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Early Use of Remdesivir in Patients Hospitalized With COVID-19 Improves Clinical Outcomes

A Retrospective Observational Study

Neha Paranjape, MD, MPH, Mir Husain, MD,† Jennifer Priestley, PhD,‡ Yashila Koonjah, MS,‡ Christopher Watts, MD,§ and Joseph Havlik, MD†*

Background: Remdesivir treatment, like most antiviral drugs, is likely to be most effective when used early in the course of coronavirus disease 2019 (COVID-19). Optimal timing of remdesivir for the treatment of COVID-19 remains unclear.

Objectives: The aim of this study was to determine whether early treatment with remdesivir improves clinical outcomes: length of stay, need for mechanical ventilation, and death.

Methods: We conducted a retrospective observational study of patients hospitalized with COVID-19 who received remdesivir therapy within 10 days of symptom onset at a large health system in Georgia, United States.

Results: We identified a total of 475 patients. Initiation of therapy 3 days or less from first positive SARS-CoV-2 improved length of stay (15.7 days) compared with those started on therapy more than 3 days after a positive test (19.3 days) ($P = 0.03$). In the ≤3 day group, further reduction in length of stay was seen in those with lower oxygen requirement at baseline ($P < 0.0001$). Length of stay was lower in the ≤3 day group both with and without the use of corticosteroids ($P = 0.0003$). The odds of requiring mechanical ventilation were higher for the >3 day group compared with the ≤3 day group (odds ratio, 1.5; 95% confidence interval, 0.8–2.7), and the odds of death were higher for the >3 day group versus the ≤3 day group (odds ratio, 1.74; 95% confidence interval, 0.9–3.2).

Conclusions: Our data show that early treatment with remdesivir in patients hospitalized with COVID-19 shortened length of stay.

Key Words: COVID-19, SARS-CoV-2, remdesivir, clinical outcomes, length of stay

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Background

As of March 2021, the coronavirus disease 2019 (COVID-19) pandemic has affected more than 121 million individuals, causing over 2.6 million deaths worldwide.[1] Remdesivir is an antiviral agent that became the first drug to be approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19.[2]

Based on the Adaptive COVID-19 Treatment Trial-1, the US FDA issued an emergency use authorization (EUA) for use of remdesivir for the treatment of patients hospitalized with COVID-19.[3,4] Our health system received federally allocated donations of this drug from May 2020 to August 2020.[5]

Since the FDA approval, remdesivir has become the standard of care for the treatment of hospitalized patients with COVID-19 in the United States.

Recently, the World Health Organization recommended against the use of remdesivir for the treatment of COVID-19 after the Solidarity trial failed to show benefit.[6]

We describe the real-world clinical outcomes of patients hospitalized with COVID-19 between May 2020 and August 2020, treated early with remdesivir at a large health system in Georgia, United States.

Objective

The aim of this study was to evaluate the effect of early treatment with remdesivir on the length of stay, need for mechanical ventilation, and death in patients hospitalized with COVID-19.

METHODS

Study Design

We conducted a retrospective observational study of patients with COVID-19, hospitalized at our health system from May 2020 to August 2020, who were treated with remdesivir within 10 days of symptom onset. The study was granted institutional review board approval by Wellstar Health System Institutional Review Board (approval number: 1625597-1). The reporting of this study adheres to the STrengthening and Reporting of OBservational studies in Epidemiology statement (Appendix I).[7]

Setting

Our health system received several allocations of donated remdesivir under the FDA EUA from the Georgia Department of Public Health, which were used across 9 community hospitals within our health system from May 2020 to August 2020. Because of the limited supply, use was restricted to infectious disease or pulmonary service. Unidentified data were extracted from electronic medical records.

Participants

Decision to treat with remdesivir under FDA EUA was determined by infectious disease or pulmonary consultation based on the following criteria:

- Positive SARS-CoV-2 polymerase chain reaction (PCR).
- Within 10 days of symptom onset.
- Age more than 18 years.
- Oxygen saturation 94% or less on room air.
- Estimated glomerular filtration rate (eGFR) greater than 30 mL/min.

From the *Department of Infectious Disease, Wellstar Kennestone Hospital; †Department of Infectious Disease, Wellstar Cobb Hospital, Marietta; ‡Analytics and Data Science Institute, Kennesaw State University, Kennesaw; and §Department of Infectious Disease, Wellstar Douglas Hospital, Marietta, GA.

Correspondence to: Neha Paranjape, MD, MPH, Department of Infectious Disease, 55 Whitcher St., Suite 220, Marietta GA 30060.
E-mail: neha.paranjape@wellstar.org.

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- Alanine transaminase (ALT) less than 5 times the upper limit of normal.

Symptoms included fevers, cough, sore throat, shortness of breath, fatigue, myalgias, loss of taste or smell, nasal congestion, nausea, vomiting, and diarrhea.

