New Perspectives on Antimicrobial Agents: Remdesivir Treatment for COVID-19

Running Title: Remdesivir for COVID-19

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Abstract

Remdesivir was recently approved by the Food and Drug Administration for the treatment of hospitalized patients with COVID-19. Remdesivir is the prodrug of an adenosine analogue that inhibits viral replication of several RNA virus families including *Coronaviridae*. Preclinical data in animal models of coronavirus diseases, including COVID-19, have demonstrated that early treatment with remdesivir leads to improved survival, decreased lung injury and decreased quantification of viral RNA. Recent clinical data have demonstrated the clinical activity of remdesivir in terms faster time to recovery in patients with severe COVID-19 and higher odds of improved clinical status in patients with moderate COVID-19. Clinical trials published to date are presented and appraised. Remdesivir's potential benefits and its favorable adverse event profile make it an option for the treatment of COVID-19. This article examines the available literature describing remdesivir's pharmacology, pharmacokinetics, and preclinical and clinical data.

Introduction

Coronaviruses (CoVs) are enveloped viruses containing a large single-stranded, positive-sense RNA genome(1). Most known CoVs include those that usually cause mild acute rhinophanryngitis (including HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43), but also others that can cause severe pulmonary disease including the Severe Acute Respiratory Syndrome (SARS), caused by SARS-CoV-1 (i.e. SARS-CoV); and Middle East Respiratory Syndrome (MERS), caused by MERS-CoV(2). In December 2019, SARS-CoV-2 was identified as the pathogen responsible for Coronavirus Disease 2019 (COVID-19). SARS-CoVs use angiotensin-converting enzyme (ACE-2) as the entry receptor to infect cells via interaction with the viral Spike protein and subsequent receptor-mediated endocytosis(3). Inside host cells, SARS-CoV-2 replicates via viral RNA-dependent RNA polymerase (RdRp) encoded by the viral genome(4).

SARS-CoV-2 is transmitted primarily through the respiratory route, both by respiratory aerosols and droplets, and less commonly by direct contact or fomites(5).Transmission can occur from people with clinical disease or asymptomatic infection(6). SARS-CoV-2's high transmissibility has resulted in a massive global outbreak of COVID-19, which was officially declared a pandemic on March 11, 2020. As of October 29, 2020, the World Health Organization (WHO) reported over 44 million confirmed COVID-19 cases and over 1.1 million deaths globally(7). Remdesivir (also known as GS-5734) is currently the most promising available direct antiviral treatment option. Based on favorable initial data from a National Institute of Allergy and Infectious Diseases (NIAID) sponsored randomized double-blind clinical trial, the United States Food and Drug Administration (FDA) granted remdesivir Emergency Use Authorization for the treatment of COVID-19 on May 1, 2020 (8). Remdesivir has also received

conditional marketing authorization in the European Union, and approval for use in Japan, Taiwan, India, Singapore, and the United Arab Emirates for the treatment of COVID-19 pneumonia(9, 10). On October 22, 2020, remdesivir received full FDA approval for treatment for hospitalized patients with COVID-19(11). In this review, we discuss the pharmacology, pharmacokinetics, pre-clinical, and clinical data for remdesivir in COVID-19.

Chemistry and pharmacology

Remdesivir is a single diastereomer monophosphoramidate prodrug of a cyano-adenosine nucleoside analog (GS-441524), a chemical structure that masks the negatively charged phosphate of GS-443902 and facilitates cellular entry. Remdesivir undergoes rapid intracellular conversion to an alanine metabolite (GS-704277), followed by the nucleoside monophosphate derivative (GS-441524), and ultimately into the pharmacologically active nucleoside triphosphate form (GS-443902) (Figure1)(12). GS-443902 acts as an analog of adenosine triphosphate (ATP) and competes with the endogenous ATP substrate for incorporation into SARS-CoV's RNA via RdRp. RdRp is a non-structural protein that is highly conserved among different viral strains, making it an attractive antiviral target(13). Remdesivir's primary mechanism of antiviral activity occurs through GS-443902 incorporation into viral RNA chains by RdRp, leading to chain termination and inhibition of viral replication (Figure 2)(14).

A challenge in the development of nucleoside analogues against CoVs is the presence of a unique CoV proofreading 3'-5, exoribonuclease (ExoN) that increases replication fidelity(15). In an *in vivo* SARS-CoV infection model, inactivation of ExoN activity due to alanine substitution of the first two active site residues resulted in a 12-fold reduced replication fidelity (16). *In vitro* resistance to ribavirin and 5-fluorouracil among CoVs has been attributed to their

removal by the proofreading ExoN(17). Thus, an effective nucleoside analogue must evade the proofreading ExoN to prevent CoV viral replication. A study using a β-coronavirus murine hepatitis virus (MHV) model illustrated that remdesivir is still able to inhibit RdRp even in the setting of intact ExoN(18). The authors of this study compared the sensitivity of Wild type (WT) MHV and revealed that it is modestly less sensitive to remdesivir compared to ExoN (-) MHV (EC_{50} 0.019 μM vs. 0.087 μM) suggesting that remdesivir is able to evade ExoN proofreading activity, which could be attributed to higher RdRp selectivity for remdesivir-triphosphate compared the natural nucleotides(18, 19). This can also indicate that ExoN activity is not sufficient to prevent potent inhibition of CoV replication(18).

Antiviral spectrum and resistance

Remdesivir is a potentially broad-spectrum antiviral agent against RNA viruses. It has been shown to reduce viral replication *in vitro* in human macrophages and lung microvascular endothelial cells infected with *Pneumoviridae* (e.g. Respiratory Syncytial Virus) and *Paramixoviridae* (e.g. measles, mumps, and Parainfluenza virus 3)(20). It has also been shown to exhibit antiviral activity against *Filiviridae* (e.g. Ebola and Marburg virus) in a variety of human cell types(21).

Importantly, remdesivir demonstrated potent inhibition of SARS-CoV-1 and MERS-CoV in primary human airway epithelial cell cultures, with an EC_{50} of 0.07 μM for both viruses(22). Remdesivir was also effective against bat CoVs; prepandemic bat CoVs, which are able to infect human cells and cause disease without adaptation; and circulating contemporary human CoV in human lung cells(22). More recently, remdesivir was shown to potently block *in vitro* SARS-

CoV-2 infection of human cells at very low concentrations with an EC_{50} and EC_{90} of 0.77 µM and 1.76 µM, respectively(23).

While several studies have demonstrated the potent inhibitory activity of remdesivir against CoVs, little is known about its resistance. When resistance against remdesivir develops, it is usually in association with decreased viral fitness, through 2 amino acid substitutions in the RdRp (F476L and V553L), and can be overcome with increased nontoxic concentrations of the drug(18). A recent case report demonstrated the occurrence of a novel mutation in the RdRp (D848Y) following remdesivir treatment in a patient with COVID-19 which was associated with treatment failure(24).

