International Journal of Educational Research and Development
www.journalofeducation.in
Online ISSN: 2664-7095
Received: 17-05-2021, Accepted: 02-06-2021, Published: 17-06-2021
Volume 3, Issue 2, 2021, Page No. 28-31

Remdesivir: A promising drug against COVID-19

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Abstract
Whole world is suffering from severe health hazards, which is in the form of Severe Acute Respiratory Syndrome. Remdesivir (G-5374) is considered to be one of the most promising drug against COVID-19 as it as antiviral properties which are helpful in decreasing the length of illness period and need of ventilators for the patients. It is a nucleoside analog which has broad spectrum antiviral activities. It has been tested for many viral diseases like EBOLA, MERS, SARS and SARS Co-V-2. It has been seen that remdesivir decreases the death rates in some of the countries. It has been approved by US and Japan for using it intravenously for treating hospitalized patients. India is also using remdesivir to overcome the present scenario as the Indian variant of COVID -19 has affected middle aged people in the second wave in India. It's a drug which was manufactured by Gilead Sciences, a pharmaceutical company which works mainly to develop antiviral drugs. It was firstly used for EBOLA virus during it's outbreak in South Africa. With the start of pandemic, the use of remdesivir started for patients of COVID -19 infections. It has been seen that it is effective when it is administered in early stages of the infection. Remdesivir interfere with the RNA replication of the virus and thus inhibit it's activity. Many clinical trials have shown that remdesivir has decreased the supplementary oxygen requirement. Many trails have also warned about the side effects of this drug. But as the infection of COVID-19 has engulfed many people. Many countries has lost most of the population and struggling with it, it has been suggested that an oral antiviral drug must be develop which must have high potential, high antiviral activity so that the present scenario of pandemic could be finished and the transmission of COVID -19 could be stopped. Still, there is need of more potential clinical trials seeking for the effectiveness of remdesivir along with other drugs. It has been suggested that more studies must be done to understand the clear side effects of the drug.

Keywords: remdesivir, clinical trials, viron, nucleoside analogue

Introduction

In December 2020, an acute respiratory syndrome called SARS Co-V 2 was detected in Wuhan, China. Soon this prevailed in whole world. Some of the worst affected countries are the USA, Italy, Spain, France, Iran, Afghanistan, etc. With the start of the pandemic, no medication was known and with the progress of the research in this field, various antiviral drugs were tested against COVID-19. On October 22, 2020, FDA approved Veklury (remdesivir) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization[1]. Remdesivir should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Researchers have tested remdesivir in clinical trials during Ebola outbreak. Various studies on animal cell have shown that it is effective against respiratory diseases caused by the coronavirus family - Middle East Respiratory Syndrome (MERS) and Severe Acute respiratory Syndrome (SARS). Researchers have done random clinical trials under controlled conditions in February2020 for testing the efficiency of remdesivir against SARS Co-V -2. By early April promising results were obtained showing that remdesivir has accelerated the recovery of patients who were hospitalized. Researchers have completed the clinical trials known as the Adaptive COVID-19 Treatment Trial (ACTT-1) The funding agency for this study was the National Institute of Allergy and Infectious diseases (NIAID). The final report of this study was published in the New England Journal of Medicine on 8th Oct. 2020.

Objectives

- To know the efficiency of remdesivir in treatment of COVID -19 infection.
- To know the mode of action of Remdesivir as a broad spectrum antiviral.
- To know the side effects of Remdesivir.

Research Methodology

To achieve the objectives, the researcher has reviewed many research papers, research articles, medical reports, medical letters, government and non- government data and reports of clinical trials.

Journey of Remdesivir with Gilead Sciences: Remdesivir was developed by Gilead Sciences. It is a biopharmaceutical company of America having Headquarter in Foster City, California. Its main function is to develop antiviral drugs used in the treatment of viral diseases like Herpes, Ebola, Hepatitis, Influenza and many more. Remdesivir is an investigational new drug created by Gilead. 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). Many Studies and

continuous researches show that remdesivir is has antiviral properties which have been confirmed by many clinical trials. (***Gilead sciences***) [2].