Patients who were pregnant, lactating, less than 18 years, or those who received remdesivir under the compassionate use program were excluded from our cohort.

As per the then FDA EUA guidelines, treatment duration was 5 days for patients not requiring mechanical ventilation and 10 days for those on mechanical ventilation. Based on published data, duration of treatment was limited to 5 days for all patients starting June 1, 2020.[8] Remdesivir treatment was discontinued before intended duration of therapy if the patients were deemed clinically stable for discharge from the hospital.

Variables

The following variables were collected:

- Demographics: age, race, sex, and body mass index (BMI).
- Comorbidities: hypertension (HTN), diabetes mellitus (DM), coronary artery disease, chronic kidney disease (CKD), chronic lung disease.
- Laboratory values: white blood cell count, total lymphocyte count, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer, ALT, and eGFR at start of remdesivir therapy.
- Vital signs: temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation at start of remdesivir therapy.
- Date of first positive SARS-CoV-2 PCR.
- Date of initiation of remdesivir from first positive SARS-CoV-2 PCR.
- Duration of remdesivir therapy.
- Use of corticosteroids.
- Need for mechanical ventilation and/or extracorporeal membrane oxygenation.
- Length of stay.
- Disposition—discharge home, facility, hospice, or death.

As per our health system's policy of universal testing, all hospitalized patients were tested for SARS-CoV-2 by nasopharyngeal PCR on day of admission. Those with a negative initial test were retested within 24 hours if clinical suspicion remained high or if a previously asymptomatic patient showed signs and symptoms of COVID-19 during the hospitalization.

Statistical Analysis

Sample size calculations were not done. Continuous variables were expressed as mean and SD, and categorical variables were reported as numbers and percentages. Differences of continuous data were evaluated using 2-sample independent *t* tests and 1-way analysis of variance. Differences of proportions were evaluated using χ^2 and tests of odds ratios. A bivariate analysis was conducted to evaluate the timing of remdesivir treatment on the outcomes of interest. A multivariate analysis using Poisson regression and generalized linear model was conducted to look for potential confounders and effect modifiers. A *P* value less than 0.05 was considered as statistically significant. All analysis was conducted using SAS Studio version 9.4.

RESULTS

Demographics

We identified a total of 475 patients. The mean age was 59 years. Fifty-six percent were of male sex. Race distribution was 36% Black, 35% White, and 28% other. The average BMI was 33. High blood pressure (HTN) and DM were the most common comorbidities (Table 1).

Clinical Characteristics

Most of the patients required oxygen supplementation, and 8.6% were on invasive ventilation at start of remdesivir therapy. Approximately 40% received corticosteroids in addition to remdesivir (Table 1).

Clinical Outcomes

Four hundred eight (86%) patients received 5 days or less of remdesivir therapy. The average duration of remdesivir therapy was 3.7 days, and the mean length of stay was 16 days. Thirty-two percent eventually required mechanical ventilation. Most of the patients (62.9%) were discharged home (Table 2). Eighty-two percent of patients who were admitted from home were discharged home. Remdesivir therapy was discontinued in 9 (1.8%) patients due to worsening renal function with eGFR less than 30, and in 11 (2.3%) patients due to elevation of ALT more than 5 times the upper limit of normal.

Timing of Remdesivir Initiation From Positive Test: 0 to 3 Days Versus More Than 3 Days

In our cohort of 475 patients, remdesivir was initiated within 3 days or less of first positive SARS-CoV-2 PCR test in 421 (88.6%) patients and more than 3 days in 54 (11.3%) patients.

Bivariate Analysis

The length of stay was shorter in those initiated on therapy 3 days or less from positive SARS-CoV-2 PCR test (15.7 days) as compared with those started on therapy more than 3 days after positive test (19.3 days). This difference was statistically significant ($P = 0.03$). The odds of requiring mechanical ventilation were higher for the >3 day group versus the ≤3 day group [odds ratio (OR), 1.5; 95% confidence interval (CI), 0.8–2.7]. The odds of death were higher for the >3 day group versus the ≤3 day group (OR, 1.74; 95% CI, 0.9–3.2) (Table 3).

Multivariate Analysis

The effect of the timing of remdesivir therapy on the length of stay was modified by oxygen requirement at baseline ($P < 0.0001$) and use of corticosteroids ($P = 0.0003$). The length of stay in the ≤3 day group was 8 days for no oxygen supplementation, 11 days for low flow oxygen, and 18.9 days for high flow oxygen, whereas in the >3 day group, the length of stay was 25 days for no oxygen supplementation, 16 days for low flow oxygen, and 24 days for high flow oxygen. There was no difference for patients who were on mechanical ventilation (20 days) between the 2 groups. In the patients who received corticosteroids, the length of stay was 16 days for the ≤3 day group and 23 days for the >3 day group, whereas for those who did not receive corticosteroids, the length of stay was 13 days for the ≤3 day group and 21 days for the >3 day group (Table 4).

