Remdesivir (GS-5734) for COVID-19 Treatment: Past and Recent Updates

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Abstract: Background: SARS-CoV-2 is a pandemic now, and several measures have been taken by countries to prevent, control, and treat the disease. WHO has been working meticulously and has been providing up to date information and statistics on incidences and death. Several broad-spectrum anti-viral drugs are available and have been used in the past to fight against the viral outbreak. Recently remdesivir, an experimental produg from Gilead Sciences, has been found to be a potential drug to be used as a therapy to treat COVID-19.

Objective: Here, we have reviewed several previous findings from the literature and present an up to date information on remdesivir.

Result: Remdesivir was initially invented for use against Ebola virus treatment and has proved effective against different strains of Ebola, Nipah, and other strains of coronaviruses. Clinical trials with remdesivir for COVID-19 patients have begun, and several off label use of remdesivir have been reported recently. Currently, the drug seems to have an effect against the SARS-CoV-2 virus, with side effects among a few patients. Although the results are not conclusive, they are partly promising. This review provides past and recent updates on the use of remdesivir.

Conclusion: From the review, we conclude that the drug remdesivir is known to exhibit its mechanism of action by terminating the RNA synthesis, and it is a potential drug against the novel coronavirus.

Keywords: SARS-CoV-2, coronavirus, remdesivir, clinical trial, RNA synthesis, mechanism, COVID-19.

1. INTRODUCTION

Novel Corona Virus (SARS-CoV-2 previously termed nCov-2019 or 2019–nCoV) causes a disease called Coronavirus disease (COVID-19) that was initially reported from Wuhan region of Hubei province in China on December 31st, 2019 and the World Health Organization (WHO) provides round the clock update about the disease [1]. WHO in Geneva, Switzerland has announced that COVID-19 is a pandemic (A health condition that has spread globally) after a 13 fold increase in the number of cases outside China were observed within the first few weeks of the first reported case [2]. The etiology of the disease is linked to a wholesale seafood market in Wuhan, China [3]. Previous incidence of Severe Acute Respiratory Syndrome (SARS) was also reported to have originated from a live animal market in China [4]. Subsequently, the intermediary transmitter was found to be a Civet cat for SARS, whereas for SARS-CoV-2, although the genome has shown higher homology with bat virus, the intermediate is not known. As of 13th March 2020, there were 3, 32, 930 confirmed cases with 14,510 death reported globally. The COVID-19 has affected 195 countries/territories, and the risk assessment from WHO is classified as “Very High”.

During an epidemic or pandemic, developing a new drug could be a challenging task. Lu Hongzhou has proposed at least three methods for the identification of new plausible drugs for the treatment of COVID-19. First, evaluate existing broad-spectrum anti-viral drugs and test them using standard assays. Second, screening chemical libraries and evaluating top hits using computational methods to identify and test favorable drugs of their efficacy in the wet lab. Third, renovation of drugs specific for COVID-19 using genome map of the viruses [5]. Broad-spectrum antiviral drugs have demonstrated potential against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) treatment and are now considered for COVID-19 treatment. Based on the first method, evaluation of remdesivir (Fig. 1) has been promising, and it had previously completed a clinical trial in Ebola-infected patients; the trial was stopped considering higher mortality in remdesivir treated patients as compared to Mab114 treated patients [6]. This review will focus on recent updates with the use of remdesivir and its demonstrated
potential against SARS-CoV-2 and other types of viruses. In this review, we show proof from the literature on the potential action of remdesivir against several classes of viruses and unravel its potential against the novel coronavirus.

2. PATHOLOGY OF THE DISEASE

In a case report of a patient presented with a COVID-19 infection, the following changes were observed in the biopsy samples: Acute Respiratory Distress Syndrome (ARDS) resulting from the desquamation of pneumocytes and hyaline membrane formation. Pulmonary edema and hyaline membrane formation indicate an early phase of ARDS. Mononuclear inflammatory infiltrates, with lymphocytes and viral cytopathic changes in the alveoli were observed. In the liver, microvesicular and slight portal activity was observed. Although the patient succumbed to heart attack, no pathological observations were noted in the heart muscle. Reduced levels of CD4 and CD8 T cells were also observed in the PBMC in the patient, and X-ray images revealed a rapid setup of pneumonia [7].

2.1. Lack of Animal Models

SARS-CoV-2 has a spike glycoprotein, which forms a complex with the host angiotensin-converting enzyme 2 (ACE2) receptor [8]. The absences of ACE2 receptors in normal mice make them inoperable to study the disease. Animal models with expressed ACE receptors are very limited and the Jackson laboratory and other breeders across the globe have seen a higher demand for humanized ACE2 protein-expressing mice [9].

