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Review Article

Safety and Efficacy of Remdesivir for the Treatment of Covid-19: A Rapid Review of Available Evidence

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Abstract

Context: Remdesivir is an antiviral drug manufactured by Gilead Sciences, Inc., in which in-vitro studies have been shown to work in COVID-19 patients. Although it's not approved by pharmaceutical authorities and has not passed the first and second phases of clinical trials, it is prescribed on a trial basis for patients with Covid-19. In more than 20 countries, researchers are monitoring the results of using Remdesivir in clinical settings to see if it can be prescribed for larger populations if patients respond positively.

Methods: This is a rapid review of the evidence for the potential effects of Remdesivir, which intended to create a policy guide. To do so, health technology assessment studies indexed in MEDLINE and Cochrane Library databases were searched using the keywords, including drug name and disease name, on April 21, 2020. In addition, references of retrieved studies were checked to ensure throughout the capture of the literature. Studies on the safety and efficacy of Remdesivir in Covid-19 patients, both in Persian or English, were included. To identify ongoing clinical trials in Iran and some countries, clinical trial registration systems were also searched.

Results: In total 90 titles were identified, which after removing duplicates and applying inclusion criteria, 32 were included, all of which were published in 2020. 25 of them were review studies, mostly on treating Covid-19 disease, and some of them were dedicated to the effects of Remdesivir in treating the disease. However, no systematic review was found. Of the remaining studies, three were finished clinical trials, two of which evaluated the safety and efficacy of Remdesivir on mild, moderate, and severe Covid-19 compared to a placebo, and the third study compared Remdesivir with routine treatment. A cohort study on the efficacy of Remdesivir in compassionate use was also found. Also, two case reports of patients receiving Remdesivir and a letter-to- editor describing Remdesivir as an appropriate treatment for Covid-19 were identified.

Moreover, registered clinical trials with different designs intended to investigate the safety and efficacy of Remdesivir in treating Covid-19 were extracted from clinical trial registration systems (Table 3). In total 15 protocols were found, which 13 were in primary stages. The other two were in phase three of clinical trials and aimed to investigate the effect of Remdesivir in treating patients with severe, moderate, or mild Covid-19. In the clinical trial registration system, it is mentioned that the first study is stopped prematurely due to the lack of a sufficient number of patients, and the second study is also suspended.

Conclusions: Evidence on the safety and efficacy of Remdesivir in treating Covid-19 are very limited to make a decision. However, if registered trials are completed, enough evidence would be available to decide whether to accept or reject the Remdesivir. Since the effectiveness of Remdesivir is not clear yet, its prescription for Covid-19 patients has so far been limited to clinical trials, compassionate use, or emergency use.

Keywords: Covid-19; Corona Virus; Remdesivir

1. Context

Remdesivir is an antiviral drug invented by Gilead Pharmaceutical Company nearly a decade ago with the drug code GS-5734. The company explored a compound with multiple potential antiviral uses to be used when new viruses have emerged around the world. Remdesivir is one of the medical compounds that its antiviral effects are evaluated in the laboratory and on animal samples during the Ebola virus outbreak in West Africa in 2014 (1), and the results showed that it works. Therefore, Remdesivir was produced at a higher scale for evaluating its safety and efficacy in humans (2).

It is a nucleotide analog that enters the genetic structure of the virus during the replication of RNA viruses, such as coronaviruses, and inhibits further replications (3).

In 2017, the antiviral effects of GS-5734 on SARS and MERS viruses were evaluated in vitro, and positive results were obtained, which increased hope for the efficacy of Remdesivir in patients infected with these viruses as well as other coronaviruses (4). Animal studies also confirmed the efficacy of Remdesivir on the causative agent of MERS (5). The safety and efficacy of this drug in humans infected with causative agents of SARS and MERS have not been evaluated in any clinical trial (6).

In a clinical trial on patients with Ebola (known as PALM study) conducted in 2018, anti-viral effects of Remdesivir are compared to other drug compounds, including monoclonal antibodies. In this trial, the highest mortality rate was observed in the Remdesivir group (even higher than the control group), and therefore, it dropped out prematurely (7).

By the emergence of the SARS-CoV-2 pandemic, efforts to evaluate the efficacy of Remdesivir increased. Some studies, such as Wang et al., reported a significant effect on the control of viral infections in cultured cells in an in vivo study (8). In January 2020, in the absence of an approved drug to be used for Covid-19 patients, Remdesivir was prescribed for patients as compassionate use without any approval. In evaluating the outcomes of the Remdesivir, of 53 patients, 36 (68%) were recovered. Although the results are promising, due to limitations such as lack of a control group, short follow-up period, and small sample size, it is not possible to draw general conclusions about the safety and efficacy of this drug, and further randomized clinical trials are needed (9).

