

CASE REPORT

Delayed Initiation of Remdesivir in a COVID-19-Positive Patient

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We present a case of late initiation of remdesivir antiviral therapy in the successful treatment of a patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a mixed medical intensive care unit of a community teaching hospital. A previously healthy 40-year-old man was admitted to the hospital 3 days after the onset of coronavirus disease 2019 (COVID-19) symptoms including dry cough, fever, and shortness of breath progressing to intubation and increased mechanical ventilator support. A request for compassionate use remdesivir was submitted on the same hospital day as the positive COVID-19 polymerase chain reaction result. Supportive measures, in addition to a 5-day course of hydroxychloroquine, were maintained until remdesivir could be supplied on day 9 of hospitalization, 13 days after symptom onset. Sixty hours after initiating remdesivir, the patient was successfully extubated and able to transition to room air within 24 hours of extubation. Late initiation of remdesivir may be effective in treating SARS-CoV-2, unlike antivirals utilized for different disease states, such as oseltamivir, that are most effective when started as soon as possible following symptom onset. Urgent action is needed by regulatory agencies to work with drug manufacturers to expedite the study and approval of investigational agents targeting SARS-CoV-2 as well as to meet manufacturing demands.

KEY WORDS COVID-19, remdesivir, SARS-CoV-2, coronavirus, pneumonia, viral pneumonia.
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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in Wuhan, China, in December 2019.¹ On January 21, 2020, the Centers for Disease Control and Prevention (CDC) announced the first case of the virus in the United States had been detected in a man with recent travel from Wuhan.² The World Health Organization declared the

outbreak a pandemic on March 11, 2020. Since that time, the number of cases worldwide continues to increase exponentially, including in the United States, with the number of cases in the United States now surpassing all other countries worldwide. No treatment or vaccination is currently approved for SARS-CoV-2. It is recommended to implement quarantine, social distancing, and infection control measures to prevent disease spread and to provide supportive care for those who become ill.³

With the number of critically ill patients overwhelming hospitals in cities across the nation, clinicians are looking to investigational antiviral agents for possible added benefit over supportive care alone. Ongoing clinical trials of investigational treatments for SARS-CoV-2 will likely not

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be completed until after the peak of this pandemic in many countries. Remdesivir (Gilead Sciences, Inc, Foster City, CA, U.S.) is an investigational antiviral that displays potent *in vitro* activity against SARS-CoV-2.⁴ It has shown promise in preclinical models as well as in case series, with clinical trials ongoing in multiple countries including the United States.^{4, 5} Because remdesivir is not approved by the Food and Drug Administration (FDA), this medication may only be obtained through participation in registered clinical trials or via a request to the manufacturer. Unfortunately, the overwhelming number of requests for remdesivir put a significant strain on the manufacturer's drug supply, and on March 22, 2020, the company halted their individual compassionate use program for most patient populations. They did, however, commit to fulfilling drug delivery for patients who had already been approved for compassionate use remdesivir.⁶ This, coupled with delays in testing across the country, may result in significant delays in starting antiviral therapy following symptom onset. For other viral illnesses, such as influenza, the efficacy of antiviral administration was shown to be most effective when administered within 48 hours after symptom onset.⁷ It is unknown whether remdesivir's antiviral activity would have a similar temporal relationship. We present the case and outcomes of a critically ill patient who tested positive for SARS-CoV-2 and met criteria for remdesivir compassionate use that was administered after symptoms had persisted for nearly 2 weeks due to a significant supply shortage and delay in delivery from the manufacturer.

Case Presentation

A 40-year-old man presented to his ambulatory provider for a COVID-19 screening with a 2-day history of dry cough, shortness of breath, and subjective fever. In accordance with CDC recommendations and state and local health officials, the patient was considered low risk and did not meet criteria to be a person under investigation or for COVID-19 testing at that time. On day 3 of illness, he had a telemedicine COVID-19 screening due to worsening symptoms and new-onset vomiting. At this time, he was advised to report to a designated COVID-19 testing center. There he was tested for COVID-19 via nasopharyngeal swab with a real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) assay (Advanced Technology Laboratories). He was advised to quarantine for

14 days and await test results. During this visit, both a rapid streptococcus antigen test (BBL Streptocard Acid Latex Test; Becton Dickinson and Company, Franklin Lakes, NJ, U.S.) and respiratory pathogen panel by multiplex PCR (BioFire; bioMerieux, Lombard, IL, U.S.) panel were negative.

