ORIGINAL ARTICLE

Clinical outcomes of remdesivir in patients with COVID-19 infection: An observational study from a tertiary care hospital in Pakistan

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ABSTRACT

Background: The primary objective was to assess the change in oxygenation status of patients after remdesivir treatment.

Material and Methods: This retrospective cross-sectional study was conducted at the Aga Khan University Hospital, Karachi from September to December 2020. All patients aged >18 years admitted with a positive reverse transcriptase-polymerase chain reaction for COVID-19 were included. Infection severity was subcategorized into two groups (moderate-to-severe and critical). We compared oxygenation status and assisted ventilation before and after remdesivir treatment. An analysis of outcomes between the groups was conducted using chi squares and the student t-test at a significance level of <0.05.

Results: We had 213 COVID-19 patients, of whom 114 (53.5%) received remdesivir during their hospital stay. 69 (60.5%) patients were male and the mean age was 52±12 years. 56 patients (49.1%) had moderate-to-severe infections. 21 out of 56 patients (37.5%) with moderate-to-severe COVID-19 infection while 47 out of 58 patients (81%) with critical COVID-19 required oxygen following remdesivir treatment (p-value: <0.001). Out of 58 critical COVID-19 patients, 46 patients (79.3%) were on non-invasive ventilation and 12 patients (20.7%) were on invasive ventilation prior to remdesivir therapy. 22 out of 46 patients (47.8%) recovered from non-invasive ventilation after remdesivir treatment (p-value: <0.001). 15 patients had mortality (13.1%) while the mean length of hospital stay with moderate-to-severe COVID-19 infection was 6.8 days and with critical COVID-19 infection was 11.3 days.

Conclusion: The study emphasizes that remdesivir was found to be clinically beneficial in patients with moderate-to-severe COVID-19 infection. Besides improving oxygenation status, it also reduced mortality and shortened hospital stays.

Keywords: Antiviral drug, COVID-19, Hypoxia, Noninvasive ventilation, Severe acute respiratory distress syndrome

BACKGROUND

Coronavirus disease of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has had a significant impact on the world.[1] The first case was reported from Wuhan, China in December 2019 and since then it has spread rapidly throughout other parts of the world.[2] The World Health Organization declared it a global pandemic on March 11, 2020.[3] The COVID-19 pandemic brought unexpected challenges to treatment and created great stress for treating physicians. As the pandemic worsens, so do the efforts to find the best treatment. A variety of medications, including antimalarials, antibiotics, antivirals, plasma, corticosteroids, and anti-interleukin 6 inhibitors, have been used to treat the virus.[4]

Remdesivir is a nucleotide analogue that inhibits viral replication and was used against Ebola virus infection.[5] In vitro trials have shown that remdesivir inhibits SARS-CoV-2.[6] There are various ongoing trials and cohort studies on the role of remdesivir in COVID-19 disease. The preliminary report from a small cohort study demonstrated various positive findings that shows improved clinical outcomes in severe COVID-19 disease.[7] Due to the favorable outcomes reported in the literature, the U.S. Food and Drug Administration (FDA) granted remdesivir Emergency Use Authorization for the treatment of COVID-19 on May 1, 2020.[8]

Despite this, the clinical impact of remdesivir on COVID-19 disease is uncertain.[9] There is consensus that remdesivir use in the early stages of the disease had a more fruitful outcome. But its clinical efficacy, side

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effects and tolerability need to be evaluated further for a better understanding of this drug.[10]

As a result of the above considerations, we are conducting this study to identify the clinical effects of remdesivir in a close surveillance environment at a tertiary care hospital in Karachi, Pakistan. The primary objective was to assess the change in oxygenation status of patients after remdesivir treatment. We also compared mortality, re-admission and length of hospital stay in moderate-to-severe and critical COVID-19 patients treated with remdesivir.

MATERIAL AND METHODS

This is an investigator initiated retrospective cross-sectional study conducted in our tertiary care hospital from September to December 2020 to identify the effectiveness and clinical outcomes of remdesivir. Ethical review committee (ERC) of the institute reviewed the study proposal and exemption was granted (ERC Number: 2020-5206-11731). The study was conducted in accordance with Strobe's guidelines. International disease classification version 9.1 was used to derive records of patients admitted to our hospital with COVID-19 infection.

