Review Article

Indian Journal of Emergency Medicine
Volume 6 Number 3, july–September 2020
DOI: http://dx.doi.org/10.21088/ijem.2395.311X.6320.6

Emergency Approval of Remdesivir for Covid-19 Infection in India

Subhrojyoti Bhowmick[1], Sanket Bandyopadhyay[2], Suddha Chatterjee[3], Debarati Kundu[4], Pankaj Kumar Singh[5], Indraneel Dasgupta[6]

Author's Affiliation: [1]Clinical Director, Department of Academics Quality Assurance and Research, Peerless Hospital and BK Roy Research Centre, Kolkata, India, [2]PG Student, Department of Biotechnology, Ramaiah College of Arts Science and Commerce Bangalore, [3]PG Student, Department of Microbiology, St. Xavier's College, Kolkata, India, [4]Clinical Research, [5]Senior Resident, [6]Clinical Director, Department. of Emergency, Peerless Hospitex Hospital and Research Center Ltd, Kolkata-700094, India.

Corresponding Author:
Subhrojyoti Bhowmick, Clinical Director, Quality and Research Departments, Peerless Hospital and B K Roy Research Centre Kolkata -700094, India.

E-mail: drsubhro@gmail.com

Abstract

Novel Coronavirus or SARS-CoV-2 has brought the entire pharmaceutical industry to a halt. The whole world is still awaiting the news of an established treatment modality or a prophylactic vaccination schedule for COVID-19. Researchers all over the world are working tirelessly to find a cure or a vaccine as early as possible to assure humankind of a recovery from this life threatening disease. On the downside, people are desperate to find a solution to this crisis and this has led to introduction of certain drugs in the market that claim to be a remedy for COVID 19. US pharmaceutical company Gilead Sciences Inc. which holds patent of antiviral drug Remdesivir joined hands with Hetero Labs Ltd. and Cipla Ltd., two major pharmaceuticals companies in India for launching the drug. On June 21, 2020 Hetero Labs Ltd. got the nod from Drugs Controller General of India (DCGI) to market the investigational antiviral medicine Remdesivir for "restricted emergency use" on COVID-19 patients. Remdesivir did not undergo any human clinical trials on Indian patients before its launch which is the protocol for launch of any investigational new drug as per the Central Drugs Standard Control Organization (CDSCO) of India. The medicine has been issued by the FDA with an Emergency Use Authorization (EUA). But it is still concerning if the decision was good enough to use the drug on Indian patients who have an entirely different ethnic background than the American patients. This article is a quick review of the efficacy and safety issues known about Remdesivir till date.

Keywords: Remdesivir Emergency; Approval; Covid 19; India.

How to cite this article:
Subhrojyoti Bhowmick, Sanket Bandyopadhyay, Suddha Chatterjee, Emergency Approval of Remdesivir for Covid-19 Infection in India. Indian J Emerg Med 2020;6(3):187–192.

Introduction

Corona viruses belong to the family Coronaviridae and are generally known to be positive-sense RNA viruses that infect humans and animals.[1] It mainly causes respiratory distress and intestinal infections in animals that were discovered in the 1960s.[2]Severe Acute Respiratory Distress Syndrome (SARS-CoV-2) caused by Coronavirus is an infectious disease that was newly identified in December 2019.[3,4] The virus is responsible for causing wide range of clinical symptoms that stretches from asymptomatic to severe manifestation of Coronavirus Disease or COVID-19.[1,4] The strains such as HCoV-229E & HCoV-OC43 are responsible for common cough but these strains got mutated in 2003 during the SARS pandemic and in 2012 with MERS outbreak.[2] Both strains of the virus were found in bats.

