The Efficacy of Remdesivir Drug to Control the Recently Emerged Novel Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2): A Review Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author HB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MB, KB, ZR, SS and GMH help and managed the analyses of the study. Authors HB and MB managed the literature searches. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Introduction: Remdesivir is among the investigational drugs which show some promising effect against COVID-19, it may be due to its broad-spectrum antiviral action against some RNA viruses. To date very few clinical studies have been conducted on the use of remdesivir to the treatment of COVID-19. The main objective of the present study was, to conduct a review on the effect of Remdesivir to the treatment of COVID-19. To the best of our knowledge, this is the first systematic review on the effect of remdesivir drug to the treatment of COVID-19.

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Methodology: We have searched PubMed, for published studies on assessing the effect of remdesivir drug among patients with confirmed COVID-19. The main search terms used were "COVID-19" or "SARS-CoV-2", "remdesivir", and "systematic review".

Results: Only 11 research articles were found eligible for enclosure in this systematic review, among selected studies only two were randomized, placebo-controlled trial of intravenous remdesivir. Data on the efficacy of remdesivir in the patients with confirmed COVID-19 from clinical Phase-III trials are still pending. Recently, in the latter half of May month, results of two hospital based randomized, double-blind, placebo-controlled phase III trials studies were reported, both the studies found that remdesivir was efficient in the treatment of patients with confirmed COVID-19. However, Wang et al., (2020) found that remdesivir treatment was not significantly associated with clinical benefits.

Conclusion: From the systematic review, the use of remdesivir to cure patients with confirms COVID-19 was found promising; however, further clinical studies with large patient size need to be considered. The efficacy and safety of remdesivir in the treatment of COVID-19 will require to be emphasized in future research studies.

1. INTRODUCTION

The latest outbreak of the novel coronavirus 2019, officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a worldwide health crisis with severe global burden [1]. Coronavirus disease 2019 (COVID-19) is a respiratory syndrome caused by novel SARS-CoV-2 infection. The novel SARS-CoV-2 was first discovered in the month of December 2019 in Wuhan City, Hubei Province of China. Usually coronavirus is enveloped, single-stranded RNA (ssRNA) and positive-sense viruses. The novel SARS-CoV-2 is RNA beta-coronavirus Lineage β, and has phylogenetic resemblance to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. The genomic size of the SARS-CoV-2 is 29.9kb [3]. Worldwide containment measure has been taken to fight the COVID-19 outbreak, however despite the global lockdown this pandemic quickly reach across the globe and constantly rises in many countries, resulting 34 396 222 COVID-19 cases and 1024675 confirmed deaths globally as of 3 October 2020 [4]. The most usual symptoms of COVID-19 onset are fever, nausea and fatigue, dry cough, diarrhea, or other type of gastrointestinal disorders. COVID-19 has milder clinical symptoms and minor casualty as compared with MERS and SARS, however it spread rapidly and can be lethal. Severe COVID-19 patients may suffer from acute respiratory distress syndrome (ARDS) and progressive respiratory failure. Regarding pathophysiology, the receptor binding domain (RBD) of S-protein on the surface of COVID-19 virus binds to the Angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface in order to entry in the host cell and release its ssRNA, after that the virus translates its RNA replicase (RNA-dependent RNA polymerase), and make an RNA replicase-transcriptase complex using it RNA template. Through replication, the RNA replicase-transcriptase complex forms RNA negative strands that will be further translated for the formation of structural proteins of the virus. Subsequently, in the cytoplasm of the infected cell the structural proteins and along with RNA produce fresh viral particles, which are released from host cells by exocytosis to infect surrounding cells. Each of the infected cells have capacity to produce thousands of new viral particles that eventually spread to bronchi, and finally get to the alveoli, and then causing pneumonia and other respiratory infections [5,6]. Researchers are extensively in progress to find out fast action drug for COVID-19. Many studies are searching into repurposing medicines that have been in practices for the therapy of other similar symptoms. However, to date no approved vaccines or effective medicines are discovered that control the widespread COVID-19; therefore continuous searching for vaccines and drugs are crucial to prevail over the COVID-19 outbreak. Numerous clinical trials have been going on for the search of different therapeutic options. At present, some drugs including hydroxychloroquine, remdesivir, ritonavir/lopinavir, chloroquine, Arbidol and interferon are under randomized controlled trials (RCTs) for their safety/efficacy assessment in COVID-19 patients [7,8].

