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Remdesivir-A Possible Therapeutic Measure to Stem the Pandemic Wave

Umer Farooq, Aroosh Shabbir, Arsalan Fazal, Maryam Khan, Saba Shamim*

Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore

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Abstract

The year 2020 will always be recalled in human history as the year of the COVID-19 pandemic. Its crisis at the global level has united scientists all over the world for the development of potential therapeutic drugs for its treatment. Remdesivir remains in limelight owing to its efficacy. The initial clinical trials showed a better benefit-ratio profile ratio. However, its safety is not established yet. The drug is under investigation. The ongoing clinical trials have proposed a better benefit-risk profile of remdesivir as compared to the placebo. Both *in vitro* and *in vivo*, remdesivir is one of the potential drugs which has demonstrated its efficacy against the Coronaviruses. It has also shown its promising support as a compassionate use drug for the clinical improvement of patients in the COVID-19 challenge. It is expected from the clinical trials progress that remdesivir will show the outstanding breakthroughs for the global COVID-19 challenge. Moreover, FDA approval has created a hope that the use of remdesivir may be helpful in the mitigation of morbidity, mortality, and the burden on the health care systems due to COVID-19 in the future.

* **Corresponding Author:** Saba Shamim ✉ sabashamimgenetics@gmail.com

Introduction

Background of COVID-19

Coronaviruses are positive-sense single-stranded RNA viruses that are enveloped, having a helically symmetrical nucleocapsid (Zumla *et al.*, 2016). They were first identified in the 1960s and had been generally known for causing the common cold for the last six decades (Vassilara *et al.*, 2018; Paules *et al.*, 2020). However, in the last twenty years, public awareness and perception have been changed after the three dangerous outbreaks which have attracted international attention for discovering the potential therapeutic options (World Health Organization, 2020). In 2002 and 2003, these viruses were identified for causing respiratory infections in human beings after the SARS outbreak in Guangdong, China caused by the SARS-CoV (Zhong *et al.*, 2003; Cui *et al.*, 2019). After a decade, the world has witnessed the MERS outbreak which was caused by the MERS-CoV in the Middle East (Zaki *et al.*, 2012; Bawazir *et al.*, 2018). Meanwhile, the researchers were busy investigating the basic mechanisms of pathogenicity and producing effective treatment strategies against the MERS, the world has seen the deadliest outbreak of COVID-19 (Khan *et al.*, 2020a).

This novel virus is much more similar to the SARS-Coronavirus than to MERS-Coronavirus. However, both SARS-CoV and SARS-CoV-2 have similar mechanisms of pathogenesis. The SARS-CoV was reported to be transmitted to humans from market civets, while the transmission of MERS-CoV was done from the dromedary camels (Guan *et al.*, 2003; Alagaili *et al.*, 2014). The transmission of new SARS-CoV-2 also occurred from wild animals to humans from the markets where they are sold. However, its transmission from the animal source is not yet confirmed. According to the previous research, the origin of the aforementioned coronaviruses is thought to be from bats (Khan *et al.*, 2020b). Its causative coronavirus was named SARS-CoV-2 because of its close resemblance to SARS-CoV (Chen *et al.*, 2020a-b; Hui *et al.*, 2020; Ji *et al.*, 2020). Its spread was very rapid after being emerged as a new infectious virus in humans in China in December 2019. The researchers have quickly isolated the virus and performed gene sequencing and started working on different possible treatments. Although the development of new drugs and vaccines takes time, these patients were in urgent need. Therefore, the use of conventional drugs has become a feasible solution. This virus is 80% homologous with the SARS-CoV, which was also emerged in China in 2002 (Morse *et al.*, 2020). It will continue its spread over time infecting 55% of the world population (Fine *et al.*, 2011; Li *et al.*, 2020).

