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A COMPLETE OVERVIEW ON REMDESIVIR

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ABSTRACT

The 2019 coronavirus disease (COVID19) pandemic has turned into a global health crisis. Human coronaviruses (HCoVs) were discovered in the 1960s and originally believed to cause only mild upper respiratory tract disorders in immunocompetent hosts to inhibit the replication of a wide variety of human and animal coronaviruses in vitro and in preclinical studies. Remdesivir inhibits SARSCoV2 replication, reduces viral load and exerts protective effects in SARS-CoV2 infected animals. Remdesivir was used as a human drug to treat COVID19 patients. Remdesivir is one of the leading candidates used against COVID 19. Remdesivir (GS5734), a viral RNA-dependent RNA polymerase (RdRP) inhibitor that can be used to treat a wide variety of RNA viral infections, is expected to be an effective treatment for severe cases of acute respiratory coronavirus infection 2 (SARSCoV2) Syndrome. The aim of this review was to study the antiviral activities of remdesivir against SARSCoV2, the causative agent of COVID19. In this article, we provide an overview of Remdesivir's discovery, mechanism of action, and recent studies examining its clinical effectiveness

Keywords: *Remdesivir, SARSCoV2, COVID 19, Systematic Review, Coronavirus*

1. INTRODUCTION

In late 2019, a new HCV called SARSCoV2 appeared in China, causing a new disease called COVID19 (Coronavirus Disease 19)[1,2]. It turned out that SARSCoV2 spreads more efficiently than the coronaviruses SARS and MERS, which makes it extremely difficult to spread worldwide and have a devastating impact on global public health and the world economy[1]. Coronaviruses (CoVs) are members of the Coronaviridae family in the order Nidovirales and the genus *Betacoronavirus* or comprise a large number of enveloped single-stranded RNA viruses with a positive sense that cause a variety of diseases in animals and humans[1,3,4]. Due to their phylogenetic relationships and genomic structures, CoVs are divided into four genera: Alpha, Beta, Gamma and Delta Coronavirus; among these, Alpha and Beta CoVs infect only mammals[1,5,6]. The 2019 coronavirus disease (COVID19) pandemic, caused by the newly emerging severe acute respiratory syndrome coronavirus 2 (SARSCoV2), has become a global health crisis (WHO, 2020b)[7]. Viral respiratory infections are a leading cause of morbidity and mortality in humans worldwide[8].

Since the late 1960s, human coronaviruses have been known to be upper respiratory pathogens associated with conditions such as the common cold and respiratory tract[8]. Recently, three types of coronaviruses have been identified that are responsible for severe pneumonitis: SARS-CoV-2, the causative agent of severe acute respiratory syndrome (SARS), MERSCoV, the Middle East respiratory syndrome, and COVID19, which is caused by a virus called SARSCoV2[9]. Several therapeutic agents have been investigated for the treatment of COVID19, including remdesivir, favipiravir, lopinavir / ritonavir, darunavir / cobicistat, nafamostat mesylate, chloroquine / hydroxychloroquine, camostat, tocilizumab, eculizumab, colchicin, barbaropicitinibic, and navicopicitinibic; however, currently only remdesivir is approved by the US Food and Drug Administration for use in COVID19 patients who require hospitalization[10,11].

Numerous drugs are being studied to treat COVID19; Among them, Remdesivir was in the limelight and named the first approval from the US Food and Drug Administration (FDA) for dealing with COVID19 [7]. Remdesivir is an inhibitor of ribonucleic acid-dependent RNA polymerase (RNA) with in vitro inhibitory activity against the coronavirus, which was originally developed to treat Ebola[2,12]. Based on the results of the National Institute of Allergies and Infectious Diseases (NIAID) and SIMPLE studies, on May 1, 2020, the FDA approved the use of remdesivir in critically ill hospital patients with COVID19 as part of an emergency approval (USA)[2].

Remdesivir is a prodrug of the parent adenosine analogue GS441524[10,13]. Remdesivir was developed pharmacologically to efficiently deliver the nucleoside monophosphate analogue GS441524 into cells. Inside cells, the monophosphate GS441524 is rapidly converted into the pharmacologically active nucleoside triphosphate of the form GS443902.The main mechanism of inhibition is the incorporation of nucleoside triphosphate GS443902 into nascent RNA strands by viral RdRp, which causes a delay in RNA strand termination during the viral replication process[8]. In summary, Remdesivir is a prodrug and inhibits viral RNA polymerases when it is metabolized intracellularly to an ATP analogue.

It was found that remdesivir is a potent inhibitor of SARSCoV2 replication in human epithelial cells of the bronchi and the nasal airways. These results encouraged its use in patients with SARSCoV2 (COVID19) infection without effective treatment[14]. Remdesivir, an adenosine nucleotide analog that

inhibits the RNA-dependent RNA polymerase of SARSCoV2, was recently approved by the US Food and Drug Administration for the treatment of COVID19 in adult and pediatric patients (≥12 years of age) and populations are poorly known due to the small number of studies available, including studies prematurely terminated due to the lack of patients with COVID19[15].

