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A Brief overview on Epidemiology of Covid-19 & Mechanism action of REMDISIVIR

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1. Introduction:

Coronaviruses are a family of intricate viruses, a single-stranded RNA genome that infects species of animals and humans. Among the coronavirus members are those who suffer from the common cold, Acute Respiratory Syndrome (SARS), Middle East Respiratory Related Syndrome (MERS), and Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), a recent cause it appears. The pathogen of the disease is COVID-19 (1).

In the current context of the public health crisis of the COVID-19 epidemic, recurrence of antimicrobials may be an effective strategy as no effective treatment is guaranteed. Published literature shows that Remdesivir has extensive anti-viral activity against many RNA viruses and has recently been recognized as a promising treatment against SARS-CoV2(2).

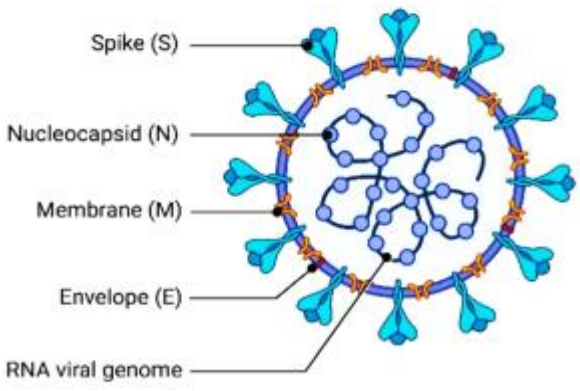


Figure 1:-Structure of Corona virus

2. History of Covid-19:-

On December 31, 2019, the Chinese Health Authority informed the World Health Organization (WHO) of several cases of unknown aetiology pneumonia in the city of Wuhan in Hubei province in central China. The cases have been reported since December 8, 2019, and many patients have been working or living near the Huanan Seafood Sea-food Market(3). although some of the original cases had no exposure to this market. On January 7, the novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was detected in a patient's throat sample(4). The pathogen was later renamed acute acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group and the disease was named coronavirus disease 2019 (COVID-19) by WHO. As of January 30, 7736 have been confirmed and 12,167 167 suspected cases have been reported in China and 82 confirmed cases have been found in 18 other countries. On the same day, WHO announced the outbreak of SARS-CoV-2 as an International Emergency Medical Concern. According to China's National Health Commission, the certified death rate in China was 2.1% since February 4 and the mortality rate was 0.2% among cases outside China. Of the hospitalized patients, the mortality rate was between 11% and 15%. COVID-19 is relatively contagious with a high mortality rate, but the information available in public reports and publications is growing rapidly. The purpose of this review is to summarize the current understanding of COVID-19 which includes causative agent, pathogenesis of disease, diagnosis and treatment of cases, and control and prevention strategies(5).