Common symptoms of COVID-19 are fever, cough, myalgia, while headache, diarrhoea, sputum production are also seen occasionally.[2] The severity of the disease is more in older populations with co-

morbid conditions such as obesity, hypertension, diabetes, and chronic kidney disease.[5] Other symptoms like neurological symptoms and coagulopathies have been reported. The Case Fatality Rate (CFR) tends to vary depending on regions, population demographics, healthcare capabilities, etc. For example, in Italy, the CFR is estimated at 14.45% that is higher compared to China (5.47%) while global CFR is 4.89% as of 1st July 2020 according to the European Center for disease prevention and control (ECDC).[6]

Through the clinical trials carried out in several countries, it has been found that the inhibitors of neuraminidase (oseltamivir, peramivir, and zanamivir) as well as other drugs like ganciclovir, acyclovir, and ribavirin have proved to be ineffective and not suitable for clinical use. Remdesivir has proven to be effective in trials related to MERS-CoV and Ebola Virus.[3] It was jointly developed by Gilead Sciences, U.S Centers for Disease Control and Prevention (CDC), and the U.S Army Medical Research Institute of Infectious Diseases (USAMRIID).[2] It has a molecular weight of 602.6g/mol with limited water solubility.[7] In the Ces1c (-/-) mouse SARS model, the trial of preventive treatment using Remdesivir achieved satisfactory results. One day after the onset of the disease, the administration of the drug resulted in a significant decrease in titres of lung viruses, with an enhancement of pulmonary function. It was observed that two days after the onset of the disease post administration of the drug, pulmonary virus titre is reduced, but the survival rate of mice is still relatively low. It can be concluded that when the pulmonary injury is at its maximum, reducing the viral load will not aid in the suppression of the strong immune responses in mice. Therefore, the drug should be administered before the virus replicates which will result in the improvement in condition of the infected mice.[3]

Mode of Action

Remdesivir (RDV) is a prodrug of nucleoside monophosphate (Nuc-MP). It is designed specifically to improve the permeability of Nuc-MP. When administered to a patient, it distributes itself into tissues and blood cells by passive diffusion. Remdesivir is then converted into Nuc-MP by intracellular hydrolases upon entering the cell. This results in the formation of active metabolite nucleoside-triphosphate (Nuc-TP) intracellularly. It bypasses the first rate-limiting phosphorylation step of the nucleoside. Thus, it cannot be administered orally because it will result in the hydrolysis of the prodrug to Nuc-MP in the gastrointestinal tract. The transformation will prevent the absorption owing to the negative charge of the phosphate group. Nuc-MP can neither be able to distribute itself into tissues nor penetrate cell membranes, which is extremely essential for antiviral activity.[8] RDV-TP (the triphosphate form of RDV) acts as a substrate for several viral RNA-dependant RNA polymerases (RdRp) complexes and it inhibits the viral RNA synthesis by delayed chain termination for SARS-CoV-2. The RDV-TP is very much similar to adenosine triphosphate (ATP) and hence competes with the nucleotide during viral RNA synthesis.[9] It is effective against lethal Ebola and Nipah virus in non-human primates. It was made for Ebola Outbreak in 2014.[2] Remdesivir triphosphate is considered to have a low potential for mitochondrial toxicity since it is a weak inhibitor of mammalian DNA and RNA polymerases.[7]

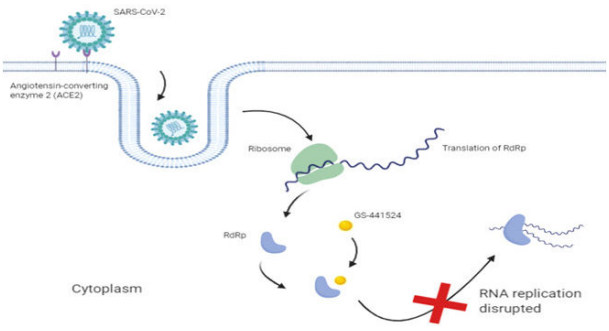

Fig. 1: Mode of action of Remdesivir under the diagram

Clinical Trials

"Clinical Trial" in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its, (i) clinical or; (ii) pharmacological including pharmacodynamics, pharmacokinetics or; (iii) adverse effects, with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug.[10]

According to a clinical trial, after the administration of Remdesivir to 53 patients, 68% showed characteristic improvement as far as oxygen support was concerned whereas 15% showed worsening. 13% died after the completion of the treatment, out of which 18% were receiving invasive ventilation and 5% non-invasive oxygen support 60% of the total patients suffered from adverse side effects such as increased hepatic enzymes, diarrhoea, rash, renal impairment, and hypotension.[11]

In a trial monitored by Hangzhou Tiger Med Consulting in China, 79 patients were assigned to receive placebo and 158 patients to receive

Remdesivir. One and three patients opted out of the study from the placebo and Remdesivir group respectively. Hence 155 and 78 patients were incorporated in the Intention-to-treat (ITT) population.[12]

Although not statistically significant, patients who received Remdesivir improved clinically faster than those who were subjected to placebo treatment, among patients with symptom duration of ≤10 days (hazard ratio 1.52 [0.95–2.43]). Adverse events were reported in 66% Remdesivir recipients versus 64% placebo recipients. Remdesivir was stopped early due to adverse events in 12% of patients versus 5% of patients who stopped the placebo early.[12] The goal was to determine the safety and efficacy of Remdesivir in patients with mild to moderate symptoms.