Remdesivir (GS5374), a monophosphoramidate prodrug of an adenosine analog and a competitive inhibitor of viral RNA-dependent RNA polymerase (RdRP), administered as a "compassionate drug" according to the principle of compassionate drug use, although it did not meet the approval requirements[16]. Finally on October 22nd, 2020, Remdesivir became the first drug with FDA approval for the treatment of COVID19[7]. Nucleoside analogs are a group of drugs that inhibit reverse transcription and are among the most powerful antivirals available to combat SARSCoV2 infection; within that group is remdesivir[3].

The symptoms of COVID-19 include fatigue, fever, cough, lack of smell/taste, dyspnoea, and shortness of breath. Some humans may also broaden ARDS (acute breathing misery syndrome) because of cytokine release, septic shock, and blood clots. In the maximum excessive instances, SARS-CoV-2 infections can cause pneumonia, acute breathing syndrome, or even loss of life because of kidney and more than one organ failure[3,10,16,17]. Severe contamination with the COVID-19 virus in being pregnant gives specific control demanding situations for the obstetrician and vital care specialist. Special attention ought to be undertaken concerning oxygenation and breathing support, fluid control, use of corticosteroids and experimental therapeutics, anticoagulation, and fetal tracking, regularly with restrained evidence-primarily based totally recommendations[18]. Isolated instances of cardiac rhythm abnormalities had been stated in sufferers on Remdesivir, such as sinus bradycardia and QTc interval prolongation, warranting near cardiac rhythm tracking during Remdesivir administration[8].

2. DISCOVERY OF REMDESIVIR

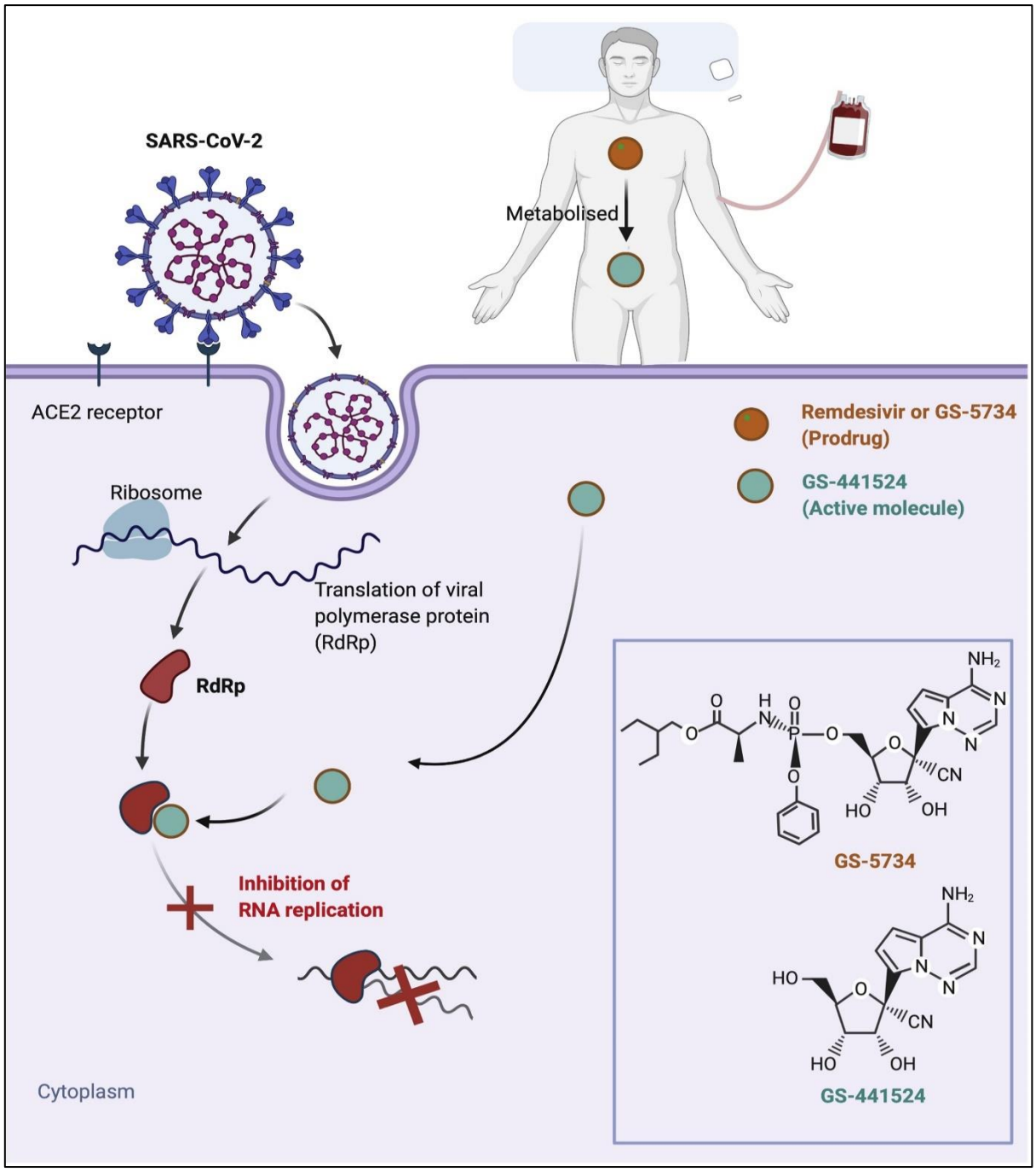
Remdesivir (GS-5734), an adenosine analogue prodrug developed by Gilead Sciences, emerged from a collaboration between Gilead Sciences, the U.S. Centres for Disease Control and Prevention (CDC) and therefore the U.S. Army Medical analysis Institute of Infectious Diseases (USAMRIID) within the conceive to determine broad spectrum small-molecule antiviral medicine effective against RNA viruses with world pandemic potential, as well as SARS and MERS coronaviruses and above all filovirus (EBOV), driven by the EBOV irruption in 2014 [1].

