The Evaluation of Remdesivir Utilization Pattern and Its Correlation with Clinical Indicators in Hospitalized Patients During COVID-19 Pandemic; A Retrospective Cross-sectional Study

Yasaman Soroush, Hadi Esmailyi*, Nasibeh Ghalandari

Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: 2023-06-24, Revised: 2023-09-20, Accepted: 2023-11-03, Published: 2023-12-31

Abstract

Background: In 2019 COVID became the cause of a pandemic, with approximately 500,000 deaths in six months worldwide. Remdesivir, the first drug approved by the U.S. Food and Drug Administration (FDA) for COVID-19 treatment, gained attention from numerous medical centers worldwide. The consecutive waves of COVID-19 peaks in Iran, coupled with the lack of widespread vaccination, and high consumption leading to a shortage of remdesivir in the country, prompted an investigation into the usage patterns of remdesivir and its correlation with clinical indicators in hospitalized patients.

Methods: A retrospective cross-sectional study was conducted using 390 patients' electronic records in seven different hospitals. Electronic records were reviewed and information was extracted under four categories: demographic data, lab test results at admission, medication information, and lab test results after completing treatment. Patients were classified into three time periods based on the date of their first remdesivir injection. Outcomes were defined as final clinical status and length of stay in hospital.

Results: A total of 390 patients were enrolled, with 198 females and 192 males. The longest hospital stay was 88 days, with an average of 7.5 days. A total of 1,979 doses of remdesivir were prescribed, with 224 doses being in accordance with the national protocol, 22 doses exceeding the protocol, and 144 doses below the protocol. The overall average dose consumption was 5.07 for each patient.

Conclusion: Overall pattern of remdesivir utilization in the hospitals evaluated in this study (affiliated with Shahid Beheshti University of Medical Sciences) has been reasonable and in accordance with national protocols for COVID-19 infection.

J Pharm Care 2023; 11(4): 226-232.

Keywords: COVID-19; Remdesivir; Drug Utilization Pattern;Cross-Sectional Study

Introduction

At the end of 2019, the World Health Organization reported a new pneumonia in Wuhan, China. The disease, named SARS-CoV-2, became the cause of a pandemic, with approximately 10 million cases and 500,000 deaths in around six months. The virus belongs to the RNA virus group and the coronavirus family, and it enters the body by binding to ACE2 receptors through its protein spikes. By using the RNA polymerase enzyme, it replicates and produces new viral components, leading to the spread of infection (1-3).

Remdesivir is a pre-viral antiviral drug developed by Gilead Sciences in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in 2009 to treat RNA viruses. It belongs to the nucleoside analogs group. Nucleoside analogs require phosphorylation for effective viral polymerization, which is a slow and time-consuming process. To overcome this issue, the addition of ester, monophosphate, and amide phosphate groups facilitates their entry into cells and expedites the phosphorylation process (4, 5).

*** Corresponding Author:** Dr Hadi Esmailyi
Address: Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Niyayesh Highway, Valiasr Ave., Tehran, Iran, Postal code: 1996835113, Telefax:+982188873704.
Email: Esmaily_hadi@sbmu.ac.ir

Remdesivir, the first drug approved by the U.S. Food and Drug Administration (FDA) for COVID-19 treatment, gained attention from numerous medical centers worldwide. Emergency use of this drug was initially announced in May 2020 and later approved for the treatment of hospitalized patients with low oxygen saturation for a 10-day period. Subsequent studies showed that a 5-day treatment course with remdesivir had similar effects to the 10-day course. Although remdesivir reduced hospitalization duration and recovery time, it did not significantly lengthen patients' survival (6, 7).

On August 15, 2020, remdesivir was approved for the treatment of COVID-19 in Iran and was included in the Iran's COVID-19 treatment protocol (8). After that, and according to the cost analysis conducted in several hospitals nationwide, remdesivir was the most expensive drug used in Iran hospitals during the spring quarter and afterward. Therefore, the consecutive waves of COVID-19 in Iran, coupled with the lack of widespread vaccination, and high consumption leading to a shortage of remdesivir in the country, prompted an investigation into the usage patterns of remdesivir and its correlation with clinical indicators in hospitalized patients at the Shahid Beheshti University of Medical Sciences hospitals in from March 2021 until September 2021.

