Review Article

# Review on Remdesivir: A Possible Therapeutic Option for the Covid-19

**Richa Chaudhary[1], Sarita Jangra Bhyan[2], Bhupinder Bhyan[3], Besty Thomas[4], Aditya Narayan Gupta[4], Kulsoom Hamid[4]**

1. Pharm D (Post Baccalaureate) Intern, Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, TMU, Moradabad, Uttar Pradesh, India.
2. Internship Coordinator, Assistant Professor, Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, TMU, Moradabad, Uttar Pradesh, India.
3. Assistant Professor, Department of Pharmaceutics, Teerthanker Mahaveer College of Pharmacy, TMU, Moradabad, Uttar Pradesh, India.
4. Pharm D Intern, Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, TMU, Moradabad, Uttar Pradesh, India.

***Corresponding author's E-mail: richachaudhary1410@gmail.com**

**Received:** 14-05-2020; **Revised:** 18-07-2020; **Accepted:** 25-07-2020.

**ABSTRACT**

Remdesivir is a broad-spectrum antiviral agent (with a development code GS-5734). This medicine is an experimental drug, and was not licensed or approved at the time this article was published. In 2017 Gilead Sciences synthesized and developed it as a treatment for Ebola virus infection. Studies in vitro have shown that Remdesivir can inhibit coronavirus, such as SARS-CoV and MERS-CoV replication. Newer randomized controlled trials recently published showed a mixed outcome. We aimed to look through the literature to understand Remdesivir's pharmacology and clinical effects in COVID-19 patients. Initial compassionate use of Remdesivir, in the absence of a control arm, has shown a fairly good result, but difficult to quantify. Although the very first double-blind, placebo-controlled, randomized trial conducted in Wuhan found no substantial advantage relative to the control, the preliminary outcome of another similar multi-country trial showed a slightly faster recovery time, but without any mortality differences. In the opening remarks by the Director-General of the World Health Organization (WHO) at the COVID-19 media briefing on 20 February 2020, it was covered that the two therapeutic Remdesivir clinical trials prioritized by the WHO R&D Blueprint are expected to deliver preliminary results in three weeks' time. On 24 February, the WHO cast a vote of confidence for the experimental antiviral drug, Remdesivir, by Gilead Sciences, suggesting that Remdesivir has great potential and could be the best choice for COVID-19 therapy.

**Keywords:** Remdesivir, COVID-19, WHO R&D, Gilead Sciences, MedRxiv.

## INTRODUCTION

In December 2019, an epidemic of pneumonia because of unknown cause occurred in Wuhan, Hubei province, China with clinical presentations greatly resembling virus infection and rapidly spread throughout the country within 1 month.[1] The pathogen of this disease was confirmed as a unique coronavirus by molecular methods and was initially named as 2019 novel coronavirus (2019-nCoV);[2] however, World health organization (WHO) announced a new name on February 11, 2020 for the epidemic disease: Corona virus disease (COVID-19).[3] COVID-19 (Coronavirus disease-2019), a disease caused by the coronavirus SARS-CoV-2 (Severe acute respiratory syndrome-coronavirus-2), has emerged as a rapidly spreading disease affecting over 200 countries across the world at the present.[4] The disease is primarily spread through large respiratory droplets, though the chance of other routes of transmission can't be ruled out, because the virus has been found in stool and urine of affected individuals.[5]

At the time of writing this article, coronavirus cases: 9,060,870 cases with 470,939 deaths & 4,847,018 recovered spanning over 213 countries and territories and a couple of international conveyance are reported.[6] On 11th March 2020, WHO declared this disease as pandemic.[7] This might be an underestimate due to the lower number of diagnostic tests and case identification partly because of poor health services in most countries. The mortality rate stands at 0.28%.[8]

Diversion of all healthcare facilities toward the COVID-19 pandemic is probably going to extend the morbidity and mortality due to other health problems.[9] Another conundrum faced could be a high secondary infection rate among high-risk healthcare workers annexing the already burdened healthcare system.[10] This is able to not only compound the approaching shortage of healthcare facilities but would also mean more pervasive spread. Prevention is thus the foremost effective strategy to not only prevent more spread and deaths but also to unburden the healthcare system. However, there are challenges involved. Although methods like mitigation, quarantine, isolation, social distancing are being employed and these don't seem to be infallible. Contact tracing for the spread of infection from asymptomatic or mild undiagnosed cases, transition to community spread, and factors

like uncertainty regarding the survival of the virus in air or fomites are cumulatively adding to the mammoth task.[11] Hence, the main focus has now been shifted toward evaluating and implementing other strategies like chemoprophylaxis and vaccination besides the continued use of the barrier system.[12] Vaccine development will take time, between 12-18 months, as human trials are under way. The incubation period of the virus is the time between the exposure and the display of symptoms. Current data recommends that the brooding period ranges from 1 to 12.5 days (with middle appraisals of 5 to 6 days), yet can be up to 14 days.[13]

