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A Review on Remdesivir: An Antiviral Drug

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Abstract

Remdesivir (GS-5734) is the first approved treatment for severe coronavirus disease 2019 (COVID-19). It is a novel nucleoside analog with a broad antiviral activity spectrum among RNA viruses, including ebolavirus (EBOV) and the respiratory pathogens Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, and SARS-CoV-2. First described in 2016, the drug was derived from an antiviral library of small molecules intended to target emerging pathogenic RNA viruses. In vivo, Remdesivir showed therapeutic and prophylactic effects in animal models of EBOV, MERS-CoV, SARS-CoV, and SARS-CoV-2 infection. Remdesivir reduces the time to recovery of hospitalized patients who require supplemental oxygen and may have a positive impact on mortality outcomes while having a favorable safety profile. Although this is an important milestone in the fight against COVID-19, approval of this drug will not be sufficient to solve the public health issues caused by the ongoing pandemic.

Keywords: COVID-19, Remdesivir, Viruses, SARS-CoV-2, Clinical Trial

Introduction

Remdesivir (Veklury) was the first drug approved by the FDA for treating the SARS-CoV-2 virus. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg. The broad-spectrum antiviral is a nucleotide analog prodrug. It is administered via injection into a vein. During the COVID-19 pandemic, remdesivir was approved or authorized for emergency use to treat COVID-19 in around 50 countries. Updated guidelines from the World Health Organization in November 2020 include a conditional recommendation against the use of Remdesivir for the treatment of COVID-19.[1]

Coronaviruses are a family of enveloped viruses with a positive-sense, single-stranded RNA genome that infects animal species and humans. Among coronavirus members are those responsible for the common cold, severe acute respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome-related coronavirus (MERS), and the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative pathogen of the disease COVID-19).[2]

COVID-19 disease appears to be a spectrum of clinical presentations ranging from asymptomatic to severe respiratory failure. Common symptomology at the onset of illness are fever, cough, and general myalgia, with less common symptoms including sputum production, headache, and diarrhoea.

Remdesivir was originally developed to treat hepatitis C and was subsequently investigated for Ebola virus disease and Marburg virus infections[3] before being studied as a post-infection treatment for COVID-19.

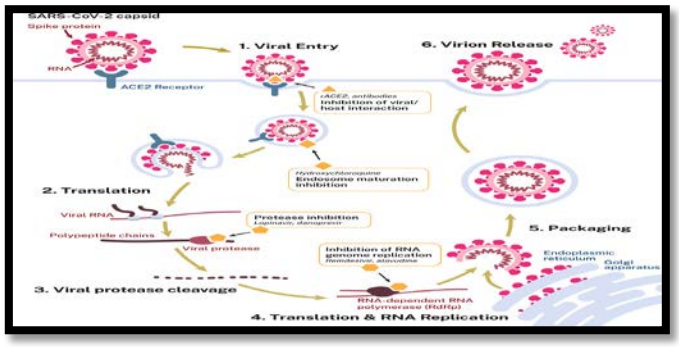

Figure 1

Development of Remdesivir

Remdesivir was invented by Gilead building on more than a decade of our research. Over that time, our research scientists have explored the compound for multiple potential uses to help address urgent and unmet medical needs around the world, including Ebola, SARS, Marburg, MERS and most recently COVID-19. Our antiviral expertise is the result of more than 30 years of research and the investment of billions of dollars in research and development. Gilead's antiviral work reflects its commitment to collaborating with the global health community and advancing potential treatments that may help in the global response to public health emergencies. The research that led to remdesivir began as early as 2009, with research programs under way in hepatitis C (HCV) and respiratory syncytial virus (RSV).[4]

Such prodrugs are typically more permeable and metabolized to liberate the nucleoside or phosphorylated nucleoside within cells. GS-5734 (remdesivir) possessed broad activity against RNA viruses, multiple groups assessed antiviral activity both in vitro and in vivo, validating its activity against coronaviruses. Antiviral activity was confirmed against SARS, MERS zoonotic coronaviruses, as well as the circulating human coronaviruses HCoV-OC43 and HCoV-229E, causative agents of the common cold.[5] Furthermore, **de Wit et al.** demonstrated that remdesivir had both prophylactic and

therapeutic activity against MERS in a nonhuman primate in vivo model.

