Evaluation of Adverse Drug Events of Remdesivir for the Treatment of COVID-19 in Patients Contacting the 13-Aban Pharmacy Drug and Poison Information Center

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Abstract

Background: One of the FDA-approved treatments for COVID-19 is remdesivir. In this study, we investigated adverse drug events (ADEs) of remdesivir in COVID-19 patients who contacted 13-Aban pharmacy's drug and poison information center (DPIC).

Methods: In this study, data of patients receiving remdesivir who contacted the 13-Aban pharmacy's DPIC between April 2021 and May 2022 were extracted. For the evaluation of potential ADEs, we reviewed all contacts related to remdesivir recipients.

Results: Out of 223 patients enrolled, 108 (48.40%) developed 120 ADEs. Elevated liver transaminase levels (26.67%) were the most common ADE, followed by weakness (7.5%), nausea, and vomiting (7.5%). The causality assessment of ADE using the Naranjo scale revealed that 41.67% were probable and 58.33% were possible.

Conclusion: Based on the results of this study, hepatic dysfunction was the most prevalent ADE among remdesivir recipients; thus, in order to ensure safe use of remdesivir, patients should be closely monitored for this ADE.

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Keywords: COVID-19; Remdesivir; Adverse Drug Event

Introduction

Since December 2019, when the first cases of coronavirus disease 2019 (COVID-19) were reported, research has been conducted in order to find an effective treatment. One of the first antiviral drugs recommended for COVID-19 treatment was remdesivir (1). Remdesivir, as an adenosine triphosphate analog, inhibits the replication of the virus by disrupting the function of the RNA polymerase enzyme (2). Remdesivir was developed as an antiviral treatment for Ebola in 2017. Remdesivir was approved by the U.S. Food and Drug Administration in October, 2020 for treating COVID-19 in adults and children 12 years of age and older weighing at least 40 kg who require hospitalization (1).

Remdesivir was recommended by the Iranian Ministry of Health and Medical Education for use in hospitalized COVID-19 patients not on mechanical ventilation (3). Because of the high number of patients and overcrowding in hospitals during the peak of the COVID-19 outbreak, many patients received remdesivir in outpatient clinics or at home.

It was initially recommended that remdesivir be administrated only to hospitalized patients, but in late 2022 it was recommended to non-hospitalized patients at high

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risk of progressing to severe COVID (4).

Adverse drug events (ADEs) are a leading cause of hospitalizations and contribute to hospital mortality and morbidity. The evaluation of ADEs plays an essential role in identifying post-marketing adverse drug reactions and ensuring their safe use. The Iranian Adverse Drug Reaction Monitoring Center provides an online system for the public and medical staff to report ADEs. Further, the drug and poison information centers (DPICs) also answer questions regarding various aspects of pharmacotherapy, such as adverse drug reactions, from general population and medical staff. Therefore, DPICs have a special role in identifying and collecting reported ADEs (5). It is common for patients, especially those suffering from chronic or serious illnesses, to have questions regarding their treatment and ADEs. In spite of the ease of accessing online information, its reliability and validity are often questioned. In this regard, patients need reliable medical information sources. DPICs can provide trusted and reliable medical information, particularly in critical situations such as the COVID-19 outbreak. They can also help patients understand their medications, administration, and even ADE risks. This role of DPICs was bold during the COVID pandemic, when patients had to be isolated without access to a doctor or other healthcare professionals (6).

The incidence of ADEs caused by remdesivir has been reported to be 51% in hospitalized COVID-19 patients. The most common ADEs associated with remdesivir are nausea, hypokalemia, and headache. There are serious but less common ADEs associated with remdesivir, such as bradycardia, hepatic impairment, renal impairment, and hypersensitivity reactions (7).

Our study was designed to investigate post-marketing ADEs of remdesivir in COVID-19 patients who contacted the DPIC of 13-Aban pharmacy.

