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Review Article

Remdesivir use in the coronavirus disease 2019 pandemic: A mini-review

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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative viral pathogen of coronavirus disease 2019 (COVID-19), appears to have various clinical presentations and may result in severe respiratory failure. The global SARS-CoV-2-associated viral pneumonia pandemic was first reported in December 2019 in China. Based on known pharmacological mechanisms, many therapeutic drugs have been repurposed to target SARS-CoV-2. Among these drugs, remdesivir appears to be the currently most promising according to several clinical trials and reports of compassionate use. In this mini-review, we summarize the current evidence on the efficacy and challenges of remdesivir for the treatment of coronavirus disease 2019 (COVID-19).

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Introduction

Coronaviruses are non-segmented, enveloped, positive-sense, and single-stranded RNA viruses that commonly exist in mammals. Human and animal coronaviruses comprise four genera, named α, β, γ, and δ. β-Coronaviruses include those that cause Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with pulmonary and parabronchial epithelial cells to enter through the epithelial cell membrane. The virus primarily spreads through saliva droplets or discharge from the nose of an infected individual after coughing or sneezing and is the causative pathogen of COVID-19, which appears to have a spectrum of clinical presentations that ranges from asymptomatic to severe respiratory failure. SARS-CoV-2 caused an outbreak of novel pathogenic viral pneumonia in December 2019, which subsequently became a global pandemic. Several preventive strategies were then implemented by governments worldwide in an attempt to control the spread of the virus, including but not limited to the shutting of air and sea borders, case identification and tracking, quarantining individuals with suspected infections, travel restrictions, big data integration, and facemask policies. Furthermore, many drugs have been proposed to control and treat COVID-19.

SARS-CoV-2 enters cells through direct interactions between the viral S protein and the cellular receptor angiotensin-converting enzyme 2. After entering a cell, the virus releases its genome, which is translated into viral replicase polyproteins and cleaved into functional proteins by proteases. Viral genome replication is mediated by the viral replication complex, which includes RNA-dependent RNA polymerase (RdRp). Viral nucleocapsids are assembled from the packaged viral genomes and translated to form viral structural proteins, which are then released by exocytosis.

Based on the currently understood mechanisms, many therapeutic drugs are being investigated and developed to fight SARS-CoV-2 during the current COVID-19 pandemic. Several ongoing clinical trials are testing the efficacy of single and combination treatments. Many different drugs are under evaluation, including antiviral nucleotide analogs such as remdesivir, antiviral nucleoside analogs such as favipiravir and ribavirin, protease inhibitors such as lopinavir/ritonavir, antimalarials such as chloroquine and hydroxychloroquine alone or combined with azithromycin, biologics such as tocilizumab, corticosteroids, colchicine, nonsteroidal anti-inflammatory drugs such as indomethacin and convalescent plasma. These candidate drugs are listed in Table 1.

Based on several clinical trials and reports on its compassionate use, remdesivir is considered by many to be the most promising drug for the treatment of COVID-19. Remdesivir (GS-5734) is a prodrug of an adenosine analog, and its triphosphate form can be used as a substrate for many viral RdRp complexes. It has been reported to inhibit viral RNA synthesis by a specific mechanism of delayed chain termination for MERS-CoV, SARS-CoV, and SARS-CoV-2.

To date, there are no Food and Drug Administration (FDA)-approved drugs for COVID-19, however, in the USA, the FDA has authorized the emergency use of remdesivir to treat hospitalized adults and pediatric patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Remdesivir has also been made available in the UK through the Early Access to Medicines Scheme (EAMS) after a positive scientific opinion from the Medicines and Healthcare Products Regulatory Agency. Similar arrangements have already been made by regulatory authorities in Japan. The EAMS scheme provides patients with COVID-19 and life-threatening or seriously debilitating conditions access to drugs that have not yet received licensing approval. Additionally, several large-scale clinical trials on the compassionate use of remdesivir have been published with varying results. In the current study, a PubMed search using a combination of the keywords "COVID-19" "SARS-CoV-2" and "remdesivir" was performed. We included all studies written in English. The initial literature search identified 39 articles, which included three large-scale randomized clinical trials. Some compassionate-use experiences were also included in this review.