Accordingly, since February 2020, clinical trials have begun on the efficacy of Remdesivir in patients with mild, moderate, and severe Covid-19. The World Health Organization (WHO) has launched a large-scale trial of Solidarity in several countries at the same time, which assesses four drugs, including Remdesivir, Lopinavir/Ritonavir, Interferon beta-1a, and Hydroxychloroquine/Chloroquine, in patients with SARS-CoV-2 infection (10). In the present study, clinical trials on the effect of Remdesivir in treating Covid-19 patients were reviewed.

This is a rapid review of the evidence for the potential effects of Remdesivir, which intended to create a policy guide. To do so, health technology assessment studies indexed in medical databases were searched.

2. Methods

Studies indexed in MEDLINE and Cochrane Library databases were searched using the keywords, including drug name and its derivatives, including GS-5734, as well as disease name. The titles and abstracts of the articles were reviewed, and the studies were selected based on the inclusion and exclusion criteria. In addition, references of retrieved studies were checked to ensure the capture of the literature. Inclusion criteria were as follow: investigating the safety and efficacy of Remdesivir in Covid-19 patients, either in Persian or English, regardless of the study design. The search was carried out on April 21, 2020.

Moreover, to identify ongoing clinical trials in Iran and some countries, clinical trial registration systems were also searched (Table 1).

Table 1. Clinical Trial Registration System

Clinical Trial Registration Systems	Website Address
Australian New Zealand Clinical Trials Registry	https://www.anzctr.org.au/
Brazilian Clinical Trials Registry	http://www.ensaiosclinicos.gov.br/
Chinese Clinical Trial Registry	http://www.chictr.org.cn/index.aspx
Clinical Research Information Service, Republic of Korea	http://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp
Clinical Trials Registry - India	http://ctri.nic.in/Clinicaltrials/login.php
Cuban Public Registry of Clinical Trials	http://registroclinico.sld.cu/en/home
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/
German Clinical Trials Register	https://www.drks.de/drks_web/
Iranian Registry of Clinical Trials	https://www.irct.ir/
ISRCTN Registry, A Primary Clinical Trial Registry Recognized by WHO and ICMJE	http://www.isrctn.com/
Japan Primary Registries Network	https://rctportal.niph.go.jp/en/
Lebanese Clinical Trials Registry	http://lbctr.emro.who.int/
Thai Clinical Trials Registry	http://www.clinicaltrials.in.th/
The Netherlands National Trial Register	https://www.trialregister.nl/
Pan African Clinical Trial Registry	https://pactr.samrc.ac.za/Search.aspx
Peruvian Clinical Trial Registry	https://ensayosclinicos-repec.ins.gob.pe/en/
ClinicalTrials.gov	https://www.clinicaltrials.gov/
UMIN Clinical Trials Registry	https://www.umin.ac.jp/ctr/index/htm/

3. Results

In total 90 titles were retrieved, which after removing duplicates and applying inclusion criteria, 32 were included, all of which were published in 2020. A cohort that declared positive response of Remdesivir efficacy in compassionate use was found. However, the authors declared that due to the limitations related to the study design, the results may not be reliable, and to obtain valid results, randomized clinical trials with sufficient confidence should be performed. Also, two studies that investigated the effects of Remdesivir on COVID-19 patients were found. A letter-to-editor that has mentioned Remdesivir as an appropriate treatment for Covid-19 was also identified.

Most of the retrieved studies had a review design (25

studies), that mainly reported the course of Covid-19 treatment and mentioned to effects of Remdesivir in the treatment of this disease. None of the retrieved studies had a systematic review design (Table 2).

