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Review Article

A Review on Utilisation of Remdesivir in Treating Covid – 19: Therapeutic Repurposing and Unmet Clinical Needs

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ABSTRACT

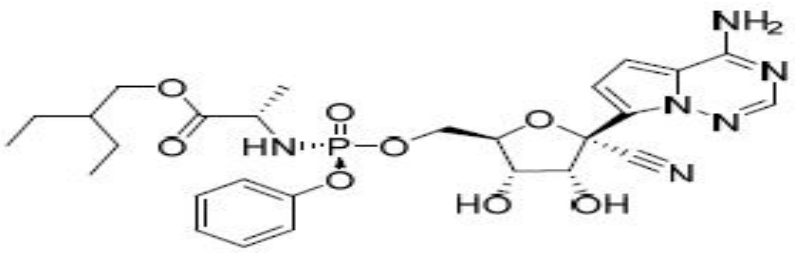
Remdesivir is the first drug that has been approved by the US Food and Drug Administration (FDA)for clinical use in hospitalized patients with COVID-19 illness. Remdesivir is a broad-spectrum antiviral agent that has previously demonstrated antiviral activity against filoviruses (Ebola viruses, Marburg virus), coronaviruses (SARS-CoV, MERS-Co-V, SARS-CoV-2), paramyxoviruses and Pnemoviridae . Remdesivir was initially developed against the Ebola virus based on its antiviralproperties demonstrated in vitro and in vivo in animal models but failed to demonstrate efficacy inrandomized clinical trials. Remdesivir was shown to exhibit antiviral activity against SARS-CoV-2 in vitro studies, and it was proposed as an investigational drug early during the pandemic. However, based on data from randomized clinical trials that demonstrated superior clinical efficacy of remdesivir to placebo, remdesivir is the first and only available therapeutic drug that has been approved by the US Food and Drug Administration (FDA) for clinical use in the management ofpatients with severe suspected or laboratory-confirmed COVID-19. COVID -19 is a disease caused by SARS-CoV-2 that can trigger what doctors call a respiratory tract infection. It can affect your upper respiratory tract (sinuses, nose, and throat) or lower respiratory tract (windpipe and lungs).It spreads the same way other coronaviruses do, mainly through person-to-person contact. Infections range from mild to deadly.

Keywords : Remedesivir, SARS-CoV-2, Food and drug administration (FDA), MERS-CoV-2, Clinical trials.

INTRODUCTION

Remdesivir (GS-5734) was developed by Gilead Sciences. Gilead, the US Centers for Disease Control and Prevention (CDC) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID) collaborated to discover drug candidates against RNA viruses with potential to induce a global pandemic (eg ; Ebola virus, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) coronaviruses). In order tofind suitable antiviral agents against the RNA viruses, a library of approximately 1000 modified nucleosides including monophosphate, ester and phosphoramidate prodrugs was compiled.Results of data screening showed that GS-441,524 (a 1′-CN modified adenosine C- nucleoside hit) along with GS-5734 (a prodrug form of the monophosphate of GS-441,524, later renamed as remdesivir) were highly potent antivirals.

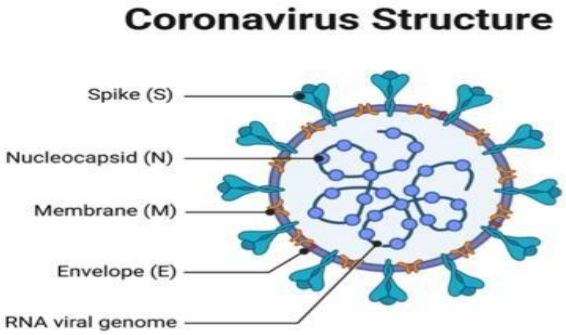
Remedesivir Structural Formula



In 2016, the first clinical experience of using remdesivir against Ebola virus in human was reported. In 2017, it was shown that remdisiver could prevent the replication of SARS and MERS coronaviruses and be effective against bat and circulating contemporary human coronaviruses in vitro. During February–March 2020, the first randomized, placebo- controlled trial of remdesivir in China showed no virological benefits or clinical effect in reducing the recovery time and deaths compared with the placebo group. Moreover, it caused several adverse effects leading to early termination of the trial . Other clinical trials of remdesivir are ongoing; preliminary data from an international multicenter, placebo- controlled double-blind randomized trial suggest that remdesivir is effective in reducing the recovery time from 15 to 11 days in hospitalized patients . On April 29, 2020, based on the Adaptive COVID-19 Treatment Trial, the National Institute of Allergy and Infectious Diseases in the United States announced that remdesivir was better than placebo in reducing recovery time in hospitalized patients with advanced COVID-19 and lung involvement . Currently, remdesivir is being tested as a specific treatment for COVID-19 and has been authorized for emergency use in people with severe symptoms in the United States .