The length of stay was 15.5 days for Black, 16 days for White, and 17.9 days for others; although this result was statistically significant ($P < 0.0001$), there was no effect modification seen with remdesivir. Similarly, other variables like BMI, CKD, chronic lung disease, and DM independently affected length of stay but did not alter the effect of timing of remdesivir therapy (Appendix II).

For probability of progression to mechanical ventilation, effect modification on the timing of remdesivir therapy was seen with oxygen supplementation at baseline ($P = 0.004$). The probability

TABLE 1. Demographic Characteristics, Comorbidities, and Clinical and Laboratory Values of Patients Treated With Remdesivir

Age	
Mean	59
SD	15.3
Minimum	21
Maximum	94
Sex, n (%)	
Male	266 (56)
Female	209 (44)
Race, n (%)	
Black	172 (36.2)
White	168 (35.4)
Other	135 (28.4)
BMI, mean (SD)	
Mean	33.5
SD	9.3
Minimum	15
Maximum	76.4
Comorbid conditions, n (%)	
HTN	329 (69)
DM	304 (64)
CKD	76 (16)
Coronary artery disease	136 (28)
Chronic lung disease	126 (26)
Vital signs, mean (SD)	
Temperature	98.6 (1.2)
Heart rate	84 (18)
Respiratory rate	22 (6.7)
Blood pressure	126/73 (20/13)
Oxygen saturation	94.3 (3.4)
Oxygen supplementation, n (%)	
None	24 (5)
Low flow ≤15 L/min*	195 (41)
High flow >15 L/min†	193 (40.6)
Mechanical ventilation	41 (8.6)
Laboratory values, mean (SD)	
Ferritin	1148.8 (2440)
LDH	433.6 (233)
CRP	13.5 (10)
D-dimer	1460 (4567)
White blood cell count	8.6 (4.5)
Absolute lymphocyte count	1.04 (1)
Other treatments, n (%)	
Corticosteroids	193 (40.6)

Missing data—0.4% for BMI, 4.6% for oxygen supplementation, 8% for ferritin, 32% for CRP, 34% for D-dimer, and 1.2% for LDH.

*Via nasal cannula.

†High-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure.

was 8% for the patients on low flow oxygen who received remdesivir 3 days or less of positive SARS-CoV-2 PCR test, whereas it was 68% for those on high flow oxygen who received remdesivir more than 3 days from positive test (Table 5). Chronic kidney disease and oxygen supplementation at baseline independently affected progression to mechanical ventilation (Appendix II).

There was no effect modification seen on mortality with timing of remdesivir therapy. Age, BMI, CKD, chronic lung disease, and oxygen supplementation at baseline independently affected the outcome of mortality (Appendix II).

DISCUSSION

The first randomized controlled trial conducted in China did not show a benefit with remdesivir in the treatment of COVID-19.[9] This study was underpowered as the desired sample size was not met. The Adaptive COVID-19 Treatment Trial-1 conducted by the National Institutes of Health demonstrated a shortened time to recovery in the remdesivir group.[3,10] Furthermore, 25% of trial enrollees reported symptom onset of less than 6 days. The primary end point of this study was to examine clinical improvement, and it was not powered for mortality. The Solidarity trial conducted by the World Health Organization did not show any benefit of remdesivir therapy; however, this study was powered for mortality and was not designed to examine clinical improvement.[6,10] In addition, the time from symptom onset was not reported.

Antivirals aimed at inhibiting viral replication are expected to be most effective when administered early in the course of the disease.[11] Consistent with this, our findings show that initiation of early treatment, that is, within 10 days of symptom onset and 3 days or less of first positive SARS-CoV-2 PCR test, shortens the length of stay by 3.6 days. Furthermore, these patients are less likely to progress to mechanical ventilation and death.

A multivariate analysis to look for potential confounders and effect modifiers showed a greater benefit of early remdesivir therapy on length of stay and progression to mechanical ventilation in the subset of patients on lower oxygen requirement at baseline. A similar advantage with early remdesivir therapy on length of stay was seen in both patients who received corticosteroids and those who did not. Early in the pandemic, use of corticosteroids was discouraged; however, after the RECOVERY trial showed a mortality benefit in patients with COVID-19 on supplemental oxygen or mechanical ventilation, corticosteroids became the standard of care of this subset of patients. Our study period extended from

TABLE 2. Clinical Outcomes of Patients Treated With Remdesivir

Duration of remdesivir	
Mean	3.7
SD	1.8
Minimum	0
Maximum	9
Length of stay	
Mean	16
SD	11.9
Minimum	2
Maximum	64
Need for mechanical ventilation, n (%)	153 (32)
Discharge from hospital, n (%)*	
Home	299 (62.9)
Rehab/nursing home/LTAC	58 (12.3)
Hospice	16 (3.4)
Died	98 (20.8)

*Missing data—0.8% for discharge from hospital.

