WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 13, Issue 1, 3071-3087. Review Article ISSN 2277–7105

REMDESIVIR AFFECT ON COVID-19

[1]Ashwini D. Pagare, [2]Ganesh B. Ahire, [3*]Rohit B. Goyekar, [4]Samadhan N. Patil, [5]Sandip D. Pagare, [6]Roshani S. Gharate

Rupesh Badhan Institute of Pharmacy, Pimpalner (Dhule).

Article Received on
20 November 2023,

Revised on 11 Dec. 2023,
Accepted on 31 Dec. 2023

DOI: 10.20959/wjpr20241-30944

***Corresponding Author**
Rohit B. Goyekar
Rupesh Badhan Institute of Pharmacy, Pimpalner (Dhule).

ABSTRACT

Pandemic Covid-19, an infectious disease brought on by SARS COV-2, starts in 2020. The respiratory system is the primary target of the illness. The Chinese city of Wuhan was the source of the first instance of respiratory tract sickness. Researchers from all around the world are conducting a variety of studies in an effort to create a medication that is both successful at treating and preventing disease. There isn't currently a prescribed treatment plan in place. Russian scientists created the SPUTNIK-V vaccine, which is meant to protect against SARS COV-2. A number of antiviral and anti-inflammatory drugs were included in the treatment plan. On May 1, 2020, the FDA approved Remdisivir's usage as an emergency use authorization to treat Covid-19. Method: The review paper was prepared by referring research and review article from various sites like PubChem, Pubmed, Google Scholar, European Medical Agency; Science Direct. Etc. Observation: Remdesivir is a drug with broad antiviral activity. It is Adenosine Triphsosphate Analogue which was developed for potential treatment of Ebola virus. Remedisivir is also active against Nipah respiratory Syncytialvirus. MERS-COV. In various studies the drug has shown clinical improvement in patient as well as optimal safety profile was observed. Several studies are still continuing to picture out the efficiency and safety of Remedisivir in Covid-19 patients.

KEYWORDS: Oseltamivir, Hydroxychloroquine, diastereomer monophosphoramidate, ebolavirus, Clavulanate.

Purpose of review

COVID-19 represents an unprecedented public health crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The antiviral remdesivir is one

component of treating COVID-19. Unfortunately, the trials evaluating remdesivir have reported mixed results, leading to uncertainty on when to use remdesivir. This review discusses the trials evaluating the efficacy of remdesivir for COVID-19 and other supporting data to help inform the role of remdesivir in patients with COVID-19.

INTRODUCTION

The WHO classified coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020, due to the disease's rapid and extensive spread. The causative agent was found one month prior by the International Committee on Taxonomy of Viruses (ICTV), who designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The genetic material of coronaviruses, which are members of the coronaviridae family and belong to the nidovirales order, is a single-stranded RNA that is 26–32 kb long. These viruses were given the name coronaviruses because of the spikes that resemble crowns on their outer surface. The coronaviruses are the novel SARS-CoV-2, which first surfaced in Wuhan City, China, in December 2019, the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), and the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV).

Covid-19 virus spreads through respiratory droplets, i.e., when the diseased person cough, sneezes or spits, the droplets from saliva or discharge from nose, carries virus and these droplets infect other individuals via contact with mucous membrane. The virus can also persist on surfaces to varying duration and this is not considered as a main route of transmission but these maybe a reason for the spread of disease. Main symptoms of disease include fever, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, sore throat, congestion or runny nose, respiratory distress and sputum production Several antiviral drugs like Oseltamivir, Ribavirin, Lopinavir, and Ritonavir are provided in some cases. FDA has also approved the use of Hydroxychloroquine and Chloroquine in case of patients with autoimmune conditions like rheumatoid arthritis and herpes. Remdesivir is also used as an antiviral drug for treatment of covid-19 which was created for the treatment of Ebola virus[8] Researchers in the U.S. say that Remdesivir helped patients in recovering from the disease 31% faster. METHOD The review is done by referring research article as well as review.[1,2,3,4,5,6,7]

METHOD

The review is done by referring research article as well as review article from various sites like Pub chem., Pub med European medical agency, Google scholar, science direct. Also information about drug was obtained from Rx list and drug bank. WHO official page was also referred to get adequate information about covid-19 and its management. The search was mainly done using keywords such as covid-19, SARS-Cov-2, management, Remdesivir, role and efficacy of Remdesivir.

