Pre-Hospital Administration of Remdesivir during a SARS-CoV-2 Outbreak in a Skilled Nursing Facility

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Published by Oxford University Press for the Infectious Diseases Society of America 2021.

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Abstract: Completion of a 5-day course of remdesivir was associated with approximately 17-fold increased odds of survival among a sample of 54 nursing home residents with SARS-CoV-2 infection during the course of an outbreak from October to December, 2020. Remdesivir was well-tolerated; administration was logistically feasible in a pre-hospital environment.

Keywords. remdesivir; COVID-19; SARS-CoV-2; SNF; LTCF.

Background

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) causes COVID-19, with manifestations ranging from asymptomatic viral carriage to severe disease. Risk factors for severe disease include advanced age, multimorbidity, diabetes mellitus (DM) and obesity.[1-2] Older adults and those residing in Long Term Care Facilities (LTCF) are among the most severely impacted, with 658,169 total confirmed cases and 133,414 COVID-attributed deaths among residents per Centers for Medicare and Medicaid Services (CMS) at the time of this writing.[3-5]

In October 2020, remdesivir received FDA-approval for the treatment of hospitalized patients with COVID-19.[6] Remdesivir is a nucleotide analogue, which inhibits viral RNA-dependent RNA polymerase.[6-8] The majority of clinical experience with remdesivir derives from use in acute care, where it has been shown to reduce time to recovery in patients hospitalized with COVID-19.[8-11] While positive trends in mortality have been observed, no statistically significant mortality reduction has been proven with remdesivir in hospitalized patients.[8-11]

This report describes our experience administering a 5-day course of remdesivir to SNF residents during a COVID-19 outbreak, prior to vaccine availability. This off-label use was undertaken in the context of a large-scale outbreak in a high-prevalence region. Our team sought to treat residents as promptly as possible following diagnosis.

Methods

Facility

The Idaho State Veteran's Home-Boise (ISVH-B) is a state-owned, 124-bed SNF. Most rooms are double-occupancy, with restrooms shared by as many as four residents. At the time of the outbreak, the facility census was 88.

SARS-CoV-2 surveillance testing was implemented for all residents and staff beginning in May 2020, pursuant to CMS and state regulations. Testing frequency was adjusted by county-level COVID-19 prevalence. Both polymerase chain reaction (PCR; Applied Biosystems TaqPath COVID-19) and rapid antigen (Becton Dickinson, BD Veritor Plus) testing were employed in twice weekly surveillance from July 2020 through January 2021.

Patients diagnosed with SARS-CoV-2 on or after October 14, 2020 were treated at the LTCF using a standardized set of supportive measures and were transferred to a higher level of care if needed, depending upon disease severity and if congruent with their goals of care. Residents who developed respiratory distress but did not desire transfer to acute care were treated with dexamethasone 6mg PO daily for 5-days, as well as mometasone furoate inhalation. Residents with secondary bacterial pneumonia were treated with amoxicillin/clavulanate; those with venous thromboembolism were treated with enoxaparin.

Beginning on October 31, 2020, all patients with a SARS-CoV-2 diagnosis within the preceding 10 days were offered a 5-day course of remdesivir. No patients were excluded due to contraindications, namely hypersensitivity to any component of the formulation. Remdesivir was administered as a 200mg IV loading dose, followed by 100mg IV daily days 2-5. Remdesivir was compounded daily in 100mL of normal saline and delivered in elastomeric infusion devices (Homepump; Halyard) over 30-60 minutes. A daily examination was performed by the attending physician during treatment. Comprehensive metabolic panel and complete blood count were monitored daily. Any resident receiving remdesivir at an acute care hospital after being diagnosed with COVID-19 in the LTCF was included as an individual receiving remdesivir. There were 34 residents treated with remdesivir, 32 of whom initiated remdesivir in the LTCF and 2 of whom received their first dose in an acute care facility. For patients lacking decision-capacity, their designated power of attorney was contacted for consent.

Statistical Analysis

Residents were considered to survive SARS-CoV-2 infection if they were alive 28-days after diagnosis. Baseline demographic and clinical characteristics of patients were collected (Table 1). Differences in age and BMI between survivors and non-survivors were tested by Student t-tests. Logistic regression analyses were completed individually against the dependent variable of death due to COVID-19. A stepwise logistic regression was also conducted to determine which of the independent variables were most significantly associated with the dependent outcome when considered simultaneously. The cutoff probability for entry into the model was set to p=0.20, while the cutoff probability for remaining in the model was p=0.05. All analyses were performed using SAS Version 9.4.

Results

Baseline characteristics of patients are summarized in Table 1. Residents who survived COVID-19 were slightly younger than those who died (p=0.0691). All residents who died did not desire cardiopulmonary resuscitation and indicated a code status of "Do Not Resuscitate (DNR)." Of the residents who survived, 35(77.8%) indicated DNR code status. Most patients in this study were asymptomatic (59.3%). Among those who were symptomatic at diagnosis, a higher mortality rate was observed (88.9%). Fourteen of the symptomatic patients received remdesivir, of whom 10 (71.4%) survived.