2.2. Limitations of Using Antibody Therapy

Although there is high sequence similarity, the spike protein of SARS-CoV-2 is significantly different from SARS-CoV-2 in two regions that bind to the ACE2 receptor limiting the use of previously developed antibody therapy to use against COVID-19 [10].

2.3. Remdesivir Use for COVID-19 Treatment

On January 20, 2020, the USA had the first confirmed case of SARS-CoV-2 infection from a person who had a travel history to Wuhan to visit his family and presented to the clinic with cough and fever on return. On day 7 the patient was treated with an intravenous dose of remdesivir and the next day, the clinical condition of the patient improved, and no adverse effects were noted. It is important to note that the stool of the patient tested positive for the virus on day 7. Overall on day 12, the oropharyngeal specimen tested negative for the virus [11].

2.4. Remdesivir Against COVID-19

Remdesivir (GS-5734) is an antiviral drug proposed for the treatment of COVID-19. Remdesivir has a chemical formula of C_{27}H_{35}N_{6}O_{8}P with a molecular mass of 602.6 g/mol and it is a prodrug that is metabolically converted into an active triphosphate GS-441524 in the cells [12]. It is a broad-spectrum antiviral drug initially reported exhibiting antiviral effects against several variants of the Ebola virus in cell-based assays [12]. Remdesivir was initially developed and synthesized by Gilead Sciences (Foster City, CA, USA) in 2017 to treat Ebola infection [13]. A drug screening \textit{in silico} analysis from China presented remdesivir as one of the putative drugs to treat COVID-19 along with 30 other agents on January 20, 2020 [14]. The structure of Remdesivir is shown in Fig. (1).

The nucleoside triphosphate, the activated form of the drug was reported to have formed in various human cell types when incubated with remdesivir. The formed nucleoside triphosphate (NTP) acts as a substrate that terminates the RNA chain in respiratory syncytial virus RNA polymerase. In a study, the authors have injected the drug intravenously into a nonhuman primate, rhesus monkey, and found nucleoside triphosphate in the peripheral blood mononuclear cells; the conversion of remdesivir required only 2 h after administration and has a half-life of 14 h. In sites of viral replication such as the brain, eyes, and testes the NTP was found 4 h. A daily dose of 10 mg/kg remdesivir for 12 days protected the Ebola-infected animal against lethality and improved several clinical features. The authors also reported the efficacy of the drug against coronavirus, marburg, ebolavirus, and filovirus. The study also reported that the NTP formed did not inhibit the human RNA polymerases [12]. A list of antiviral drugs as presented in the sixth edition of guidelines for prevention, diagnosis, and treatment of COVID-19 by the National Health Commission (NHC), China, are presented by Dong \textit{et al.} in a review [15].

![Remdesivir](image_url)

Fig. (1). Remdesivir (Pubchem CID: 121304016).

2.5. Current Clinical Trials

Several clinical trial underway as of March 12, 2020, are listed:

- A randomized, double-blind, placebo-controlled, multicentre, phase III clinical trial is underway and is expected to test the efficacy and safety of the use of remdesivir against patients hospitalized with severe COVID-19 and is expected to be completed by April [16].
- A phase III clinical trial with randomized, double-blind, placebo-controlled, multicentre study is underway to study the safety and efficacy of remdesivir against patients with mild and moderate COVID-19 infection [17].
- An expanded access treatment protocol for the intermediate-size patient population for COVID-19 using...
2.7. Remdesivir is More Potent than Other Antiviral Drugs

In a study, remdesivir showed potent antiviral activity against MERS-CoV as compared to a combination of Lopinavir/Ritonavir/IFNβ. Remdesivir acts by reducing the viral load in the lung of MERS-CoV infected mice and improves lung function and alleviates the lung pathology and therefore considered a treatment option for MERS-CoV infection [24].

Wang et al performed an in vitro evaluation with two of the existing drugs to test their efficacy against the COVID-19; they used five FDA approved drugs chloroquine, penciclovir, ibavirin, nitazoxanide, and along with two known broad-spectrum antiviral drugs favipiravir and remdesivir, on clinical isolates obtained from COVID-19 infected patients. They used cytotoxicity tests using CCK8 assay against the Vero E6 cell line. When the Vero E6 cells were infected, no obvious cytopathic changes were observed during the 48 h of infection. Researchers argue that remdesivir could be used in the fight against COVID-19 [25]. Several other possible antiviral drugs are recommended based on earlier research, safety, and clinical efficacy [26].

