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A REVIEW ON REMDESIVIR AND ITS SIGNIFICANCE

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ABSTRACT Late 2019 and early 2020 observed rampant spread of the novel corona virus disease pandemic with global death toll of 257 thousand till date. The disease originated from Wuhan, the capital of Hubei province in central China, and metastized rapidly to major cities and countries. The pathogen was identified as novel coronavirus 2019-nCoV also called SARS-CoV-2 due to its close relatedness to SARS-CoV that caused the 2004 SARS [Severe Acute Respiratory Syndrome] outbreak. Currently there is no specific treatment against 2019-nCoV. An efficient approach for treatment is to combat the symptoms or/and attack the virus directly using broad spectrum antiviral drugs that are effective in treating other related viral infections such as Ribavirin, Penciclovir, Nitazoxanide, Nafamostat, Chloroquine, Hydroxychloroquine, Favipiravir and most important Remdesivir [1]. However the use of these drugs faces conflicting ideas. The current review focuses on the use of Remdesivir as the new face of treatment for COVID-19.

KEYWORDS : Antiviral, COVID-19, Remdesivir, Treatment

INTRODUCTION:

Remdesivir produced by a pharmaceutical firm, Gilead Sciences in January 2020 as a broad spectrum antiviral agent. It was originally developed to treat Ebola, Marburg and other viral infections but was however found to be ineffective [2]. Several In-Vitro studies have proved its activity against RNA viruses. Currently Remdesivir is being tested as an effective intravenous medication to COVID-19 with an Emergency Use Authorization [EUA] label in the United States.

Remdesivir has shown broad-spectrum prophylactic and therapeutic efficacy against members of several virus families, including filoviruses (like Ebola) and coronaviruses (like SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) in nonclinical models of these viruses such as cells cultures, mice models and nonhuman primate [NHP] models [3,4]. Intravenous administration of Remdesivir in NHP models has shown complete protection against Ebola eruptions [5]. Remdesivir reduced the severity of disease, virus replication, and damage to the lungs when administered either before or after animals were infected with MERS-CoV in Non-Human primate models like Rhesus Macaque monkeys [3]. Treatment of a rhesus monkey model infected with MERS-CoV, with Remdesivir 24 h before infection can completely prevent symptoms caused by MERS-CoV, strongly inhibit viral replications in the respiratory tract, and prevent the formation of pulmonary lesions. Administering Remdesivir 12 h after infection provides clear clinical benefits, reducing clinical symptoms, lung virus replication, and lung lesions [3]. Several clinical studies have been undertaken to prove its efficacy as a potential treatment to Ebola, SARS and MERS viral infections [6].

A Chinese clinical trial in February 2020 revealed that Remdesivir caused various adverse effects in patients suffering from COVID-19 [8]. However the US-FDA has stated that the benefits of Remdesivir outweigh its associated potential risks in treating COVID-19. The National Institute of Allergy and Infectious Diseases (NIAID) announced on 29th April 2020, that Remdesivir was better than a placebo in reducing recovery time for people with advanced COVID-19 and related respiratory disorders. Recent In-Vitro study revealed that Remdesivir also inhibits viral infections in human liver cancer Huh-7 cell lines that are sensitive to 2019-nCoV [7].

This article reviews current literature available on the structural characteristics, pharmacokinetics data, novel applications of Remdesivir and its mechanism of action and the potential side effects associated with it. Several In-Vitro studies have revealed that Remdesivir is efficient in control of 2019-nCoV. Therefore it is the need of the hour to all clinicians and scientists to assess the efficacy of antiviral agents like Remdesivir to combat the pandemic and its pathogen persistent globally.

STRUCTURE OF REMDESIVIR:

Remdesivir with a synonym GS-5734, is an adenosine triphosphate [ATP] [see FIG 1] analogue first described in the literature in 2016 as a potential treatment for Ebola. Chemically it is 2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl] amino] propanoate [see FIG 2] with a molecular formula C27H35N6O8P and molecular weight of 602.6 g/mol.

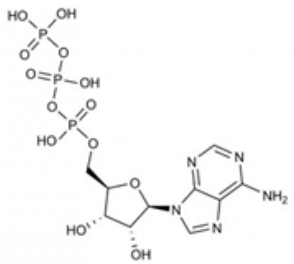

FIG 1: Structure of Adenosine triphosphate [ATP]

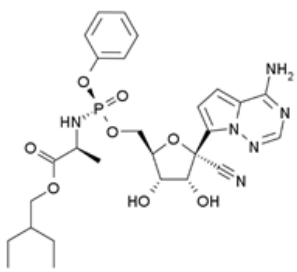

FIG 2: Structure of Remdesivir.