What is Remedisivir…?

Remedisivir is an antiviral drug from the family of nucleoside analogues developed by the Gilead Pharmaceutical Company to treat Ebola virus and Marburg virus infections. Due to its antiviral properties, it has also been used against other single-stranded RNA viruses such as respiratory syncytial virus, blood virus, lasagna virus, NIPA virus, Hendra virus and coronavirus family (including coronavirus Mers and SARS). This drug has been successful in the treatment of Quid 19 in many cases and is also being studied and researched a lot. Remdesivir is a precursor that is actively converted to GS-441524 in the body. It is an adenosine analogue that interferes with the function of the RNA-dependent RNA polymerase enzyme and prevents the virus from being sampled and genetically modified by the enzyme exoribonuclease (Exon), thus reducing virus production and replication. It is not known whether this drug terminates the RNA chain or causes a mutation in it. But like any other drug that AE has, it has been reported for Remdesivir AEs, and some AEs are associated with its use. The most common side effects in Remdesivir studies for COVID-19 include respiratory failure and organ dysfunction, including low albumin, low potassium, low red blood cell count, low platelet count, which helps clots, and yellow skin discoloration. Reported side effects include gastrointestinal upset, increased levels of transaminases in the blood (liver enzymes), and injection site reaction. Other possible side effects have been reported with remdesivir due to its injection reactions; During or around the time of remdesivir injection, it has been observed that the signs and symptoms of injection-related reactions may include: low blood pressure, nausea, vomiting, sweating and chills. Elevated levels of liver enzymes, seen in abnormal liver blood tests. Elevated levels of liver enzymes have been observed in people receiving remdesivir, which may be a sign of inflammation or damage to liver cells.

Sixty percent of remdesivir ICSRs contained at least one co-reported medicine. In the ICSRs, several COVID-19-specific medicines were used concomitantly with remdesivir.

Remdesivir is a medicine that fights viruses. It has been shown to prevent the virus that causes COVID-19 (SARS-CoV-2) from reproducing. Medical regulators have approved remdesivir for emergency use to treat people with COVID-19.

1. Description

Remdesivir (GS-5734) is the first medication for severe coronavirus disease that was approved by the FDA in 2019 (COVID-19). It is a novel nucleoside analog with broad antiviral activity against a wide range of RNA viruses, including ebolavirus (EBOV) and respiratory pathogens like Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, and SARS-CoV-2. Remdesivir, A single diastereomer monophosphoramidate as a prodrug, is converted into the active form GS-441524 after administration. GS-441524 competes with ATP for RNA incorporation and inhibits viral RNA-dependent RNA polymerase. This stops RNA transcription and reduces viral RNA replication.[8,9,10,11,12,13]

Abut Remdesivir….

Role of remdesivir (gs-5734)

In coronavirus disease Remdesivir is a drug with broad antiviral activity. The drug is developed by biopharmaceutical company, Gilead sciences. Remdesivir or GS-5734 is an adenosine Triphsosphate analogue which was first used as a potential treatment of Ebola virus. The drug was approved for use in covid-19 by emergency use authorization of FDA on 1 May 2020. The drug is authorized for emergency use in India, U.S, Singapore, Japan, and Australia for patients with severe symptoms.

Safety of remdesivir in covid-19

The data about safety of remdesivir is limited as well as not clear. Various researches are still now continued to picture out the safety of drug in covid-19 patients. Elevation of hepatic enzyme level is observed in studies, while no liver cell changes were observed increase in aminotransferases are mostly seen. There are no specific studies carried out in patients with hepatic dysfunction. Increased respiratory rates where shown by patients who are under the treatment with drug. Acute respiratory distress was experienced by some patients in clinical control studies performed in China. No adverse effect on respiration as well as on cardiovascular parameters was shown by the drug. In some patients hypotension, atrial

fibrillation as well as Hyponatremia were observed. Safety studies on cardiovascular side effects conducted in monkeys show no adverse effects. After treatment initiation 2 out of 3 patients experienced nausea as well as 1 experienced gastro paresis. 9% of patients on remdesivir experienced diarrhoea. In case of special population like pregnancy, lactation and paediatric no studies are conducted in humans. But in animal studies no adverse effect were observed in embryo-foetal development as well as male infertility.[14,15,16,17]

IUPAC NAME

1]2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate.[13]