While there was no proven effective therapy, the clinical management includes supportive measures consisting of oxygen support, treatment with antibiotics and compassionate-use therapies like antiparasitic agents, antiretrovirals, anti-inflammatory drugs, and convalescent plasma (Baden and Rubin, 2020; Cao *et al.*, 2020a; Onder *et al.*, 2020; Poston *et al.*, 2020; Shen *et al.*, 2020; Touret and Lamballerie, 2020). From the experience of dealing with SARS-CoV and MERS-CoV, it was expected to find drugs for treating COVID-19. Some drugs like lopinavir, interferon, ribavirin, and corticosteroids were being used in patients having the above diseases (Wang *et al.*, 2020a). It was found that a broad-spectrum antiviral drug, remdesivir showed strength in clinical trial against MERS-CoV and Ebola also demonstrated very significance in improving clinical symptoms of the patient with COVID-19 after 24-hour treatment in the United States. It has convinced that remdesivir has the potential of becoming a specific drug for the treatment of COVID-19 (Cao *et al.*, 2020a).

Remdesivir – a potential drug

Remdesivir is a broad-spectrum antiviral drug produced originally by Gilead Sciences Inc. for the treatment of Ebola and Marburg virus infection (Scavone *et al.*, 2020). It is a nucleoside analogue having strong antiviral activity being used in effective treatment against Ebola and Nipah virus in non-human primates (Lo *et al.*, 2019). It can inhibit the coronavirus replication in respiratory epithelial cells by competing with its counterpart ATP (Gordon *et al.*,

2020). It is an investigational antiviral drug. It is also a broad-spectrum antiviral drug that has shown activity against RNA viruses in various families, including Coronaviridae, Paramyxoviridae and Filoviridae (Warren *et al.*, 2016; Lo *et al.*, 2017; Sheahan *et al.*, 2017; Brown *et al.*, 2019; Sheahan *et al.*, 2020).

Class of Remdesivir

It is also known as GS-5734 derived from its precursor GS-411524 (Cao *et al.*, 2020a). It is phosphoramidate nucleoside analogue. It is a pro-drug that is metabolized into another triphosphate form (GS-443902) in cells (Fig. 1) and is identified as a broad RNA virus inhibitor (Lo *et al.*, 2017; Sheahan *et al.*, 2020). Prophylactically, it prevents pathology and therapeutically reduces pathology when it was given in animal models of having coronavirus infection (Sheahan *et al.*, 2020). Currently, it is under investigation as an antiviral agent for the treatment of SARS-CoV-2 infection (Gordon *et al.*, 2020). Remdesivir was developed originally by Gilead Sciences Inc. against the Ebola virus. It inhibits RdRp (RNA-dependent RNA synthetase) (Warren *et al.*, 2016; Wang *et al.*, 2020). Gilead Sciences Inc. was working with China to determine its safety and efficacy on patients with complicated COVID-19.

Mechanism of action of remdesivir

As a nucleoside analog, it targets the process of viral genome replication (Fig. 2) by inhibiting the RdRp (RNA Dependent RNA Polymerase). The RdRp is a protein complex that is used by Coronaviruses for the replication of RNA-based genomes. After metabolizing remdesivir by the host into its active form NTP (nucleoside triphosphate), metabolite competes with ATP (adenosine triphosphate, a natural nucleotide) for its incorporation into the growing RNA strand (Gordon *et al.*, 2020). This incorporation substitution into a new strand causes premature termination of RNA synthesis which halts the RNA strand growth after the addition of few more nucleotides. Although Coronaviruses possess a proofreading process that has the ability to detect and remove other nucleoside analogs, making them resistant to many drugs. But remdesivir seems to have the ability to outpace such a viral proofreading process to maintain its antiviral activity (Morse *et al.*, 2020). However, some evidence also suggests that there could have some additional mechanism of action of remdesivir (which has not been yet discovered), which allow for its partial antiviral activity instead of viral mutations enhancing replication fidelity (Agostini *et al.*, 2018; Brown *et al.*, 2019; Sheahan *et al.*, 2020).

