

## Rapid review for the anti-coronavirus effect of remdesivir

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**SUMMARY** The outbreak of SARS-CoV-2 rapidly spread across China and worldwide. Remdesivir had been proposed as a promising option for treating coronavirus disease 2019 (COVID-19). We provided a rapid review to critically assess the potential anti-coronavirus effect of remdesivir on COVID-19 and other coronaviruses based on the most up-to-date evidence. Even though remdesivir was proposed as a promising option for treating COVID-19 based on laboratory experiments and reports from compassionate use, its safety and effect in humans requires high-quality evidence from well-designed and adequately-powered clinical trials for further clarification.

**Keywords** SARS-CoV-2, COVID-19, remdesivir, safety, effect

### 1. Introduction

In early December 2019, a novel coronavirus named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan city located in Hubei province, China (1). Similar to previously identified severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is the third coronavirus that severely infects humans or even causes death (2). Initially, several SARS-CoV-2-infected pneumonia (coronavirus disease 2019, COVID-19) were identified in Wuhan. Shortly afterwards, the outbreak of COVID-19 has rapidly spread across China and worldwide, which now becomes a serious threat to global public health (3,4). While there is no specific therapy for COVID-19 available, supportive care and sometimes combined with broad-spectrum antivirals and corticosteroids remain the mainstay as the standard practice (4). Therefore, it is urgently needed to identify more effective therapeutic options in response to the rapid propagation of SARS-CoV-2. Several medications have been proposed to be tested for the prevention and treatment of COVID-19, among which remdesivir (GS-5734) has attracted substantial attention.

Remdesivir is a nucleotide analog prodrug that exhibits effective antiviral activity against a broad spectrum of human and zoonotic coronavirus in cell cultures and mouse models including SARS-CoV,

MERS-CoV, and SARS-CoV-2. In addition, a recent case report of COVID-19 indicated the recovery of a 35-year-old patient probably due to the administration of remdesivir, while no adverse events related to remdesivir was found (4). Other evidence also implicated that remdesivir may be an effective option to treat COVID-19. Therefore, in this rapid review we aimed to summarize the evidence of antiviral effect of remdesivir on the coronaviruses, and to discuss the potential application to COVID-19, after systematically searching the databases of PubMed and MEDLINE with the keywords related to remdesivir.

The potential mechanism of remdesivir for coronavirus remains unclear. Several reasons have been proposed to interpret the effect of remdesivir. First, remdesivir can interfere with the nsp12 polymerase even when the exoribonuclease proofreading activity is intact (5). Furthermore, remdesivir can efficiently generate pharmacologically active nucleoside triphosphate (NTP) that acts as an alternative substrate and RNA-chain terminator. Subsequently, NTP can inhibit coronavirus by incorporating active triphosphates into viral RNA (6). Additionally, there is a high genetic barrier to achieve resistance of coronavirus to remdesivir, which suggests that remdesivir can maintain the effectiveness of coronavirus therapies (7).

As a broad-spectrum antiviral agent, remdesivir has been reported to be effective against a group of coronavirus including alphacoronavirus (NL63) and