Corona Virus

Coronaviruses are large, enveloped, positive-stranded RNA viruses responsible for infecting a wide variety of mammalian and avian species .These viruses contain spike-like projections of glycoproteins on their surface, which appear like a crown under the electron microscope; hence, they are referred to as coronaviruses. The coronavirus genome encodes several structural and nonstructural proteins. The structural proteins are responsible for host infection membrane fusion , viral assembly , morphogenesis, and release of virus particles , among other functions, and the nonstructural proteins (nsps) facilitate viral replication and transcription .The membrane (M), the envelope (E), and the spike protein (S) make up the structural proteins and are associated with the envelope. Among these structural proteins, the trimeric S proteins protrude from the virus envelope and are the key machinery that facilitates virus entry into the host cell.



Therapeutic Repurposing Drugs

Before effective antiviral drugs for COVID-19 are available, current treatment options will come from repurposing drugs. Thus, in this review we aim to highlight potential therapeutic strategies from the viewpoints of clinicians based on updated clinical evidences, and provide a basis for future researches of effective antiviral therapies. In the future, the development of new drugs and vaccines relies on multidisciplinary cooperation among structural biologists, chemists, and medical doctors. A knowledge gap of pharmacotherapy for COVID-19 is expected to be filled up, if updated information can be shared among global research institutes .

Favipiravir

Favipiravir, an RNA polymerase inhibitor, is a prodrug of a purine nucleotide that inhibits viral replication and it demonstrated activity against SARSCoV-2 with a high EC_{50} of 61.88 μM/L . Various dosing regimens have been proposed based on the type of infection indication ; a loading dose of 2,400–3,000 mg every 12 h (two doses) has been considered for the treatment of COVID-19, followed by a maintenance dose of 1,200–1800 mg every 12 h . Favipiravir demonstrates a tolerable safety profile in terms of total and serious adverse effects compared with other drugs used for short-term treatment.

Ribavirin And Interferon

Ribavirin, a guanosine analog which has distinct antiviral mechanisms, including both indirect (inosine monophosphate dehydrogenase

inhibition and immunomodulatory effects) and direct mechanisms (interference with RNA capping, polymerase inhibition). In vitro efficacy of ribavirin against SARS-CoV-2 viral strain WIV04 has been reported.

Lopinavir /Ritonavir

Lopinavir, an inhibitor of aspartate protease of human immunodeficiency virus (HIV), has been used in the treatment of HIV infection for a long time. Ritonavir can increase the concentration of lopinavir by inhibiting cytochrome P450. Lopinavir inhibits the action of protease $3CL^{pro}$ in HIV through C2-symmetric pocket, which is absent in coronavirus . Therefore, the inhibitory effect of lopinavir on SARS-CoV-2 is uncertain. LPVr cannot be considered beneficial for patients with COVID-19 in terms of primary outcome .

Chloroquine And Hydroxychloroquine

Chloroquine has been used clinically for more than 70 years. It is an approved anti-malarial drug; it is also used for autoimmune diseases. In vitro studies showed that chloroquine was highly effective in controlling SARS-CoV-2 infection of host cells at the entry and post-entry stages . The antiviral mechanisms of chloroquine are multifaceted. It can prevent nanoparticle uptake by macrophages via inhibiting the expression of phosphatidylinositol-binding clathrin assembly protein and subsequent clathrin-mediated endocytosis. In addition, chloroquine can prevent acidification of lysosomes, thereby inhibiting their fusion with endocytic vesicles .

Interleukin 6- Inhibitors

Some patients with COVID-19 develop considerable inflammation associated with multiorgan failure requiring intensive care, and their severity and mortality of COVID-19 is associated with high levels of serum cytokines. Of note, high levels of pro-inflammatory cytokine and IL-6 were noted in severe COVID-19 patients.

Convalescent Plasma

Passive antibody administration for infectious diseases was introduced in the 1890s and has been largely replaced by antimicrobial agents in the 20th century . CP became a treatment option for severe viral diseases such as SARS, Middle East respiratory syndrome, influenza A H1N1/2009, and Ebola virus disease with variable results, because no specific treatment was available for these diseases.

