Remdesivir—Overview of the most debatable Antiviral of Recent Times

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Abstract

Viral infections constitute the biggest pandemic threat in the modern era due to lack of novel 'broad-spectrum' antiviral agents. Remdesivir is newer antiviral drug acts as RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. Therapeutic efficacy was first demonstrated by suppressing viral replication in Ebola infected infected rhesus monkeys. Then further studies show its efficacy against Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV). It is available for parenteral application with reasonable safety and tolerability profile. Recently the drug has received emergency use authorization from USFDA for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease due to lack of other approved treatment options. Multiple clinical trials are going on in many countries to evaluate its efficacy, safety and tolerability. Results are awaited in most cases and if the drug becomes a success it will be capable of meeting the demand generated by both the current pandemic and future outbreak.

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Abstract:

Viral infections constitute the biggest pandemic threat in the modern era due to lack of novel 'broad-spectrum' antiviral agents. Remdesivir is newer antiviral drug acts as RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. Therapeutic efficacy was first demonstrated by suppressing viral replication in Ebola infected infected rhesus monkeys. Then further studies show its efficacy against Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV). It is available for parenteral application with reasonable safety and tolerability profile. Recently the drug has received emergency use authorization from USFDA for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease due to lack of other approved treatment options. Multiple clinical trials are going on in many countries to evaluate its efficacy, safety and tolerability. Results are awaited in most cases and if the drug becomes a success it will be capable of meeting the demand generated by both the current pandemic and future outbreak.

Introduction:

Viral infections undoubtedly constitute the biggest pandemic threat in the modern era due to lack of 'broad-spectrum' antiviral agents. Whereas, the threat is much less in case of bacteria in spite of their more virulent natrure, due to development of multiple novel antibacterial drugs.[1] The major concern in antiviral drug development is to preserve the host cell function normal, though the viruses utilise host cell machinery due to their obligate parasite nature. Other obstacles are differences between RNA and DNA viruses, vastly different

virally encoded proteins across viral families, single or double strand genomic structure and cytoplasmic or nuclear replications cycles. Present approach remains aiming finding treatments for specific individual viruses of concern rather than their families. In most of the cases of novel viral epidemic, supportive care remains the mainstay of therapy rather than antiviral drug. So, development of novel broad spectrum antivirals is of utmost importance in present time.

Mechanism of Action Remdesivir:

Remdesivir is a prodrug of an adenosine analog developed by Gilead Sciences, Inc. It acts as a RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. After the host metabolizes remdesivir into active nucleoside triphosphate (NTP), the metabolite competes with adenosine triphosphate (ATP) for incorporation into the nascent RNA strand.[2] This unusual incorporation results in premature termination of RNA synthesis, halting the growth of the RNA strand after a few more nucleotides are added. Once remdesivir is added into the growing chain (i position), it cannot cause an immediate stop, rather it will continue to extend three more nucleotides down to pause the strand at (i+3) position.[3]

Pre-clinical data:

Therapeutic efficacy was first demonstrated by suppressing viral replication in Ebola infected infected rhesus monkeys. Prophylactic use was initiated 24 h prior to viral challenge, whereas therapeutic use was initiated 12 h after challenge. The severity of pulmonary infiltrates, were significantly better in the prophylactic and therapeutic groups, comparing each to controls.[4] Efficacy studies in Ces1c-/- mice demonstrated therapeutic efficacy of this drug against Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Sheahan et al. found that both prophylactic and therapeutic remdesivir had protective effects against MERS-CoV replication and associated pathology, generally resulting in less lung damage and better pulmonary function.[5] In 2018, Murphy et al. examined the efficacy of this drug against Feline infectious peritonitis (FIP) in 12 experimentally infected cats. In the 10 infected cats, treatment was initiated (5 cats with 5mg/kg daily and 5 cats with 2mg.kg daily) upon onset of FIP-associated clinical signs and continued for 2 weeks. All treated cats demonstrated favorable responses to remdesivir treatment within 24–48 h.[6] Pedersen et al. treated 31 cats with an initial dose of 2 mg/kg daily. A total of 25 treated cats (81%) survived FIP for at least 44 weeks of follow up, indicating that this drug is also a promising therapeutic candidate for treatment of alphacoronavirus- related disease in cats. This study was done on cats with naturally occurring CoV infection, representing real world situation.[7] Efficacy of this drug was also tested against Nipah virus Bangladesh genotype among African green monkeys and it showed all remsdesivir-treated animals survived and mild respiratory signs were observed in two out of four treated animals.[8] It also exhibited antiviral activity in vitro against other virues like Marburg virus,Paramyxoviridae (such as parainfluenza type 3 virus, Nipah virus, Hendra virus, and measles and mumps viruses) and Pneumoviridae (such as respiratory syncytial virus).[9] Wuhan Virus Research Institute carried out a vitro inhibition test and found that remdesivir can block virus infection at very low micromolar concentration of Vero E6 cells infected with virus, and the cell selectivity is high (EC50 = 0.77 μM, CC50 > 100 μM, SI > 129.87). It draws a speculation that it could also play a role (EC90 =1.76 μM) in SARS-CoV-2 infected monkeys.[10] Preclinical studies are compiled in Table 1.

