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A Potential Antiviral Treatment for COVID-19

Remdesivir

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THE BEGINNING

Sometime between October 6 and December 11, 2019, the COVID-19 pandemic began. On December 31, 2019, the World Health Organization was notified about a cluster of pneumonia cases with an unknown etiology in Wuhan, the capital of the Hubei Province, China. Initial evidence suggested that this new outbreak was associated with a seafood market in Wuhan, which was closed on January 1, 2020. The etiological agent was finally identified as a severe acute respiratory syndrome (SARS)-like betacoronavirus, later named SARS-CoV-2. Human-to-human transmission was confirmed on January 14, 2020, followed by the World Health Organization declaring COVID-19 a pandemic on March 11, 2020.[1]

For the past 2 decades, new coronaviruses (CoV) have emerged: SARS and Middle East respiratory syndrome (MERS). Severe acute respiratory syndrome emerged in 2002 from live game markets in Guangdong Province, China, as a severe atypical pneumonia and spread worldwide. The SARS outbreak was contained after 8422 cases in 32 countries with a fatality rate of 10% to 15%. With this outbreak came the alarming discovery that animal CoV were spreading to humans causing novel severe disease.[2] In 2012, the MERS-CoV was identified in Saudi Arabia as a severe respiratory syndrome. Endemic in camels, 2494 human cases were identified in 20 countries with 858 deaths, with a case fatality rate of 36% with mechanical ventilation required for 50% to 89% of patients.[2]

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Note to the reader: This article reflects evidence available at the time of article preparation or approximately 6 months after the COVID-19 pandemic began. During this time, much evidence is emerging, which is fluid requiring more testing and analysis. This article provides a glimpse of the beginning of a possible future treatment pathway for a dangerous novel virus that has affected every area of clinical nurse specialist practice in the provision of care to COVID-10 patients.

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Coronaviruses were first identified in humans in the 1960s and are responsible for approximately a third of respiratory infections in humans as well as gastrointestinal infections, the common cold, and some severe lower respiratory infections. Found in a wide range of mammals and birds, evidence suggests that SARS-CoV-2 is of zoonotic origin genetically closest to horseshoe bats. However, the zoonotic source of the virus remains in question.[1] Viral shedding occurs via fomites, airborne and fecal-oral. Coronavirus membership in the RNA family of viruses is described in the Table.[3–5]

At this time of writing (July 26, 2020), there are 16 117 992 confirmed cases of COVID-19 with 645 699 deaths in 188 countries.[6] As science pursues vaccine development, research also seeks treatment options for COVID-19 infection. One treatment with promise for COVID-19 is remdesivir previously tested in humans with Ebola virus disease and in animal models for treatment of MERS and SARS (Gilead Sciences, Foster City, California).[2,7]

POSSIBLE ANTIVIRAL THERAPY

Remdesivir is an investigational antiviral with a broad spectrum of in vitro activity against RNA viruses *Filoviridae*, *Paramyxoviridae*, *Pneumovirinae*, and *Orthocoronavirinae* and is not approved by the US Food and Drug Administration (FDA) to treat or prevent any diseases, including COVID-19. However, remdesivir has an FDA emergency use authorization (EUA) for intravenous use in persons hospitalized with severe COVID-19 defined as an Spo_2 of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Current EUA guidelines report there is insufficient evidence to support or discourage use in persons with mild or moderate COVID-19. Remdesivir can be obtained at this time through the Expanded Access or Compassionate Use program for the treatment of COVID-19.[8,9]

Healthcare providers must comply with the EUA requirements. Providers may be contacted and asked to provide information to help with the assessment of the

Table. RNA Viruses[3–5]

Virus Family	Disease Expression
Paramyxoviridae	Measles
	Mumps
	Respiratory syncytial virus
	Parainfluenza viruses: respiratory illness in children, croup, pneumonia
	Nipah virus: brain lesions, encephalitis
	Hendra: meningitis or encephalitis
Pneumovirinae	Serious virus disease in human infants
	Respiratory infection adults
Filoviridae	Ebola and Marburg virus
	Severe hemorrhagic fever in humans and nonhuman primates
Orthocoronavirinae	Subfamily of coronaviruses that are closely related
	Severe acute respiratory syndrome
	Middle East respiratory syndrome
	SARS-CoV-2 (COVID-19)

This is a summary table; not all family members are included.

use of the product during this emergency. The EUA for remdesivir will end when the FDA determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed. Adverse event reports should be submitted to FDA MedWatch online at www.fda.gov/medwatch/report.htm.[9,10]

Remdesivir is an adenosine nucleotide prodrug. Once into cells, remdesivir is metabolized to form active nucleoside triphosphate metabolite in multiple cell types and acts as an analog of adenosine triphosphate. This metabolite competes with natural adenosine triphosphate substrate to integrate into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase. This results in delayed chain termination during replication of the viral RNA. Pharmacokinetic differences based on sex, race, and age have not been evaluated. Outcomes regarding use in pregnant and breastfeeding women and children are unknown. Remdesivir use during pregnancy should only occur if the possible benefits outweigh the risks. Furthermore, the presence of remdesivir in human milk and its effects on the breastfed infant and milk production are also unknown. Finally, the pharmacokinetics of remdesivir in pediatric patients has not yet been evaluated. Pharmacokinetic modeling of data from healthy adults was used to formulate current suggested pediatric dosing.[9]

The optimal duration of treatment with remdesivir is unknown. For patients receiving mechanical ventilation or ECMO, the current recommended duration of therapy is 10 days. For patients not requiring mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days, which can be extended for up to 5 days, for a total of 10 days. Administer remdesivir via intravenous infusion for 30 to 120 minutes.[9] For information on clinical trials that are testing the use of remdesivir in COVID-19, please see www.clinicaltrials.gov.

