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A Review of Remdesivir: As a Lifesaver in the Pandemic of SARS-CoV-2

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ABSTRACT

As you people must have seen how many difficulties we had to bear during the time of Corona. Corona (SARS-CoV-2) has not ended today but due to the introduction of its vaccine, its effect has reduced. But in the beginning of the Corona period, we faced a lot of problems. Which was about medicines. At the beginning of the corona period, many drugs were used for the treatment of corona. One of those drugs was Remdesivir. At that time this medicine was received as a boon. It can also be called a miracle because many lives could be saved by this medicine. Due to which many people could get new life. In this review we will see how Remdesivir works in our body. What is its mode of action on our body. What negative effect has been seen on the body of Remdesivir since the Corona period. Will see it in this review and see how it is harming our body and we will know that the use of Remdesivir should be limited and how much should be So that we can avoid its harm effect and We will see what effect Remdesivir has on the body after the post pandemic, along with we will also study the pharmacokinetics in this review.

Keywords: SARS-CoV-2, Remdesivir, Pharmacokinetics, Pandemic, Miracle.

INTRODUCTION

COVID-19, which is triggered by the coronavirus 2 that causes severe acute respiratory syndrome is causing a global pandemic of COVID-19. This crisis poses a significant danger to worldwide public health and economic stability(1). The COVID-19 outbreak began in China's Wuhan region with certain cases of pneumonia of questionable etiology then spread to other areas of the world before being declared an international virus outbreak by the World Health Organization (WHO) on March 11, 2020. As of July 15, 2020, the WHO had recorded a total of 12,964,805 reported cases of SARS-CoV-2, counting 5,702,275 deaths(2). Aside from the reach-in African and Western Pacific regions, the United States, Europe, the Eastern Mediterranean, and South-East Asia are the regions most affected by the pandemic according to WHO. Respiratory symptoms during COVID-19 can range from a simple case of pneumonia to serious respiratory distress, which can lead to respiratory organ damage(3). At the point in time health organizations across the universe are going to review the pandemic's consequence and issuing new standards on how sponsors and MAHs should handle clinical studies and pharmacovigilance systems. In order to minimize the incidence on safety reporting and help defend patient safety in this constantly changing world, sponsors must be more vigilant and assertive in analyzing the implications of the pandemic and variations in approval standards(4). To avoid clinical trial interruptions, it is now more important than

ever to demand clear instructions and start embracing reform measures as soon as possible. Throughout the deadly COVID-19 disease, key health agencies such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the United Kingdom Medicines and Healthcare Regulatory Authority (MHRA) ensured that various stakeholders were satisfied by providing guidance and rules on clinical studies and post-marketing surveillance(5). Remdesivir, a nucleotide analogue prodrug formerly used to treat Ebola virus, has been shown in vitro and in preclinical studies to restrict the replication of a broad variety of human and animal coronaviruses. Based on the limited information available, Remdesivir for COVID-19 was approved for emergency medical care in various parts of the world in 2020 during a pandemic(6). Remdesivir, a monophosphoramidate nucleoside prodrug, was recognized as among the preponderance of viable options in opposition to coronavirus-induced incurable disease in preclinical studies in 2019. (COVID-19). It is also the first antiviral to be permitted by the FDA for the treatment of COVID-19. [4] As the use of this medicine for compassionate purposes has increased, numerous safety risks have been identified, expressing concern among clinicians(7). Various side effects have been reported and range from a mild gastrointestinal symptom such as nausea and diarrhea to increased liver enzymes, nephrotoxicity such as renal impairment or acute kidney injury, and cardiovascular adverse reactions such as hypotension or atrial fibrillation(8).

PATHOPHYSIOLOGY OF SARS-COV-2:

SARS-replication CoV-2's mechanism is still unknown. SARS-CoV-2, a coronavirus recombination, has been found to be similar to many other coronavirus class viruses, including SARS-CoV and MERS-CoV.It is possible that SARS-CoV-2 enters the body in two stages in order to spread the infection. Angiotensin-converting enzyme-2 [ACE-2] or else CD-147 or else dipeptidyl peptidase 4 [DPP-4] or else transmembrane protease serine 2 [TMPRSS2] are responsible for the attachment of SARS-CoV-2(9). It's the first step. The next step is separation of the pin protein by TMPRSS2, which discloses the combination peptide and allows it to stay alive in moderate-pH endosomes. Receptors like ACE-2 are identified similarly to the chief cellular receptors for adhesion through the receptor attachment realm of pathogen pins and as the receptors intended for human-to-human transfers of SARS-CoV(10). The ACE-2 protein is found in the alveolar respiratory epithelium of respiratory origin as well as the small intestine enterocytes. The virus first binds to an objective location on respiratory inner lining cells, according to research.ACE-2 was widely articulated in the gallbladder cells, liver cells, kidney cells, testes, gastrointestinal tract (GIT), and bladder cells, proposing that organs can exist susceptible to SARS-CoV-2 illness, which can aid in understanding the paths of illness and disease indications(11). Despite the fact that the ACE-2 receptor is commonly found in numerous organs throughout the body, sick people with SARS-CoV-2 infection mainly demonstrate respiratory system abnormalities. That link wants to be reported(12).

Furthermore, ACE-2 is upregulated in vascular endothelium cells, raising the question of whether SARS can induce vascular endothelium cell injury or impair glomerular utility. In Zhejiang, Xu et al. discovered infrequent renal harm in COVID-19 patients. It is unclear whether SARS-CoV-2 attaches only to ACE receptors or to additional receptors as well(13). According to a medical study, asking about the level of coronavirus illness causes more mortality due to several organ dysfunction syndrome or pulmonary hypertension. The SARS-CoV-2 pin glycoprotein remains bound to the ACE-2 receptor, which is required for the pathogen or virus to enter target cells. S protein

homotrimers (S1 and S2) aid in host receptor adhesion(14). The structurally similar SARS-S2 Cov-2 subunit serves as a target for antiviral treatment. A number of treatment strategies based on virus receptor attachment capacity are being researched. Individual cells that produce ACE-2 improved monitoring of SARS-CoV-2 entry, whereas individual Dipeptidyl peptidase-4 (DPP4) or APN (aminopeptidase N) did not(15). In another report, the S protein of SARS-CoV2 and ACE-2 conditional competence was found to be 10 to 20 crinkles greater than that of SARS-CoV. The Cryo-TEM configuration of the SARS-CoV-2 pin in prefusion verification attests to this(16).

Following virus entry into the cell, stimulated leukocytes start producing IL-6, which allows it to act on a wide range of cells and tissues. In SARS-CoV-2-infected patients, TNF-, IL-1, IL-8, IL-12, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1A (MIP1A), and interferon-gamma inactivating protein (IP10) levels are elevated(17). The occurrence of ARDS, shock, secondary infection, acute renal damage, and cardiac disease was markedly higher in ICU patients than in non-Intensive Care Unit patients. A major percentage of IL-6 was higher than normal in the patients, and the difference was considerably greater(18). Infection with the MERS coronavirus can lead to an increase in the concentration of pro-inflammatory cytokines. Associated Cytokine Release Syndrome (CRS) and sHLH-like serum cytokine levels suggest that severe COVID-19 cases may benefit from IL-6 pathway suppression, which may be an objective of COVID-19 disease patients' treatment. Extreme tissue necrosis occurs as a result of increased cytokine production. In certain scenarios, a reaction known as a "cytokine storm" occurs(19). This is administered in combination with its potential treatments. It has the capacity to enhance the distinction of B lymphocytes as well as enhance the growth of certain cell types while inhibiting the growth of everyone else. CD4+ and CD8+ T cell counts steadily declined until the death(20). CD4+T and CD8+T lymphocyte levels were significantly lower in critical cases, indicating that these lymphocytes were significantly suppressed. Lymphocytopenia could be induced by a cytokine storm associated with viral intrusion. When compared to severe patients, the rate of reduction of CD4+T, CD8+T, and B cells is lower in severe patients(21).

PHASES OF THE SARS-COV-2 LIFE SPAN:

Virus Entrance:

SARS-CoV-2 be capable to enter in cell by two main ways: through endosomes otherwise through plasma covering fusion. Point proteins S1and S2 of SARS-CoV-2 act as a mediator adherence to a host cell covering and engage angiotensin-converting enzyme- 2 (ACE2) seeing that the access receptor. Cell exterior vimentin (VIM) functions like an important co-receptor and it is required for effective ACE-2 binding. Heparan sulphate (HS) high affinity to the receptor binding domain (RBD) improves ACE2 linkage. Cathepsin L activates the spike protein when virions enter endosomes(22). Put another way, the spiked protein be capable of bisected amid the S1 and S2 domains via the cellular serine protease TMPRSS2 in immediate contact to the ACE2 receptor, causing the viral integument to fuse with the plasma covering. The plasma jacket combination entrance be less likely to elicit host cell antiviral body ’s immune system and thus more convenient for viral replication(23).

