Early Outpatient Administration of Remdesivir Shortens Recovery Time in Patients with Mild to Moderate COVID-19

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Abstract

Background: During COVID-19, healthcare systems in underdeveloped nations had significant challenges and were unlikely to offer the necessary care. It appears that a new, reliable healthcare model that prevents hospitalization is necessary to reduce the pressure that COVID-19 is putting on healthcare systems and patients. More particularly, as Remdesivir's use as an outpatient treatment for mild to severe SARS-CoV-2 infection has rarely been examined; we aimed to investigate in-depth comprehension of the effects of Remdesivir in these cases.

Methods: In our two-month cross-sectional study, non-hospitalized patients with mild to moderate COVID-19 who were referred to the hospital for up to 5 days of Remdesivir treatment received 200 mg of Remdesivir intravenously on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 4 days. Patients were divided into groups based on the time of starting Remdesivir treatment after the appearance of symptoms: group 1 less than and equal to 7 days, and group 2 more than 7 days. Two groups were evaluated for a correlation between Remdesivir administration time and clinical symptoms on days 1 and 14 (follow-up visits).

Results: The study enrolled 273 eligible patients with a mean age of 47.5 years, of whom 112 were males and 125 were females. Results showed that patients who received Remdesivir in the first 7 days had less dyspnea (P-value<0.0001) and lung involvement (P-value<0.0001) than those who received it after 7 days at the end of the study. Patients who came later to receive Remdesivir also showed higher fatigue, AST, and ALT levels on the first day.

Conclusion: Among patients with moderate COVID-19, those who received a 5-day course of Remdesivir within 7 days of the onset of symptoms had a statistically significant difference in clinical status compared with those who received their treatments later. However, the size of this finding has uncertain clinical importance.
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Keywords: COVID-19; SARS-CoV-2; Outpatient; Remdesivir,; Complications

Introduction

Not so far away, most of us were unfamiliar with concepts like lockdowns, mask requirements and social distancing. Today they are portion of our daily language as the

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COVID-19 pandemic continues to influence all parts of our lives (1). The central concern with the COVID-19 pandemic is that the burden of disease may surpass the healthcare resources accessible to treat patients (2). Even in developed countries, there was concern that healthcare systems would be overwhelmed if COVID-19 cases rose dramatically (2), as Italy made ventilators and ICU beds accessible only for critically ill patients during the peak of the disease (3,4) and South Korea faced a scarcity of hospital beds, resulting numerous deaths (4, 5).

Healthcare systems in developing countries faced main obstacles during COVID-19 and were unlikely to provide the care needed. The lack of health care resources, training and a small number of health experts were the major causes (1). According to the United Nations, developing countries have an average of only 113 hospital beds per 100,000, which is 80% fewer than developed countries (2). In addition, developing countries have a shortage of intensive care beds (0.1–2.5 per 100,000) compared to developed countries (5–30 beds per 100,000), in the following can lead to ethical dilemmas. This may include the necessity to care for and treat more severely ill patients while delaying treatment of others who are in better condition (3,4).

On the other hand, the pandemic has highlighted the demand for effective, available and, most importantly, affordable healthcare. Even before the crisis pandemic began, population in developing countries were paying out of pocket for more than half a trillion dollars for health care. These costly expenses cause financial hardship for more than 900 million population and push nearly 90 million populations into extreme poverty each year, a dynamic that will almost certainly be exacerbated by the ongoing pandemic (5).

It appears that a new trusted healthcare pattern that stops hospitalization is required to reducing the burden on both healthcare systems and patient in coping with COVID-19. Preventing hospitalization and its chronic effects will not simply save lives, but also support restore medical systems and other facilities that have been overwhelmed by the consequences of the pandemic. Effective early treatments maybe can fill discontinuities left by prior and ongoing prevention approaches (6).

