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A SCRUTINY ON ROLE OF REMDESIVIR IN COVID-19 PANDEMIC

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ABSTRACT

Background: The year 2020 begins with pandemic Covid-19 which is the infectious disease caused by SARS COV-2. The disease mainly affects the respiratory tract. The first case of respiratory tract illness was reported from Wuhan city in China. Researchers across the globe are carrying out various researches to develop a effective medicine for prevention and treatment of disease. Till now there is no standard treatment regiment available. A vaccine SPUTNIK-V was developed by the Russian scientists which is expected to provide immunity against SARS COV-2. Several antiviral as well as anti inflammatory agents were used as treatment regimen. Emergency use authorization of FDA approved the use of Remdisivir for the treatment of Covid-19 on 01 May 2020. The drug was authorized for emergency use in various countries like India, US, Singapore, Japan, Australia. **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. Remdisivir 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 Remdisivir in Covid-19 patients.

KEYWORDS: SARS COV-2, Sputnik-V, Remdesivir, Adenosine Triphsosphate Analogue, Antiviral.

INTRODUCTION

Corona virus disease 2019 (covid-19) is an infectious disease caused by SARS Cov-2 (Severe acute respiratory syndrome corona virus-2) which belongs to a class of novel corona virus family.[1] SARS Cov-2 was formerly known as 2019 nCov. This virus mainly triggers the respiratory tract both upper tract (sinuses, nose, throat) and lower tract (windpipe, lungs). This was first identified from a report on an outbreak of respiratory illness cases from Wuhan city of China to WHO on December 31, 2019.[1] The virus responsible for severe acute distress was named as SARS-Cov-2 by international committee on taxonomy of viruses (ICTV) on 11 February 2020. On January 30, 2020 covid 19 outbreak was declared as global health emergency by WHO and on March 11, 2020, WHO declared covid-19 as a pandemic.[1]

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.[2] Anosmia (complete or partial loss of sense of smell) is a finding in patients diagnosed with covid-19. Loss of taste is also observed in patients.

Corona virus disease may be mild, severe or critical in nature. About 81% of cases are mild cases which include patients having mild pneumonia or without pneumonia. Severe cases are patients having shortness of breath, blood oxygen saturation <93%, lung infiltrates >50% within 24-48 hrs. Critical cases include patients who suffered respiratory failure, septic shock, or multiple organ dysfunction or failure.

Adults are having risk of severe illness by corona viruses.[2] Risk factors for developing severe illness include CKD, COPD, asthma, weakened immune system due to organ transplant, bone marrow transplant, type 1 and 2 diabetes mellitus, sickle cell disease, high BP, cystic fibrosis, smoking, dementia, HIV.

About 2, 21, 34,898 cases are confirmed all over the World and 778865 deaths occurred due to the virus. In India, 27, 34,898 are affected by the disease and about 52,659 deaths were reported (data as of August 19, 2020).

Till now, there is no specific treatment available.[3] On 12 August 2020, Russia introduced the first registered vaccine against covid-19 named Sputnik V. It is a two-step vaccination procedure with ensures good immunity to the patients. WHO is now working on the pre-qualification of the vaccine.

The volunteers who were injected with the vaccine have shown to develop and improve immunity by 21 days after the injection of first dose and it was shown to double the immunity after the second dose. The vaccine is told to show its effectiveness by using the weakened form of virus and delivers small parts of a pathogen to stimulate the immune response. The phase 1 human trials began on 17 June 2020 with 76 volunteers, while phase 2 trials were started on 13 July 2020 and on 3 August 2020, completion of clinical trials were reported by the Russian media.

Patients with mild cases are provided supportive care to control the symptoms. There are several trials ongoing to find potential treatment for the cure of disease. Antihistamines, analgesics, adequate oxygen supply are provided as supportive care.[2] Several antiviral drugs like Oseltamivir, Ribavirin, Lopinavir, and Ritonavir are provided in some cases.[1] FDA has also approved the use of Hydroxychloroquine and Chloroquine in case of patients with autoimmune conditions like rheumatoid arthritis and herpes .[3]

Remdesivir is also used as an antiviral drug for treatment of covid-19 which was created for the treatment of Ebola virus[4] 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 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.

