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Remdesivir for the Treatment of COVID-19, its Safety and Clinical Effectiveness: A Clinical Review

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Authors' contributions

This work was carried out in collaboration among authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Remdesivir is a nucleotide analog pro-drug and antiviral medicine with broad spectrum effectiveness against viruses from several families. After exhibiting strong antiviral activity against coronaviruses in preclinical studies, remdesivir was approved as a specific drug for the treatment of the novel coronavirus disease 2019 (COVID-19), which was caused by the infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the current global pandemic. The Remdesivir COVID-19 phase III evaluation began in early 2020, and preliminary findings are promising. For people with severe COVID-19, Taiwan temporarily approved the use of Remdesivir in late May 2020. The approval was quickly followed by a number of conditional permits in many countries/regions, including the United States of America (USA) and Canada. Remdesivir had already been granted emergency use authorization in the USA on May 1, 2020 and special authorization for emergency use in Japan on May 7, 2020. This article provides a summary of remdesivir's development and the significant events that led to its initial conditional approval for the treatment of COVID-19.

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1. INTRODUCTION

A novel coronavirus in December 2019 in Wuhan, Hubei Province, China caused several severe viral pneumonia cases eventually spread to other parts of the world and resulted in a significant fatal pandemic. The scientific community labored assiduously to understand the biology of this unusual disease to find a workable solution. By attaching to the angiotensin-converting enzyme 2 (ACE2) receptor, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infects a host and enters the host's cells. The virus then shows a preference for the epithelial cells lining the airways of the nose and lungs as well as a number of other bodily tissues [1,2]. When the condition worsens and the coagulation cascade is set off, lung endothelial cells are affected. Due to this, a unique spectrum of clinical manifestations with multiple organ involvement is produced. The detrimental progression of the condition is now referred to as coronavirus disease, and it manifests clinically as different stages of pneumonia with or without concurrent coagulation issues (COVID-19). COVID-19 is classified as mild, moderate, severe, or critical based on clinical signs with oxygen supplementation being one of the most significant indirect measures of severity [3,4].

The COVID-19 disease appears to have a range of clinical symptoms, from asymptomatic to severe respiratory failure. The initial signs of an illness are most frequently fever, coughing, and nonspecific myalgia. Less frequent signs include sputum production, headaches, and diarrhea [5-7]. In cases from China up until mid-February 2020, a preliminary case analysis found that 14% of cases had severe disease (dyspnea, respiratory frequency > 30/min, blood oxygen saturation 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio 100, and/or lung infiltrates > 50% within 24-48 h), and 5% of cases had the critical disease (respiratory failure, septic shock, and/or multiple organ dysfunction or failure) [8]. A more extensive meta-analysis revealed that the percentage of serious diseases was slightly higher (20.3%) [9].

The disease case fatality rate (CFR) varies by geography, population demographics, and healthcare infrastructure. For instance, it is estimated that Italy's overall CFR is 7.2%, in part, because it has a higher proportion of older people than China [10]. According to data from around the world, the COVID-19 CFR based on confirmed cases is predicted to be 6.9%. Advanced age, sepsis, and aberrant blood coagulation patterns were all associated with an increased risk of mortality [11]. Acute respiratory distress syndrome typically progresses in elderly people (over 63 years old), frequently with underlying medical issues like hypertension or diabetes [12-14]. A larger body-to-mass ratio (over 30) was associated with a higher disease severity and a quicker onset of acute respiratory distress syndrome in adults under 60 [15]. Other symptoms, such as coagulo-pathies and anomalies of the nervous system, have also been observed in some afflicted individuals [16-21].

2. REMDESIVIR'S INITIAL DESIGN AND DEVELOPMENT

Remdesivir (GS-5734), a drug produced by Gilead Sciences, was developed in cooperation with the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). They looked for treatments for RNA-based viruses that still had the potential to become pandemics and spread throughout the world, like those that did so after the program's inception, like the Ebola virus (EBOV)and the Coronaviridae family viruses that are responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (SARS). A library of roughly 1,000 small compounds centered on nucleoside analogs was estabcyto protectivelished as a place to start the discovery process based on prior knowledge of effective antiviral medicines targeting RNA viruses. They made up a large portion of the library since modified nucleosides including mono-phosphate, ester, and phosphorodiamidate pro-drugs are weakly cell-permeable and can subsequently have a low hit rate in cell-based screens like antiviral screenings. The nucleoside or phosphorylated nucleoside is released by the metabolism of these prodrugs, which are typically more cellular permeable [22-24]. An extremely successful 1′-CN modified adenosine C-nucleoside hit (GS-441524) and its mono-phosphate prodrug (GS-5734, later renamed as remdesivir) was found to exist. The information from the initial full screen has not been made public [25].

