REVIEW ARTICLE JPAR 2021

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Remdesivir: A critical review

Kasturi Jahnavi[1], Bere Jyostna[2], Karangula Jyoshika[2], Ilavarapu Ashwitha[2], Diddiga Amulya[2], Kannekanti Chaitanya[2], BoggulaNarender[*2]

[1]Malla Reddy College of Pharmacy, Dulapally, Kompally, Secunderabad, Hyderabad, Telangana, India.
[2]School of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Medchal, Hyderabad, Telangana, India.

Received: 28.05.2020 Revised: 12.06.2021 Accepted: 22.06.2021 Published: 30.06.2021

ABSTRACT: The currently available antiviral drugs target three main groups of viruses that are herpes, hepatitis, and influenza viruses. Remdesivir, an antiviral prodrug originally developed to treat Ebola virus disease, has shown broad spectrum activity against the Coronavirus family. Therefore, despite supportive data from *in vitro* and *in vivo* studies, the clinical effectiveness of IV Remdesivir for treatment of COVID-19 and potential side effects remains incompletely defined in the human population. Remdesivir as a drug attracted a very serious consideration of the whole Globe in treatment of the pandemic disease COVID-19. More recently published *in vitro* inhibition activity and *in-vivo* case studies were showing promising clinical results and outcome of effective inhibition of SARS-CoV-2 virus by the use of Remdesivir. However, at the same time, use of the Remdesivir showed substantial detrimental adverse events in patients which needed special attention during treatment of COVID-19. Thus, the use of Remdesivir in treatment of COVID-19 is of current international interest although some more clinical evidence is still necessary in order to understand the actual efficiency and mechanism of Remdesivir against COVID-19.In view of this, the present literature study spotlights the current ongoing research related to use of Remdesivir which includes, pharmacology of Remdesivir, mechanism of action, pharmacokinetics and clinical use of Remdesivir against COVID-19 and other applications.

Corresponding author*
Mr. NarenderBoggula
Associate Professor,
Department of Pharmaceutical Chemistry,
School of Pharmacy, Anurag University,
Venkatapur, Ghatkesar, Medchal,
Hyderabad, Telangana - 500088, India.
Tel: +91-9666552211
E. Mail: narender.b987@gmail.com

Keywords: Remdesivir, COVID-19, antiviral drug, SARS-CoV-2 virus, RNA-dependent RNA polymerase, clinical trials.

INTRODUCTION:

Antiviral drugs are the chemotherapeutic agents which are used in treatment and prophylaxis of diseases caused by different viruses. Most antivirals are only effective while the virus is replicating. They help to stop infections from getting worse and reduce the chance of the return of an infection. They are sometimes used to prevent people whose immune systems are not working properly from infections. However, vaccination might be a better and safer option to prevent some of the viral infections, like seasonal influenza and hepatitis. Antiviral drugs are a class of medication used for

treating viral infections. Most antivirals target specific viruses, while a broad-spectrum antiviral is effective against a wide range of viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead, they inhibit its development [1,2].

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs, or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Natural viricides are produced by some plants such as eucalyptus and Australian tea trees. While most antivirals treat viral infection, vaccines are a pre-emptive first line of defense against pathogens. Vaccination involves the introduction (i.e. via injection) of a small amount of typically inactivated or attenuated antigenic material to stimulate an individual's immune system. The immune system responds by developing white blood cells to specifically combat the introduced pathogen, resulting in adaptive immunity. Vaccination in a population results in herd immunity and greatly improved population health, with significant reductions in viral infection and disease [2,3].

Antiretroviral agents (ARVs) have predictable toxicities and adverse effects because they are most chronically administered drugs. It is essential that clinicians noticeably understand ADRs, eagerly identify them in patients and manage them successfully. Information on adverse drug reactions (ADRs) associated with antiretroviral (ARV) use in public health practice is signifying the requirement for ART safety surveillance in clinical care [4].

Back ground and Chemistry:

Remdesivir is a broad-spectrum antiviral medication, developed by the Biopharmaceutical company Gilead Sciences. It is administered via injection into a vein. Remdesivir is an antiviral drug and as a nucleoside analogue. Chemically it is 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-phenoxy phospho ryl]amino]propanoate. Molecular formula is $C_{27}H_{35}N_6O_8$ Pand molecular weight is 602.58 g/mol [5]. The molecular structure of Remdesivir was shown in Fig 1.

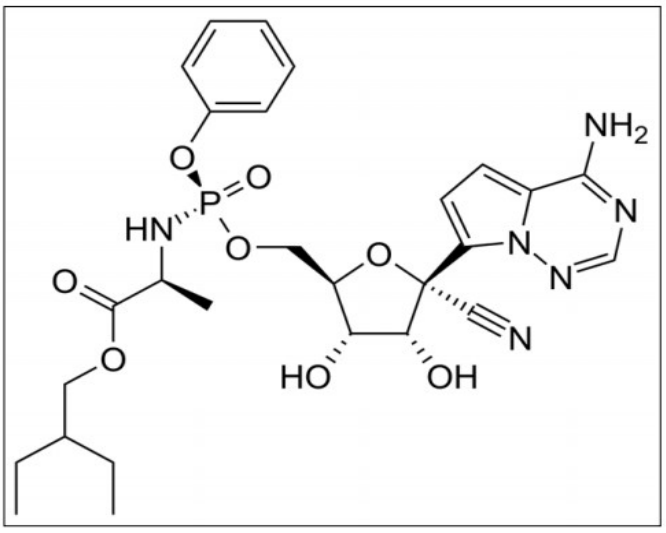

Fig 1. Molecular structure of Remdesivir.

Discovery of Remdesivir (GS-5734):

Nucleoside and nucleotide analogues as small-molecule-based antivirals have been explored for many years and form the backbone of treatment against viral infections, including HIV, hepatitis B virus, and Herpesvirus infections. In 2013, the nucleotide analogue Sofosbuvir was approved by the FDA for the treatment of chronic hepatitis C virus infections. The novel compound that targets the RNA-dependent viral polymerase (NS5B) revolutionized HCV treatment, as it is able to cure the formerly lifelong chronic progressive disease when combined with other antivirals.

