Remdesivir

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Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro and in vivo activity against SARS-CoV-2.¹

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adults and pediatric patients aged ≥28 days and weighing ≥3 kg. In nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, remdesivir should be started within 7 days of symptom onset and administered for 3 days. Hospitalized patients should receive remdesivir for 5 days or until hospital discharge, whichever comes first.² The FDA prescribing information for remdesivir indicates that if a patient does not clinically improve, clinicians may extend the treatment course for up to 5 additional days (for a total duration of 10 days). See Table 4e for more information.

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies. See Table 4a for more information.

**Recommendations**

- For the Panel’s recommendations and information on the clinical efficacy of using remdesivir to treat high-risk, nonhospitalized patients with mild to moderate COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

- For the Panel’s recommendations and information on the clinical efficacy of using remdesivir with or without immunomodulators to treat certain hospitalized patients, see Therapeutic Management of Hospitalized Adults With COVID-19.

- The data on using combinations of antiviral therapies for the treatment of COVID-19 are limited.³ Clinical trials are needed to determine the role of combination therapy in treating certain patients.

**Monitoring, Adverse Effects, and Drug-Drug Interactions**

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions.

Before starting patients on remdesivir, the FDA recommends performing liver function and prothrombin time tests as clinically appropriate and repeating these tests during treatment as clinically indicated. Remdesivir may need to be discontinued if a patient’s alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if increases in ALT levels and signs or symptoms of liver inflammation are observed.²

Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion as clinically appropriate.

Currently, no clinical drug-drug interaction studies of remdesivir have been conducted. In vitro, remdesivir is a minor substrate of cytochrome P450 (CYP) 3A4 and a substrate of the drug transporters
organic anion transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein (MATE) 1. See Table 4e for more information.

Patients Who Are Immunocompromised and Have Prolonged Symptoms and Evidence of Ongoing Viral Replication

Patients who are severely immunocompromised may have a prolonged duration of SARS-CoV-2 replication, which may lead to rapid viral evolution. There is concern that using a single antiviral agent in these patients may result in the emergence of resistant virus. Additional studies are needed to assess this risk. The role of combination antiviral therapy in the treatment of COVID-19 is not yet known.

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer COVID-19 convalescent plasma, or combination therapy.

Considerations in Patients With Renal Insufficiency

Remdesivir is formulated with sulfobutylether-beta-cyclodextrin (SBEC) sodium. SBEC is a vehicle that is primarily eliminated through the kidneys. Accumulation of SBEC in patients with renal impairment may result in liver and renal toxicities.

Basing its decision on safety data primarily from the REDPINE clinical trial and pharmacokinetic data from a Phase 1 trial, the FDA updated the prescribing information for remdesivir to indicate that it can be used without dose adjustment in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min, including those receiving dialysis.

Safety data for the use of remdesivir in patients with severely reduced kidney function are available from 2 randomized controlled trials:

- The REDPINE study was a manufacturer-sponsored, multinational, double-blind trial of remdesivir versus placebo in hospitalized adults with severe COVID-19 and an eGFR of <30 mL/min. The trial was terminated due to low enrollment. Among 163 remdesivir and 80 placebo recipients with a mean age of 69 years, there were no statistically significant differences in treatment-emergent adverse events or serious treatment-emergent adverse events, including death. Among participants with baseline acute kidney injury or chronic kidney disease, there were no statistically significant differences in the progression of acute kidney injury, the need for renal replacement therapy, or death.
- The CATCO study was a multicenter, open-label trial that compared the use of remdesivir to standard of care in hospitalized adults with COVID-19. A post hoc analysis was done for 59 patients with a baseline eGFR of <30 mL/min; 15 of these patients were on dialysis. The median age of the cohort was 74 years. Thirty-four patients received remdesivir for a median duration of 10 days, while 25 patients received standard of care. The standard of care patients had a lower median eGFR at baseline (12.4 mL/min) than patients treated with remdesivir (22.7 mL/min). There was no increased risk of renal toxicity at Day 5 among patients treated with remdesivir compared to standard of care, and there were no statistically significant differences in the need for
new dialysis, the need for mechanical ventilation, or mortality.

Although both the REDPINE and CATCO trials were underpowered to assess the clinical efficacy of remdesivir in patients with severely reduced kidney function, the available data suggest that remdesivir can be used safely in patients with an eGFR of <30 mL/min. These results are consistent with a systematic review of observational studies\textsuperscript{12} and other retrospective studies that have reported that remdesivir was not associated with an increased incidence of adverse effects in patients with COVID-19 who had baseline eGFRs of <30 mL/min.\textsuperscript{13-15}

Considerations in Pregnancy

See \textit{Pregnancy, Lactation, and COVID-19 Therapeutics} for the Panel’s guidance regarding the use of remdesivir during pregnancy and lactation.

Considerations in Children

See \textit{Special Considerations in Children, Therapeutic Management of Nonhospitalized Children With COVID-19}, and \textit{Therapeutic Management of Hospitalized Children With COVID-19}.

References

10. Santos JR, Goldman JD, Tuttle KR, et al. The REDPINE study: efficacy and safety of remdesivir in people with moderately and severely reduced kidney function hospitalised for COVID-19 pneumonia. Presented at: 33rd European Congress of Clinical Microbiology and Infectious Diseases; April 15–18, 2023; Copenhagen,