Role of remdesivir (gs-5734) in coronavirus disease

Remdesivir is a drug with broad antiviral activity[4] 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.[4] The drug was approved for use in covid-19 by emergency use authorization of FDA on 1 May 2020.[4] The drug is authorized for emergency use in India, U.S, Singapore, Japan, and Australia for patients with severe symptoms.

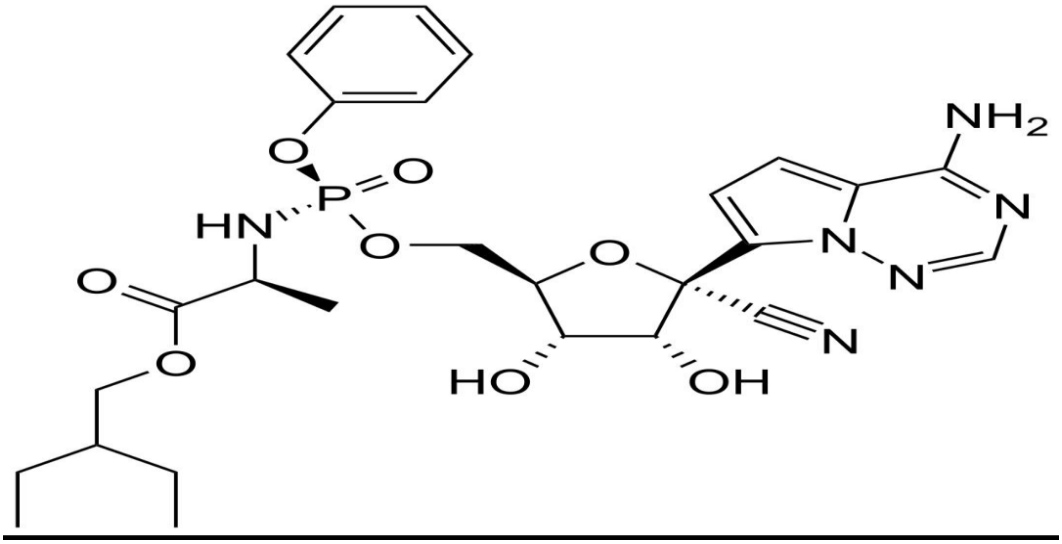

Fig. 1: Chemical structure of Remdesivir ($C_{27}H_{35}N_6O_8P$).

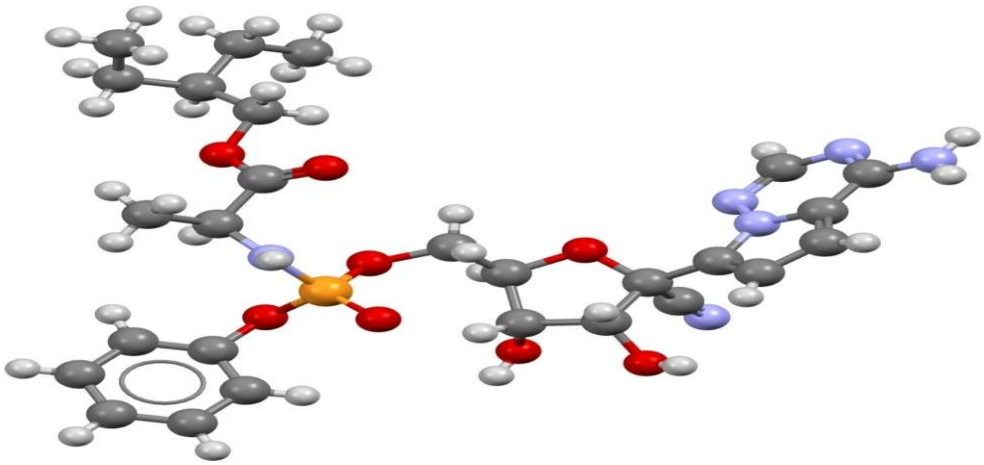

Fig. 2: Ball and stick model of Remdesivir molecule.

