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A review on Remdesivir (GS-5734) for the treatment of Covid-19

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ABSTRACT

The COVID-19 has caused a lot of fear and unease among people all around the globe. This disease is caused by the virus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Since new viruses are emerging from animal reservoirs causing diseases in humans with increasing mortality rate there is an urgent need to find an antiviral drug with a broad spectrum activity. Hence, this review article discusses about the antiviral drug remdesivir which has shown a broad spectrum activity. Remdesivir is currently approved by the FDA for the treatment of patients suffering from severe Covid-19. The scope of this review is to discuss the risks and benefits of using the drug Remdesivir, whether the treatment with it reduces mortality, whether it can reduce the time of hospitalized patients, the possible adverse effects and whether it can be used as a prophylactic agent for healthcare professionals concerned with screening and management of Covid 19 positive patients and susceptible individuals who have a high risk of developing Covid-19 will be discussed. Since this is the first and only drug that has been approved by FDA, Remdesivir should be used in patients with Covid 19 with caution owning the side effects and limited data available on it. More research should be conducted to find another drug or vaccine which would be more beneficial for patients with Covid19

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INTRODUCTION

The Coronaviruses are a group of viruses which have positive-sense single-stranded RNA virus with a nucleocapsid of helical symmetry, and they are enveloped. Three (MERS, SARS, SARS-CoV-2) among the coronaviruses have produced diseases in human beings in the past two decades which have been potentially deadly. The ongoing pandemic is caused by SARS-CoV-2.

The outbreak of Covid-19 initially began in Wuhan province in China during December 2019 and has since then spread all around the globe. So far (November 2^{nd}, 2020), the confirmed cases worldwide is 46 million, the number of people recovered is 31 million and a number of people who have lost their lives is 1.2 million. According to current evidence, the virus is transmitted by respiratory droplets and having close contact from who-so ever is inhabiting the virus. It has been also found that feces are positive for SARS-CoV2 nucleic acid, suggesting that the oral route may also be a potential route. Therefore the disease can be spread by those who have symptoms and also by those who have no symptoms at all. Symptoms start to appear from the 5th to 14th day after exposure. Hence, it is recommended to isolate for 14 days if you have been

exposed to the virus or have the clinical symptoms. The clinical symptoms of the symptomatic patient can look like the common flu. A greater number of people experience dry cough, fever, fatigue and dyspnea. While a lesser number of them experience diarrhea, headache, productive cough (Huang *et al.*, 2020; Chen *et al.*, 2020; Wang *et al.*, 2020a). While more than half of the people recover within weeks of acquiring the coronavirus, there are a few who develop severe Covid-19 requiring hospitalization. The SARS-CoV-2 seems to attack the type II pneumocytes in lower bronchi by binding the receptor-binding domain of S(spike) protein to a virus to ACE2 receptors on the cell surface of host cells (Contini *et al.*, 2020). These ACE2 receptors seem to be higher in GIT, kidneys and testes than in lungs suggesting that these organs can also be a target of the virus causing symptoms other than respiratory.

The laboratory findings in the patients affected by Covid-19 include high CRP, lymphocytopenia, neutrophilia, leukocytosis (Wu *et al.*, 2019). But these are not specific to Covid-19 disease. Since there has been no specific treatment for it various measures to prevent the spread of infection can be followed. To limit the spread of infection, frequent hand washing, maintaining physical distance from others, quarantine, wearing a mask should be done.

Since nations are gripped with fear and panic not only due the fear of contracting the disease and dying but also the economic downfalls, there is a need to explore all possible ways to find a treatment for this disease. With current research and clinical evidence, Remdesivir the only drug made available for the treatment of Covid-19. Previously, only supportive treatments were given. In this review article, the antiviral drug-Remdesivir will be discussed.

The drug Remdesivir was developed by Gilead Sciences and is said to have broad-spectrum antiviral effects. On the 11^{th} of May 2020, FDA had approved Remdesivir for Emergency Use Authorization so that healthcare providers could use it to treat patients who had severe Covid-19. Severe Covid19 is defined has those patients with SpO2 <95% on room air or requiring supplemental oxygen or mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) or heart-lung bypass machine. In October 22, 2020, FDA approved its use in patients above 12 years old with a weight of at least 40 kilograms for treatment of Covid 19 requiring hospitalization.