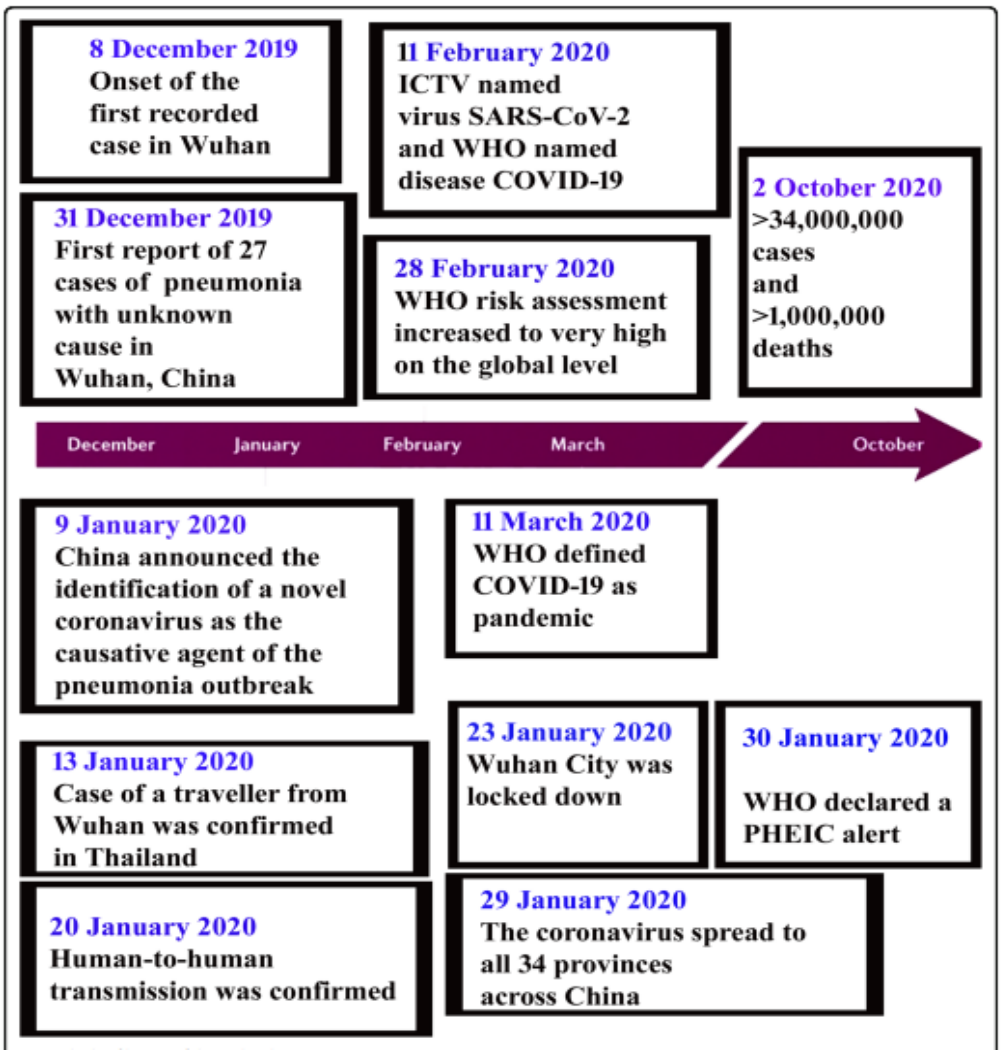


Figure 2:-Occurrence of global pandemic

3. Epidemiology: -

During December 2019 in Wuhan, the capital city of Hubei Province China, strange cases of severe pneumonia had been identified and started spreading. Most of the initial cases found had a travel history to the Hunan wholesale seafood market which also sold live animals. In China, the intelligence system which was established after the SARS outbreak in 2003 was immediately alerted and samples of the patients were sent to labs for aetiological inspection. This was followed by China notifying the world of an outbreak on December 31, 2019, subsequently, on January 1, 2020, the Hunan seafood market was sealed, on 7th January roughly a week after China's notification of a possible outbreak the disease was confirmed to be the novel coronavirus disease or COVID-19 which has more than 95% homology with bat coronavirus and almost 70% similarity to the SARS CoV-1 virus. Environmental samples collected from the Hunan seafood market were tested positive with traces of COVID-19, indicating it as the origin of the virus. In the ensuing days, more cases started to appear in China, some of which with no travel history to the Hunan seafood market, confirming that human to human transmission was taking place. The period of January being the month of Chinese New Year incited Transmission of the virus with people migrating within China as well as internationally. Cases were reported from Thailand, South Korea, Japan and those infected had a travel history to Wuhan. To contain the spread, the entire city of Wuhan was placed under lockdown on January 23, 2020, shortly after this the lockdown was extended to other parts of Hubei province. Flights were barred from China and screening of passengers with temperature monitors was started at airports. Soon local transmission was observed in diversified countries outside of China and it was found that asymptomatic carriers could also carry out load shedding of the virus following which almost all international travel came to a halt(6).

3.1 Transmission of Corona virus:-

The role of the Huanan Seafood Wholesale Market in the spread of disease is unclear. Many of the first cases of COVID-19 were linked to this market suggesting that SARS-CoV-2 was transmitted from animals to humans. However, genomic research has provided evidence that the virus was introduced to another, unknown location, in a market where it spread rapidly, even though human-to-human transmission may have occurred earlier. Groups of infected family members and medical staff have confirmed the presence of a person-to-human transmission. After January 1, less than 10% of patients in the market and more than 70% of patients had no market exposure. Human-to-human transmission is thought to occur in close-knit communities especially with respiratory drops produced when an infected person coughs or sneezes. Fomites can be a major source of transmission, as SARS-CoV has been found to persist in up to 96 hours with other coronaviruses for up to 9 days. Whether or not there is an undetectable transmission of disease is a contentious issue. One first study published on January 30 reported asymptomatic transmission, but it was later found that the researchers did not communicate directly with the patient, in fact they had symptoms before transmitting the disease. A recent study published February 21 also said that the transmission is asymptomatic, but any such research can be limited by the symptoms of reported symptoms or contact with other cases and formats. Findings about the characteristics of the disease change quickly

and depend on selection. Studies have shown that the median incubation period was 5.2 days (95% confidence interval [95% CI]. The incubation period was found to be 19 or 24 days, although the definitions of cases usually depend on a 14-day window. Basic reproductive number (R0) is measured by various results and definitions. R0 measures the average number of infections that could be a result of one person having the virus in a completely vulnerable community. A study from a previous outbreak found that R0 was 2.7 for SARS and 2.4 for the 2009 H1N1 pandemic. One study estimated that the basic birth rate (R0) was 2.2 (95% CI). However, later on an additional analysis of the 12 available studies it was found that R0 was 3.28. Because R0 represents the average value it is also important to consider the role of large broadcasters, who may be largely responsible for large-scale emergencies but may not have a significant impact on the value of R0. During a severe phase of the outbreak or pre-epidemic epidemic, the R0 may be unstable. In pregnancy, a study of nine pregnant women who received COVID-19 late pregnancy suggested that COVID-19 did not lead to worse symptoms than non-pregnant women and there was no evidence of intrauterine infection caused by direct transmission. In a hospital setting, a study involving 138 COVID-19 patients suggested that SARS-CoV-2 hospital-related transfers occurred in 41% of patients. In addition, another study of 425 patients found that the number of cases among health care workers increased steadily over time. These conditions may indicate exposure to high-viral contact through continuous contact in nearby areas. Outside of China, as of February 12, 2020, there have been 441 confirmed cases of COVID-19 reported in 24 countries where the first reported case was reported in Thailand on January 13, 2020. The highest number of cases reported in Singapore with 47 confirmed cases(7).

