New Perspectives on Antimicrobial Agents: Remdesivir Treatment 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 coronavirus disease 2019 (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 levels of viral RNA. Recent clinical data have demonstrated the clinical activity of remdesivir in terms of faster time to recovery in patients with severe COVID-19 and higher odds of improved clinical status in patients with moderate COVID-19. Here, 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.

KEYWORDS remdesivir, antiviral, COVID-19, SARS-CoV-2

Coronaviruses (CoVs) are enveloped viruses containing a large single-stranded, positive-sense RNA genome (1). Among the known CoVs, most (including human coronavirus 229E [HCoV-229E], HCoV-NL63, HCoV-HKU1, and HCoV-OC43) usually cause mild acute rhinophanryngitis, but others can cause severe pulmonary disease, including severe acute respiratory syndrome (SARS), caused by SARS coronavirus 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 2 (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 a viral RNA-dependent RNA polymerase (RdRp) encoded by the viral genome (4).

SARS-CoV-2 is transmitted primarily through the respiratory route, by both respiratory aerosols and droplets and, less commonly, by direct contact or by 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 11 March 2020. As of 11 November 2020, the World Health Organization (WHO) reported over 51 million confirmed COVID-19 cases and over 1.2 million deaths globally (7). Remdesivir (also known as GS-5734) is currently the most promising available direct antiviral treatment option. On the basis of favorable initial data from a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored randomized double-blind clinical trial, the U.S. Food and
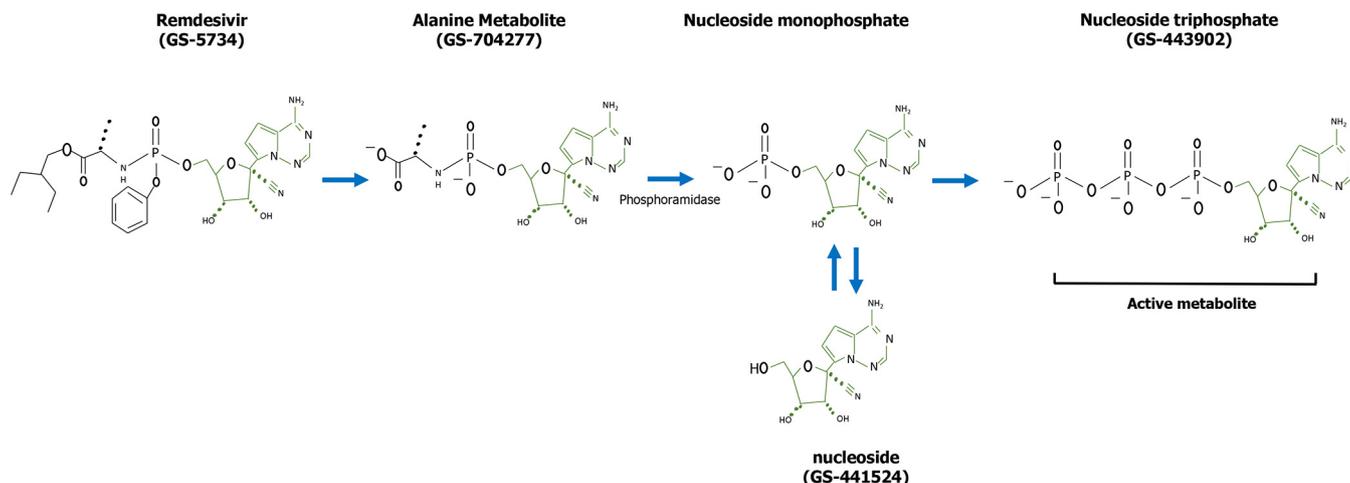
FIG 1 Chemical structure of remdesivir and its metabolites (adapted from reference 12).

Drug Administration (FDA) granted remdesivir Emergency Use Authorization for the treatment of COVID-19 on 1 May 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 22 October 2020, remdesivir received full FDA approval for treatment of hospitalized patients with COVID-19 (11). In this review, we discuss the pharmacology and pharmacokinetics of and preclinical and clinical data for remdesivir in COVID-19.