Outpatient treatments for COVID-19 would possibly have a significant impact on managing this disease, coupled with decrease in burden. Remdesivir is one of the active substance candidates for the changeover from ongoing care patterns to outpatient treatment. Remdesivir is an antiviral drug with properties to inhibit SARSCoV2 viral replication. Positive outcomes from early studies attracted media attention and led to the emergency use agreement of Remdesivir in COVID-19 (7).

A review of hospitalized patients with advanced lung disease, has showing patients on Remdesivir recovered faster than those on placebo. The classified paper on stopping COVID-19 issued by Scientists recommends widespread and rapid usage of Remdesivir and The Food and Drug Administration (FDA) approved the utility of Remdesivir under the ongoing public health emergency, but only for patients with severe illness; this approval does not seem to expressly permit outpatient use (8).

It is encouraging that effective outpatient treatments for early-stage COVID-19 are on the horizon. More specifically considering outpatient utilization of Remdesivir has seldom been studied, we are attempting to investigate in-depth understanding of the consequence of Remdesivir as an outpatient treatment for mild to moderate SARS-CoV-2 infection. Outpatient treatments for COVID-19 coupled with an effective vaccine would have a big effect on the capability to end this pandemic.

Methods

The ethics committee of educational hospital in central of Iran, Shahid Dr. Rahnemoon Hospital, approved our prospective cross-sectional study (Ethic Number: IR.SSU.SRH.REC.1400.001). In addition, the privacy and confidentiality of patient information was taken into account through electronic data protection. Also, all patients or legally authorized representatives provided written informed consent.

The study population includes non-hospitalized patients with mild to moderate COVID-19 who were referred to hospital to receive up to 5 days of Remdesivir treatment. Eligible patients were 18 years of age or older and had at least one pre-existing risk factor for progression to severe COVID-19, or were 60 years of age or older, regardless of whether they had other risk factors. Risk factors included diabetes mellitus, high blood pressure, cardiovascular or cerebrovascular disease, chronic liver disease, chronic kidney disease, chronic lung disease and immunodeficiency. Enrolled patients had SARS-CoV-2 infection confirmed by Verse-transcriptase-polymerase-chain-reaction (RT-PCR) test (using the real time PCR method with Pishtazteb kit, Pishtazteb Company, Iran) and radiological manifestations of COVID-19, chest computed tomography (CT) scan. Patients were excluded if they required hospitalization, had oxygen saturation (O2Sat) $< 93\%$, and patients with alanine aminotransferase or aspartate aminotransferase greater than 5 times the upper limit of normal or creatinine clearance of less than 50 mL/min at the time of the study. Patients need for Remdesivir was confirmed by specialists in pulmonary and infectious diseases after CT and RT-PCR examination. Due to the absence of space in the emergency ward, the sports club belonging to the hospital was converted into a rural hospital for outpatient treatment. The study center included outpatient infusion and skilled

nursing facilities.

Considering the emergency epidemic state to determine the appropriate time to start Remdesivir to improve clinical outcomes, we conducted a prospective cross-sectional study on 237 patients with mild to moderate COVID-19 who were referred to study center from July 14 to September 5, 2021 to receive an outpatient dose of Remdesivir. Eligible patients received 200 mg of Remdesivir intravenously on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 4 days, infused over 30 to 60 minutes. Based on the time of starting Remdesivir treatment, the studied patients were divided into two groups, group 1 less than and equal to 7 days and group 2 more than 7 days.

In the questionnaire prepared at the start beginning of the study, demographic characteristics and the initial symptoms of the patients were recorded. Warning signs for immediate referral were explained elucidated to patients and a leaflet documenting the contents was given to them. Patient assessments included physical examination, respiratory status (blood oxygen saturation and radiographic findings), laboratory parameters and adverse events. Correlation between Remdesivir administration time and clinical symptoms was tested between two groups on day 1 and day 14 (follow-up visit).

Statistical Analysis

Quantitative and qualitative variables were expressed as mean±standard normal deviation and number (frequency), respectively. Normally distributed quantitative variables were compared between groups utilizing the independent sample t-test. In addition, the qualitative variables were compared between two groups utilizing the chi-square test. All statistical analyzes were performed using SPSS software version 20 and differences with a P-value < 0.05 were deemed significant.