On day 5 of illness, he presented to the emergency department (ED) with worsening body aches and inability to tolerate oral intake. The COVID-19 PCR from his day 3 visit was still pending. The patient's past medical history was significant for anxiety and depression, obesity (body mass index 30.8 kg/m²), and hypercholesterolemia. His smoking history included a 5-year history of vaping with nicotine. Physical examination revealed a body temperature of 38.1°C, blood pressure of 147/93 mm Hg, pulse of 100 beats per minute, respiratory rate of 24 breaths per minute, and oxygen saturation of 93% on room air. Lungs were found to be clear to auscultation, respirations were nonlabored, and chest radiography was performed that reported areas of faint hazy opacity in the lateral left midlung and the upper right lung field, possibly related to atelectasis or infiltrate (Figure 1). After improvement following supportive care, he was discharged with a diagnosis of likely COVID-19 and was advised to return to the ED if he had worsening symptoms. Later that same day, the patient returned. Physical examination revealed body temperature of 38.5°C, blood pressure of 135/74 mm Hg, pulse of 122 beats per minute, respiratory rate of 22 breaths per minute, and oxygen saturation of 87% on room air. The remainder of the examination was unremarkable. Influenza A/B PCR (Cepheid) was negative. At this time, the patient was admitted to the hospital for suspected COVID-19 and further observation.

By day 6 of illness (hospital day 2), he was requiring 6 L of oxygen by nasal cannula with increased shortness of breath and tachypnea with his respiratory rate 25–28 breaths per minute. He was placed on 15 L of oxygen by non-rebreather mask with improvement to oxygen saturation of 95%. The intensive care team was alerted and advised to switch the patient back to 6 L of oxygen by nasal cannula non-rebreather to prevent further viral aerosolization. An hour later he was urgently intubated and transferred to the intensive care unit. A chest radiograph revealed diffuse patchy infiltrate bilaterally. A chest computed tomography without contrast revealed extensive ground glass/mosaic attenuation and consolidation opacification throughout

