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Review on Remedesivir: FDA Approved Drug for treatment of COVID- 19

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ABSTRACT :
Remdesivir, a nucleotide analogue prodrug and antiviral medication, with broad-spectrum efficacy against viruses belonging to several families (Veklury®; Gilead Sciences). Having shown in preclinical studies significant antiviral efficacy against coronaviruses,
During the present worldwide pandemic, remdesivir has become a candidate medicine for the treatment of the novel coronavirus illness 2019 (COVID-19), which is brought on by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Early in 2020, remdesivir's COVID-19 phase III evaluation got underway, and so far, the results seem encouraging. Taiwan provisionally approved the use of remdesivir in late May 2020 for individuals with severe COVID-19. A quick series of conditional licences in numerous nations/regions, including the EU and Canada, followed this. These conditional licences were preceded by an emergency usage authorization.
Keywords: Remdesivir, COVID-19, SARS-CoV-2, RNA dependent RNA polymerase, FDA Approved Drug.

I. INTRODUCTION:

Remdesivir (Veklury®; Gilead Sciences), an antiviral medication with broad-spectrum activity against viruses from various families, is a prodrug of an adenosine nucleotide analogue. Previously, Remdesivir was being developed for the treatment of Ebola virus disease in the wake of the West African Ebola outbreak from 2014 to 2016. Remdesivir, albeit a promising therapeutic treatment for Ebola virus disease in preclinical investigations , was outperformed by monoclonal antibodies in a phase III clinical trial , and it is no longer being investigated for this use. (1)

However, remdesivir's antiviral effectiveness against coronaviruses has made the medication extremely valuable during the present pandemic around the world. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that led to the new coronavirus disease 2019 (COVID-19),(1)

Remdesivir was granted an emergency use licence on May 1 in the USA and an emergency use special approval on May 7 in Japan .Remdesivir In late May 2020, Taiwan granted its first conditional permission for the drug's use in patients with severe COVID-19, with the caveat that the pharmaceutical company first execute a risk management plan to assure patient safety .(1)

Remdesivir received conditional approval in a number of other nations and regions in the world in June and July 2020, including the EU , Singapore ,Australia , South Korea and Canada . Remdesivir, the first COVID-19 drug to be approved in the EU and Canada , is indicated for the treatment of COVID-19 in adults and adolescents (aged 12).(1)

Remdesivir's safety and effectiveness are still being studied in ongoing clinical trials, particularly those involving paediatric patients and combinations with anti-inflammatory drugs.Clinical trials and initiatives for compassionate use. A phase I study for an inhalation remde- sivir solution for the potential outpatient treatment of COVID-19 was announced in July 2020.(5)

All people are susceptible to infection with the highly contagious corona virus due to the global pandemic that started in December 2019 and its epidemic corona virus sickness. The first signs of new coronavirus illness in 2019 (COVID-19) are most frequently seen are diarrhoea, myalgia, anorexia, weariness, cough, and fever.Dyspnea is the most prevalent sign of a serious illness and frequently occurs along with hypoxemia. COVID-19, an acute respiratory infectious disease that is on the rise, spreads through the respiratory system through droplets, respiratory secretions, and direct contact. The SARS-COV-2 is an enveloped, non-segmented, positive sense RNA virus belonging to the subgenus sarbecovirus and family Orthocoronavirinae.Angiotensin converting

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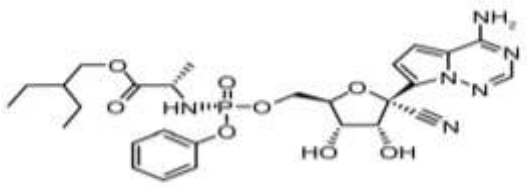
receptor 2 (ACE2) is the route by which the virus enters cells.(2)

The US Food and Drug Administration approved the investigational antiviral medication remdesivir (produced by Gilead science) for patients with severe COVID-19 who were hospitalised in May 2020.An adenosine is Remdesivir (GS-5734).triphosphate analogue was originally mentioned as a potential therapy for the Ebola virus in 2016.Its broad range action against members of the coronavirus family of viruses was also proven in 2017 .Remdesivir is additionally being studied as a possible treatment for SARS-COV-2, the corona virus that causes COVID-19.Several clinical studies using remdesivir as a COVID-19 treatment have been recorded at ClinicalTrial.gov.The majority of patients in a limited, uncontrolled, single-group clinical trial research exhibited a therapeutic benefit. Hospitalised participants in a randomised, placebo-controlled experiment demonstrated faster(2)



Chemical structure of remdesivir

Mechanism of action :

Adenosine analogue (GS-441524) monophosphoramidate prodrug Remdesivir (GS-5734). Remdesivir is metabolised into GS-441524, which is remdesivir's active form, after ingestion. (2)