At present, there's no vaccine or antiviral treatment for human and animal corona virus (COVID-19), due to its key role within the virus cell receptor interaction, the surface structure of spike glycoprotein(s) **(Figure 1)** is especially important for the event of antivirals.[14]

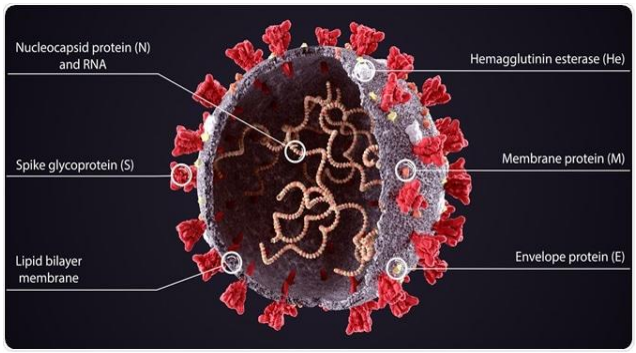


**Figure 1:** Structure of COVID-19[14]

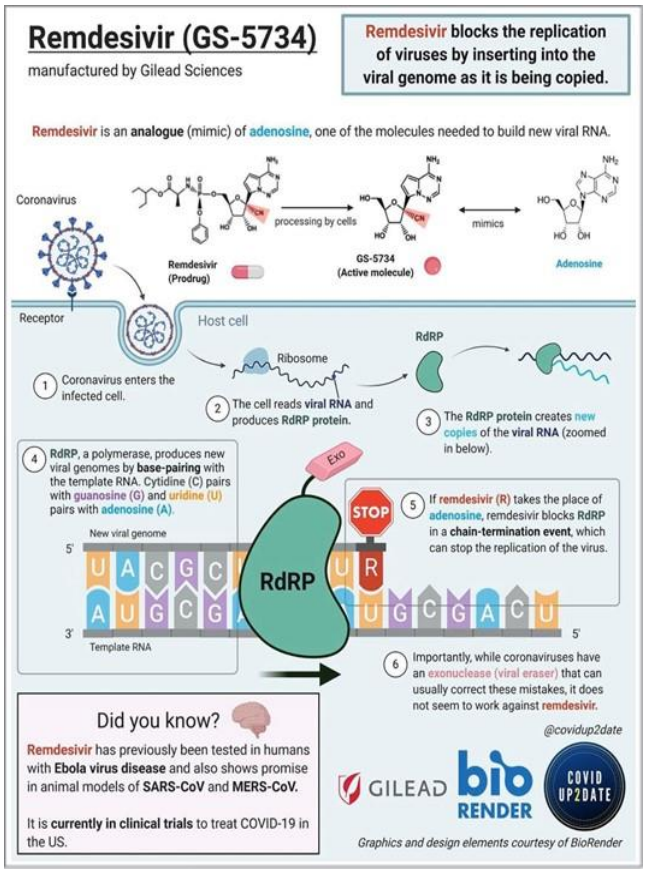


**Figure 2:** Remdesivir – Structure & Mode of action[20]

**Remdesivir Mechanism of Action**

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS- CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these corona viruses.[15]

Remdesivir, also known as GS-5734 (Figure 2), is a novel antiviral nucleotide prodrug created by Gilead Sciences for the treatment of the Ebola virus outbreak in 2016. Although it did not demonstrate efficacy in human clinical trials for this disease, it has shown efficacy against coronaviruses including SARS-CoV-1 and Middle East respiratory syndrome coronavirus.

