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Review Article

**A REVIEW: REMDESIVIR IS A HOPEFUL AGENT FOR
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Article Received: October 2020 **Accepted:** October 2020 **Published:** November 2020**Abstract:**

The pandemic COVID-19 (Coronavirus disease-19) is an extremely contagious respiratory illness due to novel coronavirus SARS CoV-2. The structure of coronavirus disease -19 has been homogeneous, coronavirus structure consisting of the four structural proteins named S (Spike), E (Envelope), M (Membrane) & N (Nucleocapsid). N protein holds the RNA genome virus & S, E, M protein create virus envelope together. For the time-consuming process to available drug remdesivir used to against covid -19. Different clinical trial of remdesivir effective on the Ebola virus has been demonstrated. Remdesivir may be effective therapy in vitro and animal models infected by SARS and MERS coronavirus. Remdesivir is a phosphoramidate pro drug of C-nucleoside. It can enter into the respiratory epithelial cells in humans, the prodrug metabolized to a nucleoside triphosphate as the active form. So much clinical trials were ongoing on COVID-19 in the health sector. In the treatment of COVID-19 with remdesivir is effective in the future along with another combination drug that may effect the treatment of Covid-19.

Key Words: Coronavirus-19, Remdesivir, COVID-19 Structure, Mode of Action of remdesivir, Clinical trials, Repurpose of Remdesivir, Future Perspective.

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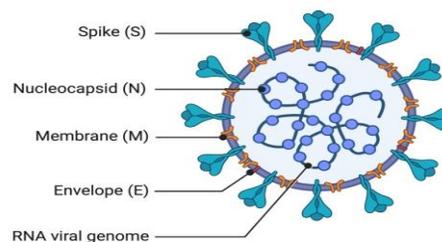
INTRODUCTION:

The novel coronavirus 2019(Covid-19), it names severe acute respiratory syndrome Coronavirus 2(SARS-CoV-2), is a novel human infectious coronavirus. Covid-19 is the disease by SARS CoV-2 that was first reported in Wuhan, China. ^[1] The covid-19 virus is commonly spread through saliva, droplets, and it affected by coughing or sneezing ^[2] The incubation period can range from two to fourteen days. ^[3] Within two to three months millions of people have been affected due to isolation, required lockdown, and quarantine. The effect of the Covid-19 pandemic has imposed the main challenges for worldwide well-being, economy, and society. ^[2, 4] Developing and manufacturing specific therapeutics and vaccines against COVID-19 is a time-consuming process. Administering conventional therapeutic along with other treatments such as inflammation control, oxygen therapy, and fluid management may be valuable to treat the clinical symptoms of the infections such as fever and difficulty in breathing ^[1] The SARS CoV-2 is a positive-sense single-stranded RNA β family corona virus that is similar to SARS corona virus. ^[5] Each virion is 50-200 nm in diameter and consists of four structural proteins named S(spike), E(envelope), M(membrane), and N(Nucleocapsid). The N-protein holds the RNA genome of the virus and S, E, and M proteins create the virus envelope together ^[6]

Corona Virus Structure:

The CoV family has a sizable homogeneous “spike protein”. The role of spike(s) protein, which is composed of 1300 amino acids, is to interact with the host cells, such as pulmonary and parabronchial epithelial cells, and assists the corona virus to enter through the membrane of the epithelial cells. ^[2,7] The alveolar epithelial cells have an expression of angiotensin-converting enzyme 2(ACE 2). The detection of ACE 2 by the S protein of the virus permits the invasion of the corona virus into the human circulation system ^[8] Single-stranded RNA (22-26 kilo bases) such as corona virus family reproduces the virus genomes by capitalizing on host cells. After corona virus comes near the ribosomes of epithelial cells or other host cells, it utilizes the ribosomes of host cells to replicate polyproteins. ^[2,9]

Coronavirus Structure



Remdesivir:

Remdesivir is investigational nucleoside analogues that act as competitive inhibitor of viral RNA dependent RNA polymerase (RdRP). ^[11] It is a pro drug with molecular formula C₂₇H₃₅N₆O₈P and an exact mass of 62.23Da. In the body, remdesivir is transformed into an active molecule known as pharmacological form with a molecular formula of C₁₂H₁₃N₅O₄(291.10)[10] The antiviral activities of remdesivir on RdRP have been reported against Ebola virus ^[12] The efficacy of remdesivir treatment was finally tested in rhesus macaque model of SARS-CoV-2 infection. ^[13] Animals became infected by with SARS-CoV-2(n=12) by combined intranasal, oral, ocular and intratracheal inoculation and were subsequently treated with intravenous placebo or remdesivir (10mg/kg loading dose followed by 5mg/kg daily) for 6 days starting at 12 h post infection ^[14] The safety and pharmacokinetics of remdesivir were assessed in single and multiple-dose phase intravenous infusions between 3 mg and 225 mg and were well tolerated without any evidence of kidney and liver toxicity. Remdesivir has shown direct pharmacokinetics within the dose range and an intracellular half-life of more than 35 h. Ensuring maximum dosage infusions, reversible aspartate aminotransferase and alanine transaminase elevation ensued ^[15]. The investigated dose of covid -19 treatments is 200mg intravenously (IV) for 1 day followed by 100 mg IV daily for up to 10 days, infused more than 30-60 min. The initial clinical use of remdesivir was conducted treat to Ebola.