Traditiona Chinese Medicine

In the early outbreak in China, no drugs approved for the treatment of COVID-19 were limited. Therefore, the China official guideline suggested traditional Chinese medicine (TCM) in combination with antiviral drugs for COVID-19 patients .Qingfei Paidu Decoction (QPD) has been strongly recommended for confirmed cases in different categories in the official guidelines based on the practical clinical experiences by the China official guideline. QPD comprises 21 traditional Chinese medicines, which are expected to have protective effects for different organs, in addition to lung.

Vaccines

In addition to antiviral agents, the global use of COVID-19 vaccine is a promising strategy to end the current pandemic. Dozens of COVID-19 vaccines designed by different organizations are at different phases of clinical trials. Saha et al. summarized a total of 146 COVID-19 vaccines, including live-attenuated vaccine, inactivated or killed vaccine, subunit vaccine,and nucleic acid-based vaccine, engaged in clinical trials , and the number of candidates will be increasing in the future. With the aid of immunoinformatics, scientists could select suitable peptide sequences which are potential B- or T-cell epitopes for the generation of epitopic vaccines against SARS-CoV-2 . Another example is the peptide vaccine against spike glycoprotein with molecular docking on toll-like receptor-5 (TLR5), which can evoke early innate immune response against COVID-19 . However, the efficacy of these candidate vaccines remains to be verified.

Clinical Trials

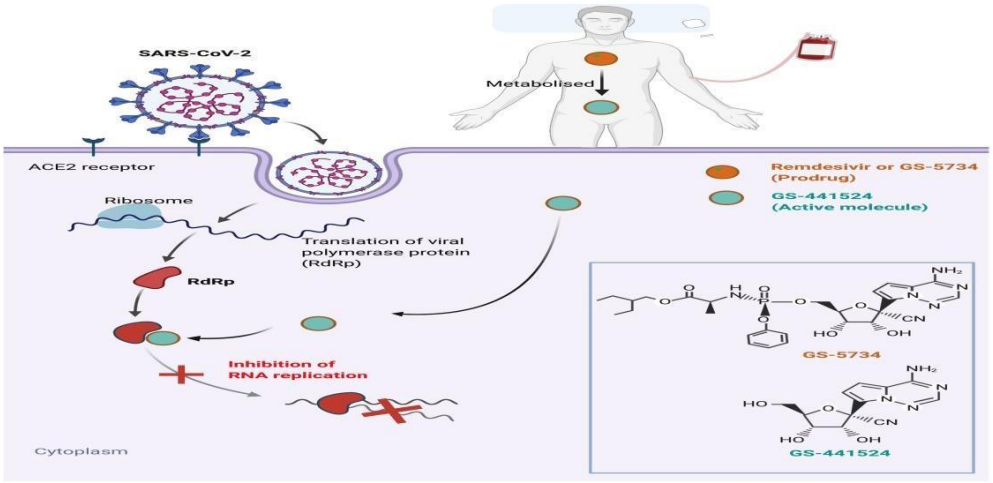
Several clinical trials of intravenous remdesivir to treat COVID-19 are ongoing.34 A double-blinded, placebo-controlled trial (ClinicalTrials.gov identifier: NCT04280705) is underway in the USA in which patients are randomly divided into two placebo and remdesivir groups. In the remdesivir group, patients receive 200 mg of parenteral remdesivir as an initial dose onthe first day, and a maintenance dose of the drug (100 mg once-daily) while hospitalized for up to 10 days.35 The primary outcome of the trial is time to recovery. Day of recovery is the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1) hospitalized, not needing supplemental oxygen – no longer needs ongoing medical care; 2) not hospitalized, limitation on activities and/or needing home oxygen; and 3) not hospitalized, no limitations on activities. The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The US National Library of

Medicine clinical trials registry described the seven category scale as follows: death, hospitalized/on invasive mechanical ventilation or ECMO, hospitalized/on noninvasive ventilation or high- flow oxygen devices, hospitalized/necessitating supplemental oxygen, hospitalized/not needing supplemental oxygen, not hospitalized/limited activity, not hospitalized/no limitations.

Mechanism Of Action

- Remdesivir (GS-5734) is a phosphoramidite prodrug of a monophosphate nucleoside analog (GS-441524) and acts as a viral RNA-dependent RNA polymerase(RdRp) inhibitor, targeting the viral genome replication process . Remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside . By entrance into respiratory epithelial cells in the human body, the prodrug may be efficiently metabolized to a nucleoside triphosphate as an active form.
- Theoretically, nucleoside analogs do not permeate through the cell wall easily. Upon their subsequent entry into the host cell, they require phosphorylation to produce nucleoside triphosphate (NTP), which resembles adenosine triphosphate (ATP) and can be used by the RdRp enzymes or complexes for genome replication.
- Once remdesivir is metabolized by the host cells into its pharmacologic active analog adenosine triphosphate (GS-443902), it competes with ATP for integration by the RdRp complex into the nascent RNA strand and, upon subsequent incorporation of a few more nucleotides, results in termination of RNA synthesis limiting viral replication.