Role in the treatment of ebola

Four decades back, Ebola virus disease had been documented for the first time during the infectious hemorrhagic fever outbreak in the DRC (Democratic Republic of Congo). After that, more than twenty outbreaks occurred intermittently. However, the outbreak which occurred recently in West Africa from 2013-2016 was considered the largest in history and resulted in a global public health emergency (World Health Organization, 2016). Ebola virus is known for its epidemic potential, sporadic outbreaks and high mortality rates (World Health Organization, 2019). It always remained a great challenge to prevent and treat negative-sense RNA viruses' infection like Ebola. In 2014, its outbreak caused almost 28000 positive cases and 11,310 deaths in West Africa (CDC, 2014-2016). Multiple drug candidates and vaccines were discovered and developed as a result of intensive research work during this outbreak (Henao-Restrepo *et al.*, 2015). Remdesivir (GS-5734) depicts its antiviral activity against various RNA viruses. This compound remained under clinical development for treating Ebola virus disease (Tchesnokov *et al.*, 2019). It was given to a British nurse as a compassionate drug who at first survived an Ebola infection but relapsed nine months later and developed meningoencephalitis (Jacobs *et al.*, 2016). It has demonstrated its antiviral properties against the various Ebola virus variants in the cell-based assays (Warren *et al.*, 2016) and also in the rhesus monkey model for the Ebola virus disease (Warren *et al.*, 2015). While its antiviral properties were demonstrated in *in vitro* cell culture and primates, its mechanism of action for the inhibition of the Ebola

virus remains to be completely elucidated. Currently, the Ebola virus RdRp complex was expressed recently and was purified which enabled the biochemical studies with its relevant remdesivir triphosphate (TP) form and its presumptive target (Tchesnokov *et al.*, 2018). Remdesivir inhibits this virus with half EC50 (maximal effective concentrations) that is relatively lower to values as reported for galidesivir or favipiravir (Oestereich *et al.*, 2014; Smither *et al.*, 2014; Warren *et al.*, 2014; Warren *et al.*, 2016; Furuta *et al.*, 2017; Siegel *et al.*, 2017). The remdesivir triphosphate form was observed for inhibiting RSV RNA-dependent RNA polymerase (RdRp) surrogate for the EBOV RdRp (Jordan *et al.*, 2018). The delayed chain termination may be a possible mechanism of action as pointed out by a recent study with NiV RdRp (Warren *et al.*, 2016; Jordan *et al.*, 20198). It is the inhibition of the synthesis of RNA some residues downstream of incorporated inhibitor. However, the results of inhibition have not been translated yet quantitatively and the data of recombinant EBOV RdRp is lacking (Fearns and Plemper, *et al.*, 2017). Currently, active EBOV RdRp was expressed containing L protein which was complexed with VP35 (viral protein 35) (Tchesnokov *et al.*, 2019). It is functionally equivalent to P proteins (Mühlberger *et al.*, 1999). In another study, it was demonstrated that nucleotide analogue incorporation at position "i" resulted in delayed chain termination especially at position i+5 (Tchesnokov *et al.*, 2019).

Role in the treatment of COVID-19

Remdesivir which is an adenosine analogue (nucleotide inhibitor) is found very effective against coronaviruses in the laboratory (Sheahan *et al.*, 2017). However, it was suggested in earlier investigations on the respiratory syncytial virus, that this drug causes delayed termination of the elongation of the RNA chain, but the mechanistic understanding of its action coronaviruses was unknown (Kirchdoerfer, 2020). Now, remdesivir is undergoing clinical trials for treating human coronavirus infections (Agostini *et al.*, 2018). At present, remdesivir has been found successful in many cases of COVID-19. The rehabilitation of the first COVID-19 patient in the US was reported in The New England Journal of Medicine. The patient visited Wuhan and returned on 15th January 2020. He had a cough with a fever for four days. On 19th January 2020, he was diagnosed with COVID-19 and was admitted. He was given remdesivir after his condition became worsened on the 6th admission day. On day 12, the clinical symptoms of the patient were improved, and oxygen saturation was increased to 94%. Although the patient was still hospitalized as of January 30, 2020, all the symptoms had been resolved except for cough and occasional running nose (Kim *et al.*, 2020). The current studies on the antiviral activity of remdesivir are of great relevance to the SARS-CoV-2, which are those done on genetically similar coronaviruses. There is some kind of genetic heterogeneity among different coronaviruses even in human strains (Vabret *et al.*, 2006). Although it is a broad-spectrum antiviral drug its effectiveness against other virus groups cannot be generalized to its efficacy against SARS-CoV-2.