When Remdesivir was administered to healthy volunteers and patients infected with COVID-19, it was noted that there is an increase in levels of transaminase. Under the Emergency Use Authorization (EUA), LFT must be performed regularly to monitor the levels of hepatic enzymes. The administration of Remdesivir must be discontinued immediately if the level of alanine transaminase is observed to be increased by more than five times than the upper limit of normal levels.[7]

Pharmacokinetics

The pharmacokinetics of the exact proposed dosing administration has not been evaluated, but sufficient clinical data exists to support this regimen. Following single-dose, 2-hour intravenous infusion of Remdesivir solution formulation at doses ranging from 3 to 225 mg, exhibited a dose-linear PK. Repetitive 1-hour infusions daily of 150 mg Remdesivir solution demonstrated time-linear PK through 14 days. It was followed by a single-dose, intravenous administration of a period of 2 hours of Remdesivir solution at doses of 75 and 150 mg, Remdesivir displayed similar PK profiles as the lyophilized formulation.[7]

100mg of lyophilized powder of Remdesivir contains 3 grams of SBECD, whereas the solution contains 6grams of SBECD. The maximum recommended dosage of SBECD is 250mg/kg per day is considered to be safe.[7]

Even though IV Remdesivir (75 mg) administered over a period of 30 minutes provided similar parent exposure as the same dose administered over 2 hours, PBMC exposure of GS443902 was observed to be higher than Remdesivir (150mg) administered IV over 2 hours. This data supports the administration over the shorter time interval of 30 minutes as a more effective dosing method, for maximizing the intracellular levels of the active metabolite GS-443902. A prolonged intracellular half-life of more than 35 hours was perceived for GS-443902 in PBMCs, aiding the once-daily dosing of Remdesivir. Pharmacokinetic data among individuals with normal kidney function demonstrated that Remdesivir and its active metabolite are predominantly (74%) renally eliminated. The plasma $t_{1/2}$of parent Remdesivir is short (1–2 hours), but the $t_{1/2}$ of the active metabolite Remdesivir triphosphate is approximately 20–25 hours,with wide distribution

Phases	Subject Type	Typical Number of Participants	Primary Goal
	Preclinical	**Cell lines (animal)**	
0	Human	About 10	Determining pharmacokinetics and Pharmacodynamics
I	Human	20-100 normal healthy volunteers (or for cancer drugs, cancer patients)	Evaluation of safety and adverse-events
II	Human	100-300 patients with specific disease	Examination of Efficacy, Side effects and Dose Range
			May help in optimizing dose, schedule, and select disease types
III	Human	200-3000 patients with specific disease	Expanded study to substantiate efficacy and safety
			Generally includes multiple sites and investigators
IV	Human	Anyone seeking treatment from their physicians	Postmarketing surveillance- watching drug use in public
			Watching the long term effects of the drug

Fig. 2. Phases of Clinical Trial

to most tissues. Concerns about the drug's potential toxicity in patients with kidney disease relate both to Remdesivir's actions and the potential accumulation of its sulfobutylether-β-cyclodextrin (SBECD) carrier.[7] The pharmacokinetics and clinical features of SBECD in kidney failure are the same as intravenous voriconazole. Voriconazole is generally administered orally to patients with renal failure, whereas intravenous administration might be required in patients with invasive fungal infections who are critically ill with poor gut perfusion that interferes with oral absorption. In this case, short courses are generally well tolerated with no observation of adverse events; with an accumulation of SBECD above levels in patients with normal kidney function.[7]

