DOI: https://doi.org/10.53350/pjmhs020241855

ORIGINAL ARTICLE

Use of Remdesivir in Mild to Moderate COVID -19 Disease and its Clinical Outcomes: A Single-Center Observational Study

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ABSTRACT

Aim: To assess the usefulness of Remdesivir in mild-moderate COVID-19 and its effects on clinical outcomes and mortality.
Methodology: This was observational study conducted at Sindh Infectious Diseases Hospital. July 2020 to March 2022. Demographic and clinical data were collected retrospectively from the patient's medical records. Patients > 18 years of age and admitted with confirmed SARS-COV 2 of the mild-moderate category were included. For analysis, patients were divided into two groups to compare those who received Remdesivir plus Standard of Care (SOC) and those receiving only Standard of Care. Outcome variables included progression to severe disease, duration of hospital stay, respiratory support, and mortality.
Results: A total of 789 patients were admitted, of which 435 (54.5%) had mild and 363 (45.5%) had moderate COVID-19 infection. Out of these**,** 46.13% received Remdesivir, while 55% of patients received SOC. The median age of patients in the Remdesivir group was 62 (IQR 50-72) years (p<0.05)**.** No significant difference in mortality was observed between the two groups. (4.4 vs. 3.2%, P>0.05). Patients in the SOC group exhibited a significant risk of disease progression [61(14%) vs23(6.3%), odds ratio (OR):2.425 95% CI: 1.45-4.06, p<0.05]. A significantly longer hospital stay in the SOC group was seen in both mild and moderate disease categories (p<0.05).
Conclusion: Remdesivir can be effective in patients with mild to moderate COVID-19 to halt the progression to severe disease and shorten the hospital stay, leading to early recovery and reduced risk of complications.
Keywords: Mild-moderate COVID-19, Remdesivir, low-flow oxygen, decreased severity, reduced mortality

INTRODUCTION

Remdesivir (RDV) was the first anti-viral to be approved for COVID-19 treatment in severe and critically ill hospitalized patients[1]. It inhibits the SARS-COV-2- RNA-dependent polymerase and has substantial activity in primary human airway epithelial cells[2]. The SARS-CoV-2 RNA-dependent RNA polymerase incorporates RDV-TP, an analog of adenosine triphosphate, into the RNA strand it replicates, and this prevents the virus from replicating by preventing cellular RNA synthesis[3].

Several health organizations have varying recommendations regarding the use of Remdesivir in COVID-19 infected patients. WHO recommends against the use of RDV regardless of the disease severity, while ESCMID (European society of clinical microbiology and infectious diseases) and IDSA (Infectious Diseases Society of America) guidelines recommend using RDV in hospitalized patients with severe COVID-19 but not those requiring mechanical ventilation[4,5,6]. NIH and NICE guidelines recommend treating patients requiring low-flow oxygen with RDV early in the course of the disease[7].

Several clinical trials and observational studies have shown the effectiveness of Remdesivir in hospitalized COVID-19 patients with low flow oxygen requirement, with reduced progression to severe disease, early recovery, and lower mortality[8]. The ACTT-1 trial showed 50% improvement in patients receiving RDV, especially with comorbidities[9]. The SOLIDARITY trial showed reduction in mortality in patients requiring low flow oxygen but not on mechanical ventilation[10]. Observational studies have also been reported from Pakistan studying the effect of Remdesivir in COVID -19 patients, and have conflicting results regarding its benefits on disease progression and mortality[11,12]. Majority of these studies did not stratify their patients according to disease severity, however, Malik et al based on their findings in patients with moderate COVID-19, reported a reduction in mortality and a shorter hospital stay[13].

