Health Information : Jurnal Penelitian
Vol. 15 No. 2 (2023): Suplemen

Effectiveness of Remdesivir for the Treatment of COVID-19 In Preclinical and Clinical Studies: A Review

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Emergency conditions in early 2020 led the government to apply various policies to increase the recovery rate of patients with COVID-19, and one of them was by administering Remdesivir as one of the treatments for patients with COVID-19. Therefore, this study aims to determine the effectiveness of Remdesivir for COVID-19 treatment in preclinical and clinical studies. The research was conducted in a Literature review method based on a research journal that focused on Remdesivir and other drugs used for COVID-19 from online libraries, using keywords such as "Effectiveness," "Remdesivir," "COVID-19", "Antiviral," "Preclinical," and "Clinical" from international journals. The results indicate that in the preclinical study, Remdesivir was shown to have a selectivity index of 129.87, which means higher than the other drugs tested in the preclinical study. During the clinical study, compassionate use of Remdesivir may result in some clinical improvement in COVID-19 patients within 5, 10, and 15 days but did not show any significant difference.

INTRODUCTION

The incubation period of SARS-CoV-2 is five days, and the basic reproduction number is 2,24-3,58 (Antinori et al., 2020; Dabbous et al., 2021) through diffuse mediated airborne droplets or close communication (Antinori et al., 2020).On January 30, 2020, WHO declared the pandemic a public health emergency needing specific attention (Salvi & Patankar, 2020). However, no antiviral drugs specifically treat COVID-19 (Cascella et al., 2020). Remdesivir is the first COVID-19 drug to be converted into an adenosine triphosphate analog in cells (Abd-Elsalam et al., 2022). Interferon, Lopinavir/Ritonavir, Ribavirin, and Remdesivir are all antiviral drugs evaluated as potential COVID-19 therapies (Dabbous et al., 2021). However, several studies and other articles have reported that Remdesivir appears to be a promising therapy in cell cultures and animal species contaminated with SARS and MERS virus pathogens (Baker et al., 2020). The RNA-dependent on polymerase inhibitor virus was found to be a promising early therapeutic approach for COVID-19 due to its benefits for inhibiting acute respiratory syndrome (SARS-CoV-2) in vitro with very small dose amounts (Galiuto & Patrono, 2020).

The public health emergency prompted authorities to speed up the regulatory process and allow hospitals to use Remdesivir conditionally before the complete clearance process (Hsu, 2020). COVID-19 patients with severe diagnosis and treatment using Remdesivir revealed medical benefits in 36 of 53 cases (68 %). Randomized, placebo-controlled trials of Remdesivir treatment are required to assess efficacy (Jonathan Grein et al., 2020). Therefore, this study aims to establish the efficacy of Remdesivir against COVID-19. Research Objectives To find relevant publications, then reviewed, and conclusions are drawn.

METHOD

The research method was carried out by a literature review of the articles obtained, deselection by inclusion and exclusion criteria, then reviewing and concluding.

RESULT AND DISCUSSION

The development of antiviral drugs for combating COVID-19 is highly necessary due to its high transmission potential and the unpredictable course of the disease (Naserghandi, et al., 2020). SARS-CoV-2 is a virus that has spread worldwide, causing public health problems everywhere (Jean et al., 2020). Fever, dry cough, and other symptoms, such as headache, weakness, and shortness of breath, are the most common symptoms of COVID-19 (Canada, 2020). Several clinical and in vitro trials for drugs that may have efficacy in treating COVID-19 have been conducted since the outbreak began (X. Wang et al., 2020). Remdesivir may benefit medical improvement and recovery of hospitalized COVID-19 patients and may be considered a clinical alternative if available (Jiang et al., 2021).