The struggle for predicting the stage of potential applicability is interrupted by the possibility that it can have other mechanisms of action which are yet to be discovered (Amiriana and Levy, *et al.*, 2020). Emetine is a potent inhibitor of protein synthesis which is used for the treatment of ameobiasis and malaria (Grollman, 1966; Wong *et al.*, 2014). The combination of remdesivir and emetine is used for the reduction of individual drug effective concentration *in vitro*. The checkerboard assay was used for the evaluation of drug interaction by diluting remdesivir and emetine two-fold (0-50 µM and 0-0.781 µM respectively) in combination. The combination of Remdesivir (6.25 µM) and emetine (0.195 µM) can lead to obtaining 64.9% viral yield inhibition that can be tested further *in vitro* (Ianevski *et al.*, 2017; Malyutina *et al.*, 2019). So, combinational therapy is suggested for reducing the effective concentration of individual drugs under maximum plasma therapeutic concentration which will lead to the identification of optimal dose combination for a better clinical outcome against the SARS-CoV-2 (Choy**a** *et al.*, 2020).

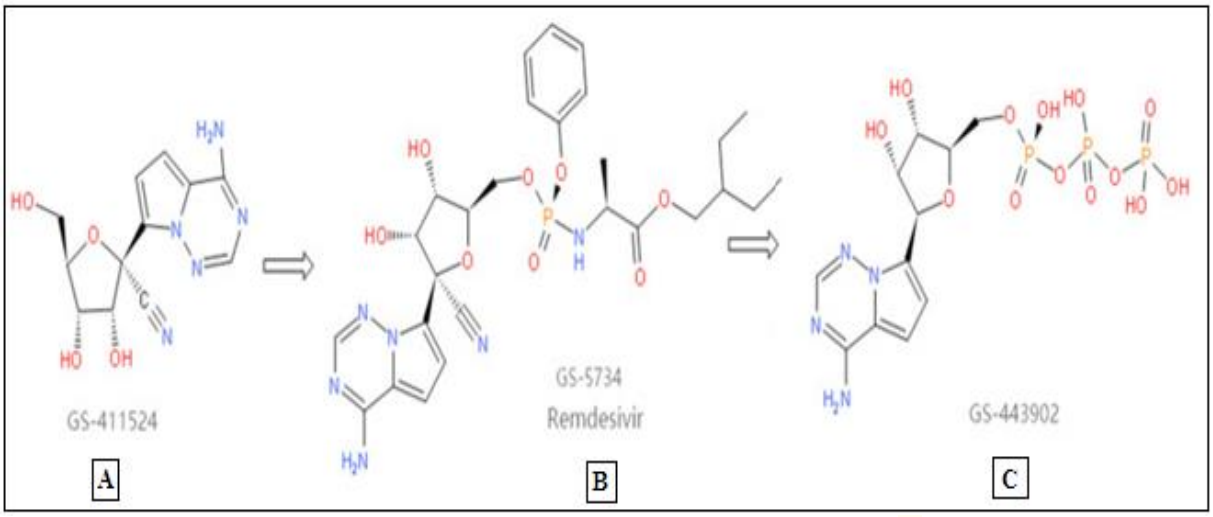

Fig. 1. Chemical structure of Remdesivir, its precursor and active metabolite (https://www.drugbank.ca. Accessed on February 25, 2020).

Efficacy of remdesivir versus other drugs used in the treatment of COIVD-19

Although at present, there is no availability of a promising antiviral drug for the effective treatment of COVID-19 there are some drugs which were very effective against MERS-CoV and SARS-CoV that may be used in treating it. *In vitro*, chloroquine and remdesivir have been observed very effective in controlling novel CoV infection (Wang *et al.*, 2020). Remdesivir alone or in combination with interferon β and chloroquine was found effective against it with no obvious side effects (Holshue *et al.*, 2020; Sheahan *et al.*, 2020; Wang *et al.*, 2020b).

Chloroquine is used for the treatment of rheumatoid arthritis and malaria. Previously it was tested *in vitro* against many viruses including SARS. It inhibited their growth but showed no remarkable benefits in animal models (Touret and Lamballerie X. 2020 *et al.*, 2020). However, it was reported to be very effective against SARS-CoV-2 but the evidence is very limited and much of the data is still not published (Gao *et al.*, 2020; Wang *et al.*, 2020b).