Methods

This retrospective study was conducted at the 13-Aban DPIC, affiliated to Tehran University of Medical Sciences. In this study, data of patients receiving remdesivir who contacted the DPIC between April 2021 and May 2022 were extracted from the center's database. We reviewed all contacts related to remdesivir recipients for potential ADEs, and among those, patients who reported ADEs were evaluated. Whenever necessary, additional information was obtained by contacting the patients and following up with them. The study excluded patients with insufficient information.

As a result of the available data in the DPIC database and the data collected from the patients, general information (such as age, sex, symptoms leading to the diagnosis of COVID-19, medications received, and underlying diseases) and information related to remdesivir prescriptions (dose, duration of remdesivir prescription, and method of preparation/administration) were extracted. In the case of adverse events, the type, onset, severity, duration, and outcome of the events were assessed. The Naranjo scale was used to assess the causality of adverse events related to remdesivir. The Naranjo scale considers a score of 1–4 as "possible," a score of 5–8 as "probable," and a score of ≥9 as "definite" for assessing the causality of ADEs (8).

The study protocol was approved by the institute of pharmaceutical sciences of Tehran University of Medical Sciences (IR.TUMS.TIPS.REC.1400.294).

Social Sciences (SPSS) version 23 was used to analyze the collected data. Categorical data were presented as frequencies and percentages. Continuous data were checked for normality using Shapiro-Wilk's test and normal data were expressed as mean ± standard deviation (SD) and non-normal data were presented as median (range). The data were analyzed using descriptive analysis, the Chi-square test, and independent sample t test.

Results

The DPIC received 680 inquiries about remdesivir in the period between April 2021 and May 2022. Among them, 236 patients received remdesivir for the treatment of COVID-19. Thirteen patients were excluded due to incomplete data. The study included 223 patients, of whom 108 (48.4%) experienced 120 adverse events. The mean age of patients developing ADRs was 45.90±14.29 years. In this study, most of the participants were female (58.7%).

Table 1 shows that 59.6% of patients had a positive COVID-19 polymerase chain reaction (PCR) test, but other patients were treated regardless of the PCR results. As a result of this study, dexamethasone (72.6%) and anticoagulants (48.4%) were the most prescribed medications along with remdesivir. There was a high prevalence of hypertension (12.5%), ischemic heart disease (9.4%), and diabetes (8.5%) in the past medical histories of the participants.

Table 1. Demographic and baseline data among remdesivir recipients.

Variable		Number (Percentage)
Sex	Male	92 (41.25)
	Female	131 (58.75)
Age (year)	<18	1 (0.45)
	≥18 -< 30	18 (8.07)
	≥30-<50	122 (54.71)
	≥50-<65	51 (22.87)
	≥65	31 (13.91)
Primary PCR	Positive	133 (59.64)
	Negative	5 (2.24)
	Unknown	85 (38.12)
Variable		Number (Percentage)
Primary O2 saturation (%)	>98	9 (4.03)
	94-98	57 (25.56)
	<94	111 (49.78)
	Unknown	46 (20.63)
Past medical history	Hypertension	28 (12.55)
	Ischemic heart disease	21 (9.41)
	Diabetes mellitus	19 (8.52)
	Thyroid disease	14 (6.28)
	Respiratory disease	12 (5.38)
	Psychiatric disease	8 (3.58)
	Gastric disease	8 (3.58)
	Hepatic disease	7 (3.14)
	Neurological disease	6 (2.69)
	Renal disease	3 (1.34)
	Other	15 (6.73)
	Without PMH	121 (54.26)
Concomitant medications	Dexamethasone	162 (72.65)
	Antibiotic (Azithromycin, levofloxacin, doxycycline)	35 (15.70)
	Favipiravir	22 (9.86)
	Hydroxychloroquine /chloroquine	5 (2.24)
	Tocilizumab	12 (5.38)
	Anticoagulant	103 (48.43)
	NSAIDs	21 (9.42)
	Interferon	6 (2.96)
	IVIG	1 (0.45)