Clinical trial data:

Remdesivir was rapidly pushed through clinical trials during the West African Ebola virus epidemic of 2013–2016. As the preliminary results were promising; it was used in the emergency period of the Kivu Ebola epidemic in 2018. But it was found less effective than monoclonal antibody treatments such as mAb114 and REGN-EB3. The trials, however, established the safety profile of the drug.[11] In Phase II clinical trials as anti-Ebola drugs, the fatality rate in remdesivir group was 53% which was not significantly less than average 50% fatality rate of the disease itself and significantly worse than that of the two monoclonal antibodies MAb114 (fatality rate 35%) and REGN-EB3 (fatality rate 33%).[12]

A nurse from Scotland with Ebola meningoencephalitis was successfully treated with high dose corticosteroids and 14 days of remdesivir therapy (once-daily infusion of 150 mg over 2 h for 2 days followed by daily 225

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mg for another 12 days).[13]

A randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China was conducted recently, recruiting adult patients of laboratory-confirmed SARS-CoV-2 infection with prefixed inclusion criteria. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days along with concomitant therapy of lopinavir–ritonavir, interferons, and corticosteroids. Though the study was limited by insufficient power to detect assumed differences in clinical outcomes and late starting of therapy, Remdesivir failed to prove statistically significant clinical improvement.[14] Few COVID-19 patients from United States were treated with Remdesivir and showed clinical improvement. On 17 March 2020, the drug was provisionally approved to be used amongCOVID-19 patients due to serious outbreak in the Czech Republic. On April 29 2020, Gilead Sciences, Inc. announced results from the open-label, Phase 3 SIMPLE trial evaluating 5-day and 10-day dosing durations of remdesivir in hospitalized patients with severe manifestations of COVID-19 disease. The study demonstrated that patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course (Odds Ratio: 0.75 [95% CI 0.51 – 1.12] on Day 14). No new safety signals were identified with remdesivir across either treatment group. More than half of patients in both treatment groups were discharged from the hospital by Day 14 with 64.5% of patients in the 5-day treatment group and 53.8% of patients in the 10-day treatment group achieved clinical recovery. In an exploratory analysis, patients in the study who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms. Pooling data across treatment arms, by Day 14, 62% of patients treated early were able to be discharged from the hospital, compared with 49% of patients who were treated late.[15]

On 1 May 2020, the U.S. Food and Drug Administration issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease..[16]

Ongoing clinical trials:

Manufacturing company has initiated two more randomized, open-label, multi-center Phase III clinical trials for remdesivir, the SIMPLE studies, in countries with high prevalence. The first SIMPLE trial is evaluating the safety and efficacy of 5-day and 10-day dosing regimens of remdesivir in hospitalized patients with severe COVID-19. The initial phase of the study randomized 397 patients in a 1:1 ratio to receive IV remdesivir 200 mg on the first day, followed by remdesivir 100 mg each day until day 5 or 10, in addition to standard of care. An expansion phase of the study was recently added and will enroll an additional 5,600 patients, including patients on mechanical ventilation. The study is being conducted at 180 trial sites around the world, including sites in the United States, China, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan and the United Kingdom. A second SIMPLE trial is evaluating the safety and efficacy of 5-day and 10-day dosing durations of remdesivir administered intravenously in patients with moderate manifestations of COVID-19, compared with standard of care. The results from the first 600 patients of this study are expected at the end of May.[15]Adaptive COVID-19 Treatment Trial (ACTT) has been conducted by the National Institute for Allergy and Infectious Diseases and help to determine the optimal duration of treatment with remdesivir. Preliminary results indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit. WHO is conducting a n adaptive, randomized, open-label, multi-center clinical trial of the safety and efficacy of remdesivir and three other investigational treatments in hospitalized adults diagnosed with COVID-19.