Because of this, Remdesivir has garnered significant attention for its potential use as a treatment option for SARS- CoV-2. As an adenosine analog, Remdesivir was shown to incorporate into growing viral RNA chains, resulting in premature termination and a decrease in viral RNA production. Due to a 96% structural similarity in its RNA-dependent RNA polymerase (RdRp) compared with the virus causing SARS-CoV-1, Remdesivir, which targets the viral RdRp, is postulated to be effective against SARS-CoV-2 as well.[16]

With the emergence of the SARS-CoV-2, the etiologic agent of (COVID-19), we are in a need for an effective antiviral agent to be able to halt the current outbreak. It had been suggested that Remdesivir might be an option for the therapy of patients with COVID-19. In a case report, Remdesivir treatment was started intravenous on day 7 in a patient with COVID-19. In vitro and animal models, Remdesivir has demonstrated activity against both SARS and MERS that also belong to coronaviruses, and theoretically provides support its effectiveness in treating COVID-19.[17]

**Possible ADRs of Remdesivir**

The common adverse event noted during compassionate use of Remdesivir in patients with COVID-19 by Grein et al. include rash, diarrhea, hypotension, abnormal liver function and renal impairment. Serious adverse events (acute kidney injury, septic shock, multi-organ failure) was noted in 23%, while 60% had at least one adverse event and 8% discontinued due to various side effect of Remdesivir.[15] Adverse events were similar in Remdesivir (66%) and control arm (64%) in study of Wang et al.[18] Although serious adverse events reported in 18% vs. 26% in Remdesivir vs. control arm respectively; more patients from the Remdesivir group discontinued Remdesivir (12%), compared to the control arm (5%) either because of adverse events or serious adverse events (notably, 5% in Remdesivir group had acute respiratory distress syndrome or respiratory failure). The most common adverse events noted in SIMPLE trial occurring in more than 10% of

patients in either group were nausea (10.0% vs. 8.6%, 5-days vs. 10-days group, respectively) and acute respiratory failure (6.0% vs.10.7%, 5-days vs. 10-days group, respectively). Grade 3 or higher liver enzyme elevations occurred in 7.3% of patients, while 5% in 5-days arm and 10% in 10-days arm had to withdraw from Remdesivir due to severe adverse events.[19]

**Remdesivir effects on Renal Functioning**

Although no evidence of nephrotoxicity was noted in healthy subjects, some caution is required while using Remdesivir. A 150-mg dose of the Remdesivir solution and lyophilized formulations of Remdesivir contains 9.0 and 4.5 g, of sulfo-butyl-ether β-cyclodextrin-sodium (SBECD), respectively (maximum recommended daily dose is approximately 250 mg/kg, based on EMA safety review). SBECD is used in the formulation as a solubilizing agent due to the limited aqueous solubility of Remdesivir. Since SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD exposures. A close look on eGFR is necessary while administrating Remdesivir, especially in patients with known renal impairment and discontinuation is required if eGFR falls to ≥50% from baseline. Although the parent compound Remdesivir has only minor renal excretion, but since urine is found to have 49% of its metabolite GS-441524, impaired renal impairment may theoretically increase plasma exposure to this metabolite. Nevertheless, given the benefit-risk ratio in patients with COVID-19, no dose modification is currently recommended in patients with mild and moderate renal impairment, although it is contraindicated in patients with severe renal impairment (eGFR <30 ml/min). It should be noted that no specific studies have been conducted with Remdesivir in patients with renal impairment.[20]

**Remdesivir effects & Hepatic Safety**

A substantial proportion of patients with acute EVD who received Remdesivir in PALM trial had moderate to severe liver and renal dysfunction, however no additional renal or hepatic function deterioration attributed to Remdesivir was noted. Remdesivir is believed to be rapidly cleaved by hydrolases and thus the effect of hepatic impairment on Remdesivir plasma levels is likely low. Given the benefit-risk ratio, no dose modification is currently recommended in patients with COVID-19, though it is contraindicated in patients with alanine transferase (ALT) > 5-times upper limit of normal or severe hepatic dysfunction. There are no specific studies conducted with Remdesivir in patients with hepatic dysfunction.[20]

**Remdesivir effects on pregnant, lactating & pediatric group**

In non-clinical reproductive toxicity studies, no adverse effect on embryo-fetal development in pregnant animal or male infertility were observed with Remdesivir, however at a systematically toxic dose an embryonic toxicity was seen. Remdesivir has not been studied in pregnancy, lactating women and pediatric population. Interestingly, in PALM study of acute EVD, 3% of pregnant women and 26% of children received Remdesivir, without any notable side effects.[20]

**Possible drug interactions of Remdesivir**

The potential of induction of CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) following exposure of human hepatocytes to Remdesivir has been seen (the reason for transient increase in liver enzymes), however, no data available currently for the drug-drug interaction.[20]

**Remdesivir Dosing Information**

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized solid that is to be reconstituted with 19 mL of sterile water for injection and diluted into 0.9% saline prior to IV administration. Remdesivir for injection, 100 mg, vials should be stored below 30 °C until time of use. Remdesivir injection, 5 mg/mL vials should be stored at refrigerated temperatures (2 °C–8 °C) until time of use. Following dilution with 0.9% saline, the solution can be stored for up to 4 h at room temperature (20 °C–25 °C) or 24 h at refrigerated temperatures (2 °C–8 °C).

