Original Research

Evaluation of the Efficacy of Remdesivir for the Treatment of Coronavirus Disease 2019

Alexandra Flannery, PharmD, BCPS[1]; Anastasia Knecht, PharmD, BCPS[1]; Koravangala Sundaresh, MD[1]

Author affiliations are listed at the end of this article.

Correspondence to: Alexandra Flannery, PharmD, BCPS (alexandra.gott@hcahealthcare.com)

Abstract

Background
Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, SARS-CoV-2, has accounted for more than 1 000 000 deaths in the United States alone. In May 2020, the Food and Drug Administration issued an Emergency Use Authorization to allow the investigational use of intravenous remdesivir for the treatment of suspected or confirmed COVID-19 in hospitalized children and adults. Several other agents, such as hydroxychloroquine, dexamethasone, and tocilizumab have been investigated as potential treatment options; however, dexamethasone is currently the only agent that has been proven to reduce mortality in patients who require supplemental oxygen. The purpose of this study was to determine if initiation of remdesivir treatment in patients who presented with early symptoms of COVID-19 (defined as symptom onset < 7 days) had a significant impact on in-patient all-cause mortality compared to initiation of remdesivir treatment in patients who presented with symptom onset of at least 7 days.

Methods
This ethics-committee-approved, retrospective, multicenter, double-arm study was conducted across 10 facilities in the HCA Healthcare West Florida Division. Adult inpatients age 18 and older with confirmed COVID-19 and administered intravenous remdesivir from May 1, 2020, to July 31, 2020, were included. Exclusion criteria included patients less than 18 years of age, the concomitant use of hydroxychloroquine or tocilizumab for any indication, or an estimated glomerular filtration rate less than 30 milliliters per minute. The primary outcome of this study was in-patient all-cause mortality. Secondary outcomes included total length of stay, time to discharge, oxygen requirements, and number of ventilator days.

Results
A total of 217 patients from facilities in the HCA Healthcare West Florida Division were evaluated for inclusion. The primary outcome of all-cause mortality occurred in 34.9% of patients with symptom onset of fewer than 7 days versus 31.0% of patients with symptom onset of at least 7 days (P = .57). There were no statistical differences found among the secondary outcomes.

Conclusion
Time since symptom onset did not result in a statistically significant difference in all-cause mortality in patients who received intravenous remdesivir for the treatment of COVID-19.

Keywords
SARS-CoV-2; COVID-19; COVID-19/therapy; antiviral agents; remdesivir; treatment outcome; hospital mortality; retrospective study

Introduction
Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, SARS-CoV-2, has accounted for more than 1 000 000 deaths in the United States alone.[1] In May 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow the investigational use of intravenous remdesivir

for the treatment of suspected or confirmed COVID-19 in hospitalized children and adults.[2] Several other agents, such as hydroxychloroquine, tocilizumab, and dexamethasone have been investigated as potential treatment options; however, dexamethasone is currently the only agent that has been proven to reduce mortality in patients who require supplemental oxygen.[3] In October 2020, the FDA approved remdesivir for the treatment of COVID-19 in hospitalized adults and pediatric patients.[4]

Results from the World Health Organization (WHO) Solidarity Trial concluded that remdesivir had a statistically significant mortality benefit at 28 days when used in patients receiving oxygen but who were not mechanically ventilated.[5] The study found no additional benefit on initiation of ventilation or hospitalization duration.[5] A recent retrospective cohort study by Chokkalingam et al found a statistically significant reduction in all-cause inpatient mortality across all supportive oxygen subgroups, including low-flow, high-flow or noninvasive ventilation, extracorporeal membrane oxygenation, and invasive mechanical ventilation.[6]

Several studies have reported conflicting results on time to clinical improvement and subsequent time to discharge in patients treated with remdesivir. A study conducted by Beigel et al concluded that remdesivir was superior to placebo in shortening the time to discharge in patients hospitalized for COVID-19.[7] Their results also suggested that remdesivir use may help to prevent the progression to a more severe respiratory status.[7] These results are consistent with a study by Gottlieb et al that found remdesivir use in the outpatient setting had a statistically significant lower risk of hospitalization related to COVID-19.[8] Contrarily, Wang et al found no statistically significant difference in time to clinical improvement.[9] Subgroup analyses related to remdesivir initiation and time from symptom onset (either > 10 days or ≤ 10 days) were also found to be not statistically significant.[9] To date, there have been no studies evaluating the time from symptom onset, relative to remdesivir treatment, and improved patient outcomes such as mortality or clinical improvement. The purpose of this study was to determine if initiation of remdesivir treatment in patients who presented with early symptoms of COVID-19 (defined as symptom onset < 7 days) had a significant impact on mortality compared to initiation of remdesivir treatment in patients who presented with a symptom onset of at least 7 days.

