about remdesivir's lacklustre performance in Solidarity the day after it signed the contract with Gilead.

To the surprise of many, on 22 October—a week after the Solidarity results became public—the FDA officially approved the drug as a covid-19 treatment for all hospitalised patients over 12 years of age.[23] FDA reviewers were aware of the Solidarity trial data, says Chanapa Tantibanchachai, a press officer at the FDA. But she added that the agency's approval of remdesivir was largely based on the NIH's ACTT-1 trial along with two Gilead sponsored trials.

It is possible for the FDA to withdraw approval of drugs for reasons of safety or effectiveness.[24] But some researchers worry that the FDA approval will make it harder to carry out additional studies, especially if some physicians are reluctant to withhold remdesivir from patients. "The FDA does not believe that the approval of remdesivir will negatively impact the clinical development of remdesivir," Tantibanchachai told *The BMJ*.

But Derek Angus, an intensive care physician and chief healthcare innovation officer at the University of Pittsburgh Medical Center, who co-authored the *JAMA* editorial on remdesivir with McCreary, says a potential side effect of the FDA approval is that it will thwart or stymie the conduct of further randomised controlled trials that would otherwise be able to help delineate exactly in whom, and at what point in the course of disease, remdesivir should be used. "The lack of benefit in the Solidarity trial only reinforces the need to better understand remdesivir's effects," he says.

A Gilead representative noted that there are multiple international clinical trials ongoing to evaluate the safety and efficacy of remdesivir for different patient populations, formulations, and in combinations with other therapies. But the company also suggested that testing remdesivir against placebo would no longer be warranted.

Bahar Turkoglu, senior director of public affairs at Gilead Sciences UK and Ireland, told *The BMJ*, "Now that the safety and efficacy of remdesevir has been assessed across multiple randomised controlled clinical trials and it is considered a standard of care, it would not be ethical to conduct a placebo controlled trial in patients who would otherwise be eligible to receive this treatment."

The next Tamiflu?

The full story of remdesivir will not be known until Gilead releases the full clinical study reports, as the pharmaceutical company Roche finally did with Tamiflu in 2013. "It was only once we looked at the whole thing that we found the benefits of Tamiflu were the shortening of the duration of illness by a few hours," says Tom Jefferson, an epidemiologist and Cochrane reviewer who is currently suing Roche under the US False Claims Act. "There was nothing credible on deaths, transmission, or hospitalisation."

There is a chance to avoid similar uncertainty hanging over remdesivir, especially with so many patients who can be enrolled in large scale clinical trials during the pandemic. Much will depend on whether future studies are designed to test remdesivir's potential effectiveness.

All this remains in the middle of a still raging pandemic, with alternative treatments now impacting discussions about remdesivir's cost effectiveness. The well known, cheap, and widely available corticosteroid dexamethasone, for example, has been proved to reduce mortality among severely ill covid-19 patients who were either on ventilators or receiving oxygen.[25] Given the apparent benefit to reducing mortality in some cases at a cost of less than $1 per day, many experts want to see studies testing remdesivir's effectiveness when given in conjunction with corticosteroids.

And then there is remdesevir's relative. In late August, the NIH began investigating the potential of GS-441524, another compound owned by Gilead that is the parent nucleoside of remdesivir. Compared with remdesivir, GS-441524 could be easier to synthesise and manufacture—and could cost much less. It could also be produced as an oral formulation—remdesivir must be given intravenously—that can be administered outside hospitals earlier following diagnosis when antiviral drugs typically show the most benefit. Preclinical animal studies suggest it may also prove less toxic to many organs of the body than remdesivir and therefore could be given at higher doses with possibly improved therapeutic effect.

"Gilead has done a considerable amount of safety and toxicity work on GS-441524, and they have data on file with the FDA," says Victoria Yan, chemist at the University of Texas MD Anderson Cancer Center, who has been pushing for a phase I trial to explore GS-441524 as a covid-19 treatment.[26]

Gilead told *The BMJ* that it chose to prioritise development of remdesivir over GS-441524 as a covid-19 treatment because of available evidence at the time from animal studies and because the company already had some safety data on remdesivir in humans from prior clinical trials focused on Ebola. But the company is currently investigating GS-441524 through animal studies.

"We have initiated additional preclinical studies to further compare remdesivir and GS-441524," Turkoglu says. "We will publish the data as soon as they become available."

Limited supplies

Supplies of remdesivir remain variable across the world. Shortages and high prices have affected the US and much of Europe. Gilead has moved to boost remdesivir production, but WHO has taken a cue from its Solidarity trial in excluding remdesivir from the list of priority drugs it's looking to supply to poor countries.[27 28]

Still, Gilead has signed licensing agreements with manufacturers in Egypt, India, and Pakistan that permit the sale of generic versions of the drug across low and middle income countries including Bangladesh and the Philippines.[29-31]

Gilead's Bahar Turkoglu told *The BMJ*, "Currently, our licensees have made generic remdesivir available to patients in need in more than 40 countries, and we expect this number will continue to grow over the coming months."

Timeline

8 April Gilead initiates a rolling new drug application for remdesivir with the FDA

29 April First randomised controlled trial published in the *Lancet* finds no significant difference between remdesivir and placebo for hospitalised patients in China

1 May FDA gives first emergency use authorisation allowing remdesivir to be given to patients hospitalised with severe covid-19

7 May Japanese Ministry of Health, Labour, and Welfare grants regulatory approval for remdesivir to be used in patients hospitalised with severe cases of covid-19 under an exceptional approval pathway

22 May ACTT-1 trial, sponsored by NIH and published in *NEJM*, finds that a 10 day course of remdesivir shortens time to clinical improvement by five days compared with placebo, but has no significant impact on mortality

27 May Gilead sponsored, open label Simple-Severe trial published in *NEJM* finds remdesivir shortens time to clinical improvement for moderately ill covid-19 patients on both five day and 10 day treatment regimens

29 June Gilead announces pricing for a six vial, five day treatment course set at $2340 for governments of developed countries. But US private insurers and the US government's Medicare and Medicaid programmes must pay $3120

3 July European Commission grants conditional marketing authorisation for remdesivir to be used in covid-19 patients with pneumonia requiring supplemental oxygen

10 August Gilead announces it has submitted the final part of its new drug application for remdesivir to the FDA

21 August Gilead sponsored, open label trial published in *JAMA* finds remdesivir shortens time to clinical improvement for moderately ill covid-19 patients on a five day treatment regimen but not a 10 day regimen

28 August FDA expands emergency use authorisation to allow remdesivir to be used in all patients hospitalised with covid-19 regardless of disease severity.

1 October Gilead takes over distribution of remdesivir from the US Department of Health and Human Services and begins selling directly to hospitals

8 October European Commission and Gilead sign a joint procurement agreement worth up to $1.2bn for up to 500 000 treatment courses over six months

15 October WHO sponsored, open label Solidarity trial (preprint) finds that remdesivir has little or no effect on overall mortality, initiation of ventilation, or duration of hospital stay

22 October FDA officially approves remdesivir for use in patients hospitalised with covid-19

Commissioned, not peer reviewed.

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