Animal studies

Given the promising antiviral effects of remdesivir *in vitro*, the drug was tested in a number of animal models in efforts to advance its development as a therapeutic option for a wide range of viral diseases.

In a mouse model of SARS-CoV-1, prophylactic subcutaneous administration of remdesivir was associated with reduced lung viral titers at days 2 and 5 post infection, reduced lung pathology, reduced intra-alveolar edema, and improved pulmonary function as compared to untreated SARS-CoV-1 mice(22). Therapeutic administration of subcutaneous remdesivir, one day post-infection, showed similarly improved pulmonary function and reduced viral lung titers when the drug was administered within one day of infection, before the peak of SARS-CoV-1 replication. In a MERS-CoV mouse model, the same research group demonstrated that prophylactic subcutaneous remdesivir administered one day prior to infection significantly reduced viral-induced weight loss, mortality, pulmonary hemorrhage, and lung viral load at days

4 and 6 post MERS-CoV infection(25). Therapeutic administration of subcutaneous remdesivir, one day post-infection, in the same model demonstrated similar effects as prophylactic dosing.

The therapeutic efficacy of remdesivir against MERS-CoV has been demonstrated in a rhesus macaque model(26). This study evaluated the effect of intravenous prophylactic and therapeutic remdesivir boluses administered over ~5 minutes in a rhesus macaque model of MERS-CoV over the course of 6 days. Prophylactic remdesivir was administered one day before inoculation and continued once daily for 6 days. Remdesivir was associated with lower respiratory rates, fewer pulmonary infiltrates on X-ray, lower lung viral loads and absent gross lung lesions on necropsy, compared to vehicle-treated subjects. When therapeutic remdesivir was administered 12 hours after inoculation and continued once daily for 6 days, it was associated with mildly elevated respiratory rates, but significantly lower than vehicle-treated group, fewer lung infiltrates on X-ray, lower viral loads and smaller areas of gross lung lesions on necropsy compared to the untreated group.

More recently, the activity of remdesivir in rhesus macaques infected with SARS-CoV-2 was demonstrated(27). Intravenous therapeutic remdesivir administered over ~5 minutes, was initiated close to the peak of viral replication, 12 hours after inoculation with SARS-CoV-2, and continued once daily for 6 days. Animals treated with remdesivir lacked clinical evidence of respiratory disease and had less severe radiographic pulmonary infiltrates and pathologic pulmonary lesions on necropsy compared to vehicle-treated controls. These findings support administration of remdesivir early in the course of COVID-19 to achieve the maximum treatment effect. Additionally, viral load was significantly lower in the lungs, while viral replication was reduced in the lower, but not the upper respiratory tract after remdesivir treatment, suggesting that a clinical improvement should not be interpreted necessarily as a lack of infectiousness (27).

Pharmacokinetics

Remdesivir is not suitable for oral administration due to complete first-pass metabolism through the liver. Consequently, intramuscular (IM) and intravenous (IV) administration of remdesivir were evaluated in male rhesus monkeys(21). The IM administration was suboptimal due to slow and variable release of remdesivir from the muscle and the pharmacokinetics of subcutaneous administration has not been evaluated in humans. In contrast, the IV administration was rapidly eliminated and converted to the nucleoside monophosphate analogue (GS-441524), indicating a more consistent and rapid delivery of remdesivir and higher maximal levels of monophosphate analogue relative to the IM administration.

Following IV administration, remdesivir has a short plasma half-life ($T_{1/2}$) of ~1 hour, as it is quickly metabolized by carboxylesterases (CES1) into the intermediate alanine metabolite (GS-704277), followed by the predominant monophosphate metabolite ($T_{1/2}$ 24.5 hours)(28-30). CES1 expression is high in the liver, with minimal expression in the type II pneumocytes in the lung, which could result in the monophosphate metabolite being present in serum at concentrations 1000-fold higher than remdesivir throughout a 7-day treatment course(29). The monophosphate metabolite is then converted into the triphosphate active metabolite of GS-443902, which has a prolonged plasma $T_{1/2}$ of over 35 hours, supporting the once daily administration of the drug(30, 31). Given the prolonged $T_{1/2}$ of the monophosphate and triphosphate metabolites, steady state is usually achieved after approximately 5 days, hence the need for a loading dose to facilitate a faster achievement of steady state. Table 1 shows a summary of the pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-443902). Interestingly, remdesivir 75 mg administered over 30 minutes provided higher peripheral blood mononuclear cell (PBMC) concentration of the triphosphate active metabolite

than remdesivir 150 mg administered over 2 hours (AUC_{inf} 394.3 h.ng/mL vs. 294.7 h.ng/mL, respectively)(30, 31). Thus, shorter infusion times of remdesivir may optimize its pharmacokinetics parameters and achieve the highest intracellular concentration of the active triphosphate metabolite.

Remdesivir has moderate protein binding, with a free fraction in humans of 12.1%. In contrast, the metabolites GS-704277 and the monophosphate metabolite exhibit very low protein binding in plasma, with mean free fraction ranging from 85% to 127%(28). *In vivo* studies demonstrated that remdesivir rapidly distributes to most tissues following IV administration(21, 28). Remdesivir levels were highest in the kidney, liver, and arterial wall(28). Remdesivir and its metabolites levels were also detected in the testes, epididymis, eyes, and brain of rhesus macaques within 4 hours of administration. Interestingly, the levels in the brain were around 8% of plasma levels at 4 hours post administration, but remained quantifiable and higher than plasma at 168 hours post-dose(21).

Remdesivir is metabolized by cytochrome P450 (CYP450). Metabolism of its metabolites has not been characterized yet (see drug-drug interactions section below).

Remdesivir and its metabolites are mainly eliminated renally (74%) and through the feces (18%). Following IV administration, the monophosphate metabolite was predominantly detected in the urine (49%), followed by remdesivir (10%), and other metabolites accounted for 6%(28). Due to remdesivir's poor water solubility, it is solubilized with sulfobutylether-β-cyclodextrin (SBECD) for IV administration, which is predominantly excreted renally(32).

Dosage and drug administration

Remdesivir is currently supplied as two different preservative-free formulations containing 5mg/mL remdesivir: aqueous-based concentrated solution and lyophilized powder formulation, both provided in 100 mg vials. The recommended dosing for adults and pediatric patients weighing ≥ 40 kg is a single loading dose of 200 mg on day 1, followed by a maintenance daily dose of 100 mg. For pediatric patients weighing between 3.5 kg and <40 kg, the lyophilized formulation is preferred. A single loading dose of 5mg/kg should be administered on day 1 followed by a maintenance dose of 2.5mg/kg. Doses should be administrated intravenously and infused over 30-120 minutes(33); however, we prefer administration over 30 minutes whenever possible to achieve higher intracellular concentrations of the active metabolite(30, 31).

