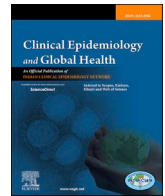




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Remdesivir and its antiviral activity against COVID-19: A systematic review

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ABSTRACT

Background: The aim of this study was to summarize the antiviral activities of remdesivir against SARS-CoV-2, the causative agent of COVID-19.

Methods: Available publications were systematically explored on some databases and gray literature was examined. Publications were discussed narratively.

Results: Remdesivir inhibits SARS-CoV-2 replication, reduces viral load, and exerts protective effects in SARS-CoV-2 infected animals. Remdesivir also reduces the pathological process, alleviates mild symptoms, and improves pulmonary lesions in SARS-CoV-2-infected animals. Remdesivir has been used as a compassionate drug for treating COVID-19 patients.

Conclusion: Although remdesivir has shown potent antiviral activities, more efficacy assessments are urgently warranted in clinical trials.

1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic, has caused considerable challenges to the national healthcare systems of most affected countries.^{1,2} The most common clinical manifestations of COVID-19 include fever, cough, dyspnea, chest pain, and pneumonia with ground-glass opacities being the most common finding in computed tomography imaging.^{3,4} Aside from respiratory symptoms, COVID-19 could involve cardiac manifestations,⁵ the digestive system,⁶ and other organs.^{7–9} The progression and severity of COVID-19 may be associated with dysregulation of host immune responses.¹⁰ As on June 8, 2020, over 7 million confirmed COVID-19 cases and 400,000 deaths were reported, according to the COVID-19 Global Cases database.¹¹ The rapid transmission of the virus is mainly owing to its high reproductive number (R_0), with a mean of 3.28,¹² implying that one infected person could transmit the virus to up to three unvaccinated individuals. The

virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the family *Coronaviridae* and genus *Betacoronavirus*, together with SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV).⁸ The virus has 79.6% sequence similarity with SARS-CoV.¹³

A specific antiviral treatment for COVID-19 is yet to be identified,¹⁴ therefore, several strategies have been proposed to treat patients, including the use of convalescent plasma and interferon (IFN), as well as interleukin 6 receptor inhibitors since they have the potential to inhibit the cytokine storm.¹⁰ Chloroquine and hydroxychloroquine that inhibit endocytosis-mediated viral entry, inhibit endosomal acidification, and disrupt glycosylation of angiotensin converting enzyme 2 (ACE2),^{15–18} as well as ivermectin that inhibits nuclear transport of viral proteins,^{19,20} have been used to treat COVID-19. In addition, antivirals that inhibit protease inhibitors^{21–25} and nucleotide or nucleoside analogs that inhibit viral RNA synthesis^{17,26–28} have been repurposed for the

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treatment of the SARS-CoV-2 infection. Nucleoside analogs represent a group of drugs that inhibit reverse transcription and are among the most potent antiviral agents available to combat the SARS-CoV-2 infection—within this group is remdesivir. The objective of this review was to summarize evidence from *in vitro* studies, *in vivo* studies, use in patients with COVID-19 under emergency protocol, and clinical trials to provide comprehensive information on the potential of remdesivir in the treatment of patients with COVID-19.

2. Materials and methods

Relevant articles were searched on PubMed and Google Scholar using the search terms “remdesivir”, AND “coronavirus”, OR “SARS-CoV”, OR “MERS-CoV”, OR “SARS-CoV-2” in the title and abstract. Recent clinical trials assessing the efficacy of remdesivir against COVID-19 were also searched on the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database. The screened publications were classified and analyzed based on the study types: *in*