CHEMISTRY AND PHARMACOLOGY

Remdesivir is a single-diastereomer monophosphoramidate prodrug of a cyano-adenosine nucleoside analogue (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 analogue (GS-441524), and, ultimately, the pharmacologically active nucleoside triphosphate form (GS-443902) (Fig. 1) (12). GS-443902 acts as an analogue of ATP and competes with the endogenous ATP substrate for incorporation into SARS-CoV's RNA via RdRp. RdRp is a nonstructural protein that is highly conserved among different virus 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 (Fig. 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 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 betacoronavirus murine hepatitis virus (MHV) model illustrated that remdesivir was still able to inhibit RdRp even in the setting of intact ExoN (18). The authors of that study compared the sensitivity of wild-type (WT) MHV to that of ExoN-negative (ExoN$^-$) MHV and revealed that it is modestly less sensitive to remdesivir (50% effective concentration [EC$_{50}$], 0.019 μM versus 0.087 μM), suggesting that remdesivir is able to evade ExoN proofreading activity, which could be attributed to higher RdRp selectivity for remdesivir triphosphate than for the natural nucleotides (18, 19). This might also indicate that ExoN activity is not sufficient to prevent potent inhibition of CoV replication (18).
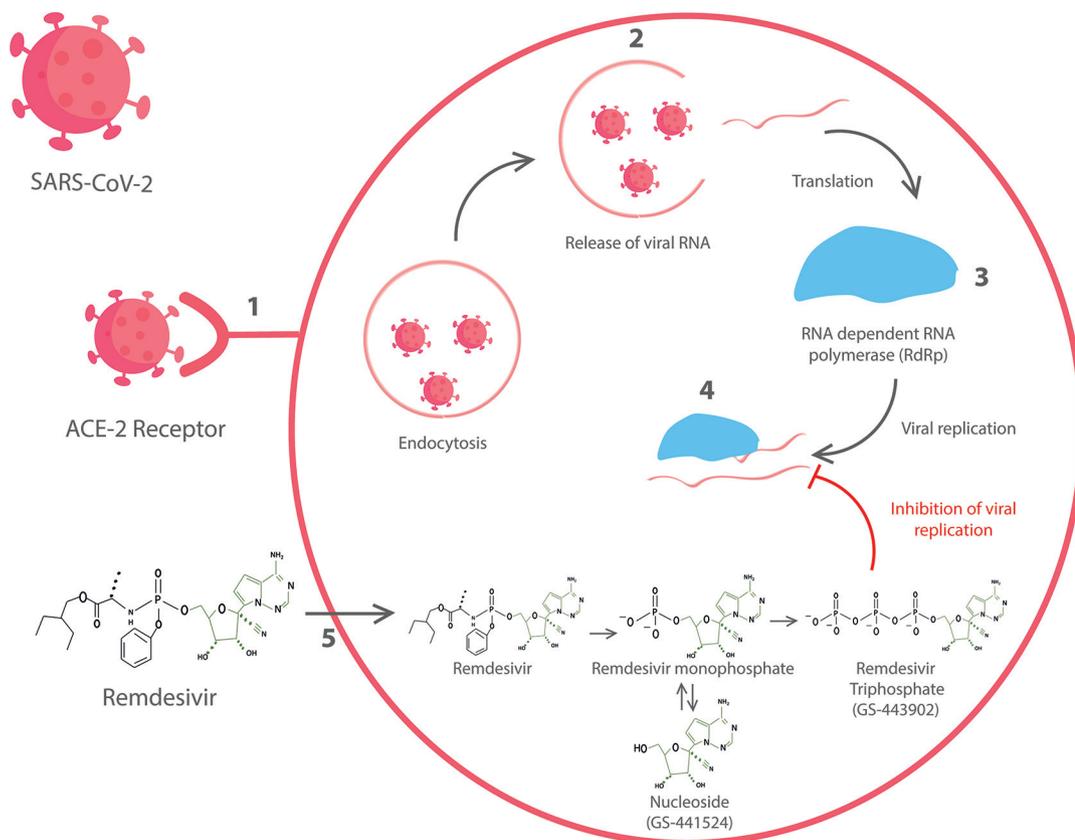
FIG 2 Mechanism of remdesivir. (Step 1) Entry of SARS-CoV-2 into the target cell by binding to the ACE-2 receptor on the cell surface. (Step 2) Once SARS-CoV-2 enters the cell, it releases its viral RNA. (Step 3) SARS-CoV-2 uses the host machinery to translate RNA into RNA-dependent RNA polymerase (RdRp). (Step 4) RdRp is then used to facilitate viral replication. (Step 5) Once remdesivir enters the cell, it is converted into remdesivir triphosphate, which competes with endogenous ATP, which is used as a source of nucleotide, for incorporation into RdRp, leading to chain termination. (Courtesy of Lama Albadi, reproduced with permission.)