MATERIALS AND METHODS

A systematic search was conducted in PubMed, New England Journal of Medicine, The Lancet, JAMA, Google Scholar.

The main description part of the article is divided into,

1. Introduction, Mechanism of action, pharmacodynamics, pharm kinetics
2. Benefits of using Remdesivir
3. Adverse effects of using the drugs
4. Whether it could be used has prophylaxis for health care professionals and others who have a high risk to develop Covid-19.

Introduction, Mechanism of action, pharmacodynamics, pharmacokinetics

Remdesivir or GS-5734, an investigational broad-spectrum anti-viral drug was developed more than a decade ago. In 2009 Remdesivir was researched has a potential treatment for Hepatitis C and Respiratory Syncytial Virus.

Antiviral profiling of remdesivir done in 2013 and early 2014 led to a suggestion that it could have broad-spectrum antiviral activity. In 2014, it was used for the Ebola outbreak in West Africa in 2014-2016 and again in 2018 outbreak. It was shown to be effective in rhesus macaques infected with Ebola virus (Warren *et al.*, 2016). Although it was found effective in animal models, it did not prove to be effective in a trial conducted in the Democratic Republic of Congo (Mulangu *et al.*, 2019).

The broad-spectrum activity of remdesivir has been shown against filoviruses, paramyxovirus, pneumoviruses (Lo *et al.*, 2017). Studies using animal models showed that remdesivir was effective against coronaviruses (Brown *et al.*, 2019), including MERS and SARS. In an vitro study which used primary human lung epithelial cell cultures, it is found to be effective against human coronaviruses and also bat coronavirus (Sheahan *et al.*, 2017). It was also found effective in Vero E6 cells with 50% effective concentration, The concentration of remdesivir was reduced when it was combined with another antiviral emetine in vitro (Wang at al,2020) (Choy *et al.*, 2020). Despite these positive preclinical data, it could not be developed clinically due to the lack of potential study participants.

Mechanism of action

It acts by inhibiting of viral RNA dependent RNA polymerase enzyme specifically nsp7. Remdesivir is a phosphoaramidate prodrug of 1'-cyano-substituted nucleotide analogue. The active form of remdesivir is the triphosphate form of Remdesivir(RDV-TP) is used has a substrate for viral dependent RNA polymerase. RDV-TP resembles the adenosine

triphosphate (ATP), and it competes with nucleotide during viral RNA synthesis. The incorporation of RDV-TP in the viral RNA it results in the termination of new RNA synthesis. The coronavirus has a proofreading process that can remove unwanted nucleotides, which lead to the development of resistance against remdesivir. But remdesivir seems to surpass this action and has a result there has been no resistance developed against remdesivir (Tchesnokov *et al.*, 2019).

Pharmacokinetics and Pharmacodynamics

Remdesivir a prodrug of nucleoside monophosphate. It cannot be given oral has it will result in the conversion of the prodrug to nucleoside monophosphate in the GI tract. This will result in poor absorption due to the change in the phosphate group. To avoid hepatic first-pass metabolism and due to low bioavailability it is given in intravenous form When administered in IV form it is distributed into the blood cells and tissues by passive diffusion and results in a transformation of the prodrug to nucleoside monophosphate and ultimately to the active metabolite nucleoside triphosphate intracellular. Remdesivir is widely distributed in most tissues which include kidney, salivary glands, liver, prostate gland. It does not cross the blood-brain barrier. Remdesivir and its active metabolites and primarily excreted renal (74%) and rest in feces (18%). Its metabolism is mediated by hydrolases. The plasma half-life of remdesivir is short (0.5-1 hour), while that of the active metabolite is long (20-25 hours). Suggestions to use a combination of IV and pulmonary administration (Sun, 2020) or just aerosolized (Contini *et al.*, 2020) suggests additional benefits against Covid 19.

