Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13385
DOI URL: http://dx.doi.org/10.21474/IJAR01/13385

RESEARCH ARTICLE

REMDESIVIR IN THE TREATMENT OF COVID-19: A SHORT OUTLINE

Pydala Sai Prasanna[1], Ragam Swetha Samrajyam[1], Kasani Chitti Ramya[1], Ambati Sujatha[1], Satheesh S. Gottipati[2] and P. Srinivasbabu[2]

1. Pharm D Intern Vignan Pharmacy College, Pin Code 522213, Vadlamudi, Guntur.
2. Department of Pharmacy Practice Vignan Pharmacy College, Pin Code 522213, Vadlamudi, Guntur.

Manuscript Info

Manuscript History
Received: 10 July 2021
Final Accepted: 13 August 2021
Published: September 2021

Key words:-
Covid, Sars-Cov-2, Mers, Remdesivir

Abstract

We look at the clinical development of remdesivir, a prodrug that has been shown to inhibit SARS-CoV-2 replication, indicating that it could be used to treat COVID-19. Remdesivir is a nucleotide analogue prodrug that disrupts viral replication and was first tested in clinical trials in 2014 to combat the Ebola outbreak.The ability of remdesivir to inhibit coronavirus replication, including SARS-CoV-2, was later demonstrated by numerous virology laboratories. We'll go over how remdesivir was discovered, how it works, and what studies are currenty being done to see how effective it is in the clinic.

Introduction:-

Coronaviruses are a group of enveloped viruses with a positive-sense, single-stranded RNA genome that infect both animals and humans.The common cold, severe acute respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome-related coronavirus (MERS), and the recently emerged severe acute respiratory syndrome coronavirus 2 are all coronavirus members (SARS-CoV-2, the causative pathogen of the disease COVID-19).[1]

As reported to the World Health Organization (WHO) in December 2019, this novel coronavirus, SARS-CoV-2, caused a pathogenic viral pneumonia outbreak in Wuhan, Hubei Province, China. As a result of the subsequent spread, a global pandemic has emerged (officially declared by the WHO on March 11, 2020)[2]

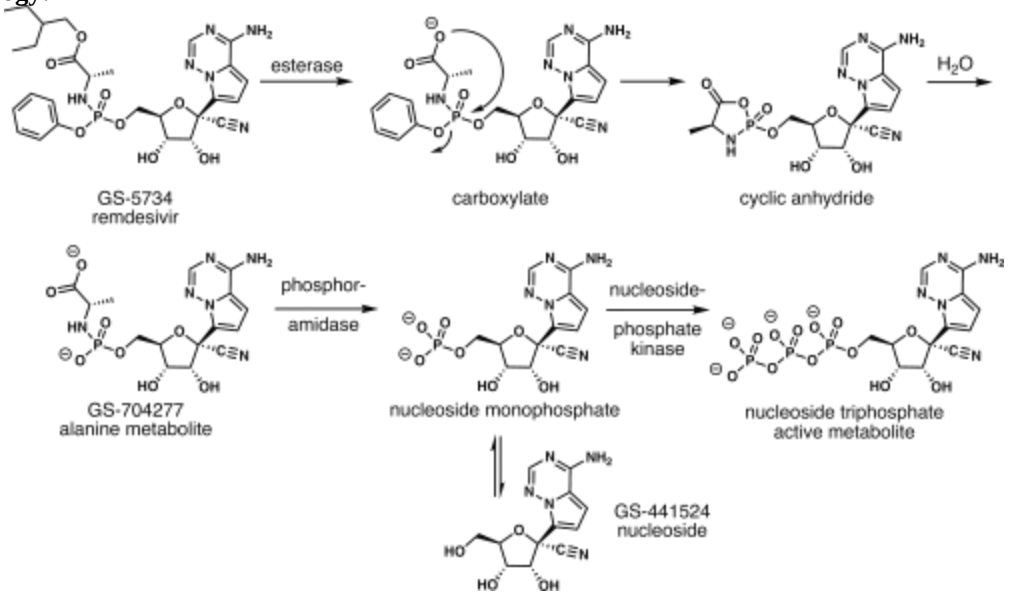
SARS-CoV-2 is a novel disease with no clinically proven treatments. In addition, there was a significant amount of preclinical research in the search for therapeutic treatments for the related viruses SARS and MERS. No therapeutic development programmes were completed because the SARS and MERS coronavirus outbreaks did not last.As a result, drug repositioning and repurposing has gotten tons of attention, and approved drugs like hydroxychloroquine, azithromycin, ritonavir, ruxolitinib, and camostat have gone into clinical trials to combat the current SARS-CoV-2 pandemic.

