Remdesivir Shows Promise for COVID-19, but Not a Game Changer

FDA grants emergency use authorization, but randomized clinical trials of the antiviral drug show mixed results.

June 3, 2020 By Liz Highleyman

On May 1, the Food and Drug Administration granted emergency use authorization (EUA) for remdesivir, an antiviral medication being developed by Gilead Sciences. The EUA covers treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.

> FDA issued an Emergency Use Authorization (EUA) to Gilead Sciences, Inc. for the investigational antiviral drug remdesivir – which has been shown to shorten recovery time in some #COVID19 clinical trial patients – to treat suspected or confirmed #COVID19. https://t.co/indPpdMi7d pic.twitter.com/4RsJ5YyK07
>
> — Dr. Stephen M. Hahn (@SteveFDA) May 1, 2020

Results from Gilead's randomized SIMPLE trials—one in patients with severe COVID-19 and one in people with moderate disease—showed that remdesivir led to promising, albeit modest, improvement. Two placebo-controlled trial, however, produced conflicting results.

Because a majority of people with COVID-19 recover without treatment, it's important to compare experimental therapies against a placebo in randomized trials to determine how much the new drug helps. Once a treatment has been found to work better than a placebo, it can then become the standard of care and the basis of comparison in randomized studies of other therapies.

As National Institutes of Health director Francis Collins, MD, PhD, described in a recent blog post, drugs may show activity against multiple viruses in the laboratory, but they must be tested in patients to determine if they actually work against a specific disease. Remdesivir was originally developed to treat Ebola virus, but proved ineffective. In animal studies, it showed activity against SARS and MERS, caused by coronaviruses related to the one that causes COVID-19 (officially known as SARS-CoV-2).

> Could a failed #Ebola drug work against #COVID19? Get the latest on early human tests of the antiviral #remdesivir. #NIH https://t.co/BheC6z4f6j
> — Francis S. Collins (@NIHDirector) April 17, 2020

Severe COVID-19 illness is caused partly by the coronavirus itself and partly by the immune system's response to it. Just as antivirals for HIV and hepatitis C work best when used early, before they cause severe immune system or liver damage, remdesivir and other medications that halt SARS-CoV-2 virus replication may be more effective when used before severe lung damage occurs. Later on, combining antivirals with anti-inflammatory drugs that control the excessive immune reaction known as a cytokine storm might produce the best outcomes.

Clinical trials are currently underway of remdesivir in combination with other medications, including the anti-inflammatory drugs Actemra (tocilizumab) and Olumiant (baricitinib). Gilead is also working on remdesivir formulations that can be administered by subcutaneous injection or inhalation, which would be more practical for people treated outside a hospital.

SIMPLE Trials

The Phase III SIMPLE trials enrolled hospitalized patients with confirmed COVID-19 in more than a dozen countries with a high prevalence of the new coronavirus, including the United States, China, Italy, Spain and the United Kingdom.

On June 1, Gilead announced results from a trial of 584 people with moderate COVID-19 who had evidence of pneumonia but did not have reduced oxygen levels at study entry. They were randomly assigned to receive IV infusions of remdesivir for five or 10 days or standard care alone. The primary endpoint was clinical status as assessed on a seven-point scale ranging from hospital discharge, to increasing need for oxygen support or mechanical ventilation, to death.

Patients who received the five-day course were 65% more likely to experience clinical improvement on Day 11 compared with the standard care group. Those treated for 10 days did somewhat better than the standard care group, but the difference did not reach statistical significance, meaning it could have been due to chance.

Those treated with remdesivir for five days were more likely to experience at least a two-point clinical improvement compared with the standard of care group (70% versus 61%), and less likely to experience at least a one-point decline (3% versus 11%). Two people receiving standard care, one person receiving the 10-day course and no one receiving the five-day course died.

Remdesivir was generally well tolerated. The most common adverse events were nausea, diarrhea, and headache. Overall adverse events (51% versus 45%) and severe events (10% versus 12%) occurred with similar frequency in the five-day remdesivir and standard care groups. Gilead indicated that the full data will be submitted for publication in a peer-reviewed medical journal.

"These study results offer additional encouraging data for remdesivir, showing that if we can intervene earlier in the disease process with a five-day treatment course, we can significantly improve clinical outcomes for these patients," Francisco Marty, MD, of Brigham and Women's Hospital and Harvard Medical School said in a Gilead press release.