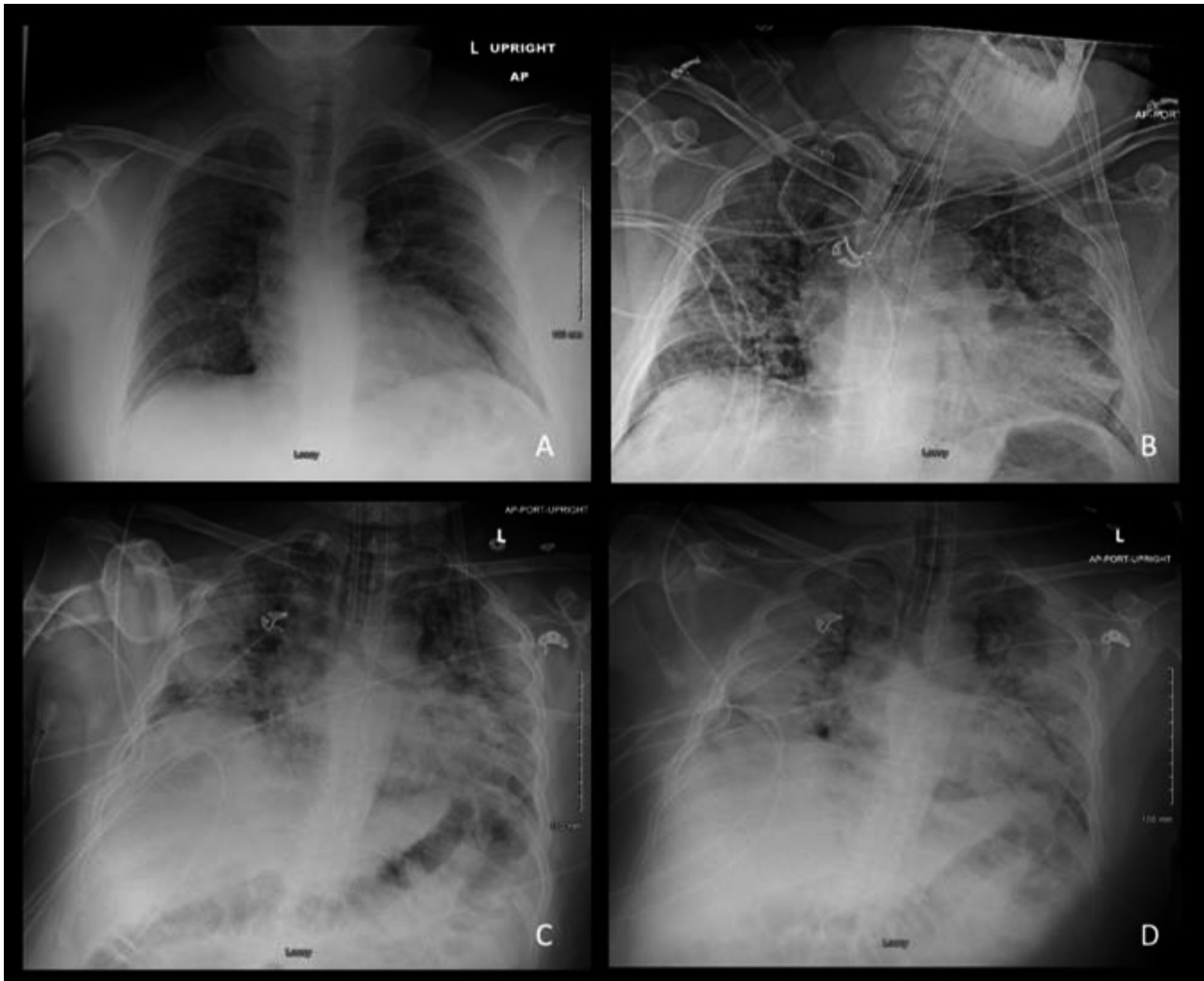


Figure 1. Demonstration of rapid progression of disease. (A) Day 5 of illness. (B) Day 6 of illness following intubation. (C) Day 7 of illness. (D) Day 8 of illness.

bilateral lung fields, highly concerning for changes secondary to viral pneumonia (Figure 2). He was initiated in an assist control mode of ventilation requiring fraction of inspired oxygen (FiO_2) of 60% with positive end-expiratory pressure (PEEP) 14 cm H_2O . The infectious diseases (ID) consultation team initiated hydroxychloroquine 400 mg enterally twice/day for 1 day followed by 200 mg enterally twice/day for 4 days. Additionally, cefepime 2 g intravenously (IV) every 8 hours and azithromycin 500 mg IV every 24 hours were recommended for possible superimposed bacterial pneumonia. A sputum culture was ordered as well as *Legionella* urine antigen testing. Later that evening his COVID-19 test was confirmed as positive. Because of his acute hypoxic respiratory failure requiring mechanical ventilation and

likely progression to acute respiratory distress syndrome (ARDS), the use of investigational remdesivir was discussed among the ID team, clinical pharmacist, and the patient's family. Following signed consent by the patient's family for treatment, the ID physician contacted Gilead via e-mail to initiate the individual compassionate use process, and approval was received early the following morning (Figures 3 and 4).

On day 7 of illness (hospital day 3), the patient's oxygen requirements increased to an FiO_2 of 70% and a PEEP of 14 cm H_2O . Furosemide as needed was initiated to maintain an even or slightly negative fluid balance. He intermittently required FiO_2 to be titrated up to 95% and PEEP 16 cm H_2O . The FDA was notified via phone of Gilead's approval for compassionate use by the ID physician, and the request was