RESULTS AND DISCUSSION

Benefits of using remdesivir

Severe Covid 19

A clinical trial conducted by (Wang *et al.*, 2020b) in China showed that remdesivir was not associated with any significant clinical benefits in adults with severe covid-19. Although not statistically significant, there was a reduction in the time to clinical improvement in the patients treated with remdisivir compared to those receiving placebo. But this trial had limitations of having not completed enrollment due to control of infection and small sample size.

National Institute for Allergy and Infectious Diseases (NIAID) conducted a clinical trial Adaptive Covid-19 Treatment Trial (ACTT-1). This was a double-blind, randomized, placebo-controlled trial where intravenous remdesivir was given to adult patients with severe Covid-19. Remdesivir was given IV 200mg on day 1 followed by 100mg/d for 10 days or until discharge or death. The preliminary report of the trial showed that a 10 days course of Remdesivir shortened the time to recovery 11 days compared to those who got placebo where the time to recovery was 15 days. However, the mortality rate remained the same in both groups suggesting that although the time to recovery is reduced, the prognosis of the both the groups remain the same. The final report of the trial in October 2020 also confirmed the same. It also suggested the use of dexamethasone along with it. Also, it was shown that there was fewer days of subsequent oxygen use for patients requiring oxygen at enrollment and shortened duration of ECMO or mechanical ventilation for those requiring these at enrollment. NIAID is conducting an ACTT-2 and ACTT-3 with remdesivir. ACTT-2 will evaluate the safety and efficacy of remdesivir in combination with the anti-inflammatory drug a Janus Kinase inhibitor- baricitinib compared to remdesivir alone and a ACTT-3 combining interferon beta 1a with remdesivir (Beigel *et al.*, 2020).

Gilead Sciences conducted the SIMPLE trial to check the safety and efficacy of two dosing durations – 5 days and 10 days – of remdesivir in adults patients diagnosed with severe COVID-19 The final result was the patient's clinical status on day 14. The clinical status was worse in 10 days group than 5 days group. The discharge rates were better in the 5 days group, and the mortality rate was also less. In this trial, there was no significant difference in 5 days treatment course or 10 days of treatment course patients with severe covid-19 who did not require mechanical ventilation. However, since no placebo was used in this trial, and it was open based the amount of benefit cannot be estimated exactly (Goldman *et al.*, 2020).

Moderate Covid 19

A randomized, open-label trial of hospitalized patients with moderate Covid19 was done to determine the efficacy of remdesivir for 5 or 10 days compared to standard care by assessing the clinical status of the patients on the 11^{th} day. Here, moderate Covid 19 pneumonia patients referred to patients having pulmonary infiltrates and SpO2>94%. These patients were divided randomly on 1:1:1 ratio to receive remdeivir for 10 day or to receive remdesivir for 5 days or standard care. Remdesivir was given IV 200mg on day 1 followed by 100mg/d. The study showed that there was no clinical benefit in 10 days of remdesivir compared to standard treatment. Although the patients that received 5

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days remdesivir showed statistically significant clinical status improvement compared to standard care alone (Spinner *et al.*, 2020).

Remdesivir and Tocilizumab

A case report on a pregnant female with severe Covid19 showed that combining the use of remdesivir and tocilizumab, which is an interleukin 6 receptor blocker seems to effective. Since patients of severe Covid19 have severe cytokine storm and hyper inflammation, this seems to be an effective combination. The patient had 7 days history of symptoms of covid19 and also high-risk factors such as hypertension, type 2 dm, intermittent asthma and a BMI of 28. The patient was given on day 3 of hospitalization due worsening of the clinical status, Tocilizumab 400mg IV followed by 5 days of remdesivir. The patient showed clinical improvement and was discharged on day 9 of hospitalization with no short term adverse effects (Naqvi *et al.*, 2020).

While another case report using the same 2 combination of drugs in 2 patients with an almost identical history resulted in 1 patient having Hemophagocytic syndrome (HLH). According to the author, this could suggest that even though tocilizumab blocks IL-6 receptor, it can leave other alternative pathways remain open causing HLH. The author, therefore, suggests to use Remdesivir before secondary uncontrolled inflammatory response takes place if the later does occur then tocilizumab is an option (Akinosoglou *et al.*, 2021). Since an increase in IL-6 seems to associated with increased association with death and critical illness combining an IL-6 receptor blocker and a viral replication inhibitor seems to work well.