Target	Drug	EC50	CC50	SI = CC 50/EC50	Source
Viral entry	Arbitol	4.11 µM	31.79 µM	7.73	Wang X et al. 2020
RNA synthesis	Remdesivir	0.77 µM	100 µM	129.87	Wang M, et al. 2020
	Ribavirin	109.50 µM	>400 µM	3.65	Wang M, et al. 2020
	Penciclovir	95.96 µM	>400 µM	4.17	Wang M, et al. 2020
	Favipiravir	61.88 µM	>400 µM	6.46	Wang M et al. 2020
Miscellaneous	Chloroquine	1.13 µM	100 µM	88.50	Wang M, et al. 2020

Table 1. *Results of Literature Review on the Effectiveness of Preclinical In Vitro Studies (Manli Wang et al., 2020; X. Wang et al., 2020)*

Research Title	Criterion	Treatment	Research Results	Author
"Remdesivir for 5 or 10 Days in Patients with Severe COVID-19"	Patients over 12 years old Infected with SARS-CoV-2 and confirmed by PCR Test Have radiographic evidence of pulmonary infiltrates Oxygen saturation 94% or less	Patients were divided into two categories of IV Remdesivir treatment 200 patients for five days and One hundred ninety-seven patients for ten days. Remdesivir IV 200mg on day 1 and 100mg for 4 and 9 days	5-day group 172 out of 200 patients completed treatment with an average duration of 5 days 10-day group 86 of the 197 patients completed treatment for an average of 10 days. Results of the 5-day group vs. 10-day group: Go back home: 60%, vs. 52% Mortality: 8%, vs. 11%	Goldman JD, et al. 2020
"Remdesivir for the Treatment of COVID-19 — Final Report"	Adults with lower respiratory tract infections	Remdesivir or placebo for up to 10 days (200 mg load dose on day 1, followed by 100 mg daily for up to 9 additional days)	541 patients were given Remdesivir, and 521 patients were given a placebo Patients receiving Remdesivir 10 days: 95% confidence interval [CI], 9 to 11	J. H beigel, et.al. 2020

			Patients receiving Remdesivir for 15 days: 95% CI, 13 to 18 Patients who received placebo on day 15: odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity	
"Remdesivir in Adults with Severe COVID-19: A Randomized, Double-blind, Placebo-controlled, Multicentre Trial"	Men and non-pregnant women over 18 years with COVID-19 infection Suffering from pneumonia Oxygen saturation 94% or lower Partial elevation of arterial oxygen to fractional inspirational oxygen of 300 mmHg within 12 days after symptom onset	Patients are separated into two categories. Group administered Remdesivir or placebo at the dose of 200mg on day one followed by 100 mg on days 2-10 in a single daily infusion	158 Patients receiving Remdesivir: hazard ratio 1·23 [95% CI 0·87–1·75]. 79 Patients receiving placebo: hazard ratio 1·52 [0·95–2·43)	Wang, Y. et al. 2020.

Table 2. *Results of Literature Review on the Effectiveness of Remdesivir in Clinical In Vivo Studies (Beigel et al., 2020; Goldman et al., 2020).*

Efficacy of Remdesivir on Covid-19 in Preclinical Trials

This study conducted research by collecting more than 30 journals to prove that Remdesivir is the best drug for treating COVID-19 patients. Three types of drugs are published in this journal, namely drugs that work on virus entry, RNA synthesis, and others.

Based on the results, the most effective drug for treating patients infected with COVID-19 is Remdesivir. This drug is considered effective for treating patients infected with COVID-19 because the selectivity index of Remdesivir is 129.87 with other drugs tested Arbitol 7.73, Ribavirin 3.65, Penciclovir 4.17, Favipiravir 6.46. Meanwhile, the selectivity index of Chloroquine is 88.50. It is proven that Remdesivir is more effective than Chloroquine.

Other drugs, such as Favipiravir (FPV), have been licensed to treat new viral diseases since 2014. It is a guanine analog that selectively inhibits RdRP RNA viruses (Lu et al., 2020). Favipiravir is still used in some countries to treat SARS-CoV-2. Nevertheless, no agreement exists on whether it is effective in treating COVID-19 (Damayanti et al., 2021). In addition, based on the results, it is not very effective for treating patients with COVID-19 infection, and other drugs mentioned in the results, such as Arbitol, Ribavirin, and Penciclovir.