Replication and Translation of Viral Replication Machinery:

Polyproteins are converted later than the viral RNA has been launched into the target cell. The SARS genetic RNA encrypts nonstructural proteins (NSPs) that are compulsory for viral RNA synthesis over and above structural group of amino acid that are essential for virion

congregation(24). First, polyproteins pp1a and pp1ab are converted and bisected via the Papain-like protease (PLpro, Nsp3) and 3C-like protease (3CLpro, Nsp5) to form functional NSPs like Helicase or the RNA replicase–transcriptase complex (RdRp). The host control valve factor Nsp1 was among the first proteins to be converted. This viral protein obstructs conversion and accelerates the dreadful conditions of host mRNA, preventing the host's innate immune comeback(25).

Viral Structure, Protein Translation, and Virus Congregation:

RdRp (Nsp12) is in charge of structural protein RNA replication. Ribosomes connected to the endoplasmic reticulum (ER) translate the structural proteins S, Envelope (E), and Membrane (M). The ER forms double membrane vesicles (DMVs), in which viral RNA replicates while being protected from the host's innate immune system(26). Nsp3 generates a porous structure through which viral RNA exits the DMVs to be assembled into a virion. The nucleocapsid proteins (N) persist in the cytoplasm and are built from genomic RNA. They bind to the virion precursor, which is then transferred via small vesicles from the ER to the surface of the cell via the Golgi apparatus(27).

Virus Exocytosis:

The release of pathogens occurs in the infected cell and targets the next cell. SARS-CoV-2 is distinguished from other coronaviruses by the presence of a second cell division site in the S protein. Furin division occurs at the S1/S2 site when virions are released via the Golgi apparatus or lysosomes. It prepares the S protein for a new cut by TMPRSS2 at the S2' site. Specific genetic changes within this region have also been discovered in SARS-CoV-2 strains of concern, including alpha, beta, delta, and omicron(28).

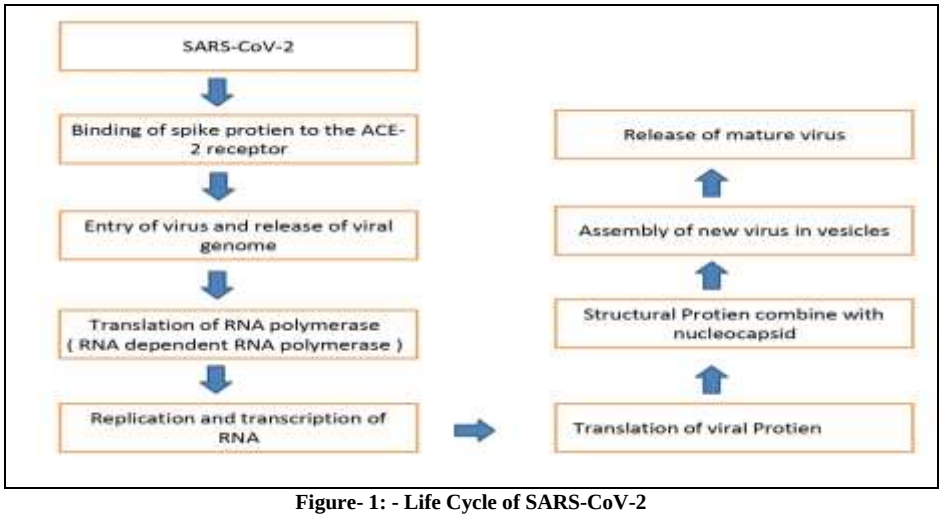

Figure- 1: - Life Cycle of SARS-CoV-2

MECHANISM OF ACTION OF REMDESIVIR:

The inactive drug, Remdesivir, is a mono-phosphoamidate nucleoside. There are changes in the active form, nucleoside triphosphate intracellularly (NTP). As previously stated, most novel direct-acting antivirals The active form of Remdesivir then identifies the machinery responsible for viral RNA genome replication, a critical component of the pathogen's life sequence. Nucleoside analogues are artificial compounds that compete with intracellular natural nucleoside pools for inclusion in replicating viral RNA(29). Whereas these compounds closely resemble their physiological equivalents, the inclusion of the previously associated particle disrupts subsequent molecular processes. The API specifically targets the process that leads to

viral replication inhibition. [20] Remdesivir triphosphate interferes with the nsp12 polymerase in SARS-CoV and MERS-CoV, which is a multisubunit RNA synthesizer multifaceted of viral non-structural proteins (nsps) formed as alkyl chains of viral polyprotein(30). Because nsp-12 is structurally similar transversely to the coronavirus relatives, it is nearly all but certain that the mode of action of remdesivir does not differ significantly between CoV and EBOV. Remdesivir triphosphate productively inhibits SARS-CoV and MERS-CoV replication by provoking delayed chain extinction when integrated into the duplicating RNA. According to several recent biochemical examinations, remdesivir triphosphate induces the termination of RNA synthesis in SARS-CoV 2 at three positions after it is integrated. This mechanism is almost identical to the RdPs (RNA-dependent RNA polymerase) of SARS-CoV-2 and MERS-CoV-2. Premature RNA synthesis termination finally prevents more transcriptional and translational procedures required for the development of newer virions. Remdesivir's antiviral activity has been studied from a variety of angles(31).

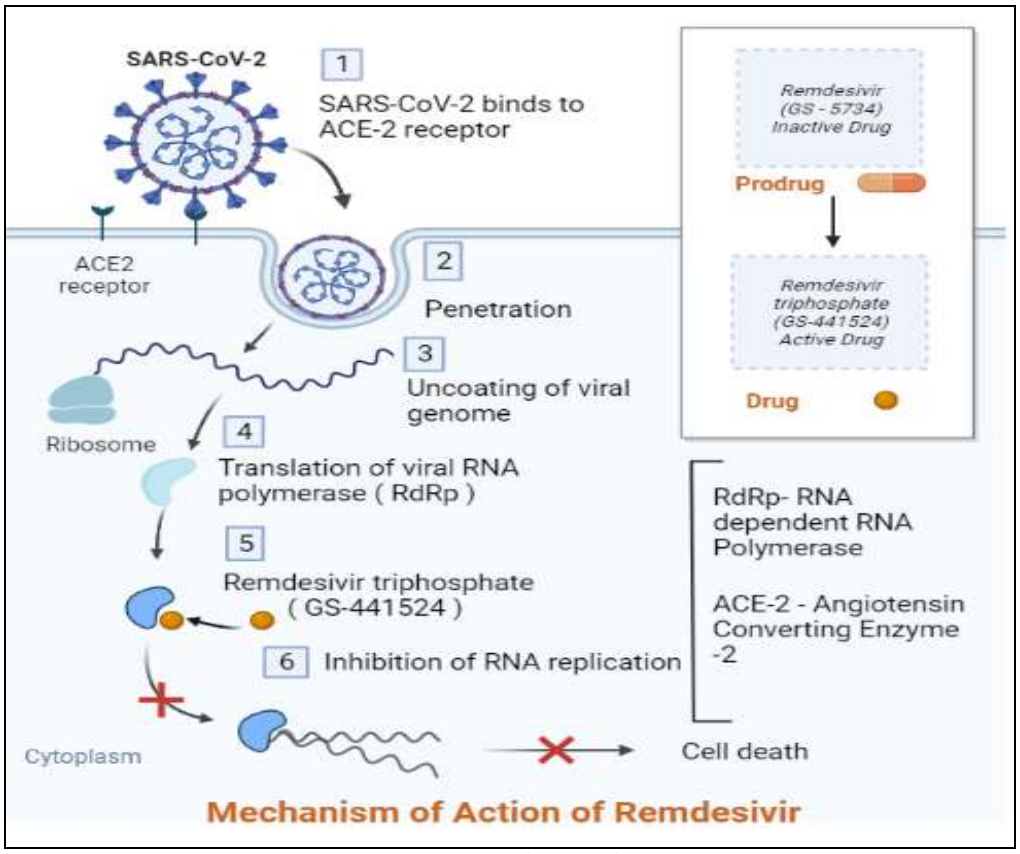

Figure -2: - Mechanism of Action of Remdesivir

Remdesivir has an effect on several organ systems:

Remdesivir is beneficial for controlling SARS-CoV-2 activity, and it falls into the broad-spectrum antiviral category. The use of remdesivir, as well as its increased use, causes many organs to become diseased, including the kidney, liver, heart, and other organs.