**Method**

We systematically searched the PubMed, ClinicalTrial.org & MedRxiv database up till June,2020 using the several specific key words “Remdesivir” & “COVID-19” etc., and retrieved all the articles published in English language that reported pharmacology and any clinical outcome with the Remdesivir in patients with COVID-19. In addition, we also searched the ClinicalTrial.Org for the ongoing trials with remdesivir in COVID-19. We compiled all the data chronologically and narrated the past, present and future of remdesivir in the context of COVID-19.

## DISCUSSION

Remdesivir is an anti-viral agent that has shown a significant inhibitory effect *in vitro* and *in vivo* studies against SARS-CoV-2 and appears to be ahead to other repurposed drug being tried for the treatment of COVID-19. Since viral shedding in COVID-19 and intensive care admission tends to be more protracted, even late administration could be useful. In this regard, FDA has currently authorized Remdesivir only in severe COVID-19 in both adults and children. With regards to the outcome of Remdesivir in COVID-19, while one RCT found no benefit, preliminary results from other RCT have shown some benefit. Therefore, the overall outcome with Remdesivir is perhaps in a stage of clinical equipoise at this point of time. The safety profile of Remdesivir in COVID-19 is incompletely characterized in COVID-19. While the safety data from the previous use during acute EVD suggest no specific alarm, COVID-19 differs profoundly in its clinical characteristics from EVD. Nevertheless, hitherto no safety findings allow Remdesivir to be used in COVID-19, under a proper pharmacovigilance. Special attention should be given for disproportionate rise in ALT or decrease in GFR, during the treatment with Remdesivir. The current contraindication of starting Remdesivir with

concomitant vasopressors use is primarily based on this being an indication of end organ failure. In contrast, once a patient initiates treatment with Remdesivir, subsequent use of vasopressors is not a reason for discontinuation of Remdesivir. Moreover, the use of vasopressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed.

**Clinical Trial Results of Remdesivir in COVID-19 Patients (Table 1)**

**Table 1:** Clinical Trial Studies on Remdesivir [19]

| Study Number | Study Title | Study Status |
|---|---|---|
| GS-US-540-5773 (SIMPLE) | A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19 | Ongoing |
| GS-US-540-5821 | Expanded Access Treatment Protocol: Remdesivir (RDV; GS5734) for the Treatment of SARS-CoV2 (CoV) Infection | Planned |
| CO-US-540-5764 | A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Mild and Moderate 2019-nCoV Respiratory Disease | Ongoing |
| CO-US-540-5824 (WHO) | Multi-center, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults | Planned |
| NCT04280705 | Adaptive COVID-19 Treatment Trial (ACTT) | Recruiting |
| ISRCTN83971151, NCT04330690 | Public Health Emergency SOLIDARITY Trial of Treatments for COVID- 19 Infection in Hospitalized Patients | Available |
| NCT04321616, 2020-000982-18 | The Efficacy of Different Antiviral Drugs in (Severe Acute Respiratory Syndrome-Corona Virus-2) SARS-CoV-2 | Not yet recruiting |
| NCT04323761 | Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV-2 (CoV) Infection | Available |

## CONCLUSION

Strategic reservation for antiviral drugs will avoid the difficulty of medicine unavailable when an outbreak comes again. Remdesivir situational and political superiority, as well as its previous research results and application effects make it imperative to carry out the clinical trials focusing on the SARS-CoV-2. Given that SARS-CoV-2 is an RNA virus that is easy to mutate, the rapid starting of clinical trials is undoubtedly a right choice to prevent the resistance mutation due to blind medication. It has been covered in the World Health Organization (WHO) Director-General's opening remarks at the media briefing on COVID-19 on 20 February 2020 that the two clinical trials on Remdesivir of therapeutics prioritized by the WHO R&D Blueprint are expected preliminary results in three weeks. On February 24, the WHO cast a vote of confidence for Gilead Sciences' experimental antiviral drug, Remdesivir, indicating that Remdesivir has great potential and may be the best candidate for the treatment of COVID-19. Whatever the progress of the clinical trials is, we are expecting that the clinical trials of Remdesivir, a starring drug, would bring outstanding breakthroughs to the treatment of COVID-19, or more promisingly, other virus infection in the future.

