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REVIEW ARTICLE **OPEN ACCESS**

Covid-19: Treatment with Remdesivir

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ABSTRACT
Corona virus disease-2019 is a pandemic and contagious respiratory infection because of a newly identified corona virus SARS-CoV-2. Some of the drugs have their protein targets and molecular pathways over disease. However, reusing of drugs can considerably reduce the time in finding outs new treatment drugs for such unforeseen illness. With this point of view, Remdesivir (RDV) has been considered as one of the potent drug treatment of COVID-19. In this manuscript, we have tried to converge the maximum information about RDV drug against covid-19. The manuscript has included the clinical trials and even the published data in relation to the therapeutic application of RDV.
Keywords: *Remdesivir (RDV), COVID-19, Repurposing, RNA Virus*

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INTRODUCTION

Remdesivir (RDV) possessed antiviral property against RNA viruse(s). Earlier studies with RNA-dependent RNA polymerase (RdRps) from both Ebola virus (EBOV) as well as Middle East respiratory syndrome coronavirus (MERS-CoV) have shown the delayed chain-termination which is an RDV's possible mode of action (Figure 1) [1-4]. Even recently, Gordon, *et al.*, 2020, demonstrated the RdRp potentially incorporates the active form of triphosphate RDV (RDV-TP) into RNA, that producing termination in the synthesis of RNA [5]. Researchers obtained similar results with the MERS-CoV, SARS-CoV, SARS-CoV-2 RdRps and it has been concluded that the distinguishing characteristics of RDV-TP is its high refinement over the incorporation of its natural nucleotide counter-part ATP. RDV drug is a prodrug of monophosphoramidate of an adenosine analogue, formerly known as GS-5734, was produced in relation to Ebola outbreak occurred in West Africa (2014). RDV drug binds to the RdRp and even acts as RNA chain terminator. Even it exhibits *in vitro* activity against SARS-CoV-2 (EC_{50} of 0.77 mM in the Vero E6 cells at 48 hours) [6]. Even it has been found effective against other zoonotic corona viruses such as MERS-CoV and SARS-CoV-1 [7-9]. The drug RDV is very much selective against viral polymerases, therefore contain low tendency to produce toxicity in humans. It has a broad therapeutic index applied in a epithelial cell of human airway model [8]. The pharmacokinetics and safety of RDV were observed in single and multiple dose phase IV infusions varied from 3- 225 mg and well-tolerated without kidney or hepatic injury. The drug also showed a linear pharmacokinetics and an intracellular half-life for more than 35 hours. The dose for the treatment of COVID-19 is about 200 mg intravenous on the first day followed by 100 mg intravenous daily for 10 days, infused over 30-60 min [10].

EFFICACY OF REMDESIVIR

In a case series, the COVID-19 infected patient received RDV on 11th day of disease, and in which on the 12th day, the improved condition was observed. Safety and efficacy reports of RDV are shown in table 1.
Reports of a five case series, in which three received a dose of RDV drug. In two patients, the RDV drug treatment provided at the time of disease's worsening. Among them, one patient has discontinued the RDV after five days and revealed the elevated ALT levels with rashes. In third patient, RDV was discontinued even after a single dose as because of renal dialysis to prevent the accumulation of drug, cyclodextrin.
The fourth study analyzes the drug treatment of a single patient on 13th day of the patient's disease. On administration of RDV, the patient was in the intensive care, and was given with hydroxychloroquine

(400 mg/day) and azithromycin for 7 days. The patient's condition was improved after 48 hours of RDV initiation. During the treatment, the patient was extubated after sixty hours and was able to breathe.
RCT involving 1061 patients with drug treatment reveal that the patients who administered RDV had a 31% faster time to recovery compared to those who received placebo (11-15 days) however the survival benefit over 1063 patients was found insignificant than those to placebo of p=0.059.
Another study reported no significant mortality and even no improvement in clinical status of 5-10 days of drug treatment. Additionally, serious toxic effects are reported in the treated patient (27.7%) including 4.7% of mild kidney injury. Moreover 7.3% of the patient that showed adverse events led to discontinuing the drug treatment [18].
In the case of safety aspects, around 32 patients (60%) observed some adverse events during their follow-up. Most common side effects were such as rash, kidney impairment, elevated liver enzymes, hypotension and diarrhoea. Twelve patients (23%) had grave and severe side effects, commonly multiple-organ-dysfunction syndrome, acute kidney injury, septic shock and hypotension. About 4 patients (8%) terminated drug treatment prematurely due to several reasons including renal failure, multiple organ failure, transaminitis with a maculopapular rash [12]. A list of ongoing clinical trials on COVID-19 patients of RDV is summarized in table 2.

