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A REVIEW ON THE ROLE OF REMDESIVIR FOR THE TREATMENT OF COVID 19

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ABSTRACT

Severe acute respiratory coronavirus-2 (SARS-CoV-2) is an RNA virus is responsible for the greatest public health challenges of our lifetime the coronavirus disease 2019 (COVID-19) pandemic. The term coronaviruses were given based on the morphology as spherical virions with a core shell and surface projections resembling a solar corona. Alpha-, beta-, gamma-and delta coronaviruses are the four subfamilies. The incubation period of five days 7 and a median incubation period of 3 days. The clinical signs of SARS-CoV-2-related disease COVID-19 which allowed case detection was pneumonia and gastrointestinal symptoms and asymptomatic infections, especially among young children. The search for effective therapies has become a worldwide priority because of the complicated postinfection sequelae and grave consequences. Several studies have showed that remdesivir an antiviral agent is useful in treatment of COVID 19. In United States through an emergency use authorization. Along with data obtained from clinical trials on the safety profile of remdesivir against Ebola virus and information obtained from in vitro studies and animal models support remdesivir as a promising agent against SARS-CoV-2. The main intention of this study is to produce a comprehensive review of the role, Pharmacology, mechanism of action, safety of remdesivir in treatment of COVID 19.

KEYWORDS: Antiviral, Remdesivir, Coronavirus, RNA Virus.

INTRODUCTION

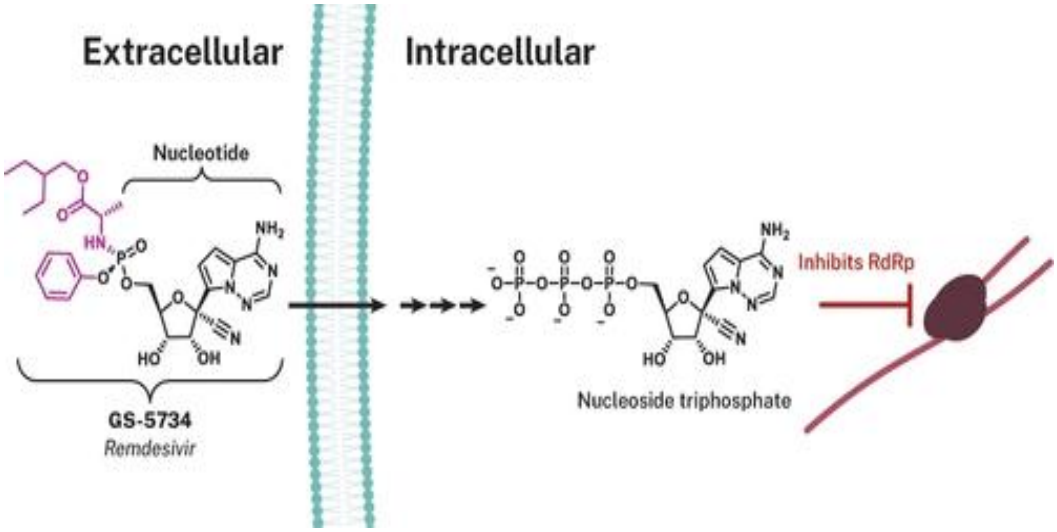
The outbreak of noval Coronavirus SARS – Co (coronavirus disease 2019; previously 2019-nCoV) occurred from Hubei province of China has non spread throughout the globe.[1] Coronaviruses are positive single-stranded large RNA viruses that are enveloped and it infect humans, but also a wide range of animals. Tyrell and Bynoe in 1966 was first to describe coronaviruses, who cultivated the viruses from patients with common colds.[2] The term coronaviruses were given based on the morphology as spherical virions with a core shell and surface projections resembling a solar corona. Alpha-, beta-, gamma-and delta coronaviruses are the four subfamilies Gamma and delta viruses originate from pigs and birds whereas alpha and beta viruses apparently originate from bats. The incubation period of five days 7 and a median incubation period of 3 days. The clinical signs of SARS-CoV-2-related disease COVID-19 which allowed case detection was pneumonia and gastrointestinal symptoms and asymptomatic infections, especially among young children.[3] The common symptoms include tiredness, fever, headache, sore throat and it can lead to serious symptoms like shortness of breath, loss movement and speech, chest pain. Various drugs are being used for the treatment and prevention of progression of diseases.[4,5]