Remdesivir (GS-5734) is an antiviral nucleotide analogue phosphoramidate prodrug developed

by an American pharmaceutical company "*Gilead Sciences*" for treatment of Hepatitis C. It was then used for the treatment of *Ebola* virus infections in Africa. Gilead Sciences initiated clinical evaluation of remdesivir for EBOV. During Ebola outbreak *Gilead Sciences* pursued FDA's Animal Rule, authorizing the confidence on efficiency result from animal study for remdesivir in which it is not ethical or viable to carry out human trials. Primary findings reported severe side effects like hypotension, prominent creatinine increase and elevated aspartate aminotransferase levels (impaired kidney) in remdesivir-treated patients. Even though remdesivir was substandard against Ebola as compared to antibody therapy, the remdesivir did offer a preliminary imminent into the safety of the patients. Remdesivir is among the investigational drugs which show some promising effect against COVID-19, it may be due to its broad-spectrum antiviral action against some RNA viruses [9,10]. Remdesivir prodrug is a 1-cyano-substituted adenosine nucleotide (ATP) analog. Remdesivir metabolized in target cells to an active nucleoside triphosphate (RDV-TP) which resembles ATP and inhibits viral RNA-dependent RNA polymerases (RdRp) enzymes and reduce viral RNA production in the early infectious stage [11,12]. Other possible mechanisms of action of this Remdesivir could be mutagenesis and chain termination of RNA transcription. It was found from *in vitro* study that the amalgamation of Remdesivir at the initial stages of replication of virus had the most effective action, meaning a time-dependent result for Remdesivir treatment [12]. We have searched PubMed, for published studies on assessing the effect of remdesivir drug among patients with confirmed COVID-19. The main search terms used were "COVID-19" or "SARS-CoV-2", "remdesivir", and "systematic review". We did not find any systematic review on the effect of drug remdesivir in treatment of COVID-19. Therefore, the chief objective of the study was to conduct a systematic review on the effect of Remdesivir drug in the treatment of COVID-19. To our best of knowledge, this is the first systematic review on the effect of remdesivir in the treatment of COVID-19.

2. METHODS

We conducted a systematic review by using online databases like MEDLINE (maintain by NCBI), Embase, Clinicaltrials.gov, ScienceDirect and Google Scholar. The searches included combinations of MeSH (Medical Subject Headings) terms describing "COVID-19", "treatment", such as "SARS- cov-2", "antiviral agents", "remdesivir", "systematic review", "nucleotide analogue", "randomized controlled trials" and "GS-5734". Data were collected from studies conducted during 2019 to 2020. Inclusion criteria of this study were as follows:

(a) The study population includes confirmed cases of COVID-19
(b) Study population includes both genders.
(c) At any clinical stage of the disease, thus mild, moderate or severe/critical case
(d) Use of Remdesivir of any dose
(e) Original and review articles published in peer reviewed journals.

The selected research articles included in the present study were critically appraised to evaluate the validity of research against error and limitation and to reduce possible bias according to the following questions:

a) What are the research objectives and the design of the study was evidently stated?
b) Is the research original?
c) Do the research articles have new findings?
d) Does the research question cover group or population of patients, intervention or therapy and significance of research outcome?
e) Do the researchers use the proper methodology, and reporting?
f) Has the study's hypothesis been properly addressed?
g) Is the analysis of the data accurate?
h) What level of uncertainty surrounds any results?
i) Are the data and analysis accurate and authors drawing the appropriate conclusions that are based on results?
j) Is the outcome of the study helpful for clinical practice?
k) Does the jeopardy of a diagnostic or treatment prevail over the potential benefits?