Preclinical evidence for the efficacy of remdesivir against sars-cov-2

Remdesivir was developed by a collaboration among Gilead Science, the U.S. Centers for Disease Control and Prevention, and the U.S. Army Medical Research Institute of Infectious Diseases. Sheahan et al. reported the in vivo efficacy of remdesivir in the inhibition of viral replication, and Gordon et al. and de Wit et al. reported a reduction in viral-related pathology of MERS-CoV and SARS-CoV infections. Furthermore, in an in vitro study, Wang et al. assessed the antiviral activity of remdesivir against SARS-CoV-2 using quantitative reverse transcription-polymerase chain reaction quantification of the viral copy number in infected Vero E6 cells. The study demonstrated that remdesivir had an IC50 of 770 nM and an IC90 equal to 1760 nM (with a cytotoxic concentration of >100 mM). Recently, remdesivir has been found to inhibit SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells, which supports the theory that remdesivir is a potential therapeutic drug against SARS-CoV-2. Furthermore, in a randomized, well-masked, controlled trial in 12 rhesus monkeys infected with SARS-CoV-2, a course of remdesivir administered 12 h after inoculation attenuated their respiratory symptoms and lung damage. At necropsy, lung viral loads were lower with less lung damage in the remdesivir-treated animals than in the controls. Thus, remdesivir treatment administered early during...
| Mechanism | Dosage | Current evidence |
|-----------|--------|------------------|
| **Antiviral agents** | | |
| Nucleotide analogsRemdesivir | RNA polymerase inhibitors | 200 mg intravenously on day 1. 100 mg intravenously on day 2–10. Based on clinical trials, the US FDA has authorized emergency use of remdesivir to treat hospitalized adult and pediatric patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19.

Nucleoside analogs | RNA polymerase inhibitors | Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily). In an open-label, control trial in China, the favipiravir arm had a higher improvement rate in chest imaging and faster viral clearance.

Ribavirin | | 400 mg orally, twice daily for 14 days. Clinical trial is ongoing.

Protease inhibitors | | 400 mg/100 mg orally twice daily for 14 days. Failed to provide benefits in a Chinese trial.

Lopinavir/ritonavir | | Fatal dysrhythmias and electrolyte shifts may occur if inappropriately used.

Antimalarials | Elevate endosomal pH and inhibit pH-dependent steps in the viral replication process | 500 mg orally twice daily for 10 days. In vitro data of chloroquine is promising, but there are safety concerns for its clinical use. Clinical trials are ongoing.

Chloroquine | | 400 mg orally twice daily for 1 day, then 200 mg twice daily for 4 days. Hydroxychloroquine has increased potency and a more tolerable safety profile compared with chloroquine. Clinical trials are ongoing.

Hydroxychloroquine | | 500 mg on day 1, followed by 250 mg per day on day 2–5. Combination treatment with azithromycin recommended for patients with moderate-to-severe COVID-19.

Azithromycin | Reinforces the efficacy of hydroxychloroquine, virus elimination | N/A Corticosteroid use is still controversial. A study in China found that the use of methylprednisolone decreases the risk of death in patients with COVID-19 who develop ARDS.

Corticosteroid | Binds to cytoplasmic receptors to change the transcription of mRNA and reduce the production of inflammatory mediators | N/A Corticosteroid use is still controversial. A study in China found that the use of methylprednisolone decreases the risk of death in patients with COVID-19 who develop ARDS.

Colchicine | Anti-inflammatory action without the adverse effects of steroids and nonsteroidal anti-inflammatory agents | Colchicine 1.5 mg loading dose followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily for 3 weeks. Participants who received colchicine had statistically significantly improved time to clinical deterioration.

