REVIEW ARTICLE

Past, Present, and Future of Remdesivir: An Overview of the Antiviral in Recent Times

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Abstract

In the current COVID-19 pandemic, evidence to justify the use of any specific antiviral drug with proven efficacy is not yet available. Antiviral drug development always remains a challenge to the scientists. Remdesivir has emerged as a promising molecule, based on results of clinical trials and observational studies and has receieved marketing approval for COVID-19 treatment under "emergency use authorization" in countries such as United States. Remdesivir is a newer antiviral drug that acts as an RNA-dependent RNA polymerase (RdRp) inhibitor targeting the viral genome replication process. Therapeutic efficacy was first demonstrated by suppressing viral replication in Ebola-infected rhesus monkeys. It is available for parenteral use with reasonable safety and tolerability profile. Multiple clinical trials are going on in many countries to evaluate its safety, efficacy and tolerability. Positive outcome will make the drug capable of meeting the demand generated by both the current pandemic and future outbreak.

Keywords: Clinical trials, COVID-19 drug treatment, Viral genome.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23491

Background

Viral infections undoubtedly constitute one of the biggest pandemic threats in the modern era. By nature, viruses are obligate intracellular pathogens that utilize host cell for their survival. Hence, an important consideration for antiviral drug candidates includes non-impairment of host cell function despite killing or arresting viral multiplication. Other considerations includes structure (i.e., differences between RNA and DNA viruses), degree of host cell interaction, and acquired drug resistance.

Of late, the mainstay of treatment for most novel viral epidemics such as COVID-19 has been primarily supportive, as evidence to justify the use of any specific drug with proven efficacy is limited. However, remdesivir has emerged as a promising molecule based on the results of recent clinical and observational studies. It has received conditional marketing approval for COVID-19 treatment under "emergency use authorization" in countries such as USA. Apart from remdesivir, several other agents are being evaluated for COVID-19 therapy including antivirals such as lopinavir-ritonavir, favipiravir, arbidol, and repurposed agents such as hydroxychloroquine, azithromycin, ivermectin, and nitazoxanide.

Remdesivir: Mechanism of Action Simplified

Remdesivir (GS-5734) has been developed by Gilead Sciences, Inc. It acts as a prodrug of adenosine analogue, inhibiting RNA-dependent RNA polymerase (RdRp) enzyme. Additionally, it also seems to block the viral genome replication process.

Remdesivir is first metabolized within the host cells into an alanine metabolite (GS-704277), which is further processed into monophosphate derivative and then ultimately into the active nucleoside triphosphate (NTP) analogue. The NTP derivative now competes with alanine metabolite to get attached to nascent RNA strand.[1] This abnormal incorporation stops the elongation of RNA strand, terminating RNA synthesis prematurely. However, addition of remdesivir in the i-position of growing chain will not immediately stop the replication process. Instead, the strand replication stops at i+3 positions after incorporation of three more nucleotides.[2] This unique mechanism of delayed chain transmission has been found to inhibit viral RNA synthesis of all three types of corona viruses including SARS CoV 2. Mechanism of action is shown schematically in Figure 1.[3]

Remdesivir: Salient PK/PD Features

Remdesivir is widely distributed in the body, predominantly in bladder, kidneys, liver, prostate, mandibular salivary gland, pancreas, seminal vesicle, epididymis, and testes. It is administered by intravenous route, with a half-life of 0.84–1.04 hours. It gets eliminated mainly by renal (63%) and biliary excretion (27.8%) and shows poor penetration across the blood -brain barrier. It is metabolized partially by CYP2C8, CYP2D6, and CYP3A4 enzymes.[4]

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How to cite this article: Choudhury S, Chakraborty DS, Lahiry S, Chatterjee S. Past, Present, and Future of Remdesivir: An Overview of the Antiviral in Recent Times. Indian J Crit Care Med 2020;24(7):570–574.