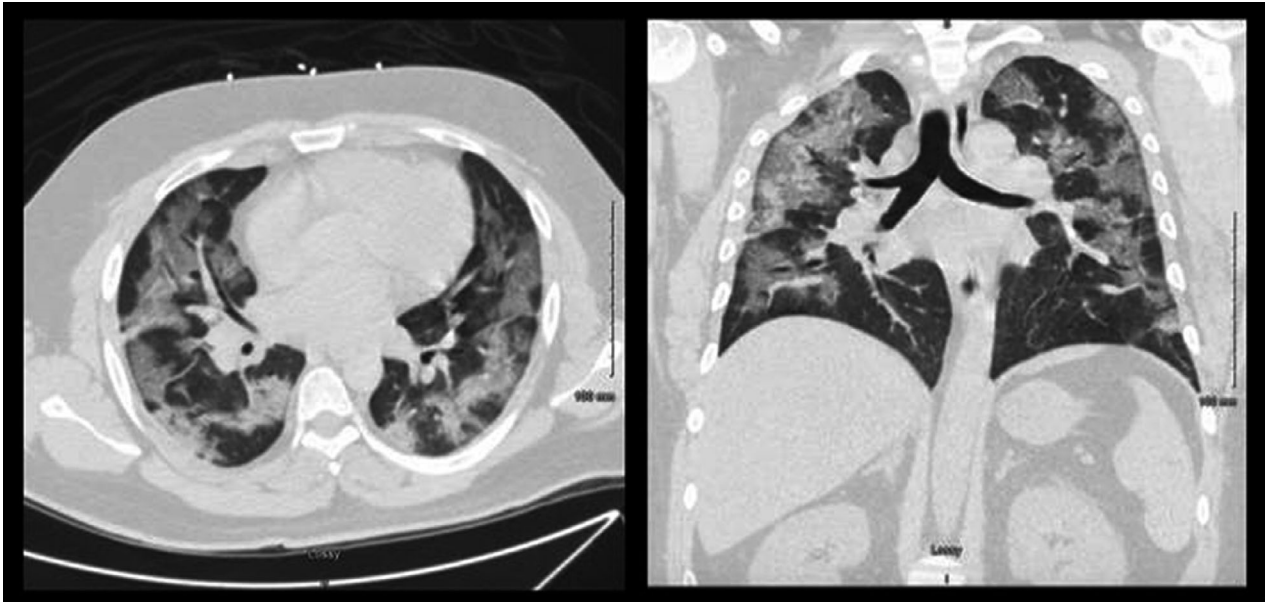


Figure 2. Chest computed tomography concerning for viral pneumonia on day 5 of illness.

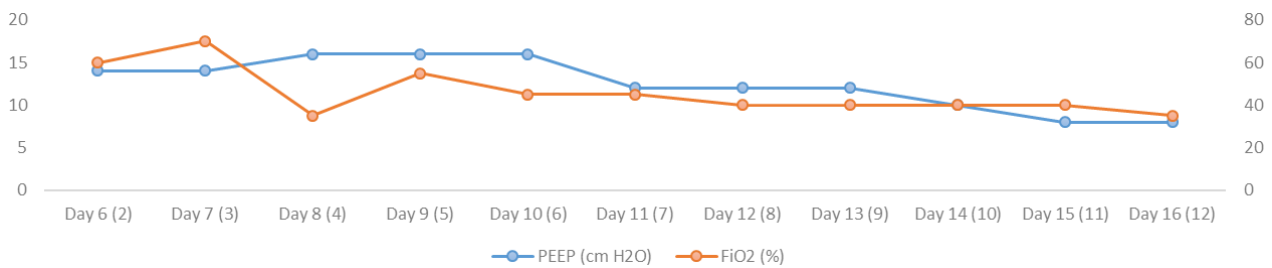


Figure 3. Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FiO₂) requirements during hospitalization days requiring mechanical ventilation. The y-axis represents the day of illness (hospital day).