Development of remdesivir started with the Ebola virus outbreak in 2014 in West Africa. Gilead worked with the U.S. CDC and the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) respectively to test collections of Gilead's antiviral molecules and confirmed remdesivir was active against Ebola and other viral pathogens representing potential global health threats. In parallel with the researches on Ebola virus, Gilead also started its researches for antiviral drugs for MERS and SARS in late 2014 in collaboration with different institutions. And soon in January 2020, with the outbreak of COVID-19 pandemic, Gilead started finding of potential of remdesivir against SARS Co-V-2.In February 2020, Gilead started multiple clinical trials to find out the potential and safety of remdesivir against COVID-19. Gilead donated study drug and provided scientific input for two clinical trials coordinated by the China-Japan Friendship Hospital in China, which began enrolling patients in early to mid-February. Gilead has provided input on the design of both WHO's global Solidarity trial and the INSERM-sponsored discovery trial in Europe. In late February, Gilead initiated its own two Phase 3 studies of remdesivir, which enrolled patients in countries globally with high numbers of diagnosed COVID-19 cases. These studies began enrolling patients in March 2020 and will evaluate two dosing durations of remdesivir. Gilead also provided study drug to two clinical trials conducted by China and Japan together in Friendship hospital of China conducted clinical trials. After positive results of administration of remdesivir in clinical trials in many countries on May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow the use of remdesivir for the treatment of suspected or laboratory-confirmed Covid-19 in adult and pediatric patients hospitalized with severe disease.

Chemical composition of Remdesivir

Remdesivir was formerly called GS-5734. It acts as a prodrug of nucleoside analogue which is effective against single stranded RNA viruses as it has direct antiviral activity against them. It is likely to have antiviral properties against novel SARS- Co-V-2. Chemically, it is a phosphoramide prodrug having 1' cyano substituted nucleoside analogue. Its molecular formula is $C_{27}H_{35}N_6O_8P$. Its 2D structure can be given as in (figure-1)

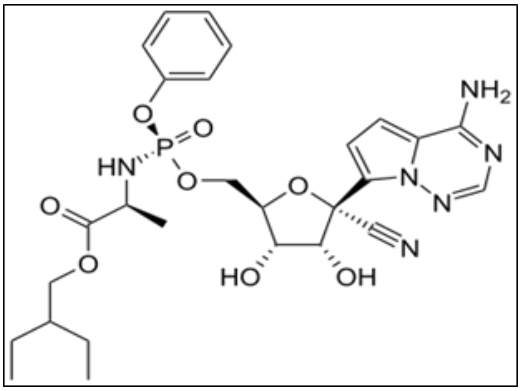

Fig 1: Chemical structure of Remedesivir

(**Source:**https://en.wikipedia.org/wiki/Remdesivir#/media/File:Remdesivir.svg) [12]

Upon administration into the body of Patient it changes itself to active form i.e., GS-441524 which is responsible for the inhibition of replication of viral RNA via RNA dependent RNA polymerase. It has chemical formula $C_{12}H_{16}N_5O_{13}P_3$. Its molecular structure can be given as in (figure 2)

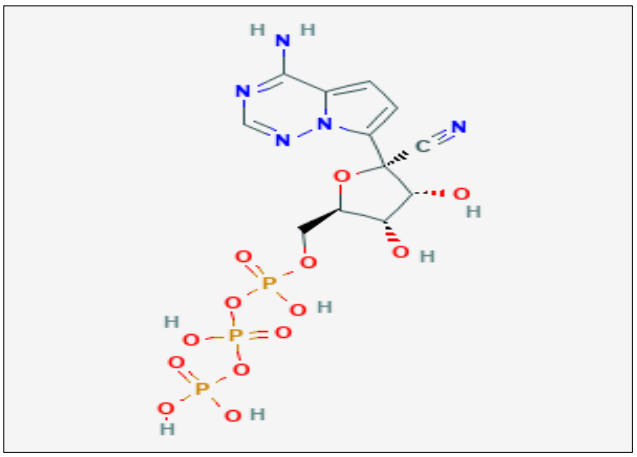

Fig 2: Chemical structure of active remdesivir (Remdesivir triphosphate)

(Source:https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir-triphosphate) [13]

Mode of Action

Remdesivir is a prodrug in the form of monophosphoramide nucleoside. After administration it undergoes metabolic conversion to form active nucleoside triphosphate. This nucleoside triphosphate is named as GS-443902 or remdesivir-TP. This metabolite targets the viral genome undergoing replication. The active form of remdesivir act as synthetic nucleoside analogue, compete with the natural one and get incorporated into the genome of the virus.This inhibits the molecular processes of the virus and makes it inactive.[3] By various studies conducted on mode of action of remdesivir, it has been clear that in case of SARS Co-V and MERS- Co-V, nsp-12 polymerase is a RNA synthesis complex[4]. Remdesivir interferes with it which causes inhibition of viral action. It causes termination of RNA replication and these results in stoppage of translational and transcriptional processes which are responsible for formation of new virions. This is how remdesivir works according to different studies based on experiments and clinical trials [5].