Remdesivir and Convalescent plasma

Another case report combined remdesivir with convalescent plasma in a pregnant patient with severe covid19. 1 unit of convalescent plasma was given on a day of admission, and remdesivir was given on day 5 of hospitalization for 10 days. The patient showed signs of clinical improvement by 5 days of initiation of remdesivir. Although there was a mild elevation of transaminases after 3days of initiation of remdesivir, it was normalized by the 6^{th} day. No other short term adverse effects was noted, and the patient was discharged on completion of remdesivir treatment (Anderson *et al.*, 2020).

Vitamin D and Remdesivir

The combination of Vitamin D and Remdesivir seems to have a synergistic effect has shown by (Arya and Dwivedi, 2020).

Remdesivir in Cancer Patient

Remdesivir given to a patient will Chronic Lymphocytic leukaemia with covid19 and resulted in temporary suppression of the infection. As such, 2 courses of remdesivir was given, but it did not result in eradication of the disease. This suggests that although it suppresses the infection, it is temporary in an immunocompromised individual (Helleberg *et al.*, 2020).

Adverse Effects of using Remdesivir

In ACTT-1 study the most common adverse effects found in the remdesivir group was anemia, acute kidney injury, decreased estimated glomerular filtration rate or creatinine clearance, or increased blood creatinine, pyrexia, increased blood glucose level and increased aminotransferase levels. Otherwise, the incidence of adverse events was not found to be significantly different between the remdesivir group and the placebo group.

In Simple Study, the most common adverse effects in either group was nausea and acute respiratory failure, increased aminotransferase levels, constipation. The patients that discontinued the treatment due to adverse effect had serious adverse effects and died during treatment was more in 10 days treatment group Serious adverse effects are Acute Respiratory failure, Septic shock, Acute respiratory distress syndrome.

Remdesivir induced liver injury is reported, and therefore remdesivir should be given with close monitoring of liver functions and with a caution in those with prior liver disease (Zampino *et al.*, 2020; Li and Su, 2020). It is contraindicated in those with liver (ALT-5 times above the baseline) or renal (eGFR<30ml/min) dysfunction. Longer duration of Remdesivir could itself lead to high mortality in the patients.

Whether it could be used has prophylaxis for health care professionals and others who have a high risk to develop Covid-19

Remdesivir has shown to have potential prophylactic and therapeutic efficacy in rhesus macaques infected with MERS-CoV. They were treated prophylactically 24 hours before inoculation with MERS-CoV. Those treated prophylactically showed a reduction of clinical signs, reduction in viral lung loads, absence gross and histologic lung lesions. Based on this study, Remdesivir could be used prophylactically in humans (de Wit *et al.*, 2020). But seeing the adverse effects and limited clinical benefits of Remdesivir it may not be wise to use the drug prophylactically.

CONCLUSION

Several questions still remain unanswered like the optimal time to start remdesivir, the optimal dose and duration, the impact on mortality, the effect of the drug in combination with other drugs, whether specific groups of patients may benefit more or less, the long term effect, the significant benefits and risks still remain unknown. It does seem to be effective in reducing the clinical time to recovery leading to a shorter duration of hospital stay. This is particularly useful in hospitals in making more beds available to other patients and also in decreasing the use of hospital resources. A subsequent reduction in oxygen use among the patients on using the drug also suggests a reduction in disease burden. Remdesivir may not be the miracle drug we hoped it to be. But seeing its slight clinical benefit and side effects in Covid 19 and since no other treatment has been approved for Covid 19, it is better to be used with caution. The still multiple ongoing trials on remdesivir may give us a clear idea of remdesivir and whether it is better to use it alone or in combination.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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REFERENCES

Akinosoglou, K., Velissaris, D., Ziazias, D., Davoulos, C., Tousis, A., Tsiotsios, K., Kalogeropoulou, C., Spyridonidis, A., Marangos, M., Fligkou, F., Gogos, C. 2021. Remdesivir and tocilizumab: Mix or match. *Journal of Medical Virology*, 93(1):56–58.