2]2-ethylbutyl(2S)-2-{[(S)-[(2R,3S,4R,5R)-5-{4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl}-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy(phenoxy)phosphoryl]amino}propanoate.[14]

Molecular formula:- $C_{27}H_{35}N_6O_8P$.[18]

Structure of Remdesivir

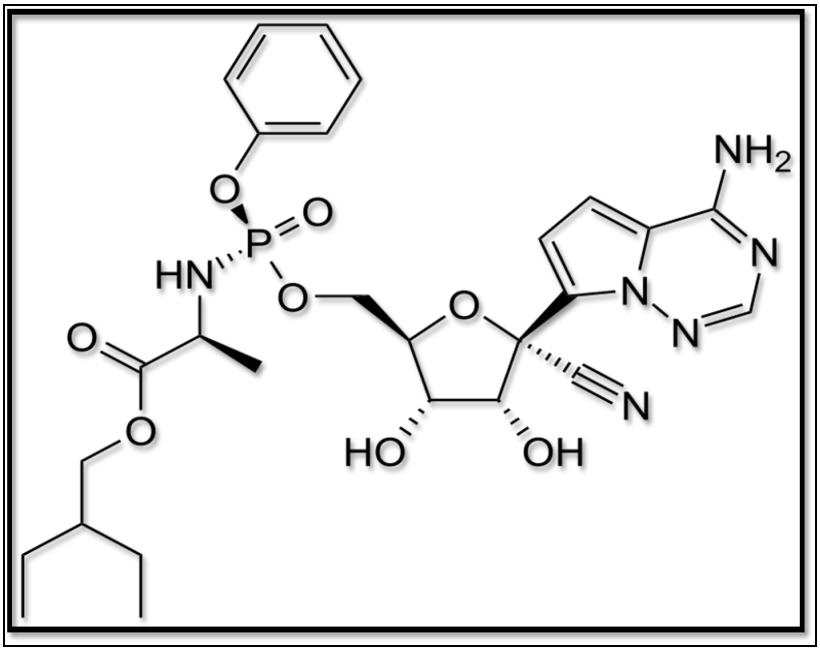

Fig. 1: Structure of Remdesivir.[19]