Remedesivir And Its Antiviral Activity Against Covid-19



- Remdesivir demonstrated potent antiviral activity against SARS-CoV-2 in vitro in primary human airway epithelial cultures and human lung cells. Remdesivir also had a dose-dependent inhibitory effect on SARS-CoV-2 replication with a half-maximal effective concentration (EC50).

Indications

REMEDESIVIR(Veklury) is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. Remedesivir should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

Formulation And Dosing

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized solid that is to be reconstituted with 19 mL of sterile water for injection and diluted into 0.9% saline prior to IV administration. Remdesivir for injection, 100 mg, vials should be stored below 30 °C until time of use. Remdesivir injection, 5 mg/mL vials should be stored at refrigerated temperatures (2 °C–8 °C) until time of use. Following dilution with 0.9% saline, the solution can be stored for up to 4 h at room temperature (20 °C–25 °C) or 24 h at refrigeratedtemperatures (2 °C–8 °C).

Remedesivir (Brand Name –Veklury) For Injection

100 mg (NDC 61958-2901-2), is supplied as a single-dose vial containing a sterile, preservative-

free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion. Discard unused portion. The container closure is not made with natural rubber latex.

Administration

The current recommended dose of remdesivir for adults and pediatric patients hospitalized with suspected or laboratory-confirmed COVID-19 infection is weight-based, and administration is via theIV route.

Adults and pediatric patients(12 years of age or older) and weighing at least 40 kgand higher
200 mg IV as a loading dose on day 1, followed by a maintenance dose of100 mg IV daily for up to 9 additional days based on the severity of the illness and clinical response to the treatment.

Remedesivir For the Treatment Of Hospitalised Patients WithSevere Covid-19 Instructions

Patient	Key Patient Factors	Loading Dose	Maintenance Dose	Clinical Considerations
Adult and Pediatric Patients > 40 kg	Mechanical ventilation and/or ECMO	200 mg IV on day 1	100 mg IV for 9 days	
	No mechanical ventilation or ECMO	200 mg IV on day 1	100 mg IV for 4 days	If no clinical improvement is seen, treatment can be extended for up to 5 additional days
Pediatric Patients 3.5 - 40 kg	Mechanical ventilation and/or ECMO	5 mg/kg IV on day 1	2.5 mg/kg IV for 9 days	Use Remdesivir for injection lyophilized powder ONLY
	No mechanical ventilation or ECMO	5 mg/kg IV on day 1	2.5 mg/kg IV for 4 days	Use remdesivir for injection lyophilized powder ONLY If no clinical improvement is seen, treatment can be extended for up to 5 additional days

Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of remedesivir injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer remedesivir via intravenous infusion over 30 to 120 minutes.

Pharmacodynamics

Remdesivir and metabolites exposure-response relationships and the time course of pharmacodynamics response are unknown.

Pharmacokinetics

The current knowledge of remdesivir in special populations such as renal or hepatic impairment is very limited with discrete reports of remdesivir PK in COVID-19 patients with renal dysfunction. In silico simulation of remdesivir pharmacokinetics suggests that age, weight, liver, and renal function status can influence its disposition since remdesivir and its active metabolite are excreted through urine , it necessitates the dose evaluation data on patients with renal impairment. The plasma concentration of remdesivir is increased in patients with chronic kidney disease. The key PK parameters of parent remdesivir such as $AUC_{0\text{-}infinity}$, Cmax, clearance, and volume distribution differ by 2.5-fold to 4-fold between healthy volunteers and renally impaired patients The FDA has outlined that remdesivir should not be given to patients with eGFR less than 30 mL/min.

Toxicity

There is a lack of robust clinical trial data describing the toxicity associated with remdesivir.

Drug Interactions

Due to potential antagonism based on data from cell culture experiments, concomitant use of REMEDESIVIR with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

Adverse Effects

Considering that remdesivir is currently considered an investigational drug, its safety profile has not yet been fully characterized.

