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A Review on in vitro and Clinical Studies Published on Remdesivir After COVID-19 Outbreak

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Abstract

It has been almost seven months since the outbreak of the novel SARS-coV-2 virus that has severely impacted global health. Researchers across the world are working towards developing a therapeutic strategy against the COVID-19 pandemic. But the development of either a development or prevention strategy against COVID-19 will take several months to a few years. To fasten this development process repurposing of drugs has also been considered as a possible treatment strategy. Remdesivir a nucleotide analog that exhibits broad-spectrum antiviral activity against RNA virus-like COVID-19. This drug has demonstrated favorable findings in a few studies which include molecular docking model, pharmacodynamic as well as clinical studies. Although not fully established, but these results collectively suggest that remdesivir may be effective to destroy the SARS-CoV-2 virus by binding to RNA dependent-RNA polymerase (RdRp). It can be used as one of the potential treatment strategies against COVID-19 after more in-depth safety and efficacy study.

Keywords: Remdesivir, SARS-coV-2, COVID-19, Repurpose, Clinical Trials.

Introduction

In December 2019, a cluster of cases of pneumonia with unknown causes in the Wuhan, Hubei sea market, China was reported to the World Health Organization (WHO) [1]. The patients exhibited symptoms associated with a variable degree of respiratory syndrome such as mild upper respiratory illness to severe interstitial pneumonia [2,3]. These cases were related to the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) infections reported in February 2003 in Asia and Saudi Arabia in September 2012 respectively [4]. On February 11, 2020, WHO named this new member of respiratory distress causing virus as SARS COV-2, and the disease was termed as novel coronavirus disease or in short "COVID". Several other cases in China, Japan, South Korea, and the USA of similar nature were also reported. Later, on March 11, 2020, the WHO declared the outbreak as a pandemic [5].

COVID-19 is an infectious disease caused by a coronavirus that belongs to the family Coronaviridae and the order Nidovirales. It consists of a positive-sense, single-stranded RNA genome that is enveloped with glycoprotein's spike which appears as crown under an electron microscope [3]. The members of this viral family are responsible for the common cold to severe acute respiratory syndrome coronavirus (SARS). The causative pathogen for the disease COVID-19 is SARS-coV-2, severe acute respiratory syndrome coronavirus 2 [6].

After studying the genomic similarity the reports suggests that the novel coronavirus had a similarity to bat virus (Betacoronavirus genus)which links its emergence from bat population [7,8]. Thereafter, the transmission of the zoonotic virus occurred to (new) human host by close contact or consumption of some infected animals [9]. Further, human-to-human transmission continued via droplets or direct contact by coughing or sneezing of the infected person eventually leading to a global outbreak of the year 2020 as shown in Figure 1 [10].

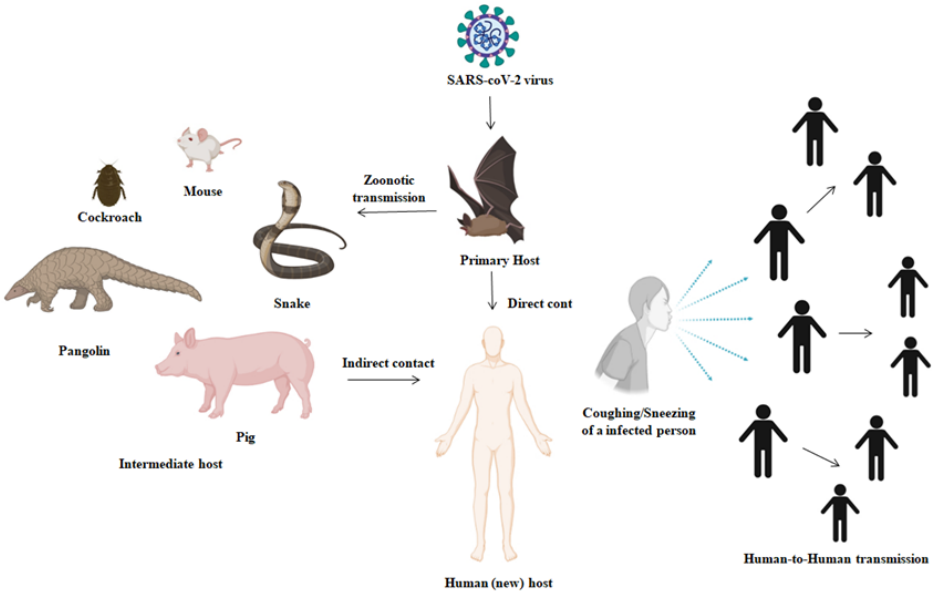

Figure 1:Transmission of the virus from the primary host to a new host [11].