Evidence from clinical trials

Many clinical trials have been conducted to make the antiviral activity of remdesivir clear and effect of administration time on SARS Co-V 2. One of the studies was done on 35 years old woman in the US which showed mild symptoms of COVID-19 which includes mild coughing and low temperature fever[6]. She had continued with the mild symptoms but after 9 days she contracted symptoms of pneumonia and decrease in the saturation of oxygen level. When she was administered with remdesivir, she started to recover fast with an increase in the level of oxygen after 11 days. At the time of discharge from the hospital, she was having only a mild cough.

A study done by Wang *et al* on remdesivir has also shown that remdesivir is able to inhibit the infection of COVID-19 in human liver Huh- 7 cells [7]. A study done by WHO as reported in World Health Organization, Coronavirus disease 2019 (COVID-19) situation report-41, remdesivir was administered in 53 patients out of which 68% recovered while mortality rate was only 13%. This study also shows that remdesivir is a potential drug against COVID -19 infections. It could not only inhibit the replication of virions but also decrease the mortality rate of the patients [8].

Gilead sciences have also conducted various clinical trials to find the efficiency of remdesivir. The clinical trials include phase 3 simple trails on the patients having moderate COVID-19 symptoms. This open-label study evaluated 5-day and 10-day courses of the investigational antiviral remdesivir plus standard of care, versus standard of care alone. The study demonstrated that patients in the 5-day remdesivir treatment group were 65 percent more likely to have clinical improvement at Day 11 compared with those in the standard of care group (OR 1.65 [95% CI 1.09-2.48]; p=0.017). The odds of improvement in clinical status with the 10-day treatment course of remdesivir versus standard of care were also favorable, trending toward but not reaching statistical significance (OR 1.31 [95% CI 0.88-1.95]; p=0.18) [9]

Adverse effects

The studies done by Gilead Sciences shows that there are various side effects of Remdesivir like the patients experience headache, ecchymosis, nausea, extreme pain and Phlebitis. The same effects are also shown by the PK studies after administration of remdesivir doses up to multiple doses of 150 mg once in a day for 7 days or 225 mg single doses for 7 days or 14 days or 200 mg once followed by 100 mg daily for 5 -10 days. It has been shown by the report dealing with the first 12 cases of US that three patients who were administered with remdesivir increased the level of Transaminase and shown various gastrointestinal symptoms [10]. The reports of FDA has reported that among 163 patients enrolled for clinical trials, overall liver function test abnormalities was 11.7% only [11].

Conclusion

Remdesivir is proactive antiviral drug which has shown promising effects on the patients enrolled in various clinical trials. It is now clear that if remdesivir is administered in early stages of the COVID-19 infection then it decreases the rate of mortality and reduce the days of illness. Administration after a delay, remdesivir may not be as effective as it could be if given at early stages. It has been also suggested that the patients with renal disorders and hepatic diseases must not be given remdesivir as it may increase various complexities in the patients. Remdesivir in the body of patients, gets converted to active drug remdesivir triphosphate which then interferes with the genome of the virus and thus interrupts the replication of RNA inside the virus. Due to such activity, Remdesivir is found active against various viral diseases like EBOLA, MERS, SARS, SARS Co-V-2. It is suggested that there must be more clinical trials for using remdesivir so that its potential becomes More clear. It has been also suggested that the clinical trials must also be done for studying the side effects of remdesivir. Various countries must come together to find out the potential antiviral drug against COVID-19 as it has affected each and every part of the World. Many people died and many are dying because of lack of efficient drug which could be effective for different variants of SARS Co-V-2.Although, remdesivir has antiviral properties but alone it could not be effective. It is not reliable that it could decrease the rate or mortality or save the life of a person suffering for severe illness of COVID-19. It could not stop the transmission of virus among the people of a community. The need of the hour is such a drug is to be designed that it must be effective in severe illness, has less side effects and prevent the deaths of the patients.

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