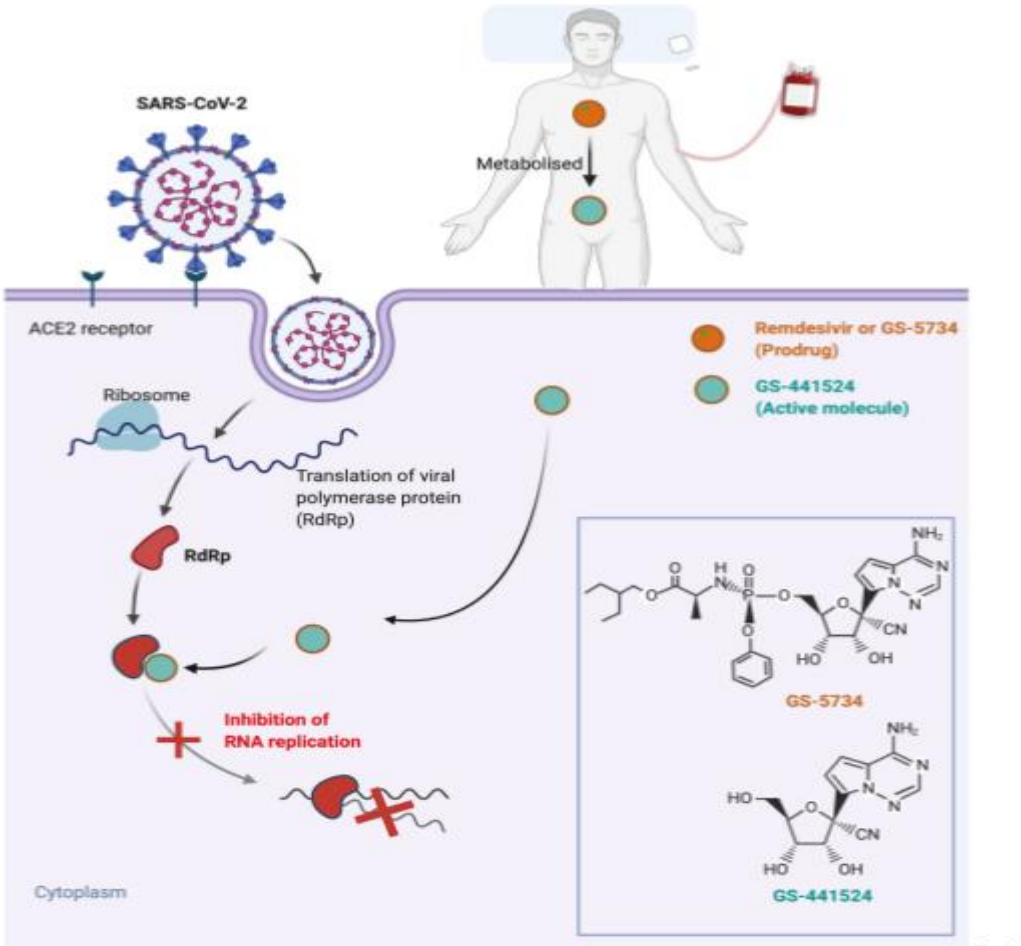


Figure 3: Diagrammatic representation of Transmission of Corona virus & Action of Remdesivir

3.2. Symptoms and effects of COVID-19

An infected COVID-19 patient can have two major states of infection, the asymptomatic state, and the symptomatic state. The symptomatic stage can develop into Acute Respiratory Disease Syndrome (ARDS) then raising infection can lead to multi-organ failure which can be fatal to the patient. An asymptomatic patient does not exhibit any symptoms of the disease due to high immunity but is still capable of infecting others, this state is extremely dangerous for the community and transmission of the virus. It is impossible to identify an asymptomatic patient without conducting an RT-PCR (Reverse transcription polymerase chain reaction) test which can be difficult for a government institution to conduct on a large scale and limits its ability to identify the amount of spread of the virus in the community(8). Symptomatic patient's exhibit varying levels of severity of the disease, most patients display mild symptoms only like fever, cough, sore throat, headache, myalgia or severe symptoms like ARDS or organ failure (Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease COVID-19, 2020). ARDS is a type of respiratory failure mainly defined by the onset of inflammation in the lungs especially in the alveoli that helps in gas exchange and maintains the stability of the flow and surface tension of the lungs. In the case of COVID-19, an extreme rise in inflammatory cytokines, monocytes, neutrophils, etc. leads to vasodilation which leads to the symptoms including shortness of breath, rapid breathing, and bluish skin coloration. (Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease COVID-19, 2020) Patients with ARDS are prescribed to be put on mechanical ventilators to aid in their breathing, therefore, the exponential rise in cases has led to an increase in the demand of such ventilators(6).

3.3 Genetic Testing (RT-PCR):

Reverse Transcriptase polymerase chain reaction (RT-PCR) is the most widely used SARS-CoV-2 detection. This test requires a nose and throat swab that is used directly to detect the presence of the virus rather than the immune system. This test detects the viral gene (RNA) that is present in a patient before the formation of antibodies or the appearance of symptoms. With this test, one can detect the presence of the virus early. Tests continue to convert viral RNA into cDNA through a process called "Reverse Transcription". RT-PCR targeted the regions of the Orf1b virus (Open Reading Frame) and N (Viral Nucleocapsid) after the release of its genome .N-genetic testing gives the first results and Orf1b testing confirms the diagnosis. Separated and isolated RNA in collected samples is written backwards to form cDNA, which is then amplified into a Real-Time Polymerase Chain Reaction thermal cycler. The probes contain the journalist's dye at the end of 50 cDNA and the dye extinguisher at the end of cDNA. The fluorescent markers produced by the journalist's dye are absorbed by the extinguishing dye, thus eliminating any traces. During the amplification process, probes combined with templates are cut by the Tag enzyme with the 5'-3 'function of the exonuclease, this separating the reporter's dye from a fluorescent signal that produces fluorescent signals. The PCR tool automatically pulls a real-time magnification curve based on fluorescent signal transduction thus providing the final dose detection of the SARS-CoV-2 virus at the nucleic acid level. RT-PCR can detect the virus in people with no symptoms, testing gives negative

negatives in about 30% of cases. Therefore, patients are screened twice before being confirmed as uninfected(9).

3.4 Pathogenesis of COVID-19: -

Although immunopathogenesis of COVID-19 is poorly understood, its clinical symptoms vary from fever and fatigue to severe respiratory problems and multiple organ failure. Understanding the immunopathogenesis of COVID-19 and the differences between affected populations is important in designing therapies and reducing mortality. One way is to study similar viruses such as SARS-CoV and MERS-CoV and learn from pre-described pathogen interactions. As discussed, SARS-CoV-2 uses ACE2 as a host cell host. ACE2 is highly expressed in a wide variety of human cell types, including alveolar epithelial cells and small intestinal epithelial cells, both of which are considered potential SARS-CoV-2 transmission pathways. Overall, ACE2 is widely distributed in the main target components of SARS-CoV-2, as well as organs that play an insignificant or unknown role in COVID-19 pathophysiology. SARS-CoV has also been reported to invade immune cells such as T lymphocytes, monocytes and macrophages, but it is still unclear how much SARS-CoV-2 reacts to these cells. Numerous studies test the immune response to SARS-CoV-2, most suggest that the immune response is disrupted due to the opposite function of monocytes / macrophages, elevated cytokines that cause inflammation, lymphocyte depletion and proliferation. Neutrophils, but the complex mechanisms involved are not yet fully understood(10).