Currently, there is no approved clinical treatment against the new virus. A significant amount of preclinical research was done to search for the treatment for related SARS and MERS viruses [12]. As this viral outbreak didn't persist for a longer time, no vaccine or treatments were developed. As the world is facing the pandemic, researchers around the globe are working towards the main goal of developing either treatment strategy or prevention against COVID-19. Developing mass prophylactic measures or the invention of a vaccine and its clinical establishment may take a few years. Similarly, the development of a new molecule and its establishment as a drug takes 10-15 years. Therefore, clinicians and researchers are considering treatment strategies like drug repurposing [13]. Repurposing of an older established drug for another purpose can fasten the process of developing a treatment strategy against COVID-19. Drugs like azithromycin, hydroxychloroquine ritonavir, ruxolitinib, and camostat are considered as potential candidates for drug repurposing in COVID-19. Out of these Remdesivir, an antiviral drug has been recognized as a promising molecule against COVID-19 [14]. It has shown highly effective in controlling coronavirus in-vitro studies in cultured cells, mice, and nonhuman primate (NHP) models [15]. All over the globe, few clinical trials are going on simultaneously to find out the safety and efficacy of remdesivir in COVID-19 infection. At the same time, few in vitro studies with notable findings are also published after the COVID-19 outbreak. This review summarizes some of the in-vitro studies and few on-going remdesivir clinical trials that were published in the early months of the year 2020, as a possible treatment against COVID-19.

Basic Information on Remdesivir

Remdesivir is an adenosine analog (figure 2). It was developed by Gilead Sciences, Unites States during anti-viral development against the Ebola virus in 2015 [15]. It exhibits broad-spectrum activity against the virus of the family filo, paramyxo, and corona with RNA as their genetic material [16].

2-ethyl butyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate

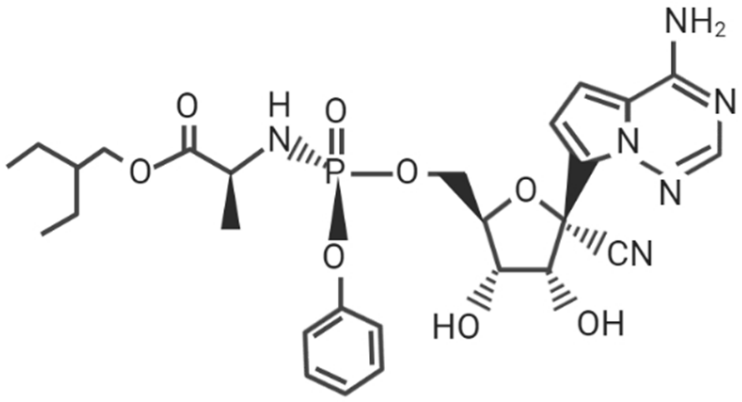

Figure 2: Structure of Remdesivir

SARS-CoV-2 enters the cell and binds to the S-protein of the ACE-2 receptor on the cell surface. After the virus enters the host it requires RNA-dependent RNA polymerase (RdRp) protein complex for replication [17]. Remdesivir functions at the post-entry stage of the virus. It is a prodrug that metabolizes into GS-441524 (active metabolite). This active metabolite competes with adenosine triphosphate (ATP) and incorporates itself into the nascent RNA chain. This incorporation of this substitute into the new strand leads to premature termination of viral RNA synthesis [18].