The COVID-19 patients requiring ICUs have 35.5% mortality and a higher risk of severe complications like thromboembolism and ARDS. [8] They also require more healthcare personnel and increase the cost of care, which in a resource-poor setting like ours can cause a substantial burden on the healthcare systems. Remdesivir, if given appropriately, can prevent progression to this critical stage, reduce mortality, and save healthcare costs and personnel. This study aimed to assess the effect of Remdesivir in COVID-19 patients with mild-moderate disease on their clinical outcomes, including mortality. The rationale was to address the paucity of local data and validate the previous studies' findings, emphasizing the usefulness of Remdesivir in patients with mild-moderate COVID-19 in our population.

Received on 05-02-2024
Accepted on 26-06-2024

METHODOLOGY

The study was conducted at the Sindh Infectious Diseases Hospital and Research Center, Karachi. The hospital was specifically built and designed to manage COVID-19-infected patients during the pandemic. It was an observational study based on data collected retrospectively from patient's medical records from July 2020-March 2022. All patients >18 years old with a positive SARS-CoV-2 NAAT/antigen test and clinical evidence of mild/moderate COVID-19 disease were included. We excluded patients categorized as severe/critical COVID-19 disease, patients with laboratory evidence (cultures/NAAT testing PCR) of bacterial or viral co-infection at hospital admission, lactating and pregnant women, patients who left against medical advice, and those who died on day one of hospitalization. Patients with a creatinine clearance of <30ml/min and SGPT >5xtimes the standard limit were also excluded.

For analysis, patients were further divided into two groups: group 1: patients who received Remdesivir with standard of care (SOC), and group 2: those who received only standard of care (SOC). Remdesivir was started in patients based on the primary physician's decision, and the dose was 200 mg IV loading followed by 100 mg IV once per day for a total of 5 days. Standard of care (SOC) included steroids, anti-coagulation, antipyretics, and antibiotics (if indicated). Low-flow oxygen was administered at < 6 L/min via nasal cannula or an oxygen mask. A case of COVID-19 was defined as acute onset of any three or more of the following: fever, myalgia, cough, fatigue/generalized weakness, headache, coryza, nausea/diarrhea/anorexia, dyspnea, sore throat) with a positive professional use of SARS-CoV-2 antigen (RDT/NAAT). A mild case was defined as apatient meeting the case definition of COVID-19 without evidence of viral pneumonia, i.e., cough,

dyspnea, tachypnea, or hypoxia. A moderate case was defined as a patient with symptoms and signs of pneumonia (fever, cough, dyspnea, and tachypnea). However, there were no signs of severe pneumonia, including SpO2 > 90% on room air[14].

After getting the IRB approval, the following data was collected on a pre-tested, pre-formed proforma. Demographic data includes the patient's age, gender, date of admission, and discharge. Clinical data included co-morbid conditions, signs, and symptoms at presentation, like fever, body aches, nausea, vomiting, cough, shortness of breath, and chest pain. Other parameters were noted, such as SpO2 on room air and oxygen requirements on admission and discharge, disease severity, complications including disease progression to severe pneumonia, ICU admission, duration of stay, and invasive/non-invasive ventilation requirement. Treatment given with dose and duration, adverse effects of RDV, and outcomes (death or discharge) were noted as well. Laboratory data included: COVID-19 PCR/antigen report, CBC and CRP,

Variables used to assess the outcomes included duration of hospital stay, progression to severe disease, and transfer to ICU with or without mechanical ventilation and oxygen requirement at discharge. Improvements in laboratory parameters like CRP and outcome, i.e., death or discharge, were also assessed. Clinical improvement was assessed within seven days after RDV administration. Clinical improvement was defined as clinical recovery, i.e., fever, respiratory rate, & oxygen saturation returned to normal, and cough relief maintained for at least 24 hours.

Data was analyzed using SPSS version 21. Categorical variables like gender, symptoms, and complications were analyzed and presented as percentages and frequencies. Continuous variables like age, duration of hospital stay, and oxygen requirements are presented as mean (standard deviations) or median (interquartile range), and the Shapiro-Wilk test was applied for the normality of the continuous data. Binary variables are expressed as proportions. Differences in continuous variables between groups were evaluated using the Wilcoxon rank-sum test, and differences in categorical variables are evaluated using chi-square or Fisher's exact test. We then compared patient characteristics between the two groups. An estimate of the odds ratio and 95% confidence interval was also reported.