Source of support: Nil

Conflict of interest: None

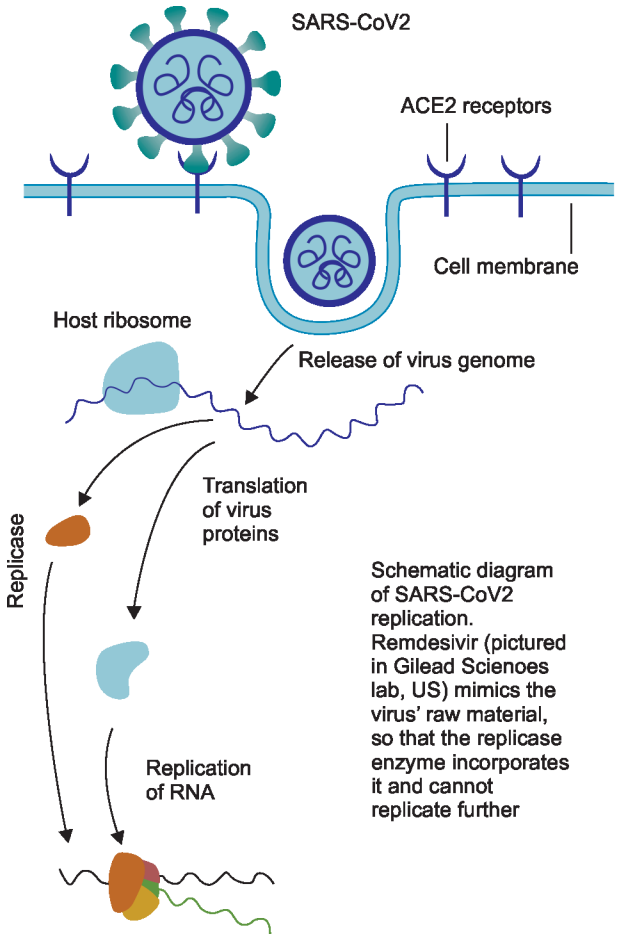

Fig. 1: Probable mechanism of action of remdesivir against SARS-CoV

In clinical pharmacokinetic studies, remdesivir expressed low bioavailability in cynomolgus monkeys. In vivo studies in rhesus monkeys have shown that remdesivir administered at a dose of 10 mg/kg by intravenous route undergoes rapid conversion to nucleoside phosphate derivative. It gets distributed in peripheral blood mononuclear cells within 2 hours of administration, followed by activation to NTP analogue to achieve a peak with 100% survival rate.[5]

A linear PK trend was seen with a single dose of 3 to 225 mg intravenous remdesivir infusion for 2 hours. However, active substance accumulated in vivo in daily administration schedule. Therefore, a maintenance dose of 100 mg is advised after a loading dose of 200 mg to maintain appropriate blood concentration in vivo.[6] As of June 2020, Phase I trials with remdesivir have demonstrated adequate safety, tolerability following intravenous use without any serious adverse effects or liver toxicity.

The US FDA has recommended different dosing regimens for remdesivir (according to age, body weight, and severity of patients) and its common adverse effects that are depicted in Table 1.

Table 1: FDA suggested dosing pattern of remdesivir in COVID-19 in different categories of patients

Category of patient	*Body weight*	*Loading dose*	*Maintenance dose*
Adult or pediatric patients requiring invasive mechanical ventilation and/or ECMO	≥40 kg	200 mg infused intravenously over 30 to 120 minutes on day 1	100 mg infused intravenously over 30 to 120 minutes for 9 days (days 2 through 10).
Adult or pediatric patients not requiring invasive mechanical ventilation and/or ECMO	≥40 kg	200 mg infused intravenously over 30 to 120 minutes on day 1	100 mg infused intravenously over 30 to 120 minutes for 9 days (days 2 through 5). If no improvement, may be extended up to 10 days.
Pediatric patients requiring invasive mechanical ventilation and/or ECMO	3.5 to 40 kg	5 mg/kg IV (infused over 30 to 120 minutes) on day 1	2.5 mg/kg IV (infused over 30 to 120 minutes) once daily for 9 days (days 2 through 10)
Pediatric patients not requiring invasive mechanical ventilation and/or ECMO	3.5 to 40 kg	5 mg/kg IV (infused over 30 to 120 minutes) on day	2.5 mg/kg IV (infused over 30 to 120 minutes) once daily for 4 days (days 2 through 5). If no improvement, may be extended up to 10 days.

Remdesivir can be used at any time after onset of symptoms in hospitalized patients

All patients must have an estimated glomerular filtration rate (eGFR) determined before dosing

Known serious adverse effects are infusion-related reaction, increased risk of transaminase elevations. Common adverse effects are nausea, diarrhea, rash hypotension etc.

Remdesivir Activity on Coronavirus: Evidence from Preclinical Studies

Table 2 depicts preclinical data on remdesivir against coronavirus. remdesivir was first found to be efficacious by successfully suppressing viral replication in Rhesus monkeys with Ebola infection.[7] Efficacy studies in Ces 1 c-/- mice demonstrated therapeutic efficacy of this molecule against both MERS-CoV and SARS-CoV. A recent study by Sheehan et al also showed the protective role of remdesivir against Middle East Respiratory System (MERS) corona virus replication in both prophylactic and therapeutic aspects.[8]

In preliminary animal study done in cats (n = 31), Pedersen et al demonstrated promising results with remdesivir at an initial dose of 2 mg/kg/day in naturally occurring SARS-CoV-2 infection.[9] Additionally, antiviral activity of remdesivir has also been established in vitro against several other viruses, including Marburg virus, Nipah virus, Measles, Mumps, Parainfluenzae, Hendra virus, Respiratory syncytial virus etc.[10]