Considering the time constraints in dealing with emerging diseases and the assessment of drug usage patterns, especially during a widespread epidemic at a national and international level, analyzing drug consumption patterns can play a significant role in improving a country's healthcare situation. Drug consumption patterns not only indicate the extent and type of therapeutic interventions used but also contribute to evaluating healthcare costs, enabling healthcare policymakers at the hospital or national level to make changes and improvements to healthcare programs.

This study's aim is to provide insights into the characteristics and outcomes of COVID-19 patients receiving remdesivir treatment in hospital setting.

Methods

This is a retrospective cross-sectional study that focuses on patients diagnosed with COVID-19, receiving remdesivir as an inpatient intervention. Based on Cochran sample size equation(9), the sample size was estimated 385 individuals and we eventually enrolled 390 patients in the study.

The researchers reviewed electronic records and extracted information under four categories: demographic data, lab test results at admission, medication information, and lab test results after completing treatment. Specifically, the total number of remdesivir was recorded and classified in three groups based on the national COVID guideline (available at Iran Medical Council website) (8). Based on this national guideline, patients receiving a total six doses were considered treated according to protocol and patients receiving less or more doses were classified accordingly. Also, Patients were classified into three time periods based on the date of their first remdesivir injection. Time A (from 21 March until 21 May), Time B (from 22 May until 21 June) and Time C (from 22 June until 22 September). Important to note, during time A and time C Iran was facing two separate waves of illness, admission and death.

Confirmation of COVID-19 infection was through a positive PCR results, COVID-19 typical lung tissue involvement in CT imaging, or clinical symptoms. Inclusion criteria were defined as patients hospitalized and receiving at least one dose of remdesivir. Exclusion criteria were defined as remdesivir usage for reasons other than COVID-19 and previous use of remdesivir in another medical centers.

The outcomes of this study were the pattern of remdesivir administration in Shahid Beheshti Medical Sciences Hospitals, determining the relationship between the dose of remdesivir received and clinical indicators (length of hospitalization, oxygen dependence, ICU admission, receiving corticosteroids, and Anti-IL-6 agents, and time of receiving drugs in disease duration), determining the relationship between the mortality of patients with the dose of remdesivir.

Data analysis was conducted using the SPSS software version 16. Descriptive results were reported as means and medians. Level of significance of 5% and a study power of 80% was chosen. Mann Whitney-U test (for two ranked independent samples), Spearman correlation (for non parametric rank correlation), Kruskal-Wallis (for two ranked dependent samples) and ANOVA (for multiple independent variance analysis) were used in analyzing data.

Results

A total of 390 patients were enrolled, with 198 females and 192 males. The average age of the patients was 56.7 years, ranging from 16 to 93 years. The highest number of patients was observed in Imam Hussein Hospital (96 patients, 24.6%), while the lowest number was in Modarres and Taleghani Hospitals (36 patients, 9.2%). The distribution of patients in other hospitals is described in detail in Table 1. The study period showed the lowest number of patients (30) in the second period (Time B) and 136 and 224 patients in the first (Time A) and third (Time C) periods, respectively. The longest hospital stay was 88 days, with an average of 7.5 days.

The drugs were categorized into three main groups: Remdesivir, other drugs prescribed for COVID-19 treatment (such as corticosteroids, antivirals, etc.), and drugs prescribed to patients for reasons other than COVID-19 treatment during their hospital stay.

Remdesivir: A total of 1,979 doses of remdesivir were prescribed, with 224 doses being in accordance with the national protocol, 22 doses exceeding the protocol, and 144 doses below the protocol. Among the 144 patients who received less than the protocol, only 29 cases resulted in death. Among these 29 cases, only 6 patients were hospitalized for more than 6 days or exactly 6 days before their death, while the remaining 23 cases died before 6 days of hospitalization. Among the 115 patients who received less than the protocol and did not die, 88 patients were hospitalized for less than 6 days, and 27 patients were hospitalized for more than 5 days. The highest number of prescribed doses of remdesivir was in Shohada Tajrish Hospital (420 doses), and the lowest number was in Sevvom Shaban Hospital (109 doses). The overall average dose consumption was 5.07 with a standard deviation of 0.5. Table 2 and 3 demonstrates the results in detail.

The relationship between the utilization of remdesivir over time and the length of hospital stay was analyzed using non-parametric tests due to the non-normal distribution. The Kruskal-Wallis test showed no significant difference in remdesivir consumption between the three time periods and between the protocol-compliant and non-compliant groups. However, the Spearman correlation test demonstrated a significant but weak relationship between remdesivir consumption and the length of hospital stay ($p < 0.001$, $r = 0.28$).