Lopinavir and ritonavir are antiviral drugs used for treating HIV. Lopinavir was used as a potential drug against SARS in 2003. However, the efficacy of lopinovir-ritonavir was tested by Chinese researchers and it was found that they gave no benefit against SARS-CoV-2 infection beyond the standard care (Cao *et al.*, 2020b). Flavipiravir is also an antiviral drug. It was reported to be preferred over arbidol (antiviral drug) in COVID-19 patients with pneumonia in less severe cases in Wuhan, China (Chen *et al.*, 2020c). Tocilizumab is a monoclonal antibody that is used for the treatment of RA (rheumatoid arthritis).

It blocks the IL-6 signaling pathway. At present, the evidence on the efficacy of this drug is limited in the treatment of SARS-CoV-2 infection (Mahase, 2020).

In another *in vitro* test which utilized human airway epithelial cell cultures, remdesivir showed effectiveness against circulating human coronavirus in lung cells (Sheahan *et al.*, 2017; Agostini *et al.*, 2018). Remdesivir and interferon β were found superior to ritonavir, lopinavir, and interferon-beta in a study both in a mouse model and *in vitro* (Sheahan *et al.*, 2020). However, there is an urgent need to treat COVID-19. Although it is very difficult to use it clinically on a very large scale while some clinical trials are underway. So, if the clinical trial results prove its potential efficacy, immediate use of remdesivir will be done in severely ill patients (Al-Tawafiq *et al.*, 2020). On 24th February 2020, World Health Organization also gave confidence by supporting the potential use of the experimental antiviral drug by Gilead Sciences Inc. and indicating that it may be best among the candidate drugs against the COVID-19 (Cao *et al.*, 2020a).

Clinical trials for the treatment of COVID-19

The first DBRCT (double-blind, placebo-controlled, randomized trial) was performed in serious COVID-19 patients with remdesivir versus placebo. It was found that there was no considerable difference in the initial outcome of time to clinical recovery within twenty-eight days (Wang *et al.*, 2020b). There was also seen no difference in twenty-eight-day mortality between remdesivir and placebo. This trial was stopped early due to the unavailability of required patients in Wuhan. Statistically, it was an underpowered trial to get any conclusive result (Norrie *et al.*, 2020). Therefore, it was suggested that there was no knowledge about the benefit of remdesivir was available in severe COVID-19 patients as compared to placebo in this trial.

On April 29, 2020, an interim result was announced about a randomized controlled trial by NIAID (National Institute of Allergy and Infectious Diseases). It was conducted in consultation with WHO (Routh, 2020). It was named ACTT (Adaptive COVID-19 Treatment Trial) (ACTT, 2020). A total of 1,063 patients have been enrolled from 21st Feb 2020 to 19th April 2020. This was sponsored by NIAD and was conducted at sixty-eight cities in the USA, Europe and Asia. The initial results have shown that 11 days was the median time to recovery for those patients receiving remdesivir while it was 15 days for the patients who were on placebo. Therefore, it was suggested that 31% faster recovery of the remdesivir receiving patients was observed as compared to those who received placebo ($p < 0.001$). The mortality rate was also lesser (8%) in remdesivir group while it was 11.6% for the placebo group (Eastman *et al.*, 2020; NIH, 2020).

Interestingly on April 29, 2020, the result of phase III open-label randomized trial by the Gilead Sciences was also announced. It was a simple trial for the comparison of the clinical improvement of a short course (5 days) with the long course (10 days) treatment of remdesivir in the severe hospitalized patients having pneumonia and decreased oxygen levels. Its secondary objective was to compare the adverse effects and the clinical outcome in both groups. The results of this study have shown that there was a significant difference in outcome between these two groups, but five days course was more impressive. The time to clinical recovery was day 10 in fifty percent of patients with 5 days course while it was day 11 in the 10 days treatment course. 60% of patients with 5 days course were discharged on day 14 while 52% of patients with 10 days course were discharged on the same day. Similarly, the clinical recovery was 64.5% vs 58.3% on the 14th day in the 5-days versus10 days treatment respectively. However, the overall mortality rate was the same (7%) on day 14 in both groups. It was also found that a larger benefit was suggested if it was used within ten days of the development of symptoms (Gilead, 2020; U.S. National Library of Medicine Clinical Trials Registry, 2020).