2.1 Limitations in This Systematic Review

1. Online search included only English written articles; we did not include articles written in other languages.
2. We considered data which were only available on PUBMED, Clinicaltrials.gov, ScienceDirect and Google Scholar and Google Scholar.
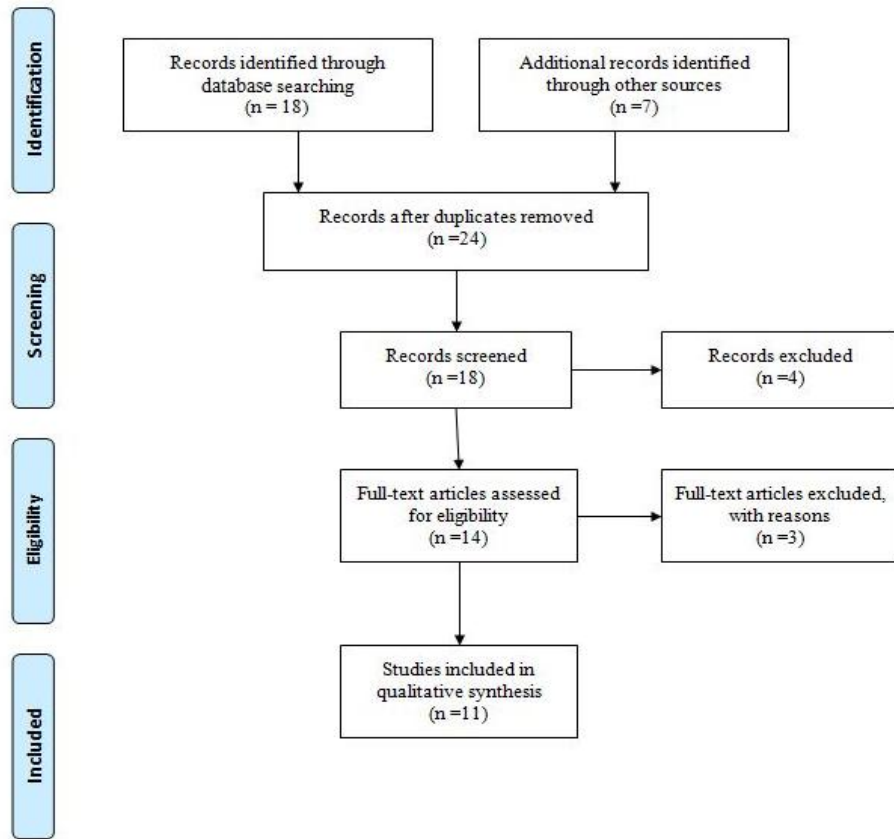
Fig. 1. Summary of PRISMA flow diagram

Table 1. Features of the studies that related eating disorder and depression

Author/DOI	Samples size/cell line	Type of study	Results
Beigel et al., [10] / DOI: 10.1056/NEJMoa2007764	538	Hospital based, randomized, placebo-controlled trial of intravenous remdesivir	They evaluated treatment of Covid-19 with remdesivir as compared with placebo. From initial observation, they found that remdesivir was better than placebo in reducing the time to recovery in adults hospitalized patients with Covid-19 and they study also confirm lower respiratory tract infection due to remdesivir treatment
Wang et al., [13] / DOI: 10.1016/S0140-6736(20)31022-9	158	Randomized, double-blind, placebo-controlled, multicentre trial	For the study it was interpreted that in case of adult COVID-19 patients, remdesivir treatment was not significantly associated with clinical benefits. Nevertheless, the study also evidence numerical reduction in time to clinical improvement in those treated earlier with remdesivir.