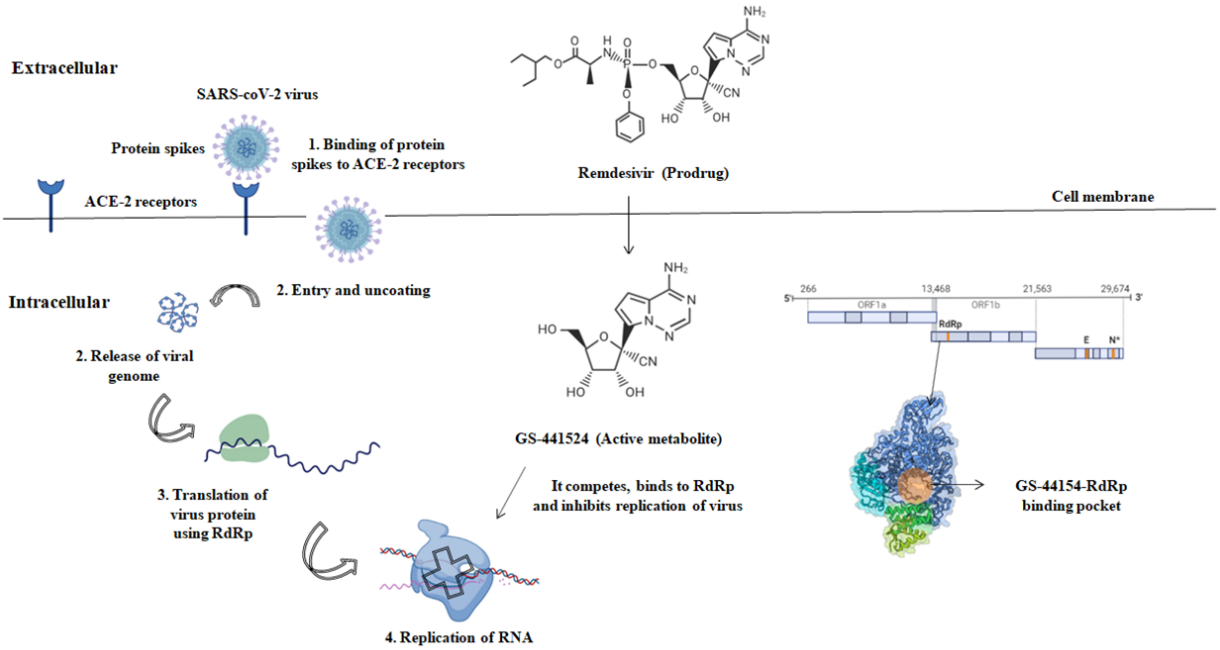

Figure 3: Mechanism of action of remdesivir against SARS-CoV-2 [17]

Molecular Docking Study

A molecular docking study entitled "Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV- 2 RNA dependent RNA polymerase (RdRp): A molecular docking" has been published in (March 25, 2020) (19). In that study Abdo, 2020 used RNA-dependent RNA polymerase (RdRp). The enzyme was targeted using different anti-polymerase drugs that are already approved as antiviral. The solved structures from the National Centre for Biotechnology Information (NCBI) protein data banks were used to build the SARS-CoV-2 RdRp Swiss model. The optimized SARS-coV-2 RDRP model was used at the molecular docking target. After the model validation test is conducted on several direct-acting antivirals (DAA) drugs. It also included 5 FDA-approved medications such as Galidesivir, Remdesivir, Tenofovir, Sofosbuvir, and Ribavirin used for the treatment of HIV, HEV, and the Ebola virus. A total of 24 compounds were tested against SARS-CoV-2, SARS HCoV, and HCV NS5B RdRps, where the four physiological nucleotides were GTP, UTP, CTP, and ATP. Currently, 13 compounds in clinical trials Uprifosbuvir, Setrobuvir, Balaprevir, MK0608, R7128, IDX-184, 2'C methylcytidine, BMS-986094, YAK, PSI-6130, PSI-6206, R1479, and Valopectibine were tested against HCV NS5B RdRp. The two negative controls, Cinnamaldehyde and Thymoquinone showed no affinity toward RdRp. All of the compounds in their active forms were optimized in physiological conditions. After docking, the structural examination was done using the protein-ligand interaction profiler (PLIP) webserver at the Technical University of Dresden. Drugs like Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir showed tight binding to its RdRp model which was considered as promising results with the possibility of inhibiting coronavirus too. Other compounds like IDX-184, Setrobuvir, and YAK also exhibited excellent binding which can be potential lead against the SARS-CoV-2 virus. It also suggested utilizing GTP can be a seed to obtain specific inhibitors against SARS-CoV-2 using a high-quality RdRp model. The overall study concluded that anti-RdRp drugs can be used to treat COVID-19 patients without toxicity measurements since these drugs are previously approved by FDA [19].

