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Role of Remdesivir in the Management of Covid-19- A Review

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Abstract

Today the world is facing a pandemic and the cause of this pandemic (Covid-19) is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As such there is no specific antiviral drug available for the treatment of Covid-19. Remdesivir is a broad-spectrum antiviral drug which act by inhibiting RNA dependent RNA polymerase. It is a prodrug and upon activation inside the host cell converted into active form, Remdesivir nucleoside triphosphate (adenosine triphosphate analogue) which compete with natural counterpart ATP, for incorporation into viral RNA. It leads to termination of chain elongation of RNA dependent RNA polymerase. In various studies Remdesivir has shown promising effect for the management of Covid-19 hence US FDA has issued an Emergency Use Authorization (EUA) for its use in the management of Covid-19 but WHO's latest recommendations do not promote it. With this background we tried to present review of Remdesivir to give details about its pharmacokinetics, pharmacodynamics, safety issues and recommendations.

***Keywords**: Remdesivir, Covid-19, WHO*

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Introduction

The cause of Covid-19 is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is a respiratory disease which can progress to viral pneumonia and acute respiratory distress syndrome (ARDS) which can be life threatening. For genomic replication SARS-CoV-2 depends on RNA dependent RNA virus which can be inhibited by nucleoside analogue type of drugs. [1]

As of now there are many antiviral drugs have been evaluated for the management of Covid-19 but so far, no antiviral drug has shown promising effects in the management of the Covid-19. Remdesivir (GS-5734) is an adenosine triphosphate analogue, an RNA dependent, RNA polymerase inhibitor is a broad-spectrum antiviral drug both in vitro and in vivo in animal models against Ebola, SARS, Marburg, MERS and SARS-CoV-2. It's activity against the *Coronaviridae* family was first described in 2017. [2] In early studies it has shown some promising effects in Covid-19 as it decreases lung viral load and decreases consequent lung damage. [3] The US FDA has issued an emergency use authorization (EUA) for the Remdesivir to treat infection SARS-CoV-2 on May 1st 2020. [4] The emergency use authorization is based on a randomized clinical trial which showed reduced recovery time of hospitalized patients who were diagnosed with Covid-19. Full approval for Remdesivir as a COVID-19 treatment was granted on October 22, 2020 by US FDA. It is presently prepared and marketed by Gilead Sciences with Veklury. [5,6] Remdesivir is a prodrug which target the RNA-dependent RNA polymerase (RdRp) of RNA viruses.

History

Pharmaceutical company Gilead Sciences developed Remdesivir in an effort to identify therapeutic agents against RNA-based viruses which has potential for global pandemic. It received wide attention when first described in literature and used against Ebola virus in 2016. The company developed nucleoside analogue GS-441524, the prodrug form of which is Remdesivir or GS-5734. It was found highly effective against RNA viruses such as yellow fever virus, Dengue virus type 2, influenza A, parainfluenza 3, and SARS. Remdesivir shown cytoprotection effect when used against SARS strain Toronto 2 in a 2012 study. During the Ebola virus outbreak in 2014, it was found that Remdesivir also has good antiviral potential against other viruses such as coronavirus. In 2017 its activity against coronavirus family was described in detail. On 1st May 2020 US FDA granted emergency use authorization for the use against SARS-CoV-2. [7,8]

Structure

Remdesivir is a 2-ethylbutyl *L*-alaninate phosphoramidate prodrug. The molecular formula of Remdesivir is $C_{27}H_{35}N_6O_{88}P$ and molecular weight is 602.6 g/mol. It is a prodrug of Adenosine Triphosphate (ATP) analogue. It is converted into its active form GS-441524 upon administration. It is available in the powder form for solution intravenous infusion. [8]

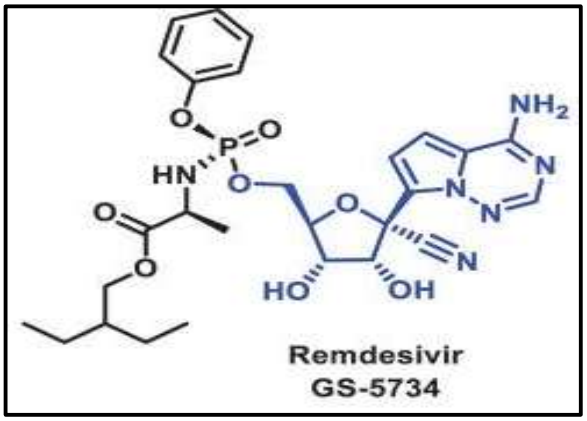

Figure 1. Remdesivir.
Source:
https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir

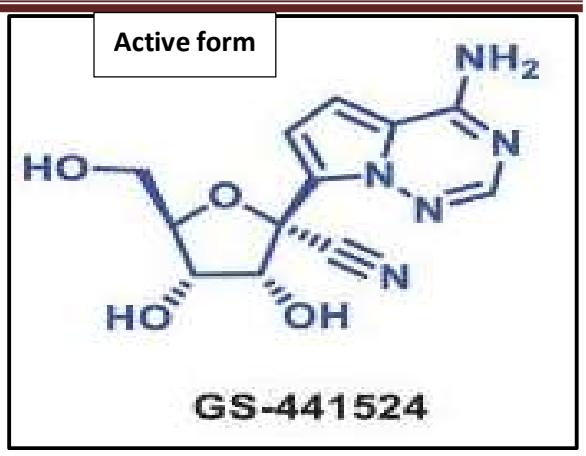

Figure 2. GS441524.
Source:
https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir

Pharmacokinetics

On oral administration, Remdesivir has very low bioavailability. After intramuscular injection the bioavailability is 50%. Remdesivir is absorbed quickly after intravenous administration. Maximal plasma concentration reaches in 0.67-0.68 hours after single dose of 30 minutes IV infusion. [9] A 10 mg/kg intravenous dose given to cynomolgus monkeys distributes to the testes, epididymis, eyes, and brain within 4 hours. Plasma protein binding of Remdesivir (GS-5734) is 88-93.6% while its active metabolite GS-441524 has 2% plasma protein binding capacity. [10]

After diffusion into the host cell Remdesivir (GS-5734) is converted into carboxylate in esterase mediated reaction which create unstable cyclic anhydride. Cyclic anhydride hydrolyzed to alanine metabolites which is converted into nucleoside monophosphate by phosphoramidase enzyme. Phosphorylation of nucleoside monophosphate leads to generation of nucleoside triphosphate derivative. [10]

Elimination of Remdesivir is mainly through urine (74%) although 18% eliminated through faeces. 49% eliminated drug is in the form of metabolite GS441524 while 10% is unchanged Remdesivir. Elimination half-life of Remdesivir is 1 hour when single dose intravenous infusion is given while GS441524 has 27 hours with the same dose. [11,6]

Mechanism of Action

Remdesivir produces antiviral activity by interfering with the activity of RNA-dependent RNA-polymerases (RdRp) through its triphosphate metabolite. [4] Since Remdesivir is a prodrug, it is converted into active metabolite GS441524 into the host cell. GS441524 is an adenosine triphosphate (ATP) analogue which compete with natural counterpart ATP, for incorporation into viral RNA. Remdesivir triphosphate has 3.65 time more selectivity for incorporation into the RNA dependent RNA polymerase complex (RdRp) of SARS-CoV-2 than endogenous adenosine triphosphate (ATP) hence incorporated very well in the SARS-CoV-2 RNA dependent RNA polymerase complex. After addition of Remdesivir triphosphate into the growing chain (i position), it does not stop the growth immediately as Remdesivir has a free 3'-hydroxyl group that allows for continued chain elongation. Extension of three more nucleotides occurs and at *i*+ 4 which corresponds to the position for the incorporation of the fourth nucleotide, the 1'-cyano group of Remdesivir sterically clashes with Ser-861 of the RNA dependent RNA polymerase, preventing further enzyme translocation and terminating replication at position *i* + 3 position (delayed chain termination). [9,12,13,14]