Gilead previously announced early results from the SIMPLE-Severe trial on April 29. Results were later published in May 27 issue of The New England Journal of Medicine.

The 397 patients in this study had evidence of pneumonia and reduced oxygen levels at study entry but did not yet require mechanical ventilation. Participants were randomized to receive IV remdesivir for five or 10 days; none received standard care alone.

Both regimens worked about equally well. At the two-week mark, 64% of people in the five-day group and 54% in the 10-day group experienced clinical improvement, defined as at least a two-point increase on the seven-point scale. However, after adjusting the data to account for baseline clinical status—those in the 10-day group were sicker—the difference did not reach statistical significance.

The median duration of hospitalization was seven days in the five-day treatment group versus eight days in the 10-day group. At the end of two weeks, 60% of people on the five-day regimen and 52% of those on the 10-day regimen had been discharged from the hospital. The discharge rate was higher for those who started remdesivir sooner after the onset of symptoms compared with those who started later (62% versus 49%).

Death rates were 8% in the five-day group and 11% in the 10-day group. The results differed somewhat by country, with patients in Italy faring worse.

Treatment was again described as "generally well tolerated" in this sicker patient population. The rate of treatment discontinuation due to adverse events was lower in the five-day group compared with the 10-day group (4% versus 10%); 6% versus 8%, respectively experienced ALT liver enzyme elevations.

"Unlike traditional drug development, we are attempting to evaluate an investigational agent alongside an evolving global pandemic," said Gilead chief medical officer Merdad Parsey, MD, PhD. "The study demonstrates the potential for some patients to be treated with a five-day regimen,

which could significantly expand the number of patients who could be treated with our current supply of remdesivir. This is particularly important in the setting of a pandemic, to help hospitals and healthcare workers treat more patients in urgent need of care."

NIAID ACTT Trial

On April 29, the National Institutes of Allergy and Infectious Diseases (NIAID) announced early data from a placebo-controlled trial showing that remdesivir led to quicker recovery in COVID-19 patients with advanced disease. These results were later published in May 22 issue of The New England Journal of Medicine.

This study showed that remdesivir "has a clear-cut, significant positive effect in diminishing the time to recovery," NIAID director Anthony Fauci, MD, said at an April 29 White House new briefing. "This is a very important proof of concept, because what is has proven is that a drug can block this virus."

"This is reminiscent of 34 years ago, in 1986, when we were struggling for drugs for HIV. We had nothing, and there were a lot of anecdotal reports that maybe they work, maybe they don't," Fauci added. "We did the first randomized, placebo-controlled trial with AZT, which turned out to give an effect that was modest, but that was not the end game. Building on that, every year after, we did better and better."

> Dr. Fauci says he was told data from a coronavirus drug trial testing Gilead's remdesivir shows that "remdesivir has a clear cut significant, positive effect in diminishing the time to recovery." https://t.co/kaovCY312w pic.twitter.com/cXcCcf750l
>
> — CNBC (@CNBC) April 29, 2020

These findings come from NIAID's Adaptive COVID-19 Treatment Trial, which has study sites in the United States and several other countries. The study included 1,063 hospitalized patients with confirmed COVID-19 with evidence of lower respiratory tract involvement. They were randomly assigned to receive remdesivir or a placebo administered intravenously for up to 10 days; results were available for 1,059 patients.

On April 27, the study's independent data and safety monitoring board notified Fauci and the trial investigators that remdesivir worked significantly better than the placebo, meaning the results

were probably not attributable to chance.People assigned to the placebo group were then offered remdesivir.

The median time to recovery was 11 days in the remdesivir group compared with 15 days in the placebo group—about a 30% improvement. The benefit was greater for those who required supplemental oxygen but not mechanical ventilation, but there was little difference for those on ventilators. The study also saw a trend toward improved survival, with mortality rates of 7% in the remdesivir group versus 12% in the placebo group, but this did not reach statistical significance.

Serious adverse events were more common in the remdesivir compared with the placebo group (21% versus 27%, respectively).