(continued on next page)
infection had a clinical benefit in SARS-CoV-2-infected rhesus macaques.\textsuperscript{56} However, \textit{in vitro} and in-animal efficacy does not always accurately predict outcomes in humans\textsuperscript{57,58}; therefore, further clinical trials are urgently needed.\textsuperscript{44}

Clinical evidence for remdesivir in sars-cov-2

Efficacy following compassionate use

Gilead Science had provided more than 1000 doses of remdesivir for compassionate use worldwide by the end of May 2020, and this was first used in China. All compassionate-use treatments and clinical trials involved the administration of remdesivir at a 200-mg loading dose on the first day, with a 100-mg maintenance dose for 9 subsequent days\textsuperscript{16,28,30,59,60}; this regime is identical to that utilized in the previous Ebola trial,\textsuperscript{61} which appears to be the model for all subsequent trials involving remdesivir.

Holshue et al. reported the first case of confirmed SARS-CoV-2 infection in the USA.\textsuperscript{62} On the patient’s seventh day of hospitalization and following clinical deterioration, the patient was administered intravenous remdesivir through the compassionate-use access scheme; no adverse events were observed on infusion. The patient received the first dose of remdesivir on hospital day 7 when they developed severe pneumonia that could not be treated successfully using the broad-spectrum antibiotics vancomycin and cefepime. The patient recovered on hospital day 8 and no longer required supplemental oxygen.

In a case series of 28 patients with severe COVID-19 in Seattle, USA, 14 eventually died and 7 received remdesivir through compassionate-use access; however, the outcomes of these patients were not reported.\textsuperscript{59} Clinically, the process of obtaining remdesivir for compassionate use is both challenging and time-consuming. For optimal results, remdesivir should be administered as soon as possible, although late administration may also be effective to treat SARS-CoV-2.\textsuperscript{63} Gerin et al.\textsuperscript{28} reported a compassionate-use
remdesivir trial of patients who were hospitalized with confirmed SARS-CoV-2 infections. All patients had an oxygen saturation of 94% or less while breathing ambient air or receiving oxygen support and received remdesivir through a compassionate-use scheme. Among the 53 patients whose data were analyzed, 22 were in the USA, 22 were in Europe or Canada, and 9 were in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) were receiving extracorporeal membrane oxygenation. (57%) were receiving mechanical ventilation and 4 (8%) showed an improvement in oxygen-support class, including 17 of the 30 patients (57%) receiving mechanical ventilation, who were extubated. A total of 25 patients (47%) were discharged and 7 patients (13%) died; the mortality rate was 18% (6 of 34) among patients who received invasive ventilation and 5% (1 of 19) among those who did not receive invasive ventilation.

**Efficacy in randomized controlled trials**

Four randomized control trials have been published to date. First, to evaluate the efficacy and safety of remdesivir in patients with COVID-19, a randomized, placebo-controlled, double-blind, multicenter, phase 3 clinical trial was launched on February 5, 2020, in China. Eligible patients were adults admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Randomization was performed according to the level of respiratory support as follows: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation. Patients were randomly assigned in a 2:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted the concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomization to the point of a decline in two levels on a six-point ordinal scale of clinical status as follows: death = 6; hospital admission for extracorporeal membrane oxygenation or mechanical ventilation = 5; hospital admission for non-invasive ventilation or high-flow oxygen therapy = 4; hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation) = 3; hospital admission but not requiring oxygen therapy = 2; and being discharged or having reached the discharge criteria (defined as clinical recovery, ie, normalization of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 h) = 1.

Overall, 237 Chinese patients who were admitted to hospital with laboratory-confirmed SARS-CoV-2 infections and who had an interval of 12 days or less from symptom onset to enrolment, an oxygen saturation of 94% or less breathing room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia were enrolled. Patients were permitted the concomitant use of lopinavir–ritonavir, interferon, and corticosteroids. The study concluded that the use of remdesivir was not associated with a significant difference in the time to clinical improvement (hazard ratio, 1.23 [95% confidence interval (CI), 0.87–1.75]). Although not statistically significant, patients with a symptom duration of 10 days or less who received remdesivir had a faster time to clinical improvement than those who received placebo (hazard ratio, 1.52 [95% CI, 0.95–2.43]). Notably, this trial was underpowered. It was terminated early, after 237 of the intended 453 patients were enrolled, because by March 12 no further patients met the eligibility criteria in Wuhan. The study closed on March 29.