Results

During the two-month, 273 eligible patients with mild to moderate COVID-19, of whom 112 were males and 125 females, were enrolled in study with a mean age and BMI of 47.5 years old and 27.19 kg/m2, respectively. The most common comorbidities were hypertension (27%), diabetes mellitus (23.2%), and ischemic heart disease (8%). One in 10 patients had previously been infected with COVID-19. Monitoring of respiratory status demonstrated that the average of CT score of all patients was 5.38 and the average of O2Sat was 94.71. The most common symptoms at the onset of the disease were fatigue (69.6%), cough (67.5%), fever (54.4%) and shortness of breath (12.2%). On average, patients received CT scan and Remdesivir injection, 6 and 8 days after symptom onset, respectively. Additional patient demographic and clinical baseline characteristics are provided in Table 1.

Table 1. Baseline Demographic and General Characteristics of Patients

Characteristic	N=237
Sex	
Male	112 (47.31)
Age (y)	47.43 (14.22)
BMI (kg/m²)	27.19 (4.53)
Vital sign	
SBP/DBP, mmhg	126.32 (14.42) / 82.18 (10.33)
T, °C	36.38 (0.76)
RR	22.49 (6.41)
HR	83.05 (12.93)
O_2Sat, %	94.71 (2.77)
CT Score	5.38 (5.61)
Concurrent comorbidities	
DM	55 (23.21)
HTN	64 (27.00)
IHD	19 (8.01)
CKD	11 (4.64)
Hypothyroeidism	16 (6.75)
Common Patients' Clinical Status	
Dyspenea	29 (12.2)
Fever	129 (54.4)
Cough	160 (67.5)
Fatigue	165 (69.6)
COVID-19 History	
Yes	26 (10.97)
Laboratory tests	
ALT (U/L)	56.24 (103.67)
AST (U/L)	63.59 (104.24)
ALP	215.81 (129.34)
WBC	9.18 (5.58)
LYM	1.12 (1.72)
NEUT	7.79 (5.29)
NLR	10.07 (8.20)
CRP positive	184 (77.62)
Time symptom to CT, day	6.95 (3.45)
Time symptom to REM, day	8.23 (3.59)

N: Number; BP: Blood Pressure; T: Temperature; [1] Data are based on frequency (%); [2] Data are based on Mean (SD); BMI: Body Mass Index; kg/m2: Kilogram force per square meter; SBP/DBP: Systolic Blood Pressure/ Diastolic Blood Pressure; RR: Respiratory Rate; HR: Heart Rate; O2Sat: Oxygen saturation; CT: Computed Tomography; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; CKD: Chronic Kidney Disease; ALT: Alanine transaminase; U/L: Unit/Liter; AST: Aspartate transaminase; ALP: Alkaline Phosphatase; WBC: White Blood Cells; LYM: Lymphocyte; NEUT: Neutrophil; NLR: Neutrophil-Lymphocyte Ratio; CRP: C-Reactive Protein; REM: Remdesivir

The relationship between clinical symptoms on day 1 and day 14 of study was tested by statistical chi-square analysis. Patients were shown to have significantly better respiratory status (Dyspnea) on day 14, after administration of 5 doses of Remdesivir (P = 0.028). Differences in other clinical status were not statistically significant (Table 2).