As promising leads from a group of 10-substituted 4-aza-7,9-dideazaadenosine C-nucleosides with broad antiviral activity against a panel of RNA viruses, including SARS, influenza A, dengue virus type 2, influenza B, and yellow fever virus, GS-441524 and its S-acyl-2-thioethyl monophosphate pro-drug were first introduced in 2012, they were then known as GS-441524 (YFV). The primary test used was the cyto-protective effect (CPE) assay in which a live virus is incubated with a target cell line and the antiviral activity is determined by the ability of a test agent to delay cell death as determined by a reference cell viability reagent. In a 2012 study, the drug GS-5734 demonstrated CPE action against the SARS strain Toronto 2 (IC50 = 2.2 M) without harming the kidney epithelial cells utilized as the host in the CPE assay, Vero African green monkeys [26,27].

3. REMDESIVIR STRUCTURE

Remdesivir (GS-5734), a nucleoside analog drug, has a broad spectrum of antiviral activity and efficiently treats Ebola and Nipah virus infections in nonhuman primates [28]. It works as an RNA-dependent RNA polymerase (RdRp) inhibitor to stop the replication of some coronaviruses in respiratory epithelial cells. A recent study found that Remdesivir competes with its natural counterpart ATP. Once it has been added to the growing chain I position, Remdesivir cannot cause an immediate halt. Rather, it will proceed three further nucleotides to end the strand at position I + 3 [29].

4. PHARMACOKINETICS / PHARMACO-DYNAMICS OF REMDESIVIR

Remdesivir must be delivered intravenously for quick and reliable delivery to target cells and peak plasma concentrations are attained for remdesivir after the infusion and for GS-441524 after one to one and a half hours. The maximum concentration (Cmax) of remdesivir is increased when the infusion period is cut from 2 hours to 30 minutes, but the Cmax of GS441524 is barely affected. Remdesivir has a half-life of roughly one hour in plasma concentrations, but GS-441524 has a longer half-life of almost 27 hours. Remdesivir has poor hepatic stability, which prevents oral administration because doing so would likely lead to total clearance following first-pass metabolism. Remdesivir has a 12.1% free fraction in humans, which indicates moderate protein binding. The plasma protein binding of the metabolites, GS-704277 and GS-441524, is incredibly low (1% and 2%, respectively).

Remdesivir and its metabolites appear to be widely distributed throughout the kidney, liver, lungs, and artery wall with only marginal penetration of the blood-brain barrier in animal studies. GS-441524 dose-proportional increases were observed in one investigation examining drug distribution into peripheral blood mononuclear cells after different single doses of remdesivir (3 to 225 mg), which is consistent with a linear pharmacokinetic model. Remdesivir undergoes substantial metabolism after intravenous injection, starting with esterases' hydrolysis of the drug which yields the intermediate alanine metabolite GS-704277. Following phosphoramide activity on GS-704277, nucleoside mono phosphate is created, which can travel through two different metabolic routes. The active nucleoside triphosphate GS-443902 is produced by phosphorylating the nucleoside monophosphate, while the nucleoside GS-441524 is produced by dephosphorylating it. Additionally, M27, a significant metabolite that has not yet been named, appears to be present in plasma [27,30,31].

5. MECHANISM OF ACTION OF REMDESIVIR

Remdesivir (GS-5734) is a prodrug of a C-adenosine nucleoside analog that inhibits the replication of the SARS-CoV-2 virus by targeting the RNA-dependent RNA polymerase (RdRp). The purpose of remdesivir as a prodrug is to encourage improved cell wall permeability. Nucleoside triphosphate GS-441524, the pharmacologically active version of remdesivir, is produced by significant metabolism after being present intracellularly. SARS-CoV-2 RdRp competes with natural adenosine triphosphate as it inserts itself into the RNA chain using GS-441524, delaying chain termination and viral replication [32-34].