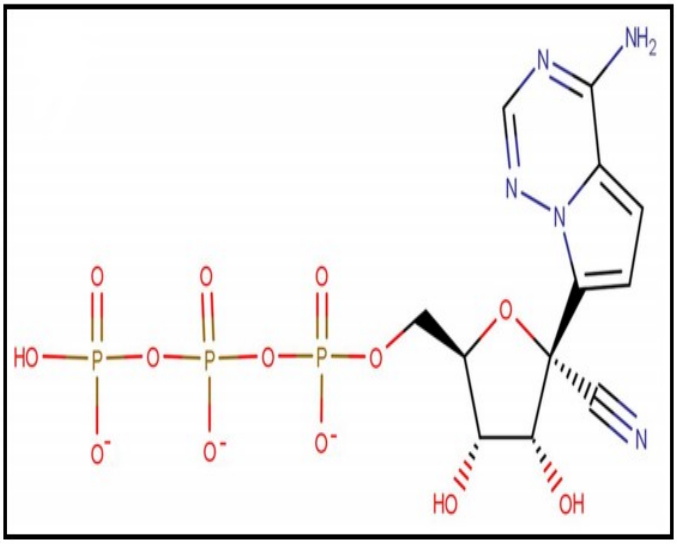

Fig 3. Pharmacologically active nucleoside triphosphate (NTP) as a viral RdRp inhibitor.

In the past years, nucleoside/nucleotide analogues were increasingly recognized as potential antivirals targeting other positive-stranded RNA viruses such as members of the Flaviviridae, Picornaviridae, Caliciviridae, and

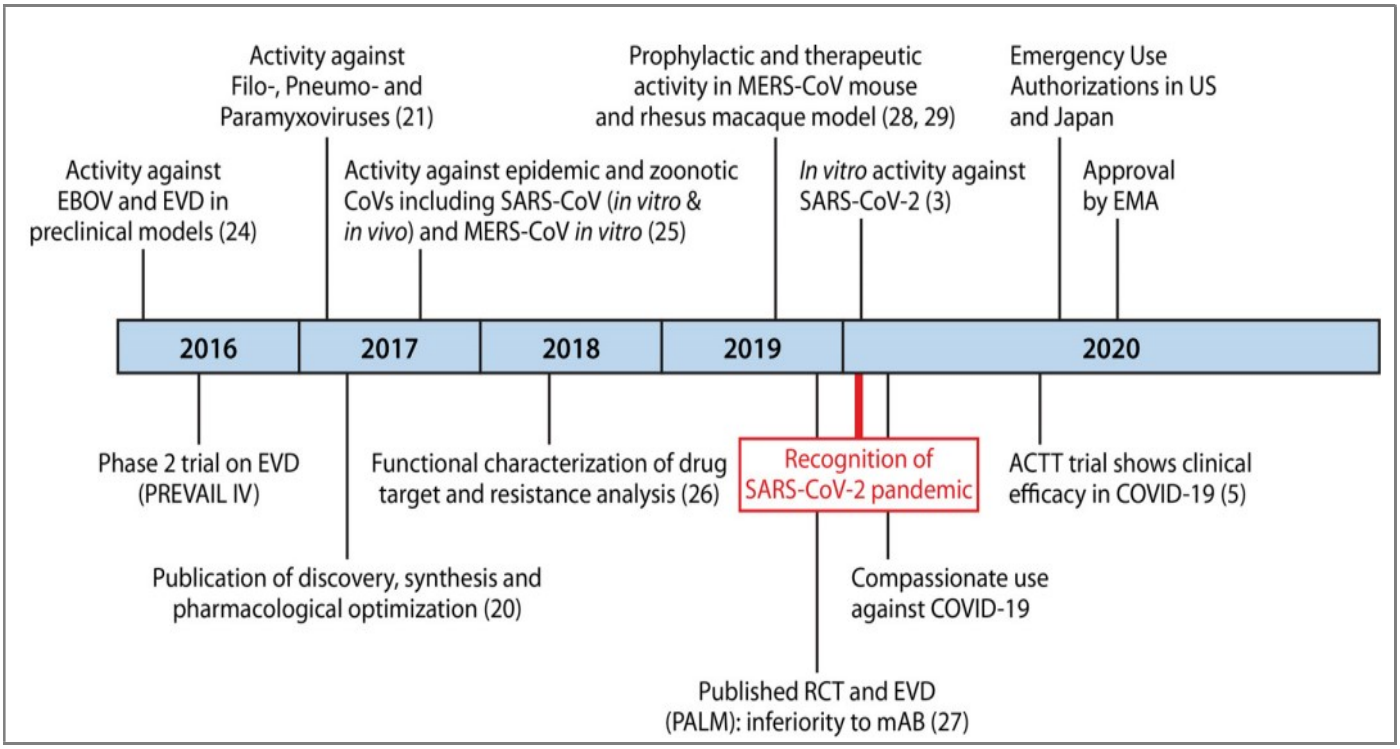

Fig 2. Milestones in the discovery of Remdesivir as an anti-COVID-19 treatment. Shown is a chronological summary of important achievements in the discovery and preclinical and clinical evaluations of Remdesivir (GS-5734).