Table 2. The Most Common Patients' Clinical Status on Study Days 1 and 14

	Groups		
Clinical Presentation	**Day 1**	**Day 14**	***P-value***
	N (%)		
Cough	160 (67.5)	61(25.7)	0.371
Taste disorder	106 (44.7)	3(1.3)	0.442
Fever	129 (54.4)	3 (1.3)	0.564
Chill	113 (47.7)	5 (2.1)	0.456
Fatigue	165 (69.6)	29 (12.2)	0.727
Vertigo	60 (25.3)	9 (3.8)	0.238
Nausea	68 (28.7)	1 (0.4)	0.287
Anorexia	128 (54)	2 (0.08)	0.561
Diarrhea	45 (19)	1 (0.4)	0.810
Myalgia	155 (65.4)	13 (5.5)	0.488
Arthralgia	110 (46.4)	7 (3)	0.168
Rhinorrhea	37 (15.6)	1 (0.4)	0.844
Sneezing	30 (12.7)	1 (0.4)	0.873
Dysuria	15 (6.3)	1 (0.4)	0.937
Anosmia	115 (48.5)	6 (2.5)	0.630
Muscular cramp	52 (21.9)	2 (0.8)	0.609
Headache	143 (60.3)	9 (3.8)	0.765
Paresthesia	67 (28.3)	12 (5.1)	0.087
Dyspnea	29 (12.2)	46 (19.4)	**0.028** *

* Statistically significant (*P-Value<0.05)*

In this study, patients were divided into two groups based on the timing of Remdesivir administration, less than and equal to 7 days and more than 7 days after symptoms onset. The results showed that at day 14 a significant difference was reported between the clinical symptoms, dyspnea and the radiological findings, the percentage of lung involvement between 2 groups. In other words, patients who received Remdesivir in the first 7 days after symptom onset had less dyspnea and lung involvement than those who received after 7 days. Also, people who came later to receive Remdesivir showed more fatigue, AST, and ALT levels on the first day (Table 3).

Table 3. Correlation between Remdesivir administration time with baseline & outcome clinical symptoms and baseline laboratory

	Variabale		Time ≤ 7day	Time > 7day	*P-value*
Base line	**Dyspenea**	N (%)	7 (24.1)	22 (75.9)	**0.017***
	Fever		53 (41.1)	76 (58.9)	0.218
	Cough		67 (41.9)	93 (58.1)	0.203
	Fatigue		66 (40)	99 (60)	**0.027***
	CRP+		86 (46.7)	98 (53.3)	0.245
	ALT (U/L)	Mean (SE)	40.95 (39.23)	68.62 (133.88)	**0.041***
	AST (U/L)		48.26 (34.39)	75.98 (135.74)	**0.042***
	ALP		200.33 (100.43)	228.34 (147.89)	0.098
	WBC		8.96 (4.86)	9.36 (6.12)	0.590
	LYM		1.00 (0.67)	1.23 (2.24)	0.308
	NEUT		7.48 (4.59)	8.03 (5.80)	0.425
	NLR		9.50 (7.09)	10.52 (9.0)	0.341
Day 14	**CT Score**		1.41 (2.74)	8.60 (5.27)	**<0.0001***
	O_2Sat		94.57 (2.82)	94.80 (2.71)	0.518
	Dyspenea	N (%)	3 (6.5)	43 (93.5)	**<0.0001***
	Fever		2 (66.7)	1 (33.3)	0.446
	Cough		27 (44.3)	34 (55.7)	0.933
	Fatigue		11 (37.9)	18 (62.1)	0.432
	CT Score		1.56 (3.03)	8.96 (5.78)	**<0.0001***
	O_2Sat	Mean (SE)	96.41 (2.77)	96.22 (2.51)	0.844
	Changes in CT scan involvement (1-14 days)		0.15 (1.42)	0.36 (2.22)	0.407

* Statistically significant (*P-Value<0.05)*

By day 14, adverse events had occurred in 77 of 237 patients. The most common non-serious side effects that occurred were headache, nausea, and cough. None of the outpatients who received Remdesivir died. Ten of these patients were hospitalized, but none of them were transferred to the intensive care unit.