Mechanism of Action:

Remdesivir is a phosphoramidate pro drug of an adenosine C- nucleoside ^[16]. Entry into the respiratory

epithelial cells in the human body, the pro drug may be efficiently metabolized to nucleoside triphosphate as an active form.^[17] The active form can prevent the replication of several corona viruses in lung epithelial cells. The nucleoside analogue drugs inhibit the RNA dependent RNA-polymerase by competing with usual

counterpart adenosine triphosphate(ATP) the nucleoside analogue is incorporated into generating RNA strand and cause a delay in the viral replication process.^[17,18] The drugs block the enzyme when it reaches up to the third position away from enzymes active site.

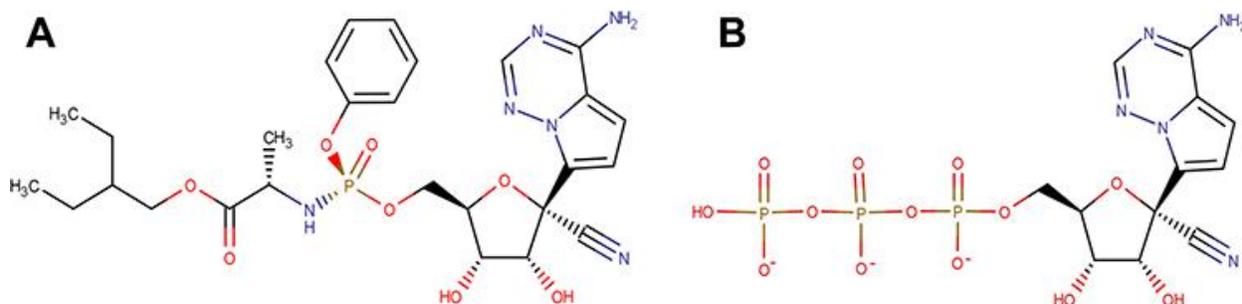


Fig.2 Chemical structure of (A) remdesivir as a phosphoramidate pro drug of an adenosine c –nucleoside and (B) pharmacologically active nucleoside triphosphate.

