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A COMPREHENSIVE INVESTIGATION INTO THE INFLUENCE OF REMDESIVIR ON MORTALITY AND MORBIDITY AMONG INDIVIDUALS AFFLICTED WITH COVID-19: RETROSPECTIVE COHORT STUDY

Sohail Khan Raja[1], Hamdah Bashir Mughal[2], Rubina Rafique Shiekh[3], Munazza Nazir[4], Bushra Bashir[5], Easha tur Razia[6], Amna Akbar[7], Sabahat Tasneem[8], Sarosh Khan Jadoon[9*], Saddam Hussain[10]

[1]Assistant Professor, Pulmonologist, AJKMC, Muzaffarabad, AJK, Pakistan, Sohailkhanraja3011@hotmail.com, https://orcid.org/0009-0009-5951-5897
[2]MBBS, RMP, AJKMC, Muzaffarabad, AJK, Pakistan, drhamdahbashirmughal@gmail.com, https://orcid.org/0009-0001-9000-9193
[3]Assistant professor Medicine AJKMC, Muzaffarabad, AJK, Pakistan, dr.robinarafique@proton.me, https://orcid.org/0009-0001-0541-139X
[4]Associate professor, Medicine, AJKMC, Muzaffarabad, AJK, Pakistan, Drmunazza778@yahoo.com, https://orcid.org/0009-0005-9901-0595
[5]Demonstrator, Department of Pathology, AJKMC, Muzaffarabad, AJK, Pakistan, Drbushrabashir1441@proton.me, https://orcid.org/0009-0008-6856-1759
[6]Resident Medicine, Abbas Institute of Medical Sciences, Muzaffarabad, AJK, Pakistan, Dr.eashatur.razia124@hotmail.com, https://orcid.org/0009-0009-0342-6377
[7]Medical Officer, Poonch Medical College Rawalakot, AJK, Pakistan, amna.akbar1324@gmail.com, https://orcid.org/0009-0009-6560-5493
[8]Public Health (MSPH), Health Services Academy, Islamabad, Pakistan, tasneem.saba30@gmail.com, https://orcid.org/0009-0004-4947-8213
[9*]Resident surgery, CMH/SKBZ, AJK Muzaffarabad, Pakistan, saroshkhanjadoon@outlook.com, https://orcid.org/0000-0002-1728-2599
[10]Senior Medical Officer, Punjab Institute of Neurosciences, Lahore, Pakistan, saddam.javaid@gmail.com

***Corresponding Author:** Sarosh Khan Jadoon
Resident surgery, CMH/SKBZ, AJK Muzaffarabad, Pakistan,
Email: saroshkhanjadoon@outlook.com, https://orcid.org/0000-0002-1728-2599

Abstract

Background: Remdesivir's distinct method of action is a promising strategy for battling viral illnesses. It assists in lowering the viral load and reducing the severity and length of infection by interfering with the replication mechanism of the virus.

Methodology: Retrospective cohort study was conducted at a tertiary care hospital in AJK, Pakistan. The data was collected from hospital records and the analysis was performed to find the effectiveness of Remdesivir.

Results: There were 62.7% males and 37.3% females, and the most common symptoms were fever, cough and shortness of breath. Remdesivir was initiated early in 126 patients. The mean number of doses is 2.0 and Remdesivir affects the recovery ($p<0.05$).

Conclusion: Remdesivir can be administered in COVID-19 patients but the results from past are mix. Remdesivir has good therapeutic efficacy.

Keywords: COVID-19, Remdesivir, morbidity, mortality

Introduction

Remdesivir serves as a phosphoramidate prodrug and is generated from an adenosine C-nucleoside. It undergoes a metabolic shift by entering human respiratory epithelial cells, becoming a nucleoside triphosphate, which is an active form. This nucleoside analog competes with its natural equivalent, adenosine triphosphate (ATP), to operate as a strong inhibitor of viral RNA-dependent RNA polymerase (RdRp). The nucleoside analog alters the normal course of viral replication by integrating into the freshly generated RNA strand, causing delayed termination of the process. Remdesivir exhibits antiviral activity by interfering with RNA-dependent RNA polymerase, which is a crucial enzyme for viral replication. This mechanism hinders the ability of the virus to multiply and spread, thereby lowering the total viral load in the infected person (1).