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 virus, mumps virus, and parainfluenza virus 3) (20). It has also been shown to exhibit antiviral activity against *Filiviridae* (e.g., Ebola virus 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} value 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 EC_{50} and EC_{90} values 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 usually occurs 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 virus titers at days 2 and 5 postinfection, reduced lung pathology, reduced intra-alveolar edema, and improved pulmonary function compared to untreated SARS-CoV-1 mice (22). Therapeutic administration of subcutaneous remdesivir, 1 day postinfection, showed similarly improved pulmonary function and reduced viral lung titers when the drug was administered within 1 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 1 day prior to infection significantly reduced virus-induced weight loss, pulmonary hemorrhage, lung viral load, and mortality at days 4 and 6 after MERS-CoV infection (25). Therapeutic administration of subcutaneous remdesivir, 1 day postinfection, in the same model demonstrated effects similar to those seen with prophylactic dosing.

The therapeutic efficacy of remdesivir against MERS-CoV has been demonstrated in a rhesus macaque model (26). That study evaluated the effect of intravenous prophylactic and therapeutic remdesivir boluses administered over ~5 min in a rhesus macaque model of MERS-CoV over the course of 6 days. Prophylactic remdesivir was administered 1 day before inoculation and was continued once daily for 6 days. Remdesivir administration 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 the results seen with vehicle-treated subjects. When therapeutic remdesivir was administered 12 h after inoculation and continued once daily for 6 days, the treatment was found to be associated with mildly elevated respiratory rates but at levels significantly lower than those seen in the vehicle-treated group, as well as with fewer lung infiltrates on X-ray, lower viral loads, and smaller areas of gross lung lesions on necropsy than in the untreated group.

More recently, the activity of remdesivir in rhesus macaques infected with SARS-CoV-2 was demonstrated (27). Administration of intravenous therapeutic remdesivir over ~5 min was initiated close to the peak of viral replication, 12 h after inoculation with SARS-CoV-2, and was continued once daily for 6 days. Animals treated with remdesivir lacked clinical evidence of respiratory disease and had less-severe radiographic pulmonary infiltrates and pathological pulmonary lesions on necropsy than 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 as necessarily representative of a lack of infectiousness (27).

PHARMACOKINETICS

Remdesivir is not suitable for oral administration due to complete first-pass metabolism through the liver. Consequently, intramuscular (i.m.) and intravenous (i.v.) administration of remdesivir was evaluated in male rhesus monkeys (21). The i.m. 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 remdesivir administered via i.v. was rapidly eliminated and converted to the nucleoside analogue (GS-441524), indicating a more consistent and rapid delivery of remdesivir and higher maximal levels of the nucleoside analogue than were seen with the i.m. administration.

Following i.v. administration, remdesivir has a short plasma half-life ($t_{1/2}$) of ~1 h, as it is quickly metabolized by carboxylesterase 1 (CES1) to the intermediate alanine metabolite (GS-704277), followed by the predominant GS-441524 metabolite ($t_{1/2}$ of

TABLE 1 Plasma and peripheral blood mononuclear cell pharmacokinetics following a single intravenous infusion of a lyophilized remdesivir formulation in human healthy adult subjects[a]

Pharmacokinetic parameter	Value(s)		
	Remdesivir 75 mg 2-h infusion ($n = 10$)	Remdesivir 150 mg 2-h infusion ($n = 10$)	Remdesivir 75 mg 30-min infusion ($n = 9$)
Remdesivir plasma			
AUC_{inf} (h · ng/ml)[b]	1,839.9	3,261.1	1,254.7
C_{max} (ng/ml)	1,720 (28.4)	2,720 (35.0)	2,930 (29.2)
$t_{1/2}$ (h)[c]	0.84 (0.8–0.96)	1.11 (0.97–1.8)	1 (0.85–1.03)
GS-441524 (nucleoside analogue) in PBMC			
AUC_{inf} (h · ng/ml)[b]	2,200	4,330	2,020
C_{max} (ng/ml)	77.5 (21.0)	148 (26.5)	69.1 (32.8)
$t_{1/2}$ (h)[c]	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)[b]	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)[c]	42.68 (30.61–47.41)	35.95 (27.27–41.5)	48.79 (26.21–69.52)
Accumulation ratio[c,d]	3.1 (2.39–3.38)	2.7 (2.19–3.03)	3.46 (2.15–4.7)

[a]The table was adapted from references 30 and 31. AUC_{inf}, area under the concentration-time curve from 0 h to infinity; C_{max}, peak plasma concentration; PBMC, peripheral blood mononuclear cell; $t_{1/2}$, half-life.
[b]Data are expressed as means.
[c]Data are expressed as median (IQR).
[d]Accumulation ratio = $1/(1 - e^{-k*tau})$; where $k = 0.693/t_{1/2}$ and tau is the dosing interval of 24 h.