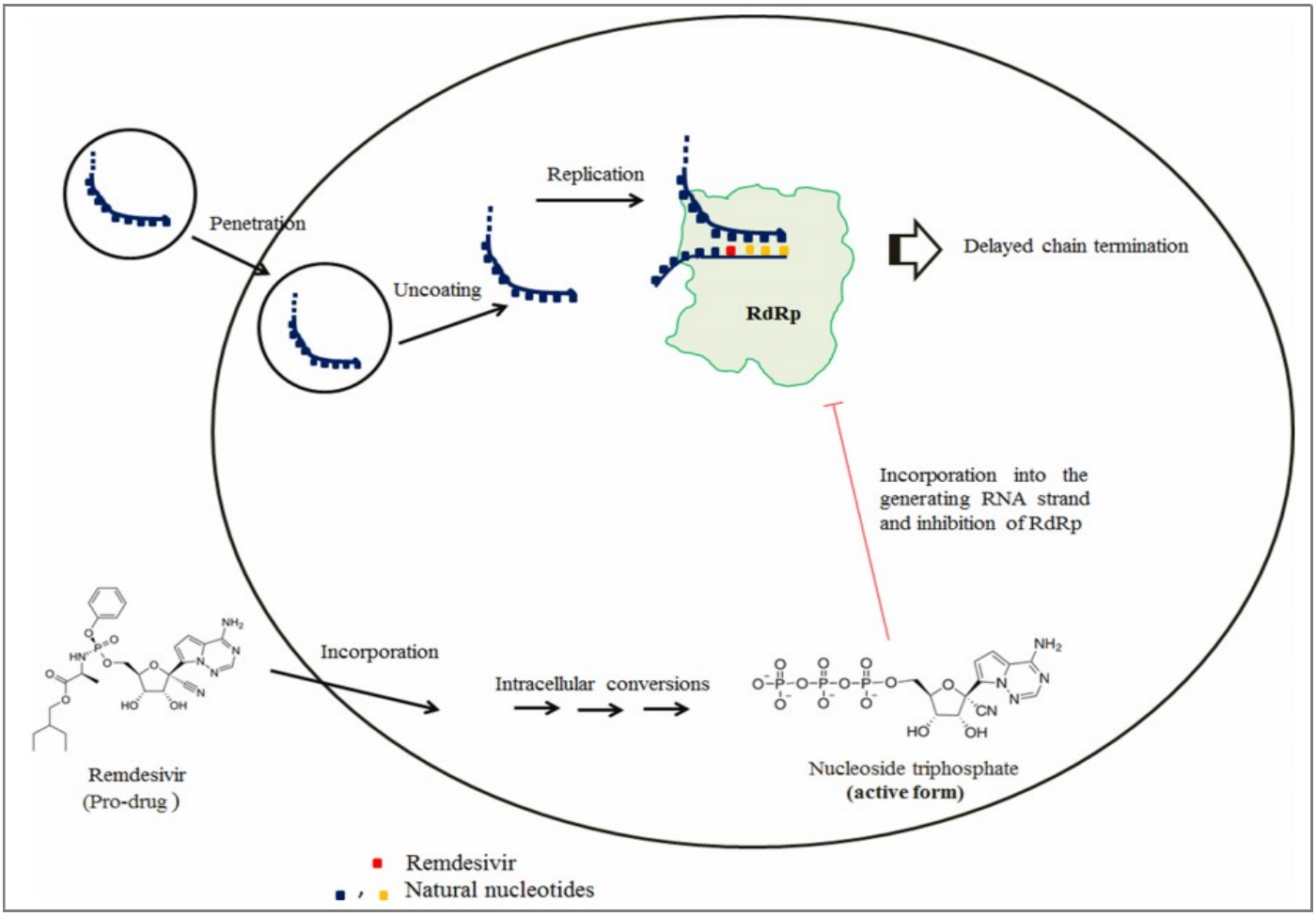

Fig 4. Mechanisms of action of Remdesivir.

Coronaviridae families, as they share relevant amino acid sequences with HCV, and the RNA-dependent polymerases are closely related phylogenetically.

This supported the assembly of antiviral compound libraries that could be screened against emerging RNA viruses. In the past years, several pharmacological advances in the development of nucleoside analogues were made based on structure-to-activity relationship (SAR) studies that improved pharmacokinetics, antiviral activity, and selectivity. A comprehensive overview of the medicinal chemistry and pharmacological evolution of antiviral nucleoside analogues can be found elsewhere. Nucleoside analogues require intracellular activation by phosphorylation in order to become their active metabolites. One of the most important milestones was the addition of a monophosphate prodrug to the nucleoside, which significantly improved intracellular delivery and activation. This so-called Pro-Tide approach was used to optimize the precursor of Remdesivir named GS-441524 [6-8].

Mechanism of Action (MoA):

Remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside (Fig 2). By entrance into respiratory epithelial cells in the human body; the prodrug may be efficiently metabolized to a nucleoside triphosphate as an active form (Fig 3). The active form can prevent the replication of several coronaviruses in the lung epithelial cells. The nucleoside analogue drug inhibits the RNA-dependent RNA polymerase (RdRp) by competing with the usual counterpart adenosine triphosphate (ATP). The nucleoside analogue is incorporated into the generating RNA strand and causes a delayed stop in the viral replication process (Fig 4). As the enzyme incorporates one, two or three more nucleotides, the incorporated nucleoside analogue moves back. The drug blocks the enzyme while it reaches into the third position away from the enzyme's active site. It crashes into a conserved serine (Ser) in the active site of the enzyme and inhibits the enzyme from moving one step forward to incorporate the next nucleotide (Fig 4). The exoribonuclease of the virus that usually proofreads and corrects the replication errors cannot work against the active form of Remdesivir [9-10].

Pharmacokinetics:

Remdesivir is a pro-drug; concentrations decline rapidly after IV administration (plasma half-life, T½ ~1 h), followed by the sequential appearance of the intermediate alanine metabolite GS-704277 and the nucleoside monophosphate metabolite GS-441524 (plasma T1⁄2 24.5 h). Inside cells, GS-441524 is rapidly converted to the pharmacologically active triphosphate analogue, GS-443902, which has a prolonged intracellular T ½ (peripheral blood mononuclear cell, PBMC T1⁄2 ~ 40 h). Both Remdesivir and GS-441524 exhibit linear PK following single doses between 3mg and 225mg and no Remdesivir accumulation was observed following once daily dosing for up to 5 days. By contrast, GS-441524 reaches steady state around day 4 and accumulates by ~2-fold after multiple once daily dosing. The Remdesivir dosing regimen being evaluated in clinical trials (200 mg IV on day 1, then 100 mg IV on days 2 through 5 or 10) was substantiated by in vitro data and bridging the PK with the rhesus monkey experience to humans [11].