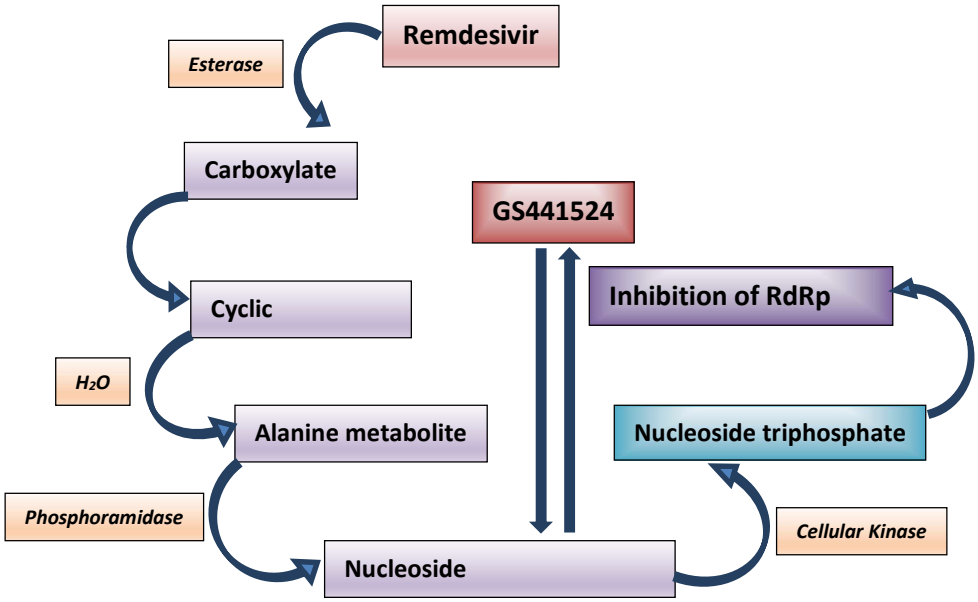

Figure 3. Inhibition of RdRp

Adverse Drug Reactions

Generally, Remdesivir is a well-tolerated drug in healthy subjects. [15] But hypersensitivity reaction can occur with the use of Remdesivir including infusion related reactions. Generalized seizure are also observed in less than 2% adult population with the use of Remdesivir. [4] Other observed adverse events are increase in hepatic enzymes (ALT, AST and transaminases), constipation, nausea, diarrhoea, vomiting poor appetite, gastroparesis, Respiratory failure or acute respiratory distress syndrome, Pneumothorax, Hypotension, atrial fibrillation, hypertnatremia, cardiac arrest, renal impairment, acute kidney injury and hematuria. [16]

Laboratory abnormalities observed in 3% or more than 3% adult population with the use of Remdesivir in a clinical trial are; decrease creatinine clearance (18%), increase creatinine (15%), decrease haemoglobin (15%), increase glucose level (12%), decrease lymphocyte (11%), increase prothrombin time (9%), increase AST (6%), increase ALT (3%) and increase bilirubin in 2%.[4]

The most common adverse events observed in the study of Grein et al [17] were increased hepatic

enzymes, diarrhoea, rash, renal impairment, and hypotension which were more common in patients who received invasive ventilation. While the most common serious adverse events observed were multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension. [17]

In the study of Wang Y 66% patients reported adverse events. Among them the most common adverse events were constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin while serious adverse events reported in 18% patients which included respiratory failure. Remdesivir has to be stopped due to adverse events which included gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin increase, and worsened cardiopulmonary status. [5]

Drug Interactions

Role of CYP isoenzymes and transporter in the overall metabolism of Remdesivir is unclear but strong CYP3A4 inducers such as Rifampicin should not be co-administered as they can lead to decrease in Remdesivir level although drug interactions with CYP3A4 inhibitors or inducers are unlikely with Remdesivir. [18,19,20,21] Co-administration of Chloroquine and hydroxychloroquine also not recommended as these drugs may decrease antiviral activity of Remdesivir. [21]

Contraindications and Precautions

Remdesivir is contraindicated in patients who have history of hypersensitivity to it. There is insufficient clinical data regarding use of Remdesivir in pregnancy and its effect on developing foetus. Animal studies indicate no adverse consequences of its use during pregnancy. Also, there is no available data regarding presence of Remdesivir in human milk and its effect on the breastfed infant but in animal studies its presence is detected in the nursing rat pups of mothers who received Remdesivir. Its safety and efficacy in paediatric population below the age of 12 years and weighing at least 3.5 kg or paediatric patients weighing 3.5 kg to less than 40 kg have not been established. Pharmacokinetics of Remdesivir in renal impairment is not known but for its use, eGFR should be greater than or equal to 30 ml/min. Also, in liver disease Remdesivir has not been evaluated.