Remdesivir is a phosphoramidate prodrug of the C-adenosine analog GS-441524 which is metabolized in the cells to the alanine metabolite (GS704277) and then processed into the monophosphate derivative and finally the active nucleoside triphosphate derivative (NTP), which is a substrate for incorporation by RNA-dependent ones viral RNA polymerase, which leads to the inhibition of viral RNA synthesis [1,19-21].

3. REMDESIVIR IN THE TREATMENT OF COVID-19

Remdesivir was identified as a promising therapeutic candidate for COVID19 in early 2020 due to its ability to inhibit SARSCoV2 in vitro [1,22]. In a subsequent study, Pruijssers and others confirmed that remdesivir was able to replicate SARSCoV2 in human lung cells Calu3 (EC50 = 0.28 mM) and in primary cultures of human airway epithelium (EC50 ¼ 0.01 mM). This study showed lower efficacy of remdesivir in established human and monkey cell lines, due to its lower metabolic ability to activate the compound remdesivir metabolism shows different levels of expression of the bioactivation enzymes of the prodrug (CES1 / CTSA / HINT1) in different tissues, with low expression in type II pneumocytes in the lungs and high expression in the GI tract, liver, and kidneys, which is probably the different area of the EC50 values of the drug in vitro [1].

In this study, the animals treated with remdesivir showed no signs of respiratory disease, unlike the vehicle-treated macaques; In addition, they showed reduced pulmonary infiltrates and reduced virus titers in bronchoalveolar lavages 12 hours after the first dose, suggesting that remdesivir treatment started early during infection had clinical benefit in SARSCoV2-infected macaques [1,23]. Profile of remdesivir in the evaluation of the EBOV clinical trial, prompted the evaluation of remdesivir as a potential therapeutic drug for reuse against the SARSCoV2 pandemic [1,24]. The final study report was published on October 8 and showed that remdesivir helped placebo to reduce recovery time Adults hospitalized with COVID19 with evidence of lower respiratory infection [1,25]. On May 1, 2020, the Food and Drug Administration (FDA) made Remdesivir (trade name VEKLURY®) available under an Emergency Use Authorization (USA) for the treatment of adults and children with severe COVID19 disease in the USA [1].



Remdesivir (GS-5734):

Remdesivir is a pyrrolotriazine derivative based on tetrahydrofuran (MF: C27H35N6O8P; MW: 602.6; CAS number: 1809249373) developed by Gilead Sciences [17,26]. In May 2020, the US Food and Drug Administration (USFDA) approved an Emergency Use Authorization (EUA) for remdesivir, and the USFDA approved it in full on October 22, 2020 [17,27]. Remdesivir is indicated for the treatment of COVID19, d under certain conditions. First, it must be given in a healthcare facility or hospital that provides acute care similar to inpatient hospital care, as the intravenous (IV) infusion of remdesivir should be administered by a trained professional. The recommended dose of remdesivir in patients with COVID19 is a single intravenous infusion of remdesivir (200 mg) on day 1 followed by a maintenance dose (100 mg) from day 2 by intravenous infusion (30-120 min). The recommended duration of treatment is not less than 5 days and not more than 10 days [17]

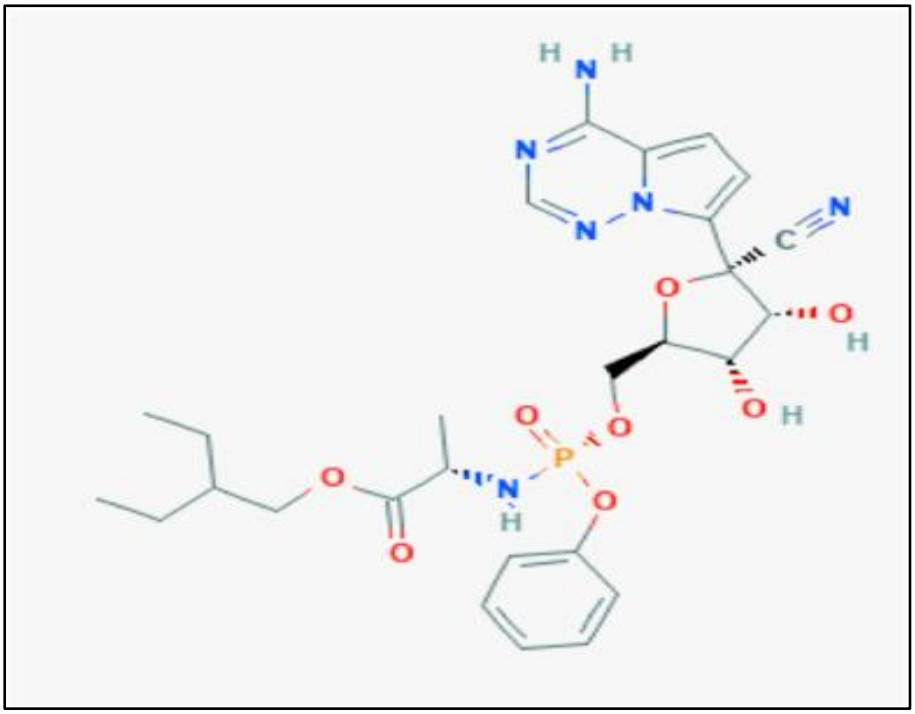


Fig: Structure of Remdesivir [1 M. Gabriella Santoro]