In Vitro Study

An in vitro experimental study entitled "Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-coV replication in vitro has reported on April 03, 2020, by Ka-Tim Choy [16]. The authors evaluated the effect of the in-vitro anti-viral effect of remdesivir, lopinavir, homoharringtonine, and emetine among other 16 compounds. These four drug candidates show inhibitory activities against the SARS-CoV-2 virus in Vero E6 cells. Remdesivir has shown to inhibit human coronavirus (SARS-CoV-2). The researchers fitted viral load in the logarithm scale (log10TCID50/ mL and log10viral RNA copies/mL) under the increasing concentration of remdesivir. Effective concentration (EC50) of remdesivir was determined at 23.15 µM. Two conserved residues F480 and V557 are mapped and were used for the experiments as reported previously to confer resistance to remdesivir in the SARS-CoV-2. Also to reduce the effective concentration of the individual compound, the combinational therapy was evaluated using the checkboard assay with 2-fold serial dilution with remdesivir (0–50 µM) and emetine (0–0.781 µM). It was observed that remdesivir and emetine showed synergism at 6.25 and 0.195 µM respectively. The studies suggested combination therapy can inhibit viral yield up to 64.9% in-vitro which can be further tested in-vivo. Further clinical benefits using this combination can be observed under the maximal therapeutic plasma concentration.

Pharmacodynamic Study in an Animal Model

A study was conducted to evaluate the clinical efficacy of

remdesivir against SARS-CoV-2 in the rhesus macaque model and published as "The clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2" on April 15, 2020. The efficacy was tested on two groups (treatment and control group) of six rhesus macaques 3 males and females each, weighed 3.6-5.7 kg. One group (treatment) of six animals was treated with 10 mg/kg remdesivir as a loading dose followed by 5 mg/kg maintenance dose. While the other (control) group animals were administered 2mg/kg as a loading dose and 1 mg/kg maintenance dose of vehicle solution (12% sulfobutyl ether-β-cyclodextrin in water and hydrochloric acid, pH 3.5). The dose administered was equivalent to a human dose used in clinical studies to treat COVID-19 patients. The dose was administered daily intravenously in the left or right cephalic or saphenous veins alternately. The animals were assessed daily for clinical signs using a standardized scoring sheet. The primary endpoint was 7 daily through 6 days post-inoculation (dpi). The anesthetized animals were examined for viral load, pulmonary infiltrates, and reduction in pulmonary pathology.

The results indicated that animals treated with remdesivir showed good efficiency against SARS-CoV-2 in comparison to animals administered with the vehicle. A significant reduction was observed in broncho-alveolar lavages indicating less viral load and reduced damage on lungs indicating the efficiency of remdesivir. The experiment concluded remdesivir had significant clinical efficacy in the rhesus macaque model against SARS-CoV-2.

Clinical Trial I

A clinical trial entitled "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial" has been conducted and published in "The Lancet journal" on April 29, 2020 (20). The study (NCT04257656) registered at ClinicalTrials.gov was conducted on 6 February 2020 to 12 March 2020 at ten hospitals in Hubei, China. It was a multicentre, randomised, placebo-controlled; the double-blind trial was conducted to assess the effectiveness and safety of intravenous remdesivir in adults. The target (eligible) populations were adult men and non-pregnant women (aged ≥18 years). The study inclusion criteria consisted of patients suffering from a severe COVID-19 infection which included (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, noninvasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation.

Initially, a total of 255 participants were screened, 14 did not meet the study inclusion criteria and then 4 withdrew. Eventually, the study was conducted on 237 on enrolled participants. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir or the same volume of placebo infusions for 10 days. After randomization, 158 participants received remdesivir and 79 placebos. The dose administered of remdesivir or placebo on day 1, 200 mg followed by 100 mg on days 2–10 in single daily infusions. The concomitant use of lopinavir-ritonavir, interferons, and corticosteroids was permitted during trial. The primary endpoint for clinical improvement was up to 28 days or death. Patients were assessed daily by a trained nurse to record safety on a six-category ordinal scale i.e. two levels from 1=discharged to 6= discharged alive/death. The study evaluated RNA quantitatively and qualitatively by collecting the upper respiratory tract specimen nasopharyngeal swab and lower respiratory tract fecal/anal swab specimen. The specimens were collected at days 1, 3, 5, 7, 10, 14, 21, and 28 as time-point for study evaluation. All the collected data were recorded into an electronic database, validated and evaluated statistically. It was found those patients with symptom duration of 10 days or less showed a faster time to clinical improvement than those receiving placebo. However, it had no statistical significance associated with a difference in time to clinical improvement. Adverse events were reported in 66%, 102 out of 155 remdesivir recipients v/s 50 (64%) of 78 placebo recipients. Administration of remdesivir was stopped early because of adverse events in 12%, 18 patients versus 5% in four patients. However, the numerical reduction in clinical requirement time in those treated earlier still requires confirmation in a larger group [20].