3.5 Prevention:-

At the time of writing this paper, neither vaccine nor approved drug treatment for COVID-19 is discovered, prevention of the disease is therefore crucial to avoid the transmission. Although certain aspects of the virus pose serious hindrances in prevention aspects, such as no onset of symptoms until an average of 5 days during the 14 days incubation period or in some cases no symptoms, while at the same time the patient is shedding viral load similar to the symptomatic patient and prolonged. This Graph depicts the viability of the SARS-CoV-2 virus in different mediums and surfaces. A Visual Representation of a cohort of >44,000 patients in China and their varying illness severity. Keeping these aspects in mind there some guidelines suggested by major institutes in a bid to prevent the spread of the virus. At the community, level to slow the spread initially avoid large gatherings, defer non-essential travel for work or recreation, it is recommended to wear masks whenever heading out of the house for essential work the mask need not be surgical like N95 a simple mask made of cloth would suffice. Further covering of hands with disposable or washable gloves would also stop the spread of the virus. Practice hand hygiene frequently; washing hands with soap for a minimum of 20 s or using an alcohol-based sanitizer with a minimum of 60% alcohol. Practicing social distancing by standing at least 6 feet apart from others and avoiding encountering people having fever, cough, or sneezing. Avoid touching your face or mouth with dirty hands(6).

4. SARS-Life cycle of SARS-CoV-2: -

A virus is a parasite that is a living cell that replicates only after the invasion of catching cells. The SARS-CoV-2 health cycle begins in the lungs, where it infects alveolar II cells. SARS-CoV2 attaches to cells by binding to an angiotensin receptor that converts the enzyme 2 (ACE2) present in the cell membrane through its spike protein (S), which is expressed in the virus site. The mutation-altering change in S protein as a result of binding promotes the entry of SARS-CoV-2 into the cell, especially with endocytosis. The S protein acts as a key, locking the ACE2 receptor; this causes cell entry to occur. Once inside the cell, the virus releases its own gene, a single-stranded RNA, and begins to synthesize replicating polyproteins in the virus using a host machine. These polyproteins bind to subunits with viral proteins and bind to RNA-dependent RNA. The repetitive complex consists of additional copies of viral RNA and a series of sub-genomic RNAs, which are translated into viral proteins into the endoplasmic reticulum membrane using translation equipment. New copies of genomic RNA and SARS-CoV-2 virus proteins are finally packaged in new viral particles or virions, and then released out of the cell by exocytosis or proptosis(11). Newly formed viruses SARS-CoV-2 can infect large numbers of healthy lung cells, thus furthering the cycle. Virions are identified by alveolar epithelial cells as well as endothelial and macrophages. The interaction of these viral cells with these cells triggers the release of cytokines, which then activate specific cell types, such as T cells, monocytes and macrophages, and promote inflammation. In many cases, the immune system reacts by producing T cells, killing SARSCoV-2 while the β-cell antibodies inhibit the interaction of the S protein-ACE2 receptor, thereby preventing further spread of other organs, leading to the patient's recovery. In contrast, in response to a weakened immune system, there is an accumulation of immune cells in the lungs that lead to the production of unpredictable levels of pro-inflammatory cytokines leading to a cytokine storm. Coincidentally, the rapid uncontrolled spread of SARS-CoV-2 in some organs causes multiple organ failure and even death. An analysis of 326 COVID-19 people from China showed that the critical time line for progression of coronavirus 2019 (COVID-19) symptoms Day 1 a Fever in 88% of people infected with the virus, often accompanied by fatigue, nausea or day lohudo. 2–4 Fever with dry cough and muscle aches Day 5-6 + Respiratory problems Day 7–8 Recovery of some patients; however, hospitalization may be necessary for patients with severe conditions (~ 15%), they may have acute respiratory distress syndrome due to congestion of fluids in the lungs. In many cases the fever goes away but the cough may go on. Day 13–14 in patients striving for recovery, respiratory problems may disappear at this stage. Day 17–18 Complete recovery; However, in some cases (5%) it may lead to death a ‘Day 1’ refers to the appearance of the first sign(12).

5. Global variability and disease resistance: -

The viral genome may accumulate genetic mutations while replicating within the host cell, thus producing genetic variation throughout the world. SARS-CoV-2 is flexible, albeit slow. Separating these conditions may be helpful in understanding how the disease works, how the virus escapes the immune system, or how it develops drug resistance. However, it can be premature to determine from the available data currently that certain mutations make the virus more dangerous. Recent research has found two major versions of

SARSCoV-2, called clade I and clade II, based on genealogical analysis of more than 100 sequences. These two categories were not found to differ in terms of infection or severity of the disease. The severity of the disease depended significantly on age factors such as age, lymphocytopenia, and cytokine-related storms, not so much on viral mutations(13). In a separate study, researchers found three blood-based biomarkers that could predict disease risk at least 10 days in more than 90% accuracy, based on a database of 485 infected patients from Wuhan, China. Based on these results, disease severity was found to be associated with higher lactate dehydrogenase levels, lower lymphocyte levels and increased levels of high-sensitivity C-reactive protein. Phylogenetic analysis of different species can also help to trace the viral trajectory around the world. Large-scale analysis based on the sequence of 3067 SARS-CoV-2 genomes revealed clonal geo distribution and a few tropical genetic mutations. Information about the most popular areas of genetic modification may be important in both treatment and vaccine formulation so that genomic regions showing high mutations can be avoided as drug targeting or vaccine development(12)

6. Development of Remdesivir:-

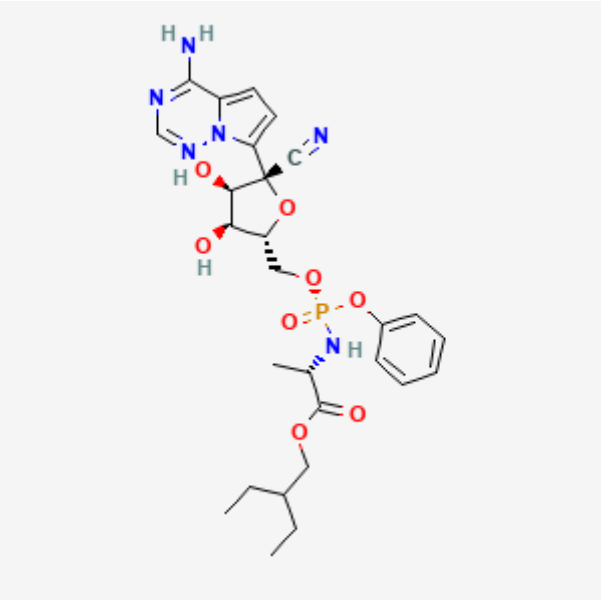


Figure 4: - Structure of Remdesivir

2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate

Remdesivir (GS-5734) was developed by Gilead Science and emerged from a collaboration between Gilead, the American Centres for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). They want to identify anti-retroviral RNA antibodies that retain the power of the global epidemic, such as those that emerged after the program began, including EBOV and the Coronaviridae family viruses exhibited by Middle East respirator syndrome (MERS) and Severe acute Respiratory disease (SARS)(14).

