Archives of Razi Institute, Vol. 78, No. 3 (2023) 935-941

DOI: 10.22092/ARI.2022.360354.2574

Original Article

A Comparative Study of Antiretroviral (Lopinavir/Ritonavir) and Remdesivir Used in the Pandemic in Iraq on the Clinical Outcome in Patients with SARS-CoV-2

Alabdalaali, M. M[1 *], Hadi, A. M[1]

1. College of Pharmacy, University of Basra, Basra, Iraq

Received 20 October 2022; Accepted 26 November 2022
Corresponding Author: mustafamufeedsch@gmail.com

Abstract

The SARS-CoV-2 virus, which emerged in December 2019, has infected millions worldwide and caused many deaths. Due to its high mortality rate, several studies assessed the effectiveness of different drugs against COVID-19, mainly in reducing the hospitalization rate among the elderly and compromised patients. Lopinavir-ritonavir combination and remdesivir were among the medications used to treat COVID-19. Due to considerable differences in the effectiveness and clinical outcomes of the two treatments, this study aimed to compare the clinical outcomes between COVID-19 patients treated with antiretrovirals (lopinavir-ritonavir) and remdesivir. A total of 33 patients on lopinavir-ritonavir and 35 on remdesivir were selected for this study. A retrospective comparative analysis was conducted based on demographic characteristics, hospital stay, laboratory parameters of C-reactive protein (CRP) and plasma blood oxygen saturation (SPO_2), clinical treatment, and a clinical outcome assessment extracted from hospital archive data. Both treatments improved patient outcomes, yet there was a significant difference between lopinavir-ritonavir and remdesivir groups in platelet count, CRP, SPO_2, and monocyte results, with remdesivir showing better clinical outcomes. No significant difference was reported in white blood cells, lymphopenia, and lactate dehydrogenase between the two treatments. It is still necessary to conduct further research to determine how effective the two treatments are in treating severe COVID-19 cases due to the limited number of available studies and the inconsistency in research methods and measurements.

Keywords: Antiretroviral drugs, Coronavirus, COVID-19, Lopinavir-ritonavir, Remdesivir, SARS-CoV-2

1. Introduction

COVID-19 was discovered in Wuhan, China, in December 2019 (1). Since then, the virus has spread worldwide and become a pandemic, infecting millions of people and contributing to a massive loss of life (2). The unique pathophysiology of the SARS-CoV-2 virus has led health organizations and governments to launch ongoing trials to find a cure and reduce morbidity and mortality. The history of the human coronavirus dates to the mid-1960s when Tyrrell and Benoy isolated coronaviruses from the nasal washes of patients with the common cold in 1966, and it was the first time to identify the virus in humans (3). Coronaviruses are viral envelopes that contain large, positive, and single-stranded RNAs. Because of their morphology, they are referred to as spherical virions with an outer shell resembling a solar corona (3). The four subfamilies of coronavirus, including alpha, beta, gamma, and delta, have different animal origins, particularly mammals, pigs, and birds (4). SARS-CoV-2 belongs to the beta Coronaviridae subfamily, similar to MERS-CoV and SARS-CoV viruses (5).

COVID-19 pathogenesis involves two processes, including the replication of SARS-CoV-2, which