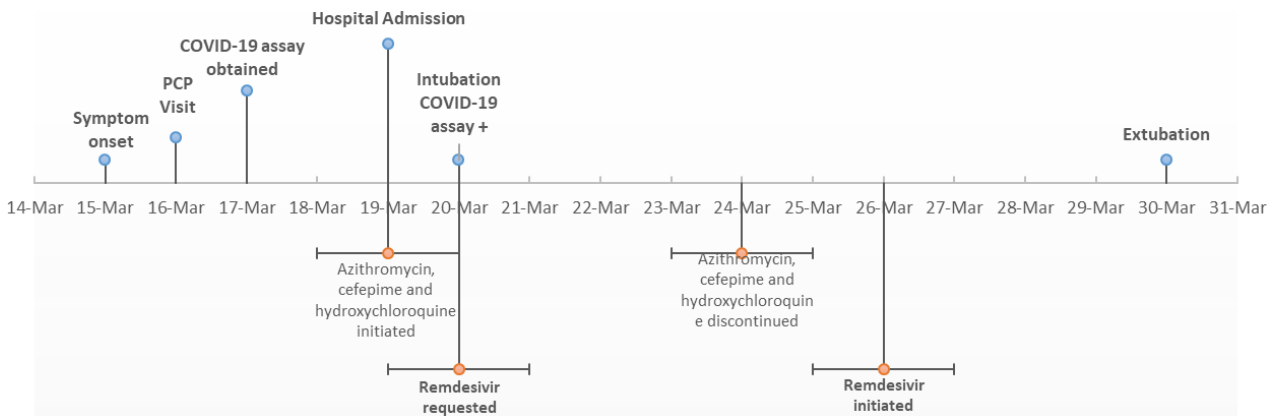


Figure 4. Clinical course of patient with COVID-19 from symptom onset until extubation. PCP = primary care provider.

made for an emergency investigational new drug (eIND). The institution’s investigational review board was also notified for approval. The ID physician and clinical pharmacist were granted

access to the Medidata system to input the patient’s baseline testing and laboratory data. Later in the day, the eIND was received from the FDA approving the use of remdesivir.

On day 8 of illness (hospital day 4), ARDS treatment was initiated with prone positioning, neuromuscular blockade, and aggressive diuresis to achieve a fluid negative balance. With maximum ventilator support achieved, there was a discussion about extracorporeal membrane oxygenation (ECMO) with a nearby hospital with capabilities. Later that afternoon, however, he tolerated a downward titration to FiO_2 of 35% with PEEP 16 cm H_2O , and methylprednisolone 100 mg IV/day was added. The FDA eIND, FDA Form 3926, patient consent form, and prescriber curriculum vitae and medical license information were e-mailed to Gilead. Following the receipt of these documents, the final steps in the process were awaiting the manufacturer to send a formal prescriber agreement for signature, shipping instructions, as well as the medication administration and handling instructions.

During the next 48 hours, mechanical ventilator settings were stable although unable to be weaned down significantly. He had been afebrile for 24 hours, and sputum culture was reported complete with normal respiratory flora; therefore, the cefepime and azithromycin were discontinued. Hydroxychloroquine was also discontinued due to upward trending alanine aminotransferase (ALT) and aspartate aminotransferase (AST). At this time, the ID team was still awaiting the prescriber agreement paperwork and shipping instructions from Gilead that were delayed due to drug supply issues and cessation of the compassionate use program.

On day 11 of illness (hospital day 7), the ID physician received the prescriber agreement from Gilead. This was returned via e-mail, and a letter of authorization was then sent from Gilead to the FDA to accompany the patient-specific eIND. Additionally, reference materials including the investigator brochure, template protocol, and pharmacy manual were received from the manufacturer. Throughout this period, the patient continued to require aggressive mechanical ventilator support. The ID pharmacist was contacted by Gilead with shipping instructions indicating medication delivery would occur within 24 hours. At this time, the medication and administration and handling instructions were built in the electronic medical record system to expedite drug compounding and delivery once the product arrived.

On day 13 of illness (hospital day 9), remdesivir arrived and a 200 mg IV loading dose was administered to the patient. This was followed by orders for a remdesivir 100 mg IV

maintenance dose every 24 hours for the next 9 days. During the following 48 hours, the patient continued to progress, he was able to tolerate aggressive mechanical ventilation weaning, and his ALT and AST were downtrending. On day 16 of illness (hospital day 12), he was extubated without incident. His oxygen saturations remained stable requiring 2–3 L of oxygen by nasal cannula and were able to maintain his oxygenation saturation on room air by day 17 of illness (hospital day 13). The patient continues to be in stable condition on room air and is progressing toward discharge.