Table 1. Frequency and Percentage of Admission time, Gender and Hospitals

		Frequency (Percentage)
Admission time	Time A	136 (34.9%)
	Time B	30 (7.7%)
	Time C	224 (57.4%)
Gender	Female	198 (50.8%)
	Male	192 (49.2%)
Hospital	Imam Hossein	96 (24.6%)
	Sevvom Shaban	22 (5.6%)
	Shohada Tajrish	78 (20%)
	Taleghani	36 (9.2%)
	Loghman	56 (14.4%)
	Modarres	36 (9.2%)
	Mofateh	66 (16.9%)

Table 2. Frequency of patients treated with different Remdesivir doses.

Total number of doses	Imam Hossein	Sevvom Shaban	Shohada. Tajrish	Taleghani	Loghman	Modarres	Mofateh	Total number of patients
	Number of patients in each hospital which received the mentioned number of doses							
1 dose	2	0	0	0	0	1	3	6
2 dose	2	4	7	4	15	1	11	44
3 dose	5	1	4	3	7	1	10	31
4 dose	8	1	2	0	4	1	9	25
5 dose	6	2	10	4	4	4	8	38
6 dose	68	14	52	20	25	28	17	224
7 dose	4	0	1	5	1	0	8	19
8 dose	1	0	1	0	0	0	0	2
9 dose	0	0	1	0	0	0	0	1
Cumulative doses	527	109	420	192	244	198	289	390
Dose per patient	5.48	4.95	5.38	5.33	4.35	5.5	4.37	5.07

Drugs prescribed for COVID treatment (other than remdesivir): Regarding other drugs effective in COVID-19 treatment, three main categories were identified: corticosteroids, IL-6 inhibitors, and other antiviral drugs. According to the data, 358 patients (91.8%) received corticosteroids, 52 patients (13.3%) received IL-6 inhibitors, and 99 patients (25.4%) received antiviral drugs other than remdesivir.

Drugs prescribed for reasons other than COVID treatment: The other drugs used by patients for reasons other than direct COVID-19 treatment were also extracted and grouped based on their therapeutic class and Drug Related Problems (DRPs). Based on this data, we analyzed the number of different drug classes used by each patient and considered it as a surrogate for comorbidities for further analyses. Distribution of DRP frequency in different disease categories mentioned in Table 4.

Final Clinical Status: Out of all the patients, information on the outcome was available for 365 patients, while 25 patients could not be followed. Among the 365 patients, 58 patients died, with only 5 deaths occurring Time B. The distribution of outcomes based on hospitals and time is shown in Tables 5 and Table 6.

Among the 58 deceased patients, half of them were hospitalized for 6 days or less, and the average length of hospital stay for the deceased patients was 10.72 days.

Final clinical status, age and gender: The association between gender and final clinical status was examined using the Mann-Whitney test, which showed no significant correlation between the two ($p=0.576$). Similarly, the Spearman test revealed a positive correlation ($p<0.001$ and $r=0.2$) between age and final clinical status.

Final Clinical status and Time periods of admission: The Kruskal-Wallis test showed no significant relationship between time of stay (time A to C) and final clinical status ($p=0.1$). However, the Spearman test indicated a significant difference ($p<0.001$) in final clinical status among different hospitals.

Final clinical status and Drugs: There was no significant correlation found between the use of remdesivir and final clinical status ($p=0.77$) according to the Spearman test. Additionally, the Mann-Whitney test did not find a significant association between the use of corticosteroids and final clinical status ($p=0.13$). However, there was a significant difference ($p=0.03$) in the final clinical status between the group that received IL-6 inhibitor and the group that did not receive it. Analysis of the results showed that patients who did not receive IL-6 inhibitors had better clinical outcomes.

Table 3.Percentage of doses in each hospital based on national protocol

	Imam Hossein	Sevvom Shaban	Shohada.Tajrish	Taleghani	Loghman	Modarres	Mofateh	Total
Less than protocol	23.96%	36.36%	29.49%	30.55	53.57%	22.22%	62.12%	36.92%
Per-Protocol	70.83	63.64%	66.66%%	55.56%	44.64%	77.78%	25.76%	57.44%
More than Protocol	5.21%	0%	3.85%	13.89%	1.79%	0%	12.12%	5.64%

Table 4.Distribution of DRP frequency in different disease categories

Disorders	**Prevalence**
Endocrine, Nutritional or Metabolic Diseases	75%
Nervous System	27%
Circulatory System	1%
Genitourinary System	2%
Factors Influencing Health Status or Contact with Health ServiceS	2%
Respiratory	34%
Skin	2%
Conditions Related to Sexual Health	<1%
Sleep-wake Disorders	15%
Disease of the Immune System	1%

Furthermore, using the Spearman test, it was found that there is a weak positive correlation (P<0.001 and r=0.27) between the frequency of using other drugs for reasons other than direct COVID-19 treatment and the final clinical status.