occurs early in the disease, and dysregulated immune/inflammatory responses, which cause tissue damage later (6). These findings suggest that therapies targeting SARS-CoV-2 early in the disease will be most effective, while immunosuppressive and anti-inflammatory therapies will be most effective later (6). Severe outcomes among COVID-19 patients were associated with many demographic characteristics, as well as behavioral, physiological, and genetic risk factors. In addition, certain disorders and diseases, such as hypertension, diabetes, chronic obstructive pulmonary disease, and coagulation disorders, have contributed significantly to health deterioration among COVID-19 patients (7). When it comes to clinical manifestations, the working case definitions for viral testing include severe acute respiratory illness with fever, cough, and respiratory symptoms (8). However, some COVID-19 patients are completely asymptomatic, while others might show mild flu and gastrointestinal symptoms or severe symptoms, such as pneumonia and respiratory distress syndrome. In the recent SARS-CoV-2 variant, symptoms begin with fatigue, muscle pain, sore throat, nasal congestion, followed by dyspnea, which may become significantly severe, and upper respiratory tract infections, which can result in severe pneumonia, according to CT images (9). Blood tests are generally taken before starting the treatment and afterward for the follow-up. This includes analyzing complete blood count, C-reactive protein (CRP) inflammatory marker, lymphopenia (LYMPH) marker for poor prognosis, and D-Dimer for deterioration (10). Conditions such as LYMPH (63%), leukocytosis (24-30%), and leukopenia (9-25%), in addition to raised aspartate, alanine aminotransferases, and high levels of inflammation indices, were the most common lab abnormalities among hospitalized pneumonia patients (11, 12).

Tremendous efforts aimed to find the most effective and safest treatment for COVID-19. Antiviral drugs were the initial therapies used for clearance; however, they showed variation between different clinical trials, either with or without benefits. While these drugs, especially those targeting viral or host proteins, have great potential for treating diseases in Iraq, access to these therapies is currently limited. One available and repurposed drug used to treat COVID-19 is lopinavir-ritonavir, a protease inhibitor approved by the U.S. Food and Drug Administration (FDA) for treating HIV infection (5). Lopinavir-ritonavir was priorly used on SARS and MERS patients as it demonstrated *in vitro* inhibition against their causing viruses, and its use to treat COVID-19 patients was based on that experience (13). To inhibit viral replication, lopinavir must be co-administered with ritonavir due to its low oral bioavailability and extensive metabolism by CYP3A4 (14, 15). Multiple studies assessed the efficacy of the lopinavir-ritonavir combination on COVID-19 patients' outcomes, reporting inconsistent findings. According to Patel, Patel (6), no benefits were observed in the virological cure, adverse events, and mortality outcomes when lopinavir-ritonavir was added to COVID-19 patients' standard care. The infectious disease society of America (IDSA) guidelines were also against using lopinavir-ritonavir for prophylaxis or the treatment of COVID-19 patients (16).

On the other hand, Luo, Zheng (17) reported the clinical improvement and effectiveness of lopinavir-ritonavir, especially in early treatment. Another FDA-approved COVID-19 drug previously used to treat the Ebola virus is remdesivir (16). This promising drug is the pharmacologically active substrate of adenosine nucleotide prodrug and acts by impeding viral RNA synthesis (18). Unlike lopinavir-ritonavir, remdesivir was recommended by IDSA and proven effective in treating COVID-19, especially when given at the early stages of the disease (16). Additionally, remdesivir exerted superior antiviral activity over lopinavir-ritonavir (14).

To ensure that this treatment line remains safe and effective for COVID-19 patients in Iraq and considering the contrary findings regarding the outcomes of the two drugs, this study aimed to compare clinical outcomes between COVID-19 patients receiving antiretroviral therapy (lopinavir-ritonavir)

and those receiving remdesivir to support treatment decision-making.

2. Materials and Methods

Our retrospective study involved all adult inpatients at Basra General Hospital (Basra, Iraq) with laboratory-confirmed COVID-19. Data were collected between September and December 2020. The study included COVID RT-PCR-positive patients aged over 18 years who were classified as severe or severely ill COVID-19 cases and required oxygen therapy within 72 h of hospital admission. The patients were classified as severe to severely ill COVID-19 based on the extent of lung involvement, blood oxygen, and oxygen support. In contrast, patients with comorbid conditions, such as heart disease, diabetes mellitus, respiratory disease, and immunosuppression, as well as those receiving continuous positive airway pressure therapy, were excluded from the study. Afterward, 33 patients on lopinavir-ritonavir and 35 on remdesivir were included in the study. The comparative analysis of survivors and non-survivors was conducted based on demographic characteristics, hospital stay, laboratory parameters of CRP and plasma blood oxygen saturation (SPO_2), clinical treatment, as well as a clinical outcome assessment extracted from hospital archive data. Patients' symptoms were also monitored and compared to verify the disappearance of symptoms associated with the type of treatment, such as fever, tachypnea, shortness of breath, and gastrointestinal symptoms.