SBECD is removed by continual Renal replacement therapy (RRT) and haemodialysis procedures; and significant accumulation is observed in patients when dialysis is held for longer periods. RRT keeps the exposure of SBECD in a limit that is considered to be safe. Though less in number, but liver function test elevation related to SBECD use in patients with kidney failure was rare.[7]

Concerns of RDV

According to the fact sheet for health care providers for the Emergency Use Authorization (EUA) of Remdesivir provided by the U.S Food and Drug Administration (FDA) "Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus".[13] The statement indicates that the administration of Remdesivir to pregnant women might not be safe and may cause harm to either the mother or the fetus. No clinical trials claim the safety of Remdesivir treatment for pregnant women so it is still unknown if RDV passes into breast milk or not. "If it does, the extent of teratogenic effects isstill unclear."

Managing the patients with kidney disease (especially dialysis patients) is even more challenging as they are vulnerable to the infection, along with those who are immunosuppressed or are with severe comorbidities.[14] The drug's potential toxicity in patients with kidney disease might be dependent on two factors-action of Remdesivir and accumulation of its (SBECD) carrier. The intravenous preparation of Remdesivir contains SBECD vehicle because the drug has limited water solubility. The accumulation of SBECD associated with liver necrosis and renal tubule obstruction is observed in animals at doses 50 to 100-fold higher than expected for a normal Remdesivir course (5-10 days).[7]

The concentration of Nuc-TP in the human lung is uncertain. No technology is available that has been able to measure the concentration of Remdesivir in the human lungs. The concentration of Nuc-TP in the human lung tissues can be estimated by assuming that human and monkey lung cells have a similar ability to uptake and accumulate Remdesivir and Nuc-TP. Therefore, it is difficult to determine the drug concentration in the human lungs.[8]

The mode of action of Remdesivir is very particular as it targets the viral RNA to break the chain of RNA synthesis but the mutation which improves proofreading and the fidelity of the base-pairing process might cause the resistance to Remdesivir.[15]

According to a clinical trial, an increase in hepatic enzymes was observed in a patient. Chronic inflammation of the liver leads to an increase in hepatic enzymes. The trial also shows occurrence of diarrhoea; a related systemic illness which is mediated by a direct response to an external factor causing an indirect inflammatory response to gut microflora-derived LPS.[16] This suggests that after treatment with Remdesivir, patients may suffer from inflammation of liver.[17]

Gilead has licensed the drug to four companies — Cipla, Mylan, Hetero and Jubilant Life Sciences for sale in India.[18] Among these Hetero, Cipla and Mylan already got a nod of approval from DCGI.[19,20] The price of Remdesivir in the Indian markets under the trade name of COVIFOR launched by Hetero Labs Ltd. is INR 5400 per 100mg vial.[21] At this point Cipla is also planning to launch Remdesivir under the trade name of CIPREMI which is priced at INR 4000.[22] Mylan is also in streamline to launch Remdesivir under brand name DESREMTM which costs INR 4800.[20] This is a matter of concern for a developing country like India, where most of the people have to pay their medical bills from their own pockets and affording this high cost medicine would prove to be very difficult.[23] Moreover, increased demand and less production have led to shortage in the availability of the drug. There have been reports of black marketing where the patient has even ended up paying INR 30,000-40,000 per vial.[22]

Conclusion

The Central Drugs Standard Control Organization (CDSCO) of India has permitted Indian pharmaceutical companies to produce Remdesivir to fight against the coronavirus based

on FDA's EUA policy without any clinical trial on Indian patients. But as the drug was developed to fight the Ebola virus, it is difficult to assume whether it is effective on COVID-19 patients as well. Although a significant reduction of viral load has been reported after getting a treatment of Remdesivir for a span of 5-10 days, there is still not enough data to establish its safe usage in Indian COVID patients.

As per the clinical reports, the drug inhibits viral replication but it plays no role in the prevention of the disease. Remdesivir performed phenomenally well in the clinical trials carried out in the US but it had its share of setbacks. This is not a vaccine but used as a treatment after the onset of the infection. As the immunity, drug resistance, genetic makeup, etc varies from person to person or from continent to continent, it can be assumed that the efficacy of the drug might be altered in case of Indian patients compared to the patients of USA. The answers to these questions can be obtained with well designed post marketing surveillance studies to identify the safety and efficacy of Remdesivir on Indian Covid19 patients.

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