Triphosphate RDV, or RDV-TP, is employed as a substrate by several viral RNA-dependent RNA polymerase (RdRp) complexes and inhibits RNA synthesis by a particular mechanism of delayed chain termination. It competes with ATP. Additionally, it prevents viralRdRp from acting on any of the three corona viruses (MERS-COV, SARS-COV, and SARS-COV-2).As a result, genome replication is stopped. (2)

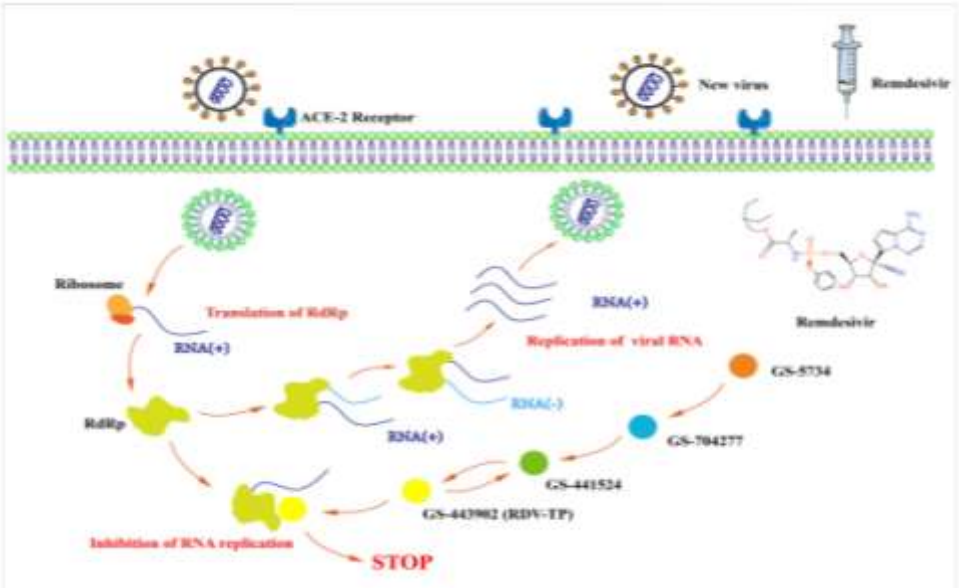


Figure 1: Probable molecular mechanism of remdesivir against SARS-COV-2. (A) Diagramatic representation shows the SARS-COV-2 viral entry and its RNA synthesis which can be blocked by Remdesivir. (B) Detail molecular mechanism of remdesivir to inhibit the synthesis of viral RNA.

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Remdesivir increased lung capacity and decreased viral load in the lungs. Thus aids in reducing lung pathology. Contrarily, therapeutic doses of lopinavir (LPV)/ritonavir (RTV)-interferon lowered viral loads only little and had no effect on other clinical indicators.
Although it did not slow down viral multiplication, LPV/RTV-IFN enhanced pulmonary function. This suggested that remdesivir has greater promise for treating MERS-COV infection than LPV/RTV-INF.(2)

Remdesivir Applications :

Summary of Antiviral Activity Against Different Viral Entities Gilead Sciences produced the drug Remdesivir (GS-5734). The US Centres for Disease Control and Prevention (CDC), the US Army Medical Research Institute of Infectious Diseases (USAMRIID), and Gilead worked together to identify drug candidates against RNA viruses that have the potential to cause a global pandemic, such as the Ebola virus, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS) coronaviruses.20–23 A library of about 1000 modified nucleosides, including monophosphate, ester, and phosphoramidate prodrugs, was created in an effort to find effective antiviral medicines to combat RNA viruses.21–23 GS-441,524 (a 1-CN modified adenosine C-nucleoside hit) and GS-5734 (a prodrug version of the monophosphate of GS-441,524, later renamed as remdesivir) were shown to be effective, according to data screening results.(3)
Remdesivir was administered randomly to 175 Ebola patients in a controlled, randomised clinical study for the disease that was carried out in the Democratic Republic of the Congo. Remdesivir wasn't a drug. effective treatment due to a significant mortality rate (53.1%).(3)

De Wit et al. conducted research on the preventative and curative effects of remdesivir against MERS in rhesus macaques (a nonhuman primate model) in 2020. Results demonstrated that the treated animals' viral loads in their lungs were lower than those of the controls.(3)

Sheahan et al. shown in 2020 that remdesivir and interferon-beta have higher antiviral effectiveness against MERS-CoV in vitro compared to lopinavir and ritonavir. In Remdesivir enhanced respiratory function in mice and reduced pulmonary virus loads and severe lung pathology when used either prophylactically or therapeutically. However, prophylactic lopinavir/ritonavir-interferon beta had no effect on the other disease-related parameters while only slightly reducing the viral loads. Although treatment did not lessen virus replication or severe lung pathology, therapeutic lopinavir/ritonavir-interferon beta improved pulmonary function.(3)