2.1. Statistical Analysis

The data were analyzed using the SPSS software (version 26.0). Descriptive statistics, including age, gender, temperature, and comorbidities, were analyzed for the study sample. An independent sample t-test was used to compare the mean differences in blood indicators between the lopinavir-ritonavir and remdesivir groups. Frequencies and percentages were also calculated and presented in tables and figures to compare the results before and after the treatment and compare them to days of hospital stay.

3. Results

Table 1 shows descriptive statistics of the study sample. The mean age of patients was 65 years (IQR: 56-71). There were 89 (56%) men and 69 (44%) women in the remdesivir group and 51 (65%) men and 27 (35%) women in the lopinavir-ritonavir group (Table 1). Hypertension was the most common comorbidity, followed by diabetes. Totally, 51.4% of patients received remdesivir, while 48.6% received lopinavir-ritonavir.

Table 1. Baseline descriptive statistics of the study sample

	Remdesivir (n=35)	**Lopinavir/ritonavir (n=33)**
Age, years	51 (32 – 69)	48 (30 – 68)
Sex, Men	25 (71%)	25 (76%
Women	10 (29%)	8 (24%)
Any comorbidities	26 (74%)	20 (61%)
Diabetes Mellites	8 (23%)	8 (24%)
Hypertension	22 (63%)	15 (45%)
Temp C	37.3 (36.9-37.6)	37.2 (36.9 – 37.5)

An independent sample t-test was used (Table 2) to compare blood test results between lopinavir-ritonavir and remdesivir groups. The results showed significant differences in the monocyte (Mono), platelet count (PLT), CRP, and SPO_2 (P<0.05) between the two groups. On the other hand, there were no statistically significant differences between the two groups in white blood cells (WBC) results (P=0.198), LYMPH (P=0.057), and lactate dehydrogenase (LDH) (P=0.085).

Table 3 illustrates the PLT results before and after medication according to the hospital stay. Based on the table 3, normal PLT among the lopinavir-ritonavir group showed an improvement from 90.9% to 97%, while the number of those above normal values reduced from 9.1% to 3%. On the other hand, normal PLT among the remdesivir group reduced from 62.9% to 62% after the medication, while the number of those above normal values increased from 37.1% to 40%. The most considerable effects were observed in patients with (1-7 days) and (7-13 days) of hospital stay

in remdesivir and lopinavir-ritonavir groups, respectively.

Table 4 illustrates CRP results before and after medication according to the hospital stay. Based on the table 4, the percentage of abnormal CRP reduced in 33.3% of the lopinavir-ritonavir group and 40% of the remdesivir group.

Figure 1 shows Mono and SPO_2 results before and after medication according to the hospital stay. The Mono test results showed an improvement in both the lopinavir-ritonavir and remdesivir groups. In the lopinavir-ritonavir group, improvements were noted in patients who stayed (1-7), (7-13), and (13-19) days (A.1). On the other hand, in the remdesivir group, improvements were observed in patients who stayed (1-7) and (7-13) days (A.2). As for the SPO_2 results, shortness of breath reduced in both treatment groups. Similar to the Mono results, improvements were noted in lopinavir-ritonavir patients who stayed (1-7), (7-13), and (13-19) days (B.1). On the other hand, improvements were noted in remdesivir patients who stayed (1-7) and (7-13) days (B.2).

