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Role of the antiviral drug Remdesivir in the treatment of Coronavirus disease 2019 (COVID-19)

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Abstract
The pandemic of COVID-19 (Coronavirus Disease-2019) is an highly contagious respiratory sickness due to a novel coronavirus, SARS-CoV-2. Remdesivir, different clinical trials has been done at different countries in their hospitals, when it was issued for emergency drug. Its safety profile has been evaluated in a merciful use setting for patients with COVID-19. The current therapeutic examination demonstrate clinical efficacy of remdesivir in COVID-19 patients by reducing time to clinical recovery, and hospitalization. In this regards, we srncerely analyze the recent evidence of remdesivir against COVID-19 and automize the aspects over its efcacy and safety. Based on available data, remdesivir can be noticed as a potential therapeutic drug against COVID-19. Further, randomized placebo-controlled clinical trials anticipate to validate these fndings.

Keywords: pandemic, coronaviruses, COVID-19, remdesivir

Introduction

Coronaviruses are belongs to enveloped viruses family along with single stranded RNA genome which transmitte mammals and humans. There are various corona virus such as Middle East respiratory syndrome-related coronavirus (MERS), severe acute respiratory syndrome coronavirus (SARS), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 the responsible pathogen of the disease COVID-19).

Corona virus first infect respiratory tract and then intestine in animals and mankind. It was first introduced in 1960s, and considered that it can cause only mild type of infection with some strains named HCoV OC43 and HCoV 229E with symptoms like common cold. But it changed in 2003 SARS pandemic and again in 2012 outbreak MERS. The mortality rate was 10% and 35%, respectively [1].

Both corona virus originated from bat populations, That keep a big diversity of this virus and were communicated via an intermideate host to mankind. Waht ever evidences come up that indicating that covid 19 that emerges in wuhan of China in 2019 also from bat only. This novel coronavirus, SARS-CoV-2, derived in an epidemic of pathogenic viral pneumonia in Wuhan city, Hubei Province in China, as revealed to the World Health Organization (WHO) in December month 2019. Sucessive spread has led to a global pandemic (officially announced by the WHO on March 11, 2020) [2]. Remdesivir is a prodrug of Adenosine triphosphate (ATP) analog, having strong antiviral effect against various RNA viruses. It is an antiviral nucleotide analogue used for treatment of severe novel coronavirus disease 2019 (COVID-19) effected by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection. Remdesivir therapy is stated intravenously for 5-10 days. After administration, Remdesivir, being a prodrug, is digested into its active form. As an ATP analog active form competes with ATP for consolidation into RNA and controls the action of viral RNA-dependent RNA polymerase. This wallops in the termination of RNA transcription and reduces viral RNA production [3, 4].

Coronavirus (CoV) structure

Coronaviruses are roughly spherical particles, large with special suface projections [5]. They are available in different sizes ranging from 80-120 nm [6]. The maximum size indentified from 50 to 200 nm in diameter. The overall molecular mass is on average 40 thausand kDa. They are surrounded in an envelope fixed with a number of protein molecules [7]. The membrane protein, lipid bilayer envelope and nucleocapsid save the virus whenever it is outside of the host cell [8].

The viral cover is made up of a lipid bilayer in that membrane (M), spike (S) and envelope (E) structural proteins are binded [9]. The ratio of E: S: M in the lipid bilayer is around 1:20:300 [10]. The structural proteins E and M combined with lipid bilayer to give shape the viral cover and gives a proper morphology to it. To interact with the host cells the S proteins are needed [11].

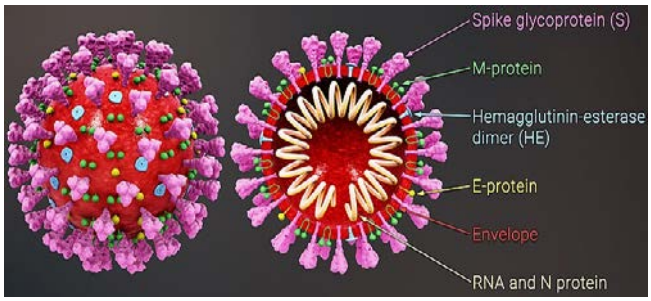

Fig 1: Structure of Corona Virus.

Search for treatment

When pandemic started, various types of medications or combinations have been used in different countreies [12]. The safety aspect, pharmacodynamics and pharmacokinetics of existing viral treatments have already been established [13]. Various drugs have many protein targets and sevral illnesses share overlapping molecular paths. In cases like this, reusing drugs for more than one purpose and finding their biggner uses can considerably reduces the time in finding new cures for unpredicted diseases [14].

Remdisivir (RDV)

Against RNA viruses, RDV exhibits broad-spectrum antiviral activity. It is sold in the brand name Veklury [15, 16]. The route of administration is through injections in vein [17, 18]. During the first and second wave of COVID-19 pandemic it was authorized for urgent use to tret COVID-19 in over 50 countries [19, 20]. Recent guidelines from the World Health Organization (WHO) in November 2020 involve a conditional recommendation against the use of remdesivir for the treatment of COVID-19 [21, 22].