Adult and pediatric patients with moderate or severe COVID-19 can receive a treatment duration of 5 days, which can be extended for up to 10 days if patients do not demonstrate clinical improvement(33, 34). Although rare to date, in some patients with severe immunocompromising conditions, especially those who receive combined T cell and B cell depleting agents for hematological malignancies or autoimmune diseases, we have had to administer additional courses of remdesivir over time for recrudescent clinical disease(35).

Drug interactions

Drug-drug interactions of remdesivir in humans have not been reported and their clinical relevance has not yet been established. As remdesivir is a prodrug, the potential for significant drug-drug interactions is limited due to the transient exposure of intact remdesivir following IV administration. However, *in vitro* studies demonstrated that remdesivir is a substrate for the

CYP450 enzymes (CYP2C8, CYP2D6, and CYP3A4), Organic Anion Transporting Polypeptides 1B1 (OAPT1B1), and P-glycoprotein (P-gp) proteins. In addition, remdesivir can act as an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, OAPT1B1, OATP1B3, multidrug resistance-associated protein 4 (MRP4), and sodium-taurocholate cotransporting polypeptide (NCTP) (33). *In vitro* data demonstrated an antagonistic effect of chloroquine on the intracellular activation and antiviral activity of remdesivir. Thus, co-administration of remdesivir and chloroquine or hydroxychloroquine is not recommended as it may result in reduced antiviral activity of remdesivir(33).

Clinical data

The first randomized, double-blind, placebo-controlled trial evaluating remdesivir in hospitalized patients with severe COVID-19 included 236 participants in China enrolled between early February and mid-March 2020—158 were randomized to remdesivir and 78 to placebo)(36). Remdesivir was administered intravenously over 30 to 60 minutes as a 200 mg loading dose on day 1, followed by a 100 mg daily maintenance dose on days 2 through 10. The primary clinical endpoint was time to clinical improvement, defined as a two-point reduction in patients' baseline clinical ordinal scale (Table 2), or live discharge from the hospital, within 28 days after randomization(37). The median time from symptom onset to starting study treatment was 10 days (interquartile range [IQR], 9-12 days). More patients in the remdesivir arm had a baseline respiratory rate of more than 24 breaths per min compared to placebo (23% vs. 14%), and more patients in the control group had been symptomatic for $\leq$ 10 days at the time of starting remdesivir or placebo compared to the remdesivir arm. The time to clinical improvement in the remdesivir group (median 21 days; IQR, 13-28) was not significantly different to that of the

placebo group (median 23 days; IQR, 15–28; hazard ratio [HR] 1.23; 95% CI, 0.87–1.75 [a HR>1 indicates shorter time to clinical improvement with remdesivir]). Nasopharyngeal virus load reduction, or day 28 mortality (14% in the remdesivir arm vs. 13% in the placebo arm) were similar in both groups. In a subgroup analysis of patients enrolled within 10 days of symptom onset, there was no statistically significant difference in 28-day mortality (11% among those treated with remdesivir vs. 15% among those who received placebo), or time to clinical improvement (hazard ratio 1.52; 95% CI 0.95–2.43). Importantly, this trial failed to complete enrollment, due to steep reductions in COVID-19 incidence in China as the trial proceeded, and had a low statistical power (58%), which may explain in part why it was unable to demonstrate any statistically significant clinical benefits of remdesivir. Unlike subsequent clinical trials of remdesivir for COVID-19 published to date, 66% of patients in this study also received corticosteroids, though there was no difference in the proportion between the remdesivir and placebo arms (Table 3).

Subsequently, the international double-blind, randomized, placebo-controlled trial, known as the Adaptive Covid-19 Treatment Trial (ACTT-1) met its primary endpoint of a faster time to recovery in patients who received remdesivir relative to placebo(38). This study included 1062 patients enrolled between late February and mid-April 2020, with 541 were allocated to the remdesivir group and 521 were allocated to placebo. Remdesivir was administered intravenously over 30 to 120 minutes as a 200-mg loading dose on day 1, followed by a 100-mg daily maintenance dose on days 2 through 10 or until hospital discharge or death. The primary outcome was initially defined as the difference in clinical status, as ascertained by an eight-category ordinal scale, among patients treated with remdesivir as compared with placebo at day 15. However, on March 22, 2020, trial statisticians, who were unaware of treatment assignments

and had no knowledge of outcome data, suggested changing this primary outcome to time to clinical recovery based on evolving understanding that severe COVID-19 often has more a prolonged clinical course than many other acute respiratory viral infections(38). Overall, the baseline characteristics were balanced between the two groups. Median duration of symptoms before initiation of study drug was 9 days in both groups (IQR, 6-12 days). At baseline, 131 (24.2%) were receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) in the remdesivir group, compared to 154 (29.6%) in the placebo arm. Remdesivir was superior to placebo in shortening the time to recovery by day 29 (median, 10 days vs. 15 days; rate ratio [RR] for recovery 1.29; CI 1.12–1.49 [a RR >1 indicates faster time to recovery with remdesivir]). This benefit was most apparent in patients requiring supplemental oxygen by nasal cannula at treatment initiation (RR 1.45; CI, 1.18–1.79). The benefit of remdesivir was larger when given earlier in the illness. Patients who received remdesivir within the first 10 days of symptom onset had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64) vs. patients who received remdesivir more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI, 0.94 to 1.52); The rate ratio of recovery for patients who began remdesivir within 6 days from symptom onset was 1.92 (95% CI, 1.41-2.60). The odds of clinical improvement at day 15 were higher in the remdesivir group, (OR 1.50; 95% CI, 1.18 – 1.91). The time to an improvement by at least one or two category in the ordinal scale by day-29 was significantly shorter in the remdesivir arm compared to placebo (one category improvement: median 7 days vs. 9 days; rate ratio 1.23; CI, 1.08-1.41; two category improvement: median 11 days vs. 14 days; rate ratio 1.29; 95% CI, 1.1-1.46). Remdesivir was associated with a significant reduction in median hospital length of stay (12 days vs. 17 days). Mortality rate was significantly lower by day 14 (6.7% vs. 11.9%; HR 0.55, 95% CI, 0.36-0.83), but not by day 29 (11.4% vs.

15.2%; HR 0.73; 95% CI, 0.52-1.03) in the remdesivir group compared to the placebo group. A lower mortality was particularly apparent in patients requiring supplemental oxygen at baseline (HR 0.3; 95% CI, 0.14-0.64). Interestingly, remdesivir was associated with lower incidence of new oxygen use among patients who were not receiving oxygen at baseline (36% vs. 44%). Treatment with remdesivir was also associated with fewer days of subsequent oxygen use for patients receiving oxygen at enrollment (13 days vs. 21 days) and shorter subsequent duration of mechanical ventilation or ECMO for those receiving these interventions at baseline (17 days vs. 20 days). The incidence of adverse events was similar between the remdesivir group and the placebo group (Table 3).