Another study was conducted in which a follow-up (median) of 18 days was done after getting the first dose of remdesivir in 53 patients. 68% of patients (36 of 53) have demonstrated an improvement in the oxygen support category while 15% of patients (8 of 53) showed worsening of disease. All 12 patients were improved who were getting ambient air. The 71% of patients (5 of 7) receiving non-invasive oxygen support have also shown improvement. It was also observed that 57% of patients (17 of 30) who have been getting invasive mechanical ventilation got improved and were extubated. The 47% of patients (25 of 53) who were receiving invasive and non-invasive ventilation) were discharged on the recent follow-up. The clinical improvement was observed less frequently among the patients who were getting invasive ventilation than those receiving non-invasive ventilation and among the older patients of 70 years of age or above (Grein *et al.*, 2020).

Dosage and Safety of Remdesivir

The recommended route of administration of remdesivir is intravenous for 30-120 minutes. The recommended standard dose is a loading dose of 200 mg followed by 100 mg once daily for patients with weight more than 40 kg for a period of 5 days who do

not need mechanical ventilation but can be extended to 10 days for those patients with no clinical improvement and for 10 days for patients who are on mechanical ventilation. Dose adjustment is required for pediatric patients with weight-less than 40 kg (Food and Drug Administration, 2020).

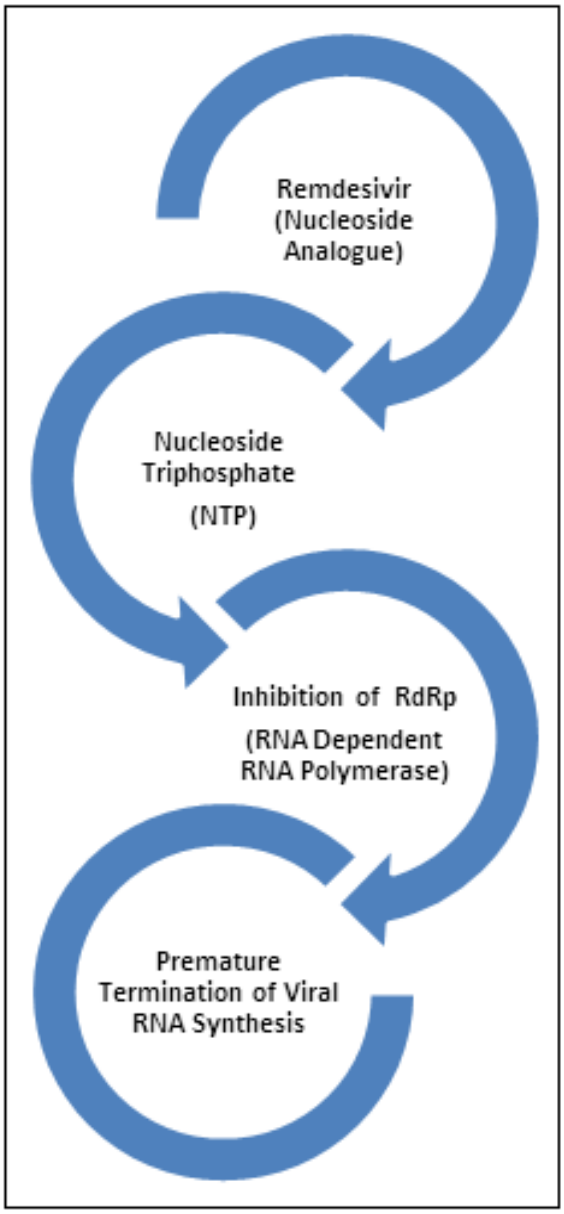

Fig. 2. Mechanism of action of Remdesivir.

Intravenous infusions of remdesivir showed good pharmacokinetics and safety in phase I trials previously with no hepatorenal toxicity, cytotoxicity, or serious adverse reactions were observed. Patients showed tolerance to intravenous 150 mg daily dosage for one to two weeks with no renal injuries in studies. After entering the body, it is distributed very quickly to the epididymis, testis, eyes and brain but in the eyes and brainless relatively (Warren *et al.*, 2016). This indicates the ineffective control of the Ebola virus by Remdesivir in tissues of high lethality. The Wuhan Institute of Virus Research has found that it is the most powerful and fastest-acting antiviral drug after conducting *in vitro* experiments on SARS-CoV-2 infection (Wang *et al.*, 2020b).