Synthesis of Remdesivir

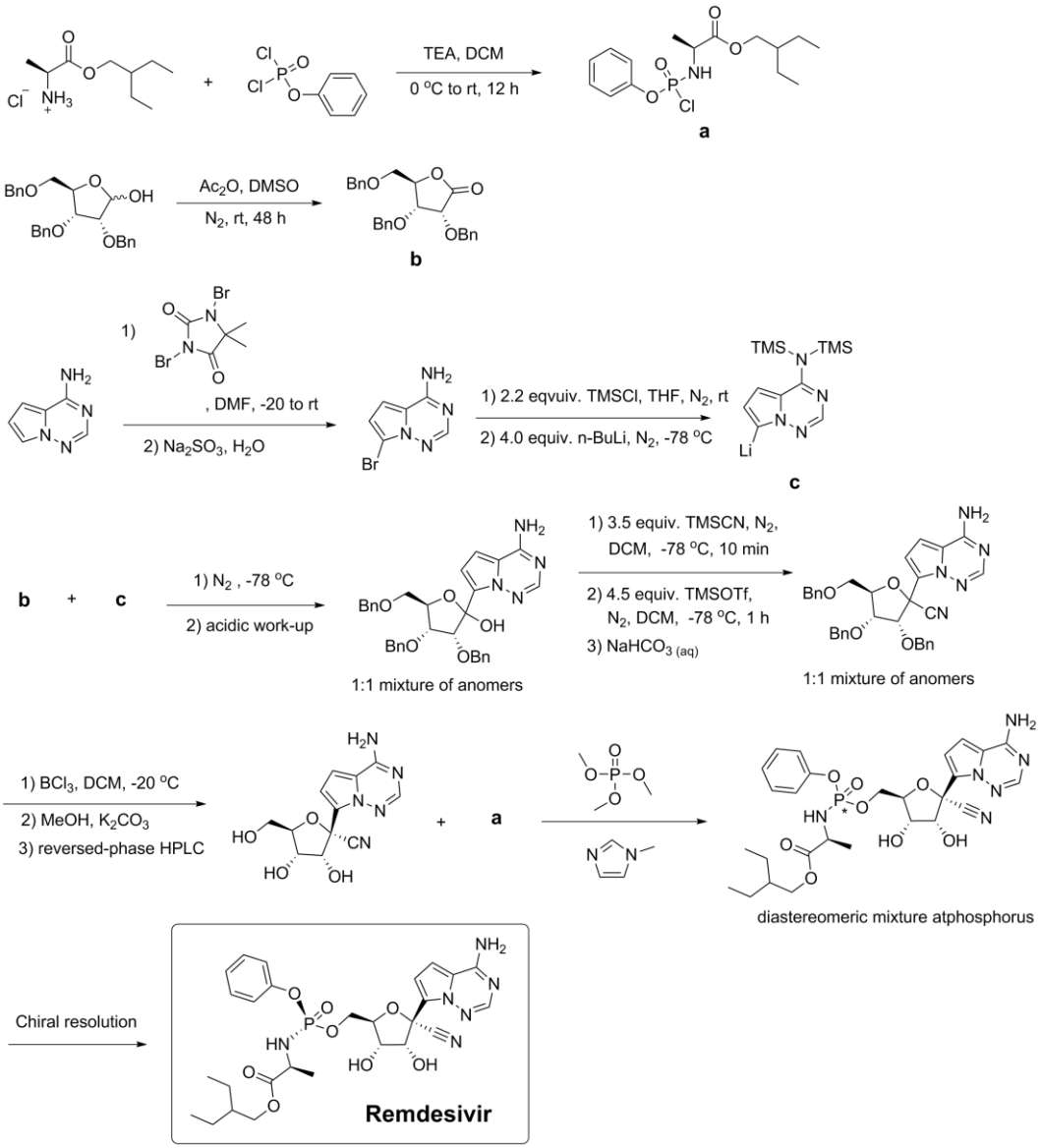

Fig. 2: Synthesis of Remdesivir.[20]

Route of elimination

Remdesivir is 74% eliminated in the urine and 18% eliminated in the feces. 49% of the recovered dose is in the form of the metabolite GS-441524, and 10% is recovered as the unmetabolized parent compound. A small amount (0.5%) of the GS-441524 metabolite is found in feces.[21]

Route of Administration:- Intravenous.[22]

Category of Remedisivir:- Antiviral.[23]

Mechanism of Action

Remdesivir is a monophosphoramidate nucleoside prodrug that undergoes intracellular metabolic conversion to its active metabolite nucleoside triphosphate (NTP). As described for several other direct-acting antivirals, the active metabolite of remdesivir (remdesivir triphosphate [remdesivir-TP] or GS-443902) subsequently targets the machinery responsible for the replication of the viral RNA genome, a highly conserved element of the viral life cycle. Nucleoside analogs are synthetic compounds that work by competition with endogenous natural nucleoside pools for incorporation into replicating viral RNA. While these compounds mimic their physiological counterparts, the incorporation of the analog molecule disrupts subsequent molecular processes. The drug target and the exact processes that lead to the inhibition of viral replication have been studied extensively in ebolavirus. The suggested drug target, the EBOV RNA-dependent RNA polymerase (RdRp) complex, was only recently biochemically purified, which allowed for in-depth molecular analyses. Viral RdRp is the target protein for the active metabolite remdesivir-TP. Remdesivir-TP acts as the substrate for RdRp where it competes with ATP for incorporation into new strands. Inhibition of EBOV RdRp most probably results from delayed chain termination, a mechanism that is known from approved antivirals against human immunodeficiency virus type 1 (HIV-1) and HBV (26-30). In the case of EBOV, the incorporation of remdesivir-TP into replicating RNA was observed to cause chain termination predominantly at five positions downstream ($i + 5$). Importantly, the activity of human RNA polymerase is not inhibited in the presence of remdesivir-TP.

In SARS-CoV and MERS-CoV, remdesivir-TP interferes with the nsp12 polymerase, which is a multisubunit RNA synthesis complex of viral nonstructural proteins (nsp's) produced as cleavage products of viral polyproteins. As nsp12 is highly conserved across the coronavirus family, it is most likely that the mechanism of action (MOA) of remdesivir does not differ significantly among CoVs. Like in EBOV, remdesivir-TP efficiently inhibits the replication of SARS-CoV and MERS-CoV by causing delayed chain termination when being incorporated into the replicating RNA. A recent biochemical analysis revealed that in SARS-CoV-2, remdesivir-TP causes the termination of RNA synthesis at three positions after the position where it is incorporated ($i + 3$). This mechanism was nearly identical in RdRps of SARS-CoV and MERS-CoV. The premature termination of RNA synthesis ultimately abrogates further transcriptional and translational processes needed for the generation of new

virions (Fig.3). The resulting antiviral effects of remdesivir have been studied in different cell-based models.[24,25,26 30,31,32,33]