Author/DOI	Samples size/cell line	Type of study	Results
Wang et al., [14] / DOI: 10.1038/s41422-020-0282-0	Human liver cancer Huh7 cell line	*In vitro*	Remdesivir inhibited COVID-19 virus infection efficiently in a human cell line (Huh-7 cell line), which is sensitive to SARS- cov-2.
Khujawski et al., [15] / DOI: 10.1101/2020.03.09.20032896	3	Trial of intravenous remdesivir	Since remdesivir drug was not given as part of a RCT, study unable to evaluate remdesivir effectiveness or safety
Gordon et al., [16] / DOI: 10.1074/jbc.RA120.013679	Insect cells (Sf9)	*In Vitro*	Study provides evidence for the target specificity action of remdesivir, as RDV-TP* was less efficiently integrated by the distantly related Lassa virus RdRp, and termination of RNA synthesis was not found. Study provides a novel unifying, developed mechanism of RDV-mediated RNA synthesis inhibition in SARS- cov-2 and identify remdesivir as a direct-acting antiviral.
Cao et al., [9] / DOI: 10.1016/j.tmaid.**2020**.101647	-	Review	The study demonstrated structure, immunogenicity, and pathogenesis of SARS- cov-2. Additionally, they analyzed the pharmacological actions of remdesivir to recognize the viability of conducting research on remdesivir and COVID-19
Huang et al., [7] / DOI: 10.1128/mBio.00221-18	-	Review	Discussed the development of effective and thriving RdRp** inhibitors.
Barlow et al., [2] / DOI:10.1371/journal.ppat.1008536	-	Review	Discussed remdesivir and it mode of action and side effects
McCreary et al., [17] DOI: 1041-1042. doi:10.1001/jama.2020.16337	-	Review editorial	RCT results hint remdesivir may improve recovery COVID-19 patients. Nevertheless, whether the use of remdesivir (expensive) over corticosteroids, (commonly available and reasonably priced), is productive or not. Therefore further assessment of remdesivir in large-scale RCTs requires.
Grein et al., [18] DOI: 10.1056/NEJMoa2007016		Case study	Severe Covid-19 treated with remdesivir showed clinical improvement in 68% of patients. Further evaluations require confirming efficacy of remdesivir therapy.
Wang et al., [19] DOI: 10.1016/S0140-6736(20)32021-3		Correspondence	Remdesivir may need introduction before the viral replication peak, which seems not clinically possible in the human presentation of COVID-19

* RDV-TP: active triphosphate form of remdesivir; *RdRp: RNA-dependent RNA polymerases; *RCT: randomized controlled trial

3. RESULTS

We have selected 21 studies after online search, however after screening only 11 studies were found eligible for the study of the use of remdesivir in the treatment of COVID-19. To date very few clinical studied have been conducted on use of remdesivir in the treatment of COVID-19. The existing data on remdesivir use are mostly available on *in vitro* human cell culture, *in vivo* mouse and nonhuman primate studies. Of the 11 eligible studies, only 2 were hospital based randomized, placebo-controlled trial of intravenous remdesivir, 3 *in vitro* studies on remdesivir and COVID-19, 5 reviews relevant articles and only one trial of intravenous remdesivir (not considered randomized controlled trial during study). Wang et al., (2020) conducted an *in vitro* study on remdesivir and found that remdesivir have efficacy to inhibit SARS-CoV-2 replication, they conducted the study using Human Huh7 cell line [14]. Even though in phase II remdesivir was not as efficient as other competitive drugs, remdesivir showed good safety and pharmacokinetics in the phases II clinical trials. Phase III clinical trials of remdesivir in COVID-19 patients are under progress. Whether the outcome of phase III trial will make remdesivir comeback as antiviral drug is worthy of expectation [5]. Wang et al., (2020) published (available on May 16) first randomized, double-blind, placebo controlled clinical trial evaluating the effect of intravenous remdesivir among hospitalized adults with confirmed Covid-19. They reported that in the intention-to-treat, the main endpoint of time to clinical progress was not significant among the remdesivir groups; however clinical improvement was found better in the remdesivir group as compared to control group, mostly in those patients treated within 10 days of symptom onset. For the study it was interpreted that in case of adult COVID-19 patients, remdesivir treatment was not significantly associated with clinical benefits. Nevertheless, the study also demonstrated numerical reduction in time to clinical improvement in those treated earlier with remdesivir. Beigel et al., (2020) conducted a series of phase III, randomized, double-blind, placebo-controlled trials to assess the clinical efficacy and safety of remdesivir in adults admitted to hospital with COVID-19. Their study was published online on May 22. In that study, they evaluated treatment of Covid-19 with remdesivir as compared with placebo. From initial observation, they found that remdesivir was better than placebo in reducing the time to recovery in adults hospitalized patients with Covid-19 and their study also confirm lower respiratory tract infection due to remdesivir treatment, however it requires confirmation in larger population studies [10].