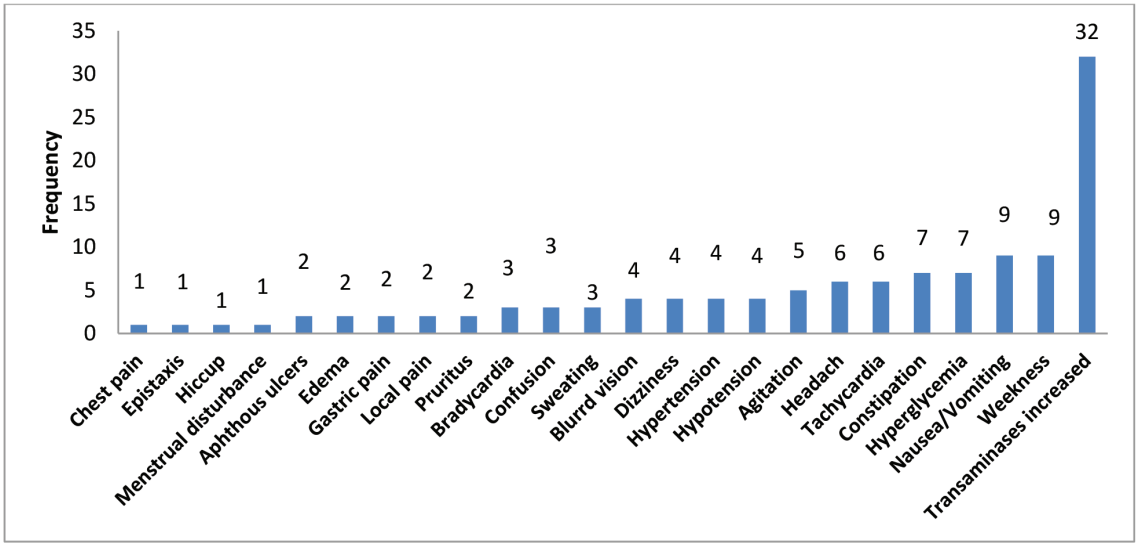

Figure1. Distribution of ADEs among remdesivir recipients.

According to Table 2, there was no statistically significant difference between patients with and without ADEs in demographic data and in the setting for receiving remdesivir, or in the history of receiving the COVID-19 vaccine. Data collected from the patients were analyzed to determine the occurrence of medication errors in remdesivir dose, infusion duration, and preparation/administration. There was no statistically significant difference between the occurrence of medication errors in patients with ADE and patients without ADE (P: 0.21), but the majority of medication errors were associated with the simultaneous administration of other drugs especially dexamethasone in serum containing remdesivir (73.2%) and rapid infusion of remdesivir (25.3%).

Among the patients, increased liver transaminase, weakness, nausea, and vomiting were the most common ADEs (Figure 1). Remdesivir-related ADEs were analyzed with the Naranjo scale, which indicated that 70 (58.3%) ADEs had possible causality and 50 (41.6%) had probable causality (Table 3).

Eighty-five of the 108 patients with ADE recovered, but 11 patients declared that the ADE remained, and 12 patients had an unknown outcome.

Table 2. Comparison of demographic data and other characteristics between patients with and without ADEs.

Variable, n (%)		Patients with ADR, 108 (48.4)	Patients without ADR, 115 (51.6)	P-value
Age	<18	0	1 (0.87)	0.81
	≥18 -< 30	8 (7.41)	10 (8.69)	
	≥30-<50	56 (51.85)	66 (57.40)	
	≥50-<65	28 (25.93)	23 (20)	
	≥65	16 (14.81)	15 (13.04)	
Sex	Male	47 (43.52)	45 (39.13)	0.59
	Female	61 (56.48)	70 (60.87)	
Setting for receiving remdesivir	Hospital (inpatient)	23 (21.30)	18 (15.65)	0.54
	Clinic (outpatient)	57 (52.78)	65 (56.53)	
	Home	13 (12.04)	11 (9.56)	
	Unknown	15 (13.88)	21 (18.26)	
History of receiving COVID-19 vaccine	Yes	34 (31.48)	28 (24.35)	0.18
	No	44 (40.74)	42 (36.52)	
	Unknown	30 (27.78)	45 (39.13)	
Medication errors occurrence	Dose	0	1 (0.87)	0.21
	Infusion time	8 (7.41)	10 (8.69)	
	Preparation/administration	32 (29.63)	20 (17.39)	

Table 3: Assessment of the causality of ADEs associated with remdesivir.