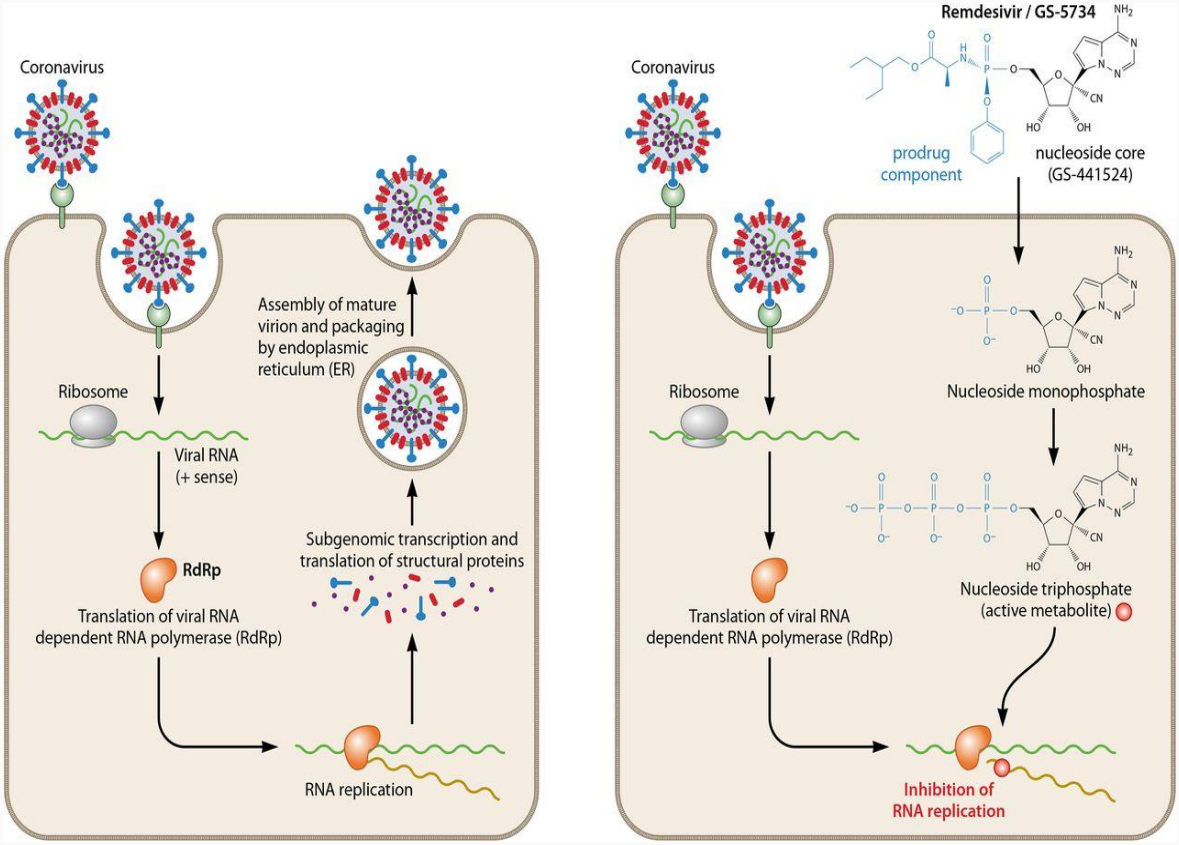

Fig. 3: MOA of Remedisivir.[34]

Drug Interactions

Interaction Between Remdesivir and Antibiotics: Azithromycin, Clavulanate, Doxycycline, Erythromycin, LevofloxacinRegarding antibiotic prescription, great care Must be taken with the macrolides, so azithro-Mycin should be avoided when dealing with oral Cavity infections. Likewise, clarithromycin and Erythromycin must be avoided as it is an estab-Lished fact that erythromycin (in particular) is a Potent inhibitor of the hepatic oxidative enzyme System (oxidases) of the P450 cytochrome sys-Tem15, which will aggravate hepatoxic damage if Patients are in treatment with Remdesivir. Prescribing these antibiotics for orofacial infec-Tion must be avoided, particularly levofloxacin (an-Tibacterial fluoroquinolone that acts on the DNA Gyrase-DNA complex and on topoisomerase IV), Which is used to treat acute bacterial sinusitis and Complicated skin and soft tissue infections. When there is no alternative therapeutic option Available, current recommendation, are for dental Professionals to carefully adjust the dose of the Antibiotic and monitor liver function closely.[35]