The duration of remdesivir treatment in hospitalized patients with severe COVID-19 was evaluated in a randomized, open-label, phase 3 trial (SIMPLE Severe) (39). A total of 402 patients were enrolled in the randomized part of the study (200 patients started a 5-day and 197 started a 10-day course). Overall, baseline characteristics were compatible between the two groups. However, the 10-day group had a larger proportion of patients in the two highest disease-severity groups compared to the 5-day group (5% vs. 2% were receiving mechanical ventilation or ECMO, and 30% vs. 24% were receiving non-invasive ventilation or high-flow oxygen). The median duration of symptoms before initiation of remdesivir was 8 days in the 5-day group and 9 days in the 10-day group. Of the 200 patients in the 5-day group, 172 patients (86%) completed the full course of trial treatment, with a median duration of 5 days. Reasons for early termination of remdesivir treatment included hospital discharge (8%) and adverse events (4%). Of the 197 patients in the 10-day group, 86 patients (44%) completed the full course of treatment, with a median duration of 9 days. The proportion of patients who experienced clinical improvement of at least two points on the study's 7-point clinical ordinal scale at day 14 was not significantly

different between the 5-day and 10-day groups (65% vs. 54%). There was no significant difference in the median time to recovery between the 5-day group compared with 10-day group (10 days vs. 11 days, similar to the 10 days in the ACTT-1 trial), median duration of hospitalization among patients discharged on or before day 14 (7 days vs. 8 days), or mortality (8% vs. 11%). Interestingly, among patients receiving mechanical ventilation or ECMO on day 5, mortality by day 14 occurred in 40% (10 of 25) in the 5-day group, compared with 17% (7 of 41) in the 10-day group. However, this benefit was not seen in patients receiving non-invasive ventilation or high flow-flow oxygen on day 5, mortality by day 14 occurred in 10% in the 5-day group, compared with 15% in the 10-day group. Discharge rates were higher among patients who were symptomatic <10 days before initiating remdesivir compared to those who had symptoms for >10 days prior to their first dose (62% vs. 49%). There was no difference in the rate of adverse events in the two groups (Table 3).

Additionally, the effect of remdesivir in hospitalized patients with moderate COVID-19 pneumonia was evaluated in a randomized, open-label, phase 3 trial (SIMPLE Moderate)(40) . A total of 584 patients were enrolled in the randomized part of this study (193 received a 10-day course, 191 received a 5-day course, and 200 received standard care). The median duration of symptoms before initiation of remdesivir was 8 days in the 5-day and 10-day group, compared with 9 days in the standard of care group. On day 11, patients in the 5-day remdesivir treatment group had a significantly higher odds of better clinical status distribution on the 7-point ordinal scale compared to the standard of care group (odds ratio [OR] 1.65; 95% CI 1.09-2.48 [a OR >1 indicates a difference in clinical status towards discharge for the remdesivir group compared to standard care]). There was no significant difference observed in the odds of improvement in clinical status with the 10-day treatment course of remdesivir compared to standard of care

(p=0.18). The results of the primary endpoint did not change in post hoc analyses adjusting for day-1 clinical status score, symptom duration, inputting patients with missing status as dead, and using the intention-to-treat population. Interestingly, by day 14, the clinical status of the 5-day group and 10-group were significantly different compared to standard of care (p=0.03) with 76% of patients being discharged in the 5-day and 10-day groups and 67% in the standard of care group. The difference in clinical status by day-28 remained significant for the 10-group (p=0.03) with 90% of patients not being hospitalized compared with 83% in the standard of care group. The lack of difference in clinical status observed in the 10-day group was possibly due to the open-label design of the study and the requirement for intravenous dosing of remdesivir, which could influence discharge (Table 3).

On 15 October 2020, an interim report of a randomized open-label adaptive trial sponsored by the World Health Organization evaluating remdesivir, hydroxychloroquine. lopinavir/ritonavir, interferon-beta vs. standard of care (SOLIDARITY trial) was posted as a preprint manuscript(41, 42). A total of 11,266 patients from 405 centers in 30 countries were included in the study, of which 2750 patients were allocated to the remdesivir group and compared with 2708 patients who were allocated to receive standard of care. Overall in-hospital mortality, the trial's primary endpoint, was similar between remdesivir and the standard of care arm (11% vs. 11.2%; rate ratio [RR], 0.95; 95%CI, 0.81-1.11; p=0.50). In-hospital mortality among patients on any supplemental oxygen at enrollment was 12.2% in the remdesivir group compared to 13.8% in the standard of care arm (RR, 0.85; 95% CI, 0.66-1.09); the mortality among patients ventilated at enrollment was 43.0% vs. 37.8% (RR, 1.20; 95% CI 0.80-1.80), respectively.

It is hard to make conclusions on the effect of remdesivir in this trial, despite its larger sample size, with the information currently available(41). Major issues, include the open-label design of SOLIDARITY which places the study results at increased risk of bias compared to the double-blind, placebo-controlled design of ACTT-1(43). Furthermore, it was up to the local physician to decide what of the four treatment arms the patient could be randomized to, not only to the availability of particular drugs, without providing protocol-specific criteria for eligibility. There is no specific definition of COVID-19, or how the presence of SARS-CoV-2 infection was assessed to make a patient eligible for the study—bias towards no effect would increase with the proportion of patients without confirmed SARS-CoV2 infection. No time from symptom onset to randomization and treatment is provided, an important covariate to assess antiviral treatment effect. The trial states that patients stopped being followed at discharge, even though possible outcomes were transfer to other facilities or hospice discharge, making in patient mortality potentially biased; in ACTT-1 all patients were followed through study day 29 whether discharged or not(44).

There are additional ongoing trials of remdesivir for COVID-19 that have yet to report results. These include DisCoVeRy, a randomized open-label trial sponsored by INSERM across seven European countries assessing the same treatments as SOLIDARITY(45); ACTT-2, a randomized double-blinded trial sponsored by NIAID evaluating remdesivir and baricitinib vs. remdesivir alone(46); ACTT-3, a randomized double-blinded trial sponsored by NIAID evaluating remdesivir and interferon beta-1a vs. remdesivir alone(47); REMDACTA, a randomized, double-blind, multicenter study sponsored by Hoffmann-La Roche evaluating the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir and placebo in patients(48).

Special populations

Pregnancy and Lactation

There is currently limited information on the use of remdesivir during pregnancy and lactation. Remdesivir has not shown genotoxicity *in vitro* or adverse embryo-fetal developmental effects in animal models(33). Pregnant patients and nursing mothers have been excluded thus far from clinical trials evaluating remdesivir treatment against SARS-CoV-2. A case series of three pregnant patients with severe COVID-19 pneumonia who required supplemental oxygen, demonstrated resolution of this requirement after initiation of remdesivir. In this series, remdesivir was overall well tolerated, with only one patient experiencing elevation in liver function enzymes that required discontinuation of remdesivir(49). Another report of 67 pregnant patient who received remdesivir through the compassionate use program demonstrated that 93% recovered within 28 days. Pregnant women not requiring invasive ventilation at baseline had the highest rates of recovery (98%) and shortest median time to recovery (5 days), of whom 98% recovered, 95% were discharged. Treatment with remdesivir was well tolerated, no new safety signals were detected among pregnant patients(50). Overall, remdesivir should be used during pregnancy only if the potential benefit justifies the potential risks for mother and fetus.