Due to the near complete first-pass effect of phosphoramidates, Remdesivir is expected to have poor oral bioavailability. Plasma protein binding for Remdesivir is moderate (Free fraction of 12.1 %). By contrast, metabolites GS-704277 and GS-441524 exhibit low plasma protein binding with mean free fractions ≥ 85%. In cynomolgus monkeys, radiolabeled Remdesivir or its metabolites were detectable in the testes, epididymis, eyes, and brain 4 h after a 10mg/kg dose (equivalent to 200 mg in humans). Levels in the brain were significantly lower than in other tissues but accumulated over time. Distribution studies in humans have not yet been reported [12].

Remdesivir is a substrate of several cytochrome P450 enzymes *in vitro*, however clinical implications are unclear since the pro-drug is rapidly metabolized by plasma hydrolases. By similar reasoning, the effect of hepatic impairment on Remdesivir plasma levels should be low although specific studies have not been conducted in patients with hepatic impairment and the drug is contraindicated in patients with severe hepatic impairment. Metabolism of metabolites GS-704277, GS-441524, and GS-443902 has not been characterized [13].

Remdesivir exhibits low renal excretion (< 10 %). However, 49 % of a radiolabeled dose was recovered as GS-441524 in urine. Theoretically, plasma exposure of GS-441524 may be increased in patients with renal impairment. Remdesivir formulations contain sulfobutylether b-cyclodextrin sodium (SBECD) as a solubility enhancer. Formulations containing SBECD have historically been cautioned against in patients with

renal impairment, although clinical data suggest SBECD accumulation does not increase the risk of acute kidney injury. There are no recommendations for dose adjustments in patients with mild to moderate renal impairment at this time. Under the FDA emergency use authorization guidance, Remdesivir is not recommended in patients with an estimated glomerular filtration rate (eGFR) < 30 ml/min or serum creatinine ≥ 1mg/dl unless the potential benefit outweighs the potential risk. Patients with an eGFR< 30 ml/min and those who are receiving hemodialysis or hemofiltration are excluded from the EMA compassionate use program. There are no pharmacokinetic data available for children or women who are pregnant or breastfeeding [14].

Resistance:

The development of Remdesivir resistance in coronaviruses has been assessed by cell culture in MHV, which has similar EC_{50} values to SARS-CoV-1, SARS-CoV-2, and MERS-CoV. Following > 20 *in-vitro* passages, two non-synonymous mutations were selected in the nsp12 RdRp: F476L and V553L. Neither of the mutations directly altered RdRp's catalytic site or substrate binding pocket, but they did cause minor structural alterations that are thought to impact RdRp's fidelity checking step before catalysis. Compared to wild-type viruses, these mutations conferred 2.4d and 5 fold reduced susceptibility to Remdesivir, respectively, while the double mutant showed 5.6-fold reduced susceptibility *in-vitro*. The EC_{50} values of the mutants (0.057 to 0.13 µmol/L), however, remained below achievable human drug exposures. Furthermore, the mutations appear to confer a fitness cost, with wild-type virus rapidly out competing the mutants in the absence of Remdesivir. Of concern, however, the affected residues are conserved across coronaviruses raising the possibility of a common pathway to resistance. In fact, substitutions at homologous SARS-CoV-1 residues conferred a 6-fold decrease in susceptibility to Remdesivir (EC50 0.01µmol/L to 0.06µmol/L). No data specific to SARS-CoV-2 Remdesivir resistance have been published [15,16].

Drug interactions:

At the time of writing, no *in vivo* drug interaction studies of Remdesivir have been published but the ability of Remdesivir to inhibit or induce cytochrome P450 (CYP450) enzymes and transporters has been tested *in vitro*. Importantly however, as a pro-drug, Remdesivir is rapidly degraded *in vivo* so the potential for clinically significant drug interactions is likely limited. Data on the potential for Remdesivir metabolites to perpetrate drug interactions are even scarcer. In *in vitro* studies, Remdesivir was a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Remdesivir's IC_{50} for CYP3A was 1.6 µmol/L, suggesting inhibition may occur briefly with standard human exposures. Inhibition of CYP450 enzymes by metabolites was not investigated. Tests of Remdesivir CYP450 induction have been inconsistent; it may induce CYP1A2 and CYP2B6. Again, the clinical importance of this is questionable. GS-441524 and GS-704277 demonstrated no CYP450 induction in these studies. Remdesivir was found to be a substrate (OATP1B, P-glycoprotein) or inhibitor (OAT1B1, OAT1B3) of several drug transporters. There are no exclusion criteria relate to drug-drug interactions in current Remdesivir clinical studies [17,18].

Dosage and Administration:

Remdesivir is available in two bioequivalent formulations: a concentrated solution (5mg/mL) and a lyophilized powder formulation. Vials contain 100mg of Remdesivir and are preservative free. Readers are referred to the FDA Fact Sheet for full storage, preparation, and administration instructions. For adults and children weighing ≥ 40kg requiring invasive mechanical ventilation or ECMO, the recommended dose is 200 mg IV on day 1 followed by 100 mg IV once daily on days 2 to 10. For those not requiring invasive mechanical ventilation or ECMO, a 5-day regimen is recommended. Doses should be administered over 30 min to 2 h. Readers are referred to the FDA Fact Sheet for full pediatric dosing recommendations. There is no information on direct IV push, intramuscular, or subcutaneous administration at this time [19,20].