Discussion

In this study of non-hospitalized patients with mild to moderate COVID-19 who were at risk of severe disease referred to hospital, received up to 5 days of Remdesivir administration at one of the hospital sites. We found that patients who received Remdesivir in the first 7 days after symptom onset had considerably less shortness of breath and lung involvement by day 14 than patients who received it after 7 days. Also, people who came later to receive Remdesivir illustrated more fatigue and higher AST and ALT levels on day one. In addition, no significant differences in the CT scan were reported between the two time points of referral, which may signify that the later

referral led to an additional exacerbation of the disease, which did not enhance even with the administration of Remdesivir after two weeks. As consequence, early referral and administration of Remdesivir recommended. Also, treatment with Remdesivir had an acceptable safety profile.

According to a previous study in reviewing the financial burden of coronavirus disease in Iran, a severe status of the disease in COVID-19 cases would cause the too high medical costs. It is estimated that the high prevalence incidence rate of COVID-19 has directly imposed a heavy financial burden on the country and healthcare system, which may lead to rationing or painful cost control approaches (9). Therapeutic options could reduce the burden on both healthcare systems and patients, and one of those options is out-of-hospital therapy.

One of the suggestive drugs used for systemic treatment of COVID-19 is Remdesivir because of its wide variety of effects including expedite the advancement in several biomarkers of COVID-19 severity, comprising a decrease in the soluble angiopoietin-2, D-dimer and neutrophil to lymphocyte ratio and an increment in lymphocyte counts associated with better clinical results during infection (10).

Consistent with our study, the observations of a controlled study by Gottlieb et al. demonstrated that in non-hospitalized patients at high danger for progression of COVID-19, 3-day treatment with Remdesivir had a satisfactory safety profile and resulted in an 87% lower risk for hospitalization or death as a placebo (11). Also, Piccicacco et al., showed in a retrospective cohort study that outpatients at highest risk with Omicron-associated COVID-19 who received early Sotrovimab or Remdesivir had a considerably smaller possibility of hospitalization and/or emergency room visits (12).

The results of a prospective observational study indicated in outpatients receiving Molnupiravir, Nirmatrelvir/ Ritonavir, or Remdesivir, hospitalization or death did not change in high-risk COVID-19 outpatients, but safety and time up to negative test were different in the patients. Recipient group of Remdesivir showed more safety while the time up to navigate test was higher comparing to other antiviral drugs (13). A prospective comparative cohort study conducted by Rajme-Lpez et al., illustrated that early outpatient treatment with Remdesivir greatly reduced death or hospitalization by 84% in high-risk patients with primarily immunocompromised patients with Omicron variant COVID-19 (14).

A meta-analysis by Rezagholizadeh et al., provided an updated review of the scientific proof on the advantage of Remdesivir in COVID-19 patients. The outcome of the randomized controlled trial studies illustrated a substantial improvement in recovery rate, low-flow oxygen assistance, and invasive mechanical ventilation or extracorporeal membrane oxygenation requirements in the Remdesivir group. In addition, the danger of suffering serious adverse drug reactions was considerably smaller in the Remdesivir group (15).

Although the observations of the current research are interesting, caution should be exercised when adopting the results and the limitations of the study should be taken into account. First, the major limitation was the small size of the sample group. Second, due to the urgency of the condition under which the study was conducted, the influence of Remdesivir on SARS-CoV-2 viral load was not evaluated. Third, other laboratory parameters such as AST, ALT, CBC, CRP, which may have been helpful in identifying other predictors of findings, were not complete at day 14 because patients did not cooperate in performing the collected tests. Given the small sample size and absence of power to present a variation in efficacy outcome, we carefully interpret this information to suggest the probability of advantageous effect and the absence of harm. Therefore, we conclude that additional efficacy evaluation in the type of a larger clinical trial is warranted. In the campaign toward ending the COVID-19 pandemic, these data add another choice for the treatment of patients who are at high risk for progression to severe COVID-19 with a stable condition.

Among patients with moderate COVID-19, those who received a 5-day course of Remdesivir within 7 days of the onset of symptoms had a statistically significant difference in clinical status compared with those who received their treatments later. However, the size of this finding has uncertain clinical importance. We have come to the conclusion that an additional clinical trial with more participants is necessary to complete the efficacy evaluation.

Conflict of interest

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

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