De Wit et al.[6] that remdesivir had both prophylactic and therapeutic activity against MERS in a nonhuman primate in vivo model. Remdesivir is administered via an intravenous injection (IV) with a loading dose on day 1 (200 mg in adults, adjusted for body weight in pediatric patients) followed by a daily maintenance dose (100 mg in adults) for up to 10 days. In nonhuman primates, daily administration of 10 mg/kg of remdesivir yielded a short plasma half-life of the prodrug ($t_{1/2}$= 0.39 h), but sustained intracellular levels of the triphosphate form.

Mechanism of action

Remdesivir is a monophosphoramidate nucleoside prodrug that undergoes intracellular metabolic conversion to its active metabolite nucleoside triphosphate (NTP). As described for several other direct-acting antivirals, the active metabolite of remdesivir (remdesivir triphosphate [remdesivir-TP] or GS-443902) subsequently targets the machinery responsible for the replication of the viral RNA genome, a highly conserved element of the viral life cycle. Nucleoside analogs are synthetic compounds that work by competition with endogenous natural nucleoside pools for incorporation into replicating viral RNA. While these compounds mimic their physiological counterparts, the incorporation of the analog molecule disrupts subsequent molecular processes. The drug target and the exact processes that lead to the inhibition of viral replication have been studied extensively in ebolavirus.[7] (The suggested drug target, the EBOV RNA-dependent RNA polymerase (RdRp) complex, was only recently biochemically purified, which allowed for in-depth molecular analyses. Viral RdRp is the target protein for the active metabolite remdesivir-TP. Remdesivir-TP acts as the substrate for RdRp where it competes with ATP for incorporation into new strands. Inhibition of EBOV RdRp most probably results from delayed chain termination, a mechanism that is known from approved antivirals against human immunodeficiency virus type 1 (HIV-1) and HBV.[8] In the case of EBOV, the incorporation of remdesivir-TP into replicating RNA was observed to cause chain termination predominantly at five positions downstream (i + 5). Importantly, the activity of human RNA polymerase is not inhibited in the presence of remdesivir-TP.

Clinical Studies

Among 1,200 adult patients, 76 pediatric patients, and 96 pregnant women with COVID-19 were treated with remdesivir through the compassionate-use program according to the manufacturer Gilead Sciences. Liver function test abnormalities were reported in 19 of 163 evaluated cases. Once the COVID-19 epidemic started in China, at a time when there was no clinical trial in preparation, the first observational data for remdesivir arose from patients treated under compassionate use. In a prospective cohort study funded by Gilead Sciences, 61 patients with COVID-19 were treated with remdesivir for a 10-day course (200 mg on day 1, followed by 100 mg daily). Clinical improvement was observed in 36 (68%) of 53 evaluable patients. Another study from Italy reported on 35 patients treated with remdesivir in a general infectious disease ward. Interpretations of data from this study are very limited due to the low sample size, as only 22 patients completed a 10-day treatment course. The most frequent adverse events (AEs) were elevations of liver transaminase levels (15/35 patients) and acute kidney injury (8/35 patients).[9] As there were no control groups, no efficacy statements can be made based on these studies. One approach with a simulated control group is currently under peer review and suggests reductions in mortality with remdesivir.[10] Several clinical trials were conducted to evaluate its efficacy against EVD and COVID-19.