Table 2. Comparison of blood test results among Lopinavir/ritonavir and Remdesivir groups

	Drugs	Mean +SD	Sig
WBC	Lopinavir/ritonavir Remdesivir	11.072+3.947 9.727+4.546	0.198
MONO	Lopinavir/ritonavir Remdesivir	12.072+5.904 5.485+3.23	0.000
LYMPH	Lopinavir/ritonavir Remdesivir	12.306+5.645 9.142+7.621	0.057
LDH	Lopinavir/ritonavir Remdesivir	528.397+145.04 453.7+193.788	0.085
PLT	Lopinavir/ritonavir Remdesivir	239.454+78.564 364.457+120.482	0.000
CRP	Lopinavir/ritonavir Remdesivir	65.303+75.903 24.628+25.738	0.004
SPO_2	Lopinavir/ritonavir Remdesivir	89.393+11.562 94.171+7.0938	0.043

Table 3. Platelet count results before and after medication according to the hospital stay

Lopinavir/Ritonavir							Remdesivir					
Platelet Count		Before		After		Total		Before		After		Total
		Normal	Above	Normal	Above			Normal	Above	Normal	Above	
1-7 days	c	4	0	4	0	4	c	12	4	8	8	16
	%	100	0	100	0	100	%	75	25	50	50	100
7-13 days	c	15	3	18	0	18	c	10	7	11	6	17
	%	83.3	16.7	100	0	100	%	58.8	41.2	64.7	35.3	100
13-19 days	c	9	0	8	1	9	c	-	1	1	-	1
	%	100	0	88.9	11.1	10	%	-	100	100	-	100
19 & more days	c	2	0	2	0	2	c	-	1	1	-	1
	%	100	0	100	0	100	%	-	100	100	-	100
total	c	30	3	32	1	33	c	22	13	21	14	35
	%	90.9	9.1	97	3	100	%	62.9	37.1	60	40	100

Table 4. C-Reactive Protein results before and after medication according to the hospital stay

CRP		Lopinavir/Ritonavir					Remdesivir			
		Before	After		Total		Before	After		Total
		Abnormal	Normal	Abnormal			Abnormal	Normal	Abnormal	
1-7 days	c	4	2	2	4	C	16	10	6	16
	%	100	50	50	100	%	100	62.5	37.5	100
7-13 days	c	18	7	11	18	C	17	4	13	17
	%	100	38.9	61.1	100	%	100	23.5	76.5	100
13-19 days	c	9	2	7	9	C	1	-	1	1
	%	100	22.2	77.8	100	%	100	-	100	100
19 & more days	c	2	0	2	2	C	1	-	1	1
	%	100	0	100	100	%	100	-	100	100
total	c	33	11	22	33	C	35	14	21	35
	%	100	33.3	66.7	100	%	100	40	60	100

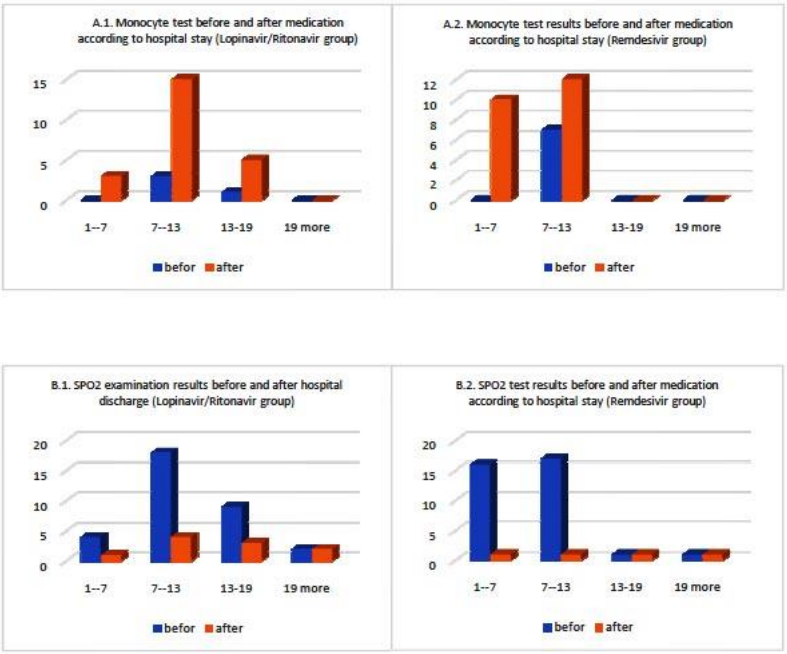

Figure 1. Monocyte and SPO_2 results before and after medication according to the hospital stay