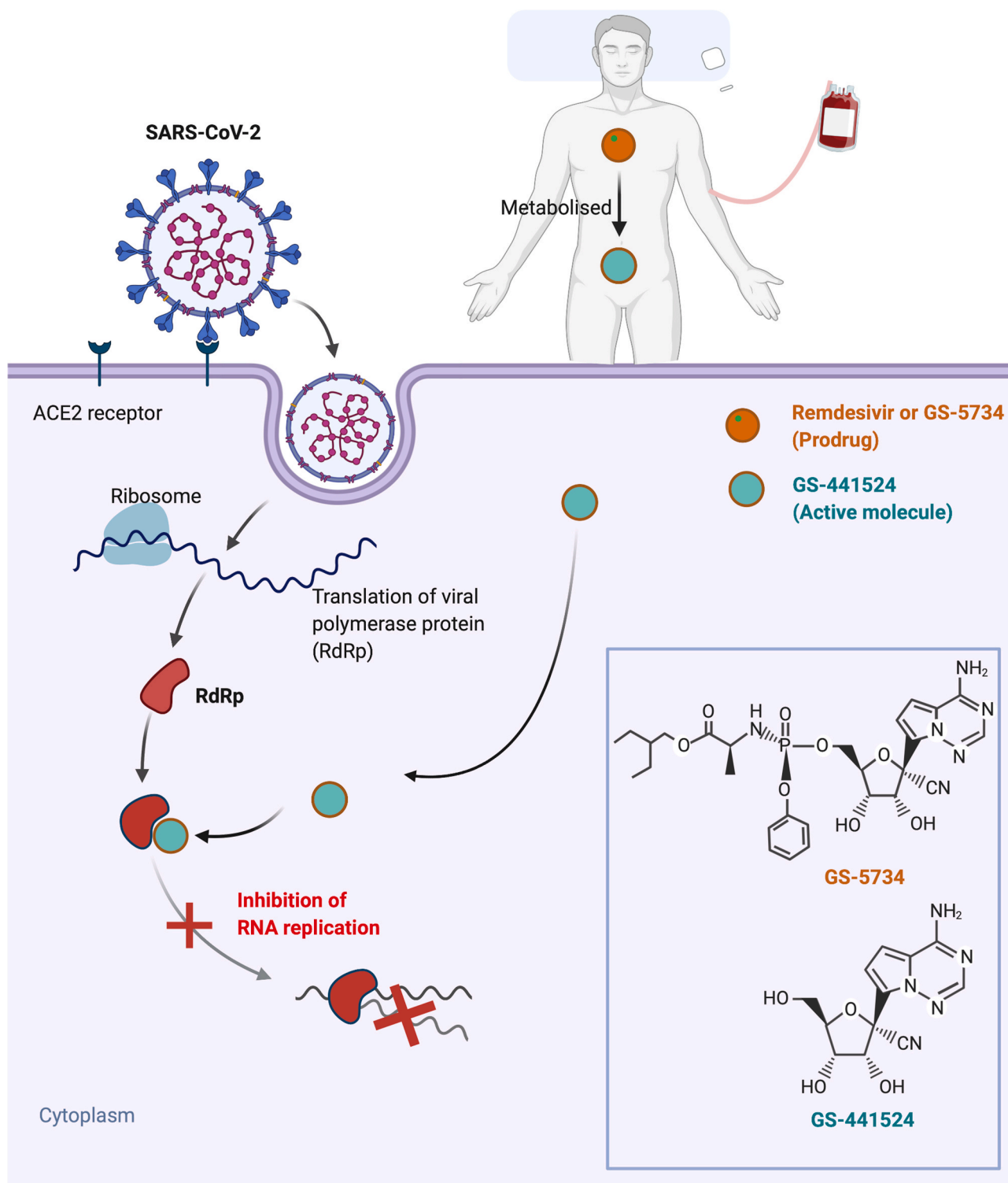


Fig. 1. Structure and mechanism of action of remdesivir (GS-5734) and its pharmacological active form (GS-441524).

in vitro, *in vivo*, emergency use in hospitals, and clinical trials. All available articles until May 4, 2020 were considered eligible.

3. Results

The search combinations yielded 21 main references related to remdesivir. Antiviral activity and mechanism of remdesivir in both non- and coronaviruses have been reported in several *in vitro* studies.^{17,29–39} *In vivo* studies have been conducted to assess antiviral effect of remdesivir on non-coronaviruses using rhesus monkeys³⁰ and African green monkeys⁴⁰ as well as on coronavirus such as in mice^{34,41} and rhesus macaques.^{42,43} The antiviral effect of remdesivir also have been assessed in humans⁴⁴ and it have been used to treat severe COVID-19 patients, as an emergency use.^{45–47} Although only one clinical trial has been conducted to assess the effectiveness and safety of remdesivir for COVID-19,⁴⁸ several clinical trials are ongoing in some countries.