Methods

Study Design

This was a multi-center, retrospective, double-arm study that included adult patients admitted to 10 facilities in the HCA Healthcare West Florida Division from May 1, 2020, to July 31, 2020. Approval for this study was obtained by the primary institution's Ethics and Compliance Committee. Additionally, this study was determined to be exempt from Institutional Review Board (IRB) oversight by C.A.R.R.I.E (Centralized Algorithms for Research Rules on IRB Exemption), an HCA Healthcare IRB platform.

Stratification

Subjects were grouped based on their self-reported symptom onset upon initial presentation to the emergency department, as symptom onset of fewer than 7 days or symptom onset of at least 7 days **(Figure 1)**.

Inclusion/Exclusion Criteria

Patients were included if they were admitted to a facility in the HCA Healthcare West Florida Division from May 1, 2020, to July 31, 2020, were 18 years of age or older, had a confirmed diagnosis of COVID-19, and subsequent administration of at least 1 dose of intravenous remdesivir. Patients were excluded if they were less than 18 years of age, had concomitant use of hydroxychloroquine or tocilizumab, or had an estimated glomerular filtration rate less than 30 milliliters per minute.

Outcomes

The primary outcome was in-hospital all-cause mortality. Secondary outcomes included total hospital length of stay, time to discharge from initial remdesivir administration, oxygen requirements, and total number of ventilator days.

Data Collection

The data collected included patient baseline demographics, concomitant comorbidities such as hypertension, heart disease (defined as hav-

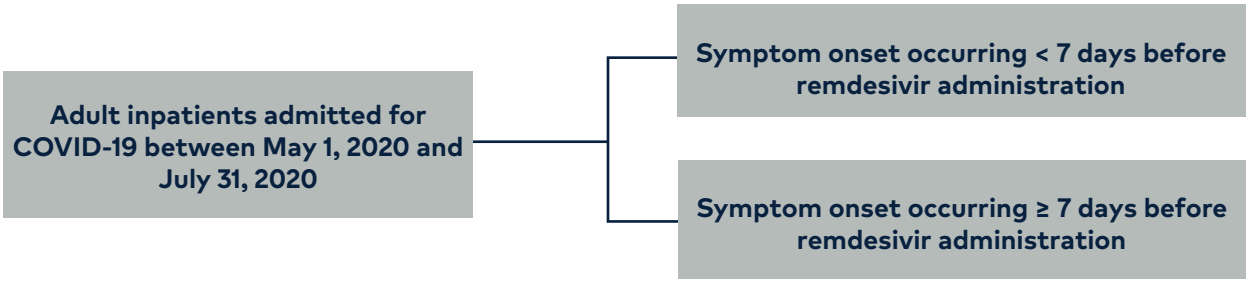

Figure 1. The flow chart illustrates the stratification methods used in the study.

ing coronary artery disease, arrhythmias, heart failure, history of stroke, or cardiac arrest), diabetes mellitus, chronic obstructive pulmonary disorder (COPD), and body mass index (BMI). Outcome data were also collected including in-hospital mortality, length of stay (overall hospital stay), time to discharge from initial remdesivir administration, oxygen requirements, and total number of ventilator days.

Statistical Analysis

Nominal data were evaluated utilizing a chi-square test, while continuous data were evaluated using a 2-sided student *t* test. A *P* value of less than .05 indicated statistical significance.

Results

Baseline Demographics

From May 1, 2020, to July 31, 2020, a total of 217 patients from 10 facilities in the HCA Healthcare West Florida Division were evaluated for inclusion. A total of 24 patients were excluded from further evaluation (**Figure 2**). Of the remaining 193 patients, 109 patients reported symptom onset of less than 7 days before remdesivir administration, and 84 patients reported symptom onset of at least 7 days before remdesivir administration. The 2 arms were similar in age, gender, and race (**Table 1**). The average age of patients with symptom onset of less than 7 days versus at least 7 days was 64.7 and 61.1 (*P* = .19), respectively. The percentage of males was greater than 60% in each study arm and the majority of patients in each arm were Caucasian (*P* = .06). In patients who presented with symptom onset of less than 7 days versus at least 7 days, the prevalence of hypertension, heart disease, diabetes, and COPD was 57.8% and 59.5% (*P* = .81), 25.7% and 20.2% (*P* = .37), 26.6% and 38.1% (*P* = .09), and 18.3% and 11.9% (*P* = .22), respectively. BMI information was also collected to assess the relationship between BMI and mortality rates. In patients who presented with early symptom onset compared to later symptom onset, most had a BMI between 25.0 to 29.9 (*P* = .76). There was no statistical difference in baseline characteristics between the 2 groups.

Primary Outcome Results

There was no statistically significant difference in in-hospital all-cause mortality between patients with symptom onset of fewer than 7 days (34.9%) versus patients with symptom onset of at least 7 days (31.0%) (*P* = .57, **Table 2**).