Indication

Remdesivir was investigated as treatment for Ebola virus. But it helps in treatment of a variety of RNA viruses. It is active against Nipah, respiratory syncytial virus and corona virus

categories like SARS-Cov and MERS-Cov[4,5] The activity of remdesivir against corona virus categories SARS-Cov and MERS-Cov was found out in 2017 and also the FDA emergency drug authorization approved use of remdesivir for use in children and adults with confirmed cases of covid-19 who are hospitalised and have a low oxygen saturation that is $SPO_2 \leq 94\%$.

Dose

FDA emergency use authorization suggest loading dose 200mg once daily in patients ≥ 40kg followed by maintenance of 100mg once daily. In patients having 3.5 kg less than 40kg, 5mg/kg once daily is given as loading dose and is followed by a maintenance dose of 2.5 mg/kg once daily. In patients who do not need extracorporeal membrane oxygenation or mechanical ventilation should be treated for 5-10 days, if they do not have any improvement. Also in patients who require mechanical ventilation and extracorporeal membrane oxygenation, 10 days treatment should be provided.

Clinical trial was conducted using 200mg once daily for first day as loading dose and followed by 100mg once daily for 9 days as maintenance dose. Some of data suggest patients will show improvement within 5 days of treatment with the drug.

Synthesis

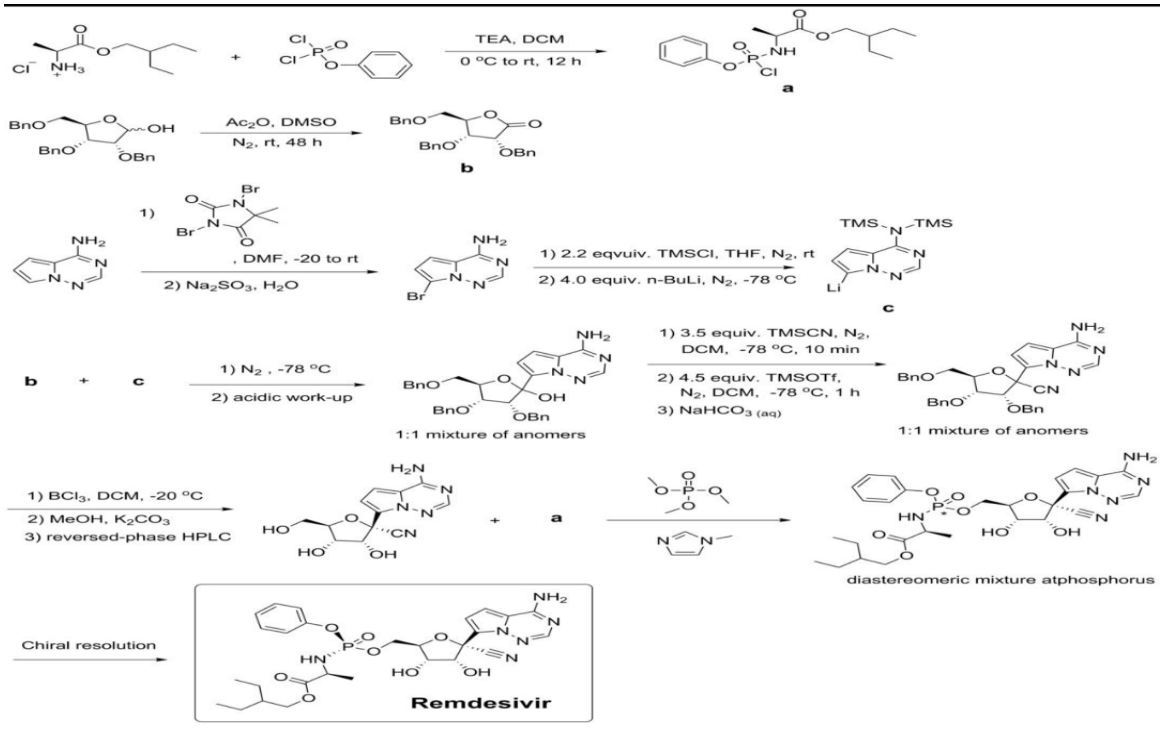

Fig. 3: synthesis of remdesivir invented by byoung kwan chun et.al. from gilead sciences.