Prophylactic use and side effects:

Very few reports are available for the proposed prophylactic use of Remdesivir against COVID-19. European medicine agency documented the prophylactic use of Remdesivir which reduces the viral load significantly. Prophylactic use of the Remdesivir may prevent the physiological defect that occurred due to SARS-CoV-2 infection. The prophylactic efficacy of Remdesivir against various coronavirus diseases. Thus, from the available literature it may be possible that Remdesivir showed its effective prophylactic and therapeutic use against COVID-19. However, more evidence is still waiting in order to understand the efficient prophylactic use of Remdesivir against

COVID-19. Further, it is noteworthy to mention the adverse influence of Remdesivir in the present medical emergency scenario.

Adverse events of use of Remdesivir which involves the nausea (in 9 % patients), worsening or respiratory failure (in 8 % patients), increased alanine aminotransferase level (in 7 % patients), and constipation (in 7% patients), anaemia (in 7.9 % patients than 9.0 % of control group); pyrexia (in 5.0 % patients than 3 % of control group); hyperglycemia (in 4.1 % patient than 3 % of control group) and increased aminotransferase. Adverse events in 60 % patients during treatment which involves the increased liver enzymes, diarrhea, renal impairment, and hypotension, while 23 % patients showed severe adverse effects such as multiple-organ dysfunctioning, septic shock, kidney injury. Common side effects in use of Remdesivir which involves constipation, hypoalbuminemia, anaemia, thrombocytopenia, and elevated bilirubin. Thus, the Remdesivir should be administered only under medical supervision as it may have severe side effects [21-23].

Dosing recommendations:

Remdesivir is administered by intravenous infusion over 30 to 120 min. The standard dose for adults and pediatric patients weighing 40kg and higher is a loading dose of 200mg followed by once-daily doses of 100 mg. Dose adjustments are necessary for pediatric patients weighing less than 40kg. It is not known if dose adjustments based on kidney or liver function are necessary. Administration in patients with a glomerular filtration rate (GFR) below 30ml/min is not recommended based on the potential accumulation of sulfobutylether-β-cyclodextrin sodium salt present in both formulations of Remdesivir. The optimal treatment duration for COVID-19 is still unknown. In phase 3 trials, a treatment course of 5 or 10 days was investigated. Based on these data, the actual recommendations in the context of emergency authorizations are 5 days for patients who do not require mechanical ventilation, which can be extended up to 10 days if patients do not demonstrate clinical improvement. For patients on mechanical ventilation, the recommended treatment duration is 10 days [24-26].

Therapeutic uses of Remdesivir:

Remdesivir as an analogue of Ribonucleotideadenosine monophosphate has the potential to compromise RNA synthesis in viral RNA infections. It was tested against various RNA viruses with more or less success. Remdesivir was tested against Ebola, Nipah virus, and Middle East respiratory syndrome (MERS) in human medicine and feline infectious peritonitis. Currently, the world is following numerous clinical trials in which Remdesiviris tested in patients' with COVID-19 [27].

The in vitro and in vivo testing of Remdesivir:

At the start of the COVID-19 pandemic, no specific therapy or specific preventive therapeutic agents were known and available. Various drugs were repurposed from other indications, and the information regarding their *in-vitro* and *in-vivo* activity in various cells, and also humans were from the time when these drugs were investigated against other infections. In the case of Remdesivir, Ebola infection use gave some information about its possible therapeutic activity, as it was studied in vitro on its ability to be incorporated into the RNA structure, and on its ability to inhibit various RNA polymerases. Additionally, it has already been studied in a non-human primate model with an Ebola infection. Many studies on the Remdesivir activation and mechanism of action were performed on cellular or sub-cellular models. For example, Agostini and her team used in her study murine astrocytoma cells and baby hamster kidney 21 cells expressing the murine hepatitis virus receptor. She also used the human lung epithelial cells Calu-3 and human tracheobronchial epithelial cells. As much as her data are interesting, they were not obtained specifically for SARS-CoV-2. Sheahan and his team used in their experiment the primary human lung epithelial cell cultures. They studied Remdesivir activity on circulating contemporary human CoVs-i.e., SARS-CoV, but not SARS-CoV-2. Only newer scientific reports deal with SARS-CoV. Choy studied the activity of Remdesivir and other substances against the SARS-CoV-2 virus in Vero E6 cells. A nice summary of Remdesivir preclinical *in vitro* and *in vivo* data was published just at the end of May 2020. Another summarization of the *in vitro* data for Remdesivir and several other therapeutics used in COVID-19 appeared online also very recently in May 2020. As for *in vivo* studies, the preference is given to primate models, as discussed in the sections on Ebola and MERS [28-30].

Ebola:

Remdesivir was used in the treatment of Ebola cases based on preclinical data showing that it had blocked Ebola virus replication in primates. It was used in Ebola patients in emergency settings during the Kivu Ebola epidemic in 2018-2019. Then, it was shown that Remdesiviris inferior to the affectivity of monoclonal

antibodies. An excellent review of therapeutic strategies that may be useful against the Ebola infection was published only recently. Similarly, to the situation with other RNA viruses, Remdesivirrivals adenosine triphosphate for incorporation into RNA. Kinetic experiments demonstrated that GS-441524triphosphate (the active molecule of Remdesivir) is similar to adenosine triphosphate in its incorporation efficiency. However, the selectivity of this incorporation is approximately 4 times higher for adenosine triphosphate compared to GS-441524triphosphate. On the other hand, human mitochondrial RNA polymerase effectively distinguishes these two substrates, and the selectivity ratio for adenosine triphosphate and GS-441524 triphosphate is approximately 500. The presence of activated Remdesivirin cells results in delayed chain termination in the synthesis of RNA. Remdesivir was used in two patients with Ebola successfully-both patients survived.

This moved Remdesivir into Phase 2 of clinical development for its use in Ebola patients. Additionally, when used in a new born from an Ebola virus-positive lady on the day of birth (together with monoclonal antibodies ZMapp), Remdesivir contributed to the eradication of the virus in the child (as proved by PCR) and it seems to be doing well at the 12 months of age. Despite these and some other positive records, potential Ebola outbreaks still represent a danger for affected populations, especially due to the ways of transmission, various social aspects, and current limits of therapeutic interventions [31-34].