24.5 h) (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 GS-441524 metabolite being present in serum at concentrations 1,000-fold higher than remdesivir throughout a 7-day treatment course (29). The GS-441524 metabolite is then converted into the active triphosphate metabolite of GS-443902, which has a prolonged plasma $t_{1/2}$ of over 35 h, supporting the idea of once-daily administration of the drug (30, 31). Given the prolonged $t_{1/2}$ of the GS-441524 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 min provided a higher peripheral blood mononuclear cell (PBMC) concentration of the triphosphate active metabolite than remdesivir 150 mg administered over 2 h (area under the concentration-time curve from 0 h to infinity [AUC_{inf}], 394.3 h · ng/ml versus 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 GS-441524 exhibit very low protein binding in plasma, with mean free fraction values ranging from 85% to 127% (28). *In vivo* studies demonstrated that remdesivir rapidly distributes to most tissues following i.v. administration (21, 28). Remdesivir levels were highest in the kidney, liver, and arterial wall (28). Remdesivir and its metabolites were also detected at various levels in the testes, epididymis, eyes, and brain of rhesus macaques within 4 h of administration. Interestingly, the levels in the brain were around 8% of plasma levels at 4 h postadministration but remained quantifiable and higher than the plasma levels at 168 h postdose (21).

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

Remdesivir and its metabolites are mainly eliminated renally (74%) and through the feces (18%). Following i.v. administration, the metabolite predominantly detected in the urine was the monophosphate metabolite (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 i.v. administration, which is predominantly excreted renally (32).

DOSAGE AND DRUG ADMINISTRATION

Remdesivir is currently supplied as two different preservative-free formulations containing 5 mg/ml remdesivir, including a water-based concentrated solution and a lyophilized powder formulation, both provided in 100-mg vials. The recommended dosing for adults and for pediatric patients weighing ≥40 kg is a single loading dose of 200 mg on day 1, followed by a daily maintenance dose of 100 mg. For pediatric patients weighing more than 3.5 kg and less than 40 kg, the lyophilized formulation is preferred. A single loading dose of 5 mg/kg of body weight should be administered on day 1 followed by a maintenance dose of 2.5 mg/kg. Doses should be administered intravenously and infused over 30 to 120 min (33); however, we prefer administration over 30 min 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 up to 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-depleting 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, 55, 56).

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 i.v. administration. However, in vitro studies demonstrated that remdesivir is a substrate for the CYP450 enzymes (CYP2C8, CYP2D6, and CYP3A4), organic anion-transporting polypeptide 1B1 (OAPT1B1), and P-glycoprotein (P-gp) proteins. In addition, remdesivir can act as an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; of OAPT1B1 and OATP1B3; of multidrug resistance-associated protein 4 (MRP4), and of 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, coadministration 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 administration of 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 min 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 to 12 days). More patients in the remdesivir arm than in the placebo arm had a baseline respiratory rate of more than 24 breaths per min (23% versus 14%), and more patients in the control group than in the remdesivir arm had been symptomatic for ≤10 days at the time of starting remdesivir or placebo. The time to clinical improvement in the remdesivir group (median, 21 days; IQR, 13 to 28) was not significantly different from that in the placebo group (median, 23 days; IQR, 15 to 28; hazard ratio [HR], 1.23 [a HR value of >1 indicates shorter time to clinical improvement with remdesivir]; 95% confidence interval [CI], 0.87 to 1.75). Levels of

TABLE 2 Ordinal scales used for clinical status in clinical trials

Scale used by Wang et al. (36) and in ACTT trials (37, 38)	Clinical status	Scale used in the SIMPLE Severe Trial and SIMPLE Moderate Trial (39, 40, 59, 60)
8	Death	1
7	Hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation	2
6	Hospitalized, on noninvasive 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

nasopharyngeal virus load reduction and rates of day 28 mortality (14% in the remdesivir arm versus 13% in the placebo arm) were similar in the two groups. In a subgroup analysis of patients enrolled within 10 days of symptom onset, there was no statistically significant difference in 28-day mortality rates (11% among those treated with remdesivir versus 15% among those who received placebo) or in the time to clinical improvement (hazard ratio, 1.52; 95% CI, 0.95 to 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 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 that study also received corticosteroids, though there was no difference in the proportions of administration 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 than in those who received placebo (38). That study included 1,062 patients enrolled between late February and mid-April 2020, with 541 allocated to the remdesivir group and 521 allocated to placebo. Remdesivir was administered intravenously over 30 to 120 min 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 compared with those treated with placebo at day 15. However, on 22 March 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 the 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. The median duration of symptoms before initiation of study drug was 9 days in both groups (IQR, 6 to 12 days). At baseline, 131 (24.2%) patients 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 versus 15 days; rate ratio [RR] for recovery, 1.29 [a RR of >1 indicates faster time to recovery with remdesivir]; 95% CI, 1.12 to 1.49). This benefit was most apparent in patients requiring supplemental oxygen by nasal cannula at treatment initiation (RR, 1.45; 95% CI, 1.18 to 1.79). The benefit of remdesivir was greater when it was 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); in comparison, 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