Based on the results from this study and the SIMPLE-Severe trial, Raphael Dolin, MD, of Beth Israel Deaconess Hospital, and Martin Hirsch, MD, of Massachusetts General Hospital wrote in an accompanying editorial, "In our current era of limited remdesivir supplies, priority should be given to a five-day remdesivir regimen at the early stages of severe disease (i.e., when they are receiving supplemental oxygen but have not been intubated) since the evidence of benefit is clearest in this population."

Of note, however, neither of these study reports included data on DARS-CoV-2 viral load data, which would be an important indicator of whether an antiviral medication is working as expected.

Randomized Trial in China

On April 23, STAT leaked results from a randomized clinical trial of remdesivir in China, which was stopped early because there were no longer enough patients once the COVID-19 epidemic there was brought under control. The results were accidentally posted to the World Health Organization website but quickly taken down. Results from that trial were later published in the April 29 online edition of The Lancet.

The study enrolled 237 adults with COVID-19 at 10 hospitals in Hubei, China. They had an oxygen saturation of 94% or less or another measure of impaired respiration as well as confirmed pneumonia as indicated by lung scans. They were randomly assigned to receive IV remdesivir or a placebo for 10 days. They were allowed to also use other medications including Kaletra (lopinavir/ritonavir), interferons and corticosteroids.

Remdesivir did not significantly speed up improvement of symptoms or reduce the likelihood of death compared with the placebo. The researchers also saw no significant differences in length of hospitals stay, time on ventilators or how long to took to clear the coronavirus. The study did suggest faster improvement among those treated earlier—within 10 days of symptom onset—but that difference was not statistically significant. Adverse events were about equally common in both groups, but more people using remdesivir stopped treatment early due to adverse events (12% versus 5%).

"In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not

associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies," the researchers concluded.

Responding to the leaked data, a Gilead spokesperson said that the company still believes "trends in the data suggest a potential benefit for remdesivir, particularly among patients treated early in disease." However, Andrew Hill, PhD, of the University of Liverpool, told STAT, "If there is no benefit to remdesivir in a study this size, this suggests that the overall benefit of remdesivir in this population with advanced infection is likely to be small in the larger Gilead trial."

More Leaked Trial Data

On April 17, STAT reported on preliminary outcomes at a Chicago hospital that is treating severely ill COVID-19 patients as part of a Phase III trial. This study site enrolled 125 participants, 113 of whom had severe disease. They were all treated with daily IV infusions of remdesivir, with no placebo group.

> A Chicago hospital treating severe Covid-19 patients with Gilead Sciences' antiviral medicine remdesivir in a closely watched clinical trial is seeing rapid recoveries in fever & respiratory symptoms, with nearly all patients discharged in less than a week https://t.co/YeePsK5ymW
>
> — STAT (@statnews) April 17, 2020

The report was based on comments from study investigator Kathleen Mullane, DO, PharmD, of the University of Chicago, made during a video discussion with colleagues. Her remarks were not intended for the public, and the study results have not yet been peer-reviewed or published in a scientific journal.

The patients recovered more quickly than would have been expected without treatment. Their fevers decreased rapidly, respiratory symptoms improved and some were able to come off ventilators soon after starting treatment.

"The best news is that most of our patients have already been discharged, which is great," STAT quoted Mullane as saying in the video. "We've only had two patients perish."

Although preliminary, these results were greeted with optimism.

“Even without a control, if those results hold up, that’s awfully promising,” Bob Wachter, MD, chair of the Department of Medicine at the University of California at San Francisco tweeted after seeing the leaked findings.

Gilead declined to provide further information about the Chicago findings. “We understand the urgent need for a COVID-19 treatment and the resulting interest in data on our investigational antiviral drug remdesivir,” the company said in a statement. “The totality of the data need to be analyzed in order to draw any conclusions from the trial. Anecdotal reports, while encouraging, do not provide the statistical power necessary to determine the safety and efficacy profile of remdesivir as a treatment for COVID-19.”

Compassionate Use Findings

In the April 10 online edition of The New England Journal of Medicine, investigators published early data from Gilead’s compassionate use program, which provided remdesivir to people with advanced disease outside of formal trials.

This analysis included 61 hospitalized COVID-19 patients who had low oxygen levels or were receiving oxygen support. A majority were men over 60 with underlying health conditions including hypertension or diabetes—a population known to be at higher risk for more severe disease.