RESULTS

The study consisted of a total of 789 admitted COVID-19 patients, of which 435(54.5%) belonged to mild (no supplemental oxygen requirement) and 363(45.5%) were moderate (requiring oxygen) category. The clinical characteristics of the patients are shown in Table 1. The median age was 60 (IQR=50-70) years. Most patients had comorbidities (60.7%), including Hypertension (46.7%) followed by Diabetes Mellitus (36.6%). More than half of the patients were males (61.2%), and almost all the patients had symptoms, most commonly fever (81%), shortness of breath (67.4%) and cough (68%) at presentation.

Out of the 789 patients, 364(46.13%) received Remdesivir (RDV), while 434(55%) patients were given standard of care (SOC) but no RDV during hospital stay. There were no significant differences between the clinical characteristics of the two groups, except in the age and duration between onsets of symptoms. The median age of patients not receiving RDV was younger 60 (50-69) compared to patients who received RDV 62(50-72) years (p<0.05).

The clinical course and outcomes of the patients are presented in Tables 2 and 3. Regarding mortality, no significant differences were observed between the two groups of patients. (4.4 vs. 3.2%, P>0.05). However, patients who did not receive RDV exhibited a significant risk of disease progression compared to those who received RDV [61(14%) vs 23(6.3%), odds ratio (OR):2.425 95% CI: 1.45-4.06, p<0.05]. When comparing the status at discharge, 38(8.7%) of patients were discharged while still requiring oxygen, in contrast to only 11(3.02%) patients discharged with an oxygen requirement, who received RDV (p<0.05).

Table 1: Comparison of Clinical Characteristics of COVID -19 patients. Standard of care vs. Remdesivir therapy

Variables	Total (798)	SOC (434)	RDV (364)	p-Value
Median (IQR) Age	60 (50-70)	60 (50-69)	62 (50-72)	0.012
Gender n (%)				
Male	488 (61.2)	266 (61.3)	222 (61)	0.942
Female	310 (38.8)	168 (38.7)	142 (39)	
Onset of Symptoms n (IQR)	7 (4-10)	6 (4-7)	7 (5-12)	0.001
Symptoms n (%)	794 (99.5)	430 (99.1)	364 (100)	0.13
Cough	543 (68)	297 (68.4)	246 (67.6)	0.819
Fever	646 (81)	353 (81.3)	293 (80.5)	0.786
Shortness Of Breath	538 (67.4)	276 (63.6)	262 (72)	0.012
Sore Throat	22 (2.8)	12 (2.8)	10 (2.7)	1
Diarrhea	26 (3.3)	15 (3.5)	11 (3)	0.84
Headache	3 (0.4)	2 (0.5)	1 (0.3)	1
Flu Like Symptoms	19 (2.4)	11 (2.5)	8 (2.2)	0.819
Loss of Sense of Smell & Taste	5 (0.6)	4 (0.9)	1 (0.3)	0.383
Disease Category n (%)				
Mild	435 (54.5)	282 (65)	153 (42)	0.0001
Moderate	363 (45.5)	152 (35)	211 (58)	
Comorbidities n (%)	540 (67.7)	288 (66.4)	252 (69.2)	0.404
Diabetes mellitus	292 (36.6)	150 (34.6)	142 (39)	0.21
Hypertension	373 (46.7)	197 (45.4)	176 (48.4)	0.433
Smoker	17 (2.1)	12 (2.8)	5 (1.4)	0.221
Asthma	23 (2.9)	17 (3.9)	6 (1.6)	0.87
Ischemic heart disease	89 (11.2)	53 (12.2)	36 (9.9)	0.312
Cerebral vascular accident	14 (1.8)	7 (1.6)	7 (1.9)	0.791
Chronic kidney disease	27 (3.4)	16 (3.7)	11 (3)	0.696
Thyroid abnormalities	22 (2.8)	9 (2.1)	13 (3.6)	0.278
COPD	10 (1.3)	8 (1.8)	2 (0.5)	0.121
Biomarkers at Day1 median (IQR)				
Hb	12.6 (11.2-13.9)	12 (10.98-14.0)	12.6 (11.3-13.7)	0.608
TLC	8.1 (5.8-11.2)	8.5 (6.2-12.38)	7.5 (5.4-10.5)	0.006
PLATELETS	238 (173-325)	247 (178-334)	227(171-320)	0.157
CRP	65 (27-129)	54.5 (18.3-123)	76 (36-141)	0.0001