The National Institute of Allergies and Infectious Diseases and the National Institute of Health initiated the Adaptive COVID-19 Treatment Trial, a double-blind, randomized, placebo-controlled phase 3 trial designed to evaluate the safety and efficacy of remdesivir compared with a placebo-control. The preliminary data were reported by Beigel et al. The study enrolled 60 trial sites and 13 subsites worldwide. The primary outcome was initially defined as the difference in clinical status, defined using an eight-category ordinal scale, among patients treated with remdesivir compared with placebo at day 15. Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. A total of 1063 patients underwent randomization and preliminary results were obtained from 1059. Those who received remdesivir had a median recovery time of 11 days (95% CI, 9–12), compared with 15 days (95% CI, 13–19) for those who received the placebo (rate ratio for recovery, 1.32; 95% CI, 1.12–1.55; P < 0.001). The Kaplan–Meier estimates of mortality at 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47–1.04). The authors concluded that remdesivir was superior to the placebo and shortened the recovery time for adults hospitalized with COVID-19 who had evidence of a lower respiratory tract infection. Based on this study, the US FDA provided emergency use authorization for the use of remdesivir for COVID-19 on May 1, 2020.

Trials led by Beigel et al. and Grein et al. showed favorable results. Additionally, the first COVID-19 case in the US responded well to remdesivir. However, these results are different from those of another large-scale trial by Wang et al. in Hubei, China, in which the time to clinical improvement was unchanged following remdesivir treatment. All enrolled patients in this clinical trial were Asian and only 4.9% and 16.7% of the enrolled patients were Asian in the trials by Beigel and Grein, respectively. Furthermore, in the trial by Beigel, subgroup analysis revealed that Asian patients showed the poorest response to remdesivir. Further pharmacogenetic studies of the efficacy of remdesivir for the treatment of COVID-19 in patients of different races are urgently needed.

Recently, the results of the third randomized remdesivir trial were published. The SIMPLE trial was designed to evaluate the efficacy of 5- and 10-day treatments with intravenous remdesivir. The eligible patients were hospitalized patients with confirmed SARS-CoV-2 infection who...
| Study                | Enrolled Cases | Asian Ratio | Case Definition                                                                 | Trial Design                                      | Countries/sites                                                                 | Remdesivir: Placebo Ratio | Primary Endpoint | Dosage Result |
|---------------------|----------------|-------------|---------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|---------------------------|-----------------|---------------|
| Wang et al.         | N = 237        | 100% (all Chinese) | RT-PCR positive for SARS-CoV-2, had pneumonia, SpO2 ≤ 94% or a ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤ 300 mmHg, and were within 12 days of symptom onset | Double-blind, randomized, placebo-controlled multicenter trial | Ten hospitals in Hubei, China. | 2 : 1 permitted concomitant use of lopinavir–ritonavir, interferon, and corticosteroids | Time to clinical improvement | Intravenous remdesivir 200 mg on day 1, followed by 100 mg on days 2–10 in all four trials |
| Beigel et al.       | N = 1603       | 4.9%        | Laboratory-confirmed SARS-CoV-2 infection, with lower respiratory tract involvement | Double-blind, randomized, placebo-controlled multicenter trial | Sixty trial sites globally | 1 : 1 | Time to recovery | Rate ratio for recovery, 1.32; 95% CI, 1.12–1.55; *P* < 0.001; median recovery time of 11 |
| Grein et al.        | N = 61 (53 were analyzed) | 16.7% | RT-PCR positive for SARS-CoV-2, SpO2 ≤ 94% or a need for oxygen support, and radiologic evidence of pneumonia | Compassionate use | Twenty-two cases in United States, 22 cases in Europe or Canada, and 9 cases in Japan. | All received remdesivir (1:1 ratio to receive for 5 or 10 days) | Clinical improvement | 68% of patients had an improvement in oxygen-support class. |
| Goldman et al.      | N = 397        | 11.47%      | RT-PCR positive for SARS-CoV-2, SpO2 ≤ 94% or a need for oxygen support, and radiologic evidence of pneumonia | Open-label, randomized, phase 3 trial, multicenter trial (SIMPLE trial) | Fifty-five hospitals in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan | | Clinical improvement | On day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day |
| Spinner et al.      | N = 584        | 17.98%      | RT-PCR positive for SARS-CoV-2 within 4 days of randomization and moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air) | Randomized, open-label, phase 3, multicenter trial | 105 hospitals in the United States, Europe, and Asia | | Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). Clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7). |
days (95% CI, 9–12) compared with 15 days (95% CI, 13–19) in those who received placebo
group and 54% in the 10-day group.
distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09–2.48; P = .02). The clinical status
distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different
(P = .18)