TABLE 3 Published randomized trials of remdesivir in COVID-19[a]

Study	Method(s)	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 yrs; 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 23 days), day 28 mortality (14% vs 13%), or viral load reduction observed between remdesivir and placebo; incidences of adverse events similar between the two groups	Strengths: randomized controlled trial, low loss to follow-up, evaluated SARS-CoV-2 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 et 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 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 ≤ 94% or requiring supplemental oxygen, mechanical ventilation, or ECMO; ALT or AST < 5× 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 (RR, 1.45); day 14 and 29 mortality were lower for the remdesivir group (7% vs 12% and 11% vs 15%, respectively), 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 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 Trial) (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 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 ≤ 94% or requiring supplemental oxygen; ALT or AST < 5× 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 10-day courses (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 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-day course

TABLE 3 (Continued)

Study	Method(s)	Study population	Key results	Strengths/limitations	Interpretation
Spinner et al., JAMA 2020 (SIMPLE Moderate Trial) (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, standard care)	Age ≥12 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 > 94% and breathing on room air at screening; ALT or AST < 5× 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 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
Pan et al. (SOLIDARITY Trial) (41)	Randomized, open-label, phase 3 trial (remdesivir 200 mg loading dose, 100 mg maintenance dose for up to 9 days or standard of care)	Age ≥18 yrs; 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 reduced 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, inclusion criteria not clearly defined, patients who were discharged were not followed, did not use WHO ordinal scale	Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19

[a]ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; SpO2, oxygen saturation; NEJM, New England Journal of Medicine; ULN, upper limit of normal.

1.92 (95% CI, 1.41 to 2.60). The odds of clinical improvement at day 15 were higher in the remdesivir group (odds ratio [OR], 1.50; 95% CI, 1.18 to 1.91). The time to an improvement by at least one or two categories in the ordinal scale by day 29 was significantly shorter in the remdesivir arm than in the placebo arm (for improvement by one category, median, 7 days versus 9 days; rate ratio, 1.23; 95% CI, 1.08 to 1.41; for improvement by two categories, median, 11 days versus 14 days; rate ratio, 1.29; 95% CI, 1.1 to 1.46). Remdesivir was associated with a significant reduction in median hospital length of stay (12 days versus 17 days). The mortality rate was significantly lower by day 14 (6.7% versus 11.9%; HR, 0.55; 95% CI, 0.36 to 0.83) but not by day 29 (11.4% versus 15.2%; HR, 0.73; 95% CI, 0.52 to 1.03) in the remdesivir group than in the placebo group. A lower mortality rate was particularly apparent in patients requiring supplemental oxygen at baseline (HR, 0.3; 95% CI, 0.14 to 0.64). Interestingly, remdesivir was associated with a lower incidence of new oxygen use among patients who had not been receiving oxygen at baseline (36% versus 44%). Treatment with remdesivir was also associated with fewer days of subsequent oxygen use for patients receiving oxygen at enrollment (13 days versus 21 days) and with a shorter subsequent duration of mechanical ventilation or ECMO for those receiving these interventions at baseline (17 days versus 20 days). The incidences of adverse events were 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 (the SIMPLE Severe Trial) (39). A total of 402 patients were enrolled in the randomized part of the study (200 patients started a 5-day course, and 197 started a 10-day course). Overall, baseline characteristics were comparable between the two groups. However, the 10-day group had a larger proportion of patients in the two highest disease severity groups than the 5-day group (5% versus 2% were receiving mechanical ventilation or ECMO, and 30% versus 24% were receiving noninvasive ventilation or high-flow oxygen). The median durations of symptoms before initiation of remdesivir were 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 (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 proportions of patients who experienced clinical improvement of at least 2 points on the study's 7-point clinical ordinal scale at day 14 were not significantly different between the 5-day and 10-day groups (65% versus 54%). There was no significant difference in the median time to recovery between the 5-day group and 10-day group (10 days versus 11 days, similar to the 10 days in the ACTT-1 trial), in the median duration of hospitalization among patients discharged on or before day 14 (7 days versus 8 days), or mortality (8% versus 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 noninvasive ventilation or high-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 than among those who had symptoms for >10 days prior to their first dose (62% versus 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 (the SIMPLE Moderate Trial) (40). A total of 584 patients were enrolled in the randomized part of that 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 groups, compared with 9 days in the standard-of-care group. On day 11, patients in the 5-day remdesivir treatment group had significantly higher odds of a better clinical status distribution on the 7-point ordinal