Although some candidates have prior data to support coronavirus activity, other repurposing candidates for potential use against SARS-CoV-2 are supported on their ability to inhibit SARS-CoV-2 viral replication in vitro. Among these are hydroxychloroquine, a known autophagy inhibitor that suppresses lysosomal function, and camostat, a serine protease inhibitor.Although clinical trials of several of these potential therapeutics are currently underway, the ability of these compounds to act as prophylactic agents, treat disease, or even modulate viral replication in vivo has not been demonstrated.

Corresponding Author:- Pydala Sai Prasanna
Address:- Pharm D Intern Vignan Pharmacy College, Pin Code 522213, Vadlamudi, Guntur.

Remdesivir, a pre-existing drug candidate developed by Gilead Sciences as part of an antiviral development effort, was one of the first clinical candidates to receive attention, with preliminary results against Ebola virus (EBOV) reported in 2015.It was recently authorized for compassionate use and has now entered controlled clinical trials. Like all other therapeutic approaches for patients with COVID-19, remdesivir wasn't developed specifically to treat COVID-19, and here we review its mode of action.[2]

Pharmacology:



Remdesivir is a ProTide medication (Prodrug of nucleoTide). It can enter cells and be converted to GS-441524 monophosphate by esterases (CES1 and CTSA) and a phosphoamidase (HINT1), which is then phosphorylated to its active metabolite triphosphate by nucleoside-phosphate kinases.This bioactivation pathway is intended to occur intracellularly, but a significant amount of remdesivir is prematurely hydrolyzed in plasma, with GS-441524 being the major metabolite in plasma and the only metabolite remaining two hours after dosing.[3]

Mechanism of Action

The active metabolite of remdesivir, an adenosine nucleoside triphosphate analogue (GS-443902), inhibits viral RNA-dependent RNA polymerase and avoids proofreading by viral exoribonuclease (ExoN), resulting in a decrease in viral RNA production.It causes RNA-dependent RNA polymerases to pause in some viruses, such as respiratory syncytial virus, but its main effect (as in Ebola) is to induce irreversible chain termination.Unlike many other chain terminators, this is accomplished by delaying the addition of the next nucleotide, which occurs after five additional bases have been added to the growing RNA chain.MERS-CoV, SARS-CoV-1, and SARS-CoV-2 RNA-Dependent RNA Polymerase arrests RNA synthesis after the incorporation of three additional nucleotides.Hence, remdesivir is assessed as a direct-acting antiviral that works as a delayed chain terminator.[4]

Pharmacoknetics

In humans, remdesivir had intermediate protein binding (80–90%) and GS-441524 had very low protein binding (20%) in plasma. Preliminary findings from healthy human donors show that remdesivir is substantially processed by the cytochrome P450 enzyme (CYP) (CYP2C8, CYP2D6 and CYP3A4).On GS-441524, no specific metabolic data has been reported. Remdesivir and GS-441524 have half-lives of roughly 0.89 and 25 hours, respectively. Remdesivir is mostly eliminated through the urine (about 74 percent). GS-441524 was the most common species found in urine, followed by remdesivir and other metabolites.[5]

Resistance

In 2018, researchers discovered mutations with in the mouse hepatitis virus RNA replicase that cause partial resistance to remdesivir. These mutations make the viruses less effective in nature, and the researchers believe they will die out if the drug is not used.