Remdesivir molecule can be synthesised from ribose derivatives using multiple steps.

In the presence of trimethylamine and dichloromethane intermediate ‘a’ is prepared from L-alanine and phosphorodichloridate. Lactone intermediate bis produced from the oxidation of triple benzyl protected ribose by active anhydride along with dimethyl sulfoxide. Trimethylsilyl chloride biominatesand protects pyrole (2,1-f)(1,2,4) triazin 4-amine. Intermediate C is obtained from n-butylithium. N-butylithium undergoes a halogen- lithium exchange reaction with bromide at -78℃ (-108° F). To the solution containing intermediate C, intermediated b is added drop by drop and the reaction is carried out in a weakly acidic aqueous solution to obtain a mixture of 1:1 anomer. Then this mixture was reacted with trimethylsilyl cyanide in dichloromethane at -78℃ or -108°F for 10 minutes. To obtain a nitrileintermediate the mixture was quenched in aqueous sodium hydrogen carbonate after reacting for an hour by adding trimethylsilyltriflate. The protective benzene group was removed using boron trichloride in dichloro methane at -20° C. A benzyl free intermediate is obtained after quenching boron trichloride in a mixture of potassium carbonate and methanol. By performing reverse phase High Performance Liquid Chromatography (HPLC), the isomer were separated.[6,7]

Activation

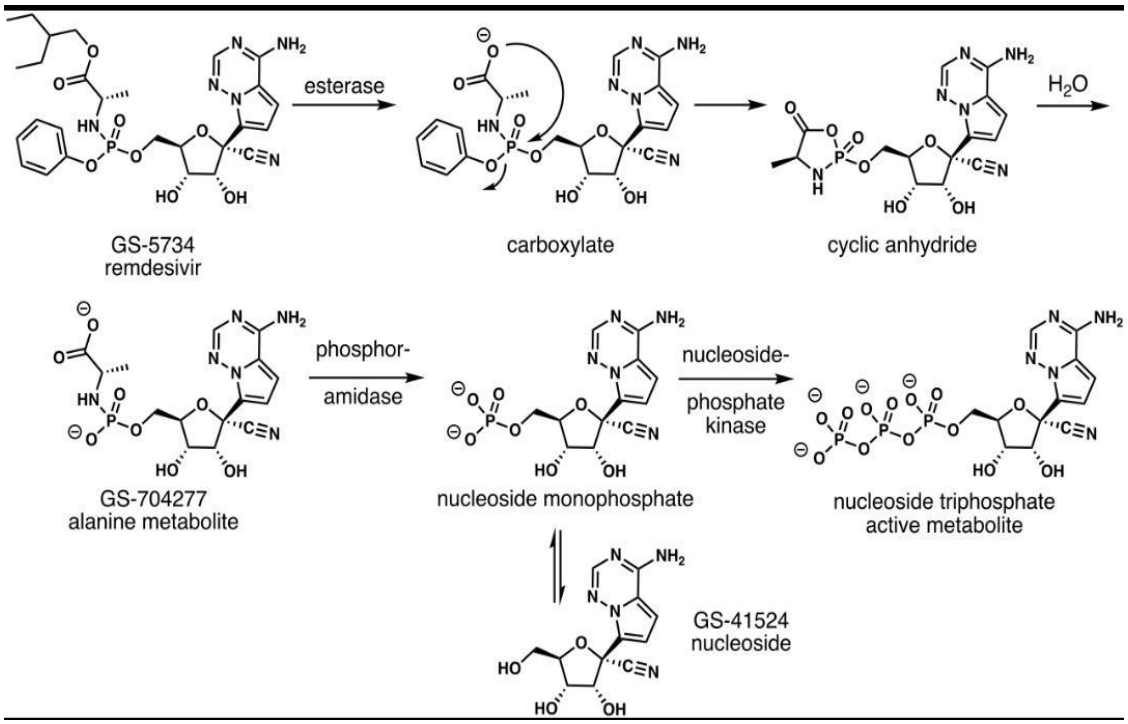

Fig. 4: activation of remdesivir into metabolite triphosphate form.