Clinical Efficacy of Remdesivir to Treat COVID-19 :

Information on the remdesivir's potential efficacy Animal models and in vitro research are the only forms of defence against coronaviruses, although knowledge about COVID-19 is expanding quickly.(3)

A COVID-19-infected 35-year-old man who had pneumonia in the USA in January 2020 was kindly treated with intravenous remdesivir. The patient was hospitalised for more than 12 days, intravenous remdesivir was administered for seven days, and on the eighth day, the patient's health appeared to have improved.Remde-sivir administration was observed to have no side effects.(3)

The first 12 COVID-19 patients in the USA were the subject of a preprint reporting new medical research; nevertheless, the authors noted that the study has not yet been evaluated and therefore should not be used as a benchmark for clinical practise.In the report, data on the subjects' clinical and demographic characteristics, the progression of their infections, and their clinical care were analysed. In the second week of the illness, 7 out of 12 patients (58%) with radiographic evidence of pneumonia and clinical or laboratory clues of deterioration were hospitalised. Experimental antiviral Remdesivir was administered to three hospitalised patients for a period of 4 to 10 days. Following the introduction of remdesivir, aminotransferase levels were raised in all patients, and transient gastrointestinal symptoms, such as nausea, vomiting, gastroparesis, or rectal haemorrhage, were noted. There were no post-remdesivir symptoms found.(3)

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S.N.	Adverse effect
1.	General major side effects: chills or shivering, sweating, dizziness upon standing up.
2.	Gastrointestinal symptoms: constipation, nausea, vomiting, diarrhea, poor appetite.
3.	Respiratory toxicity: respiratory failure or acute respiratory distress syndrome, pneumothorax.
4.	Cardiovascular toxicity: Hypotension, Atrial fibrillation, hypernatremia, cardiac arrest.
5.	Nephrotoxicity: Renal impairment, acute kidney injury, hematuria.

Table 1: Ref:(2) Anjali Shivaji Shilimkar ,REMDESIVIR FOR COVID-19: A REVIEW. WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES ,Volume 10, Issue 1, 340-349.

Dosage :

1. For adult patients weighing 40 kg or more, the suggested dose is 200 mg on day 1 and 100 mg on day 2.(2)

2. For paediatric patients weighing 3.5 kg to less than 40 kg, the suggested dose is 5 mg/kg on day 1 and 2.5 mg/kg once daily starting on day 2.(2)

Registration Number	Official Title	Status	Country	Estimated Study Completion Date
NCT04257656	A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with severe COVID-19	Terminated	China	April 10, 2020
NCT04365725	A multicenter, retrospective study of the effects of remdesivir in the treatment of severe COVID-19 infections	Recruiting	France	June 2020
NCT04302766	An intermediate-size patient population expanded access treatment protocol for coronavirus disease 2019 (COVID-19) using remdesivir (RDV; GS-5734™)	Available	–	–
NCT04252664	A phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with mild and moderate COVID-19	Suspended	China	April 27, 2020
NCT04323761	Expanded access treatment protocol: remdesivir (RDV; GS-5734) for the treatment of SARS-CoV-2 (CoV) infection	Available	–	–
NCT04410354	A phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of oral merimepodib in combination with intravenous remdesivir in adult patients with advanced coronavirus disease 2019 (COVID-19)	Recruiting	USA	August 2020
NCT04292730	A phase 3, randomized study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with severe COVID-19	Active, not recruiting	–	June 2020

Table 2 : Ref:(3) Seyed MohammadReza Hashemian 1,2 Tayebeh Farhadi2 Ali Akbar Velayati2 , A Review on Remdesivir: A Possible Promising Agent for the Treatment of COVID-19, Drug Design, Development and Therapy,2020:14 3215–3222

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Contra indications:
Remdesivir is contraindicated in people who have experienced an allergic reaction to any of its ingredients.(2)

II. CONCLUSION

Numerous medications have been developed since the WHO classified COVID-19 disease to be a pandemic. attempted as a cure. Remdesivir is one of the antiviral drugs that were tried during the EBOLA outbreak, however the Food and Drug Administration (FDA) of the USA rejected the drug since there wasn't enough convincing data to support it. Remdesivir was once again considered to be one of the most promising treatments for COVID-19 patients based on a few laboratory tests, reports from some compassionate use, and case studies. For a precise judgement, the safety and effectiveness of this medication in COVID-19 instances require high-quality evidence from clinical trials that are well powered, well-designed, and with the right sample size.

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