Remdesivir for COVID-19 Shows No Survival Benefit in Large Study

None of the four drugs tested in the WHO's Solidarity trial reduced mortality or duration of hospitalization.

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The experimental antiviral drug remdesivir (Veklury) did not reduce the risk of death, the chances of being put on a ventilator or the length of hospital stays in the World Health Organization's large Solidarity trial, according to results released this week. Other drugs tested in the study—hydroxychloroquine, Kaletra (lopinavir/ritonavir) and interferon beta—also failed to improve these outcomes.

"The unpromising overall findings from the regimens tested suffice to refute early hopes, based on smaller or non-randomized studies, that any will substantially reduce inpatient mortality, initiation of ventilation or hospitalization duration," the investigators concluded.

However, remdesivir's manufacturer, Gilead Sciences, noted that the results conflict with those of prior randomized clinical trials and suggested that the complex study design of Solidarity does not provide definitive answers.

Remdesivir is a nucleotide analogue, in the same class as several widely used medications for HIV and hepatitis B and C. These drugs interfere with the viral polymerase enzyme, acting as defective building blocks that prevent viruses from copying their genetic material.

On May 1, the Food and Drug Administration (FDA) granted emergency use authorization (EUA) for remdesivir for people hospitalized with severe COVID-19. In August, the FDA expanded the EUA to include all hospitalized patients regardless of disease severity. COVID-19 treatment guidelines from the National Institutes of Health (NIH) recommend remdesivir for first-line treatment of patients who require supplemental oxygen. Gilead filed for regular approval of remdesivir in August.

Previously, Gilead's Phase III SIMPLE trials showed that remdesivir led to promising, albeit modest, improvement. Patients with moderate disease who received a five-day course of remdesivir by IV infusion were 65% more likely to experience clinical improvement compared with a standard of care group. For people with severe disease, two thirds of those who received a five-day course and 64% who received a 10-day course experienced clinical improvement; the latter trial had no

standard care control group.

The Adaptive COVID-19 Treatment Trial (ACTT-1), sponsored by the National Institutes of Allergy and Infectious Diseases, showed that hospitalized patients randomly assigned to remdesivir recovered faster than those who received a placebo (10 days versus 15 days, respectively). There was a trend toward reduced mortality at 29 days (11% versus 15%, respectively), but the difference did not reach the threshold for statistical significance. An earlier study in China found that remdesivir did not significantly speed recovery or reduce the likelihood of death compared with a placebo.

The latest results come from the ongoing Solidarity trial, which is comparing multiple treatments for COVID-19. So far, the study has enrolled nearly 12,000 participants in more than 30 countries.

On October 15, trial investigators reported results in a preprint (meaning a scientific paper that has not yet been peer reviewed) showing that all the treatments evaluated—remdesivir, the malaria drug hydroxychloroquine, the HIV combination pill Kaletra and interferon beta—had "little or no effect" on mortality, the need for ventilation or duration of hospital stays. So far, only the steroid dexamethasone has been shown to improve survival in people with severe COVID-19.

Between March 22 and October 4, the Solidarity investigators collected data from 11,266 adults hospitalized with COVID-19 who were randomly assigned to receive locally available medications or standard care. More than half (62%) were men, and about 20% were age 70 or older. About 8% were already on a ventilator at the start of treatment.

Of these, 2,750 received remdesivir, 954 received hydroxychloroquine, 651 received Kaletra plus interferon beta, 1,411 received Kaletra alone, 1,412 received interferon alone and 4,088 received none of the study drugs. The hydroxychloroquine and Kaletra arms were halted early after preliminary results showed no benefit.

A total of 1,253 deaths were reported, for an overall mortality rate of 12% at 28 days. This rose to 20% for people age 70 or older and to 39% for those on a ventilator. Mortality rates were statistically similar in all treatment groups.

Further, there were no significant differences between the remdesivir and standard-of-care groups in the proportion of people who needed to be put on ventilators or the proportion still hospitalized after seven days (69% versus 59%, respectively).

The treatments were generally well tolerated. There were few deaths related to heart problems (a potential side effect of hydroxychloroquine) in any of the treatment groups. Although many COVID-19 deaths involved multi-organ failure, no deaths in the study drug groups were attributed to kidney or liver disease, which could potentially indicate drug toxicity, the researchers reported.

In Search of Better Outcomes

Gilead argued that the number of different drugs and combinations tested in Solidarity, the

variable circumstances of the participants and local standards of care and missing data mean the results are less informative than those of traditional randomized clinical trials.

“We are concerned that the data from this open-label global trial have not undergone the rigorous review required to allow for constructive scientific discussion, particularly given the limitations of the trial design,” the company said in a statement. “The trial design prioritized broad access, resulting in significant heterogeneity in trial adoption, implementation, controls and patient populations, and consequently, it is unclear if any conclusive findings can be drawn from the study results.”

What’s more, some experts think remdesivir still holds promise for specific subsets of patients, including those treated earlier in the course of illness or as part of a combination regimen. Early symptoms of COVID-19 are generally attributable to the SARS-CoV-2 virus itself, but in people with advanced disease, an excessive immune response can cause severe lung and other organ damage.

Final results from an analysis of 1,062 hospitalized patients in the ACTT-1 study, published this month in The New England Journal of Medicine, showed that while people assigned to receive remdesivir recovered five days sooner than the placebo group overall, those who required oxygen support recovered seven days faster (11 versus 18 days). Remdesivir reduced the likelihood of needing mechanical ventilation or external blood oxygenation (13% versus 23%). Those on low-flow oxygen support—the largest group of patients in the study—had a significant 70% reduction in mortality in an unplanned post hoc analysis, Gilead chairman and CEO Daniel O’Day noted in a statement.

Researchers are now testing remdesivir in various combination regimens.

The ACTT-2 study is evaluating remdesivir with barcitinib (Olumiant), an anti-inflammatory JAK1/JAK2 inhibitor approved as a treatment for rheumatoid arthritis. Data presented at a recent COVID-19 therapeutics conference showed that remdesivir plus baricitinib reduced time to recovery (seven versus eight days) and mortality (5% versus 8%) compared with remdesivir alone, though the latter difference was not statistically significant. Here, too, patients who required supplemental oxygen saw the largest benefits, according to a press release from barcitinib manufacturer Eli Lilly and Company.

The ACTT-3 trial is evaluating remdesivir plus interferon beta-1a, an immunomodulator used to treat multiple sclerosis. It mimics natural interferon beta, a cytokine produced by immune cells that has both antiviral and anti-inflammatory properties.

Last week, the NIH announced the launch of the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) trial, which will test a combination of remdesivir plus hyperimmune intravenous immunoglobulin, a preparation that contains a higher concentration of SARS-CoV-2 neutralizing antibodies than convalescent plasma from recovered COVID-19 patients.

The current intravenous formulation of remdesivir is mainly suitable for hospitalized patients. Gilead and others are working on other formulations that can be administered by subcutaneous injection or inhalation, which would be more practical for people treated outside a hospital.