In a recent in vitro study conducted at Wuhan Virus Research Institute, China, virus-infected Vero E6 cells treated with remdesivir

Table 2: Summary of *in vitro* studies on remdesivir (GS-5734) efficacy against coronaviruses

Study	*Coronavirus*	*Cell line*	*EC50 or IC50*
Sheahan et al.	MERS-CoV	Calu-3 2B4	IC50 = 0.025 μM
	SARS-CoV	HAE	IC50 = 0.074 μM
		HAE	IC50 = 0.069 μM
Agostini et al.	SARS-CoV	HAE	EC50 = 0.07 μM
	MERS-CoV	HAE	EC50 = 0.07 μM
	MHV[†]	DBT	EC50 = 0.03 μM
Brown et al.	HCoV-OC43	Huh7	EC50 = 0.15 μM
	HCoV-229E	Huh7	EC50 = 0.024 μM
	PDCoV[‡]	LLC-PK1	EC50 = 3.8 μM
		LLC-PK1	Not reached
		Huh7	EC50 = 0.02 μM
Sheahan et al.	MERS-CoV	Calu-3 2B4	EC50 = 0.09 μM
Wang et al.	SARS-CoV-2	Vero E6	EC50 = 0.77 μM
Murphy et al.	FIPV[¥]	CRFK	EC50 = 0.78 μM
Agostini et al.	SARS-CoV	HAE	EC50 = 0.18 μM
	MERS-CoV	HAE	EC50 = 0.86 μM
	MHV†	DBT	EC50 = 1.1 μM

Calu-3, human bronchial epithelial cells; HAE, human airway epithelial cells; DBT, mouse delayed brain tumor; Huh7, human liver cells; LLC-PK1, porcine kidney cells; Vero E6, African green monkey kidney epithelial cells; CRFK: feline kidney cells. EC50 = Half maximal effective concentration; IC50 = half maximal inhibitory concentration. EC50 or IC50 provided as reported by each respective study. [†]MHV = murine hepatitis virus. [‡]PDCoV = porcine deltacoronavirus. [¥]FIPV = feline infectious peritonitis virus

showed that it blocked virus replication even at very low micro-molecular concentration with high cell selectivity. The result assumed its effective role in monkeys with SARS-Co-2 infection.[11]

Remdesivir in COVID-19: Evidences from Clinical Studies

In recent years, remdesivir has been tested extensively for its efficacy, especially during the West African Ebola virus epidemic. It has also shown promising results during the 2018 Kivu Ebola epidemic. Starting March 17, 2020, remdesivir has been provisionally approved in Czech Republic for use in COVID-19 patients.

In the ongoing COVID-19 pandemic, a double blind, placebo-controlled trial was carried out in China across ten hospitals, using remdesivir in microbiologically confirmed SARS-CoV-2-infected adult patients. Subjects were assigned to test and control groups randomly in 2:1 ratio. In the test group, remdesivir was initiated at a loading dose of 200 mg on first day followed by a daily dose of 100 mg once from day 2 to day 10 by intravenous infusion. Concomitant therapy with lopinavir -ritonavir, corticosteroids, and interferons was given in both groups. However, there was no statistically significant clinical improvement in the test drug group. It is important to know that, therapy was started late and power of the study was insufficient to identify clinical improvement in both the groups.[12]

Data from preliminary studies conducted in US demonstrate significant clinical improvement in COVID-19 patients when treated with remdesivir. On 29 April, 2020, results of the SIMPLE (trial), a phase III open label study was declared by Gilead Sciences Inc. wherein remdesivir was tested in severe cases of COVID-19 hospitalized patients, with two dosing schedules of 5 days and 10 days. Results showed similar clinical improvement in 10-day treatment group in comparison to 5-day group with an odds ratio of 0.75 (95% CI: 0.51–1.12). Clinical recovery was achieved in 53.8% patients of 10-day group and 64.5% in 5-day group. A total of >50% patients were discharged from both groups by day 14. Exploratory analysis revealed that outcome was better when the therapy was initiated within 10 days of onset of symptoms. Additionally, 62% patients with early-onset treatment could be discharged in comparison to 49% discharge rates for subject with late-onset treatment by day 14. Safety and tolerability data were similar for both groups without any new safety signal.[13]

Grein et al. also demonstrated favorable outcome with remdesivir in hospitalized patients having severe COVID-19. remdesivir was primarily used on a compassionate basis in this cohort. Study eligibility criteria included patients requiring oxygen support or having oxygen saturation <94% in room air. Dosing schedule was a single loading dose of 200 mg on first day followed by a daily dose of 100 mg once from day 2 to 10 intravenously by infusion. Preliminary results indicated that 57% patients could be extubated from mechanical ventilation; improvement in oxygen status was recorded in 68% patients. Overall mortality rate was 13% over 18 days follow up-period. Data regarding viral load, a useful surrogate for antiviral efficacy, were not recorded in this study, although clinical improvement was noted in patients across different geographies.[14]