scale than those in the standard-of-care group (odds ratio [OR], 1.65 [an OR of >1 indicates a difference in clinical status toward discharge between the remdesivir group and the standard-of-care group]; 95% CI, 1.09 to 2.48). There was no significant difference observed in the odds of improvement in clinical status with the 10-day treatment course of remdesivir compared to the standard of care ($P = 0.18$). The results corresponding to 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 statuses of the 5-day group and 10-day group were significantly different from those of patients receiving the 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-day group ($P = 0.03$), with 90% of those 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 have influenced 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, and interferon-beta versus standard of care (the 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, among which 2,750 patients were allocated to the remdesivir group and compared with 2,708 patients who were allocated to receive the standard of care. Overall rates of in-hospital mortality, the trial's primary endpoint, were similar between the remdesivir arm and the standard-of-care arm (11% versus 11.2%; rate ratio [RR], 0.95; 95% CI, 0.81 to 1.11; $P = 0.50$). In-hospital mortality among patients on any form of 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 to 1.09); the mortality rates among patients ventilated at enrollment were 43.0% and 37.8% (RR, 1.20; 95% CI, 0.80 to 1.80), respectively.

It is hard to draw conclusions on the effect of remdesivir in that trial, despite its larger sample size, with the information currently available (41). Major issues include the open-label design of the SOLIDARITY Trial, 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 which of the four treatment arms the patient could be randomized to (i.e., the decision was based on the availability of particular drugs, and the trial instructions did not provide protocol-specific criteria for eligibility). There is no specific definition of COVID-19 or description of how the presence of SARS-CoV-2 infection was to be assessed to make a patient eligible for the study—bias toward no-effect data would increase with the proportion of patients without confirmed SARS-CoV2 infection. No specification of time from symptom onset to randomization and treatment is provided, an important covariate in assessing antiviral treatment effects. The trial data state that patients stopped being followed at discharge, even though possible outcomes included transfer to other facilities or hospice discharge, making in-patient mortality data 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 and assessing the same treatments as the SOLIDARITY Trial (ClinicalTrials registration no. NCT04315948; accessed 13 June 2020); ACTT-2, a randomized double-blind trial sponsored by NIAID evaluating administration of remdesivir and baricitinib versus remdesivir alone (ClinicalTrials registration no. NCT04401579; accessed 13 June 2020); ACTT-3, a randomized double-blind trial sponsored by NIAID evaluating administration of remdesivir and interferon beta-1a versus remdesivir alone (ClinicalTrials registration no. NCT04492475; accessed 8 October 2020);

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 (ClinicalTrials registration no. NCT04409262; accessed 13 June 2020).

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 well tolerated overall, with only one patient experiencing elevation in the levels of liver function enzymes that required discontinuation of remdesivir (45). Another report of 67 pregnant patients 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); among those women, 98% recovered and 95% were discharged. Treatment with remdesivir was well tolerated; no new safety signals were detected among pregnant patients (46). 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 (47). Moreover, given that remdesivir has poor oral absorption due to extensive first-pass metabolism, infants are unlikely to absorb a clinically important amount of the drug from breastmilk. Newborn infants who received remdesivir for the treatment of Ebola did not experience any adverse events (47, 48). 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 of the three randomized, controlled trials evaluating administration of remdesivir in COVID-19 included patients who were ≥12 years of age. In the phase 3 trial of remdesivir in Ebola virus disease, 43 patients who were ≤18 years of age, including two neonates, received remdesivir, with no serious adverse events reported (47). 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 (49).

Renal dysfunction. Safety data of remdesivir in patients with estimated glomerular filtration rate (eGFR) values of <30 ml/min per 1.73 m² and in 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 adverse renal events were not reported when remdesivir was used in the phase 3 Ebola clinical trial (47). 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 dose of 250 mg/kg/day (for patients weighing over 24 kg) (50). Animal studies showed an association of SBECD accumulation with renal tubular obstruction at doses 50 to 100 times higher than that of remdesivir (51). Given the short remdesivir treatment duration, and the relatively low daily amounts of SBECD administered, we think that its benefit outweighs the risk for patients with eGFR values of <30 ml/min per 1.73 m², especially for patients with severe COVID-19. Moreover, SBECD is readily removed by continuous RRT and hemodialysis (52). Thus, RRT would keep SBECD exposure within a limit that is generally considered safe, and significant accumulation occurs only if dialysis is held for prolonged periods. A recent report demonstrated that around 59%

of the GS-441524 metabolite was removed after a 4-h hemodialysis session in a patient with COVID-19 treated with remdesivir (53). A case series of 46 patients with acute or chronic renal disease who received remdesivir demonstrated that it was well tolerated. These patients did not experience worsening renal function or clinically significant elevations in liver function enzymes that were attributed to remdesivir (54). Renal experts of the American Society of Nephrology suggest that patients without under-lying liver disease who are expected to undergo continuous or intermittent dialysis or those with acute kidney injury that is expected to be transient may be the best initial candidates to receive remdesivir (50).