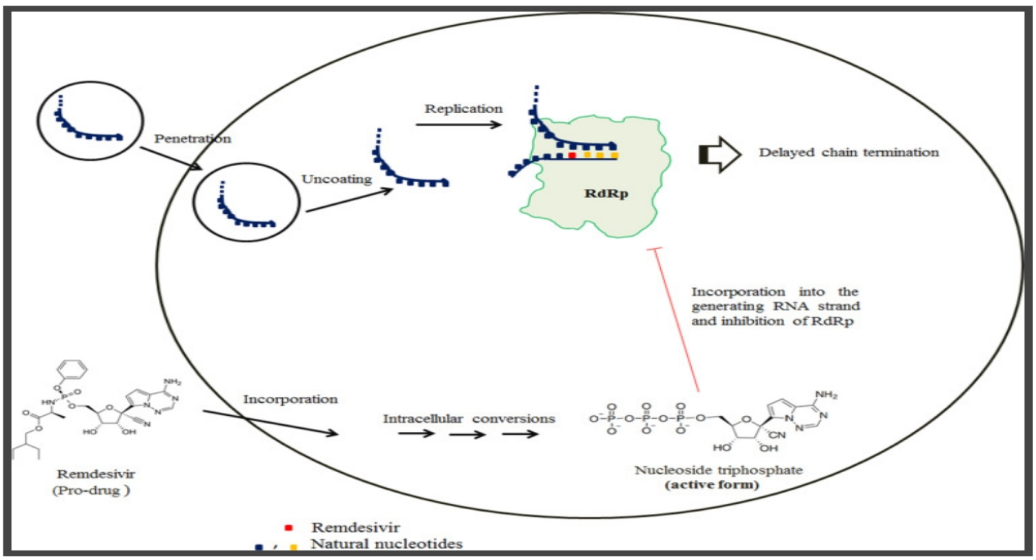
Various classes of drugs are used for the treatment in of COVID 19 particularly in patients with moderate to severe COVID-19 based on the pathological features and different clinical phases of COVID-19. The drugs used are inflammation inhibitors/antirheumatic drugs, antiviral agents, plasma, and hyperimmune immunoglobulins, low molecular weight heparins. Clinical researchers are using and testing a variety of possible treatments during emergency period of the COVID-19 outbreak.[6] A pro drug Remdesivir an antiviral agent is included in treatment of COVID 19. It inhibit viral RdRp4 and stopping viral replication by the entry and accumulation into cell by the active analogue of remdesivir.[7] “Proofreading “ enzyme exoribonuclease in coronaviruses corrects errors in the RNA sequence, potentially limiting the effects of analogues.[8,9] Remdesivir can evade this proofreading.[10]

Mechanism of action

Remdesivir is a prodrug, it is the phosphoramidate prodrug of an adenosine C-nucleoside. The prodrug may be efficiently metabolized to a nucleoside triphosphate as an active form by entrance into respiratory epithelial cells in the human body.[11,12] The active form can prevent the replication of several coronaviruses in the lung epithelial cells. The RNA-dependent RNA

polymerase (RdRp) is inhibited by nucleoside analog drug by competing with the usual counterpart adenosine triphosphate (ATP). The nucleoside analog causes a delayed stop in the viral replication process by incorporating into generating RNA strand.[12,13]





The incorporated nucleoside analog moves back as the enzyme incorporates one, two or three more nucleotides. Remdesivir blocks the enzyme while it reaches into the third position away from the enzyme's active site. It crashes into active site of the enzyme into the conserved serine (Ser) and inhibits the enzyme from moving one step forward to incorporate the next nucleotide.[14,15] The viral exoribonuclease that usually proofreads and corrects replication errors cannot work against the active form of remdesivir.

Clinical efficacy of remdesivir in COVID-19

Potential efficacy of remdesivir against coronaviruses is restricted to knowledge about in vitro studies and animal models, information related to COVID-19 is rapidly growing.[16] The patient of age 35 was hospitalized with COVID 19 in January 2020 and was treated with intravenous remdesivir after developing pneumonia in the USA.[17] The patient was administered with intravenous remdesivir for 7 days out of the 12 days of hospitalization the patient's condition was apparently improved on the eighth day and no adverse effects were reported.(h). Information about using remdesivir for COVID-19 can be obtained from studies on compassionate use of the drug before the clinical trials are completed.