4. Discussion

Viral infections are more challenging to treat. They are generally self-resolving and do not require treatment. However, some viruses require antiviral medications to alleviate symptoms. For COVID-19, multiple medications have been recommended to relieve the symptoms, such as lopinavir-ritonavir and remdesivir, with varying effectiveness. In the present study, both treatments improved patient outcomes; however, there was a significant difference between lopinavir-ritonavir and remdesivir groups in PLT, CRP, SPO_2, and Mono results, with remdesivir showing better clinical outcomes (Table 2). The PLT was improved in 6.1% of patients when lopinavir-ritonavir was administered; however, no improvements were noted in the remdesivir group (Table 3). Kalantari, Fard (19) found opposite results, with both groups improving and the remdesivir group showing a more significant improvement. Nevertheless, this improvement was not statistically significant. On the

other hand, Cao, Wang (20) reported no differences in PLT before and after the administration of lopinavir-ritonavir. As for the CRP, the value reduced among 40% of the remdesivir group and 33.3% of the lopinavir-ritonavir group (Table 4). This finding was supported by Kalantari, Fard (19), who reported a significant reduction in CRP between admission and discharge, which was higher among patients who received remdesivir from (43.88±9.50) to (16.88±14.27), compared to the lopinavir-ritonavir group from (44.73±10.85) to (31.64±19.37). Another study by Castle, Williams (21) reported considerable regulating effects of remdesivir on CRP levels among COVID-19 patients. The results of the Sevilla-Castillo, Roque-Reyes (22) study, however, reported that lopinavir-ritonavir is ineffective in treating COVID-19 patients as it fails to reduce CRP, LDH, D-Dimer, and LYMPH. When it comes to SPO_2, shortness of breath was improved when both lopinavir-ritonavir and remdesivir were administered (Figure 1.B.1 and B.2). However, the mean of the remdesivir group (94.171±7.0938) showed significantly better improvements, compared to the mean of the lopinavir-ritonavir group (89.393±11.562) as shown in table 2. This was supported by Castle, Williams (21), who found that remdesivir effectively improved the clinical condition of 68% of COVID-19 patients with an oxygen saturation of 94% or less. Lopinavir-ritonavir, on the other hand, did not significantly improve oxygen saturation among patients in Baden and Rubin (23) clinical study. Our study also reported significantly different Mono results between both groups, with numerous patients responding to the remdesivir treatment (5.485±3.23), while the lopinavir-ritonavir group made a slight improvement (12.072±5.904). Unlike our findings, Castle, Williams (21) reported remdesivir to have only a slight regulating effect on Mono counts.

The current study had some limitations. First, due to the lack of a control group, neither treatment regimen could be compared to standard care. Second, the sample size in our study was relatively small, which makes it difficult to verify whether a particular outcome was actual. Therefore, similar studies are recommended with a larger sample size, more laboratory parameters, and a control group to compare both treatments to one another and standard care.

With an extensive array of antiviral treatments available for COVID-19, it is challenging to determine which treatment is effective and which patients can benefit from it. Many studies and comparative analyses were conducted to measure the effectiveness of these treatments. In the current study, the remdesivir treatment showed noticeable advantages and a significant difference in improving CRP, SPO_2, Mono, and PLT among patients, compared to the lopinavir-ritonavir treatment. The improvements were mainly noted in patients with shorter hospital stays. Other laboratory parameters, such as WBC, LYMPH, and LDH, were not significantly different between the two treatments. While some studies supported these findings, others found contradicting results. Therefore, more studies are required to compare both treatments and assess their effectiveness in treating patients with severe COVID-19.