Additionally, remdesivir has been used without reported fetal toxicity in six pregnant women with Ebola(51). Moreover, given that remdesivir has poor oral absorption due to extensive first-pass metabolism, infants are unlikely to absorb clinically important amount of the drug from breastmilk. Newborn infants who have received remdesivir for the treatment of Ebola did not experience any adverse events(51, 52). As a result, it does not appear that remdesivir should be avoided in the setting of lactation. However, careful infant monitoring during breastfeeding is warranted.

Pediatrics

As of June 2020, only two out of the three randomized, controlled trials evaluating remdesivir in COVID-19 included patients ≥12 years of age. In the phase 3 trial of remdesivir in Ebola virus disease, 43 patients ≤ 18 years, including two neonates, received remdesivir, with no serious adverse events reported(51). The Pediatric Infectious Diseases Society currently recommends the use of remdesivir as the preferred antiviral agent for patients with severe COVID-19 when antiviral use is indicated(53).

Renal dysfunction

Safety data of remdesivir in patients with eGFR <30 mL/min per 1.73 m^2 and those requiring renal replacement therapy (RRT) are lacking, as these patients have been excluded from clinical trials to date. Available data from published controlled trials in COVID-19 do not demonstrate an increased risk of renal adverse events in patients who received remdesivir compared to placebo(36, 38). In addition, significant renal adverse events were not reported when remdesivir was used in the phase 3 Ebola clinical trial(51). Concerns of using remdesivir in patients with renal dysfunction may arise from the presence of the excipient sulfobutylether-β-cyclodextrin (SBECD). Each 100 mg of lyophilized powder and aqueous solution of remdesivir contains 3 and 6 g of SBECD, respectively, which is below the maximum recommended safety threshold of dose of 250 mg/kg/day (for patients weighing over 24 kg)(54). Animal studies associated SBECD accumulation with renal tubular obstruction at doses 50-100 times higher than that of remdesivir(55). Given the short treatment duration of remdesivir, and the relatively low daily amounts of SBECD administered, we think its benefit outweighs the risk for patients

426 with eGFR <30 mL/min per 1.73 m^2, especially for patients with severe COVID-19. Moreover,
427 SBECD is readily removed by continuous RRT and hemodialysis(56). Thus, RRT would keep
428 SBECD exposure within a limit that is generally considered safe and significant accumulation
429 only occurs if dialysis is held for prolonged periods. A recent report demonstrated that around
430 59% of the monophosphate metabolite (GS-441524) was removed after a four-hour hemodialysis
431 session in a patient with COVID-19 treated with remdesivir(57). A case series of 46 patients with
432 acute or chronic renal disease who received remdesivir demonstrated that it was well tolerated.
433 These patients did not experience worsening renal function or clinically significant elevations in
434 liver function enzymes that were attributed to remdesivir(58). Renal experts from the American
435 Society of Nephrology suggest that patients without underlying liver disease who are expected to
436 undergo continuous or intermittent dialysis or those with acute kidney injury that is expected to
437 be transient may be the best initial candidates to receive remdesivir(54).
438
439 *Immunocompromised hosts*
440 Although immunocompromising conditions including solid-organ or hematopoietic-cell
441 transplantation, hematological malignancies, autoimmune or rheumatologic diseases have not
442 been exclusionary from the remdesivir controlled trials published to date, there have not been
443 specific reports on remdesivir effects in these populations that participated in those trials. Recent
444 reports of chronic COVID-19 in two immunocompromised patients with lymphoma and
445 associated B-cell immunodeficiency illustrated prolonged viral replication and shedding(59, 60).
446 These patients required additional courses of remdesivir over time and received convalescent
447 plasma with eventual resolution of symptoms. We have encountered patients that developed
448 COVID-19 during chemotherapy for B-cell malignancies (with agents that also affect T cells)

449 experience similar protracted courses of Covid-19 requiring additional courses of remdesivir due
450 to recrudescent disease. Solid organ and hematopoietic cell transplant recipients we have treated
451 to date have responded to single courses of treatment without recrudescent disease.
452
453 **Adverse events**
454 There are limited data evaluating the adverse event profile of remdesivir. Although
455 relatively rare, hypersensitivity reactions, including infusion-related and anaphylactic reactions,
456 have been observed during and following administration of remdesivir(33). In phase 1 studies of
457 138 healthy volunteers, transient elevations in aminotransferases were observed with remdesivir
458 administration(33). The Ebola phase 3 trial reported one serious adverse effect, a fatal episode of
459 peri-infusional hypotension, deemed potentially related to remdesivir administration(51).
460 In clinical trials, remdesivir adverse event profile has been favorable overall. Wang et al.
461 reported 102 patients (66%) in the remdesivir group experienced any adverse event compared
462 with 50 patients (64%) in the placebo arm(36). The percentage of serious of adverse event
463 reported was 18% in the remdesivir arm compared with 26% the control group. The most
464 common adverse events reported were constipation (14% vs. 15% in the remdesivir vs. placebo
465 group), hypoalbuminemia (13% vs. 15%), hypokalemia (12% vs. 14%), elevation in total
466 bilirubin (10% vs. 9%). Remdesivir discontinuation due to adverse events occurred in 18 patients
467 (12%) compared with four patients (5%) in the placebo arm. In the ACTT-1 trial, serious adverse
468 events occurred in 24% of patients in the remdesivir group vs. 32% in the placebo group. The
469 most common serious adverse event was respiratory failure, which occurred in 7.3% of patients
470 treated with remdesivir and 12.8% of patients treated with placebo(61). Non-serious grade ≥3
471 adverse events occurred in 52% in the remdesivir group vs. 57% in the placebo group. The most

common non-serious adverse events reported in the remdesivir group vs. placebo were anemia (16.5% vs. 21.7%), decrease in renal function (16.0% vs. 20.3%), hyperglycemia (13.7% vs. 11.8%), and increased liver aminotransferases (6.0% vs. 10.7%). In addition, in the SIMPLE Severe trial, the percentages of patients who experienced adverse events were similar in the two groups (70% in the 5-day group vs. 74% in the 10-day group)(39). The percentage of serious adverse events was 21% in the 5-day group and 35% in the 10-day group. The most common adverse events overall were nausea (10% in the 5-day group vs. 9% in the 10-day group), acute respiratory failure (6% vs. 11%), increased alanine aminotransferase (6% vs. 8%), and constipation (7% in both groups). Discontinuation rates due to adverse events were similar in the 5-day and 10-day groups (4% and 10% respectively) and discontinuation due to aminotransferase elevations were (2.5% and 3.6%, respectively). In the SIMPLE Moderate trial, the percentage of patients who experienced adverse events were similar in 5-day group vs. standard care (51% vs. 47%, respectively)(40). However, the percentage of adverse events was significantly higher in the 10-day group compared with placebo (59% vs. 47%, respectively). The most common adverse events in the remdesivir groups were nausea (9.6% in the remdesivir groups vs. 3% in the standard of care group), hypokalemia (6% vs. 2%), and headache (1.3% vs. 2.5%). Serious adverse events were reported in 5% of patients in the remdesivir groups and 10% in the standard care group.