Pharmacokinetics of remdesivir:

RDV is a nucleoside analog prodrug that can be metabolized in cells to adenosine triphosphate analogs, which inhibit viral RNA polymerase. Remdesivir has a broad spectrum of activity against members of several virus families, including filoviruses (e.g., Ebola virus) and coronaviruses (e. SARS-CoV-2). and the Middle East respiratory syndrome coronavirus [MERSCoV]). It is essentially a modified version of the natural component of adenosine, which is essential for DNA and RNA. The active form of RDV contains three phosphate groups; This form is recognized by the virus' RNA polymerase enzyme. Once RDV is built into the RNA growth chain, the presence of carbon-nitrogen (CN) groups can cause the sugar to bend, which in turn distorts the shape of the RNA chain. Therefore, only three additional nucleotides can be added. This stops the production of strands of RNA and eventually stops the virus from replicating. The main structural feature that distinguishes RDV from adenosine is the modification of specific chemical bonds in the molecule. Instead of binding a carbon and a nitrogen atom, the chemist replaces the nitrogen with another carbon to form a carbon-carbon bond, which is essential for the success of this drug because the coronavirus has a special enzyme, the artificial one Can recognize and remove nucleosides. By modifying the chemical bond, the enzyme cannot eliminate RDV, so it remains in the growing chain and prevents replication [15]

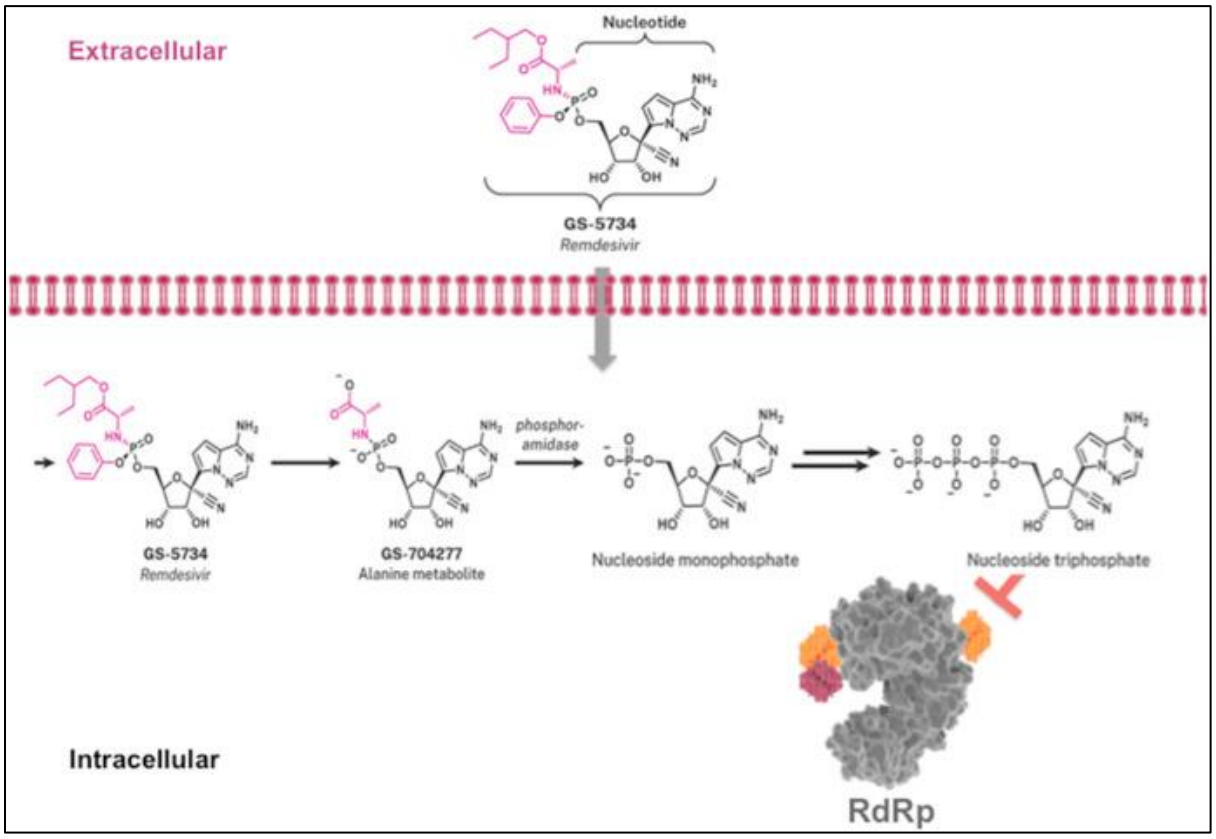


Fig: Intracellular processing of remdesivir (GS-5734) [1 M. Gabriella Santoro]