All patients aged >18 years admitted to the hospital with a positive reverse transcriptase-polymerase chain reaction for SARS-CoV-2 were included. Patients with suspected COVID-19 and those diagnosed on computed tomography of the chest were excluded from the study. The patients were recommended to use remdesivir after consulting with an infectious disease specialist.

All patients who received intravenous remdesivir (200mg on day 1 followed by 100mg once daily infusion for 4 more days) were further studied. After enrollment, their demographic information, co-morbid conditions, clinical presentation, management, oxygen and assisted ventilation requirements, and clinical outcomes were recorded. Severity of COVID-19 infection was subcategorized into two groups i.e. group 1 was moderate-to-severe in which patients were symptomatic and hypoxic that required supplemental oxygen only and group 2 was labelled as critical in which patients had hypoxic respiratory failure and with supplemental oxygen required assisted ventilation.[(11)]

Patients were further classified into pre- and post-remdesivir categories. The oxygenation status and assisted ventilation prior to remdesivir administration were called "pre-remdesivir", and on day six (after completing a 5-day course of remdesivir) were labelled as "post-remdesivir". The primary outcome was to compare oxygenation status and assisted ventilation after remdesivir treatment. Secondary outcomes were mortality, re-admission, and length of hospital stay in both groups of patients.

Clinical data was filled out with designed pro-forma and entered into the system software. Statistical Package for the Social Sciences (SPSS) Version 23, IBM, Chicago, USA was applied for data analysis. Number and percentages of categorical variables were compared between groups using chi square with a level of significance of <0.05. Mean and standard deviation of continuous variables were compared between groups using an independent student t-test with 95% confidence interval.

RESULTS

A total of 213 patients were admitted to our tertiary care hospital from September to December 2020 with COVID-19 infection. Out of these 213 patients, 114 (53.5%) patients received remdesivir during their hospital stay. 69 (60.5%) of the patients were male and the mean age was 59±12 years. The main co-morbidities in these individuals were hypertension in 69 patients (60.5%), diabetes in 57 patients (50%) and ischemic heart disease in 17 patients (14.9%). Fever was the major presenting complaint in 77 (67.5%), followed by cough in 62 (54.4%) and dyspnea in 61 (53.5%). 56 patients (49.1%) had moderate to severe COVID-19 infection. All patients (100.0%) required supplemental oxygen therapy during their hospital stay. 46 patients (40.3%) used non-invasive ventilation while 12 patients (10.5%) required invasive ventilation for hypoxic respiratory failure due to COVID-19. 15 patients (13.2%) had mortality from COVID-19 infections. Table-I shows the detailed demographics, clinical characteristics and outcomes of these patients.

All patients received supplemental oxygen prior to hospital admission. At day 6 following a five-day course of remdesivir, 21 out of 56 patients (37.5%) with moderate-to-severe COVID-19 infection still used supplemental oxygen. Based on this, 47 out of 58 patients (81%) with critical COVID-19 required oxygen after treatment with remdesivir (p-value <0.001). Figure-I shows the comparison of the proportion of oxygenation improvement after remdesivir treatment in both groups.

From 58 Critical COVID-19 patients, 46 patients (79.3%) were on non-invasive ventilation and 12 patients (20.7%) were on invasive ventilation prior to remdesivir therapy. 22 patients (47.9%) recovered from non-invasive ventilation after completing remdesivir treatment (p-value: <0.001). Figure 2 compares the ventilation status of patients before and after treatment with remdesivir.

Our study found that 15 patients (25.8%) died in the critical COVID-19 group. The causes of mortality were septic shock with multi-organ failure in 9 patients (60%) and hypoxic respiratory failure in 6 patients (40%). We also identified various complications with COVID-19 infection. 2 patients with moderate-to-severe COVID-19 infection had pulmonary embolisms. Pneumothorax and/or pneumomediastinum was identified in 1 patient with moderate-to-severe and 6 patients with critical COVID-19 infection. 99 patients were discharged from the hospital and 5 patients (5%) were re-admitted to the hospital again in a one-week period. The re-admission reasons were hospital acquired pneumonia in 2 patients, super-added fungal pneumonia in 2 patients and pulmonary embolism in 1 patient. The mean length of hospital stay with moderate-to-severe COVID-19 infection was 6.8 days and with critical COVID-19 infection was 11.3 days. Table-II demonstrates secondary outcomes among patients with moderate-to-severe and critical COVID-19 infection.