Purpose of Medication
Remdesivir injection is used in hospitalised adults and children 12 years of age and older who weigh at least 88 pounds to treat coronavirus disease 2019 (COVID-19 infection) caused by the SARS-CoV-2 virus (40 kg). Remdesivir belongs to the antiviral medication class. It works by preventing the virus from spreading throughout the body.[6]

Route of Administration
Remdesivir is available as a solution (liquid) and as a powder to be mixed with liquid and infused (slowly injected) into a vein by a doctor or nurse in a hospital over 30 to 120 min. It is generally given once daily for 5 to 10 days. The duration of your treatment is determined by how well your body reacts to the medication.[6]

Routes	Dosage Forms	Strengths
Parenteral	Powder for injection, for IV infusion only	100 mg
	Concentrate for injection, for IV infusion only	100 mg/20 mL (5 mg/mL)

Side Effects
An infusion reaction can occur with remdesivir, causing symptoms such as low blood pressure, nausea, vomiting, sweating, and shivering. The healthcare professional should keep an eye out for any side effects while administering remdesivir.

There is currently insufficient information to determine whether remdesivir causes serious side effects.

Symptoms of a severe allergic reaction may include: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, and difficulty breathing.[6]

Dosing instructions, potential side effects, and drug interactions for remdesivir in treating COVID-19 should be made known to health care providers and patients. Increased levels of liver enzymes, which could indicate inflammation or damage to liver cells; and infusion-related symptoms, such as low blood pressure, nausea, and vomiting are all possible side effects of remdesivir.

Interactions
Remdesivir is at least partially metabolised by the cytochrome P450 enzymes CYP2C8, CYP2D6, and CYP3A4.Remdesivir blood plasma concentrations are expected to fall when combined with cytochrome P450 inducers such as rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, etc.

The use of chloroquine or hydroxychloroquine with remdesivir may reduce its antiviral activity. Because in vitro data show that chloroquine has an antagonistic effect on remdesivir's intracellular metabolic activation and antiviral activity, coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended.[6]

Precautions
1. It is critical that you keep a written record of all prescription and nonprescription (over-the-counter) medications you are taking, as well as any vitamins, minerals, or other dietary supplements. You should bring this list with you whenever you go to the doctor or are admitted to the hospital. It is also important to have this information on hand in case of an emergency.
2. Notify your doctor and pharmacist if you have an allergy to remdesivir, any other medications, or any of the ingredients in remdesivir injection. Request a list of the ingredients from your pharmacist.
3. Tell your doctor if you have liver or kidney disease or if you have ever had it.
4. Let your doctor know if you are pregnant, intend to become pregnant, or are breastfeeding.[6]

Conclusion:-
Despite the FDA approval, several current RCTs should be completed to determine remdesivir's clinical efficacy and risk profile. We cannot infer that remdesivir is effective for treating COVID-19 until more evidence becomes available.[8]

At 11 days after starting therapy, hospitalised patients with moderate COVID-19 who were assigned to a 5-day course of remdesivir had a statistically significantly better clinical status than those randomised to standard care, but the difference was of questionable clinical significance.[9]

Acknowledgement:-

I would like to express my deep gratitude to professor Dr.P. Srinivasa Babu and professor Dr. Satheesh.S. Gottipati, and my classmates, for patient guidance, enthusiastic encouragement and useful critiques of this work
Finally, I wish to thank my parents for their support and encouragement throughout my study.

Conflict of Interest
No conflict of interest.

References:-

1. Richard T. Eastman,† Jacob S. Roth et al.,Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19ACS Cent Sci. 2020 May 27; 6(5): 672–683.
2. WHO Director-General's opening remarks at the media briefing on COVID-19. In *WHO Newsletter*; https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--13-april-2020. Accessed April 13, 2020.
3. Morse J. S.; Lalonde T.; Xu S.; Liu W. R. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. *ChemBioChem* 2020, 21, 730–738. 10.1002/cbic.202000047. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. *Yan VC, Muller FL (14 May 2020).* "Gilead should ditch remdesivir and focus on its simpler and safer ancestor". *Stat. Boston Globe Media Partners.*
5. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.
6. https://www.webmd.com/drugs/2/drug-179015/remdesivir-intravenous/details
7. https://medlineplus.gov/druginfo/meds/a620033.html
8. Alejandro Piscoya, Luis F. Ng-Sueng,etal.,Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. December 10, 2020
9. Christoph D. Spinner, MD[1] et al.,Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19A Randomized Clinical Trial**n** JAMA. 2020;324(11):1048-1057.