Results of logistic regression are summarized in Table 2. Subsequent stepwise logistic regression modeling revealed two variables significantly predictive of survival when independent variables were considered simultaneously: completion of a 5-day remdesivir course (p=0.0044) and diabetes mellitus (p=0.0221), Wald $\chi^2(2)=9.8245$, p=0.0074. Completion of a 5-day course of remdesivir increased the odds of survival almost 17-fold (adjusted OR=16.9,

95% CI=2.4, 118.5). A diagnosis of diabetes reduced the odds of survival by 90% (adjusted OR=0.1, 95% CI=0.014, 0.719). The Hosmer-Lemeshow test showed adequate model fit to the data [$\chi^2(2)=0.2058$, p=0.9022]. The model provided a prediction classification rate of 83.6%. Age, weight, other co-existing conditions and concomitant therapies were not found to be significant predictors of mortality (Table 2).

Safety Outcomes

One resident developed transaminitis following receipt of two doses of remdesivir. He had baseline elevation of liver enzymes secondary to congestive hepatopathy. Transaminitis following remdesivir administration was mild, compared to baseline values, and occurred in the context of septic shock related to COVID-19; this resident died of septic shock.

One resident expired within several hours of receipt of a single dose of remdesivir. This resident was noted to have signs and symptoms of septic shock several hours prior to remdesivir administration but did not desire hospitalization or aggressive interventions. A compassionate dose of remdesivir was given, per the family's wishes.

Three residents developed hyperkalemia while receiving remdesivir; of these, one required transfer to a higher level of care for management. Hyperglycemia was observed in many residents receiving remdesivir and the supportive measures described above. Dexamethasone was implicated in most cases of hyperglycemia.

Discussion

Observational data from this cohort demonstrate nearly 17-fold increased odds of survival at 28-days among SNF residents receiving a 5-day course of remdesivir. SNF residents were administered remdesivir promptly upon diagnosis of SARS-CoV-2 infection, with an

average of 2.4 days from diagnosis to remdesivir-initiation. Prompt remdesivir administration in a pre-hospital setting, regardless of symptoms, is a novel approach to COVID-19 management and is hypothesized to account for the profound survival benefit observed here, which has not been observed in other studies of remdesivir.[8-11]

While our approach was novel, early treatment with remdesivir has been efficacious in experimental models of viral infection, and early antiviral therapy is well-aligned with the treatment paradigm of influenza in LTCF.[12] Antiviral therapy for influenza exerts greatest clinical benefit when initiated as soon as possible after symptom onset.[12] Reduction in influenza transmission has also been observed in LTCF settings with early antiviral treatment, and it is reasonable to hypothesize a similar effect with early initiation of remdesivir for SARS-CoV-2. As the outbreak progressed, we initiated remdesivir more quickly, often on the day of diagnosis. That said, receipt of remdesivir within 48-hours of diagnosis did not reach statistical significance (p=0.0539), likely due to small sample size.

Increased mortality was observed among our patients with diabetes, consistent with findings in other settings.[4,13] In our sample, completion of a 5-day course of remdesivir among residents with diabetes was protective, even when accounting for the influence of diabetes in reducing survival.

In addition to demonstrating clinical benefit, this study demonstrates the plausibility of administering remdesivir in the LTCF setting. The utilization of elastomeric balls for intravenous infusion obviated the need for IV pumps. No complications related to use of the infusion device were encountered. Adverse events were uncommon.

Limitations

This observational study is limited by small sample size, and by the homogeneity in gender and race among the residents observed: the population of the ISVH-B is predominantly male and white. Due to the small sample size, extended statistical analyses, such as exploration of interactions between independent variables, were not possible.

This study required resources not always available in LTCF. Coordination with an infusion pharmacy and frequent deliveries are critical due to the short stability of remdesivir. Nurses skilled in IV placement and monitoring, as well as phlebotomy staff, were essential. Finally, close monitoring of clinical status through daily physician rounding is requisite.

Asymptomatic patients accounted for the majority of patients observed in this study, perhaps contributing to the profound mortality benefit described. Thus, the role of antivirals in asymptomatic positive patients is unclear but should be considered in LTCF outbreak contexts.

While vaccination stands to mitigate SARS-CoV-2 severity among LTCF populations, challenges in vaccine uptake and emerging variants remain, analogous to seasonal influenza. Additionally, the extent and duration of protection conferred by vaccination in frail, multimorbid older adults remains to be seen. Thus, access to and guidelines for use of, broad-spectrum antiviral agents with activity against SARS-CoV-2 and other respiratory viruses of pandemic potential are of paramount importance.