| Result in Asian patients | N/A | Rate ratio for recovery is worst in the Asian subgroup [1.20, 95% CI, 0.65–2.22] | N/A | N/A |
|--------------------------|-----|--------------------------------------------------------------------------------------------|-----|-----|
| Grade 3 adverse events   | 18% vs 26% | 21.1% vs 27% | 23% |

18% vs 26% 21.1% vs 27% 23% 27% in 5-day group; 34% in 10-day group
12%, 10%, 12% in 5-day group, 10-day group and standard care. Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care.

* Indicates statistical significance.
had radiographic evidence of pulmonary infiltrates and either oxygen saturation of 94% or less while they were breathing ambient air or were receiving supplemental oxygen. Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation at screening were excluded, as were patients with signs of multiorgan failure. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent treatment days. In total, 397 patients underwent randomization and began treatment. More than 50% of patients in both treatment groups were discharged from hospital by day 14 (5 days: 60.0%, vs. 10 days: 52.3%; P = 0.14). On day 14, 64.5% patients in the 5-day treatment group and 53.8% patients in the 10-day treatment group achieved clinical recovery. The overall mortality rate on day 14 was 7% in both treatment groups, with 64% of the patients showing clinical improvement and 61% being discharged from the hospital. The trial did not show a significant difference between a 5- and 10-day course of remdesivir in patients with severe COVID-19 not requiring mechanical ventilation.25

Recently, Spinnet al. conducted a randomized trial to determine the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status on day 11 after the initiation of treatment.26 Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/day. On day 11, patients in the 5-day remdesivir group had a statistically significantly higher odds of a better clinical status than those receiving standard care (odds ratio, 1.65; 95% Cl, 1.09–2.48; P = .02). There was no significant difference in clinical status on day 11 between the 10-day remdesivir and standard care groups.28 All of these large-scale remdesivir trials are summarized in Table 2.

Safety in trials

A lyophilized formulation of remdesivir was evaluated in a phase 1 trial for potential future use in clinical trials owing to its storage stability in resource-limited settings. All adverse events were grade 1 or 2 in severity.60 Clinically, common adverse drug reactions (ADRs) noted during the compassionate use of remdesivir in patients with COVID-19 reported by Grein et al. included increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension.28 Four patients (8%) discontinued remdesivir treatment prematurely, one due to a worsening of preexisting renal failure, one because of multiple organ failure, and two because of elevated aminotransferases, one of whom had a maculopapular rash.

In a trial conducted by Wang et al.30 in Wuhan, China, adverse events were reported in 66% of patients in the remdesivir group and 64% in the control group. The most common adverse events in the remdesivir group were constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin. The incidence of serious adverse events was 18% in the remdesivir group and 26% in the control group. In the trial led by Beigel et al.,26 serious adverse events occurred in 21.1% of the remdesivir group and 27.0% of the placebo group. The most common adverse events were anemia and decreased hemoglobin (7.9% and 9.0% in the remdesivir and placebo groups, respectively). Overall, the incidence of adverse events was not significantly different between the remdesivir and placebo groups. Furthermore, in the 5- and 10-day remdesivir treatment trial led by Goldman et al.,27 the percentage of patients who experienced ADRs was similar between the groups: 70% in the 5-day group and 74% in the 10-day group. Overall, 21% of the patients in the 5-day group and 35% in the 10-day group had serious adverse events. The most common adverse events were nausea (10% in the 5-day group vs. 9% in the 10-day group), acute respiratory failure (6% vs. 11%), increased alanine transferase (6% vs. 8%), and constipation (7% in both groups). Laboratory abnormalities of grade 3 or higher occurred in 27% of the patients in the 5-day group and 34% of the patients in the 10-day group. Most abnormalities were transient, with no significant difference in the median change between the groups on day 14, which indicated that the ADRs for the 10-day remdesivir treatment course were acceptable.