**Table 1. Antiviral effect of remdesivir on SARS-CoV, MERS-CoV and SARS-CoV-2**

Virus type	Experimental studies	Human studies
SARS-CoV	<ul style="list-style-type: none"> <li>Remdesivir prophylactically inhibited SARS-CoV replication in human airway epithelial cell cultures. Prophylactic and early-stage therapeutic (within 1 day after infection) effects against SARS-CoV were demonstrated in animal experiments (8).</li> </ul>	<ul style="list-style-type: none"> <li>No evidence in human was reported.</li> </ul>
MERS-CoV	<ul style="list-style-type: none"> <li>Calu-3 cell cultures and animal experiments indicated the prophylactic and therapeutic effects of remdesivir on MERS-CoV, and the effects were found to be superior to the other anti-viral medications (9).</li> </ul>	<ul style="list-style-type: none"> <li>No evidence in human was reported.</li> </ul>
SARS-CoV-2	<ul style="list-style-type: none"> <li>In time-of-addition assay using Vero E6 cells, remdesivir therapeutically (administered 2 hours after infection) inhibited SARS-CoV-2 replication, while no prophylactic effect was found. Remdesivir could inhibit SARS-CoV-2 infection in human liver cancer Huh-7 cells (10).</li> </ul>	<ul style="list-style-type: none"> <li>A case report in the United States of COVID-19 indicated the recovery of a patient probably due to the administration of remdesivir (4).</li> <li>A study of compassionate-use remdesivir reported clinical improvement in 68% of the 53 recruited patients who had severe COVID-19 (11).</li> <li>As of 28<sup>th</sup> April 2020, seven RCTs have been initiated, aiming to evaluate the benefit and harm effects of remdesivir for COVID-19 patients. No results have been available in the literature.</li> </ul>

COVID-19: coronavirus disease 2019; MERS-CoV: Middle East respiratory syndrome coronavirus; SARS-CoV: severe acute respiratory syndrome coronavirus.

several SARS/MERS-CoV-like bat coronavirus (8). Below we summarized the most up-to-date evidence of remdesivir for SARS-CoV, MERS-CoV, and the SARS-CoV-2 of concern (Table 1).

## 2. MERS-CoV

A recent study compared antiviral effect on MERS-CoV of several medications including remdesivir, lopinavir (LPV), ritonavir (RTV) and interferon beta (IFN- $\beta$ ) and the combination of LPV/RTV-IFN- $\beta$  (9). The prophylactic and therapeutic effect of remdesivir on MERS-CoV was found to be superior to the other medications. Specifically, results from the *in vitro* experiments showed that remdesivir had superior antiviral effect with a selectivity index (concentration causing a 50% reduction in replication/concentration causing a 50% cytotoxication) > 100 on Calu-3 cells, which was significantly higher than IFN- $\beta$  (> 16), LPV (> 4.3) and RTV (> 2). Likewise, findings from the animal experiments demonstrated that prophylactic remdesivir could significantly inhibit MERS-CoV replication and diminish the pathological features of acute lung injury (ALI) in MERS-CoV-infected *Ces1c*<sup>-/-</sup> mice, while only minimal effect was found in other antiviral medications. When the agents were given on the first day after low-dose infection (5E + 04 pfu), improved pulmonary functions were observed in both remdesivir and LPV/RTV-IFN- $\beta$  groups. Nevertheless, reductions in several indices (including virus lung titers, viral antigen labeling in lung tissue sections, body weight loss, lung hemorrhage and signs of ALI) were only detected in the group treated with remdesivir.

Furthermore, when a lethal dose of MERS-CoV (5E + 05 pfu) was used, a reduced lung viral load in infected mice was only observed in remdesivir group, while no effect was found in other groups.

## 3. SARS-CoV-2

Wang *et al.* conducted an experiment to evaluate the anti-SARS-CoV-2 effect of remdesivir (10). In time-of-addition assay using Vero E6 cells, remdesivir was found to be effective when administered 2 hours after infection at a multiplicity of infection (MOI) of 0.05. However, no prophylactic effect was observed when remdesivir was administered prior to the SARS-CoV-2 infection. The concentration for 90% of maximal effect (EC<sub>90</sub>) value of remdesivir against SARS-CoV-2 was found to be 1.76  $\mu$ M. This study also revealed that remdesivir could inhibit SARS-CoV-2 infection in human liver cancer Huh-7 cells.