Immunocompromised hosts. Although immunocompromising conditions, includ-ing solid-organ or hematopoietic cell transplantation, hematological malignancies, and autoimmune or rheumatologic diseases, have not been exclusionary factors in the controlled remdesivir trials published to date, there have not been specific reports on the effects of remdesivir in these populations that participated in those trials. Recent reports of chronic COVID-19 in two immunocompromised patients with lymphoma and associated B-cell immunodeficiency illustrated prolonged viral replication and shedding (55, 56). Those patients required additional courses of remdesivir over time and received convalescent plasma, with eventual resolution of symptoms. We have encoun-tered patients that developed COVID-19 during chemotherapy for B-cell malignancies (with agents that also affect T cells) who experienced similar protracted courses of Covid-19 requiring additional courses of remdesivir due to recrudescent disease. Solid-organ and hematopoietic cell transplant recipients whom we have treated to date have responded to single courses of treatment without recrudescent disease.

ADVERSE EVENTS

There are limited data evaluating the adverse-event profile of remdesivir. Although relatively rare, hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of remdesivir (33). In phase 1 studies of 138 healthy volunteers, transient elevations in aminotransferases were observed with remdesivir administration (33). The Ebola phase 3 trial reported one serious adverse effect, a fatal episode of peri-infusional hypotension, deemed poten-tially related to remdesivir administration (47).

In clinical trials, the adverse-event profile of remdesivir has been favorable overall. Wang et al. reported that 102 patients (66%) in a remdesivir group experienced at least one adverse event compared with 50 patients (64%) in the placebo arm (36). The proportion of serious adverse events reported was 18% in the remdesivir arm com-pared with 26% in the control group. The most common adverse events reported were constipation (14% versus 15% in the remdesivir group versus the placebo group, respectively), hypoalbuminemia (13% versus 15%), hypokalemia (12% versus 14%), and elevation in total bilirubin (10% versus 9%). Remdesivir discontinuation due to adverse events occurred in 18 patients arm (12%) compared with 4 patients (5%) in the placebo arm. In the ACTT-1 trial, serious adverse events occurred in 24% of patients in the remdesivir group versus 32% in the placebo group. The most common serious adverse event was respiratory failure, which occurred in 7.3% of patients treated with remdesivir and 12.8% of patients treated with placebo (38). Nonserious grade ≥3 adverse events occurred in 52% in the remdesivir group versus 57% in the placebo group. The most common nonserious adverse events reported in the remdesivir group versus the placebo group were anemia (16.5% versus 21.7%), decrease in renal function (16.0% versus 20.3%), hyperglycemia (13.7% versus 11.8%), and increased levels of liver aminotransferases (6.0% versus 10.7%). In addition, in the SIMPLE Severe Trial, the proportions of patients who experienced adverse events were similar in the two groups (70% in the 5-day group versus 74% in the 10-day group) (39). The proportions of serious adverse events were 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 versus 9% in the 10-day group), acute respiratory failure (6% versus 11%), increased alanine aminotransferase (6% versus 8%), and constipation (7% in both groups). Discontinua-

tion rates due to adverse events were similar in the 5-day and 10-day groups (4% and 10%, respectively), and discontinuation rates due to aminotransferase elevations were 2.5% and 3.6%, respectively. In the SIMPLE Moderate Trial, the proportions of patients who experienced adverse events were similar in 5-day group and the standard-of-care group (51% and 47%, respectively) (40). However, the proportion of adverse events was significantly higher in the 10-day group versus the placebo group (59% versus 47%, respectively). The most common adverse events in the remdesivir groups were nausea (9.6% in the remdesivir groups versus 3% in the standard-of-care group), hypokalemia (6% versus 2%), and headache (1.3% versus 2.5%). Serious adverse events were reported in 5% of patients in the remdesivir groups and 10% in the standard-of-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 (ClinicalTrials registration no. NCT04501952). The pharmacokinetics of an inhaled version of remdesivir is currently being evaluated in a phase 1a trial (ClinicalTrials registration no. NCT04539262). The availability of a nebulized or dry powder formulation of remdesivir could provide more-targeted delivery of the drug and potentially lower levels of systemic exposure and toxicity, as has been demonstrated with the inhaled formulation of the neuraminidase inhibitor zanamivir for influenza A and B virus (57). Moreover, a single rapidly administered bolus of remdesivir that resulted in a high intracellular concentration of remdesivir triphosphate could theoretically be enough treat patients who present earlier on in the course of diease. Other ways to potentially expand the use of remdesivir to the outpatient setting include evaluation of 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 enable studies of the use of remdesivir as a postexposure prophylaxis to prevent symptomatic infection or reduce the infectious burden after exposure to COVID-19. Additionally, given the limited data on remdesivir in pregnancy and pediatrics, future studies evaluating the safety and efficacy of remdesivir should consider inclusion of these patient populations to prevent delays associated with drug acquisition through the compassionate use programs.
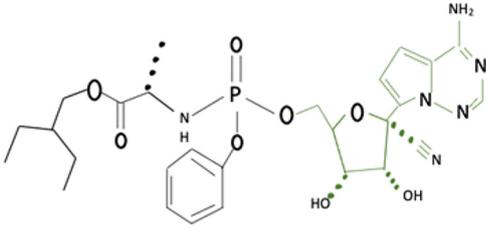
We favor confirmation of the subgroup findings of the ACTT-1 trial in at least an additional double-blind, placebo-controlled trial that explicitly targets and is powered to demonstrate a benefit of remdesivir in different strata of COVID-19 severity. Further studies are needed to assess remdesivir in 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) (58).