6. EFFECTIVENESS OF REMDESIVIR IN COVID-19; CLINICAL EVIDENCE

On October 22, 2020, the U. S. Food and Drug Administration (FDA) approved Veklury (remdesivir) as the initial antiviral medication for COVID-19. Gilead Sciences developed the antiviral drug Remdesivir (GS-5734) as the result of significant research that started in 2009 and was first concentrated on the hepatitis C virus and respiratory syncytial virus. However, the antiviral profiling that started in 2013 and 2014 suggests that Remdesivir may have a broad-spectrum effect against several viruses. Gilead

Sciences researched remdesivir's effectiveness against Ebola, SARS, and MERS infections in collaboration with federal agencies and university institutions. Remdesivir, a novel investigational drug, just passed SARS-CoV-2 testing [36]. The prodrug remdesivir (GS-5734), an adenosine nucleotide analog, is converted to nucleoside monophosphate and phosphorylated to produce the nucleoside triphosphate derivative [37]. The essential enzyme for viral replication, viral RNA-dependent RNA-polymerase (RdRp), competes with native ATP to utilize the nucleoside triphosphate derivative, resulting in the premature termination of the viral RNA strand (Al-Tannak, Novotny, & Alhunayan, 2020; Calvin J Gordon et al. 2020). Additionally, the integrated nucleoside triphosphate form is not recognized by viral exoribonuclease-mediated proofreading (Agostini et al. 2018). According to molecular docking research, Remdesivir would bind to SARS-CoV-2 RdRp with a strong affinity, indicating its molecular mode of action [38].

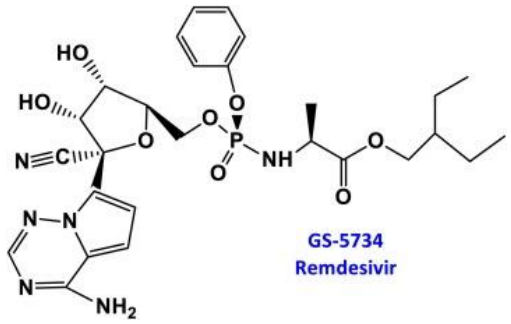

Fig. 1. Structure of Remdesivir [29]

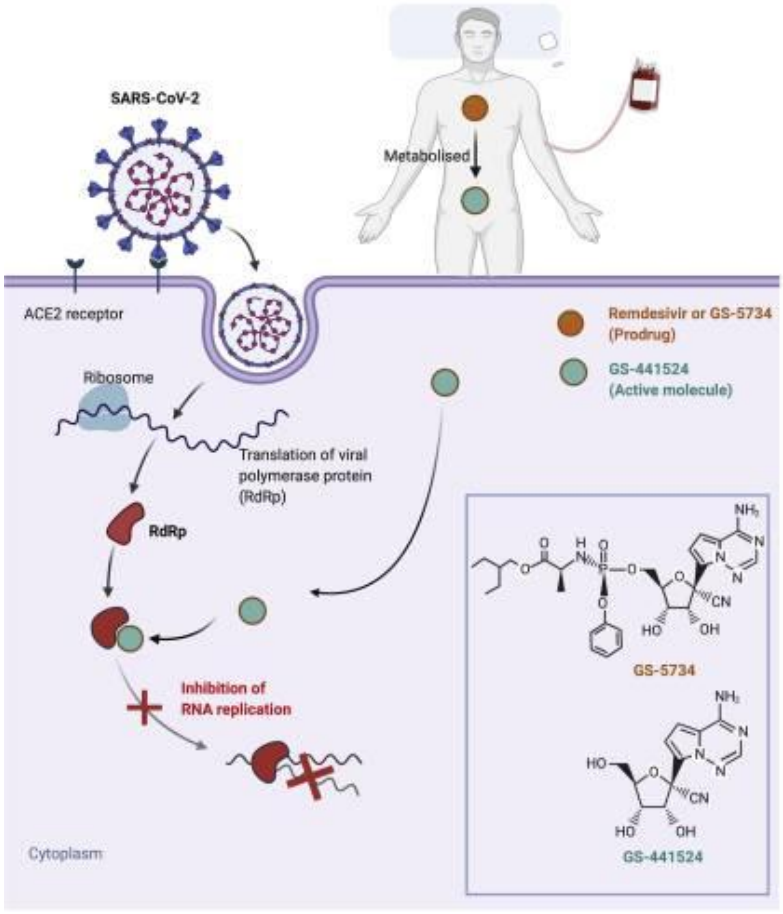

Fig. 2. Structure and mechanism of action [35]