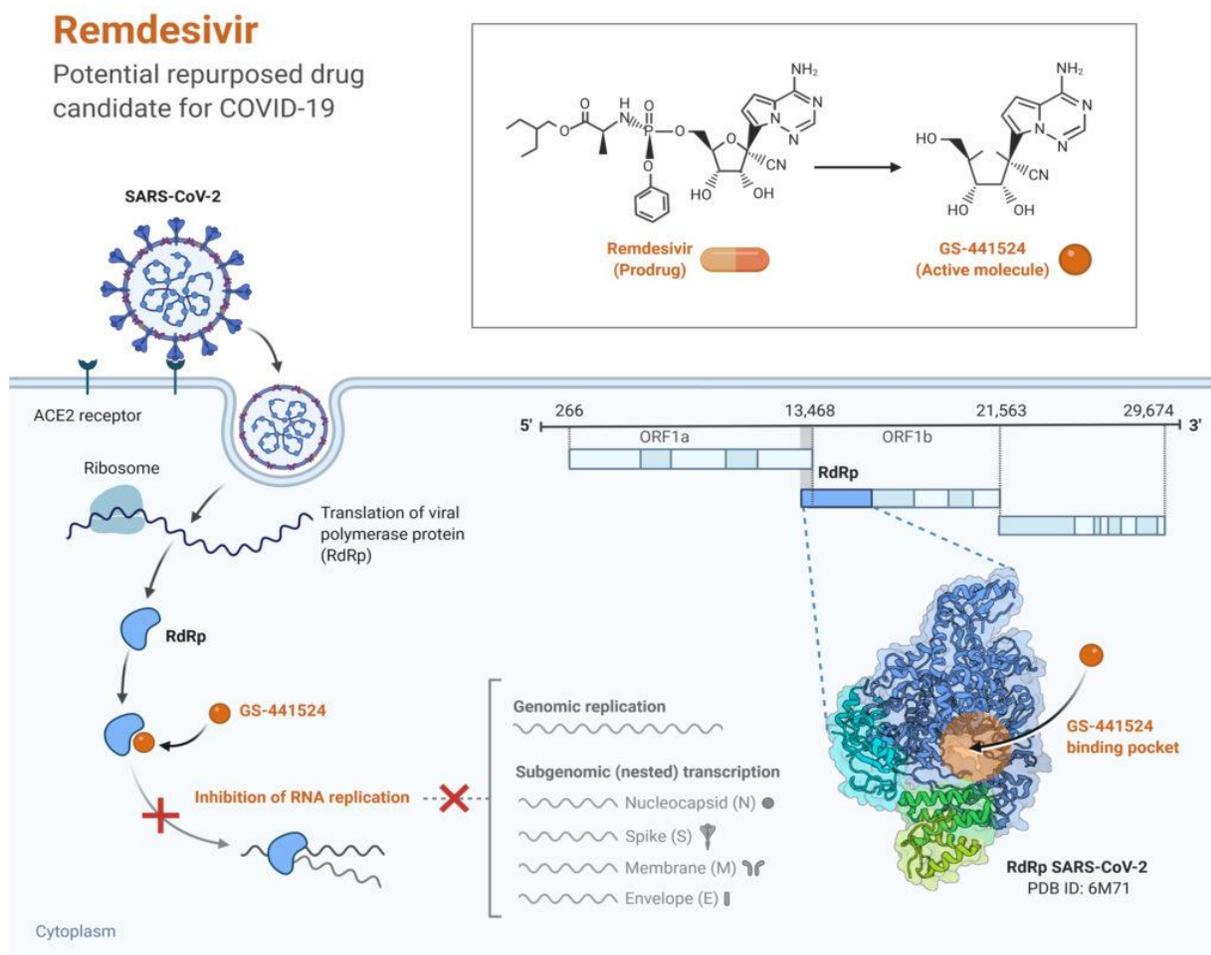


Fig.3 Mode of action of Remdesivir

Clinical Trials:

The US National library of medicine clinical trials registry described the seven-category scale is:

- i. Death
- ii. Hospitalized /on non-invasive ventilation or high flow oxygen device
- iii. Hospitalized/on invasive ventilation or ECMO
- iv. Hospitalized supplemental oxygen
- v. Hospitalized not needing supplemental oxygen
- vi. Not hospitalized
- vii. No limitations ^[19]

Table 1: Registered clinical trials to investigate the efficacy or safety of remdesivir for covid -19

Registration number	Title	Status	Country	Study completion date
NCT04257656	Phase 3, randomized, double-blind, placebo-controlled, multi-test study to evaluate the efficacy and safety of remdesivir in hospital older patients with severe covid -19	Terminated	China	April10,2020
NCT04365725	A multicenter, retrospective study of the effects of remdesivir in treatment of severe covid-19 infections	Recruiting	France	June 2020
NCT04302766	An intermediate-size patient population expanded access treatment protocol for covid-19 using remdesivir	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 for treatment of SARS cov-2 infection.	Available	–	–
NCT04410354	A phase 2, randomized, double-blind, placebo-controlled study of efficacy and safety of oral merimpodib in combination with intravenous remdesivir in adult patients with advanced covid-19	Recruiting	USA	August 2020
NCT04292730	A phase 3, randomized study to evaluate the safety and antiviral activity of remdesivir in participants with severe covid -19	Active, not recruiting	–	June 2020
NCT04409262	A phase 3, randomized double blind, multicenter study to evaluate the efficacy and safety of remdesivir plus tocilizumb compared with remdesivir plus placebo in hospitalized patients with severe covid-19 pneumonia.	Recruiting	–	July 31,2020
NCT04431453	A phase 2/3, single-arm, open label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir in participants from birth to <18 years age with covid-19.	Not yet recruiting	–	December 2020
NCT04330690	A multicenter ,adaptive, randomized , open label, controlled clinical trial of the safety and efficacy of investigational therapeutics for covid-19 in hospitalized patients in conjunction with the Public Health Emergency Solidarity trial (WHO)	Recruiting	Canada	May 18, 2022

Repurpose of Remdesivir:

On the basis of current knowledge about the use of remdesivir in SARS CoV 2 infection, remdesivir is considered as the potential drug candidate for repurposing against COVID-19. Remdesivir is a nucleoside analogue originally developed against Ebola viruses. [19] Remdesivir efficiently inhibited SARS CoV 2 infection in Human liver cancer Huh 7 cells. [11] In rhesus macaques, the drug showed therapeutic and prophylactic efficacy against both SARS and MERS corona viruses, indicating its potential against diverse corona virus including SARS CoV-2. [20]

Future Perspective:

After decades of research on direct-acting antiviral drugs, remdesivir is the first nucleoside analogue that can be used to treat infections caused by a respiratory virus. The drug is already available in the united state and Japan based on emergency use authorization and was recently approved in Europe. [21] The therapeutic efficacy of remdesivir might be improved by the addition of other antiviral or immunomodulatory agents. It has been recently shown at glucocorticoids are able to improve clinical outcomes in cases severe and critical COVID-19 [22] Another Approach that may improve clinical outcomes could be combination therapy with direct antiviral drugs that target several processes within the viral life cycle. Clinical trials are estimated to combination therapy are effective in the case of COVID-19.

CONCLUSION:

We conclude the remdesivir is might be a promising agent to be COVID-19. In clinical trial has developed the efficacy of remdesivir against COVID-19. Due to today's pandemic situation indications that remdesivir needs to be some clinical improvement for COVID-19.

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