Indications

Remdesivir is indicated for the treatment of hospitalized Covid-19 adult and paediatric patients aged 12 years and over weighing at least 40 kg. Duration of treatment for the patients who does not require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) is 5 days while it is 10 days for those who require it. [10]

Dosage

The dose of Remdesivir is once daily since it's duration of action is moderate. The loading dose of Remdesivir is 200 mg intravenously diluted in normal saline (0.9%) or 5% dextrose to be given over 60 minutes on 1st day followed by a 100 mg maintenance dose intravenously diluted over 60 minutes for another 9 days. [22,23]

Clinical Studies

Beigel JH et al; conducted a double-blind, placebo-controlled, randomized, clinical trial. 1062 cases (541 in Remdesivir group and 521 in placebo group) of diagnosed hospitalized Covid-19 patients with lower respiratory tract infection were included in the study. Intravenous Remdesivir 200 mg (loading dose) was administered on day one while 100 mg in remaining 9 days, placebo was given to another group. The median recovery time for Remdesivir group was 10 days while it was 15 days in placebo group. According to Kaplan-Meier estimates, mortality rate was 6.7% in Remdesivir group while it was 11.9% in placebo group. Serious adverse events were observed in 24.6% patients of Remdesivir group while it was 31.6% in placebo group. The study concluded with the opinion that "Remdesivir shorten the recovery time". [22]

Goldman JD et al. in their randomized, open-label, phase 3 trial on confirmed hospitalized Covid-19 patients with oxygen saturation of 94% or less and radiologic evidence of pneumonia administered intravenous Remdesivir as 200 mg bolus dose one day 1 and 100 mg on subsequent daily dose for 5 days

group and 10 days group in 397 patients. The clinical status of 10 days group was worse in comparison to 5 days group. They observed clinical improvement in 64% patients of 5 days group while it 54% in 10 days group. After adjustment of baseline clinical status in 10 days group on 14th day, they found that the clinical condition was similar to 5 days group. The observed adverse events were nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). They concluded that there is no significant differences among the groups although they were not able to define the level of benefit of Remdesivir due to absence of placebo control. [24]

According to Christopher D Spinner et al. Remdesivir has superior efficacy in comparison to placebo in severe Covid-19 cases. It is also effective in 5 days course in patients of moderate Covid-19 but clinical status is insignificant if patients treated with Remdesivir for 10 days. Hence, they were uncertain about its efficacy in moderate Covid-19. Their study was randomized, open label in hospitalized moderate and severe Covid-19 cases with 200 mg loading dose on day 1 and subsequent maintenance dose of 100 mg. They compared the efficacy of Remdesivir of 5 days and 10 days with standard care with end point as clinical status on day 11. It was a multicentric study conducted in USA, Europe and Asia in which 533 patients completed the study. Adverse events observed with Remdesivir were nausea (10%), hypokalemia (6%), headache (5%). [25]

As per the WHO Solidarity trial in which 11266 adults participated and conducted in 405 hospitals in 30 countries shows that "Remdesivir does not produce any measurable benefit in mortality or disease course". Although the report is preliminary but conclusive. According to the study, Remdesivir does not shows any real trend towards improved survival, even a non-significant one. [26]

Low value on small and uncertain benefits and important adverse consequences and additionally contextual factors such as resources, feasibility, acceptability, and equity for countries and health care systems promoted WHO to discourage its use in Covid-19 patients.[27] Hence WHO suspended it from prequalification list. [28]

Conclusion

Remdesivir is a broad-spectrum antiviral drug. It inhibits RNA dependent RNA polymerase by incorporation of its active form "Remdesivir nucleoside triphosphate" into the viral RNA. It competes with natural counterpart ATP, for incorporation into viral RNA. It has favorable pharmacokinetics and generally well tolerated drug although hepatic and renal adverse events have been reported with its use in Covid-19 patients. Earlier it was reported to be superior to placebo in shortening the time of recovery in hospitalized Covid-19 patients. But as per the latest (November 2020) recommendation of WHO, it does not provide any additional advantages in Covid-19 patients hence WHO is now not recommending it for the management of Covid-19 patients.

Conflict of Interest: *None declared*
Source of Support: *Nil*

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