Nipah Virus:

Nipah virus (Paramyxoviridae) is another pathogenic RNA virus. This virus was transmitted to humans from fruit bats. Additionally, transmission between persons was confirmed. Similarly, to COVID-19 infection, Nipah virus also causes respiratory and neurological disorders, with a 40 to 75 % mortality according to the World Health Organization. Treatment, similarly to the treatment of the COVID-19 infection, is still under development. Remdesivir represents a viable option, as it seems to be highly effective in the African green monkey model. Experiments performed using this model with infecting the experimental animals with a lethal dose of virus have shown that Remdesivir administered in one dose daily during 12 days saved all the treated animals compared to the monkeys that were not treated. All the animals left without treatment died during the experiment. It indicates that Remdesivirmay represent a suitable treatment also for the Nipah virus [35-37].

Middle East Respiratory Syndrome (MERS):

Coronaviruses belong to the Orthocoronavirinae family and transmission between various species is one of their properties. At present, therapeutic strategies for these viruses do not exist, but the present crisis has made researchers and medical doctors pay increasing attention to this issue. Remdesivir seems to represent a viable option in the treatment of various corona (and other) infections through the inhibition of the viral RNA dependent RNA polymerase. Middle East Respiratory Syndrome coronavirus (MERS-CoV) serves as the causative agent of respiratory disease that has caused over 2468 infections in humans, with more than 851 deaths registered in 27 states during the last 8 years. MERS-CoV infection seems to respond to the Remdesivir therapy, as shown in the nonhuman primate model through the inhibition of viral replication, as demonstrated *in vitro*. Treatment by Remdesivir (starting 24 h before infection by MERS-CoV) resulted in the full inhibition of clinical symptoms by inhibiting MERS-CoV replication in the lungs, thus preventing the appearance of lung tissue lesions. The treatment with Remdesivir in the early stages of MERS infection has shown significant clinical benefit, accompanied by the diminished formation and severity of lung lesions. Compared to other agents (Lopinavir, ritonavir, and possibly interferon beta), Remdesivir shows the highest anti-MERS activity *in-vitro*, and it improves various pulmonary functions in a murine model *in-vivo*. This effect is achieved through the competition of the triphosphate of activated Remdesivir (10-cyano analogue of adenosine with adenine replaced by 4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl-) competing with ATP via various mechanisms [37,38].

COVID-19:

Clinical Trials Evaluating Remdesivir as a Treatment for COVID-19 Originally, within the period of January to March 2020, Remdesivir was given to individual COVID-19 patients on a compassionate-use basis. Remdesivir was administered for 10 days (200 mg intravenously on day 1, and 100 mg per day on the day 2 to 10). An analysis of data for 53 patients (22 in the USA, 22 in Europe or Canada, and 9 in Japan) has shown that 25 patients (47 %) were treated successfully and 7 patients (13 %) died. Clinical improvement was seen in 36 of 53 patients (68 %). On 6 February 2020,

the first global clinical trial began in China, specifically in Hubei. The designed clinical trial was a randomized, double-blind, placebo-controlled, and multi-center study, with a participation of 237 hospitalized patients (aged≥18 years). The study found that there were no statistically significant clinical benefits associated with Remdesivir use. However, the clinical improvement time for the patients was shorter while using the antiviral drug compared to those receiving placebo. The first randomized and controlled clinical trial for Remdesivir in the United States has been begun by the University of Nebraska Medical Center (UNMC) in Omaha to evaluate Remdesivir's safety and efficacy in hospitalized adults diagnosed with COVID-19. The trial was overseen by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The participants in the trial should be examined and diagnosed with SARS-CoV-2 infection as well as evidence of lung association, such as speedy sounds when breathing (rales), with a need for supplemental oxygen or abnormal chest X-rays, or barely breathing and requiring mechanical ventilation. Individuals with confirmed infection who have mild symptoms or no symptoms will not be involved in the study. The preliminary data analysis, as well as results, was released on 29 April 2020. The study showed that the recovery time was reduced by 31 % for the patients who received Remdesivir compared to the placebo group. Moreover, the mortality rate was 8.0 % for the group receiving Remdesivir, while it was 11 % for the group who received a placebo. Moreover, Gilead Sciences Inc. released data on a Gilead sponsored Phase 3 randomized trial in 12 years and older hospitalized patients with severe COVID-19 disease. The design of the study was randomized, open-label, and multicentre, and the estimated enrolment of the study was 6000 patients. The data revealed that patients who were treated for 5 days with Remdesivir had a comparable clinical improvement compared to the patients who were treated for 10 days with Remdesivir. Additionally, the study indicated the proposed treatment duration for severe cases, which can aid in monitoring other COVID-19 cases that require treatment in an intensive care unit. In the United States, a clinical trial phase 3 has been launched on 21 February 2020. The study is designed to be an adaptive, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of Remdesivir in hospitalized adults (aged ≥ 18 years) diagnosed with COVID-19. The study was proposed to be a multicenter trial that will be conducted in roughly 100 sites all over the world. The study will compare different investigational therapeutic agents, including Remdesivir, to a control. The project originally enrolled 394 patients, however, with the recent enrolment rates the total sample size could reach 600 or even more than 800. To date, the study results have not been posted or may not yet be posted because they are pending a quality control (QC) review by the National Library of Medicine (NLM) or the sponsor or investigator is addressing QC review comments provided by the NLM. After all this, the clinical trials showed diverse results that were due to the different rules of patients' enrolment and different endpoints. The clinical trials performed in China had stricter conditions for the enrolment of patients, such as having an interval from symptom onset to the enrolment of 12 days or less. Besides this, the time (in days) from randomization to the point of a decline of two levels on a six-point ordinal scale of clinical status (1 = discharged and 6 = death) was the primary endpoint for the China trial. In contrast, in the National Institute of Allergy and Infectious Diseases trial, the primary endpoint was time to recuperation, which was indicated as recovered enough to leave hospital or a resumption of normal activity level. Currently, the ClinicalTrials.gov database registers 30 trials for Remdesivir (6 trials are using the term "GS-57340" instead of Remdesivir) concerning COVID-19. However, more time is needed to evaluate all the data and information from these trials. Currently, three clinical trials are enrolling patients to study the therapeutic usefulness of Remdesivir. One trial is organized in Hospital Cochin in Paris, France, and two are in the USA. One clinical trial organized in Wuhan, China, was suspended [38-42].