Table 2. List of Enrolled Studies

No.	Title	Type of study	Reference
1	A phase 3 randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of Remdesivir in hospitalized adult patients with mild and moderate 2019-nCoV respiratory disease	Randomized clinical trial controlled with placebo	(11)
2	A phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Remdesivir in hospitalized adult patients with severe 2019-nCoV respiratory disease	Randomized clinical trial controlled with placebo	(12)
3	A phase 3 randomized study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment	Randomized clinical trial controlled with routine treatment	(13)
4	Delayed initiation of Remdesivir in a COVID-19 positive patient	Case report	(14)
5	The first case of 2019 novel coronavirus in the United States	Case report	(15)
6	Compassionate use of Remdesivir for patients with severe Covid-19	Cohort	(9)
7	Remdesivir as a possible therapeutic option for the COVID-19	Letter to editor	(16)
8	Arguments in favor of Remdesivir for treating SARS-CoV-2 infections	Review	(17)
9	Current knowledge about the antivirals Remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses	Review	(18)
10	Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence	Review	(19)
11	COVID-19: An update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of Integrative Chinese–Western Medicine for the Management of 2019 novel coronavirus disease	Review	(20)
12	SARS-CoV-2: Recent reports on antiviral therapies based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other drugs for the treatment of the new coronavirus	Review	(21)
13	Cardiovascular considerations in treating patients with coronavirus (COVID-19)	Review	(22)
14	Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic	Review	(23)
15	Discovering drugs to treat coronavirus disease 2019 (COVID-19)	Review	(24)
16	Pharmacological therapeutics targeting RNA-dependent RNA polymerase, proteinase, and spike protein: From mechanistic studies to clinical trials for COVID-19	Review	(25)
17	Treatment options for COVID-19: The reality and challenges	Review	(26)
18	A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19)	Review	(27)
19	Potential therapeutic agents against COVID-19: What we know so far	Review	(28)
20	Drug treatment options for the 2019-new coronavirus (2019-nCoV)	Review	(29)
21	Compounds with therapeutic potential against novel respiratory 2019 coronavirus	Review	(30)
22	Coronavirus disease 2019 treatment: a review of early and emerging options	Review	(31)
23	Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets	Review	(32)
24	Clinical trials on drug repositioning for COVID-19 treatment	Review	(33)
25	COVID-2019: update on epidemiology, disease spread, and management	Review	(34)
26	Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review	Review	(35)
27	Antiviral treatment of COVID-19	Review	(36)
28	COVID-19: A brief overview of the discovery clinical trial	Review	(6)
29	Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods	Review	(37)
30	Insight into 2019 novel coronavirus - an updated interim review and lessons from SARS-CoV and MERS-CoV	Review	(38)
31	The epidemiology, diagnosis, and treatment of COVID-19	Review	(39)
32	Controversial treatments: An updated understanding of the coronavirus disease in 2019	Review	(40)

3.1. Randomized Clinical Trials

Registered clinical trials with different designs intended to investigate the safety and efficacy of Remdesivir in the treatment of Covid-19 were extracted from clinical trial registration systems (Table 3). In total, 15 protocols were found, which 13 were in primary stages. The other two were in phase three of clinical trials and aimed to investigate the effect of Remdesivir in treating patients with severe, moderate, or mild Covid-19. In the clinical trial registration system, it is mentioned that the first study is stopped prematurely due to the lack of a sufficient number of patients, and the second study is also suspended.

Table 3. List of Clinical Trials

No.	Title	Study Design	Comparison Groups	Country	Status
1	A phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Remdesivir in hospitalized adult patients with severe COVID-19	Phase III	Remdesivir Placebo	China	Terminated
2	A phase 3 randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of Remdesivir in hospitalized adult patients with mild and moderate COVID-19.	Phase III	Remdesivir Placebo	China	Suspended
3	Multicenter, retrospective study of the effects of Remdesivir in the treatment of severe Covid-19 infections	Retrospective Cohort	Remdesivir	France	Not yet recruiting
4	An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care (solidarity trial)	Phase II & Phase III	Chloroquine or hydroxychloroquine Local standard of care Lopinavir with Ritonavir (ditto) plus Interferon Lopinavir with Ritonavir (orally twice daily for 14 days) Remdesivir	Argentina, Brazil, Canada, Germany, India, Indonesia, Iran (Islamic Republic of), Norway, Peru, Qatar, South Africa, Spain, Switzerland, Thailand	Open to Recruitment
5	Expanded access treatment protocol: Remdesivir (RDV; GS-5734) for the treatment of SARS-CoV2 (CoV) infection- COVID-19	Phase IV	Remdesivir	France, Germany, Italy, Spain, Switzerland, United Kingdom	Ongoing (Available)
6	A phase 3 randomized study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with severe COVID-19	Phase III	Remdesivir Standard of Care	China, France, Germany, Hong Kong, Italy, Japan, Korea, Republic of Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States	Ongoing (Recruiting)
7	A phase 3 randomized study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment	Randomized Open-label Phase III	Remdesivir Standard of Care	China, France, Germany, Hong Kong, Italy, Japan, Korea, Republic of, Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States	Ongoing (Recruiting)