4. DISCUSSION

Remdesivir is an inhibitor of the viral RNA replication and was effectively used against RNA virus like SARS-CoV and MERS-CoV. It was also used against SARS- cov-2 infection, initially in *in-vitro* and nonhuman cell, remdesivir showed promising therapeutic results for the control of COVID-19. However, data of efficacy of remdesivir in the patients of confirm COVID-19 from clinical Phase trials are still in progress. Recently, in the latter half of May month, results of two hospital based randomized, double-blind, placebo-controlled phase III trials studies were reported, both the studies found efficacy of remdesivir in the patients with confirmed COVID-19 [10,13]. However, Wang et al., (2020) found that remdesivir treatment was not significantly associated with clinical benefits [13]. Wang et al., randomized trials study compared 10-day route of remdesivir with placebo in only 237 COVID-19 patients and which may have been underpowered [17]. The National Institutes of Health–sponsored Adaptive COVID-19 Treatment Trial (ACTT-1), conducted randomized clinical trials (RCT) on 1063 patients and observed that those given remdesivir (10-

Table 2. Practical Considerations of Remdesivir antiviral treatment proposed against COVID-19

Nature	Dose	Administration	Drug interactions	Side effects
Nucleotide Analog (GS-5734), Contains β-cyclodextrin, $C_{27}H_{35}N_6O_8P$ (molecular formula), 602.6g/mol (Molecular weight)	Remdesivir with a dose of 200 mg intravenously followed by 100 mg/day intravenously for 5-10 days [20]	30 minutes	Remdesivir is metabolized to the active, a triphosphorylated nucleoside, via anabolic intracellular kinase and terminate viral RNA production in initial phases of infection.	vomiting, Nausea, gastroparesis, or rectal bleeding

day course) had a recovery rate shorter by four days as compared with placebo [17]. Genetic factors are capable of influencing drug's efficiency and toxicity. Genetic variations (polymorphism, mutations etc.) of diverse populations could cause the efficiency inconsistency of remdesivir in randomized clinical trials [19].

5. CONCLUSION

To our knowledge this is the first systematic review on the effect of remdesivir drug in the treatment of COVID-19. Only 11 research articles were found eligible for inclusion in this systematic review, among selected studies only two were randomized, placebo-controlled trial of intravenous remdesivir. From the systematic review, the use of remdesivir to cure patients with confirmed COVID-19 was found indecisive; however, further clinical studies with large patient size and diverse population need to be considered. Considering the current situation where there is no precise targeting medicine treatment of COVID-19, remdesivir can be used as a repurposed drug on the basis of its broad-spectrum antiviral action against RNA viruses. The pharmacogenomic studies of remdesivir drug in the treatments of COVID-19 will require to be emphasized in future research studies.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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