Adverse effects

- Back pain
- Chest tightness
- Chills
- Cough
- Dark-colored urine
- Difficulty swallowing
- Fast heartbeat
- Fever
- Flushing
- Headache
- Hives, itching
- Light-colored stools
- Nausea and vomiting
- Puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue
- Stomach pain, continuing
- Trouble breathing
- Unusual tiredness or weakness
- Yellow eyes or skin
- Seizures
- Skin rash
- Bleeding
- Blistering
- burning, coldness
- discoloration of skin
- feeling of pressure
- hives
- infection
- inflammation, itching
- lumps, numbness
- pain, rash, redness, scarring, soreness, stinging
- swelling, tenderness
- tingling, ulceration
- warmth at the injection site

- Cardiovascular: Hypotension, arrhythmias, and cardiac arrest
- Pulmonary: Dyspnea, Acute respiratory failure, acute respiratory distress, pneumothorax, pulmonary embolism
- Hematological: Anemia, lymphopenia
- Endocrine: Hyperglycemia
- Infectious: Pneumonia, septic shock
- Gastrointestinal: elevated lipase, nausea, vomiting, diarrhea, constipation, poor appetite, gastroparesis, and lower GI bleeding
- Hepatic: Hepatic manifestation characterized by Grade 1-4 increase in serum transaminases (ALT and/or AST) are the most common adverse effects in patients treated with remdesivir. Other abnormalities include hyperbilirubinemia
- Renal and Metabolic: Acute kidney injury or worsening of underlying chronic kidney disease, hypernatremia, hypokalemia
- Neurological: Headache, lightheadedness
- Skin: Rash, contact dermatitis, pruritus
- Psychiatric: Delirium
- Other adverse effects: Pyrexia, insomnia, multi-organ dysfunction, DVT, and hypersensitivity/anaphylactic reactions related to the infusion.[36,39,41-47]

Contradictions

Based on the guidance from the documentation published by the European Medicines Agency (EMA, 2020) and U.S FDA issued EUA, remdesivir is contraindicated in the following clinical situations unless the potential benefit of the use of remdesivir outweighs the potential risks:

Patients with alanine aminotransferase (ALT) levels >5-times upper limit of normal or severe hepatic dysfunction

Adult and pediatric patients (>28 days old) with severe renal impairment described as eGFR < 30 ml/min

Neonates (at least seven days to ≤ 28 days old) with serum creatinine ≥1 mg/dL.[38]

Uses

Remdesivir is used to treat coronavirus disease, also known as COVID-19, for certain patients who are in the hospital. Remdesivir is an antiviral drug. Remdesivir may also be used to treat patients with COVID-19 who are not in the hospital, but have a high risk for COVID-

19 complications due to older age, obesity, or ongoing medical conditions (such as lung, kidney, or heart disease, diabetes).[40]

Dosage Forms & Strengths

Injection, lyophilized powder for reconstitution

100mg/vial

Injection, concentrated solution

100mg/20mL (5mg/mL).[37]

CONCLUSION

Remdesivir has demonstrated some benefit in alleviating COVID-19 symptoms and shortening recovery time for hospitalized patients who require supplemental oxygen or ventilation. However, its impact on mortality rates remains inconclusive. While initial studies and compassionate use cases were promising, larger clinical trials revealed modest effects. Therefore, remdesivir's use should be limited to specific patient populations and further research is necessary to assess its long-term efficacy and resistance potential.

Remedisivir show either positive or negative side effect but I conclude on above study of remedisivir drug is some patient therapatic and some patient do not show good effect, totally the remedisivir drug is show various side affect after the treatment of covid 19. afer long period of time of treatment they show various side effect on those person who have some medicinal history.