HEPATOTOXICITY:

Recent animal investigations of remdesivir revealed no liver variations, whereas transient treatment-emergent increases in aminotransferases were observed in research trials of remdesivir. The most common remdesivir-induced ADE was an increase in liver enzymes. On the whole, nearly one-

third of patients who received remdesivir experienced an increase in liver enzymes. In a case series, three COVID-19 patients had enhanced aminotransferases after starting remdesivir. One COVID-19 patient stopped taking remdesivir due to an increase in alanine aminotransferase and a rash that went away after three days. According to Grein et al.'s studies on compassionate-use remdesivir in combination with COVID-19, 23 percent of the sick people had elevated liver enzymes, and two of them had to discontinue remdesivir treatment prematurely. A recent randomized controlled trial (RCT) in China also concluded that whole bilirubin, aspartate, and alanine aminotransferase levels were enhanced in 9%, 6%, and 1% of COVID-19 sick people in the remdesivir class, compared to 8%, 11%, and none of the COVID-19 sick people in the placebo class. Because of the increased aminotransferase and bilirubin levels, many people with the disease in the remdesivir class withdrew the study drug compared to the placebo group. Even so, it should be noted that hepatic atrophy was common in COVID-19 patients, making it difficult to determine whether the increases in aminotransferases and bilirubin were caused by remdesivir or the pathological conditions. Remdesivir is not supposed to be used in conjunction with other hepatotoxic drugs, as suggested by the European Medicines Agency, and hepatic mechanism observation is considered necessary throughout treatment. Because the majority of COVID-19-infected individuals with hepatic problems had a mild increase in aminotransferases and bilirubin, if abnormalities in hepatic enzymes take place behind remdesivir's onset, particularly at high levels, adverse effects must be considered and the drug must be discontinued if yet needed.

CLINICAL MANIFESTATIONS ORIGINATING IN THE GASTROINTESTINAL SYSTEM:

According to case reports in which three COVID-19 patients were allowed to be treated with remdesivir, two experienced nausea and one experienced gastroparesis after starting therapy. Diarrhea was noticed in 8% of Remdesivir recipients. According to a Chinese RCT, a higher percentage of remdesivir recipients than placebo recipients had their dosage interrupted due to anorexia, nausea, and vomiting(32).

TOXICITY IN THE LUNGS:

Except for temporarily increased respiration rates, animal safety testing of remdesivir revealed no adverse effects on respiration. Even so, acute respiratory distress syndrome (5%) and pneumothorax (3%) were reported following remdesivir I.V. According to the research results of a Chinese RCT, so many people with the disease in the remdesivir class in comparison to the placebo group experienced respiratory failure and acute respiratory suffering syndrome, and thus the study drug was delisted(33).

TOXICITY TO THE HEART:

In the monkey safety assessment, there were no consequences of remdesivir on cardiovascular factors. However, in a randomized controlled trial of investigational Ebola therapies, one example of hypotension was determined to be probably connected to remdesivir. A COVID-19-infected person treated with remdesivir experienced hypotension (9%), atrial fibrillation (7%), and hypernatremia (5%). Furthermore, one example of heart failure was confirmed in the remdesivir class in a Chinese RCT(34). Some patients receiving remdesivir for COVID-19 disease can experience sinus and bradycardia, hypotension, T-wave alteration, AF, and a prolonged QT gap. There have also been a few reports of cardiac suppression as a result of remdesivir infusion. Remdesivir appears to have a few cardiotoxic and proarrhythmic effects, which are more pronounced in patients with prior cardio-vascular disease. A nonstop heart rhythm monitor is advised for sick people receiving Remdesivir therapies(35).