In 2016, the first use of remdesivir was reported against Ebola virus disease in humans. It was given to a Scottish female nurse who had already developed Ebola meningoencephalitis after it was confirmed by the Ebola virus RNA detection in cerebrospinal fluid and plasma (Jacobs *et al.*, 2016). She was treated very successfully with fourteen days remdesivir therapy and high-dose corticosteroids. She did not develop any serious biochemical or clinical events during this period of remdesivir therapy except a mild raise in serum amylase level (Ko *et al.*, 2020).

Another study was conducted on the compassionate use of remdesivir on severe COVID-19 patients. About 60% of patients were reported to show adverse reactions during the follow-up. These include raised hepatic enzymes, rash, diarrhea, hypotension and renal impairment. Generally, these adverse events occur more commonly in patients needing ventilator support. The 23% of patients had shown very serious adverse events including acute renal injury, septic shock, hypotension and multiple organ dysfunction syndromes in the hospitalized patients receiving ventilator support at baseline. The 8% of patients had discontinued the treatment prematurely due to worsening of renal failure, one due to multi-organ failure, and two due to raised aminotransferases, with one patient having maculopapular rash (Grein *et al.*, 2020). Although remdesivir use is not associated with any evidence of nephrotoxicity some kind of caution is needed (Singh *et al.*, 2020). The patient reported cardiovascular side effects including arrhythmias and hypotension (Mulangu *et al.*, 2019; Long *et al.*, 2020), while the risk of cardiovascular events associated with remdesivir use is largely unknown (Kumar *et al.*, 2020). Respiratory system adverse

effects include acute respiratory distress or failure were reported in patients receiving remdesivir but these may be caused due to the underlying disease rather than using it (Wang *et al*., 2020a; Gilead, 2020). Gastrointestinal side effects include raised hepatic enzymes and diarrhea in addition to lower GIT (gastrointestinal tract) haemorrhage (Mulangu *et al*., 2019; Clinical Trials, 2020; Boettler *et al*., 2020; Jean *et al*., 2020). Remdesivir showed no adverse events on the embryo-fetal development however embryonic toxicity was seen at a toxic dose (systemic) in reproductive toxicity studies. In a study, 26% of children and 3% of pregnant females had received remdesivir with no prominent side effects (Gilead, 2020).

It was found in a study conducted about the tolerance and safety of remdesivir, that the number of patients having serious adverse effects was lesser in remdesivir receiving patients than the placebo recipients (Wang *et al*., 2020b). FDA gave emergency use authorization to remdesivir for the hospitalized patients of COVID-19 on 1st May 2020 and finally approved it on 22nd October 2020 (Food and Drug Administation, 2020; Lamb, 2020).

Future prospects

With the passage of time COVID-19 pandemic is spreading across the globe. The scientists and researchers are vigorously working day and night for the development and evaluation of vaccines and the potential therapeutic drug for the effective treatment of SARS-CoV2 infection (Amanat and Krammer, 2020; Hodgson, 2020; Chen *et al*., 2020a; Philippidis, 2020). The results of the initial clinical trials have proposed a better benefit-risk profile of remdesivir as compared to the placebo. Currently, there is a limitation on the availability of safety. There is a need for further trials to analyse the expected risks and benefits. However, the incorporation of the data from the ongoing clinical trials into a framework may give an updated assessment of risks and benefits (Davies *et al*., 2020). Both *in vitro* and *in vivo*, remdesivir is one of the potential drugs which has demonstrated its efficacy against the Coronaviruses. It has also shown its promising support as a compassionate use drug for the clinical improvement of patients in COVID-19 challenge (Grein *et al*., 2020). The repositioning of the small molecule may provide the most rapid therapeutic measure to stem the pandemic wave (Allison, 2012; Kouznetsova *et al*., 2014). The results of ongoing clinical trials will further provide insights into the use of approved and experimental drugs against the COVID-19. It is expected from the clinical trials progress that remdesivir will show the outstanding breakthroughs for the global COVID-19 challenge. Moreover, FDA approval has created a hope that the use of remdesivir may be helpful in the mitigation of morbidity, mortality and the burden on the health care systems due to COVID-19 in the future.

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