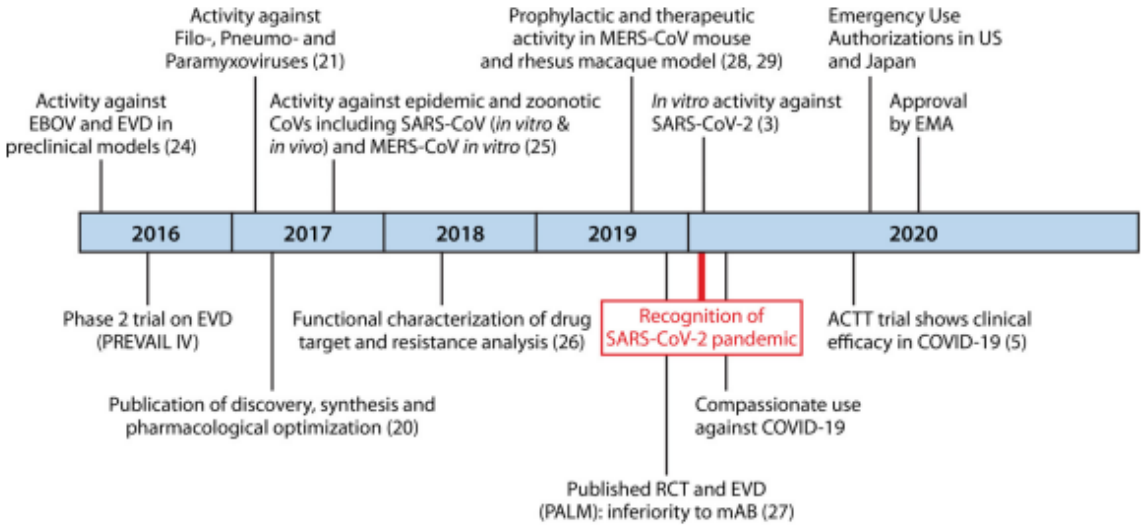


FIG 1 Milestones in the discovery of remdesivir as an anti-COVID-19 treatment. Shown is a chronological summary of important achievements in the discovery and preclinical and clinical evaluations of remdesivir (GS-5734). Achievements appear according to the year of manuscript publication or reception at a peer-reviewed journal. COVID-19, coronavirus disease 2019; EBOV, ebolavirus; EMA, European Medicines Agency; EVD, ebolavirus disease; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV(-2), severe acute respiratory distress syndrome coronavirus (2); RCT, randomized controlled clinical trial; mAB, monoclonal antibody. (See references 3, 5, 20, 21, and 24–29.)

Figure 5. Discovery of Remdesivir

As a prelude to the discovery, a library of 1000 small molecules focused on nucleoside analogue, based on prior knowledge of active antibacterial compounds targeted at RNA viruses, was compiled. Nucleosides are not easily accessible to cells (so they may have a lower rate of cell-based screening such as anti-bacterial screens), so modified nucleosides such as monophosphate, ester, and phosphoramidate prodrugs form a large part of the library. Such products are usually more accessible and digested to release nucleoside or phosphorylated nucleoside within cells. Although the data from the full real screen appears to be undisclosed, 1'-CN modified adenosine C-nucleoside hit (GS-441524), as well as the prodrug form of monophosphate GS-441524 (GS-5734, was later renamed remdesivir), was found to be highly potent. GS-441524 and its S-acyl-2-thioethyyl monophosphate prodrug was previously reported in 2012 as a potent lead in the 4-aza-7 series ranked 10, I- 9-dideazaadenosine C-nucleosides, with extensive activity against the RNA viral panel: yellow fever virus (YFV), Dengue virus type 2 (DENV-2), influenza A, parainfluenza 3, and SARS. The main test used was a cyto-protection effect (CPE) assay, in which a live virus was injected into a target cell line and the antiviral function was guided by the test agent's ability to rescue cell death, measured using a standard reagent cell function. -2012, GS-5734 demonstrated CPE activity against SARS type Toronto 2 (IC50 = 2.2 μm) without causing cytotoxicity towa Vero African green monkey kidney epithelial cells used in CPE testing.

When the Ebola outbreak occurred in 2014, an integrated library was used to identify and prioritize effective combinations against EBOV. A study by Madelaine et al. found that GS-5734 reduced EBOV duplication in HeLa cells by IC50≈ 100 NM, and retained power in non-human EBOV infection models, while GS-441524 was ineffective. In addition to demonstrating the anti-EBOV activity, Warren et al. has shown that remdesivir also has anti-viral activity against several other viruses, including coronavirus MERS, which has an IC50 of 340 NM in vitro.

By demonstrating that GS-5734 (remdesivir) has extensive anti-viral RNA activity, many groups have tested antibodies in both in vitro and in vivo, confirming their activity against coronaviruses. Antiviral activity was confirmed against SARS, MERS zoonotic coronaviruses, and the human coronavirus surrounding HCoV-OC43 and HCoV-229E, the virus-causing agents. In addition, De Wit et al. has shown that remdesivir has both preventive and therapeutic activity against MERS in a non-human in vivo model(1).