8	A phase 3 randomized study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with severe COVID-19	Randomized Open-label Phase III	Remdesivir Standard of care	China, France, Germany, Hong Kong, Italy, Japan, Korea, Republic of Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States	Ongoing (Recruiting)
9	Adverse events related to treatments used against coronavirus disease 2019	Observational (Cross-sectional case-only	Any drug used to treat Covid-19	France	Recruiting
10	Effect of treatments in patients hospitalized for severe COVID-19 pneumonia: a multicenter cohort study	Observational (Retrospective case-only)	Any drug used to treat Covid-19	France	Recruiting
11	A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalised adults	Phase III	Remdesivir Placebo	Denmark, Germany, Greece, Italy, Portugal, Spain, United Kingdom, Japan, Korea, Republic of Mexico, Singapore	Ongoing (recruiting)
12	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults (DisCoVeRy Trial)	Phase III	Remdesivir Lopinavir/ritonavir Interferon Beta-1A Hydroxychloroquine Standard of care	France	Ongoing (Recruiting)
13	A single-arm multicenter clinical trial to evaluate the safety and efficacy of Remdesivir in COVID-19 patients with progressive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)		Standard Treatment Remdesivir	IR Iran	Recruiting
14	A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults	Phase III	Remdesivir Placebo	USA, KOREA, Japan	Recruiting
15	The fleming [FMTVDM] directed CoVid-19 treatment protocol	Phase II & Phase III	Hydroxychloroquine, Azithromycin Hydroxychloroquine, Doxycycline Hydroxychloroquine, Clindamycin Hydroxychloroquine, Clindamycin, Primaquine-low dose, Hydroxychloroquine, Clindamycin, Primaquine-high dose Remdesivir Tocilizumab Methylprednisolone Interferon-Alpha2B Losartan Convalescent Serum	United States	Enrolling by invitation

On April 24, 2020, the results of the first trial on using Remdesivir to treat Covid-19 were posted on the World Health Organization's website, stating that Remdesivir had no effect on infected patients who were hospitalized due to the severe form of Covid-19. However, the report was removed shortly afterwards and a spokesman for the organization announced that the publication was wrong and premature (41).

Again, on April 29, 2020, the results of the above-mentioned trial were published in the Lancet after confirming the results through peer review. In that study, as the first controlled randomized clinical trial with placebo, 237 patients were divided into the control and Remdesivir groups (with a 1:2 ratio). The results obtained on the 28th day of the trial showed that; although the rate of recovery in the Remdesivir group was numerically better than the placebo group (65% vs. 58%), this 7% difference was not statistically significant [CI = -5.7 to 20.7]. Hence, further studies with larger sample sizes are needed to confirm the significance of this difference. On the other hand, samples isolated from the upper respiratory tract revealed that the drug couldn't decrease the viral load.

In a study of Remdesivir safety by Wang et al., the results showed that 66% of the drug-receiving group developed side effects, while in the control group, 64% of patients experienced such outcomes. In addition, 12% of patients in the Remdesivir group discontinued the treatment due to developing serious side effects, while in the control group, 5% of patients were dropped out.

Although the results of the study are published, the lack of definitive treatment for Covid-19 forced the US Food and Drug Administration (FDA) to release a letter on May 1, 2020, giving Gilead the right to distribute Remdesivir under an emergency use authorization (EUA). Under this license, Remdesivir is allowed to be prescribed only for hospitalized patients with severe Covid-19, including those with $SpO_2 \leq 94\%$ and requiring supplemental oxygen or mechanical respiratory support, under the supervision of health care professionals and by observing strict EUA conditions.

One of the most important issues noted in this letter is stating the following issues in all descriptive printed materials, including advertising materials related to the use of Remdesivir:

A) Remdesivir has not received FDA approval;

B) The FDA has authorized the use of Remdesivir under the EUA;

C) Remdesivir can only be prescribed as long as the emergency persists.

4. Conclusions

Based on the findings, evidence on the safety and efficacy of Remdesivir on patients with Covid-19 patients is not sufficient. However, if currently implementing clinical trials be completed, enough evidence would be available to decide whether to accept or reject the Remdesivir prescription. Since the effectiveness of Remdesivir is not clear yet, its prescription for Covid-19 patients has so far been limited to clinical trials, compassionate use, or emergency use.

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