Actually this drug was originally developed to treat the hepatitis C [23]. and was investigated for Marburg and Ebola virus infection. Afterwards it also being examined as a post-infection treatment for COVID-19 [24]. The most common side effect in healthy volunteers is raised blood levels of liver enzymes (a sign of liver problems) [25]. The most common side effect in people with COVID-19 is nausea [26]. Side effects may include liver inflammation and an infusion-related reaction with nausea, low blood pressure, and sweating [27].

Remdesivir is a prodrug that is deliberated to allow intracellular delivery of GS-441524 monophosphate and following biotransformation into GS-441524 triphosphate, a ribo nucleotide analogue inhibitor of viral RNA polymerase [28]. The U.S. Food and Drug Administration (FDA) considers it to be a first-in-class medication. Remdesivir is the international nonproprietary name (INN) while the development code name was GS-5734 [29].

RDV is very judicious for viral polymerases, consequently a low propensity to cause human toxicity. In addition, it has shown to have a wide therapeutic index in a human airway epithelial cell model [29]. The drug also exhibits a high genetic hurdle to resistance in coronaviruses and has an extended intracellular half-life that permits for once-daily dosing [30].

The safety and pharmacokinetics of RDV were assessed in single- and multiple-dose phase Intravenous infusions between 3 mg and 225 mg and were well-tolerated without any evidence of kidney or liver toxicity. RDV showed linear pharmacokinetics within this dose range and an intracellular half-life of more than 35 h. Ensuing multiple-dose infusions, reversible aspartate aminotransferase and alanine transaminase elevations ensued (WHO, 2020b).

The dose under investigation for treatment of COVID-19 is 200 mg intravenously (IV) on day 1 followed by 100 mg IV daily for up to 10 days, infused over 30–60 min. The initial clinical use of RDV was conducted by Jacob *et al* in 2016 to treat Ebola [31], followed by case series [32].

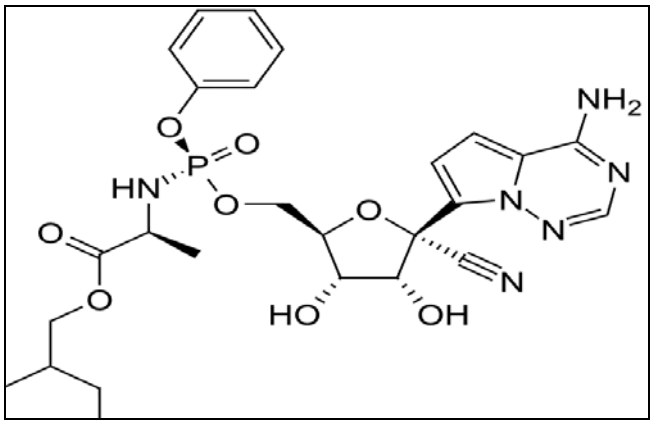

Fig 1: Structure of Ramdesivir

Clinical Trials

Article published in the New England Journal of Medicine, examiners have used RDV on a compassionate use basis to patients hospitalized by Covid-19. Those who Participated were patients with confirmed SARS-CoV-2 positive and who had been observed oxygen saturation of upto 94% or less at room air or who were on oxygen support. Patients administered a 10-day dose of RDV, comprising of 200 mg received intravenously on day 1, folloewd by 100 mg/day for the rest of 9 days of treatment. Overall, 61 patients were assigned but only 53 patients data were analyzed. Participants were from the Canada, United States, Europe and Japan. More than 50% of patients (n ¼ 30) were receiving mechanical ventilation and almost 10 % (n ¼ 4) were receiving extracorporeal membrane oxygenation. On follow-up (median ¼18 days), 36 patients (68%) had an amelioration in oxygen-support, including 17 of 30 patients (57%) getting mechanical ventilation who were extubated. Moreover, 25 patients (47%) were discharged, and 7 patients (13%) expired. The writers concluded that administration RDV, led to clinical progression in 36 of 53 patients (68%) infected with Covid-19.

In terms of safety, 32 patients (60%) revealed adverse events during regular follow-up. The most common adverse effect were rash, renal impairment, diarrhea, increased hepatic enzymes, and low BP. Overall, side events were more common also in patients on invasive ventilation. Total of 12 patients (23%) had grave adverse events, most commonly multiple-organ-dysfunction syndrome, septic shock, acute kidney injury and hypotension. Four patients (8%) aborted RDV treatment prematurely: one due to deteriorating of preexisting renal failure, one due to multiple organ failure, and two due to transaminitis, including one patient with a maculopapular rash [34].