Hypersensitivity and anaphylactic reactions have been observed during and after administration of remdesivir. Signs and symptoms can include hypotension, arrhythmia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Limited evidence suggests that these signs and symptoms could be reduced with slower infusion rates (a maximum infusion time of 120 minutes). If signs and symptoms are significant, stop the infusion and begin treatment.[9]

Patients should have hepatic testing before receiving remdesivir and every day while on therapy. Discontinue remdesivir in patients who develop an alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal during treatment or when ALT elevation is accompanied by signs or symptoms of liver inflammation, increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio. Remdesivir may be restarted when ALT is less than 5 times the upper limit of normal.[8,9] Healthcare providers must submit a report on all medication errors and all serious adverse events related to the administration of remdesivir. Limited evidence suggests that there is a risk of reduced antiviral action of remdesivir with concomitant chloroquine or hydroxychloroquine therapy and is not recommended.[9]

Every patient or parent/caregiver should be provided drug information consistent with the "Fact Sheet for Patients and Parents/Caregivers."[9] Essential elements provided include the following: (1) The FDA has authorized the emergency use of remdesivir, which is not an FDA-approved drug; (2) the patient or parent/caregiver can accept or refuse remdesivir; (3) known and potential risks and benefits of remdesivir are unknown; and (4) available alternative treatments that include the risks and benefits of those alternatives.[9] Additional information on other COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html (accessed July 26, 2020). If providing this information would delay the administration of remdesivir that endangers the life of the patient, this information must be provided to the patients as soon as is practical after remdesivir is administered.[9,11]

EMERGING EVIDENCE

Remdesivir was tested in a double-blind, randomized, placebo-controlled trial of 1063 hospitalized adult patients with COVID-19 and evidence of lower respiratory tract involvement. The primary trial outcome was time to recovery. Preliminary analysis revealed that those who

received remdesivir had a median recovery time of 11 days (95% confidence interval, 9-12) compared with 15 days (95% confidence interval, 13-19) for those who received placebo. For the 541 patients who received remdesivir, 114 serious adverse events were reported compared with the placebo group (n = 522), of which 141 experienced serious adverse events. In this early trial, remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection (study funded by the National Institute of Allergy and Infectious Diseases and others; ACCT-1 ClinicalTrials.gov number: NCT04280705).[12]

In a randomized, open-label, phase 3 trial of hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less on room air and radiological evidence of pneumonia were found. Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 or 10 days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale. For this trial of patients with severe COVID-19 not receiving mechanical ventilation, there were no significant differences between 5- or 10-day courses of remdesivir. Significance of results cannot be evaluated because there was no placebo control (funded by Gilead Sciences; GS-US-540-5773, ClinicalTrials.gov number: NCT04292899).[13]

ONE EMERGING CONCERN

An emerging concern is a possible interaction of remdesivir with P-glycoprotein inhibitors resulting in hepatotoxicity due to inhibition of remdesivir elimination from hepatocytes.[14] P-glycoprotein is an efflux transporter found in the abdomen that can significantly modify therapeutic concentrations of many drugs, and many drug doses are factored to account for this transporter activity. Inhibition of P-glycoprotein results in higher concentrations of drug effluxed into the gut by the transporter, resulting in higher blood concentrations. A P-glycoprotein inducer increases the activity of the transporter pumping more drug into the gut and away from circulation and lower blood concentrations. Many drugs that affect P-glycoprotein also impact CYP3A4. Common P-glycoprotein inhibitors include amiodarone, carvedilol, macrolides, some azole antifungals, and verapamil (list not inclusive).[15,16]

Research on outpatient use of remdesivir has begun. This phase 1a study beginning in July 2020 will examine the safety and pharmacokinetics of inhaled remdesivir in healthy volunteers. On the basis of evidence that the upper respiratory tract is the most prevalent site for SARS-CoV-2, providing remdesivir directly to the infection site using a nebulized, inhaled solution may provide a targeted, effective, and accessible treatment for nonhospitalized patients. Additional trials are also planned to evaluate remdesivir in combination with anti-inflammatory medications.[17]

GOING FORWARD

As remdesivir becomes more available with further research, perhaps the populations that most benefit from remdesivir therapy can be identified. These early studies are important and a beginning to develop the most effective therapy for SARS-CoV-2 infections.[18]

The genetically diverse *Orthocoronavirinae* (CoV) family is prone to cross-species transmission with disease emergence in both humans and livestock. Viruses such as known epidemic strains circulating in wild and domestic animals increase the probability of further emergence in the future. Effective antiviral therapies are needed now to provide treatment options. Currently, available agents such as ribavirin, interferon, lopinavir/ritonavir, and corticosteroids currently seem not effective in improving outcomes compared with supportive care. The antiviral activity of remdesivir against CoV disease now and in the future may provide much needed treatment options if there is evidence of an acceptable safety profile.[19,20]

Emerging CoV will probably remain a constant global public health threat. Considering the variance in the CoV family expression and increasing human interactions with wild, domestic, and companion animals, the next CoV outbreak may be immune to vaccines and antivirals being developed now for SARS-CoV, MERS-CoV, and novel CoV (SARS-CoV-2). The battle may have just begun.[21]

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