Interestingly, the National Institute for Allergy and Infectious Disease (NIAID) has conducted an Adaptive COVID-19 Treatment Trial. The objective of this study was to find out the optimal duration of remdesivir therapy in SARS-CoV-2 infection. It was a double blind, placebo-controlled, multicentric study with 1,063 randomized patients. Results showed that remdesivir use was associated with survival benefit and faster recovery rates with a median time to recovery of 11 days compared to 15 days with placebo. All hospitalized patients requiring oxygen therapy showed significant clinical improvement. However, the mortality rate was high (7.1% in the remdesivir group versus 11.9% in the placebo group by day 14), indicating that antiviral monotherapy may not be sufficient for COVID-19.[15]

Currently, remdesivir is only approved in Japan for patients with SARS-CoV-2 infection. Outside Japan, it is still an investigational drug. The US-FDA has granted remdesivir "emergency use authorization" on May 1, 2020, for treatment of suspected or microbiologically confirmed hospitalized patients with severe COVID-19.[16] This authorization is temporary.

Remdesivir in COVID-19: Data from Ongoing Clinical Studies

As of June 2020, two phase III open-label trials (SIMPLE) are underway recruiting patients from countries with high infection rates/burden.[13,17] The first trial is evaluating the safety and efficacy of remdesivir in hospitalized patients with severe COVID-19 infection, having oxygen saturation<94% and radiological proof of pneumonia. The second trial includes confirmed cases with moderate manifestations of COVID-19. Both studies have similar intravenous dosing regimens of 5-day and 10-day duration of therapy.

The first study has already recruited 397 patients (1:1) in both groups (i.e., 5-day vs 10-day) in its initial recruitment phase. A loading dose of remdesivir being 200 mg on first day, followed by 100 mg once daily intravenous infusion up to 5 days or 10 days, along with standard care. Preliminary results indicate that efficacy was not significantly different between groups for severe cases not

Table 3: List of ongoing trials on remdesivir in the treatment of COVID-19

Clinical trial ID (registry)	*Intervention*	*Size*	*Randomized*	*Blinded*	*Status*	*Country of origin (pharma sponsor)*
NCT04302766 (ClinicalTrials.gov)	Arm A: remdesivir	Unspecified	Unspecified	Unspecified	Available	USA
NCT04292899 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment	400	Yes	No	Recruiting	USA and Asia
NCT04292730 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment	600	Yes	No	Recruiting	USA and Asia
NCT04280705* (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	394	Yes	Double	Recruiting	USA and South Korea
2020-000841-15 (EU-CTR)	Arm A: remdesivir Arm B: standard treatment	400	Yes	No	Recruiting	Worldwide
2020-000842-32 (EU-CTR)	Arm A: remdesivir Arm B: standard treatment	600	Yes	No	Recruiting	Worldwide
NCT04252664 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	308	Yes	Quadruple	Recruiting	China
NCT04257656 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	453	Yes	Quadruple	Recruiting	China
NCT04315948 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: lopinavir/ritonavir Arm C: lopinavir/ritonavir and interferon beta 1a Arm D: hydroxychloroquine Arm E: standard treatment	3100	Yes	No	Recruiting	France

*Preliminary result published

requiring mechanical ventilation. Incidence of adverse reactions and tolerability profile were also comparable. However, cases requiring mechanical ventilation in due course may benefit with 10-day therapy. This study is slated to expand through recruitment of 5,600 severely ill patients from 180 study sites worldwide. Study sites already listed include United States, United Kingdom, Japan, Italy, China, France, Singapore, Spain, Germany etc.[13] The second study in moderately ill COVID-19 patients is expected to publish its study results of first 600 patients.[17]

The WHO is also conducting a Phase III-IV SOLIDARITY trial globally and partners to compare four treatment options (including remdesivir) for hospitalized cases of severe COVID-19 illness. The study was launched on March 18, 2020, and as of April 21, 2020, over 100 nations were participating.

Comments

Currently, nine clinical studies evaluating the role of remdesivir in COVID-19 is underway (Table 3). Results of these trials will present evidence about the status of this drug, as a treatment option in SARS-CoV-2 infection. In most published studies, remdesivir was found to decrease the duration of recovery time making faster healing in some COVID-19 illness, but the effectiveness and safety of this molecule is yet to be known.[16] Hopefully, there will be encouraging study results favoring remdesivir, which could be a potential game changer.

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