4. Discussion

4.1. Remdesivir: an introduction

Remdesivir (GS-5734; Gilead Sciences Inc., US) is an investigational nucleoside analog that acts as a competitive inhibitor of viral RNA-dependent RNA polymerase (RdRp) (Fig. 1).¹³ It is a prodrug with a molecular formula of $C_{27}H_{35}N_6O_8P$ and an exact mass of 602.23 Da. In the body, remdesivir is transformed into an active molecule known as GS-441524 (Fig. 1), with a molecular formula of $C_{12}H_{13}N_5O_4$ (291.10 Da). Remdesivir was previously proposed for the treatment of Ebola^{29,30,44} and is yet to be approved or licensed by the US Food and Drug Administration (FDA) or any other drug regulatory authority worldwide. The antiviral activities of remdesivir on RdRp have been reported against Ebola virus,^{36,37} MERS-CoV,³³ SARS-CoV,^{33,34} and other coronaviruses such as CoV-OC43, CoV-229E, and PDCoV.³⁵

4.2. Evidence from *in vitro* studies

In 2015, a study showed that remdesivir is an effective inhibitor of the Ebola virus.²⁹ Its half-maximal effective concentration (EC_{50}), the drug concentration that induces a response halfway between the baseline and maximum after a specified exposure time, varied between 0.07 and 0.14 μM in Ebola-infected cells such as HeLa, HFF-1, HMVEC-TERT, and Huh-7.³⁰ Studies on the inhibitory effects of remdesivir against various viruses have been conducted using seven virus families, namely, filo-, paramyxo-, pneumo-, bunya-, arena-, rhabdo-, and flaviviruses.³¹ Another study showed that phosphorylated GS-441524, the active molecule of remdesivir, inhibited feline infectious peritonitis in CRFK cells, with a half maximal inhibitory concentration (IC_{50}); the drug concentration at which half of the peak inhibiting effect of the drug against a specific viral function is achieved) of 0.78 μM .³² The EC_{50} of remdesivir against the murine hepatitis virus is 0.03 μM .³³ Remdesivir also exerts antiviral activities against MERS-CoV, Junin virus, and Lassa fever virus in HeLa cells, with EC_{50} values of 0.34, 0.47, and 1.48 μM , respectively.³⁰ Another study revealed that remdesivir inhibits SARS-CoV and MERS-CoV in human airway epithelial (HAE) cells, with EC_{50} values of 0.069 and 0.074 μM , respectively.³⁴ The summary of the EC_{50} and IC_{50} of remdesivir and its active component GS-441524 against highly pathogenic human coronaviruses (MERS-CoV and SARS-CoV) is presented in Table 1.

Remdesivir inhibits RdRp; its antiviral activity against RdRp has been reported in Huh7 human cells infected with CoV-OC43, CoV-229E, and PDCoV, with EC_{50} values ranging between 0.02 and 0.17 μM .³⁵ The same mechanism, i.e., the inhibition of RdRp, has also been reported in Ebola virus.^{36,37} In 2020, a study revealed that the inhibitory mechanism of the active triphosphate molecule of remdesivir against MERS-CoV in insect cells involved various nonstructural proteins (nsp), such as nsp5, nsp7, nsp8, and nsp12 (RdRp).³⁸

Table 1

In vitro studies on efficacy of remdesivir and its active component against highly pathogenic Coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2).

Component	Virus	Cell line	IC_{50} or EC_{50}	Reference
Remdesivir	MERS-CoV	Calu-3 2B4	$IC_{50} = 0.025 \mu M^a$	34
		HAE	$IC_{50} = 0.074 \mu M^a$	34
		Calu-3 2B4	$EC_{50} = 0.09 \mu M^a$	41
	SARS-CoV	HAE	$EC_{50} = 0.07 \mu M^a$	33
		HAE	$IC_{50} = 0.069 \mu M^a$	34
		HAE	$EC_{50} = 0.07 \mu M^a$	33
SARS-CoV-2	Vero E6	$EC_{50} = 0.77 \mu M^a$	17	
	Vero E6	$EC_{50} = 23.15 \mu M^b$	39	
GS-441524	MERS-CoV	HAE	$EC_{50} = 0.86 \mu M^a$	33
	SARS-CoV	HAE	$EC_{50} = 0.18 \mu M^a$	33

Calu-3: human bronchial epithelial cells; HAE: human airway epithelial cells; MERS-CoV: Middle East respiratory syndrome-related coronavirus; SARS-CoV-2: The virus, severe acute respiratory syndrome coronavirus 2; SARS-CoV: severe acute respiratory syndrome-related coronavirus; Vero E6: African green monkey kidney epithelial cells.