Table-I: Demographics, Clinical Characteristics & Outcomes of COVID-19 patients (N: 114)

		N (%)
Age		
	Mean ± S.D.	59 ± 12
	Range	29 – 84 Years
Gender		
	Male	69 (60.5%)
	Female	45 (39.5%)
Co-Morbid		
	Diabetes	57 (50.0%)
	Hypertension	69 (60.5%)
	Ischemic heart disease	17 (14.9%)
	Chronic kidney disease	2 (1.8%)
	Chronic obstructive pulmonary disease	8 (7.0%)
Clinical Symptoms		
	Fever	77 (67.5%)
	Cough	62 (54.4%)
	Dyspnea	61 (53.5%)
	Sore Throat	26 (22.8%)
	Myalgia	23 (20.2%)
Severity		
	Moderate to Severe	56 (49.1%)
	Critical	58 (50.9%)
Management		
	Steroids	113 (99.1%)
	Tocilizumab	46 (40.3%)
Outcomes		
	Supplemental oxygen	114 (100.0%)
	Non-invasive ventilation	46 (40.3%)
	Invasive ventilation	12 (10.5%)
	Mortality	15 (13.2%)
	Length of hospital stay (mean ± S.D.)	9 ± 4 days

Table-II: Outcomes of patients with COVID-19 infection received remdesivir.

	Moderate - Severe	Critical	p-value
Mortality – N (%) *	0	15 (100)	<0.001
Re-admission – N (%) *	2 (40)	3 (60)	0.676
Length of Hospital Stay (days) – mean ± S.D. **	6.8 ± 3.2	11.3 ± 4.8	<0.001

***Chi-square tests were used with a level of significance at p-value <0.05, ** Independent student t-test was used with a level of significance at p-value <0.05**

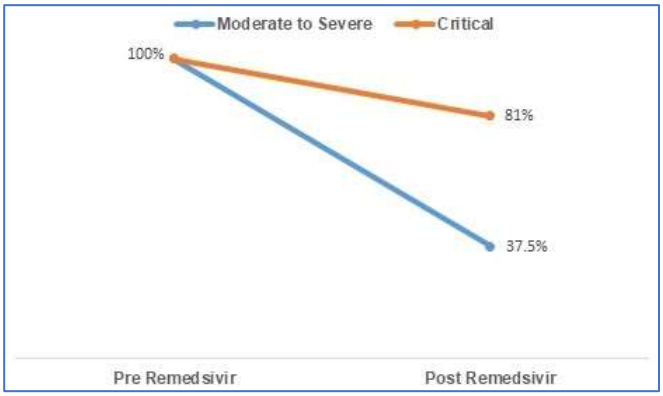

Figure-1: Improvement in oxygenation status after remdesivir treatment.

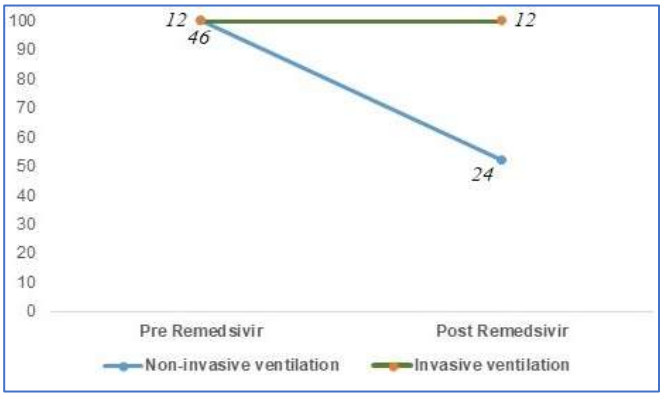

Figure-II: Ventilation status of patients before and after remdesivir treatment.