6.1 Pharmacokinetics: -

The pharmacokinetics of remdesivir are summarized in the literature on sensitivity published by the European Medicines Agency (EMA, 2020). Remdesivir is administered intravenous (IV) injection with a 1-day loading dose (200 mg for adults, adjusted for weight loss in paediatric patients) followed by a daily maintenance dose (100 mg for adults) for up to 10 days. In non-human tissues, daily administration of 10 mg / kg of remdesivir revealed a shorter plasma fraction of prodrug (t1/2= 0.39 h), but continuous intracellular levels of the triphosphate form. Efficacy of remdesivir against SARS-CoV-2 and related coronaviruses. This includes a recent in vitro study of remdesivir testing for antiviral activity against SARS-CoV-2 (formerly known as 2019-nCov, strain nCoV-2019 BetaCoV / Wuhan / WIV04 / 2019) using -RT-PCR for viral copy number in Vero E6 infected cells. This study showed an IC50 of 770 NM and an IC90 equal to 1,760 NM (with cytotoxic concentration> 100 mm) .In addition, it was performed by Sheehan et al. and de Wit et al. demonstrated in vivo the effectiveness of remdesivir in preventing viral replication and reducing viral-related infections against coronaviruses-related. These findings, along with the remdesivir safety profile in clinical trial trials against EBOV 54 support the remdesivir trial as a potential re-therapeutic drug against the SARS-CoV-2 epidemic. Driven by the EBOV outbreak in 2014 and based on an in vitro and animal model in vivo efficacy against EBOV, 45 Gilead Sciences has launched a clinical trial of the EBOV remdesivir. Gilead pursued FDA testing under the FDA Veterinary Act, which allows reliance on performance-based results from animal studies of drugs where it is not possible or inconvenient to perform human trials. Thus, remdesivir was included in a randomized, controlled trial of the treatment of Ebola virus in patients within the Democratic Republic of the Congo (NCT02818582); however, the main analysis of the intermediate study found that remdesivir was less antibody based therapeutics MAb114 and REGN-EB3, in terms of mortality and arm remdesivir intervention was discontinued. Malang et al. reported one adverse event related to remdesivir, for example hypotension, and high levels of creatinine and aspartate aminotransferase plasma (suggesting renal or liver dysfunction, respectively) in patients treated with antibodies based on antibodies. Although remdesivir was relatively low compared with EBOV based on efficacy compared with antibody treatment, the research arm provided initial insight into patient safety profiles.

6.2 Remdesivir as Nucleoside Analogues:

Nucleoside and nucleotide analogue as an antiviral based on small molecules have been tested for many years and form the basis of treatment against viral infections, including HIV, hepatitis B virus, and herpesvirus infections. Pharmacological advances in the development of nucleoside analogues were made

based on structural-to-activity (SAR) relationship studies that improved pharmacokinetics, antiviral activity, and selectivity. A comprehensive overview of medical chemistry and the evolution of antiviral nucleoside analogues can be found elsewhere. Nucleoside analogues require intracellular activation by phosphorylation in order to be their active metabolites. One of the most important factors was the addition of monophosphate prodrug to the nucleoside, which greatly improved intracellular delivery and function. This method called Pro Tide, developed by McGuigan et al, was also used to amplify remdesivir precursor named GS-441524(15).

6.3 Preclinical Studies:-

Evidence from in vivo studies: - In 2016, in vivo studies were performed using rhesus rats with Ebola (non-human primate) and various doses of intramuscular injection remdesivir injections. Post-exposure revealed that remdesivir has protective effects by preventing the recurrence of the virus. The concentration of remdesivir type, was 10 μm in mononuclear blood cells after administration of remdesivir 10 mg / kg. A study of green African monkeys infected with the Nipah virus showed the protective effects of remdesivir: half of monkeys treated with remdesivir (n = 4) developed mild respiratory symptoms and the other half recovered; those in the control group developed severe respiratory disease. Remdesivir has also been shown to perform antiviral activity against coronaviruses. Remdesivir treatment was found to reduce viral load in MERS-CoV-infected hDPP4 mice and was significantly associated with improved lung function and reduced risk of developing lung injury in infected animals. In addition, remdesivir inhibited MERS-CoV recurrence in rhesus macaques and led to a reduction in lung ulcers. Remdesivir also reduced viral load in the lungs and improved respiratory function in mice infected with the SARS-CoV MA15. Recent studies have shown that administration of remdesivir to rhesus macaques infected with SARS-CoV-2 improved lung ulcers, according to radiographs; reducing viral titters in Broncho alveolar lavage after 12 hours of treatment; and reduces the amount of virus in the lungs after 7 days of treatment. In addition, animals treated with remdesivir showed no signs of lung disease.

In vitro study: -

Remdesivir has been tested against various viruses in different cell-based systems and targeted cells. When comparing the results of antiviral testing, one should consider that different test methods and parameters such as target cell type and viral infiltration may have a significant impact on the outcome of effective performance. Various methods are available to test the antiviral function of candidate compounds in cell-based models. The targeted cells are simplified, vulnerable to allowing viral replication and are then exposed to successive concentrations of test compounds. Historically, compounds were evaluated for their ability to reduce the amount of PFU virus in cell membranes. Although this approach is beneficial in dealing with the overall viral health cycle, it has largely been replaced by molecular mechanisms that allow for automatic measurement. The antibacterial effects of test compounds can be tested by monitoring viral replication by measuring viral RNA levels using real-time PCR (RT-PCR) or fluorescent reporter gene expression (RGE) measurements from genetically modified viruses. A special type of reporter genetic testing is viral replicon testing (REPL) using genetically modified viral genes that perform the process of

transcribing and translating within a target cell but do not produce infectious offspring. Often, genetically engineered proteins are exchanged by the reporter's genes for that(16).