Remdesivir is a nucleotide prodrug. Bioactivation of the drug is meant to occur intracellularly, but in plasma itself, an amount of drug is prematurely hydrolysed. Remdesivir is able to diffuse into cell only after its conversion into GS-441524 monophosphate. The conversion occur due to the action of esterases and phosphoamidase. GS-441524 monophosphate is then phosphorylated by nucleoside phosphate kinase into triphosphate form which is its active metabolite.

Mechanism of action

The active metabolite form of remdesivir nucleoside triphosphate analogue inhibits RNA synthesis by interfering viral RNA dependent RNA polymerase synthesis by a mechanism of chain termination reaction.

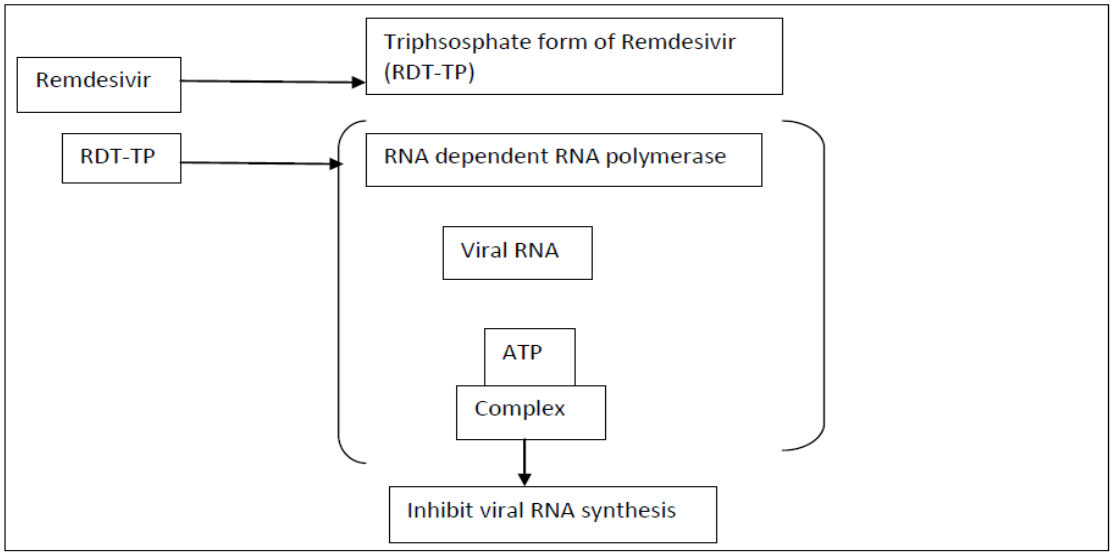

Fig. 5: mechanism of action of Remdesivir.

Fig: mechanism of action of remdesivir against SARS-Cov-2. Diagram represent SARS-Cov-2 viral entry and RNA synthesis blockade by the drug.

During viral RNA synthesis the remdesivir triphosphate which resembles as adenosine triphosphate competes with viral nucleotide.[4,6] The 3'hydroxyl group of remdesivir triphosphate forms a phosphodiester bond and become a part of new RNA strand. And hence RNA subunit formation by polymerase enzyme is reduced as well as genome replication do not occur.[4,6] It is not clear that whether the prodrug terminates the RNA chain or the mutation of RNA is caused by the drug. Studies are still carried out to make classification on these.[6]

Pharmacological actions

After intravenous administration of 10mg/kg of drug it was seento be distributed to the testes, epididymis, eye and brain with four hours. Plasma half life in non-human primates is 14 hours and in humans is approximately 20 hours.[1]

74% of drug is eliminated in urine and 18% in faeces. 49% of the drug recovered is in metabolite form and 10% recovered is the unmetabolized. No data is available till now about volume of distribution, protein binding, decrease and toxicity.[1]

Side effects

Increased liver enzyme levels are the most experienced side effect. Liver damage may occur due to the increase in liver enzyme. Allergic reaction like hives, difficulty in breathing, swelling of face, lips, tongue may occur. Infusion related reaction like nausea, vomiting, chills, as well as increased sweating may occur.