Remdesivir was provided on a compassionate-use basis to patients with severe COVID-19 in 2020, in a published study in New England Journal of Medicine. The patients included in the study were confirmed SARS-CoV-2 infection and breathing oxygen support or receiving ambient air. The saturation level of patients were 94% or less. For 10 days the drugs were administered. The patients received 200 mg of the drug intravenously at the first day and 100 mg of remdesivir was daily used in the remaining 9 days. Out of 53 patients in the cohort study, clinical improvement was observed in 36 subjects (68%).[18,16,19,20]

The study conducted by Beigel et al which was a double-blind, randomized, placebo-controlled trial in patients with COVID-19 under intravenous remdesivir. Patients were divided into treatment and placebo groups receiving remdesivir for up to 10 days randomly. The time of recovery in placebo group was longer than patients who received remdesivir.[21]

The study conducted by Wang et al (2020) randomized, double-blind, placebo-controlled, multicenter trial in adult patients with COVID-19 at ten hospitals in China. The total number of patients involved were 237 and they were divided randomly into remdesivir and placebo groups. 158 patients were there in remdesivir group and 79 cases in placebo group. The results in the study showed that the remdesivir administration is not related to a significant change in the time of clinical improvement. However the recovery time of patients receiving remdesivir were shorter compared to those in placebo group.[22]

A randomized, open-label, phase 3 trial including hospitalized patients with COVID-19 conducted by Goldman et al (2020). Patients were divided to two groups one group receiving intravenous remdesivir for 5 days and another for 10 days. In patients not in need of mechanical ventilation but were in severe condition, there was not any significant difference

between the 5-day and 10-daythe degree of benefit cannot be ascertained. The degree of benefit cannot be ascertained due to the lack of placebo control.[23]

The results of in vitro and in vivo studies have demonstrated the efficacy of remdesivir against coronaviruses. Some evidence indicates that compassionate use of remdesivir may cause some clinical improvement in patients with COVID-19.[18]

The pharmacokinetics and pharmacodynamics of remdesivir

In the documentation published by the US Food and Drug Administration (FDA) the pharmacokinetics of remdesivir has been summarized. To license the emergency use of the remdesivir for management of suspected or laboratory-confirmed SARS-CoV-2 infection in adults and pediatric patients hospitalized with severe disease the FDA has issued an emergency use authorization (EUA).[24]

Remdesivir is administered via an intravenous injection (IV) over 30 to 120 minutes considering the EUA licensed by FDA. For both adult patients and pediatric patients the drug was given. A single loading dose of the drug (200 mg on day 1) followed by once-daily maintenance doses (100 mg from day 2) for adults and the dosage of the product should be adjusted for body weight in pediatrics patients. For patients not requiring invasive mechanical ventilation and/or ECMO and patients requiring invasive mechanical ventilation and/or ECMO, treatment courses are 10 days and 5 days, respectively. Administration of remdesivir may be continued for up to 5 additional days for a total treatment course of up to 10 days if clinical improvement is not seen in the patients who do not need invasive mechanical ventilation and/or ECMO.[25]

From in vitro studies and animal models the efficacy of remdesivir against SARS-CoV-2 and associated coronaviruses can be deduced. Prophylaxis and early treatment in a mouse model with SARS-CoV infection using remdesivir led to a decrease of the viral load in the lungs and improvement of the respiratory function (r). Wang et al investigated efficacy of remdesivir against SARS-CoV-2 in infected Vero E6 cells. The results from this investigation showed that the IC50 and IC90 values of remdesivir against SARS-CoV-2 were 770 nM and 1760 nM, respectively (cytotoxic concentration >100 mM). The study suggested that remdesivir as a highly effective agent against SARS-CoV-2 infection in vitro.[26]

Along with data obtained from clinical trials on the safety profile of remdesivir against Ebola virus and information obtained from in vitro studies and animal models[27] support remdesivir as a promising agent against SARS-CoV-2.[28,10]

Safety of remdesivir in COVID-19

There is nausea, vomiting and diarrhoea, including any grade, were numerically higher in the 10-days arm of remdesivir compared with the control but not significant with absolute difference of 4%. In the control, the elevation of ALT and AST, and the decreased creatinine clearance (Grade 3 or 4) were also numerically higher by absolute 1%, 2% and 1%, respectively. Because of significant heterogeneity ($p = 0.05$) detected in AST analysis, the random-effect model was used and showed RD = −0.02 and 95% CI = −0.04 to 0.01. Serious adverse effects were significantly lower in 10-days remdesivir arm compared with the control with absolute difference = 6%.[29]

Risk of remdesivir

As remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases remdesivir is considered to have low potential for mitochondrial toxicity. Other nucleotide/nucleoside antivirals (i.e., tenofovir) can lead to mitochondrial injury in renal tubular epithelial cells but kidney toxicity occurs after prolonged exposure. There is very rare chance for the toxicity to occur within a 5- or 10-day therapy course. Toxicology studies in rhesus monkeys showed kidney injury at doses of 5, 10, and 20 mg/kg for 7 days, considerably higher than the EUA dose. An increased risk of renal adverse events in patients randomized to receive remdesivir was not demonstrated in datas from single randomized, controlled trial in COVID-19. When remdesivir was used in a clinical trial for Ebola significant renal adverse events were not reported.