The recent case report recorded the administration of compassionate-use remdesivir on the 35-year-old man with COVID-19 in the United States (4). The patient had initial symptoms of mild cough and low-grade intermittent fevers; subsequently his nasopharyngeal and oropharyngeal swabs were tested positive for SARS-CoV-2 by real-time reverse-transcriptase-polymerase-chain-reaction assay. His vital signs and respiratory status remained largely stable before the 9<sup>th</sup> day of COVID-19 except for intermittent fevers and nonproductive cough. Since from day 9, the patient began to develop atypical pneumonia, with worsening chest radiograph, decreasing oxygen saturation values and substantial rales in both lungs. With remdesivir

administered on day 11, significant improvements in oxygen saturation values, rates and other symptoms were observed on day 12, indicating the rapid benefit of remdesivir. Subsequently, the patient returned to be afebrile, and all symptoms had resolved with the exception of mild cough. Besides, a recently published study revealed results of compassionate use of remdesivir for patients with severe COVID-19 (11). In 53 patients who received at least one dose of remdesivir, 36 (68%) had clinical improvements, including changes on oxygen-support and extubation of mechanical ventilation. The mortality of the patients was 13%, which was lower than the general mortality of severe patients with COVID-19 (over 50%), as reported by the WHO (12).

The current evidence on experimental studies and clinical observation indicated that remdesivir has the potential for treating COVID-19. Nevertheless, findings from the compassionate-use study were not adequately powered with a randomized controlled design to assess the safety and efficacy of remdesivir in patients with severe COVID-19. Therefore, more evidence from randomized clinical trials (RCTs) of high quality is eventually needed to confirm its safety and efficacy. Two phase III clinical trials had been launched in Hubei and Beijing in China in early February 2020, aiming to evaluate the safety and efficacy of remdesivir for adult patients with COVID-19 and with mild-moderate (NCT04252664, sample size: 308) and severe (NCT04257656, sample size: 452) symptoms. Subsequently, other five RCTs with similar objectives were further registered on *clinicaltrials.gov*. However, as of 28<sup>th</sup> April 2020, there has not been published results available in the literature. Therefore, it remains largely unknown currently regarding the benefit-harm profile of remdesivir for COVID-19.

In brief, remdesivir has been found to inhibit coronavirus and improve pulmonary functions prophylactically and therapeutically (in early stage of infection) based on evidence from both *in vitro* and *in vivo* experiments. However, evidence in patients with COVID-19 remained limited and sparse.

The ongoing clinical trials will provide more high-quality evidence on the benefit-harm effect of remdesivir. Nevertheless, there are several issues of concern regarding their protocols. First, the inclusion/exclusion criteria and the outcome measurements do not include chest radiography that is one of the key elements for disease diagnosis and criteria for recovery according to Guidelines for the Diagnosis and Treatment of Novel Coronavirus (SARS-CoV-2) Infection by the National Health Commission (Trial Version 5) published by National Health and Health Commission of the people's Republic of China (13). Thus, it may incur selection and reporting bias to weaken the results. Secondly, based on the previous experiments on SARS-CoV, remdesivir was effective only when it was administered

at the early stage of infection (before the initiation of the immunopathological phase of pneumonia) (8). By contrast, another study showed that remdesivir was found to be functional for SARS-CoV-2 when administered 2 hours after infection (10). These results indicated the benefit of remdesivir may heavily depend on the time of administration. No predefined plans of trial designs or statistical analyses are given in their protocols related to the optimum time of administration. Thirdly, the current evidence was insufficient to support the safety of remdesivir in humans. Even though some cytotoxicity tests suggested that remdesivir could be effective at a relatively low micromolar concentration compared with its cytotoxic concentration (8,9), the safety test in humans is still ongoing currently. Moreover, a previous randomized controlled trial reported that in patients with Ebola virus disease, the overall mortality was even higher in remdesivir group (53%) than the control group (a triple monoclonal antibody agent; 50%), although without significance (14). Therefore, extreme cautions and monitoring should be taken in the ongoing trials for COVID-19 given the safety of remdesivir remains largely unconfirmed and unknown.

To summarize, even though remdesivir was proposed as a promising option for treating COVID-19 based on laboratory experiments and reports from compassionate use, its safety and effect in humans requires high-quality evidence from well-designed and adequately-powered clinical trials for further clarification. Similar to the inconclusive effect on SARS-CoV and MERS-CoV, the impact of remdesivir on the SARS-CoV-2 outbreak should not be overestimated in the current clinical practice. Further explorations remain urgently needed to treat the COVID-19 and bring the SARS-CoV-2 under control.

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