Pharmacology of remdesivir:

SARSCov2 primarily affects the respiratory tract and enterocytes of the gastrointestinal tract. It requires RNA-dependent RNA polymerase (RdRP) in order to replicate [17,28,29,30]. Remdesivir, a phosphoramidite prodrug, enters the cell and is broken down into its monophosphate form. This form of monophosphate is converted into remdesivir triphosphate (RDVTP, GS443902) after phosphorylation. RDVTP is incorporated into the RdRp complex instead of ATP and inhibits its activity [31]. Remdesivir has a low affinity for RNA polymerase II and mitochondrial RNA polymerase [32]. Hence it is considered to have a good safety profile in humans (3- 225 mg) [32]. Clinical studies with remdesivir have shown its tolerable and non-toxic effects. excreted in the urine [32]. The major metabolites of remdesivir are GS704277, GS441524MP, and GS441524 [33,34]. Nausea is the most common side effect of remdesivir. Remdesivir can cause allergic reactions during its infusion or after the infusion. Consequently, the remdesivir treatment must be discontinued in patients showing clinically significant hypersensitivity to remdesivir or any component of its product. The remdesivir dose (150 mg) for 7–14 days revealed a reversible increase in the liver enzymes, for example, alanine aminotransferase and aspartate transaminase [32].

Besides, remdesivir can also lead to an increase in the prothrombin time. Therefore, liver function tests and determination of the prothrombin time are recommended before and during the remdesivir therapy. The injection of remdesivir is prepared in sulfobutylether cyclodextrin (SBECD), which can cause renal dysfunction due to its accumulation in the kidney. Consequently, patients exhibiting an eGFR of all;30ml/min are not recommended to take remdesivir. Accordingly, the testing of the eGFR has to do done before the start of remdesivir therapy.AS of date, there is no data on the overdose and antidote of remdesivir. Cases of overdose should be monitored and managed according to the signs, symptoms, and clinical status of the patient. No published report provides evidence of the developmental, teratogenic, and reproductive toxicity of remdesivir [17].

Mechanism of action:

Remdesivir is an RdRP inhibitor that can achieve antiviral effects by inhibiting viral nucleic acid synthesis [16,35-37]. SARSCoV2 is an enveloped, positive-meaning, single-stranded RNA virus [16,38], and the genomic replication process of RNA viruses is dominated by RdRP, which is encoded by the virus itself [16,39,40]. After the virus has entered the host cell, the viral genomic RNA is used directly as a template and the protein synthesis system of the host cell is used for the translation of RdRP [16,41-43]. used to complete transcriptional synthesis of negative strand sub genomic RNA, synthesis of various mRNAs related to structural proteins, and replication of viral genomic RNA [16,44-46].

The virus penetrates the host cell [47,48]. RDRP is a potent target of broad-spectrum antiviral drugs, and today most anti-coronavirus drugs that target RdRPs are nucleoside analogs (Nuc) or RNA interferons [16,49]. Remdesivir, a monophosphoramidate prodrug of an adenosine analog, enters the host cell as a prodrug, is converted to nucleoside monophosphate (NMP) and then dephosphorylated to active nucleoside triphosphate (NTP). Adenosine (ATP) has a similar structure and is competitive in binding viral RdRP similar efficiency. NTP is inserted into the RNA synthesis strand by RdRP recognition at position i, and this process results in the termination of the RNA strand at a position a few bases downstream from position i. This process is called

"chain termination" and takes place predominantly at position i+5 [16,50]. This process suppresses the virus from multiplying. As a broad-spectrum antiviral agent, Remdesivir has good antiviral effects on coronaviruses, including MERSCoV and SARS-CoV-2. Previous studies have shown that almost 80% of the SARSCoV2 genome is homologous to that of SARS-CoV-2 and almost all SARSCoV2 proteins are homologous to SARS-CoV-2 proteins [16,51]