EXPERT OPINION

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

Based on overall current trial results and clinical experience, remdesivir treatment should be considered as early as clinically possible to prevent progression of COVID-19 pneumonia and other complications in patients who are hospitalized. A new trial is evaluating remdesivir treatment of outpatients who are at higher risk of hospitalization and death to prevent progression to severe disease (ClinicalTrials registration no. NCT04501952; accessed 20 September 2020). A sizeable proportion of patients in the trials to date who received treatment early have not needed to complete a treatment course of 5 days and had a shorter duration of hospitalization. Additionally, the largest benefit of remdesivir seems to occur among patients who require supplemental oxygen at baseline, as this is the group that had the most mortality

TABLE 4 Remdesivir characteristics and clinical guide[a]

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 name	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 defect (18); D848Y mutation in RdRp can lead to treatment failure (24)	There is currently no available remdesivir resistance testing
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, and 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 solution; remdesivir is also supplied as an water-based concentrated 5 mg/ml solution; remdesivir is solubilized with SBECD; each vial of lyophilized remdesivir powder contains 3 grams of SBECD, while each aqueous-solution vial contains 6 grams of SBECD	Available only for i.v. administration as of October 2020; the lyophilized formulation allows longer-term storage than a water-based concentrated solution
Dosage	For adult patients and for pediatric patients weighing ≥40 kg, loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg; for pediatric patients weighing 3.5 to 40 kg, loading dose of 5 mg/kg, followed by a maintenance dose 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	We favor a 30-min infusion time to maximize the intracellular concn of the pharmacologically active metabolite; from clinical trials data and our 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) and transporters OATP1B1 and P-gp; distribution: remdesivir is widely distributed into tissues but has poor blood-brain barrier penetration; elimination: 74% excreted renally and 18% in the feces	Remdesivir should be administered only via the i.v. route

(Continued on next page)

TABLE 4 (Continued)

Characteristic	Key information	Practical recommendations by authors
Drug interactions	Inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, OAPT1B1, OATP1B3, MRP4, and NCTP; substrate of CYP2C8, CYP2D6, and CYP3A, OATP1B1, and P-gp; chloroquine and hydroxychloroquine reduce remdesivir's antiviral activity *in vitro*	Currently, drug-drug interactions of remdesivir in humans have not been evaluated and their clinical relevance has not been established; chloroquine or hydroxychloroquine should not be coadministered 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 of <30 ml/min or those requiring renal replacement therapy, due to the presence of the excipient SBECD	Given the short duration of remdesivir activity and the relatively low SBECD content, we think the benefit of its administration 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 levels of 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

[a]RSV, respiratory syncytial virus; SBECD, sulfobutylether-β-cyclodextrin.

benefit based on results from ACTT-1 (38). Older patients hospitalized with moderate COVID-19 (not requiring supplemental oxygen at rest) and those with comorbidities and who are at higher risk for mortality likely benefit from early remdesivir administration (40); thus, we do not think that waiting for clinical deterioration before deciding on antiviral treatment is a prudent or practical approach. While critically ill patients requiring mechanical ventilation or ECMO could benefit as well, given the advanced lung damage sustained on presentation due to acute respiratory distress syndrome, recovery would likely take longer and depend on additional interventions other than remdesivir. Detailed remdesivir characteristics and authors' recommendations are presented in Table 4.

CONCLUSION

Remdesivir seems to be the most promising antiviral currently available for the treatment of moderate and severe COVID-19 pneumonia based on preclinical and clinical data and represents the only treatment currently approved by the FDA 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.

ACKNOWLEDGMENTS

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