Abbreviations : SOC =Standard of care, RDV= Remdesivir, IQR=Interquartile range, COPD=Chronic Obstructive Pulmonary Disease, Hb=Hemoglobin, TLC= Total leukocyte count.

Table 2: Comparison of Outcomes; Standard of care vs. Remdesivir therapy

Overall Outcomes Comparison						
Variables n (%)	**Total n=798 (%)**	**SOC n=434 (%)**	**RDV n=364 (%)**	**Odd ratio**	**CI**	**P-Value**
ICU stay	46 (5.8)	24 (5.5)	22 (6)	0.915	0.522-1.604	0.763
Median Hospital Stay (IQR)	5 (3-7)	5 (4-8)	4 (2-6)		-	0.001
Discharged	768 (96.2)	420 (96.8)	348 (95.6)	1.012	0.984-1.041	0.456
Mortality	30 (3.8)	14 (3.2)	16 (4.4)	0.734	0.363-1.483	
Disease Progression	84 (10.5)	61 (14.0)	23 (6.3)	2.425	1.455 to 4.067	0.0001
Discharge on Oxygen	49 (6.1)	38 (8.7)	11 (3.02)			0.0001
CRP improved	579 (72.6)	270 (74.2)	309 (71.2)	0.96	0.881-1.045	0.381

Abbreviations : SOC =Standard of care, RDV= Remdesivir, IQR=Interquartile range, ICU=Intensive care unit, CRP= C-reactive protein, CI= Confidence interval

Table 3: Comparison of outcomes of COVID-19 patients receiving RDV vs. SOC based on disease severity

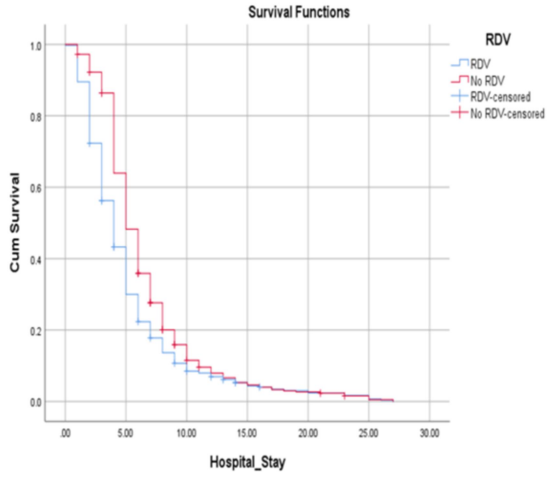
Mild n (%)	**Total n= 435 (%)**	**SOC n=282 (64.82%)**	**RDV n=153 (35.17%)**	**Odd ratio**	**CI**	**P-Value**
ICU stay	24 (5.5)	14 (5)	10 (6.5)	0.76	0.346-1.669	0.514
Hospital Stay	4 (2-6)	5 (4-7)	4 (2-6)			0.0001
Discharged	420 (96.6)	271 (96.1)	149 (97.4)	0.98	0.953-1.022	0.59
Mortality	15 (3.4)	11 (3.9)	4 (2.6)	1.492	0.483-4.606	
Disease Progression	41 (9.4)	28 (9.93)	13 (8.5)	1.187	0.5981 to 2.441	0.732
CRP improved	304 (69.9)	198 (70.2)	106(69.3)			0.913
Moderate n (%)	Total n= 363 (%)	SOC 152 (41.87%)	RDV n=211 (58.12%)	Odd ratio	CI	p-Value
ICU stay	22 (6.1)	10 (6.6)	12 (5.7)	0.856	0.360-2.036	0.824
Hospital Stay	5 (4-7)	6 (4-8)	4 (3-6)			0.0001
Discharged	348 (95.9)	149 (98)	199 (94.3)	1.012	0.984-1.041	0.108
Mortality	15 (3.4)	3 (2)	12 (5.7)	0.734	0.363-1.483	
Disease Progression	43 (11.8)	33(14.10)	10 (7.75)	5.574	2.636 to 11.28	<0.0001
CRP improved	275 (75.8)	111 (73)	164 (77.7)			0.322