^a The viral load was fit in a linear scale (the percentage of inhibition) under increasing concentrations of remdesivir or GS-441524.

^b The viral load was fit in a logarithmic scale ($\log_{10}TCID_{50}/mL$ and \log_{10} viral RNA copies/mL) under increasing concentrations of remdesivir.

The RdRp sequences of SARS-CoV-2 and SARS-CoV display more than 80% similarity.^{49,50} Therefore, it was suggested that remdesivir could potentially exert antiviral activities against SARS-CoV-2. Remdesivir was found to have an EC_{50} of 0.77 against SARS-CoV-2 in Vero E6 cells (Table 1).¹⁷ This activity of remdesivir was higher than that of the other drugs used in the study, such as ribavirin, penciclovir, favipiravir, nafamostat, nitazoxanide, and chloroquine, which showed EC_{50} values of 109.5, 95.96, 61.88, 22.50, 2.12, and 1.13 μM , respectively.¹⁷ Another study in Vero E6 cells also revealed that remdesivir inhibited the replication of SARS-CoV-2, with an EC_{50} of 23.15 μM , showing the strongest antiviral activity among the tested drugs.³⁹ In this study, the viral load was fit in a logarithmic scale under increasing remdesivir concentrations, rather than a linear scale reported previously.¹⁷ These initial studies suggest that remdesivir inhibits the replication of SARS-CoV-2 and has the potential to be used in the treatment of COVID-19.

4.3. Evidence from *in vivo* studies

In 2016, an *in vivo* study was conducted using Ebola-infected rhesus monkeys (a non-human primate) and various doses of remdesivir intramuscular injections.³⁰ Post-exposure revealed that remdesivir exerted protective effects by inhibiting viral replication.³⁰ The concentration of form of remdesivir, was 10 μM in peripheral blood mononuclear cells after administration of 10 mg/kg remdesivir.³⁰ A study in Nipah virus-infected African green monkeys showed the protective effects of remdesivir: half of the remdesivir-treated monkeys ($n = 4$) developed mild respiratory symptoms and the other half recovered; those in the control group developed severe respiratory disease.⁴⁰

Remdesivir has also been shown to exert antiviral activity against coronaviruses. Remdesivir treatment was found to reduce the viral load in MERS-CoV-infected $Ces1c^{-/-}$ hDPP4 mice and was phenotypically associated with improved pulmonary function and decreased likelihood of acute lung injury development in infected animals.⁴¹ In addition, remdesivir inhibited MERS-CoV replication in the pulmonary organs of rhesus macaques and led to a reduction in lung lesions.⁴² Remdesivir also reduced the viral load in the lung and improved the respiratory function of SARS-CoV MA15-infected mice.³⁴ A recent study showed that remdesivir administration to SARS-CoV-2-infected rhesus macaques improved pulmonary lesions, according to radiographs; reduced viral titers in bronchoalveolar lavage after 12 h of treatment; and reduced the viral load in the lungs after 7 days of treatment. Moreover, the remdesivir-treated animals did not show any signs of pulmonary disease.⁴³

4.4. Results from patients with COVID-19 and clinical trials

Historically, remdesivir was tested to treat patients with Ebola in a randomized clinical trial in the Democratic Republic of the Congo in 2018.⁴⁴ In 2020, remdesivir was included in the “Solidarity” international clinical trial conducted by the World Health Organization in an attempt to find an effective treatment for COVID-19.⁵¹ As a timely response to the pandemic, patients with COVID-19 have been treated with remdesivir in emergency protocols. In the first patient with COVID-19 treated with remdesivir, a 35-year-old from Washington, pneumonia improved after 7 days of treatment.⁴⁵ In Seattle, USA, remdesivir was used as a compassionate drug to treat seven critically ill patients.⁴⁶ A larger study found that, following a 10-day course of remdesivir treatment (intravenous administration at 200 mg on day 1, followed by 100 mg daily), 68% (36 of 53) of patients with COVID-19 showed clinical improvement; however, there was no control group in this study.⁴⁷ Therefore, this information is insufficient to confirm the efficacy of remdesivir in treating patients with COVID-19.