Future directions

There are currently no approved treatments for COVID-19 patients who are not hospitalized. A trial has opened recently comparing remdesvir to placebo for early outpatient treatment of COVID-19 in patients with comorbidities that increase their risk of hospitalization

and death (62). The pharmacokinetics of an inhaled version of remdesivir are currently being evaluated in a phase 1a trial(62). The availability of a nebulized or dry powder formulation of remdesivir could provide more targeted delivery of the drug and potentially lower systemic exposure and toxicity, as has been demonstrated with the inhaled formulation of the neuraminidase inhibitor zanamivir for influenza A and B (63). Moreover, a single rapid bolus of remdesivir, which results in a high intracellular concentration of remdesivir-triphosphate, could theoretically be enough treat patients who present earlier on in their course. Other ways to potentially expand the use of remdesivir to the outpatient setting is to evaluate the pharmacokinetics of subcutaneous administration of remdesivir in humans. Subcutaneous remdesivir was used successfully in mouse models with SARS-CoV-1 and MERS-CoV. Expanding access to the outpatient setting could potentially allow for remdesivir to be studied as post-exposure prophylaxis, to prevent symptomatic infection or lower infectious burden after exposure to COVID-19. Additionally, given the limited data of remdesivir in pregnancy and pediatrics, future studies evaluating the safety and efficacy of remdesivir should consider including these patient populations, to prevent delays associated with drug acquisition through the compassionate use programs.

We favor confirmation of the subgroup findings of the ACTT-1 trial in at least an additional double-blind, placebo-controlled trial that explicitly targets and is powered to demonstrate a benefit of remdesivir in different strata of COVID-19 severity. Further studies are needed to assess remdesivir in combination with other antiviral drugs and immunomodulatory agents such as dexamethasone (the one treatment to demonstrate a mortality benefit to date in patients with severe or critical COVID-19 disease)(64).

518 **Expert opinion**

519 Remdesivir is currently indicated for adults and pediatric patients 12 years of age or older
520 weighing ≥ 40 kg for the treatment of COVID-19 requiring hospitalization(11).

521 Based on overall current trial results and clinical experience, remdesivir treatment should
522 be considered as early as clinically possible to prevent progression of COVID-19 pneumonia and
523 other complications in patients who are hospitalized. A new trial is evaluating remdesivir
524 treatment of outpatients who are at higher risk of hospitalization and death to prevent progression
525 to severe disease(65). A sizeable proportion of patient in the trials to date who receive treatment
526 early on have not needed to complete a treatment course of 5 days and have a shorter
527 hospitalization. Additionally, the largest benefit of remdesivir seems to be among patients who
528 require supplemental oxygen at baseline, as this is the group that had the most mortality benefit
529 based on results from ACTT-1(38). Older patients hospitalized with moderate COVID-19 (not
530 requiring supplemental oxygen at rest) and those with co-morbidities at higher risk for mortality
531 likely benefit from early remdesivir administration (40), and thus, we do not think that waiting
532 for clinical deterioration to decide on antiviral treatment is a prudent or practical approach.
533 While critically ill patients requiring mechanical ventilation or ECMO could benefit as well,
534 given the advanced lung damage sustained on presentation due to acute respiratory distress
535 syndrome, recovery will likely take longer and depend on additional interventions other than
536 remdesivir. Detailed remdesivir characteristics and authors' recommendations are presented
537 in Table 4.
538
539
540

Conclusion

Remdesivir seems to be the most promising currently available antiviral for the treatment of moderate and severe COVID-19 pneumonia based on pre-clinical and clinical data and is currently the only FDA-approved treatment for COVID-19. Further studies are needed to evaluate shorter and earlier courses of remdesivir, as well as to assess remdesivir in combination with other antiviral drugs and immunomodulatory agents.

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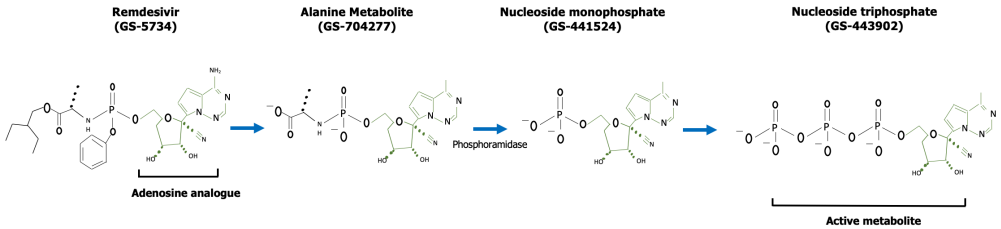
823 **Figure 1: Chemical structure of remdesivir and its metabolites (modified from(12))**



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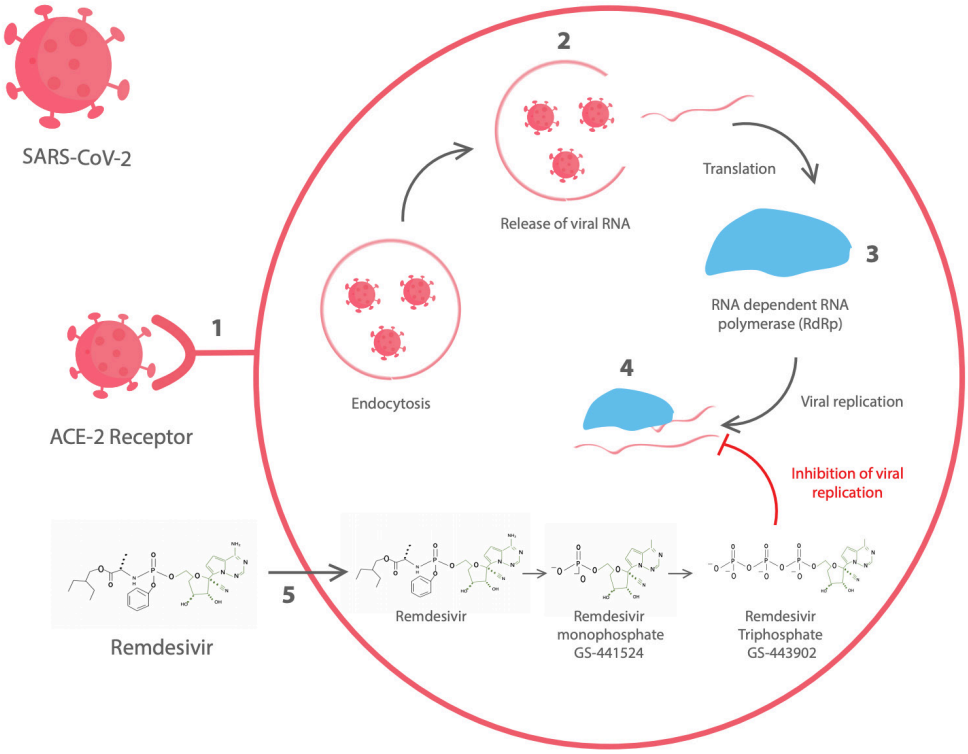
842 **Figure 2: Mechanism of remdesivir***