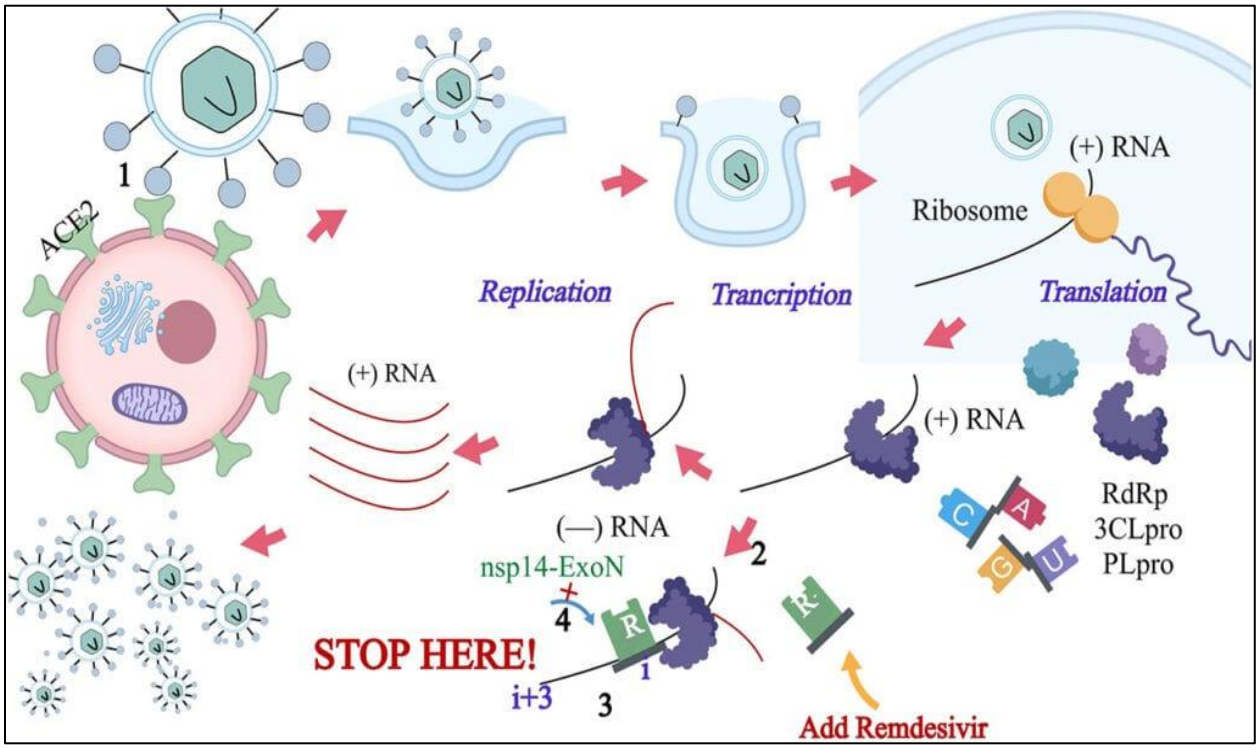


Fig : MOA

Potential molecular targets of remdesivir on SARS-CoV-2:

There are at least eleven different strains of SARSCoV2 as a result of viral mutations. ARSCoV2 replicates within the host cells by the virus' RNA-dependent RNA polymerase (RdRp), which is a highly conserved protein among various virus strains; Therefore, SARSCoV2 RdRp could be a potential antiviral target [51]. In addition, the main protease (Mpro), also known as chymotrypsin-like cysteine protease (3CLPro), which clears the central part of polyproteins and releases proteins with replication functions, plays a crucial role in coordinating the life cycle of SARSCoV2 through its replication and transcription [52]. Consequently, Mpro becomes another potential target for experimental SARSCoV2 drugs. Remdesivir has an inhibitory effect on the viral RdRp and exerts its antiviral effects by disrupting viral replication within the host cell. (GS441524) was able to form a good complex with SARSCoV2 NSP12 RdRp, terminate the RNA strand, and stop RNA replication. In addition, both remdesivir and GS441524 could bind to Mpro which, when combined with their RdRp antagonizing effects, could lead to synergistic effects. RdRp and Mpro through different binding mechanisms and has somewhat stronger interactions with RdRp than with Mpro [7,52,53].

The 5-day and 10-day remdesivir courses comparison

Remdesivir showed significant beneficial effects at all three levels of respiratory support as assessed during days 1 through 14 in both treatment regimens and 10 days. The fixed-effect approach was used for all events evaluated [7].

4. SAFETY OF REMDESIVIR IN COVID-19 STUDIES

1. Renal safety

Although no evidence of nephrotoxicity was observed in healthy volunteers, some caution should be exercised when using remdesivir. A 150 mg dose of Remdesivir solution and lyophilized Remdesivir formulations contain 9.0 or approx. 250 mg/kg, based on the EMA safety review.) SBECD is used in the formulation as a solubilizer due to the limited water solubility of Remdesivir. Close monitoring of eGFR is required during the administration of remdesivir, especially in patients with known renal impairment, and discontinuation is required if eGFR decreases to 50% of baseline. 49% of its metabolite GS441524, renal insufficiency can theoretically increase plasma exposure of this metabolite. However, given the benefit-risk balance in patients with COVID19, it is currently not recommended to change the dose in patients with mild and moderate renal impairment, although it is contraindicated in patients with severe renal impairment (eGFR <30 ml/min). that no specific studies have been carried out with remdesivir in patients with impaired renal function [14].

2. Hepatic safety

A significant proportion of patients with acute EVD who received remdesivir in the PALM study had moderate to severe hepatic and renal impairment; however, no further deterioration in kidney or liver function due to remdesivir was observed. Remdesivir is believed to be rapidly cleaved by hydrolases and therefore the effect of liver dysfunction on remdesivir plasma levels is likely to be small. In view of the risk-benefit ratio, dose adjustment in patients with COVID19 is not currently recommended, although it is contraindicated in patients with alanine transferase (ALT)> 5 times the upper limit of normal or severe hepatic impairment [14].

3. Pregnancy, Lactation and pediatric population

In preclinical reproductive toxicity studies, no adverse effects on embryo-fetal development in pregnant animals or male infertility were observed with remdesivir; however, at a consistently toxic dose, embryonic toxicity was observed. Remdesivir has not been studied in pregnancy, in women who are breastfeeding, or in children and adolescents., in the PALM study on acute EVD, 3% of pregnant women and 26% of children received remdesivir without any significant side effects [14].