Salient pharmacological features:

This drug is widely distributed in the body, predominantly in bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas, seminal vesicle, epididymis and testes. It is administered via intravenous

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route. Half life of the drug is 0.84-1.04 hr. It gets elimintated majorly by renal (63%) and billiary excretion (27.8%). It poorly crosses blood-brain barrier. Remdesivir is partially metabolized by the cytochrome P450 enzymes CYP2C8, 2D6, and 3A4.[17] Pharmacokinetic experiments in cynomolgus monkeys demonstrated low bioavailability of the drug. Intramuscular injection of 3 mg/kg had a 50% survival rate compared with the control group. Intravenous administration at a dose of 10 mg/kg got rapidly converted into nucleoside phosphate in rhesus monkeys. Within 2 hr, remdesivir quickly gets distributed in peripheral blood mononuclear cells (PBMCs), and soon afterwards activated to nucleoside triphosphate to reach a peak, with a survival rate of 100%.[18] Pharmacokinetic studies performed in vivo showed after the intravenous infusion at a single dose of 3–225 mg for 2 h, it showed dose-linear pharmacokinetics. In the case of daily administration, the active substance of the drug will be accumulated in vivo. As a result, in large-scale clinical trials, after the first dose of 200 mg is administered, the subsequent dose is adjusted to 100 mg to ensure the proper blood concentration in vivo.[19]Intravenous infusions in previously phase I clinical trials have good safety and pharmacokinetic properties without any cytotoxicity, hepatorenal toxicity, or no serious adverse reactions.

Conclusion:

Currently Nine trials (Table-2) on Remdesivir are ongoing to evaluate its safety and efficacy in the treatment of Covid 19. Results of these clinical trials will provide crucial information about whether remdesivir represents a viable treatment option for COVID-19 . While there is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19, the investigational drug was shown in clinical trial to shorten the time to recovery in some patients.[16] If the trial findings are ultimately positive, it will be imperative to ensure that the drug is produced on a commercial scale capable of meeting the demand generated by both the current pandemic and future outbreaks.

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Table-1 : Summary of in-vitro studies on remdesivir (GS-5734) efficacy against coronaviruses

Study	Coronavirus	Cell line	EC50 or IC50
Sheahan et al.	MERS-CoV SARS-CoV	Calu-3 2B4 HAE HAE	IC50 = 0.025 μM IC50 = 0.074 μM IC50 = 0.069 μM
Agostini et al.	SARS-CoV MERS-CoV MHV+	HAE HAE DBT	EC50 = 0.07 μM EC50 = 0.07 μM EC50 = 0.03 μM
Brown et al.	HCoV-OC43 HCoV-229E PDCoV ++	Huh7 Huh7 LLC-PK1 LLC-PK1 Huh7	EC50 = 0.15 μM EC50 = 0.024 μM EC50 = 3.8 μM Not reached 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 MERS-CoV MHV+	HAE HAE DBT	EC50 = 0.18 μM EC50 = 0.86 μM 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.

Table 2— List of Ongoing trials on Remdesivir in the treatment of COVID-19

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Clinical trial ID (Registry)	Intervention
NCT04302766 (ClinicalTrials.gov)	Arm A: remdesivir
NCT04292899 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment
NCT04292730 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment
NCT04280705 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo
2020-000841-15 (EU-CTR)	Arm A: remdesivir Arm B: standard treatment
2020-000842-32 (EU-CTR)	) Arm A: remdesivir Arm B: standard treatment
NCT04252664 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo
NCT04257656 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo
NCT04315948 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: lopinavir/ritonavir Arm C: lopinavir/ritonavir and interferc

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