Length of hospital stay: The length of hospital-stay, calculated as the number of days, ranged from 0 to 88 days, with an average of 7.55 days and a standard deviation of 0.41. The Shapiro test indicated that the distribution of hospital stay duration was non-normal (P<0.001), so non-parametric tests were used for data analysis.

Length of hospital stay and the time period of admission (A, B or C): Using the Kruskal-Wallis test, it was determined that there is no significant relationship between the time of stay and the length of hospital stay (P=0.3).

Length of hospital stay and Drugs: The Mann-Whitney test revealed a significant association between the length of hospital stay and corticosteroids, with longer stays observed in the group that used these medications (p=0.03). The average length of hospital stay was 7.71 days for patients who received corticosteroids compared to 5.84 days for those who did not. The Mann-Whitney test showed a significant association between the length of hospital stay and the use of both IL-6 inhibitor and antiviral medications other than remdesivir separately, with not using these drugs associated with shorter hospital stays (P=0.001 for IL-6 inhibitor and p=0.03 for antiviral drugs other than remdesivir).

Length of stay and number of comorbidities: Using Spearman test it was determined that there was a significant relation between the length of stay and the number of comorbidities (P<0.001, r=0.38)

Table 5. Frequency of final clinical status of patients across 3 time periods

	Time A	Time B	Time C	total
Complete recovery	27	5	58	90
Partial recovery[1]	74	18	125	217
Death	26	5	27	58
Total	127	28	210	365

1: Defined as still having symptoms when discharged but were not known as infected

Table 6. Final clinical status for each hospital

	Imam hossein	Sevvom Shaban	Shohada.Tajrish	Taleghani	Loghman	Modarres	Mofateh	Total
Complete recovery	0	3	56	0	27	2	2	90
Partial recovery	77	15	9	25	14	26	51	217
Death	11	3	10	10	11	6	7	58
Total	88	21	75	35	52	34	60	365

Discussion

The results of this study can be examined under two main headings, considering the initial objectives of the study: an investigation of the rate and pattern of remdesivir usage, and the final clinical status of the patients.

Remdesivir Usage Pattern: Given the policies of the Ministry of Health and the crucial role of this drug in the treatment protocol for COVID-19 patients, examining the usage pattern of remdesivir is important. The average of 5.07 doses per person and 144 patients receiving fewer doses than the protocol are not favorable facts. However, it should be noted that treatment was discontinued for 111 patients before 6 days, including those who died (23 individuals) and those discharged (88 individuals). Furthermore, the data of this study were extracted from patients who received remdesivir during hospitalization. Additionally, it was shown that there is a weak correlation between the number of doses received and the length of hospital stay. One possible reason for this analysis is that the 88 individuals who were discharged before receiving 6 doses had completed their treatment protocol adequately.

An important point in this study is the lack of correlation between the number of remdesivir doses and the length of hospital stay. As mentioned, patients were selected and examined in three-time intervals: two peaks and the interval between them. This may indicate the lack of changes in the hospital treatment protocol over time. Increased usage during the peak or deviation from the protocol during a decline in disease prevalence can both have economic and clinical implications.

Patient Outcomes: The second part of the study, which focuses on the clinical outcomes of patients who received remdesivir, is also of particular importance. The outcomes in this study were examined based on the final clinical status and the length of hospital stay.

The final clinical status in this study was ultimately significantly associated with five factors: younger age, type of hospital, non-users of IL-6 inhibitor medication, and a lower number of medications used. On the other hand, it should be noted that factors such as the using or not using corticosteroids and antiviral drugs and the duration of hospital stay (during the peak or outside the peak) did not have a significant correlation with the final clinical status of patients.

Numerous studies and inconclusive meta-analyses have been conducted regarding the mentioned factors. Regarding corticosteroid use, two meta-analyses (10, 11) suggest that the use of these drugs can slightly reduce overall mortality for symptomatic patients, which contradicts the findings of this study. However, it is important to note that the current study was only conducted on remdesivir-treated patients.