Clinical Trial II

In another clinical trial (Enlisted as NC04292899in Clinicaltrials.gov.in), Gilead Sciences the developer biopharmaceutical company of remdesivir conducted a "clinical trial to evaluate the safety and efficacy in two treatment groups evaluating at 5-day and 10-day. The report has been published in The New England Journal of Medicine on May 27(21) On April 29, 2020 [21]. The Phase-3 randomized, open-labeled conducted in 400 patients at multiple centers with severe COVID-19 participated in the study. The study inclusion criterion was patients with pneumonia, reduced oxygen levels, and no requirement of mechanical ventilation.

The study showed improvement in patients receiving a 10-day treatment course of remdesivir in comparison to those receiving a 5-day treatment course. Clinical improvement time in 50% of the patients was 10 days in a 5-day treatment course and 11 days in a 10-day treatment course respectively. It was observed that 50% of patients in both the treatment group were discharged from the hospital by 14-day. In a 5-day treatment course, 64.5% and in 10-day treatment 53.8% achieved clinical recovery. The overall mortality rate was 7%, clinical improvement observed in 61%, and patient discharging 61% on 14-day. No adverse effect of remdesivir was observed in either of the treatment group [22].

Conclusion

Recently, studies have demonstrated the therapeutic effects of remdesivir in in-vivo and in-vitro models. This has opened a new window for efficient usage of the repurposed antiviral drug for treating COVID-19. The reports have suggested that respiratory problems caused by SARS-CoV-2 can be treated with promising antiviral therapies. Remdesivir can be a viable treatment option based on the available recent reports. However, the adoption of remdesivir as a treatment option for the COVID-19 outbreak needs more clinical study to ensure its efficacy and safety.

Conflict of Interest

The authors declare no conflict of interest on the article.

References

1. Gralinski LE, Menachery VD (2020) Return of the coronavirus: 2019-nCoV. Viruses 12:1-8.
2. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E (2020) COVID-19, SARS and MERS: are they closely related? Clinical Microbiology and Infection 26:729-34.
3. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, Evaluation and Treatment Coronavirus (COVID-19) StatPearls.
4. National Institute of Allergy and Infectious Disease (2020) COVID-19, MERS & SARS.
5. World Health Organization (WHO) (2020) Rolling updates on coronavirus disease (COVID-19).
6. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, et al (2020) Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for

Treatment of COVID-19. ACS Central Science 6:672-683.

7. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R (2020) COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research 24:91-98.
8. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579:270-273.
9. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, (2020) Zoonotic origins of human coronaviruses. International journal of biological sciences 16:1686-1697.
10. Singhal T (2020) A Review of Coronavirus Disease-2019 (COVID-19). Indian Journal of Pediatrics 87:281-286.
11. Ko W, Rolain J, Lee N, Chen P, Huang C (2020) Arguments in favour of remdesivir for treating SARS-CoV-2 infections. International Journal of Antimicrobial Agents 55:1-3.
12. Li H, Liu SM, Yu XH, Tang SL TC (2020) Coronavirus disease 2019 (COVID-19): current status and future perspective. International journal of antimicrobial agents 55:1-6.
13. Li G, De Clercq E (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews Drug discovery 19:149-150.
14. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M (2020) The antiviral compound remdesivir potently inhibits RNAdependent RNA polymerase from Middle East respiratory syndrome coronavirus. Journal of Biological Chemistry 295:4773-4779.
15. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 30:269-271.
16. Choy KT, Wong AYL, Kaewpreedee P, Sia SF, Chen D, et al. (2020) Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Research 178:104786.
17. Cao Y chen, Deng Q xin, Dai S xue (2020) Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Medicine and Infectious Disease
18. Amirian ES, Levy JK (2020) Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. One Health 9:100128.
19. El AA (2020) Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS- CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study 253
20. Wang Y, Zhang D, Du G, Du R, Zhao J, et al. (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet 395:1569-1578.
21. Gilead (2020) Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. Gilead Sciences
22. Hendaus MA (2020) Remdesivir in the treatment of coronavirus disease 2019 (COVID-19): a simplified summary. Journal of Biomolecular Structure and Dynamics 0(0):1-6.