LTAC indicates long-term acute care facility.

TABLE 3. Comparison of Clinical Outcomes Between Patients Initiated on Remdesivir Therapy ≤3 Days Versus >3 Days of First Positive SARS-CoV-2 PCR Test

Initiation of Remdesivir From PCR Positive Test	≤3 Days	>3 Days	Significance
Total n (%)	421 (88.6)	54 (11.3)	
Length of stay			$P = 0.03$
Mean	15.7	19.3	
SD	12	10.9	
Minimum	2	7	
Maximum	63	64	
Need for mechanical ventilation	127 (30%)	21 (39%)	(OR, 1.5; CI, 0.8–2.7) $P = 0.19$
Death	82 (19.4%)	16 (29.6%)	(OR, 1.74; CI, 0.9–3.2) $P = 0.08$

May to August; therefore, the widespread use of corticosteroids was implemented halfway through the study in July 2020.[12]

Last, our health system consists of 9 community hospitals with demographics that are representative of patients hospitalized with COVID-19 in the United States, and present real-world outcomes of early remdesivir treatment contrary to a controlled trial setting.[13]

Limitations

- Because of the retrospective observational design of our study, we were unable to fully control for possible confounders; however, we did conduct multivariable analysis to lessen this limitation.
- Data extraction was conducted from electronic medical records; therefore, the accuracy could not be independently verified.
- To gather and process data quickly, the study period remained short, that is, duration of hospitalization. We did not collect follow-up data after hospital discharge.
- Length of stay was reported as total time that the patient required hospitalization and included delays related to discharge to facilities such as nursing homes, rehabilitation centers, etc., due to repeat testing requirements at that time. Patient transfer policies differed by facility and changed through the study period. However, only 12% of our cohort was discharged to facilities, and those with discharge delays due to a repeat positive SARS-CoV-2 PCR test were a fraction of those patients.

CONCLUSIONS

To summarize, we conducted a retrospective observational study of 475 patients hospitalized with COVID-19 who were treated with remdesivir at a large health system in Georgia, United States. We concluded that early treatment (symptom onset <10 days and within 3 days of first positive SARS-CoV-2 PCR test) led to improved clinical outcomes. This effect was more pronounced in patients on lower oxygen requirement at baseline and was seen both with and without the use of corticosteroids. Since FDA approval, remdesivir is increasingly prescribed in the hospital setting. Given the high cost of the medication, optimal timing of remdesivir treatment remains vital to improving outcomes

TABLE 4. Effect of Oxygen Supplementation at Baseline and Corticosteroid Use With Timing of Remdesivir Therapy on Length of Stay

Oxygen Supplementation at Baseline	Timing of RDV From First Positive PCR Test	Total n	Length of Stay, Mean (SD)	$P < 0.0001$
None	≤3 d	20	8.1 (3.6)	
	>4 d	4	25 (25.5)	
Low flow*	≤3 d	179	11 (8.3)	
	>4 d	16	15.5 (5.2)	
High flow†	≤3 d	150	18.9 (13.4)	
	>4 d	44	24 (13.7)	
Mechanical ventilation	≤3 d	14	20.6 (9.2)	
	>4 d	29	20.5 (11.6)	
Corticosteroid Use	**Timing of RDV from first positive PCR test**	**Total n**	**Length of Stay, Mean (SD)**	**$P = 0.0003$**
No	≤3 d	215	13 (10.7)	
	>4 d	67	21 (12.9)	
Yes	≤3 d	161	16.9 (11.7)	
	>4 d	32	23 (12.4)	

Missing data—4.6% for oxygen supplementation.

*Via nasal cannula.

†High-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure.

RDV indicates remdesivir.

TABLE 5. Effect of Oxygen Supplementation at Baseline With Timing of Remdesivir Therapy on Progression to Mechanical Ventilation

Oxygen Supplementation at Baseline	Timing of RDV From First Positive PCR Test	Total n	Progression to Mechanical Ventilation (%)	$P = 0.004$
None	≤3 d	20	10	
	>4 d	4	50	
Low flow*	≤3 d	179	8	
	>4 d	16	31	
High flow†	≤3 d	150	23	
	>4 d	44	68	
Mechanical ventilation	≤3 d	14	100	
	>4 d	29	100	

Missing data—4.6% for oxygen supplementation.

*Via nasal cannula.

†High-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure.

RDV indicates remdesivir.

and maintaining cost-effectiveness. This is especially relevant to facilities experiencing a surge in cases and/or those with limited resources, both domestically and internationally.

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