Although none of these therapies have been shown to help fight COVID-19, some have shown promise in early-stage studies.

Efficacy of Remdesivir on COVID-19 in Clinical Studies

Some researchers have found it to have antiviral properties of SARS-CoV-2 and speed recovery. Others attribute its ineffectiveness to the increased danger of unnecessary treatment (Vitiello et al., 2021). Meanwhile, the use of Remdesivir was found to have no benefit in terms of mortality in the WHO solidarity trial. Even though it was an accessible study, there was less risk of bias in assessing objective outcomes, such as mortality (Pan H, 2021; Yan & Muller, 2021).

Based on the results of clinical studies about Remdesivir. The study was conducted on patients over 12 years of age, with some studies conducted on patients with problems suffering from pneumonia, having oxygen lower than 94%, and the criteria mentioned in Table 2. In this trial, the study was

separated into two categories: patients taking placebo and patients taking Remdesivir with the same dose of 200mg on day 1 and 100mg on the rest of the treatment i.e. 4 and 9 days after the first day. Based on the results, Remdesivir showed promising results for treating COVID-19 infection in the treatment of 5, 10, and 15, but it was no change.

The efficacy of Remdesivir may be limited, even if it holds promise in current randomized controlled trials. In order to produce potentially more potent COVID-19 antiviral drugs, a combination of IV and pulmonary injection dosing regimens should be examined immediately (Sun, 2020). Since Remdesivir is the primary FDA-approved antiviral drug for treating hospitalized SARS, coV-2 patients is critical to investigate its efficacy on the new variants of SARS-CoV-2. In addition, those who have been infected with the virus are known as Covid patients (Taha et al., 2021).

In another study, Remdesivir reduced the time it took hospitalized people undergoing supplemental oxygen to recover and may improve mortality outcomes while maintaining good effectiveness and safety. At 14 days, Remdesivir had less SAE than the placebo but did not reduce all-cause mortality or the need for invasive air circulation. Compared to 10 days of therapy, five days of Remdesivir it reduced the need for invasive ventilation and SAEs (Goldman et al., 2020). Remdesivir is the drug now receiving the most attention as a treatment that inhibits replication by interfering with the function of RNA-dependent RNA polymerase (RdRp). Nucleosides are the most fundamental structure of remdesivir (nucleotides). Elongation of the RNA chain of the coronavirus is no longer possible because this structure acts as a nucleoside analog. As a result, RdRp is suppressed by stopping the virus from replicating (Yoo, 2020). Another point is that Remdesivir has become a new antiviral drug that suppresses viral replication by prematurely stopping RNA transcription and potentially affecting various RNA viruses (Ferrara et al., 2020; Glaus et al., 2020).

Remdesivir is currently only available in controlled clinical studies. However, for those who are not eligible for clinical testing in the laboratory, Remdesivir can also be obtained through attention schemes and expansion programs. The true efficacy and safety of the drug will only be revealed through the results of these carefully controlled clinical trials (Selker et al., 2018). Furthermore, ethnic diversity was found in pharmacogenes associated with other drugs, such as chloroquine, in treating COVID-19 similar to Remdesivir. In conclusion, pharmacogenomic research for COVID-19 therapy seems urgently needed (D. Wang et al., 2020).

CONCLUSION

Remdesivir works by inhibiting the virus in the post-entry stage, based on preclinical studies with an EC 50 of 0.77 M CC50 of 100μM, resulting in a selectivity index of 129.87. During clinical studies, compassionate use of Remdesivir may produce some clinical improvements in COVID-19 patients in 5, 10, and 15 days but does not show significant difference results. Therefore, the drug can be used as the first treatment for patients with COVID-19 infection. Although it can be used to treat COVID-19 infection, the researchers did not include data on the types of patients for which the drug is effective. More research needs to be carried out to find which patients can use this drug and to see the safety of this drug for our bodies.

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