**Acknowledgment:** We acknowledge Teerthanker Mahaveer University for providing resources & valuable support.

## REFERENCES

1. Huang C, Wang YJ, Cao B, Xingwang L, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet. 395(10223), 2020, 497-506, DOI: 10.1016/S0140-6736(20)30183-5, PMID: 31986264.
2. WHO. (2020, Jan 12). Novel coronavirus – China. http://www.who.int/csr/don/12-january-2020novel-coronavirus-china/en/.
3. Lai CC, Liu YH, Wang CY, Hsueh PR, Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths, Journal of Microbial, Immunology and Infection, 4(20), 2020, 30040-2, DOI: 10.1016/j.jmii.2020.02.012, PMID: 32173241.
4. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic, Diabetes and Metabolism Syndrome Clinical Research and Reviews, 14(3), 2020, 211-2. DOI: 10.1016/j.dsx.2020.03.002, PMID: 32172175.
5. Del RC, Malani PN, COVID-19—New Insights on a Rapidly Changing Epidemic, Journal of the American Medical Association, 323(14), 2020, 1339–1340, DOI: 10.1001/jama.2020.3072, PMID: 32108857.

6. World Health Organization. (2020), Coronavirus Disease 2019 (COVID- 19) Situation Report – 64, https://www.who.int/docs/default-source/coronavirus/situation-reports/20200324-sitrep-64-covid-19.pdf?sfvrsn=703b2c40_2.
7. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 14, 2020, 241-246, DOI: 10.1016/j.dsx.2020.03.011.
8. Baud D, Qi X, Saines NK, Musso D, Pomar L, Favre G, Real estimates of mortality following COVID-19 infection, Lancet Infectious Diseases, 20(7), 2020, 773, DOI: 10.1016/S1473-3099(20)30195-X, PMID: 32171390.
9. Shah S, Das S, Jain A, Misra DP, Negi VS, A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19), International Journal of Rheumatoid Diseases, 23(5), 2020, 1–7. DOI: 10.1111/1756-185X.13842, PMID: 32281213.
10. The Lancet, COVID-19: protecting health-care workers, Lancet, 395, 2020, 922, DOI: 10.1016/S0140-6736(20)30644-9, PMID: 32199474
11. Bai Y, Yao L, Wei T, Presumed Asymptomatic Carrier Transmission of COVID-19, Journal of the American Medical Association, 323(14), 2020, 1406–1407, DOI: 10.1001/jama.2020.2565, PMID: 32083643.
12. Gao J, Tian Z, Yang X, Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience Trends, 14(1), 2020, 72-73, DOI: 10.5582/bst.2020.01047, PMID: 32074550.
13. Ministry of Health and Family Welfare Government of India. (2020), www.mohfw.gov.in
14. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, Drug treatment options for the 2019-new coronavirus (2019-nCoV), Bioscience Trends, 14, 2020, 69-71, DOI: 10.5582/bst.2020.01020, PMID: 31996494.
15. Grein J, Ohmagari N, Shin D, Timothy F, Compassionate Use of Remdesivir for Patients with Severe Covid-19, The New England Journal of Medicine, 382(24), 2020, 2327-2336, DOI: 10.1056/NEJMoa2007016, PMID: 32275812.
16. Hillaker E, Belfer JJ, Bondici A, Murad H, Dumkow LE, Delayed Initiation of Remdesivir in a COVID-19 Positive Patient, Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(6), 2020, 592-598, DOI: 10.1002/phar.2403, PMID: 32281114.
17. Al-Tawfiq JA, Al-Homoud AH, Memish ZA, Remdesivir as a possible therapeutic option for the COVID-19, Travel Medicine and Infectious Disease , 34, 2020, 101615, DOI: 10.1016/j.tmaid.2020.101615, PMID: 32145386.
18. Wang Y, Zhang D, Du G, Remdesivir in adults with severe COVID-19: A randomized, double-blind, placebo-controlled, multicenter trial, Lancet, 395, 2020, 1569-1578, DOI: 10.1016/S0140-6736(20)31022-9, PMID: 32423584.
19. Gilead Creating Possible. (2020, April 29th). Gilead announces results from phase 3 trial of investigational antiviral Remdesivir in patients with severe COVID-19, https://www.gilead.com/news–and–press/press–room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-inpatients–with – severe-covid-19.
20. Gilead Creating Possible, (2020, June 25th), Summary on compassionate use Remdesivir Gilead, https://www.ema.europa.Eu/en/documents/other/summary-compassionate-use– Remdesivir-gilead.en.pdf


**Source of Support:** None declared.

**Conflict of Interest:** None declared.