REFERENCE

1. Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options.*Biomed Pharmacother*, 2020; 129: 110493. https://doi.org/10.1016/j.biopha.2020.110493. Google Scholar Crossref PubMed
2. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci., 2020; 6(5): 672–83. https://doi.org/10.1021/acscentsci.0c00489 Google Scholar Crossref PubMed
3. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, A systematic review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect*., 2021; 54(1): 12–6. Google Scholar Crossref PubMed

4. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res.*, 2020; 2491–8. https://doi.org/10.1016/j.jare.2020.03.005. Google Scholar Crossref PubMed
5. J. Grein, N Ohmagari, D Shin, G Diaz, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med., June, 2020; 382(2327-2336): DOI: 10.1056/NEJMoa2007016.
6. Al-Tannak NF, Novotny L, Alhunayan A. Remdesivir—Bringing Hope for COVID-19 Treatment. ScientiaPharmaceutica [Internet]. MDPI AG, 2020; 12, 88(2): 29.
7. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, 2020; 395(10223): 1569-78.
8. A Saha, AR Sharma, M Bhattacharya, G Sharma, SS Lee et al. Probable Molecular Mechanism of Remdesivir for the Treatment of COVID-19: Need to Know More. ARCMED, 2020; 621.
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC ACTT-1 Study Group Members. Remdesivir for the treatment of COVID-19. *N Engl J Med.*, 2020; 383: 1813–1826. [PMC free article] [PubMed] [Google Scholar]
10. Yang CJ, Wei YJ, Chang HL, Chang PY, Tsai CC, Chen YH, Hsueh PR. Remdesivir use in the coronavirus disease 2019 pandemic: a mini-review. *J Microbiol Immunol Infect.*, 2021; 54: 27. [PMC free article] [PubMed] [Google Scholar
11. Fan Q, Zhang B, Ma J, Zhang S. Safety profile of the antiviral drug remdesivir: an update. *Biomed Pharmacother,* 2020; 130: 110532. [PMC free article] [PubMed] [Google Scholar]
12. J.J. Malin, I. Suárez, V. Priesner, G. Fätkenheuer, J. RybnikerRemdesivir against COVID-19 and other viral diseases Clin. Microbiol. Rev., 2020; 34(1): e00162-20. Google Scholar
13. Remdesivir (Compound)[cited 2022 24 March]; from https://pubchem.ncbi.nlm.nih.gov/compound/121304016#section=3D-Conformer (2022). Google Scholar

14. Remdesivir (HMDB0304869)The Metabolomics Innovation Centre (TMIC)[cited 2022 24 March]; from https://hmdb.ca/metabolites/HMDB0304869 (2022). Google Scholar
15. Fan Q, Zhang B, Ma J, Zhang S. Safety profile of the antiviral drug remdesivir: An update. Biomed Pharmacother, 2020; 130: 110532; PMID: 32707440.
16. Y Zhu, Z Teng, L Yang, SXJ Liu, Y Teng et al. Efficacy and Safety of Remdesivir for COVID-19 Treatment: An Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. medRxiv, 2020.
17. Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies. Diabetes MetabSyndr, 2020; 14(4): 641- 648. 202 2. PMID: 32428865; PMCID: PMC7214279; doi: 10.1016/j.dsx.2020.05.018.
18. https://pubchem.ncbi.nlm.nih.gov/#query=C27H35N6O8P
19. https://upload.wikimedia.org/wikipedia/commons/b/bc/Remdesivir.svg
20. https://upload.wikimedia.org/wikipedia/commons/thumb/0/08/Remdesivir_activation.svg/1024px-Remdesivir_activation.svg.png
21. https://go.drugbank.com/drugs/DB14761#:~:text=Remdesivir%20is%2074%25%20eliminated%20in%20the%20urine%20and%2018%25%20eliminated%20in%20the%20feces.16%2049%25%20of%20the%20recovered%20dose%20is%20in%20the%20form%20of%20the%20metabolite%20GS%2D441524%2C%20and%2010%25%20is%20recovered%20as%20the%20unmetabolized%20parent%20compound.16%20A%20small%20amount%20(0.5%25)%20of%20the%20GS%2D441524%20metabolite%20is%20found%20in%20feces.
22. https://en.wikipedia.org/wiki/Route_of_administration
23. https://medlineplus.gov/druginfo/meds/a620033.html#:~:text=Remdesivir%20is%20in%20a%20class,from%20spreading%20in%20the%20body.
24. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, Larson N, Strickley R, Wells J, Stuthman KS, Van Tongeren SA, Garza NL, Donnelly G, Shurtleff AC, Retterer CJ, Gharaibeh D, Zamani R, Kenny T, Eaton BP, Grimes E, Welch LS, Gomba L, Wilhelmsen CL, Nichols DK, Nuss JE, Nagle ER, Kugelman JR, Palacios G, Doerffler E, Neville S, Carra E, Clarke MO, Zhang L, Lew W, Ross B, Wang Q, Chun K, Wolfe L, Babusis D, Park Y, Stray KM, Trancheva I, Feng JY, Barauskas O, Xu Y, Wong P, Braun MR, Flint M, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.*, 2016; 531: 381–385. Crossref PubMed ISI Google Scholar

25. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.*, 9: eaal3653. Crossref PubMed Google Scholar
26. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS, Cihlar T, Siegel D, Mackman RL, Clarke MO, Baric RS, Denison MR. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio*, 2018; 9(2): e00221-18. Crossref PubMed Google Scholar
27. Mulangu S, Dodd LE, Davey RT, Jr, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum J-J, PALM Writing Group, Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallee D, Nordwall J, PALM Consortium Study Team. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med.*, 2019; 381: 2293–2303. Crossref PubMed ISI Google Scholar
28. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*, 2020; 11: 222. Crossref PubMed Google Scholar
29. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A.*, 2020; 117: 6771–6776. Crossref PubMed ISI Google Scholar
30. Tchesnokov EP, Feng JY, Porter DP, Gotte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses*, 2019; 11: 326. Crossref PubMed Google Scholar
31. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, Wang T, Sun Q, Ming Z, Zhang L, Ge J, Zheng L, Zhang Y, Wang H, Zhu Y, Zhu C, Hu T, Hua T, Zhang B, Yang X, Li J, Yang

H, Liu Z, Xu W, Guddat LW, Wang Q, Lou Z, Rao Z. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science.*, 2020; 368: 779–782. Go to Citation Crossref PubMed ISI Google Scholar

32. Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun*, 2019; 10: 2342. Go to Citation Crossref PubMed Google Scholar
33. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem.*, 2020; 295: 6785–6797. Crossref PubMed ISI Google Scholar
34. https.://journals.asm.org/cms/10.1128/cmr.00162-20/asset/990a6144-1477-4771-b739-dace61f07962/assets/graphic/cmr.00162-20-f0002.jpeg
35. 15) Gómez-Moreno G, Guardia J, Cutando A, Cal-Vo-Guirado Jl. Pharmacological interactions of Anti-microbial agents in odontology. Med Oral Pa-Tol Oral Cir Bucal, 2009; 14: E123-E128.
36. https://www.mayoclinic.org/drugs-supplements/remdesivir-intravenous-route/side-effects/drg-20503608
37. https://reference.medscape.com/drug/veklury-remdesivir-4000090
38. https://www.ncbi.nlm.nih.gov/books/NBK563261/#_article-122861_s6_
39. https://www.ncbi.nlm.nih.gov/books/NBK563261/#_article-122861_s6_
40. https://www.webmd.com/drugs/2/drug-179015/remdesivir-intravenous/details
41. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanigan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med., Jun. 11, 2020; 382(24): 2327-2336. [PMC free article] [PubMed].
42. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ, PALM Writing Group.

Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallée D, Nordwall J., PALM Consortium Study Team. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med., Dec. 12, 2019; 381(24): 2293-2303. [PMC free article] [PubMed]

43. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet, May 16, 2020; 395(10236): 1569-1578. [PMC free article] [PubMed]
44. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S, Yazdanpanah Y. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis., Jun., 2020; 20(6): 697-706. [PMC free article] [PubMed]
45. COVID-19 Investigation Team. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat Med., Jun, 2020; 26(6): 861-868. [PubMed]
46. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A., GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med., Nov. 05, 2020; 383(19): 1827-1837. [PMC free article] [PubMed]
47. Burwick RM, Yawetz S, Stephenson KE, Collier AY, Sen P, Blackburn BG, Kojic EM, Hirshberg A, Suarez JF, Sobieszczyk ME, Marks KM, Mazur S, Big C, Manuel O, Morlin G, Rose SJ, Naqvi M, Goldfarb IT, DeZure A, Telep L, Tan SK, Zhao Y, Hahambis T, Hindman J, Chokkalingam AP, Carter C, Das M, Osinusi AO, Brainard DM, Varughese TA, Kovalenko O, Sims MD, Desai S, Swamy G, Sheffield JS, Zash R,

Short WR. Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019. Clin Infect Dis., Dec 06, 2021; 73(11): e3996-e4004. [PMC free article] [PubMed]