Anderson, J., Schauer, J., Bryant, S., Graves, C. R. 2020. The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. *Case Reports in Women's Health*, 27:e00221–e00221.

Arya, A., Dwivedi, V. D. 2020. Synergistic effect of vitamin D and remdesivir can fight COVID-19. *Journal of Biomolecular Structure and Dynamics*, pages 1–2.

Beigel, J. H., Tomashek, K. M., Lane, H. C. 2020. Remdesivir for the Treatment of Covid-19 - Final Report. *New England Journal of Medicine*, 383(19):1813–1826.

Brown, A. J., Won, J. J., Sheahan, T. P. 2019. Broad-spectrum antiviral remdesivir inhibits human endemic and zoonotic delta coronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Research*, 169.

Chen, N., Zhou, M., Zhang, L. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, 395(10223):30211–30218.

Choy, K. T., Wong, A., Yen, H. L. 2020. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Research*, 178.

Contini, C., Gallenga, C. E., Neri, G., Maritati, M., Conti, P. 2020. A new pharmacological approach based on remdesivir aerosolized administration on SARS-CoV-2 pulmonary inflammation: A possible and rational therapeutic application. *Medical Hypotheses*, 144:109876–109876.

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., Scott, D., Cihlar, T., Feldmann, H. 2020. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences*, 117(12):6771–6776.

Goldman, J. D., Lye, D., Towner, W. J. 2020. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *The New England journal of medicine*, 383:1827–1837.

Helleberg, M., Niemann, C. U., Moestrup, K. S., Kirk, O., Lebech, A.-M., Lane, C., Lundgren, J. 2020. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. *The Journal of Infectious Diseases*, 222(7):1103–1107.

Huang, C., Wang, Y., Cao, B. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *The Lancet*, 395(10223):30183–30188.

Li, Y., Su, Y. 2020. Remdesivir attenuates high-fat diet (HFD)-induced NAFLD by regulating hepatocyte dyslipidemia and inflammation via the suppression of STING. *Biochemical and Biophysical Research Communications*, 526(2):381–388.

Lo, M. K., Jordan, R., Spiropoulou, C. F. 2017. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Scientific reports*, 7.

Mulangu, S., Dodd, L. E., Davey, R. 2019. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *New England Journal of Medicine*, 381(24):2293–2303.

Naqvi, M., Zakowski, P., Glucksman, L., Smithson, S., Burwick, R. M. 2020. Tocilizumab and Remde-

sivir in a Pregnant Patient With Coronavirus Disease 2019 (COVID-19). *Obstetrics & Gynecology*, 136(5):1025–1029.

Sheahan, T. P., Sims, A. C., Baric, R. S. 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science Translational Medicine*, 9(396).

Spinner, C. D., Gottlieb, R. L., Marty, F. M. 2020. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. *JAMA*, 324(11).

Sun, D. 2020. Remdesivir for Treatment of COVID-19: Combination of Pulmonary and IV Administration May Offer Aditional Benefit. *American Association of Pharmaceutical Scientists Journal*, 22(4).

Tchesnokov, E., Feng, J., Porter, D., Götte, M. 2019. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses*, 11(4):326–326.

Wang, D., Hu, B., Peng, Z. 2020a. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, 323(11):1061–1061.

Wang, M., Cao, R., Xiao, G. 2020b. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, 30(3):269–271.

Warren, T. K., Jordan, R., Bavari, S. 2016. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*, 531(7594):381–385.

Wu, C., Chen, X., Song, Y. 2019. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease. *JAMA Internal Medicine*, 180(7).

Zampino, R., Mele, F., Florio, L. L., Bertolino, L., Andini, R., Galdo, M., Rosa, R. D., Corcione, A., Durante-Mangoni, E. 2020. Liver injury in remdesivir-treated COVID-19 patients. *Hepatology International*, 14(5):881–883.