To adequately assess the efficacy of remdesivir, clinical trials are ongoing in countries such as USA, Norway, Canada, France, and China. A list of currently ongoing clinical trials has been presented in Table 2. Although the length of treatment differs slightly, the dose of remdesivir is similar: 200 mg on day 1, followed by 100 mg for the rest of the treatment period.

The first randomized, double-blind, placebo-controlled, multicenter clinical trial was reported on April 29, 2020.⁴⁸ The study was conducted in China with 237 patients (158 in the remdesivir group and 79 in the placebo control group), and the primary endpoint was the time taken to achieve clinical improvement. The study revealed that treatment with remdesivir did not lead to a significant reduction in the time taken to achieve clinical improvement. In addition, mortality and viral clearance time in patients with severe COVID-19 were not significantly different from those in the placebo group, suggesting that remdesivir had poor clinical benefits. This further suggests that in COVID-19, viral propagation is not the main factor responsible for disease severity. On this account, the antiviral properties of remdesivir will not be beneficial. The severity of COVID-19 has been associated with the cytokine release storm,⁵² suggesting that host immune responses play an important role in this event. Therefore, a combination of remdesivir with immunosuppressants (for example sarilumab, an IL-6 the inhibitor) and/or other antiviral agents might potentiate the antiviral activity of remdesivir and mitigate the immunopathological injury caused by excessive immune effectors.⁵²

Nonetheless, during the same trial,⁵² in remdesivir-treated patients with COVID-19, especially those treated within 10 days of symptom onset, faster clinical improvement was observed than that in the placebo group. Unfortunately, the study was terminated prematurely owing to the occurrence of more frequent adverse events in the remdesivir group than in the placebo group.⁵² Considering these findings, the small sample size, and because the study was unexpectedly terminated, it may be insufficient to elucidate the efficacy of remdesivir.⁵³ Furthermore, the pharmacokinetics of remdesivir and its active metabolite in the respiratory tracts and/or other infected organs remain largely unknown in patients with COVID-19.³⁶ Therefore, the results of ongoing clinical trials (Table 1) are warranted to provide conclusive evidence regarding the efficacy of remdesivir in patients with COVID-19.

The pharmacokinetic profile of remdesivir, particularly the concentrations of the active metabolite, GS-441524, in the respiratory tract or other infected tissues in patients with severe COVID-19 are unknown.⁴⁸ In addition, currently available data on remdesivir are lacking, in particular those in drug–drug, drug–gene, and drug–disease interactions. This information is important in predicting possible negative outcomes that may arise during treatment.

Table 2

A list of ongoing clinical trials of remdesivir registered on ClinicalTrials.gov.

Identifier number	Title	Expected participants	Length of treatment	Location
NCT04292899	Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with severe coronavirus disease (COVID-19)	6000	5–10 days (and possibly extension)	USA
NCT04292730	Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment	1600	5–10 days (and possibly extension)	USA
NCT04321616	The efficacy of different antiviral drugs in COVID 19 infected patients	700	10 days	Norway
NCT04330690	Treatments for COVID-19: Canadian Arm of the Solidarity Trial (CATCO)	440	9 days	Canada
NCT04280705	Adaptive COVID-19 treatment Trial (ACTT)	800	10 days	USA
NCT04315948	Trial of treatments for COVID-19 in hospitalized adults (DisCoVeRy)	3100	10 days	France
NCT04349410	The Fleming [FMTVDM] directed CoVid-19 treatment protocol	500	10 days	USA
NCT04365725	Multicenter, retrospective study of the effects of remdesivir in the treatment of severe covid-19 infections (REMDECO-19)	200	15 days	France

5. Conclusion

Remdesivir is a nucleotide analog prodrug that inhibits SARS-CoV-2 RdRp. Its viral activities against SARS-CoV-2 have been shown in both *in vitro* and *in vivo* studies. Remdesivir has been used in several countries as an emergency drug for patients with COVID-19, and some patients showed improved clinical outcomes. However, large-scale clinical trials should be conducted to confirm the efficacy of remdesivir in treating patients with COVID-19.

Authors' contributions

AF and HH conceived and designed the study. AF, FN, and HH were responsible for data collection. AF and HH wrote the initial manuscript. KD, MM, and HH critically revised the manuscript. All authors have read the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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