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 activity against SARS-CoV-2. In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals. Remdesivir is expected to be active against the B.1.1.529 (Omicron) variant of concern.

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is approved for the treatment of mild to moderate COVID-19 in high-risk, nonhospitalized patients (i.e., a 3-day course initiated within 7 days of symptom onset) and for the treatment of hospitalized patients with COVID-19 (i.e., a 5-day course). See Table 2f for more information. It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in nonhospitalized and hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.

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 2a for more information.

Recommendations

For the Panel’s recommendations and information on the clinical efficacy of remdesivir in high-risk, nonhospitalized patients with mild to moderate COVID-19 and on the order of preference for outpatient antiviral therapies, see Therapeutic Management of Nonhospitalized Adults With COVID-19. There are no data on the use of combination antiviral therapies or the combination of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

For the Panel’s recommendations and information on the clinical efficacy of remdesivir with or without immunomodulators in certain hospitalized patients, see Therapeutic Management of Hospitalized Adults With COVID-19. Data on the safety and efficacy of using remdesivir in combination with corticosteroids are primarily derived from observational studies, with some (but not all) of these studies suggesting that remdesivir plus dexamethasone provides a clinical benefit for hospitalized patients with COVID-19.

In the CATCO study, patients hospitalized with COVID-19 were randomized to receive remdesivir plus standard care or standard care alone. Among patients who were not receiving mechanical ventilation at baseline, remdesivir significantly reduced the need for mechanical ventilation. About 87% of participants in the trial received corticosteroids as part of their standard care.

Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized trial. However, there are theoretical reasons that combination therapy may be beneficial for some patients with severe COVID-19. Remdesivir has also been studied in combination with other immunomodulators, including baricitinib and tocilizumab.
Monitoring and Adverse Effects

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, it is recommended that estimated glomerular filtration rate (eGFR), liver function, and prothrombin time tests be performed as clinically appropriate and be repeated during treatment as clinically indicated. However, it should be noted that in the PINETREE study, in which outpatients with mild to moderate COVID-19 received remdesivir for 3 days, baseline serum creatinine was not required in patients weighing >48 kg. 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.

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

Patients who are severely immunocompromised may have prolonged SARS-CoV-2 replication, which may lead to rapid viral evolution. There is a theoretical concern that the use of 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 is not yet known.

Considerations in Patients With Renal Insufficiency

Each 100 mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECSD), and each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECSD. SBECSD is a vehicle that is primarily eliminated through the kidneys. A patient with COVID-19 who receives a loading dose of remdesivir 200 mg would receive 6 g to 12 g of SBECSD, depending on the formulation. This amount of SBECSD is within the safety threshold for patients with normal renal function. Accumulation of SBECSD in patients with renal impairment may result in liver and renal toxicities. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECSD) in patients with renal impairment.

Because both remdesivir formulations contain SBECSD, patients with an eGFR of <50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of <30 mL/min. The FDA product label does not recommend using remdesivir in patients with an eGFR of <30 mL/min due to a lack of data.

In 2 observational studies that evaluated the use of the solution formulation of remdesivir (not the reconstituted lyophilized powder formulation) in hospitalized patients with COVID-19, no significant differences were reported in the incidences of adverse effects or acute kidney injury between patients with an estimated creatinine clearance (CrCl) of <30 mL/min and those with an estimated CrCl of ≥30 mL/min. In 1 study, 20 patients had an estimated CrCl of <30 mL/min and 115 had an estimated CrCl of ≥30 mL/min; the other study included 40 patients who had an estimated CrCl of <30 mL/min and 307 patients who had an estimated CrCl of ≥30 mL/min. These observational data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.

Drug-Drug Interactions

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 1 (MATE1).\(^5\)

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020).

See Table 2f for more information.

**Considerations in Pregnancy**

Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from small studies and case reports are reassuring.\(^17\) Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well-tolerated, with a low rate of serious adverse effects.\(^18\)

**Considerations in Children**

Remdesivir is available through an FDA EUA for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to \(<40\) kg or aged \(<12\) years and weighing \(\geq3.5\) kg or in nonhospitalized pediatric patients with mild to moderate COVID-19 and at high risk for disease progression. There are insufficient data on the safety and efficacy of using remdesivir to treat COVID-19 in hospitalized or nonhospitalized pediatric patients aged \(<12\) years or weighing \(<40\) kg, because these populations have not been evaluated in clinical trials for remdesivir. The limited data from the compassionate use program and small-case series suggest that remdesivir was well-tolerated in children who met the EUA criteria, but the data on young infants and neonates are extremely limited.\(^19-23\) A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov Identifier NCT04431453).

**Clinical Trials**

Several clinical trials that are evaluating the use of remdesivir for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.

**References**

5. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf).