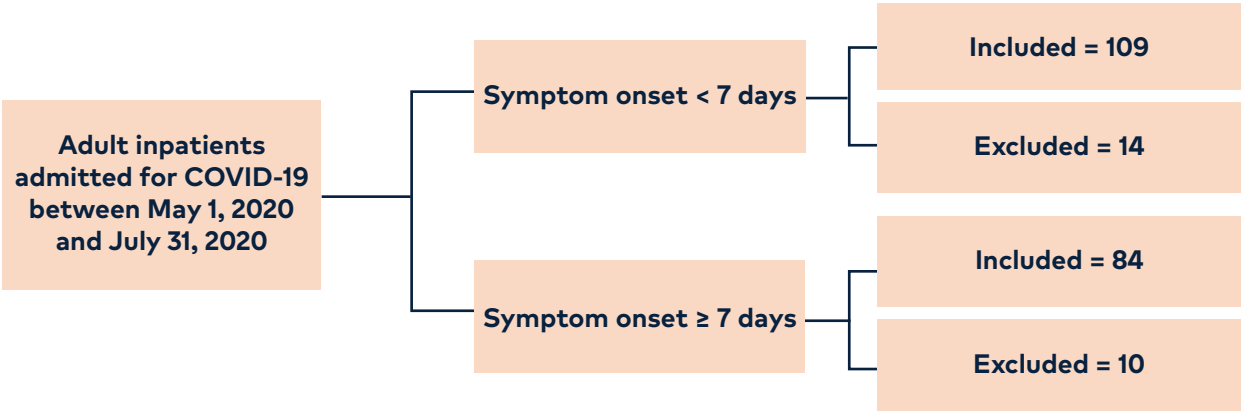

Figure 2. The flow chart illustrates the inclusion and exclusion criteria used in the study.

Table 1. Baseline Characteristics

Characteristic	Symptom onset < 7 days (n = 109)	Symptom onset ≥ 7 days (n = 84)	*P* value
Age, year	64.7 (18-91)	61.1 (18-91)	.19
Female, %	32.1% (35)	35.7% (30)	.59
Race, %			
Caucasian	72.5% (79)	59.5% (50)	.06
Black or African American	8.3% (9)	10.7% (9)	.56
Asian	2.3% (3)	3.6% (3)	.74
Hispanic	16.5% (18)	26.2% (22)	.10
Comorbidities, %			
Hypertension	57.8% (63)	59.5% (50)	.81
Heart disease	25.7% (28)	20.2% (17)	.37
Diabetes	26.6% (29)	38.1% (32)	.09
Chronic obstructive pulmonary disease	18.3% (20)	11.9% (10)	.22
Body Mass Index, %			
≤ 18.4	1.8% (2)	0% (0)	-
18.5 to 24.9	14.7% (16)	23.8% (20)	.11
25.0 to 29.9	29.4% (32)	27.4% (23)	.76
30.0 to 34.9	27.5% (30)	23.8% (20)	.56
35.0 to 39.9	11.0% (12)	16.7% (14)	.25
≥ 40	15.6% (17)	8.3% (7)	.13

Secondary Outcome Results

There were no statistically significant differences in total length of stay, time to discharge, oxygen requirements, or number of ventilator days between patients with symptom onset of fewer than 7 days compared to symptom onset of at least 7 days (**Table 3**).

Exploratory Outcome R esults

There were no statistically significant differences in mortality between groups when the data were categorized by BMI (**Table 4**).

Discussion

Overall, we hypothesized that patients who received earlier treatment (within 1 week of symptom onset) would have better outcomes compared to patients who had a delay in receiving medical treatment. Our outcome data did not support this hypothesis as our primary and secondary outcomes did not prove to be statistically significant.

The benefit of reduced mortality linked to remdesivir treatment has been described in many studies since the introduction of remdesivir for the treatment of COVID-19. The final results from the WHO Solidarity Trial found a statistically significant decrease in mortality when remdesivir was used in patients receiving supplemental oxygen, but who were not mechanically ventilated.[5] In contrast, Chokkalingham et al found a statistically significant reduction in all-cause inpatient mortality across all supportive oxygen subgroups, including

Table 2. Primary Outcome Results

Characteristic	Symptom onset < 7 days (n = 109)	Symptom onset ≥ 7 days (n = 84)	*P* value
All-cause mortality, %	34.9% (38)	31.0% (26)	.57