Notes

Acknowledgements. The authors would like to thank Boise VAMC leadership and staff, including: Kimberly Belongie, Taylor Dahmer, Brittany Bartron, Annie Ortiz, and the inpatient pharmacy staff for acquisition and preparation of remdesivir. David Wood (Facility Director), Andrew Wilper (Chief of Staff), Angelina Knesel (Associate Director of Patient Care Services/Chief Nurse Executive), and Tim Santos (Chief of Pharmacy), for support of the project. Jamie Kellar and Rene Haugen for lab coordination and phlebotomy services. The authors would also like to thank Idaho State Veteran's Home Boise Leadership, including: Rachael Knight, Director of Nursing Services, and Lydia Thompson, Interim Director of Nursing Services, for coordination of resident care during the outbreak. Amber Goodchild, Deputy Administrator, for leadership during the outbreak.

Disclaimer. The views, opinions, and findings contained herein are those of the author and should not be construed as an official Department of the Army or Department of Veterans Affairs position, policy, or decision unless so designated by other documentation.

Financial support. The author(s) received no specific funding for this work.

Potential Conflicts of Interest. MAD reports participation in a single Merck advisory board; received a single honorarium as an expert panelist regarding development of an oral antiviral agent for COVID once in December of 2020, after the present study was well-underway and nearly completed.

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Table 1: Baseline Demographic and Clinical Characteristics of the Patients

		Died (N=9)	Survived (N=45)	Total (N=54)
Category	**Characteristic**	**n (%)**	**n (%)**	**n**
Antiviral Treatment	Received any RDV	5 (55.6)	34 (75.6)	39
	Days on RDV, mean ± SD	1.60 ± 2.07	3.70 ± 2.16	--
	Started RDV within 48hr of diagnosis	1 (11.1)	23 (51.1)	24
	Days from diagnosis to RDV, mean ± SD	4.40 ± 1.95	2.10 ± 2.55	--
	Completed 5-day course of RDV	2 (22.2)	32 (71.1)	34
Disease Burden	Symptomatic at diagnosis	8 (88.9)	14 (31.1)	22
	Received any RDV and symptomatic	4 (50)	10 (71.4)	14
Demographics	Age (years), mean ± SD	85.30 ± 8.86	79.4 ± 8.81	--
	Race, White	9 (100)	44 (97.8)	53
	Race, Hispanic or Latino	0	1 (2.2)	1
	Code Status			
	DNR	9 (100)	35 (77.8)	44
	FULL	0	10 (22.2)	10
	BMI, mean ± SD	30.50 ± 5.89	28.20 ± 6.04	--
	BMI Category			
	Underweight	0	1 (2.2)	1
	Normal	1 (11.1)	13 (28.9)	14
	Overweight	3 (33.3)	17 (37.8)	20
	Obese	5 (55.6)	14 (31.1)	19
Concomitant Therapy	Dexamethasone	7 (77.8)	23 (51.1)	30
	Days of dexamethasone, mean ± SD	4.80 ± 3.73	4.70 ± 4.96	--
	Apixaban	1 (11.1)	5 (11.1)	6

	Baseline Supplemental Oxygen	4 (44.4)	6 (13.3)	10
Co-existing Conditions	Smoking	3 (33.3)	12 (26.7)	15
	Diabetes mellitus	7 (77.8)	20 (44.4)	27
	Hypertension	8 (88.9)	38 (84.4)	46
	Cardiovascular Disease	6 (66.7)	38 (84.4)	44
	Respiratory Disease	4 (44.4)	15 (33.3)	19
	Cancer	1 (11.1)	10 (22.2)	11
	Dementia	7 (77.8)	23 (51.1)	30
	Chronic Kidney Disease	2 (22.2)	9 (20.0)	11
	Liver Disease	0	4 (8.9)	4

Table 2: Predictors of Mortality

Category	Variable	p value
Antiviral Treatment	Received any RDV	0.2306
	Started RDV within 48hr of diagnosis	0.0539*
	Completed 5-day course of RDV	**0.0130***,†
	Days on RDV	**0.0160***
Demographics	Age	0.0811*
	BMI	0.2957
	Overweight or Obese BMI	0.2465
	Obese BMI	0.1713*
Concomitant Therapy	Dexamethasone	0.1578*
	Days on Dexamethasone	0.9690
	Apixaban	1.0000
	Baseline Supplemental Oxygen	**0.0397***
Co-existing Conditions	Smoking	0.6843
	Hypertension	0.7335
	Cardiovascular Disease	0.2222
	Respiratory Disease	0.5261
	Cancer	0.4603
	Dementia	0.1578*
	Chronic Kidney Disease	0.8800
	Diabetes mellitus	0.0847*,†

* indicates variable was entered in stepwise logistic regression; † indicates variable was included in final stepwise regression model. The model did not converge for race, BMI category, baseline liver disease, and code status.