4. Drug interaction

The potential to induce CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) has been observed following exposure to remdesivir in human hepatocytes (the cause of the transient increase in liver enzymes), but no data on the interaction is currently available drug [14].

5. Formulation and dosing Remdesivir

For injection, 100 mg, is a sterile, lyophilized, preservative-free solid that must be reconstituted with 19 ml of sterile water for injection and diluted in 0.9% saline before intravenous administration. 30 C until the moment of use. Remdesivir 5 mg/ml injectable vials should be stored at refrigerated temperature (2 Ce8 C) until the time of use. After dilution with 0.9% saline solution, the solution can be stored for up to 4 hours (20 Ce25 C) or 24 hours at refrigerated temperature (2 Ce8 C). The currently recommended dose of remdesivir for COVID19 is 200 mg IV. Bolus diluted in normal saline (0.9%) or 5 dextrose to be administered over 60 min on day 1, followed by 100 mg i.v. diluted over 60 min over the next 9 days Two previous clinical trials of EVD as PALM and PREVAIL IV, the dose used to give remdesivir one hour on day 1 as a loading dose and then 100 mg i.v. or 1 hour daily for 4 days (for PREVAIL IV) or 9-13 days (for PALM) as a maintenance dose [14].

5. STUDY ABOUT CARDIAC PATIENTS:

The cardiovascular effects of SarsCOV2 infection are well documented and have been associated with a poor prognosis that can be made worse by underlying cardiovascular disease. Therefore, evaluating potential adjuvant cardiovascular toxicity is critical, especially since there are no cardiovascular toxicity data for some of the few therapeutic drugs. Available options such as Remdesivir, an antiviral polymerase prodrug with inhibitory activity against the RNA-dependent viral RNA polymerase of the SARS-CoV-2 virus. In vitro studies demonstrated a marked affinity of remdesivir for human cardiomyocytes with higher local concentrations and activity, which partially explained the reported proarrhythmic effects of five days of treatment with remdesivir on cardiac rhythm. In addition to isolated reports of transient bradycardia detected by clinical observation or with a single EKG during antiviral treatment, heart rate was monitored using waist pulse before and during the administration of remdesivir or only two EKGs were performed before and after administration of remdesivir antiviral treatment raised treatment.

Our data seem to confirm previous observations of a decrease in heart rate after administration of remdesivir, although this was never associated with bradycardia, symptomatic bradycardia, or significant QTc prolongation that led to remdesivir discontinuation. higher baseline heart rate, which supports the hypothesis that the main reason for the decrease in heart rate was not remdesivir, but presumably to improve the clinical baseline conditions responsible for tachycardia (fever, hypoxia, inflammation, anxiety). in patients with a less severe clinical condition, a finding that also reassures doctors that there are no contraindications to the use of remdesivir in critically ill patients, at least regarding cardiac function. Also, no significant correlation with age, cardiovascular risk factors, comorbidities, and troponin levels were observed. The limitations of the study are the limited number of participants and lack of a control arm without remdesivir. However, as far as our sample shows, remdesivir showed a favourable toxicity profile, although it was accompanied by a significant decrease in incidence. Research is needed to confirm this preliminary observation in larger numbers of subjects [8].

Pregnancy:

Dexamethasone can provide significant maternal benefits and lower mortality in pregnant women with severe COVID19 infection who require mechanical ventilation, while also promoting fetal lung maturity. Overall, the maternal benefit of this protocol outweighs the risks of neonatal damage in critically ill patients. None of the experimental clinical therapies are considered contraindicated and compassionate use of these therapies should be considered in pregnant women with severe illness due to COVID19. Pulmonary respiratory protection strategies for COVID-associated ARDS are well tolerated by pregnant patients. The use of the prone position in the pregnant patient was achieved safely, with the benefit of oxygenation and without sustained discomfort to the fetus, during the 16-to-18-hour prone routine., a late vertical tilt to the left was used to avoid compression of the inferior vena cava and aorta by the pregnant uterus. A conservative approach to fluid management can be used with ARDS and urination during pregnancy. Fetal heart rate monitoring can be an additional clinical indicator of maternal oxygenation and should be used in critically ill pregnant patients. Permissive hypoxia can be considered to promote fetal maturity and minimize barotrauma, but this approach should be used with caution and only with continuous EFM to ensure fetal tolerance [18].

6. RESULTS FROM PATIENTS WITH COVID-19 AND CLINICAL TRIALS

Historically, remdesivir was tested to treat patients with Ebola hemorrhagic fever in {an exceedingly in a very} irregular clinical test within the Democratic Republic of the Congo in 2018 In 2020, remdesivir was enclosed in the "Solidarity" international clinical trial conducted by the globe Health Organization in an commit to notice an efficient treatment for COVID-19. As a timely response to the pandemic, patients with COVID-19 are treated with remdesivir in emergency protocols. within the 1st patient with COVID-19 treated with remdesivir, a 35-year-old from Washington, respiratory illness improved once seven days of treatment. In Seattle, USA, remdesivir was used as a compassionate drug to treat seven critically unwell patients. The larger study found that following a 10-day course of remdesivir treatment (intravenous administration at two hundred mg on day 1, followed by one hundred mg daily), 68% (36 of 53) of patients with COVID-19 showed clinical improvement; however, there was no management cluster during this study.