Future Perspective:

After decades of research on direct-acting antiviral drugs, Remdesivir is the first nucleoside analogue that can be used to treat infections caused by a respiratory virus. In the light of its beneficial clinical effects, its favourable safety profile, and the absence of alternatives to treat COVID-19, Remdesivir will increasingly be used outside the context of clinical trials or compassionate-use programs. The drug is already available in the United States and Japan based on emergency-use authorizations and was recently approved in Europe. However, treatment with the antiviral drug Remdesivir alone will not be sufficient to reliably save the lives of patients suffering from

COVID-19 or to solve the hazardous public health issues caused by the ongoing COVID-19 pandemic. Antiviral therapy in hospitalized patients cannot prevent the virus from being transmitted among communities and cannot reverse pathophysiological processes that have occurred already at the time of diagnosis. In general, prophylactic measures would be much more efficient in reducing COVID-19-associated morbidity and mortality as well as economic implications. The prophylactic use of Remdesivir might be effective, as it completely protected exposed macaques from MERS-CoV-induced clinical disease.

Prophylactic effects are also known from other virostatic-acting drugs like neuraminidase inhibitors that may prevent influenza virus infections and can also be used as post exposition prophylaxis. However, the prophylactic use of Remdesivir is generally hampered by its poor oral bioavailability and the absence of an oral formulation. Further pharmacological efforts are needed to make the drug accessible to an outpatient population. Recently, the manufacturer announced in an open letter that a phase 1 trial with Remdesivir inhalation is being planned and already accepted by the FDA. Interestingly, another SARS-CoV-2 active nucleoside analogue called EIDD-1931, which is orally bioavailable, is currently in preclinical evaluation. Finally, it should be mentioned that drug pricing will also have significant implications for the possibility of applying Remdesivir with a broader scope.

The therapeutic efficacy of Remdesivir might be improved by the addition of other antivirals or immunomodulatory agents. It has recently been shown that glucocorticoids are able to improve clinical outcomes in cases of severe and critical COVID-19. Based on these data, it can be expected that physicians will use both Remdesivir and glucocorticoids to treat patients with severe or critical COVID-19. However, combination therapy should be used with caution, as drug interactions may occur. In vitro, Remdesivir acts as the substrate or inhibitor of several drug-metabolizing enzymes (e.g., CYP3A4), which could influence the exposure levels of other therapeutic agents. In addition, these agents may interfere with the pharmacokinetics of Remdesivir.

The immunomodulatory drug hydroxychloroquine, for example, seems to reduce the antiviral activity of Remdesivir by impairing its intracellular metabolic activation. Another approach that may improve clinical outcomes could be combination therapy with direct antiviral drugs that target several processes within the viral life cycle. Although this strategy is highly effective in the therapy of chronic infections with HIV and HCV, it is unclear if this is true for acute infections with SARS-CoV-2. Clinical trials evaluating combination therapy are needed to estimate their role in COVID-19.

CONCLUSION:

This study was an attempt to descriptively analyse ADEs reported to date for Remdesivir to add to the information about the safety of Remdesivir reported to date from published clinical trials in patients with COVID-19 given potential concerns. The most important ADEs were elevation of liver enzymes and those arising from kidney injury, which is in line with the product information given by the FDA. These findings call for greater monitoring of liver enzymes during treatment, building on existing guidance, with the potential for dose adjustments, as well as monitoring renal function before and during treatment with Remdesivir. Greater guidance can also be given by the authorities as more knowledge becomes available including potential doses of Remdesivir in patients with COVID-19 with existing hepatic impairment or poor renal function.

There is both *in-vitro* and limited clinical evidence that supports the use of Remdesivir to treat SARS-CoV-2. However, Phase 3 clinical trials have not yet been completed and partial data has not yet been reported. The side-effects profile of Remdesivir remains similarly not well defined. Until high-quality studies report significant improvements with administration of IV Remdesivir, the use of this experimental drug should be limited to randomized controlled trials. Therefore, the potential of Remdesivir as a standard of care therapy for COVID-19 remains to be determined.The use of Remdesivir for COVID-19 treatment has not been clarified yet, and more detailed studies are needed on these drugs.

The ongoing studies will provide more high-quality evidence on the benefit and harmful effects of Remdesivir.

ACKNOWLEDGEMENT:

The authors wish to thank the management of Malla Reddy College of Pharmacy, Dulapally, Kompally, Secunderabad, Hyderabad, Telangana, India, and School of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Hyderabad, Telangana, India for providing necessary equipment, constant encouragement, praiseworthy inspiration, facilities and support.