Authors' Contribution

Study concept and design: M. M. A.
Acquisition of data: A. M. H.
Analysis and interpretation of data: M. M. A.
Drafting of the manuscript: A. M. H.
Critical revision of the manuscript for important intellectual content: A. M. H.
Statistical analysis: M. M. A.
Administrative, technical, and material support: M. M. A.

Ethics

The study protocol approved by the Ethics Committee of the University of Baghdad, Baghdad, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Ahmad T, Khan M, Haroon, Musa TH, Nasir S, Hui J, et al. COVID-19: Zoonotic aspects. Travel Med Infect Dis. 2020;36:101607.
2. Chang D, Chang X, He Y, Tan KJK. The determinants of COVID-19 morbidity and mortality across countries. Sci Rep. 2022;12(1):5888.
3. Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020;25(3):278-80.
4. Hameed RY, Nathir I, Abdulsahib WK, Almashhadani HA. Study the effect of biosynthesized gold nanoparticles on the enzymatic activity of alpha-Amylase. Res J Pharm. 2022;15(8):3459-65.
5. Nabi G, Khan S. Risk of COVID-19 pneumonia in aquatic mammals. Environ Res. 2020;188:109732.
6. Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, Khosla PP. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. J Infect Public Health. 2021;14(6):740-8.
7. NIH. Clinical Management of Adults Summary. COVID-19 Treatment Guidelines 2022 [Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights.
8. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-55.
9. SAl-Shaheeb H, Hashim K, Mohammed AK, Almashhadani HA, Al Fandi A. Assessment of lipid profile with HbA1c in type 2 diabetic Iraqi patients. Revis Bionatura 2022;7(3):29.
10. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, Jacquerioz F. Clinical features of covid-19. BMJ. 2020;369:1470.
11. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-23.
12. van Eijk LE, Binkhorst M, Bourgonje AR, Offringa AK, Mulder DJ, Bos EM, et al. COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. J Pathol. 2021;254(4):307-31.
13. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488-94.
14. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis. 2015;212(12):1904-13.
15. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
16. Cooper CL, van Heeswijk RP, Gallicano K, Cameron DW. A review of low-dose ritonavir in protease inhibitor combination therapy. Clin Infect Dis. 2003;36(12):1585-92.
17. Luo P, Zheng JL, Liu Y, Qiu L, Liu XL, Xue HY, et al. Effectiveness of early treatment of lopinavir-ritonavir in patients with severe COVID-19: a case series. Clin Med (Lond). 2021;21(1):e80-e3.
18. IDSA. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. 2020.
19. Kalantari S, Fard SR, Maleki D, Taher MT, Yassin Z, Alimohamadi Y, et al. Comparing the effectiveness of Atazanavir/Ritonavir/Dolutegravir/Hydroxychloroquine and Lopinavir/Ritonavir/Hydroxychloroquine treatment regimens in COVID-19 patients. J Med Virol. 2021;93(12):6557-65.
20. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-99.
21. Castle RD, Williams MA, Bushell WC, Rindfleisch JA, Peterson CT, Marzolf J, et al. Implications for Systemic Approaches to COVID-19: Effect Sizes of Remdesivir, Tocilizumab, Melatonin, Vitamin D3, and Meditation. J Inflamm Res. 2021;14:4859-76.
22. Sevilla-Castillo F, Roque-Reyes OJ, Romero-Lechuga F, Gomez-Nunez MF, Castillo-Lopez M, Medina-Santos D, et al. Both Chloroquine and Lopinavir/Ritonavir Are Ineffective for COVID-19 Treatment and Combined Worsen the Pathology: A Single-Center Experience with Severely Ill Patients. Biomed Res Int. 2021;2021:8821318.
23. Baden LR, Rubin EJ. Covid-19 - The Search for Effective Therapy. N Engl J Med. 2020;382(19):1851-2.