SAFETY ASPECTS

While analysing the toxicity aspects of the drug, RDV in *in-vivo* models resulted no hepatic alterations, but short-term treatment reflected the incipient elevations in the levels of transaminases were observed in the clinical studies. This has been supported in the case series in which the increased aminotransferases levels followed by initiation of RDV were perceived and noticed in approximately three viral infected patients [20]. Lescure *et al.* 2020, also described a patient of COVID-19 has discontinued the administration of drug due to an enhanced level of alanine aminotransferase and rashes, which has been then reduced within almost three days [21]. Additionally, according to Grein *et al.* 2020 experiment, the beneficent-usage of drug against COVID-19 would increase hepatic enzymes in 23 % of the patients and even some of the patients have discontinued the intake of RDV in early stage [12]. Randomized controlled trial (RCT) conducted in China by Wang, *et al.*, 2020, revealed the levels of total bilirubin (10 %), aspartate aminotransferase (5 %) and alanine aminotransferase (1 %) elevated in infected patients treated with the RDV drug compared to 9 %, 12 % and 0% of the viral infected patients in the placebo group [22]. Observations revealed that large frequency of patients in RDV group has terminated the drug due to the elevated levels of bilirubin or aminotransferases. Moreover, the recurrent incident hepatic injury was examined in the patients by Li, J., & Fan, J. G. (2020) hence it has been exigent to differentiate whether the elevated levels in the aminotransferases and/or bilirubin have been attributed due to the administration of RDV or to the underlying disease(s) [23]. European Medicines Agency has recommended that the RDV should not be administered along with another hepatotoxic drug(s), and thereby the monitoring of liver function is required in the treatment [24]. Since most of the infected patients with hepatic alterations had mildly elevated levels of the aminotransferases and/or bilirubin [23], and if some abnormalities concerned with hepatic enzymes appear after RDV intake, mainly in elevated levels, the adverse drug reactions (ADRs) are considered; thereby if necessary, the discontinuation of the drug is to be done.

Symptoms of Gastrointestinal Tract

Three COVID-19 infected patients were treated with the drug, in which two patients had nausea and even one of them was suffered from gastroparesis [20]. Even diarrhoea was also recorded in approximately 9 % of RDV recipients [12]. According to RCT (China), a greater proportion of RDV recipients than placebo group had stopped dosing in a prematurely stage due to nausea, vomiting and anorexia [25].

Symptoms of Respiratory Toxicity

The safety concerned of RDV in animal models revealed negligible side effects on respiratory system except for ephemeral enhanced respiration rates [26]. In addition, 4% of acute respiratory distress syndrome as well as pneumothorax were revealed after drug administration [12]. More patients in RDV group were suffered from respiratory disorder or even due to acute respiratory distress syndrome (10%) than placebo group (8%); however discontinued the RDV drug; as all these data have been reported in RCT studies taken place in China [25].

Symptoms of Cardiovascular Toxicity

Safety studies of drug reported that no side effects were noticed in monkey against cardiovascular parameters [26]. Although, one case study of hypotension was observed potentially related to remdesivirv drug against Ebola in an RCT of experimental studies [27]. According to Grein *et al*. 2020, hypotension (8%), atrial fibrillation (6%), hypernatremia (6%) were reported in COVID-19 infected patients treated with the study drug [12].

Symptoms of Nephrotoxicity

No evidence of nephrotoxicity observed in Phase I of clinical studies of RDV, although the dose-dependent declined kidney function or even injury was examined in the repeated administration of remdesivir in animal models, that has been corresponded to the histopathological observations of basophilia, casts and renal tubular atrophy [24]. In addition to these Grein *et al*., 2020 reported that the kidney injury, hematuria and renal impairments were found within the range of 4-8 % in RDV recipients [12].

Symptoms of Reproductive Toxicity

No effects/alterations observed on the reproductive functions of males/ or embryo-fetal and/ the peri-postnatal development, although the effects were notably observed on fertility parameters in the female rat models [24]. Even it has not been recommended to use in pregnant women. Whereas based on previous experiments the application of the study drug against Ebola, it has been analyzed that the drug found safer in the human pregnancies [27].

Miscellaneous Side Effects

The sudden elevation in the serum amylase observed in an Ebola-infected patient that was treated with RDV drug [10]. The multiple-organ-dysfunction syndrome, rash, delirium, pyrexia, septic shock and deep-vein thrombosis as adverse toxic effects observed in RDV recipients [12]. Though some of the toxic side effects such as circulatory, hematologic, and endocrine systems were also observed by Wang, *et al.,* 2020, in RDV group in the clinical trials (China) [22].

RECENT CASE STUDIES WITH US PRESIDENT DONALD TRUMP

US President Donald Trump tested COVID-19 positive; is being administered with the drug RDV, antiviral drug sold by Gilead Sciences Inc., American Pharmaceutical Company.

In the *Lancet*, it has been published that the drug RDV does not find to reduce the SARS-CoV-2 viral load or even death rate as compared to placebo recipients. Over 10 years ago the medicine, RDV was first produced and manufactured by Gilead Sciences for the treatment of Hepatitis C. Later, it was screened as significant and potential drug treatment for Ebola as well as Marburg viral infection(s). However, the COVID-19 outbreak has made the drug RDV a comeback after some clinical trial studies which revealed that it helps in preventing the replication of virus [28].

CONCLUSION

RDV drug might be found very important and crucial for ensuring an efficient and effective treatment, decrease mortality rate and also allow the early discharge of virus. Therefore, the ongoing randomized, placebo-controlled trials are crucial in the delineating its efficacy.

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