Causality assessment*	Possible, n (%)	Probable, n (%)	Definite, n (%)
Naranjo scale	70 (58.33)	50 (41.67)	0

Discussion

Remdesivir is a broad-spectrum antiviral drug approved for treating severe cases of COVID-19. At the time of writing this manuscript, remdesivir is recommended for COVID-19 hospitalized patients as well as non-hospitalized patients at risk of severe COVID-19 infections (4).

Approximately 48% of patients reported ADEs in this study, which is in line with Singh et al.'s findings, which demonstrated 50% of ADEs were caused by remdesivir (9). The most common ADE reported by patients was an increase in liver transaminase. Moreover, Falcao et al., and Singh et al. noted liver disorders as one of the most common remdesivir complications (9, 10). Induction of an inflammatory pathway and hypoxia may be responsible for liver injury caused by the virus (11). Furthermore, the present study reports weakness and nausea/vomiting as other common ADEs of remdesivir. It is possible that COVID-19 itself can cause weakness, or that it can be caused by the treatment (such as sedatives) (12). Symptoms of nausea/vomiting can be caused by both COVID-19 and remdesivir. Based on a Gilead study (13), remdesivir has been linked to gastrointestinal adverse effects, including nausea and diarrhea. In the present study, nausea/vomiting episodes reported during or after remdesivir administration were considered. As another complication, hyperglycemia can occur as a result of remdesivir adverse effects (14), concurrent use of corticosteroids, or the illness itself (11).

In this study, a number of ADEs were reported as "possible" causalities (58.3%), which could have been attributed to the inability to prescribe a placebo, rechallenging with remdesivir, or complications associated with COVID-19 or its other treatment options. Similarly, Bashini et al. found 53.57% causality for remdesivir ADE in their study (2).

Due to the fact that medication errors can endanger treatment safety and exacerbate ADE risk (15), errors in dose, duration of infusion, and administration of remdesivir were investigated. It was fortunate that most patients (99%) received their remdesivir dosage in accordance with the medical guidelines (4, 16). Eighteen patients did not report infusion times of 30 to 120 minutes. It was found that 52 patients had an error during the preparation and injection of their medication. A major error was not paying attention to the importance of not mixing intravenous medications with other drugs (17). A combination of dexamethasone or vitamin C with remdesivir was administered to 23% of patients. There could be several reasons for this, including a lack of adequate knowledge among nurses about how to correctly prepare remdesivir. In addition, a high workload, limitations of serum, and other treatment facilities during COVID-19 pandemics. As a result of the small number of participants, no significant association between medication errors and ADEs was found in this study (P: 0.15).

Remdesivir was administered to 41 patients during hospitalization, 122 patients received treatment in outpatient clinics, and 24 patients received treatment at home. Some patients were treated with remdesivir at home or in the clinic despite the fact that outpatient treatment with remdesivir was not recommended at that time. This was because of the large number of patients and limited hospital beds.

This study was limited by two factors: the limited number of participants, the inaccessibility of the required information due to incomplete data in the center's database, and the patient's refusal to respond when contacted again.

During this study, ADEs associated with remdesivir were evaluated in patients who contacted the DPIC following administration of the drug. There have been a high number of reports of increase in liver transaminase as a result of the ADE of remdesivir. Since remdesivir has been used more frequently since the COVID-19 pandemic, examining complications in these patients may be beneficial in the area of safety.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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