To adequately assess the effectuality of remdesivir, tests are currently in countries appreciate the USA, Norway, Canada, France, and China. a listing of presently ongoing clinical trials. though the length of treatment differs slightly, the dose of remdesivir is similar: two hundred mg on day 1, followed by one hundred mg for the remainder of the treatment period. The study was conducted in China with 237 patients (158 within the remdesivir cluster and seventy-nine within the placebo management group), and also the primary termination was the time taken to attain clinical improvement.

The study unconcealed that treatment with remdesivir failed to result in a big reduction in the time taken to achieve clinical improvement. In addition, mortality associate degreed microorganism clearance time in patients with severe COVID-19 wasn't considerably completely different from those within the placebo group, suggesting that remdesivir had poor clinical benefits. This additional suggests that in COVID-19, viral propagation isn't the most issue chargeable for malady severity. The severity of COVID-19 has been related to the protein unharness storm, suggesting that host immune responses play a vital role during this event. Therefore, a mix of remdesivir with immunosuppressants (for example sarilumab, an IL-6 inhibitor) and/or alternative antiviral agents may heighten the antiviral activity of remdesivir and mitigate the immunopathological injury caused by excessive immune impact

nonetheless, throughout an equivalent trial, in remdesivir-treated patients with COVID-19, particularly those treated inside ten days of symptom onset, quicker clinical improvement was determined than that within the placebo cluster. Considering these findings, the tiny sample size, and since the study was unexpectedly terminated, it should be insufficient to elucidate the efficaciousness of remdesivir. Furthermore, the pharmacology of remdesivir and its active substance within the metastasis tracts and/or alternative infected organs stay mostly unknown in patients with COVID-19.36 Therefore, the results of in-progress clinical trials are guaranteed to supply conclusive proof concerning the efficacy of remdesivir in patients with COVID19.

The pharmacokinetic profile of remdesivir, notably the concentrations of the active metabolite, GS-441524, within the tract or different infected tissues in patients with severe COVID-19 is unknown. In addition, presently obtainable knowledge on remdesivir is lacking, in particular, those in drug-drug, drug-gene, and drug-disease interactions. This info is very important in predicting potential negative outcomes which will arise throughout treatment.

Concerns about the clinical use of remdesivir in COVID-19:

There are some worrying questions about remdesivir. Due to its pharmacokinetic and physicochemical properties, it appears unlikely that remdesivir and its active metabolite could reach therapeutic levels in human lung cells to inhibit SARSCoV2 with the current route of administration and dosage. Based on the chemical structure of the prodrug, the active metabolite of remdesivir would accumulate significantly in the liver, kidneys, and gastrointestinal tract (GI). This problem prevents the administration of remdesivir in doses greater than 200 mg/day to achieve the therapeutic effect. Concentration in lung cells due to non-target organ-related side effects and dose-related toxicities. Recommended against the use of Remdesivir in pregnancy, breastfeeding, with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels higher than five times the upper limit of normal (ULN), patients with renal insufficiency with an estimated glomerular filtration rate (eGFR) less than 30 ml/min or haemodialysis required.

The effect of Remdesivir in combination with other active substances is not yet clear; however, the simultaneous use of hydroxychloroquine or chloroquine with remdesivir is not recommended due to the antagonistic effect of these agents on the intracellular metabolic activation and the antiviral activity of remdesivir, there is still no optimal start time, dose, and duration for Remdesivir. It is too early to confirm the long-term post-market safety of remdesivir. The only way of administration IV by Remdesivir limits its applicability to the configuration of hospital patients. In addition, in vitro and vivo studies show the remarkable safety profile for GS441524.

7. CONCLUSION

The current meta-analysis provides an updated assessment of the scientific evidence on the use of remdesivir in patients with COVID19. The results of the RCT studies showed a significant improvement in the 28-day recovery rate, the support of low oxygen flow from the line base through day 14, and the requirement from IMV or ECMO. During days 14 to 28 of the follow-up period in the remdesivir group. Also, the risk of the side effects was lower in the remdesivir group than in control group. Support of oxygen flow during days 14-28 and the need for IMV or ECMO from baseline up to day 28 of the follow-up period. In addition, the risk of death after 28 days was lower in the remdesivir group than in the no remdesivir group. There were no significant differences between the 5-day and 10-day remdesivir treatments in any of the clinical results evaluated. In addition, 5 days of treatment with remdesivir may produce similar results. These results, combined with problems related to synthetic difficulties, pharmacological properties, clinical and physicochemical properties of remdesivir, underscore the importance of performing appropriate and well-designed RCTs before starting it can be used in patients with COVID19. However, the results of ongoing clinical studies would be useful for future systematic reviews and meta-analyses to obtain more reliable results.

Limitations:

The severity of COVID19 differed among the included participants, which could affect treatment. The meta-analysis was limited by the lack of a comparison/control group in three of the ten included studies. There are no consistent guidelines for administering additional treatments and providing supportive care to COVID19 patients in clinical trials, which can lead to inaccurate and unreliable clinical outcomes. The follow-up times were not the same in all meta-analysed studies. Longer consistent follow-up periods are preferred as they would provide more reliable end results.

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Conflict of interest:

The author declares no conflict of interest, financial or otherwise.

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