DISCUSSION

Our study highlights that remdesivir significantly improves oxygenation status in patients with moderate-to-severe COVID-19 infection. In nearly half of our study participants, non-invasive ventilation was also discontinued after a complete course of remdesivir treatment in critically infected COVID-19 patients. Despite remdesivir treatment, mortality was high in patients critically ill due to COVID-19 infection. The duration of hospital stay was also much lower in the moderate-to-severe group compared to the critical group.

Our findings are consistent with the current and recent COVID-19 guidelines.[12] Two major studies SOLIDARITY and ACTT-1 both concluded that remdesivir reduces the time to clinical recovery, resulting in earlier discharge and a shorter hospital stay.[13-15] In our study, remdesivir showed significant clinical improvement when used earlier in the course of illness. Supplemental oxygen was successfully removed from 62.5% in moderate-to-severe and 19% in critical COVID-19 disease. Non-invasive ventilation was discontinued in 47.8% of our study population with critical infections. Patients who were started on remdesivir earlier also had reduced oxygen demand and could therefore be discharged earlier on room air.

Remdesivir shortens the length of hospital stay in patients with mild to moderate disease.[16, 17] Our study found that patients with critical illness had a longer hospital stay (11.3 days versus 6.8 days, p = 0.000). Prolong hospital stay is one of the many risk factors for acquiring nosocomial infections thus patients who were discharged earlier have less chance of acquiring these infections. This also reduces the financial burden on patients, hospital resources and stabilizes the current economic situation.

The significance of our study lies in its conformity to recent guidelines. However, our study was conducted in Pakistan, an Asian country. The study helps understand the impact of racial characteristics on COVD-19 management. It is reassuring and satisfying to know that remdesivir lowers oxygen demand in patients requiring either non-invasive or invasive ventilation. A study in India and Egypt also depicted similar results with remdesivir usage in their population when used in moderate-to-severe disease.[18,19] The ultimate goal of our study was to understand the role of remdesivir in our population. It clearly demonstrates in our study that patient on remdesivir had an early clinical recovery and reduce hospital stay.

In a cohort study by Diaz *et al*. they reported a lower mortality in the group of patients who received remdesivir.[20] In a cross-sectional study, it is not possible to predict the mortality rate. Additionally, we observed all of the mortality in patients with critical infections. Only 6 patients (5.2%) died due to hypoxic respiratory failure. Remdesivir given in the initial stages of illness (when the patient had a mild disease) drastically decreased hospital re-admissions.[21] This shows that remdesivir reduced disease progression. There was no significant difference in re-admission rates between the two groups. However, these re-admissions are primarily due to complications related to health care.

COVID infection can result in pneumomediastinum and pneumothorax.[22] We also identified in this study, more cases of pneumothorax in patients with critical COVID infection compared to those who had moderate-to-severe COVID infection. Thromboembolism is another entity associated with COVID infection.[23] In our study, only two patients had a pulmonary embolism.

Our study has some limitations. The retrospective nature of the study with a small sample size cannot be generalized to the whole population. The cause/reason of disease progression, risk factors for superadded infections, and impact of concurrent other COVID management strategies were not included in our study.

The strength of our study is that it compares clinical effects on oxygenation and ventilation status before and after remdesivir treatment. The severity of COVID illness was also compared to better identify remdesivir's usefulness in the illness phase. Besides this, we also report mortality and re-admission rates in these patients after remdesivir treatment. Ideally the role of remdesivir in early stages of disease in all patients including those with low to no risk of disease progression should be studied. The dosage and duration of remdesivir according to the stage of illness should be studied especially in resource-limited countries like Pakistan.

CONCLUSION

The study emphasizes that remdesivir was found to be clinically beneficial in patients with moderate-to-severe COVID-19 infection. Besides improving oxygenation status, it also reduced mortality and shortened hospital stays.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Sher Muhammad Sethi: Concept and study design; data analysis; initial manuscript writing

Memoona Irshad: Concept and study design; proof reading and reviewing

Rodaba Iqbal: Data collection, manuscript reviewing

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