NEPHROTOXICITY:

Although there is no scientific proof of remdesivir-related kidney disorder in stage I medical studies, repetitive dose adverse effect study results of remdesivir in flora and fauna revealed dose-dependent kidney injury and reduced activity that were associated with ancient results of renal atrophy, basophilia, and casts. A 150-mg dose of remdesivir dosages and lipid-soluble dosage forms of remdesivir contain 9.0 and 4.5 g of sulfo-butyl-ether b-cyclodextrin-sodium (SBECD), respectively (the maximum recommended daily dose is approximately 250 mg/kg, according to the EMA safety review)(36). Because remdesivir has poor water solubility, SBECD is used as a solubilizing agent in the preparation. Because SBECD is a renal clearance test, participants with modest and chronic kidney dysfunction can be exposed to it. When administering remdesivir, it is essential to monitor eGFR closely, particularly in sick people with recognized kidney disorders, and termination is needed if eGFR goes below 50% of the base line(37). Even though remdesivir has minimal renal excretion, urine contains 49 percent of its active form, so an impaired kidney disorder may possibly enhance plasma introduction to this biotransformation. Renal disorders, kidney injury, and hematuria occurred in 8%, 6%, and 4%, respectively, of Remdesivir receivers. After using remdesivir, a COVID-19 patient medicated by our side in Wuhan in 2020 developed kidney failure. This complaint was also concluded in a Chinese RCT(38).

TOXIC TO REPRODUCTION:

Animal reproductive and progression toxicity studies revealed that remdesivir had no effect on male reproductive function or embryo-fetal/peri-postnatal progression, but it did have a significant effect on fertility factors in mice. Despite the fact that it is not recommended for use in pregnant women, remdesivir medication may be necessary in certain cases after weighing the pros and cons. Remdesivir has proven to be useful in human births due to its previous use alongside Ebola. However, the security of remdesivir for that specific number of sick people needs to be assessed through a therapeutic experiment that includes COVID-19 with pregnant women(39).

OTHER NEGATIVE CONSEQUENCES:

Remdesivir treatment resulted in a temporary increase in serum amylase in an Ebola patient. Rash and multiple organ dysfunction syndrome, deep-vein thrombosis, delirium, septic shock, and pyrexia were all reported side effects of remdesivir. Adverse events affecting the blood, cardiac, and vascular systems, as well as the endocrine and supplementary mechanisms, were also observed in the Remdesivir cohort in the Chinese RCT(40). Because knowledge of remdesivir usage in the new and up-and-coming COVID-19 is still restricted, adverse effects must be closely monitored. Some normal adverse effects are also found, like blurred vision, hives, fever, abdominal pain, dark urine, and yellowing of the skin or eyes(41).

DRUG INTERACTION WITH REMDESIVIR:

Remdesivir interacts with 362 different medications. There have been two significant interactions recorded, 277 mild drug interactions, and one with alcohol/food. The drug interactions concerning medicines administered in are all modest and are as follows (by drug group): (1) antibiotics: gentamycin, clarithromycin, doxycycline, amphotericin-B, amikacin; (2) antifungals: clotrimazole, fluconazole, itraconazole, (3) nonsteroidal anti-inflammatories (NSAIDs): rifocoxib diclofenac, etodolac, flurbiprofen, ibuprofen, ketoprofen. Remdesivir are interact with the majorly two medicines chloroquine and hydroxychloroquine; moderately interact with the 360 medicines(42).

DISCUSSION

Many adverse effects were reported according to data. The kidney and liver organs were the most commonly documented adverse effects associated with remdesivir use, including an increase in liver enzymes and acute kidney damage, respectively. A disproportionate representation was performed to examine the incidence of adverse outcomes with remdesivir as a suspected drug. With the use of remdesivir, there were a lot more reports of elevated hepatic enzymes, acute renal diseases and kidney irregularities, bradycardia, cardiac arrest, and death (ROR below 95 percent CI >1) than with some of the other medicines in the collection.

CONCLUSION

In this review, we have presented another benefit of COVID-19, known as Remdesivir. We can talk about the remdesivir's disadvantages and one of them is an adverse effect. Remdesivir has the greatest impact on the liver, kidneys, and heart. Remdesivir causes renal impairment in the kidney by increasing the hepatic enzyme. The main side effect of remdesivir is an increase in liver enzymes. It's also caused vomiting, diarrhea, and other common side effects. It must be required to investigate potential changes in medication labelling to incorporate the discovered potential renal and cardiac safety issues.

Declaration by Authors

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