What is the role of the antiviral drug remdesivir in the treatment of coronavirus disease 2019 (COVID-19)?

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References

ANSWER

Remdesivir (Veklury) was the first drug approved by the FDA for treating the SARS-CoV-2 virus. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg. The broad-spectrum antiviral is a nucleotide analog prodrug. [21] Full approval was preceded by the US FDA issuing an EUA (emergency use authorization) on May 1, 2020 to allow prescribing remdesivir for severe COVID-19 (confirmed or suspected) in hospitalized adults and children. [158] Upon approval of remdesivir in adults and adolescents, the EUA was updated to maintain the ability for prescribers to treat pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg. [137]

The remdesivir EUA was expanded to include moderate disease August 28, 2020. This expands the previous authorization to treat all hospitalized patients with COVID-19 regardless of oxygen status. [159] A new drug application (NDA) for remdesivir was submitted to the FDA in August 2020. A phase 1b trial of an inhaled nebulized version was initiated in late June 2020 to determine if remdesivir can be used on an outpatient basis and at earlier stages of disease. [160] As of October 1, 2020, remdesivir is available from the distributor (ie, AmerisourceBergen). Wholesale acquisition cost is approximately $520/100-mg vial, totaling $3,120 for a 5-day treatment course.

Several phase 3 clinical trials have tested remdesivir for treatment of COVID-19. Positive results were seen with remdesivir after use by the University of Washington in the first case of COVID-19 documented on US soil in January 2020. [161] An adaptive randomized trial of remdesivir coordinated by the National Institute of Health (NCT04280705) was started first against placebo, but additional therapies were added to the protocol as evidence emerged and treatment evolved. The first experience with this study involved passengers of the Diamond Princess cruise ship in quarantine at the University of Nebraska Medical Center in February 2020 after returning to the United States from Japan following an on-board outbreak of COVID-19. [162] Trials of remdesivir for moderate and severe COVID-19 compared with standard of care and varying treatment durations are ongoing.

The initial EUA of remdesivir was based on preliminary data analysis of the Adaptive COVID-19 Treatment Trial (ACTT) was announced April 29, 2020. The final analysis included 1,062 hospitalized patients with advanced COVID-19 and lung involvement, showing that patients treated with 10-days of remdesivir recovered faster than similar patients who received placebo. Results showed that patients who received remdesivir had a 31% faster time to recovery compared with those who received placebo ($P < 0.001$). Specifically, the median time to recovery was 10 days in patients treated with remdesivir compared with 15 days in those who received placebo ($P < 0.001$). Patients with severe disease (n = 957) had a median time to recovery of 11 days compared with 18 days for placebo. A statistically significant difference was not reached for mortality by day 15 (remdesivir 6.7% vs placebo 11.9%) or by day 29 (remdesivir 11.4% vs placebo 15.2%). [163]

The final ACTT-1 results for shortening the time to recovery differed from interim results from the WHO SOLIDARITY trial for remdesivir. These discordant conclusions are complicated and confusing as the SOLIDARITY trial included patients from ACTT-1. [146] An editorial by Harrington and colleagues [164] notes the complexity of the SOLIDARITY trial and the variation within and between countries in the standard of care and in the burden of disease in patients who arrive at hospitals. The authors also mention that trials solely focused on remdesivir were able to observe nuanced outcomes (ie, ability to change the course of hospitalization), whereas the larger, simple randomized SOLIDARITY trial focused on more easily defined outcomes.

The open-label phase 3 SIMPLE trial (n = 397) in hospitalized patients with severe COVID-19 disease not requiring mechanical ventilation showed similar improvement in clinical status with the 5-day remdesivir regimen compared with the 10-day regimen on day 14 (OR: 0.75 [95% CI 0.51-1.12]). In this study, 65% of patients who received a 5-day course of remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at day 14, compared with 54% of patients who received a 10-day course. After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course ($P = 0.14$). The study demonstrates the potential for some patients to be treated with a 5-day regimen, which could significantly expand the number of patients who could be treated with the current supply of remdesivir. The trial is continuing with an enrollment goal of 6,000 patients. [165]

Similarly, the phase 3 SIMPLE II trial in patients with moderate COVID-19 disease (n = 596) showed that 5 days of remdesivir treatment had a statistically significant higher odds of a better clinical status distribution on Day 11 compared with those receiving standard care (odds ratio, 1.65; $p = 0.02$). Improvement on Day 11 did not differ between the 10-day remdesivir group and standard of care ($P = 0.18$). [166]

Remdesivir use in children

Remdesivir emergency use authorization includes pediatric dosing that was derived from pharmacokinetic data in healthy adults. Remdesivir has been available through compassionate use to children with severe COVID-19 since February 2020. A phase 2/3 trial (CARAVAN) of remdesivir was

initiated in June 2020 to assess safety, tolerability, pharmacokinetics, and efficacy in children with moderate-to-severe COVID-19. CARAVAN is an open-label, single-arm study of remdesivir in children from birth to age 18 years.Data were presented on compassionate use of remdesivir in children at the virtual COVID-19 Conference held July 10-11, 2020. Results showed most of the 77 children with severe COVID-19 improved with remdesivir. Clinical recovery was observed in 80% of children on ventilators or ECMO and in 87% of those not on invasive oxygen support. [168]

For additional information, see Coronavirus Disease 2019 (COVID-19) in Children.

Remdesivir use in pregnant women

Outcomes in the first 86 pregnant women who were treated with remdesivir (March 21 to June 16, 2020) have been published. Recovery rates were high among women who received remdesivir (67 while pregnant and 19 on postpartum days 0-3). No new safety signals were observed. At baseline, 40% of pregnant women (median gestational age 28 weeks) required invasive ventilation compared with 95% of postpartum women (median gestational age at delivery 30 weeks). Among pregnant women, 93% of those on mechanical ventilation were extubated, 93% recovered, and 90% were discharged. Among postpartum women, 89% were extubated, 89% recovered, and 84% were discharged. There was 1 maternal death attributed to underlying disease and no neonatal deaths. [169]

Data continue to emerge. A case series of 5 patients describe successful treatment and monitoring throughout treatment with remdesivir in pregnant women with COVID-19. [170]

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