Abbreviations: SOC =Standard of care, RDV= Remdesivir, IQR=Interquartile range, ICU=Intensive care unit, CRP= C-reactive protein. CI= Confidence Interval

When analyzed based on disease severity, Table 3 reveals a significantly more extended hospital stay for patients not receiving RDV in both mild and moderate disease categories ($p<0.05$). In terms of mortality, patients with mild disease exhibited a 1.49 times higher risk of mortality (OR: 1.492, CI: 0.483-4.606) in the SOC group. Patients with mild disease who did not receive RDV showed a 1.18 times higher risk of disease progression than those who received RDV (9.93% vs. 8.5%, OR: 1.187, CI: 0.598-2.441, $p<0.05$). In moderate category patients, there is a significantly higher risk of disease progression (14.10% vs. 7.75%, $p<0.0001$) and hospital stay (median (IQR) 6 (4-8 vs. 4 (3-6) for those who did not receive Remdesivir.

Figure 1 shows the Kaplan-Meier 30-day survival curve for hospitalized mild and moderate COVID-19 patients, grouped according to their RDV administration status. It was found that the patients who received RDV had a significant survival rate at 30 days than patients who did not receive Remdesivir.

Figure 1: Kaplan-Meyer 30-day survival curve in patients who received Remdesivir vs Standard of careAbbreviations: RDV= Remdesivir



DISCUSSION

We conducted this study to assess the effects of Remdesivir on patients admitted with mild-moderate COVID-19, i.e., patients with no or low oxygen requirement and having a high risk for progression because of older age, and pre-existing conditions like diabetes, chronic kidney disease, ischemic heart disease, and other co-morbid conditions. Several international observational studies and clinical trials with Remdesivir involving similar patients have shown favorable outcomes with a good safety profile[8,17,18].

The most notable finding of our study was reduced risk of progression to severe COVID-19 disease, including the need to shift to the ICU, use of mechanical ventilation, a shorter hospital stay, and fewer patients requiring oxygen at discharge with a 5-day course of Remdesivir. This difference was more pronounced in patients with moderate disease at presentation than those with mild disease. This result is in line with the outcomes of some large-scale RCTs, including the ACTT-1 and SIMPLE trials, both comprising patients with moderate COVID-19. These trials demonstrated that RDV significantly prevented progression to severe disease and led to lower requirement for invasive/non-invasive ventilation with better clinical outcomes[9,18,19].

In contrast, a non-placebo multi-center RCT conducted by WHO failed to demonstrate any beneficial effect of RDV on mortality, need for ventilation, and duration of hospitalization. However, this study stratified patients according to respiratory support instead of disease severity, in contrast to other clinical trials[20]. Another multi-center RCT in China did not show any clinical improvement in patients receiving RDV when compared to a placebo[21]. However, in the same trial, clinical improvement was accelerated when symptoms duration was <10 days at the time of RDV administration. Similar observations were seen with a supplemental analysis of the ACTT-1 trial when early recovery was noted in patients receiving RDV, with symptoms onset < 6 days[9]. Interestingly, in our study, patients who received Remdesivir responded well regarding disease progression and early discharge, irrespective of the duration of symptom onset (median=5-12 days). This could be because low-dose parenteral steroids were also given to all patients requiring oxygen simultaneously, which may have confounded our results.