Infusion-related reactions have also been reported. In COVID-19–infected patients and healthy volunteers receiving remdesivir transaminase elevations have been reported. Liver function tests must be monitored daily, under the EUA and remdesivir is discontinued in patients with alanine aminotransferase more than five times the upper limit of normal. Reaction related to infusion have also been reported.[30]

CONCLUSION

Remdesivir is an antiviral agents which is a nucleotide analog prodrug that inhibits SARS-CoV-2 RdRp. It has antiviral activities against SARS-CoV-2 have been shown in both in

vitro and in vivo studies. Several countries uses remdesivir as an emergency drug for patients with COVID-19, and some patients showed improved clinical outcomes. To confirm the efficacy of remdesivir in treating patients with COVID-19 large-scale clinical trials should be conducted.

REFERENCES

1. Thirumalaisamy P Velavan, Christian G Meyer, The COVID-19 epidemic, The COVID 19 epidemic, Tropical medicine & international health, 2020; 25(3): 278.
2. Tyrrell and Bynoe ML, cultivation of viruses from a high proportion of patients with cold, Lancet, 1966; 1: 76-77.
3. Chan JF, Yuan S, Kok KH et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet, 2020; S0140-6736(20): 30154-9. 10.1016/S0140-6736(20)30154-9
4. Li Q, Guan X, Wu P et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020. 10.1056/NEJMoa2001316
5. Guan W, Ni Z, Yu H, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv preprint posted online on Feb, 2020; 9.
6. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem, 2020; 295: 4773-9.
7. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio, 2018; 9: e00221-18. Doi:10.1128/mBio.00221-18 pmid:29511076
8. Pruijssers AJ, Denison MR. Nucleoside analogues for the treatment of coronavirus infections. Curr Opin Virol, 2019; 35: 57-62. Doi:10.1016/j.coviro.2019.04.002 pmid:31125806
9. Robin E Ferner, Jeffrey K Aronson et al. Remdesivir in covid-19 , BMJ 2020;369:m1610
10. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature, 2016; 531: 381-5. Doi:10.1038/nature17180 pmid:26934220
11. Siegel D, Hui HC, Doerffler E, et al. Discovery and synthesis of a phosphoramidate prodrug of a Pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem, 2017; 60(5): 1648–1661.

12. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature, 2016; 531(7594): 381–385. Doi:10.1038/nature17180
13. Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses, 2019; 11(4): 326. Doi:10.3390/v11040326
14. Liu W, Morse JS, Lalonde T, Xu S. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. Chembiochem, 2020; 21(5): 730–738. Doi:10.1002/cbic.202000047
15. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio, 2018; 9(2): e00221–18. Doi:10.1128/mBio.00221-18
16. Amirian ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. One Health, 2020; 9: 100128. Doi:10.1016/j.onehlt.2020.100128
17. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med, 2020; 382(10): 929–936. Doi:10.1056/NEJMoa2001191
18. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med, 2020; 382(24): 2327–2336. Doi:10.1056/NEJMoa2007016
19. Kujawski SA, Wong KK, Collins JP, et al. First 12 Patients with Coronavirus Disease 2019 (COVID-19) in the United States. medRxiv, 2020.
20. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis, 2020; 20(6): 697–706. Doi:10.1016/S1473-3099(20)30200-0
21. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med, 2020. Doi:10.1056/NEJMoa2007764
22. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a Randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2020; 395(10236): 1569–1578. Doi:10.1016/S0140-6736(20)31022-9
23. Goldman JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med, 2020. Doi:10.1056/NEJMoa2015301

24. Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci, 2020; 6: 672–683.
25. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med, 2017; 9(396): eaal3653. Doi:10.1126/scitranslmed.aal3653
26. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res, 2020; 30(3): 269–271. Doi:10.1038/s41422-020-0282-0
27. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med, 2019; 381(24): 2293–2303. Doi:10.1056/NEJMoa1910993
28. De Wit E, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A, 2020; 117(12): 6771–6776. Doi:10.1073/pnas.1922083117
29. Hozaifa Khalil Elsawah, Mohamed Ahmed Elsokary, Mahmoud Samy Abdallah, Ahmed Hanei ElShafie; Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis; Reviews in medical virology, 2020; e2187.
30. Meagan L Adamsick, Ronak G Gandhi e.tal, Remdesivir in patients with acute or chronic kidney disease and COVID-19, Journal of the American Society of Nephrology, 2020; 31(7): 1384-1386.