Covid-19

The first randomized-double-blind, placebo-controlled, multicenter clinical trial was reported on April 29, 2020.[11] The study was conducted in China with 237 patients (158 in the remdesivir group and 79 in the placebo control group), and the primary endpoint was the time taken to achieve clinical improvement. The study revealed that treatment with remdesivir did not lead to a significant reduction in the time taken to achieve clinical improvement. In addition, mortality and viral clearance time in patients with severe COVID-19 were not significantly different from those in the placebo group, suggesting that remdesivir had poor clinical benefits. This further suggests that in COVID-19, viral propagation is not the main factor responsible for disease severity. On this account, the antiviral properties of remdesivir will not be beneficial. The severity of COVID-19 has been associated with the cytokine release storm, suggesting that host immune responses play an important role in this event. Therefore, a combination of remdesivir with immunosuppressants (for example sarilumab, an IL-6 the inhibitor) and/or other antiviral agents might potentiate the antiviral activity of remdesivir and mitigate the immunopathological injury caused by excessive immune effectors.[11]

Adverse Effects

1. Phlebitis
2. Constipation
3. Headache
4. Ecchymosis
5. Nausea
6. Pain in extremities
7. Elevations of ALT and AST
8. Mild Hyperglycemia
9. Prolonged Prothrombin

There is no evidence for grade 3 to 4 or even severe adverse events resulting from once-daily doses of remdesivir (75 mg up to 225 mg i.v.) for treatment durations of up to 14 days. The drug seems to be well tolerated.[12] Grade 1 and 2 adverse events have been described in healthy volunteers and patients with COVID-19 treated with remdesivir and mainly refer to transient elevations of ALT or AST levels. There are not sufficient data on the safety of remdesivir in patients younger than 18 years of age and pregnant women. Long-term toxicities are known from other nucleoside analogs used for sustained antiviral treatments of chronic infections with HIV or HBV but should not be of relevance for the relatively short-term treatments with remdesivir.

Future Vista

Remdesivir is the first nucleoside analog that can be used to treat infections caused by a respiratory virus. In the light of its beneficial clinical effects, its favorable safety profile, and the absence of alternatives to treat COVID-19, remdesivir will increasingly be used outside the context of clinical trials or compassionate-use programs. The drug is already available in the United States and Japan based on emergency-use authorizations and was recently approved in Europe. However, treatment with the antiviral drug remdesivir alone will not be sufficient to reliably save the lives of patients suffering from COVID-19 or to solve the hazardous public health issues caused by the ongoing COVID-19 pandemic.

Antiviral therapy in hospitalized patients cannot prevent the virus from being transmitted among communities and cannot reverse patho-physiological processes that have occurred already at the time of diagnosis. In general, prophylactic measures would be much more efficient in reducing COVID-19-associated morbidity and mortality as well as economic implications.

The therapeutic efficacy of remdesivir might be improved by the addition of other antivirals or immunomodulatory agents. It has recently been shown that glucocorticoids are able to improve clinical outcomes in cases of severe and critical COVID-19.[13]Based on these data, it can be expected that physicians will use both remdesivir and glucocorticoids to treat patients with severe or critical COVID-19. However, combination therapy should be used with caution, as drug interactions may occur. In vitro, remdesivir acts as the substrate or inhibitor of several drug-metabolizing enzymes (e.g., CYP3A4), which could influence the exposure levels of other therapeutic agents. In addition, these agents may interfere with the pharmacokinetics of Remdesivir. The immunomodulatory drug hydroxychloroquine seems to reduce the antiviral activity of Remdesivir by impairing its metabolic activation.

Conclusion

Remdesivir is a nucleotide analog prodrug that inhibits SARS-CoV-2 RdRp. Its viral activities against SARS-CoV-2 have been shown in both in vitro and in vivo studies. Remdesivir has been used in several countries as an emergency drug for patients with COVID-19, and some patients showed improved clinical outcomes. However, large-scale clinical trials should be conducted to confirm the efficacy of remdesivir in treating patients with COVID-19. Further scientific efforts are needed to evaluate the full potential of nucleoside analogs as treatment or prophylaxis of viral respiratory infections and to develop effective antivirals that are orally bioavailable.

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