PHARMACOKINETICS DATA:

Remdesivir is an intravenously administered drug which readily absorbs into the eyes, brain, epididymis and testes. Data regarding the route of elimination and volume of clearance is currently unavailable. Remdesivir is predominantly metabolized to a triphosphate metabolite.

The plasma Half-life of Remdesivir in Non-Human primates is 20 min [or 0.39h]. The plasma of half-life of its activated

metabolite triphosphate form is 14 hours in Non-Human primates and 20 hours in Humans [9].

MECHANISM OF ACTION:

Remdesivir [GS-5734] is a nucleoside analogues drug with extensive antiviral activity. It has proved to be effective treatment to Ebola and Nipah virus in Non-Human Primates [10]. Remdesivir is a nucleotide analogue and exists as a prodrug. It has to be activated upon intracellular diffusion in host tissue.

ACTIVATION:

Remdesivir is a precursor of nucleotide. It is called hence as the ProTide [Prodrug of nucleotide]. Remdesivir diffuses into the cells where it is phosphorylated by the action of enzymes like esterases and phosphoramidases to get converted to mono-phosphates. The mono-phosphates in turn get phosphorylated to an active metabolite triphosphate by nucleoside-phosphate kinases [4].

MODE OF ACTION:

The antiviral potential and the mechanism of action of Remdesivir post viral entry can be correlated to its structural attributes [1]. Remdesivir prodrug gets metabolized intracellularly to an active analogue of adenosine triphosphate. This active metabolite is observed to behave as an inhibitor of viral RNA-dependent RNA polymerases [RdRps]. This further disables the replication and curbs the spread of viral RNA genomes in multiple coronaviruses. The mechanism can be associated with its prominent In-Vitro activity against SARS-CoV-2 [11].

Remdesivir metabolite being a nucleotide analogue, post host entry gets incorporated into nascent RNA chains of the virus and results in premature chain termination [5]. The Remdesivir triphosphate competes with ATP [Adenosine triphosphate] and binds more effectively to the viral RNA-dependent RNA polymerases [RdRps] that incorporates Remdesivir triphosphate into the nascent RNA chain instead of ATP. Following the incorporation into RNA chain, Remdesivir triphosphate enables addition of three more nucleotide triphosphates followed by arrest of RNA synthesis leading to early Chain termination. If the Remdesivir triphosphate is incorporated at position n, RNA synthesis by RdRps is arrested at position n+3. The additional three nucleotides incorporated can be considered as an adaptation to protect and stabilize the inhibitor, Remdesivir triphosphate from the viral 3 –5 exoribonuclease or proofreading activity [12].

In support to this data, studies have shown that models like MHV mutant lacking proofreading activity were significantly more sensitive to Remdesivir [13]. The In-Vitro studies conducted by Wuhan Virus Research Institute revealed that Remdesivir triphosphate cannot be removed by nsp14-ExoN, a non-structural protein RNA dependent RNA polymerase [14].

SIDE EFFECTS/COMPLICATIONS associated with REMDESIVIR:

Remdesivir is associated with adverse effects like respiratory failure, impairment of vital organ biomarkers, inflammation of liver and damage to hepatocytes. It is also viewed to cause low albumin, low potassium, anaemia, low platelet count, delayed clotting and jaundice [8]. Other reported side effects include Infusion-related reactions like gastrointestinal distress, low blood pressure, sweating, shivering, nausea and vomiting and elevated levels of liver enzymes like transaminase in the blood [15].

CONCLUSION:

Remdesivir is a broad spectrum antiviral pharmaceutical used to treat viral infections like SARS, MERS, Ebola, Nipah, Marburg and now COVID-19. Several In-Vitro studies have proved its efficiency against members of viral families like Filoviridae and Coronaviridae. Administered intravenously Remdesivir which is a structural analogue to nucleotide triphosphates intervenes in viral genome replication especially in a phase post viral entry into the host cell. Structural characteristics of Remdesivir correlate to its clinical benefits that include direct arrest of viral particles to prevent further spread within the host cells or inhibit manifestation of symptoms like lesions in respiratory track. The currently prevailing pandemic caused by SARS-CoV-2 which has no specific established treatment requires the use of such broad spectrum antiviral drugs like Remdesivir. Clinical studies undertaken globally have used Remdesivir in Human volunteers and established a safety profile. Although the molecule possesses notable side effects, its benefits outweigh the offshoots making it an effective support system to treat various viral diseases. However its use is restricted or faces conflicting ideas due to lack of sufficient scientific data validation. This review highlights the greater requirements to gather more information through clinical studies worldwide and establish Remdesivir as the new face of treatment for COVID-19.

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