The National Institute of Allergy and Infectious Diseases (NIAID), published on April 29, 2020, preliminary results on the action RVD on covid-19 disease. The randomized, controlled trial which was started on February 21, 2020 involved 1063 patients. The mortality rate for the group of individuals those received RVD was 8 % as compared to 11.6% in the placebo group (p ¼ 0.059). The patients who survived the illness, the average time to recovery was 31% quicker for patients those received RVD compared with who received placebo (11 vs 15 days) (p < 0.001) (NIH, 2020).

Gilead revealed results On April 29, 2020, from the openlabel, Phase 3 SIMPLE trial evaluating 10-day and 5-day dosing durations of the investigational anti-viral remdesivir in patients who hospitalized with severe manifestations of COVID-19 illness. admittance criteria was reduced oxygen levels and pneumonia that did not require mechanical ventilation at the time of investigation. The study revealed that patients those received a 10-day of treatment course for remdesivir attained comparable advancement in clinical status compared with who taking a 5-day treatment dose (Odds Ratio: 0.75 [95% CI 0.51 – 1.12] on Day 14).

The time to clinical advancement for 50 percent of patients was 10 days in the 5-day treatment class and 11 days in the 10-day treatment class. More than 50% of patients in both treatment classes were discharged from the hospital through Day 14 (5-day: 60.0%, n ¼ 120/200 vs. 10-day: 52.3% n ¼ 103/197; p ¼ 0.14). At Day 14, 64.5 % (n ¼ 129/200) of patients in the 5-day treatment class and 53.8 % (n ¼

106/197) of patients in the 10-day treatment class achieved clinical recovery. The overall mortality rate on Day 14 was 7 % (n ¼ 23/320) across both treatment classes, with 64 % (n ¼ 205/320) of patients revealing clinical advancement at Day 14 and 61 % (n ¼ 196/320) of patients discharged from the hospital. No unforeseen side effects were detected with the use of RDV across either treatment group [35]. The Food and Drug Administration (FDA) on May 1, 2020, issued an Emergency Use Authorization (EUA) for emergency adoption of RDV for the treatment of patients those who hospitalized by 2019 coronavirus disease (COVID-19) based on audit of the topline data obtained from the Gilead-sponsored open-label trial which evaluated different time durations of RDV (NCT04292899), and from the double-blinded, randomized, placebo-controlled trial conducted by NIAID (NCT04280705) (FDA, 2020).

The 'agreemental trial' conducted by WHO in 30 countries at 405 hospitals. 2,750 were assigned to receive Remdesivir. The results published by WHO on December 2020 revealed that on to the hospitalized patients suffering from COVID-19, this drug has minor or no side effects in respevt of hospital stay timing, starting of ventilation and consolidated mortality. From the above information the present drug should be administered only on either moderate or servere hospitalized patients suffering from COVID-19 and on oxygen. Since limited scientific evidences available world wide this drug is reserve drug and approved under emergency application. Doctors have beed adviced to practice extreme caution while giving Remdesivir to minimize its abuse since it is experimental drug [36].

The central and state goveronments have taken all the precausionery measures right from the beigning then also the number of COVID-19 positive cases keep on increasing. Thus with currently positive advancement with remdesivir, health system required to be ready to make sure the procurements of remdesivir to such a big population at affordable cost [37]. However, The price of the drug may not be affordable for country like us. Hence, according to Indian Patent Act 1970, Goveronment of India holds the authority to issue compulsory license to pharmaceutical company of India for the sale and production of it [38].

Remdesivir is a new drug should undergo clinical trial before receiving marketing approval. Currently, two pharmaceutical companies of India, Hetero and Cipla Labs Ltd., have desired clinical trial waiver from DCGI. However, the policy of charitable use of drugs in India is also being improved. ICMR, CDSCO, AIIMS, and other collaborator already had three rounds of brain assault sessions [39]. Since limited toxicity/safety information of remdesivir are present in COVID-19 patients, a booming pharmacovigilance will be mandatory. Pharmacokinetics of remdesivir has not been determined in patients with hepatic impairment, renal and geriatric patients above 65 years with COVID-19. Furthermore, transaminase ascent has been detected during clinical development with unknown mechanism [40].

The FDA endorse determination of predicted glomerular filtration rate before giving remdesivir, as a rsults of sulfobutylether-β-cyclodextrin sodium employed as an excipient accumulates in reduced renal function [41]. Suspecious adverse drug effects associated with remdesivir can be described as usual by any health-care professionals or the patient by calling at Pharmacovigilance Program toll free number of India 1800-180-3024 [41].

Conclusion

Remdesivir can be crucial for ensuring an adequate treatment, allow early discharge and decrease mortality in relation to Covid-19. Current placebo-controlled trials, randomized are critical in define its efficacy. To conclude, glance at the disease that drown more than 3 lakhs people and US-FDA has allowed emergency use authorization based on exploratory results revealing it superior to placebo, remdesivir looks to be strong candidate. Furthermore, results of currently going trial will give much needed clarity in coming future. Meantime, India has to plan appropriately focusing on its affordability, availability and safety for Indian community.

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Conflicts of Interest

Authors do not have any conflict of interest.

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