Regarding the use of IL-6 inhibitors, the study seems to be in line with previous researches. A meta-analysis conducted in December 2021 demonstrated that IL-6 inhibitors may reduce mortality.(12) Another meta-analysis on the role of IL-6 in the severity of COVID-19 has shown a significant correlation between disease severity and IL-6.(13)

Regarding the length of hospital stay as a secondary outcome, several factors were effective in reducing hospitalization: nonuse of corticosteroids, nonuse of antiviral drugs, nonuse of IL-6 inhibitors, and a lower number of comorbidities. Considering the large number of patients discharged within the first few days, it is challenging to make accurate judgments about factors that reduce hospitalization in COVID-19 patients. The mentioned factors are mostly related to the number of hospitalization days, disease severity, and the presence of comorbidities. Naturally, patients with more severe symptoms will have longer hospital stays. Among them, it can be said that patients who use a greater number of medications, often accompanied by more comorbidities, have longer hospital stays.

These data play a crucial role in analyzing many other variables, and without considering these factors, any general conclusions about patient outcomes would be incomplete. Another significant phenomenon in COVID-19 patients is re-admission or new complications due to incomplete recovery or new involvement. Although the current study did not aim to investigate such cases, a separate study could be designed and conducted to explore the association of various factors with this subgroup of patients.

Several important limitations exist in this study. Firstly, the study population consisted of patients who received remdesivir, thus the findings cannot be easily generalized to the entire population of COVID-19 patients despite an adequate sample size. Unfortunately, respiratory status (spontaneous or mechanical ventilation) and oxygen saturation levels were not fully and accurately reported in patient records, which significantly limited the analysis and inclusion in the study.

Based on our study, it can be suggested that the overall pattern of remdesivir utilization in the hospitals evaluated in this study (affiliated with Shahid Beheshti University of Medical Sciences) has been reasonable and in accordance with national protocols for COVID-19 infection. There were no significant differences in the pattern of remdesivir utilization between the waves of the pandemic in the hospitals. It seems that younger age, fewer comorbidities, and no concurrent use of multiple drugs for COVID-19 or other diseases may have a significant positive impact on the final clinical status and length of hospital stay.

Conflict of interest

The authors declare that they have no conflict of interest in this work.

References

1. Coronavirus (COVID-19) events as they happen. cited in 5/24/2023 URL: https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklury-remdesivir-include-all-hospitalized
2. Bourgonje AR, Abdulle AE, Timens W, et al.Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol. 2020;251(3):228-248.
3. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS Cent Sci. 2020;6(5):672-683.
4. FDA Approves First Treatment for COVID-19 | FDA. cited in 5/24/2023 URL: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19
5. COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19 |

FDA.

6. Mehellou Y, Rattan HS, Balzarini J. The ProTide Prodrug Technology: From the Concept to the Clinic. J Med Chem. 2018;61(6):2211-2226.
7. Slusarczyk M, Serpi M, Pertusati F. Phosphoramidates and phosphonamidates (ProTides) with antiviral activity. Antivir Chem Chemother. 2018;26:2040206618775243.
8. Last Edition of National COVID guidelines | URL: https://irimc.org/news/id/49153
9. Chaokromthong K, Sintao N. Sample size estimation using Yamane and Cochran and Krejcie and Morgan and green formulas and Cohen statistical power analysis by G* Power and comparisions. Apheit International Journal, 2021;10(2):76-86.
10. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020;24(1):696.
11. Wagner C, Griesel M, Mikolajewska A,et al. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev. 2021;8(8):CD014963.
12. Crichton ML, Goeminne PC, Tuand K,et al; European Respiratory Society COVID-19 Task Force. The impact of therapeutics on mortality in hospitalised patients with COVID-19: systematic review and meta-analyses informing the European Respiratory Society living guideline. Eur Respir Rev. 2021;30(162):210171.
13. Mojtabavi H, Saghazadeh A, Rezaei N. Interleukin-6 and severe COVID-19: a systematic review and meta-analysis. Eur Cytokine Netw. 2020;31(2):44-49.

PLEASE CITE THIS PAPER AS:

Soroush Y, Esmailyi H, Ghalandari N. The Evaluation of Remdesivir Utilization Pattern and Its Correlation with Clinical Indicators in Hospitalized Patients During COVID-19 Pandemic; A Retrospective Cross-sectional Study. J Pharm Care 2023;11(4):226-232.