Similar to our study, results from the multi-center SOLIDARITY trial and data from multiple real-world observational studies also demonstrated a faster recovery in lower-risk (with low flow oxygen requirement) than high-risk patients[22]. A study by Malin et al showed 31% faster recovery in patients receiving Remdesivir[23]. Clinical studies have provided evidence that viral replication is maximal at the time of symptom onset and its inhibition by Remdesivir can lead to an early recovery[19,24].

We also analyzed the effects of Remdesivir on mortality but could not find a statistically significant difference between the two groups, which remained unchanged even after subgroup analysis. The evidence regarding the mortality benefits of Remdesivir in COVID-19 remains controversial as there are conflicting results[8,19]. Clinical trials like the DISCOVERY and initial evidence from the SOLIDARITY trials failed to show a mortality benefit of using Remdesivir in COVID-19 infected patients, irrespective of the disease severity. [20] [25] However, results from the sub-group analysis of the ACTT-1 trial showed a statistically significant 28-day mortality benefit in patients with low flow oxygen requirement when given earlier in the course[9]. Updated results of the SOLIDARITY and the SIMPLE trials showed a similar trend of lower mortality in patients not receiving mechanical ventilation. Data from several observational studies in large cohorts of patients also corroborated the benefits of RDV on mortality in patients with moderate COVID-19[18]. A retrospective cohort study demonstrated the mortality benefit of RDV when given within six days of symptom onset[26]. A study from Pakistan on utility of RDV in moderate COVID-19 also reported decreased mortality and a shorter hospital stay[13]. Although our findings may not corroborate the evidence from the above studies, different outcomes may have been possible if RDV was administered earlier, i.e., < 6 days after symptom onset.

Unlike the patients with moderate COVID-19, those with mild disease (i.e., no oxygen requirement) did not show any statistically significant reduction in risk of disease progression with RDV. We included this patient population because there had been compelling evidence from existing studies recommending RDV in patients with mild COVID-19 having risk factors for progression.[19] The multi-center PINE-TREE trial showed an 87% reduction in hospitalization and all-cause mortality at day 28 with a three-day RDV treatment given as outpatient to high-risk patients with mild COVID-19 symptoms[1,19]. Several other observational studies have also validated these results[8]. However, a meta-analysis by Lee et al. also concluded that the benefit of giving RDV to non-hypoxemic patients remains small[17]. This entails further research with future multi-center trials, especially assessing for response in our population.

Our study has several limitations, including its retrospective, single-centered design, which makes it less generalizable.We were unable to retrieve radiological and laboratory data in all the patients as well. However, our strength lies in the fact that the study was done at the largest COVID-19 facility in the city, and we got a good sample size in both patient groups and were able to achieve a comprehensive analysis on disease outcome with regard to disease recovery, hospital stay and mortality.

CONCLUSION

In conclusion, this study provides additional evidence that patients with mild-moderate COVID-19 disease can benefit from a short course of Remdesivir in terms of reduced risk of disease progression and early recovery. However, it failed to demonstrate an improvement in the mortality rate. These findings might be useful in devising management plans in the future so that morbidity and mortality risks can be minimized, especially in the local population.

Authorship and contribution declaration: Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

Ethical approval: Ethical approval was taken from the Institutional Review Board (IRB) of Dow University of Health Sciences, Karachi, Pakistan (Ref Number)

Data availability: The data presented in this study are available on request from the corresponding author

Conflict of interest: The authors declared no conflict of interest.

Funding: This study not funded by any company or institution

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This article may be cited as: Syed b, shalim E, Memon I, Farhan A: Use of Remdesivir in Mild to Moderate COVID -19 Disease and its Clinical Outcomes: A Single-Center Observational Study. Pak J Med Health Sci, 2024;18(5): 21-25