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844 Shown here (1) entry of SARS-CoV-2 into the target cell by binding to the ACE-2 receptor on
845 the cell surface; (2) once SARS-CoV-2 enters the cell, it releases its viral RNA; (3) SARS-CoV-
846 2 uses the host machinery to translate RNA into RNA-dependent RNA polymerase (RdRp); (4)
847 RdRp is then used to facilitate viral replication; 5. once remdesivir enters the cell, it is converted
848 into remdesivir triphosphate, which competes with endogenous ATP, that is used as a source of
849 nucleotide, for incorporation into RdRp and leading to chain termination.

850

851 *Courtesy of Lama Albadi

852 **Table 1:** Plasma and peripheral blood mononuclear cell (PBMC) pharmacokinetics following a
853 single intravenous infusion remdesivir lyophilized formulation in human healthy adult subjects
854 (adopted from (30, 31))

Pharmacokinetic parameter	**Remdesivir 75 mg 2-hour infusion (n = 10)**	**Remdesivir 150 mg 2-hour infusion (n = 10)**	**Remdesivir 75 mg 30-minute infusion (n = 9)**
Remdesivir plasma			
AUC_{inf} (h.ng/mL)[a]	1839.9	3261.1	1254.7
C_{max} (ng/mL)	1720 (28.4)	2720 (35.0)	2930 (29.2)
$T_{1/2}$ (h)[b]	0.84 (0.8-0.96)	1.11 (0.97-1.8)	1 (0.85-1.03)
GS-441524 (monophosphate metabolite) in PBMC			
AUC_{inf} (h.ng/mL)[a]	2200	4330	2020
C_{max} (ng/mL)	77.5 (21.0)	148 (26.5)	69.1 (32.8)
T1/2 (h)[b]	22.9 (21.7-27.0)	26.3 (24.2-28.7)	26.7 (25.0-26.9)
GS-443902 (triphosphate metabolite) in PBMC			
AUC_{inf} (h. µM)[a]	176.2	294.7	394.3
C_{max} (µM)	2.5 (16.2)	6.0 (46.1)	5.9 (37.7)
$T_{1/2}$ (h)[b]	42.68 (30.61-47.41)	35.95 (27.27-41.5)	48.79 (26.21-69.52)
Accumulation ratio[b,c]	3.1 (2.39-3.38)	2.7 (2.19-3.03)	3.46 (2.15-4.7)

855 a Data expressed as mean

856 b Data expressed as median (IQR)

857 c Accumulation ratio = $1/(1-e^{-k*tau})$; where $k = 0.693/t_{1/2}$ and tau is dosing interval of 24 hours

858 AUC, area under the curve; C_{max}, peak plasma concentration; $T_{1/2}$, half-life

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860 **Table 2:** Ordinal Scales used for Clinical Status in Clinical Trials
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Scale used in Wang et al. and ACTT Trials (37)	**Clinical Status**	**Scale used in the SIMPLE severe and SIMPLE moderate trials(66, 67)**
8	Death	1
7	Hospitalized on invaseive mechanical ventilation or extracorpeal membrane oxygenation	2
6	Hospitalized, on non-invasive ventilation or high-flow oxygen devices	3
5	Hospitalized, requiring low-flow supplemental oxygen	4
4	Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related or not to COVID-19)	5
3	Hospitalized, not requiring supplemental oxygen or requiring ongoing medical care (other than that specified in the protocol for remdesivir administration)	6
1-2	Not hospitalized	7

862 **Table 3:** Published randomized trials of remdesivir in COVID-19

Study	Methods	Study Population	Key results	Strengths/ Limitations	Interpretation
Wang et al. Lancet 2020 (36)	Double-blind, randomized, placebo-controlled trial (200 mg loading dose, 100 mg maintenance dose on days 2-10 or placebo)	• Age ≥18 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% on room air • Symptomatic ≤ 12 days • ALT or AST < 5x ULN • eGFR > 30 mL/min	• No difference in time to clinical recovery (21 days vs. 23days), day-28 mortality (15% vs. 13%), or viral load reduction observed between remdesivir and placebo • Incidence of adverse events was similar between the two groups	• Strengths: randomized controlled trial; low loss to follow-up; evaluated SARS-CoV-2 viral-load • Limitations: did not complete enrollment due to the control of the outbreak, resulting in low power for the study	Given that the study was underpowered, results are inconclusive

Beigel etl al. NEJM 2020 (ACTT-1) (38)	Double-blind, randomized, placebo-controlled trial (200 mg loading dose, 100 mg maintenance dose for up to 9 days or placebo)	• Age ≥18 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% or requiring supplemental oxygen, mechanical ventilation or ECMO • ALT or AST < 5x ULN • eGFR > 30 mL/min	• Patients who received remdesivir had a significantly shorter recovery time by day-29 (10 vs. 15 days). The odds of clinical improvement at day 15 were higher in the remdesivir group (OR 1.50). This change was more evident in patients requiring supplemental oxygen (OR 1.47) • Day-14 and -29 mortality were lower for the remdesivir group (7% vs. 12%) and (11% vs. 15%) though not statistically significant • No difference in incidence of serious adverse events	• Strengths: Adequate power; high protocol adherence • Limitations: did not evaluate SARS-CoV-2 viral-load	Remdesivir is effective at improving clinical recovery in COVID-19 patients. Remdesivir may be beneficial in preventing progression to more severe respiratory disease and its benefit is most apparent in those requiring supplemental oxygen.