2.8. Mechanism of Action of Remdesivir

In a recent study, authors have reported the mechanism of action of remdesivir in an insect model where they have coexpressed the MERS-CoV non-structural proteins to study the interaction of remdesivir with MERS-CoV RNA dependent RNA polymerase. The results showed that the active form of the drug remdesivir-triphosphate competes with ATP, a natural counterpart, and found that the remdesivir-triphosphate is more efficient than ATP is incorporating itself into the site. When the NTP is incorporated, it inhibits the RNA synthesis by mediating delayed RNA termination. This termination, however, is not immediate, the presence of the 3'-hydroxyl group in the complex allows the addition of three more nucleotides till the RNA synthesis is arrested at the i+3 region. Between EBOV RdRp and MERS-CoV RdRp, there is a difference in the mechanism of action [27]. Earlier reports from de Wit et al showed that remdesivir pretreatment to Rhesus macaque model of MERS-CoV prevented MERS-CoV infection and disease, therefore, could be used as a prophylactic; the authors also demonstrated that remdesivir administration after 12 h of infection alleviate clinical symptoms in the animal model. Therefore, it can also be used as a therapeutic drug [28]. The mechanism of action of remdesivir is illustrated in Fig. (2).

The clinical manifestation of the disease with other relevant statistical data updated as of February 11, 2020, is reported in a study [29]. In a recent letter to the editor, authors have argued that remdesivir and chloroquine, an antimarial drug, have proved to be effective against the SARS-CoV-2 in vitro. The results demonstrated an EC50 of 1.76 μM against the 2019-nCoV in Vero E6 cells and remdesivir had inhibited the viral infection in human liver cancer cell line Huh-7 cells. The chloroquine treatment was tested pre and post-infection period and had an EC50 value of 6.90 μM against SARS-CoV-2 in Vero E6 cells [30]. However, Chloroquine failed to inhibit the SARS-CoV in a mouse model [31].

2.9. Remdesivir Against Ebola

During the Ebola outbreak, remdesivir showed inhibitory effect against Ituri Ebola strain (EC50 12 nM) and Makona Ebola strain (EC50 13 nM) [32] and the mechanism of action involves the competition of NTP with ATP for incorporation into the site of synthesis and a delayed chain termination was noted at i+5 position, and the drug did not affect RNA polymerase isolated from human mitochondria [33].
activity and activity of remdesivir against the Ebola virus [38]. In addition to targeting the said classes of viruses, remdesivir is active against the Ebola virus [42]. A previous study demonstrated that remdesivir inhibited human coronavirus OC43, 229E, and the porcine delta coronavirus and has been suggested to be used for any emerging CoV if proved safe to use in the affected patient [45]. The study demonstrated the effect of remdesivir against bat-CoVs, against circulating human CoV in human primary lung cells and also against the MERS-CoV; therefore considered a possible therapeutic for any emerging CoV in the future [46].

2.11. Remdesivir Against Other Viruses

Remdesivir and its other parent compounds were found to inhibit virus belonging to the families Paramyxoviridae, Coronaviridae, and Filoviridae [47] and exhibit broad antiviral activity and inhibited the replication of several alpha and beta-coronaviruses in human airway epithelial cell (HAE) cultures and showed low in vitro cytotoxicity in many human cell types [48].

2.12. Recent Updates with Remdesivir

Compassionate use of remdesivir was performed on a patient in the USA [49] and recently, three patients were treated with remdesivir in the USA, all the treated patients had nausea, vomiting, and rectal bleeding. Remdesivir was discontinued after the respiratory symptoms of patients improved [50]. This raises the question of considering the use of remdesivir in patients. Since safety is a concern, we need more clinical trials to assess the safety, which is lacking right now.

CONCLUSION

We have summarized the known up to date literature on remdesivir for possible use as an antiviral to control the pandemic SARS-CoV-2. This pandemic might teach us a lesson to have better preparedness to contain any future outbreak of such viral spread and diseases. An immediate way of controlling could be to use existing broad-spectrum drugs that had shown a potential effect in similar classes of an organism in the past. We must be future-ready to fight such a viral outbreak before it progresses to a pandemic. Although the mechanism of action of remdesivir is demonstrated, safety considerations might keep the drug on the waiting list. Remdesivir needs further proof of safety from clinical trials for consideration as a potential COVID-19 treatment drug.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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