Regarding the renal and hepatic toxicity of remdesivir, patients with severe acute kidney injury and end-stage renal disease were excluded from the current remdesivir trials based on estimated glomerular filtration rate (eGFR) cutoffs (either 50 or 30 mL/min per 1.73 m²), and safety data for remdesivir among individuals with an eGFR < 30 mL/min per 1.73 m² are insufficient.65 The current pharmacokinetic evidence indicates that remdesivir is rapidly cleaved by hydrolys; thus, the effect of hepatic impairment on remdesivir plasma levels is likely to be low. No dose modification is currently recommended, however remdesivir is still contraindicated in patients with severe hepatic dysfunction.28,29

Discussion

There is currently a need for effective drugs to treat COVID-19 and control the pandemic. According to the included clinical trials, remdesivir can play a crucial role in the fight against COVID-19 as it can lead to clinical improvements with no additional ADRs. However, it is important to note that remdesivir failed to treat patients with COVID-19 in a randomized controlled trial in China. These clinical trials suggest that remdesivir may be useful for the treatment of COVID-19, at least as a backbone of combination therapy. For example, a study to evaluate the use of remdesivir combined with a Janus kinase inhibitor, baricitinib, for the treatment of COVID-19 is ongoing.66 No different clinical efficacies or ADRs have been observed between 5- and 10-day treatment courses; thus, a short course of remdesivir is possible. Upcoming large-scale, randomized, placebo-controlled trials may provide additional evidence for the efficacy and safety of remdesivir for the treatment of COVID-19. Importantly, pharmacogenetic studies of remdesivir are urgently needed to explain the different effects of remdesivir in Western and Eastern countries and different races.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.
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References

1. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J 2019;16:69. https://doi.org/10.1186/s12985-019-1182-0.
2. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A 2009;106:5871–6.
3. Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J Biomat Struct Dyn 2020:1–10. https://doi.org/10.1080/07391102.2020.1758788.
4. Chang HL, Chen YH, Taiwan HC, Yang CJ. EGFR tyrosine kinase inhibitor-associated interstitial lung disease during the coronavirus disease 2019 pandemic. J Thorac Oncol 2020. https://doi.org/10.1016/j.jtho.2020.04.029.
5. Chang HL, Wei PJ, Wu KL, Huang HL, Yang CJ. Checkpoint inhibitor pneumonitis mimicking COVID-19 infection during the COVID-19 pandemic. Lung Canc 2020. https://doi.org/10.1016/j.juncanc.2020.06.013.
6. Sanville B, Corbett R, Pigdock W, Hardin K, Sebat C, Nguyen MV, et al. A community transmitted case of severe acute respiratory distress syndrome due to SARS CoV2 in the United States. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa347.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.1585.
8. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
9. Chen FM, Feng MC, Chen TC, Hsieh MH, Kuo SH, Chang HL, et al. Big data integration and analytics to prevent a potential hospital outbreak of COVID-19 in Taiwan. J Microbiol Immunol Infect 2020. https://doi.org/10.1016/j.jmii.2020.04.010.
10. Hsiao SH, Chen TC, Chien HC, Yang CJ, Chen YH. Measurement of body temperature to prevent pandemic COVID-19 in hospitals in Taiwan: repeated measurement is necessary. J Hosp Infect 2020;105:360–1. https://doi.org/10.1016/j.jhin.2020.04.004.
11. Huang HT, Chen TC, Liu TY, Chiu CF, Hsieh WC, Yang CJ, et al. How to prevent outbreak of a hospital-affiliated dementia day-care facility in the pandemic COVID-19 infection in Taiwan. J Microbiol Immunol Infect 2020;53:394–5. https://doi.org/10.1016/j.jmii.2020.04.007.
12. Yang CJ, Chen TC, Chen YH. The preventive strategies of community hospital in the battle of fighting pandemic COVID-19 in Taiwan. J Microbiol Immunol Infect 2020;53:381–3. https://doi.org/10.1016/j.jmii.2020.03.019.
13. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020;53:436–43.
14. Jorgensen SC, Kebrai B, Dresser LD. Remdesivir: review of pharmacology, pre-clinical data and emerging clinical experience for COVID-19. Pharmacotherapy 2020. https://doi.org/10.1002/phar.2429.
15. Khan SA, Zia K, Ashraf S, Uddin R, Ul-Haq Z. Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach. J Biomat Struct Dyn 2020;1–10. https://doi.org/10.1080/07391102.2020.1751298.
16. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80. https://doi.org/10.1016/j.cell.2020.02.052. e8.
17. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. bioRxiv 2020. https://doi.org/10.1101/2020.02.11.944652.
18. Elfishy AA, Azzam EB. Novel guanosine derivatives against MERS CoV polymerase: an in silico perspective. J Biomat Struct Dyn 2020:1–9. https://doi.org/10.1080/07391102.2020.1758789.
19. Amiran ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. One Health 2020;9:100128. https://doi.org/10.1016/j.ohnhlet.2020.100128.
20. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;295:4773–9.
21. Gupta MK, Vemula S, Donde R, Gouda G, Behera L, Vaddre R. In silico approaches to detect inhibitors of the human severe acute respiratory syndrome coronavirus envelope protein ion channel. J Biomat Struct Dyn 2020 Apr 15:1–11. https://doi.org/10.1080/07391102.2020.1751300.
22. Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies. Diabetes Metab Syndr 2020:14:641–8.
23. Davies M, Osborne V, Lane S, Roy D, Dhania S, Evans A, et al. Remdesivir in treatment of COVID-19: a systematic benefit-risk assessment. Drug Saf 2020;43:645–56.
24. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7:11. https://doi.org/10.1186/s40779-020-00240-0.
25. Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID-19: A narrative review for emergency providers. Am J Emerg Med 2020. https://doi.org/10.1016/j.ajem.2020.04.035.
26. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 - preliminary report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoA2007764.
27. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med 2020 May 27. https://doi.org/10.1056/NEJMoA2015301.
28. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. The Lancet. 2020;395:1569–78.
29. Nasir M, Talha KA, Islam T, Saha SK, Selina F, Parveen RA. Use of remdesivir in the management of COVID-19: a systematic review on current evidences. Mymsensingh Med J 2020;29:481–7.
30. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78.
31. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with Favipiravir for COVID-19: an open-label control study. Engineering (Beijing) 2020. https://doi.org/10.1016/j.ajeng.2020.03.007.
32. Khalili JS, Zhu H, Mak NSA, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: groundwork for an evaluation concerning COVID-19. J Med Virol 2020;92:740–6.
33. Cao B, Wang Y, Wen D, Liu M, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020;382:1787–99.
34. Weehuizen JM, Hoepelman AIM. An open-label cluster-randomized controlled trial of chloroquine, hydroxychloroquine or
only supportive care in patients admitted with moderate to severe COVID-19 (ARCHAIC)-protocol publication. *Eur J Clin Invest* 2020:e13297. https://doi.org/10.1111/eci.13297.

35. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;10549.

36. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in >80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Trav Med Infect Dis* 2020;34:101663.

37. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020;117:10970–5.

38. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020. https://doi.org/10.1001/jama. internmed.2020.0994.

39. Russell CD, Miliar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473–5.

40. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open* 2020;3:e2013136.

41. Gomeni R, Xu T, Gao X, Bressolle-Gomeni F. Model based approach for estimating the dosage regimen of indomethacin a potential antiviral treatment of patients infected with SARS-CoV-2. *J Pharmacokinet Pharmacodyn* 2020;47:189–98.

42. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. *Int J Clin Pract* 2020:e13535. https://doi.org/10.1111/i jcp.13535.

43. Olivares-Gazca JC, Priesca-Marin JM, Ojeda-Laguna M, Garces-Eisele J, Soto-Olvera S, Palacios-Alonso A, et al. Infusion of convalescent plasma Is associated with clinical improvement in critically ill patients with COVID-19: a pilot study. *Rev Invest Clin* 2020;72:159–64.

44. Ferrier RE, Aronson JK. Remdesivir in COVID-19. *BMJ* 2020;369:m1610. https://doi.org/10.1136/bmj.m1610.

45. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: a review of its discovery and development leading to Emergency Use Authorization for the treatment of COVID-19. *Arch Med Res* 2020:1–9. https://doi.org/10.1080/07391102.2017.1767691.

46. Tchesnokov EP, Feng JY, Porter DP, Gotte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses* 2019;11. https://doi.org/10.3390/v11040326.

47. Saha A, Sharma AR, Bhatchcharaya M, Sharma G, Lee SS, Chakraborty C. Probable molecular mechanism of remdesivir for the treatment of COVID-19: need to know more. *Arch Med Res*. 2020. https://doi.org/10.1016/j.arcmed.2020.05.001.

48. Kmietowicz Z. COVID-19: selected NHS patients will be treated with remdesivir. *BMJ* 2020;369:m2097. https://doi.org/10.1136/bmj.m2097.

49. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020;11:222.

50. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 2020;117:6771–6. https://doi.org/10.1073/pnas.1922083117.

51. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.

52. Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.

53. Liang C, Tian L, Liu Y, Hui N, Qiao G, Li H, et al. A promising antiviral candidate drug for the COVID-19 pandemic: a mini-review of remdesivir. *Eur J Med Chem* 2020;115:12527.

54. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature* 2020. https://doi.org/10.1038/s41586-020-2423-5.

55. Sisay M. Available evidence and ongoing clinical trials of remdesivir: could it be a promising therapeutic option for COVID-19? *Front Pharmacol* 2020;11:791.

56. Yoo JH. Uncertainty about the efficacy of remdesivir on COVID-19. *J Kor Med Sci* 2020;35:e221. https://doi.org/10.3346/jkms.2020.35.e221.

57. Bhattraj PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382:2012–22.

58. Wang Y, Zhou F, Zhang D, Zhao J, Du R, Hu Y, et al. Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. *Trials* 2020;21:422.

59. Jacobs M, Rodger A, Bell DJ, Bhagani S, Crolepy I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet* 2016;388:498–503.

60. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382:929–36.

61. Hilliker E, Beifer JJ, Bondici A, Murad H, Dumkow LE. Delayed initiation of remdesivir in a COVID-19-positive patient. *Pharmaco therapy* 2020;40:592–8.

62. Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. *Lancet* 2020;395:1525–7.

63. Adamsick ML, Gandhi RG, Bidel DR, Elshaboury RH, Bhattcharya RP, Kim AY, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol* 2020. https://doi.org/10.1681/ASN.2020050598.

64. Mahase E. COVID-19: remdesivir is helpful but not a wonder drug, say researchers. *BMJ* 2020;369:m1798. https://doi.org/10.1136/bmj.m1798.

65. Naksuk N, Lazar S, Peerapradit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. *Eur Heart J Acute Cardiovasc Care* 2020;9:215–21. https://doi.org/10.1177/2048872620922784.

66. Nasim S, Kumar S, Azim D, Ashraf Z, Azeem Q. Corticosteroid use for 2019-nCoV infection: a double-edged sword. *Infect Control Hosp Epidemiol* 2020. https://doi.org/10.1017/ice.2020.165.

67. Bozkurt B, Kovacs R, Harrington B. Joint HSFSA/ACC/AHA Statement addresses concerns Re: using RAAS antagonists in COVID-19. *J Card Fail* 2020;26:370.

68. Spanner CD, Gottlieb RL, Power GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu L, et al. Effect of remdesivir on standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *J Am Med Assoc* 2020. https://doi.org/10.1001/jama.2020.16349.