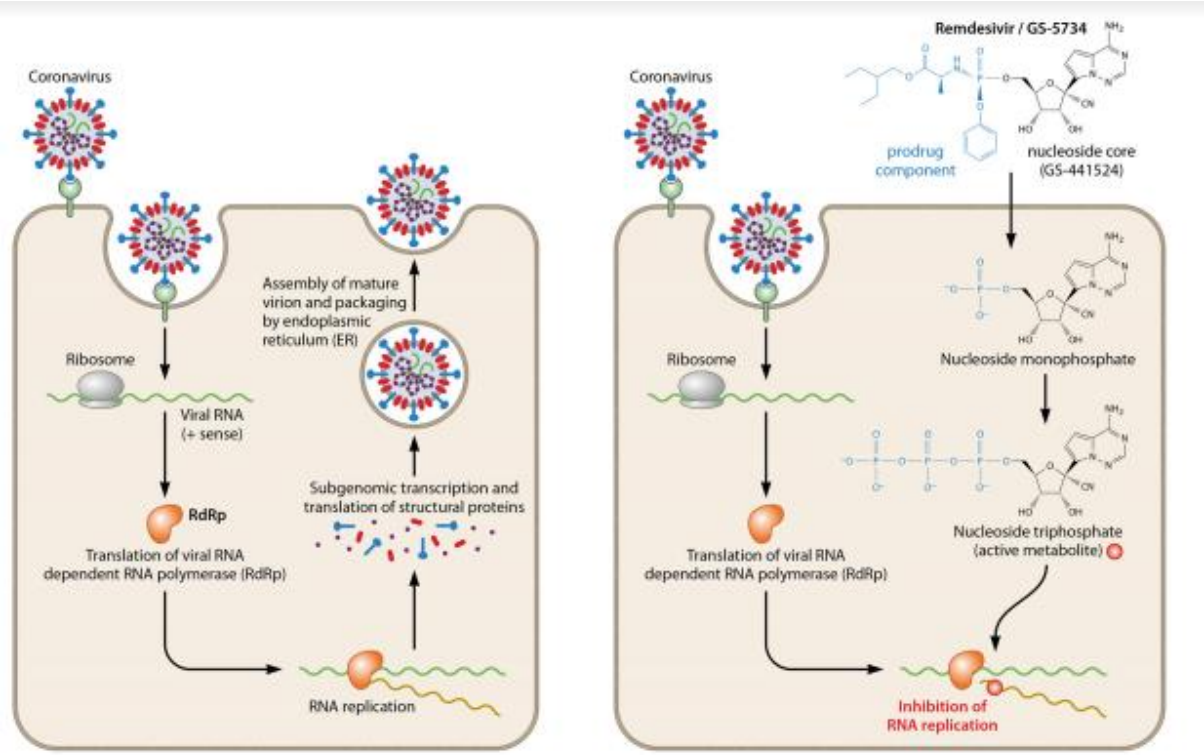


FIG 2 Intracellular activation of remdesivir (GS-5734) and inhibition of coronavirus replication. Passage through the cell membrane by remdesivir is facilitated by the prodrug component attached to the nucleoside core. Upon entering the target cell, the pronucleotide undergoes further phosphorylation steps to become the active triphosphate metabolite that effectively inhibits viral RNA replication. Delayed chain termination is caused by the following processes: (i) misintegration of nucleoside triphosphate (NTP) into replicating RNA by RdRp, (ii) prevention of further chain elongation after NTP plus 3 additional nucleosides, and (iii) premature termination of RNA synthesis.

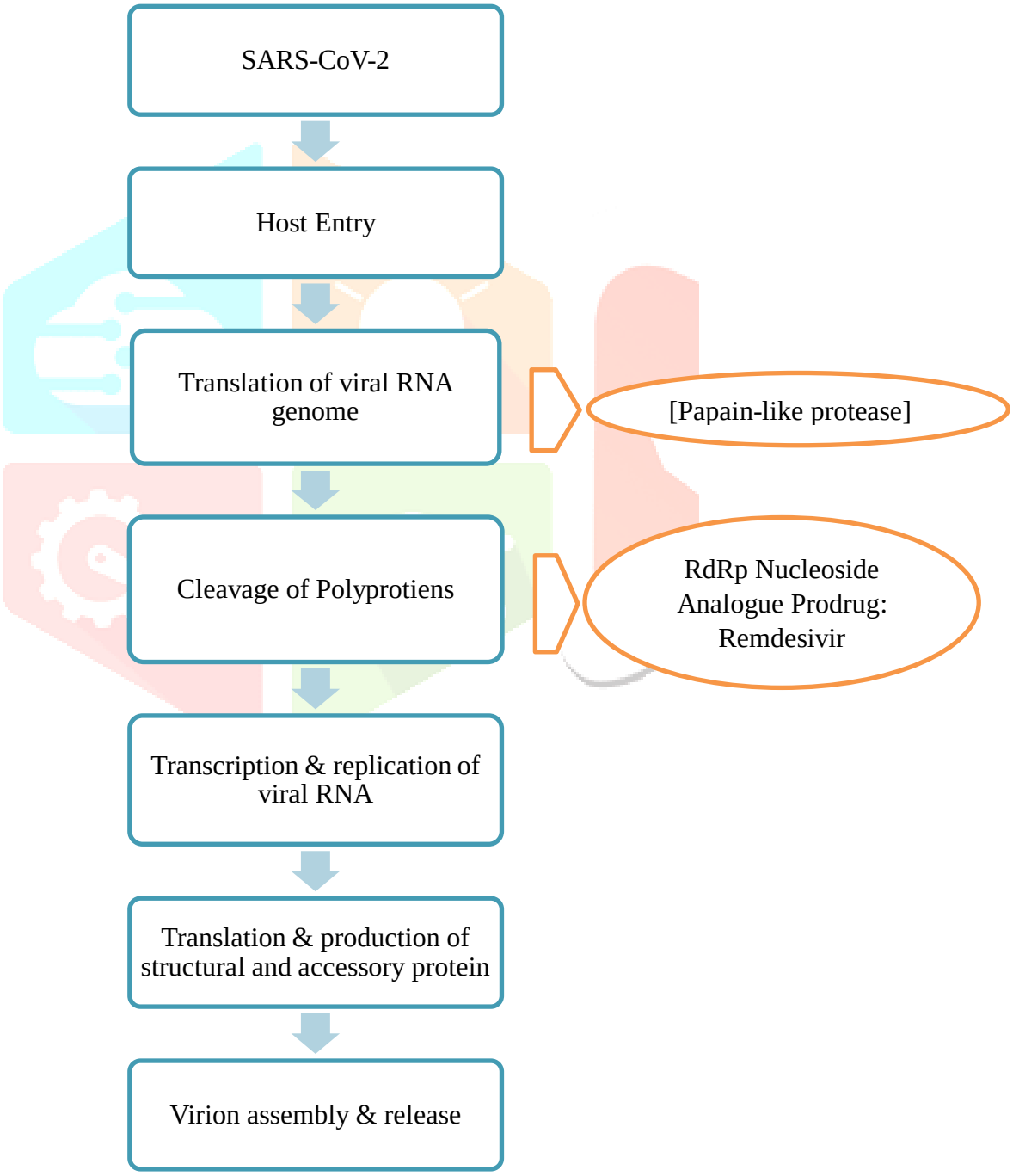
Figure 6:-Mechanism of Action of Remdesivir