Discussion

Remdesivir, also known as GS-5734, is a novel antiviral nucleotide prodrug created by Gilead Sciences for the treatment of the Ebola virus outbreak in 2016.⁸ Although it did not demonstrate efficacy in human clinical trials for this disease, it has shown efficacy against coronaviruses including SARS-CoV-1 and Middle East respiratory syndrome coronavirus.^{9–13} Because of this, remdesivir has garnered significant attention for its potential use as a treatment option for SARS-CoV-2. As an adenosine analog, remdesivir was shown to incorporate into growing viral RNA chains, resulting in premature termination and a decrease in viral RNA production.⁴ Due to a 96% structural similarity in its RNA-dependent RNA polymerase (RdRp) compared with the virus causing SARS-CoV-1, remdesivir, which targets the viral RdRp, is postulated to be effective against SARS-CoV-2 as well.¹³ Previous literature showed significantly reduced lung viral load and improved clinical signs of disease as well as respiratory function following remdesivir administration.¹¹ Its favorable safety profile demonstrated in multiple case reports, randomized trials of Ebola virus disease, as well as currently ongoing phase 3 randomized double-blind placebo-controlled clinical trials in China, further expand interest in this potentially lifesaving drug.^{9, 13}

Unfortunately, the process to obtain remdesivir for compassionate use is both challenging and time consuming. Although the manufacturer cautions prescribers that the process to obtain the medication typically takes a minimum of 72 hours, for our patient this process took more than double the estimated time expected. This delay in obtaining medication is concerning because other antivirals, such as oseltamivir for influenza or acyclovir for herpes viruses, are effective only if given within a small window of time

after symptom onset.^{7, 14, 15} Additionally, many patients hospitalized with SARS-CoV-2 may have already been symptomatic for several days, self-isolating while awaiting test results or until symptoms have worsened before presenting to the hospital, further delaying time to therapy. Fortunately, our patient made significant improvement in oxygenation and was able to be extubated less than 72 hours after starting remdesivir despite this delay in therapy. Thus administration of remdesivir, regardless of time from symptom onset, may still have clinical benefits for patients with SARS-CoV-2. Another report detailing the first case of community-transmitted SARS-CoV-2 in the United States demonstrated similar complications of delayed diagnosis and treatment with remdesivir was recently published. Similar to our case, the authors observed clinical improvement after treatment with remdesivir initiated on day 11 of illness.¹⁶

The rapid increase in critically ill COVID-19 cases reported across the country and subsequent demand for remdesivir has resulted in a supply shortage with the manufacturer halting the individual compassionate use process outside of patients who are pregnant or pediatric with severe disease manifestations. At this time Gilead is moving toward an expanded access program for future institutional use of remdesivir outside of clinical trials; however, details of that program are still forthcoming, and the procedure is expected to be similarly cumbersome as the previous individual compassionate use process. Enrollment in ongoing clinical trials to obtain remdesivir may also be difficult for institutions, especially community hospitals with less investigational research support. This case highlights significant issues that must be addressed as a health care and regulatory system in the United States. As the COVID-19 global pandemic continues to spread, it is critical that access to potentially lifesaving treatments be quickly available to patients. The FDA and government regulatory agencies must be called on to take urgent action to work with drug manufacturers of promising investigational therapies to ensure adequate supply and rapidly evaluate safety and efficacy data. Changes to improve and accelerate the processes of drug manufacturing, FDA evaluation, and approval during times of pandemic are paramount to expedite access to treatment for critically ill patients.

This report has limitations that must be considered. Our perspective comes from a single patient treated with remdesivir late in the course of disease. This patient also received hydroxychloroquine and

azithromycin for 5 days, and although he did not initially show clinical improvement after the duration of these therapies, this combination is also being investigated as potential therapy for SARS-CoV-2.¹⁷ It is possible these medications may have impacted his clinical course. He is also a younger patient with few comorbidities. His most significant risk factor for mortality was obesity; because the mortality rate in his demographic in the United States is less than 1%, it is possible that he would have improved without remdesivir.^{18, 19} Further study and clinical trials evaluating the efficacy of remdesivir are required to confirm its efficacy against COVID-19 including if efficacy differences exist between early and delayed administration.

Conclusion

Late initiation of remdesivir may be effective in treating SARS-CoV-2, unlike antivirals such as oseltamivir and acyclovir, which are most effective when started as soon as possible following symptom onset. This case highlights the urgent need for action by regulatory agencies to work with drug manufacturers to expedite the study and approval of investigational agents targeting SARS-CoV-2 as well as to meet manufacturing demands.

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