All patients were treated with a 10-day course of remdesivir given by IV infusion. Post-treatment data were available for 53 of them (22 in the United States, 22 in Europe or Canada and 9 in Japan). Of these, 30 (57%) were on mechanical ventilators and four (8%) were receiving extracorporeal membrane oxygenation, a method that withdraws blood, adds oxygen and returns it to the body.

Over a median follow-up period of 18 days, 36 patients (68%) needed less oxygen support, including 17 who were able to come off ventilators. Nearly half the patients (47%) were discharged from the hospital. Seven people died, yielding mortality rates of 18% among those on ventilators and 5% (representing one patient) among those who did not need ventilators. Everyone who was taken off a ventilator survived.

No unexpected side effects were reported. About a quarter of the patients experienced mild to moderate ALT or AST liver enzyme elevations, and two of the four people who stopped treatment prematurely did so due to elevated liver enzymes. Twelve people on ventilators experienced serious adverse outcomes, including multiple organ failure, septic shock, acute kidney injury or shock.

“Currently there is no proven treatment for COVID-19. We cannot draw definitive conclusions from these data, but the observations from this group of hospitalized patients who received remdesivir are hopeful,” lead study investigator Jonathan Grein, MD, of Cedars-Sinai Medical Center in Los Angeles, said in a Gilead press release. “We look forward to the results of controlled clinical trials to potentially validate these findings.”

Remdesivir in Monkeys

On April 17, NIAID announced findings from an animal study of remdesivir in rhesus macaque monkeys infected with SARS-CoV-2. These results were posted on the preprint server bioRxiv and have not yet been peer-reviewed.

Like human, infected moneys had evidence of pneumonia on lung scans and high viral loads in swab samples from the nose and throat as well as in lung fluid.

Two groups of six monkeys were infected with SARS-CoV-2. Twelve hours later, one group received a dose of IV remdesivir, followed by a daily booster dose for the next six days. Researchers timed the initial treatment to occur shortly before the virus reached its highest level in the lungs, according to a NIAID press release. The other six monkeys did not receive any treatment.

The monkeys who were treated early with remdesivir had significantly less breathing difficulty, lower virus levels in the lungs and less lung damage compared with untreated animals. Twelve hours after the first dose of remdesivir, the six treated monkeys showed mild breathing difficulty while all six untreated animals showed rapid and difficult breathing.

Importantly, although remdesivir improved clinical outcomes, it did not reduce virus shedding. If this finding is confirmed in humans, it would suggest that people can still transmit the coronavirus while being treated with remdesivir.

“The efficacy of direct-acting antivirals against acute viral respiratory tract infections typically decreases with delays in treatment initiation,” the study authors wrote. “Thus, remdesivir treatment in COVID-19 patients should be initiated as early as possible to achieve the maximum treatment effect.”

Commenting on these and other study findings in an April 10 open letter, Gilead chairman and CEO Daniel O’Day wrote, “In studying remdesivir, the question is not just whether it is safe and effective against COVID-19 but in which patients it shows activity, how long should they receive treatment and at what stage of their disease would treatment be most beneficial. Many answers are needed, which is why we need multiple types of studies involving many types of patients.”

Other Drugs in the Pipeline

Researchers are testing dozens of other treatment candidates for COVID-19, many of which are currently approved for other conditions. Hundreds of clinical trials of potential therapies are now underway.

Studies of chloroquine and hydroxychloroquine (Plaquenil), two inexpensive malaria medications touted by President Donald Trump, have so far have yielded largely disappointing results. A study in Brazil was recently halted after patients receiving high doses of chloroquine experienced serious cardiac side effects.

As POZ previousy reported, the HIV antiretroviral pill Kaletra (lopinavir/ritonavir) proved no more

effective than standard supportive care in one of the first clinical trials of the drug. The company that manufactures another HIV protease inhibitor, Prezista (darunavir), warned that it is unlikely the drug will have significant activity against the coronavirus.

Doctors are permitted to prescribe drugs that are approved for other conditions “off label” for COVID-19. However, medical experts and advocates urge caution about the premature use of experimental therapies before randomized clinical trials prove they are safe and effective.

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http://beta.docker.covidhealth.com/article/remdesivir-shows-promise-covid-19-game-changer