- **Cardiovascular**: Hypotension, arrhythmias, and cardiac arrest
- **Pulmonary**: Dyspnea,
- **Hematological**: Anemia, lymphopenia
- **Endocrine**: Hyperglycemia
- **Infectious**: Pneumonia, septic shock
- **Gastrointestinal**: elevated lipase, nausea, vomiting, diarrhea, constipation, poor appetite, gastroparesis, and lower GI bleeding
- **Hepatic**: Hepatic manifestation characterized by Grade 1-4 increase in serum transaminases (ALT and/or AST) are the most common adverse effects seen in patients

treated with remdesivir. Other abnormalities include hyperbilirubinemia

- **Renal and Metabolic**: Acute kidney injury or worsening of underlying chronic kidney disease, hypernatremia, hypokalemia
- **Neurological**: Headache, lightheadedness
- **Skin**: Rash, contact dermatitis, pruritus
- **Psychiatric**: Delirium
- **Other adverse effects**: Pyrexia, insomnia,multi-organ dysfunction, DVT, and hypersensitivity/anaphylactic reactions related to the infusion.

Overdose

There is no human experience of acute overdosage with remedesivir.Treatment of overdose with remedesivir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remedesivir.

Contraindications

Remedesivir is contraindicated in patients with a history of clinically significant hypersensitivity reactions to remedesivir or any components of the product .

Based on the guidance from the documentation published by the European Medicines Agency (EMA, 2020) and U.S FDA issued EUA, remdesivir is contraindicated in the following clinical situations unless the potential benefit of the use of remdesivir outweighs the potential risks:

- Patients with alanine aminotransferase (ALT) levels >5-times upper limit of normal or severe hepatic dysfunction
- Adult and pediatric patients (>28 days old) with severe renal impairment described as eGFR < 30 ml/min
- Neonates (at least 7 days to ≤ 28 days old) with serum creatinine ≥1 mg/Dl.

Monitoring

Due to limited clinical experience with remdesivir, robust clinical data evaluating the adverse drug reactions and possible drug-drug interactions is limited. Considering that remdesivir is metabolized by cytochrome P450 (CYP450) there is definitely a potential for drug-drug interaction.RDV is extensively metabolized in the liver by carboxylesterase 1 and primarily eliminated in urine as the nucleoside metabolite GS-441524 based on results of human mass balance studies.

Published data evaluating the safety of remdesivir in pediatric patients (<12 years of age) and pregnant or breastfeeding women is limited. Compassionate use of remdesivir was well tolerated and demonstrated the highest rates of recovery and shortest median time to recovery in pregnant women and postpartum women with severe COVID-19.

Enhancing Healthcare Outcomes

Although remdesivir has been approved by the FDA, there is limited published data regarding its adverse effects and its interaction with other drugs. Hence its clinical use in patients hospitalized with COVID-19 illness requires an interprofessional team that includes physicians across specialties, nurses, and pharmacists who should be aware of the mechanism of action reported, potential side effects, drug-drug interactions, and recommended doses. The patient should receive the fact sheet issued by the US FDA before they receive the drug. There should be close communication between the ordering physician, the pharmacist, and the nurse. Such a holistic approach would lead to the early identification of potential side effects and drug-drug interactions associated with this drug.

Clinical Context

Remdesivir was the first antiviral therapy to demonstrate significant clinical benefit for COVID-19 in the context of a RCT. On 26 May 2020 the UK Medicines and Healthcare products Regulatory Agency (MHRA) gave a positive scientific opinion for use of remdesivir in severe COVID-19 disease requiring supplemental oxygen, leading to its availability via the Early Access to Medicine scheme (EAMS). Remdesivir (marketed as Veklury) received a conditional marketing authorisation for use in the EU from the European Medicines Agency on 3 July 2020. This authorisation also applies in the UK during the post-Brexit transition period to December 2020, with an interim clinical commissioning policy in place to define routine access to remdesivir which replaces the EAMS (Box (Box1).1). Secondary criteria are included to be used should there be limitations in the supply of remdesivir in the UK.

DISCUSSION

Remdesivir is an anti-viral agent that has shown a significant inhibitory effect in vitro and in vivo studies against SARS-CoV-2 and appears to be ahead to other repurposed drug being tried for the treatment of COVID-19. In this regard, FDA has currently authorized remdesivir only in severe COVID-19 in both adults and children.

CONCLUSION

Repurposing or repositioning available therapeutics is the fastest way to manage a pandemic situation. In vitro and in vivo studies

have demonstrated the efficacy of remdesivir against coronaviruses. Moreover, in the current pandemic, some evidence indicates that compassionate use of remdesivir may cause some clinical improvement in patients with COVID-19. Remdesivir appears to have optimal safety profile although its efficacy in the treatment of COVID-19 appears to have a mixed outcome at the moment. Jury is still out and future trials should further enlighten its cost-effectiveness, in particular when the results of head-to-head trial with other low-cost repurposed drugs is available.

CONFLICT OF INTEREST

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

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