Remdesivir was given by Gilead Sciences to 61 patients with severe COVID-19 disease whose oxygen saturation was below 94% on a compassionate basis. About 68% of these patients demonstrated clinical improvement. Therefore, assessing remdesivir's efficacy in the management of COVID-19 was of utmost significance. Remdesivir was administered therapeutically in all clinical studies at doses of 200 mg intravenously on day 1 and 100 mg everyday thereafter. The effectiveness of remdesivir was assessed in the first randomized, double-blinded, placebo-controlled clinical trial in patients with severe COVID-19 who had pneumonia and oxygen saturation below 94%. For 10 days, patients were given remdesivir (n=158) or a placebo (n=79). Due to local efforts to contain the outbreak in Wuhan, China, this study did not reach its intended recruitment goal and was not statistically powered. Remdesivir had no impact on the length of oxygen therapy, length of hospital stay, viral load, mortality rate, or time until clinical improvement. However, remdesivir patients required less time for mechanical ventilation than those who got a placebo, even though this difference was not statistically significant. The study was stopped more frequently by individuals in the remdesivir arm due to significant side events such as respiratory failure and acute respiratory disease syndrome (ARDS).Although patients receiving remdesivir had clinical improvement more quickly than those receiving a placebo, this difference was still not statistically significant. Therefore, additional clinical research is required before drawing strong conclusions [39,40].

Remdesivir is now being tested in 45 registered clinical trials for COVID-19 patients that are in the recruitment stage. Due to a lack of supporting data, the World Health Organization (WHO) issued a conditional recommendation on the use of remdesivir in hospitalized patients on November 20, 2020 [41].

7. EFFICACY AND SAFETY OF REMDESIVIR

Remdesivir was generally well tolerated and119 adverse events were observed. The most frequent of which were nausea and vomiting (45.40% of patients), followed by elevated liver enzymes (14.28%). At the time of data collection, 8.4% of patients had been treated or made improvements, 6.77% had passed away, and 9.16% had no improvement. According to subgroup studies, patients under 60 years old had a considerably lower mortality rate than patients over 60 years old. Patients undergoing oxygen therapy had a considerably greater cure/improvement rate when given standard low-flow oxygen as opposed to mechanical ventilation, non-invasive ventilation, or high-flow oxygen. Age > 60 years, heart disease, diabetes, high flow oxygen, non-invasive ventilation, and mechanical ventilation were factors linked to greater mortality. Remdesivir is well tolerated and has an acceptable safety profile, according to research. (Vaishali Gupte et al.) The clinical outcome of cure or improvement was 84% and patients under 60 years old and using regular low-flow oxygen showed greater improvements [42].

8. CONCLUSIONS

The unique coronavirus infection, originally discovered in Wuhan at the end of 2019, has drawn much attention. Although the number of infectious cases has reached over 100,000 worldwide and is now regarded as a pandemic, a "specific treatment" hasn't yet been made available. Relevant research reveals that the new coronavirus and SARS are genetically very similar, sharing 80% of their genes. The problem that emerges when newly created pharmaceuticals cannot be given to patients straight away has a workable solution: "Conventional drug in novel use". Because Remdesivir was the first treatment the recovered patients used in the US, it earned the nickname "specific drug."

"Remdesivir has also been quickly enrolled in clinical studies in China to be used as a clinical treatment for the Corona Virus Disease that would be prevalent in 2019 (COVID-19). The starting points were the structure, immunogenicity, and patho-physiology of coronavirus infections brought on by the novel coronavirus. Analyses of the pharmacological outcomes of previous trials with Remdesivir were reviewed to assess the feasibility of investigating COVID-19. As the COVID-19 epidemic spreads across the globe, the scientific community has come together to research and evaluate novel drugs and vaccines, from government laboratories to small biotechnology companies to large pharmaceutical companies. Repurposing or repositioning an effective small-molecule medicine is the fastest treatment strategy to limit the pandemic's progress. One of the potential medicines, remdesivir, has demonstrated coronavirus effectiveness both in vitro and in

vivo. Recent studies on Remdesivir's ability to help COVID-19 patients experience some treatment improvement in accordance with a compassionate use indication are encouraging [43-48].

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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