Goldman et al. NEJM 2020 (SIMPLE Severe) (39)	Randomized, open-label, phase 3 trial (Group 1: 200 mg loading dose, 100 mg maintenance dose for up to 4 days Group 2: 200 mg loading dose, 100 mg maintenance dose for up to 9 days)	• Age ≥12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% or requiring supplemental oxygen • ALT or AST < 5x ULN • eGFR > 50 mL/min	• There was no difference in clinical improvement of at least 2-points in the ordinal scale between 5-day and a 10-day course (65% vs. 54%) • Among patients receiving noninvasive ventilation or high-flow oxygen on day 5, day-14 mortality was 10% in the 5-day group vs. 15% in the 10-day group • Among patients receiving mechanical ventilation or ECMO on day 5, day-14 mortality was 40% in the 5-day group vs. 17% in the 10-day group	• Strengths: first study to evaluate optimal duration of remdesivir in COVID-19; adequate power; high protocol adherence • Limitations: did not evaluate SARS-CoV-2 viral-loads; excluded patients on mechanical ventilation or ECMO	5 days of remdesivir is sufficient to treat COVID-19 patients who are not receiving mechanical ventilation/ECMO. Patients who progress to mechanical ventilation or ECMO may benefit from a 10 days course

Spinner et al. JAMA, 2020 (SIMPLE Moderate) (40)	Randomized, open-label, phase 3 trial (Group 1: 200 mg loading dose, 100 mg maintenance dose for up to 4 days Group 2: 200 mg loading dose, 100 mg maintenance dose for up to 9 days Group 3:	• Age ≥12 years • Positive SARS-CoV-2 PCR • Radiographic evidence of pulmonary infiltrates • SpO2 >94% and breathing on room air at screening • ALT or AST < 5x ULN • eGFR > 50 mL/min	• Those randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard of care at day 11, but not those randomized to a 10-day group. This difference was of uncertain clinical importance	• Strengths: first study to evaluate remdesivir in patients with moderate COVID-19 pneumonia; had adequate power • Limitations: did not evaluate SARS-CoV-2 viral-loads; did not stratify by sites, which could have influenced the results, given the differences in patient care and discharge practices	A 5-day course of remdesivir may be sufficient to treat patients with moderate COVID-19 pneumonia

	standard care)				
Pan et al. (SOLIDARITY) (41)	Randomized, open-label, phase 3 trial (Remdesivir 200 mg loading dose, 100 mg maintenance dose for up to 9 days or standard of	• Age ≥18 years • Diagnosis of Definitive COVID-19	• Remdesivir was not associated with a reduction in in-hospital mortality compared to standard of care (11% vs. 11.2%) • Remdesivir was not associated with educed initiation of ventilation or hospital length of stay	• Strengths: large sample size • Limitations: open-label study; no definition of COVID-19 or definitive COVID-19, did not stratify by oxygen requirements or site; has not reported duration of symptoms prior to start of treatment;	Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19

	care)			inclusion criteria unclearly defined; patients who are discharged were not followed; did not use WHO ordinal scale	

863 ALT: alanine aminotransferase

864 AST: aspartate aminotransferase

865 ULN: upper limit of normal

866 eGFR: estimated glomerular filtration rate

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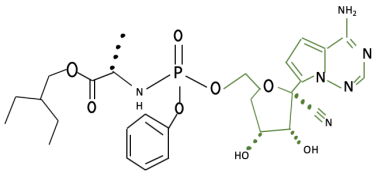
874 **Table 4:** Remdesivir characteristics and clinical guide

Characteristic	**Key Information**	**Practical recommendations by authors**
Chemical name	2-ethylbutyl N-{(S)-[2-C-(4- aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-O-yl]phenoxyphosphoryl}-L-alaninate	
Chemical structure		
Other names	GS-5734	
Mechanism of action	Inhibition of viral replication by competing with endogenous ATP for incorporation into viral RNA via RNA-dependent RNA polymerase, leading to chain termination.	
Antiviral activity	Active against coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2), filoviruses (Ebola virus, Marburg virus), and paramyxoviruses (RSV, Nipah virus, and Hendra virus) EC_{50} and EC_{90} 0.77 µM and 1.76 µM respectively against SARS-CoV-2(23).	
Remdesivir resistance	F476L and V553L mutations mediate resistance to remdesivir and are associated with a fitness	There is currently no available remdesivir resistance testing.

	defect(18). D848Y mutation in RdRp can lead to treatment failure(24).	
Authorized indication	FDA-approved for pediatric and adult patients hospitalized with COVID-19 in the United States(11). Conditional marketing authorization in the European Union(9). Approved in Japan, Taiwan, India, Singapore, the United Arab Emirates(10).	
Formulation	A remdesivir 100 mg lyophilized powder vial is reconstituted with 19 mL of sterile water for injection and diluted into 0.9% saline. Remdesivir is also supplied as aqueous-based concentrated 5 mg/mL solution. Remdesivir is solubilized with sulfobutylether-β-cyclodextrin (SBECD). Each vial of remdesivir lyophilized powder contains 3 grams of SBECD, while each aqueous solution vial contains 6 grams of SBECD each.	Only available for IV administration, as of October 2020 The lyophilized formulation allows for longer-term storage compared to aqueous-based concentrated solution.
Dosage	Adults and pediatrics weighing ≥ 40: loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg. Pediatric patients weighing 3.5-40 kg: loading dose of 5 mg/kg, followed by a maintenance dose	We favor a 30 minutes infusion time to maximize intracellular concentration of the pharmacologically active metabolite. From clinical trials data and our

	of 2.5 mg/kg. Treatment duration is up to 5 days, and can be extended to 10 days if patients do not experience clinical improvement. For mechanically ventilated patients or those receiving ECMO 10 days of treatment is recommended.	experience, patients in general wards can recover quickly (no longer need oxygen, no constitutional symptoms) and are ready for discharge before 5 days of treatment. These patients do not need to complete 5 days of treatment.
Pharmacokinetics	Absorption: remdesivir is not suitable for oral administration due to extensive first pass metabolism resulting in poor bioavailability and low systemic absorption. Metabolism: Remdesivir is a substrate of metabolizing CYP450 enzymes (CYP2C8, CYP2D6, and CYP3A); transporters OATP1B1 and P-gp. Distribution: remdesivir widely distributed into tissues, but has poor blood-brain barrier penetration. Elimination: 74% excreted renally and 18% in the feces.	Remdesivir should only be administered via the IV route.
Drug interactions	Inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, OAPT1B1, OATP1B3, MRP4, and NCTP	Currently, drug-drug interactions of remdesivir in humans have not been evaluated and their clinical relevance

	Substrate of of CYP2C8, CYP2D6, and CYP3A, OATP1B1 and P-gp Chloroquine and hydroxychloroquine reduce remdesivir's antiviral activity *in vitro*.	has not been established. Chloroquine or hydroxychloroquine should not be co-administered with remdesivir.
Adverse events of note	Possible risk of elevation in liver function enzymes.	Frequent monitoring of liver function enzymes while on remdesivir should be performed.
Renal dysfunction	No recommendations regarding dose adjustment for renal dysfunction. Current trials have exclusion criteria for eGFR <30 mL/min or those requiring renal replacement therapy, due to the presence of the excipient SBECD.	Given the short duration of remdesivir and the relatively low SBECD content, we think benefit outweighs the risk for patients hospitalized with COVID-19 and renal dysfunction.
Hepatic dysfunction	No recommendations regarding dose adjustment for hepatic dysfunction. Current trials have exclusion criteria for elevated liver function enzymes.	Given the risk of liver function enzyme elevation with remdesivir, it should be used with caution in patients with underlying hepatic dysfunction when the benefits outweigh the risks.

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