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.[8]

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.[9] 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.[8] 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.[5]

Efficacy of remdesivir

Certain trial studies showed that remdesivir in effective against certain enzymes present in SARS-Cov-2, virus which is responsible for covid-19. Remdesivir was found highly effective

against inhibiting replication of coronavirus. The first double blind, placebo controlled, randomised clinical trial conducted in Wuhan with 236 severe covid-19 patients using remdesivir as well as placebo did not show any significant clinical outcome.[5] While other studies shown significant clinical improvement. In a double blind control trial study conducted in China with 1063 patients in which 538 receive drug and 521 receive placebo, the remdesivir shows a decrease in recovery time as compared to placebo group.[10,11] Also remdesivir shows lower mortality rate as compared to placebo group. Among 53 patients with covid-19 there was 68% improvement shown when the patient was given remdesivir.[3] Also a randomized control study was conducted in 397 patients, to check the efficacy od duration of treatment that is, 10 days versus 5 day treatment.[11] results show that shorter duration improve clinical outcome as well as hospitalization is reduced.[10] There are no sufficient clinical data on efficacy of the drug as the efficacy trial studies are carrying out. Also the use of drug is authorized by FDA emergency use authorization for the treatment of covid-19 due to the improvement shown in some patients who were involved in the clinical trial studies. The drug shows some adverse effects like increasing hepatic enzyme levels, increased respiratory rates, etc. But there is no data available showing any adverse effects on cardiovascular, respiratory as well as evidence for any liver damage.[1,5]

CONCLUSION

The global pandemic Covid-19 cases are increasing day by day. Researchers are still continuing to develop a potential treatment for the disease. Russia has developed world's first corona virus vaccine Sputnik-V. The vaccine is expected to provide immunity from SARS covid virus. Several drugs like antiviral drugs and anti inflammatory agents were used in treatment of corona viral disease. Among the antivirus used patient treatment with Remdesivir has shown clinical improvement in several studies. The drug also shows optional safety profile. Several trial studies carried out to get clear picture about efficiency and safety of Remdesivir in Covid-19 patients.

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Declaration of competing interest

None declared.

REFERENCES

1. Al-Tannak NF, Novotny L, Alhunayan A. Remdesivir—Bringing Hope for COVID-19 Treatment. ScientiaPharmaceutica [Internet]. MDPI AG, 2020; 12, 88(2): 29.
2. 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.
3. 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.
4. 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.
5. 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.
6. F Mokobi. Remdesivir- Mechanism of Action, Uses, Synthesis & COVID-19. Microbe Notes, 2020; 18.
7. S Maier. Continuous Flow Process for Remdesivir Synthesis. Organic Process Research & Development/ACS Publications, 2020; 16.
8. Fan Q, Zhang B, Ma J, Zhang S. Safety profile of the antiviral drug remdesivir: An update. Biomed Pharmacother, 2020; 130; 110532; PMID: 32707440.
9. 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.
10. L.F. Lopez-Cortes, R. Ruiz-Valderas, E. Sánchez-Rivas, A. Lluch, A. Gutierrez-Valencia, A. Torres-Cornejo, et al. Lopinavir plasma concentrations and virological outcome with lopinavir-ritonavir monotherapy in HIV-1-infected patients. Antimicrob Agents Chemother, 2013; 57(8): 3746-3751, 10.1128/AAC.00315-13.
11. S Jomah, S Mohammed, BA Mohammed, J Al-Yamani. Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review. Journal of Infection and Public Health august, 2020.
12. Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment. U.S. Food and Drug Administration, 2020.

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.

13. Coronavirus Disease (COVID-19) - events as they happen [Internet]. Who.int. 2020:https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen.
14. European Medicines Agency, 2020. Summary on compassionate use Remdesivir Gilead, EMA/178637/2020 – Rev.2*; https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.