Table 3. Secondary Outcome Results

Characteristic	Symptom onset < 7 days (n = 109)	Symptom onset ≥ 7 days (n = 84)	*P* value
Total length of stay, median days	15.5 (2-40)	15.0 (2-45)	.69
Time to discharge, median days	10.6 (1-32)	10.9 (1-37)	.83
Oxygen requirements, %			
Requires supplemental oxygen	98.2% (107)	100% (84)	.21
Requires non-invasive ventilation	59.6% (65)	54.8% (46)	.49
Requires invasive ventilation	36.7% (40)	35.7% (30)	.89
Number of ventilator days, median days	10.7 (1-25)	12.0 (1-30)	.67

mechanical ventilation.[6] A recent retrospective cohort by Diaz et al also found a statistically significant (40%) decrease in mortality for patients who received remdesivir compared to those who received standard of care only.[10] Very few published studies stratified their mortality data for patients based on the time from symptom onset, which was the purpose of this study. Wang et al conducted a study in Wuhan, China that used data from February 2020 to March 2020 and looked specifically at 28-day mortality, stratified by early and late symptom onset (defined as ≤ 10 days of symptom onset and > 10 days of symptom onset, respectively).[9] These results were not found to be significant; however, the results of the late-onset group treated with remdesivir had a higher mortality trend than patients who received earlier treatment[9]. In contrast, the results of our study had a non-significant trend of increased mortality in the early symptom onset group. This trend could partly be explained by the timing of data collection; Wang et al collected data from February 2020 to March 2020, the beginning of the COVID-19 pandemic[9]; whereas, in this study, we collected data from May 2020 to July 2020, a time in which the state of Florida had a very high mortality rate due to severity of disease. The question of whether a specific patient population (early vs. late symptom onset) improves mortality remains to be answered.

Wang et al and Ali et al found no difference in total hospital length of stay, results consistent with this study.[9,11] Ali et al found a statistically significant decrease in the need for mechanical ventilation in patients treated with remdesivir compared to patients receiving standard of care, suggesting that patients with less severe disease could potentially benefit from remdesivir the most as it could prevent them from requiring mechanical ventilation.[11] Ali et al did not specifically assess the number of ventilator days to compare to our study[11]; however, Wang et al did not find a significant difference in the number of ventilator days, though their data favored remdesivir.[9]

Several studies have assessed the relationship between BMI and other important clinical outcomes. Tumminia et al found a statistically significant linear correlation between BMI and longer time to clinical improvement.[12] Chetboun et al also found a nonlinear relationship between BMI and mortality; however, these results were not found to be statistically signif-

Table 4. Exploratory Outcome Results (Relationship Between Mortality and Body Mass Index)

Body Mass Index	Symptom onset < 7 days (n = 38)	Symptom onset ≥ 7 days (n = 26)	*P* value
≤ 18.4	5.3% (2)	0% (0)	-
18.5 to 24.9	18.4% (7)	30.8% (8)	.25
25.0 to 29.9	23.7% (9)	23.1% (6)	.96
30.0 to 34.9	28.9% (11)	26.9% (7)	.86
35.0 to 39.9	13.2% (5)	15.4% (4)	.80
≥ 40.0	10.5% (4)	3.8% (1)	.33

icant.[13] Additionally, Chetboun et al found statistically significant correlations between BMI and an increased need for invasive mechanical ventilation.[13] We found no difference between a specific BMI class and an increased risk of mortality in patients treated with remdesivir.

Our study had quite a few limitations, which must be discussed. First, the primary outcome of in-hospital all-cause mortality does not specify if the patients who expired after receiving remdesivir did so due to COVID-19 or from other causes. Therefore, we cannot conclude that remdesivir use in either arm of the study was attributed to time from symptom onset. Second, the time frame in which data were collected occurred during a "peak" in COVID-19 cases and, subsequently, deaths in the state of Florida. The increased number of COVID-related deaths during this time frame, in part, may help to explain why nearly one-third of the study population met the primary outcome of all-cause mortality. Third, data were collected from multiple facilities in the HCA Healthcare West Florida Division. Despite standardization within the division, each hospital/physician may practice slightly differently than if the data all came from the same institution. Fourth, patient-reported symptom onset recorded in physician notes is subjective and should be interpreted with caution. Fifth, our study looked at patients who received remdesivir during their hospital admission but did not distinguish between whether the patient received the full recommended treatment duration or if they only received 1 dose. Lastly, this study had a relatively small sample size and we were, therefore, not able to reach the required power to show statistical significance. Post-hoc power analysis revealed we would need a sample size of approximately 2300 patients per study arm to reach 80% power. Larger trials would be required to show a true statistical significance, if any, between remdesivir use and symptom onset compared to mortality.

Conclusion

Time since symptom onset did not result in a statistically significant difference in in-hospital all-cause mortality in patients who received intravenous remdesivir for the treatment of COVID-19.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of HCA Florida Trinity Hospital, a hospital affiliated with the journal's publisher.

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Author Affiliations

1. HCA Florida Trinity Hospital, Trinity, FL

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