REFERENCES:

1. Schnitzler, P,Schon, K,Reichling J. Antiviral activity of Australian tea tree oil and eucalyptus oil against herpes simplex virus in cell culture. Die Pharmazie, 2001; 56(4): 343-347.
2. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J BiolChem, 2020; 295(15): 4773-4779.
3. Yan VC, Muller FL. Advantages of the parent nucleoside GS-441524 over Remdesivir for COVID-19 treatment. ACS Med ChemLett, 2020; 11(7): 1361-1366.
4. Menachery VD, Graham RL, Baric RS. Jumping species-a mechanism for coronavirus persistence and survival. CurrOpinVirol, 2017; 23: 1-7.
5. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. Clin Infectious Dis, 2007; 45: 1093-1101.
6. Musa A. Addendum to Systematic Review of Remdesivir for the Treatment of COVID-19. West J Emerg Med, 2020; 21(4): 742-743.
7. Mulangu S, Dodd LE, Davey RT. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med, 2019; 381: 2293-2303.
8. Boggula N, Vijay KN, Satheesh J, Jiji AG. Highly Active Antiretroviral Therapy: The Issues and Factors Deciding Adverse Drug Reactions. Am J Pharm Health Res, 2016; 4(3): 87-101.
9. Wang M, Cao R, Zhang L. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res, 2020; 30(3): 269-271.
10. Ieppala S, Vishal RA, Nellutla S, Narender B. Novel Coronavirus Disease (COVID-19): A Literature Based Review. Res Adv Pharmacy Life Sci, 2020; 2(2): 9-20.
11. Raoult D, Zumla A, Locatelli F. Coronavirus infections: epidemiological, clinical, and immunological features and hypotheses. Cell Stress, 2020; 4(4): 66-74.
12. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol, 2004; 203(2): 631-637.
13. Vander T, Medvedovsky M, Herishanu Y. Encephalopathy induced by oral acyclovir in a patient with normal renal function. J Infect, 2003; 46(4): 286.
14. Tchesnokov EP, Feng JY, Porter DP, Gotte M. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. Viruses, 2019; 11(4): 326-341.
15. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, *et al*. Remdesivir: A Review of Its Discovery and Development leading to emergency use Authorization for Treatment of COVID-19. ACS Cent Sci, 2020; 6(5): 672-683.
16. Warren TK, Jordan R, Lo MK. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature, 2016; 531: 381-385.
17. Ram AH, Badgujar KC, Zanznay R, Kadam H, Badgujar VC.Remdesivir for COVID-19: A review of pharmacology, mechanism of action, *invitro* activity and clinical use based on available case studies. J Drug DelivdTher, 2020; 10(4-s): 264-270.
18. Andersen KG, Rambaut A,Lipkin WI, Holmes EC, GarryRF. The proximal origin of SARS-CoV-2. Nat Med, 2020; 26: 450-452.
19. Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, *et al*. Safety, tolerability, and pharmacokinetics of Remdesivir, an antiviral for treatment of COVID-19 in healthy subjects. ClinTranslSci, 2020; 13: 896-906.
20. Innaimo SF, Seifer M, Bisacchi GS, Standring DN, Zahler R, Colonno RJ.Identification of BMS-200475 as a potent and selective inhibitor of hepatitis B virus. Antimicrob Agents Chemother, 1997; 41: 1444-1448.
21. Liu W, Morse JS, Lalonde T, Xu S. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. Chembiochem, 2020; 21(5): 730-738.
22. Li G, Cleraq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov, 2020; 19(3): 149-150.
23. Sheahan TP, Sims AC, Leist SR. Comparative therapeutic efficacy of Remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun, 2020; 11(1): 1-4.
24. Eastman RT, Roth JS, Brimacombe KR. Remdesivir: a review of its discovery and development leading to emergency use authorization

for treatment of COVID-19. ACS Cent Sci, 2020; 6: 672-683.
25. Holshue ML, DeBolt C, Lindquist S. First case of 2019 novel coronavirus in the United States. N Engl J Med, 2020; 382(10): 929-936.
26. Wang Y, Zhang D, Du G. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multi-centre trial. Lancet, 2020; 395(10236): 1569-1578.
27. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395(10223): 507-513.
28. Huang C. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020; 395: 497-506.
29. Li Q. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med, 2020; 382: 1199-1207.
30. Feng JY. Role of Mitochondrial RNA Polymerase in the Toxicity of Nucleotide Inhibitors of Hepatitis C Virus. Antimicrob Agents Chemother, 2016; 60(2): 806-817.
31. Venkatachalam, TK. Protease-mediated enzymatic hydrolysis and activation of aryl phosphoramidate derivatives of stavudine. Eur J Med Chem, 2005; 40(5): 452-466.
32. Schneider B. Pre-steady state of reaction of nucleoside diphosphate kinase with anti-HIV nucleotides. J BiolChem, 1998; 273(19): 11491-11497.
33. Munch-Petersen B. Diverging substrate specificity of pure human thymidine kinases 1 and 2 against antiviral dideoxynucleosides. J BiolChem, 1991; 266(14): 9032-9038.
34. Grein J, Ohmagari N, Shin D. Compassionate use of Remdesivir for patients with severe COVID-19. N Engl J Med, 2020; 382: 2327-2336.
35. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA, 2020; 323: 1824-1836.
36. Gordon CJ, Tchesnokov EP, Woolner E. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J BiolChem, 2020; 295: 6785-6797.
37. Muller MP, McGeer A, Straus SE, Hawryluck L, Gold WL. Clinical trials and novel pathogens: lessons learned from SARS. Emerg Infect Dis, 2004; 3: 389-394.
38. Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a Drug-Target Interaction Deep Learning Model. ComputStructBiotechnol J, 2020; 18: 784-790.
39. Namdeo P. A Review on Herbal Immunity Booster and Nutrition – To Fight against COVID-19. J Pharm Adv Res, 2021; 4(5): 1226- 1237.
40. Prasad H. Coronavirus: A World Threaten infectious agent. J Pharm Adv Res, 2020; 3(1): 754-756.
41. DornemannJ,Burzio C,Ronsse A,Sprecher A, De Clerck H, Van Herp M,*et al*. First newborn baby to receive experimental therapies survives Ebola virus disease. J Infect Dis, 2017; 215: 171-174.
42. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, *et al*. Discovery and Synthesis of a PhosphoramidateProdrug of a Pyrrolo[2,1-*f*][Triazin-4-Amino] Adenine *C* -Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. J Med Chem, 2017; 60(5): 1648-1661.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Jahnavi K, Jyostna B, Jyoshika K, Ashwitha[2],Diddiga Amulya I, Chaitanya K, Narender B[*]. Remdesivir: A critical review. J Pharm Adv Res, 2021; 4(6): 1285-1295.