Enable monitoring of viral replication. This method was used to study the prevention of HCV recurrence. Alternatively, viral antigens (AGs) can be measured by fluorescence- or chemiluminescence-based immunostaining. Antibacterial effects can be measured indirectly by examining cytopathic effects (CPE) where there are experimental combinations. CPE dosage tests can show not only the direct antiviral effects but also the beneficial effects of compounds with antibacterial properties. This is a benefit of high-performance testing due to signal gain. Additionally, CPE can be used to measure antiviral activity if no RGE- or RT-PCR measurements are available. It is not yet clear which type of test provides the best information that can predict vivo efficacy. However, comparisons of results from direct methods of measuring viral replication and CPE-based tests are determined by the fact that viral load in the blood and related CPE do not automatically have linear fusion.

Target cell selection indicates another important factor. The activity against filovirus-ruses is typically tested on Vero E6 cells found in the death of African monkey kidney cells. This cell line is known for producing high levels of the angiotensin-converting enzyme 2 (ACE-2) receptor, which is required for viral transmission of both SARS-CoV and SARS-CoV-2 to the target cell. In addition, Vero E6 cells support SARS-CoV replication at high titres, making them a typical cell model for the study of related viruses. In addition to the normal target cells, the antiviral activity of remdesivir was tested in human cell lines and key cells representing in vitro-focused in vitro systems. The activity against filoviruses was tested

in the human liver cancer cell line (Huh-7) and human macrophages (hPMs). Anti-CoV activity was tested in the line of epithelial lung cells (Calu-3), primary HAE cells, and endothelial endothelial cells (HMVECs) in immortal human foreskin. In contrast to the SARS-CoV tests performed on HAE cells, tests against SARS-CoV-2 were performed on Vero E6 cells, which may explain 1-log-low antiviral effectiveness measured by SARS-CoV- 2. Recent comparisons of replication kinetics with CARS of SARS-CoV and SARS-CoV-2 in Vero E6 cells concluded that there was no significant difference in drug sensitivity to remdesivir, thus supporting this hypothesis(15).

6.4 Inhibition of viral infection by Remdesivir:



7. Results from patients with COVID-19 and clinical trials:-

Historically, remdesivir was tested to treat patients with Ebola in a randomized clinical trial in the Democratic Republic of the Congo in 2018. By 2020, remdesivir was included in an international clinical trial of "Solidarity". Conducted by the World Health Organization in an effort to find effective treatment for COVID-19. As a timely response to the epidemic, patients with COVID-19 were treated with remdesivir on emergency contraceptive methods. In the first patient treated with COVID-19 with remdesivir, a native of Washington, pneumonia improved after 7 days of treatment(17). In Seattle, USA, remdesivir was used as a sensitive drug in the treatment of seven critically ill patients. A larger study found that, following a 10-day course of remdesivir treatment (intravenous administration of 200 mg on day 1, followed by 100 mg daily), 68% (36 of 53) of patients with COVID -19 indicating clinical improvement; However, there is no control group in this study. Therefore, this information is not sufficient to confirm the effectiveness of remdesivir in the treatment of patients with COVID-19.

To test the effectiveness of remdesivir, clinical trials are ongoing in countries such as the USA, Norway, Canada, France, and China. A list of continuous clinical trials is presented in Table 2. Although the duration of treatment varies slightly, the dose of remdesivir is the same: 200 mg per 1 day, followed by 100 mg for the entire duration of treatment.

The first randomized, double-blind, placebo-controlled, placebo-controlled trial was reported on April 29, 2020. The study was conducted in China with 237 patients (158 in the remdesivir group and 79 in the placebo control group, and the second. The end was the time taken to achieve clinical improvement. Studies have shown that remdesivir treatment did not lead to a significant decrease in the time it took to improve the clinic. In addition, the mortality time and prognosis time of patients with severe COVID-19 were not significantly different from those in the placebo group, suggesting that remdesivir had negative clinical benefits(18). This also suggests that in COVID-19, the spread of the virus is not a major cause of complications. In this account, remdesivir antiviral properties will not be helpful. The complexity of COVID-19 is associated with a storm of cytokine release, which suggests that immune responses play an important role in this event. Therefore, a combination of remdesivir containing an immunosuppressant (e.g. sarilumab, IL-6 the inhibitor) and/or other antivirals can do antimicrobial activity and reduce the immune-pathological damage caused by the effect of the immune system. However, at the same time. In the study, in patients treated with CODID-19 remedies, especially those treated within 10 days of starting symptoms, rapid clinical improvement was observed in that in the placebo group. Unfortunately, the study was terminated prematurely due to the occurrence of adverse events in the remdesivir group than in the placebo group. Considering these findings, the small sample size, and because the study was abruptly terminated, may not be sufficient to determine the effectiveness of remdesivir. In addition, the pharmacokinetics of remdesivir and its active metabolite in respiratory tract and / or other organs are often unknown to patients with COVID-19.36 Therefore, the results of further clinical trials are authorized to provide conclusive evidence regarding efficacy of remdesivir in patients with COVID-19.

The pharmacokinetic profile of remdesivir, in particular the concentration of the active metabolite, GS-441524, in the respiratory tract or other infected tissues in patients with severe COVID-19 is unknown. In addition, the data currently available on remdesivir is lacking, especially those involving drugs, genes, and drug-related diseases. This information is important in predicting possible side effects during treatment(16).-*clinical epidemiology & global health*

8. Conclusions: -

The current COVID-19 pandemic is clearly an international public health problem. There have been rapid advances in what we know about the pathogen, how it infects cells and causes disease, and clinical characteristics of disease. 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.

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