The genetically heterogeneous ortho-corona virus (CoV) family is susceptible to interspecies disease transmission and emergence in both humans and livestock. Future outbreaks are more likely if viruses that resemble known epidemic strains are found in wild and domestic animals. Currently, no human CoV that presents a clear unmet medical need has licensed treatment. Porcine delta-corona virus (PDCoV), a virus that affects pigs, has been successfully treated with remdesivir (RDV) and has shown extraordinary effectiveness. This antiviral drug has demonstrated exceptional anti-PDCoV efficacy, highlighting its potential as an important tool in the therapy and control of delta-corona virus infections (2).

The Food and Drug Administration (FDA) has granted approval for the intravenous administration of remdesivir for the treatment of COVID-19 in adults and children who are at least 28 days old and weigh less than 3 kg. Remdesivir should be started within 7 days of the onset of symptoms and provided for 3 days to non-hospitalized patients with mild-to-moderate COVID-19 who are at a high risk of developing severe disease. Remdesivir should be administered to hospitalized patients for five days or until they are released from the facility, whichever occurs first. Each 100-mg vial of remdesivir solution had 6 g of SBECD, while each 100-mg/20-ml vial of remdesivir lyophilized power included 3 g of Sulfobutylether beta-cyclodextrin sodium (SBECD) (3).

The kidneys are the primary organs used for the elimination of SBECD. Depending on the formulation, 6–12 g of SBECD was administered to a patient with COVID-19 who received a loading dose of remdesivir 200 mg. For patients with normal renal function, the SBECD level was within the safe range. SBECD buildups in patients with renal insufficiency may result in toxicity to the liver and kidneys. Clinicians may consider utilizing the lyophilized powder formulation, which has less SBECD preferentially in patients with renal impairment. Remdesivir use in patients with an eGFR less than 30 is not advised by the FDA product label (4,5).

Remdesivir's distinct method of action is a promising strategy for battling viral illnesses. It assists in lowering the viral load and reducing the severity and length of infection by interfering with the replication mechanism of the virus. It gives the immune system a chance to create a more potent defense against invasive infection, since it can stop viral multiplication. Remdesivir should only be used in situations where it is possible to control severe hypersensitivity responses such as anaphylaxis.

Patients should be closely monitored during the infusion and for at least an hour after it, if clinically necessary. This study aimed to investigate the impact of remdesivir on mortality and morbidity in COVID-19 patients. This study aimed to evaluate the efficacy of remdesivir in lowering mortality and enhancing clinical outcomes, as it has been widely used as an antiviral medication for COVID-19. The results of this study will aid in clinical decision-making for COVID-19 treatment and provide insightful information about the use of remdesivir.

Methodology

Study design and patient selection: The study was conducted at a tertiary care facility in Muzaffarabad, which has been actively treating COVID-19 patients and has incorporated the use of remdesivir in its treatment procedures. A retrospective cohort of patients with COVID-19 who were treated with remdesivir was included in this study. To identify eligible participants, medical records from the hospitals were examined. The inclusion criteria were based on a confirmed diagnosis of COVID-19, availability of remdesivir treatment data, and sufficient follow-up data. Patients who did not receive remdesivir, those with incomplete medical data, and those with concomitant conditions that had a serious negative influence on mortality and morbidity outcomes where all potential exclusion criteria patients and were excluded. After careful observation of the inclusion and exclusion criteria, 228 patients were included.

Data Collection: The following details about each participant were gathered in full from their medical records: demographic factors, age, gender, and marital status and type of household.

Clinical Characteristics: Comorbidities, symptoms (presence or absence of typical symptoms of COVID-19), illness severity at presentation, and laboratory results.

Remdesivir: Details of the Remdesivir treatment (first dose administration, dosage, duration, and timing of administration of the first dose)

Clinical results: Outcomes of drug administration such as recovery or no recovery, death during hospital stay, hospital stay duration, requirement for critical care, need for mechanical ventilation, and illness progression and concurrent therapies (e.g., corticosteroids and other antiviral medications).

Data Analysis: Demographic facts, clinical traits, remdesivir treatment information, and clinical results of the study population were analyzed using descriptive statistics. The frequency of events was determined. The frequencies of the number of patients with comorbidities, hypertension, diabetes mellitus, ischemic heart disease, and COPD were determined. The frequency of the outcomes was first calculated to determine whether the patient had recovered or not, and then the outcomes were divided into the number of patients who recovered, died, or were referred to other facilities for further evaluation. To determine whether the outcomes in patients were related to treatment with remdesivir, a 2×2 contingency was built using the chi-square test. A p-value of less than 0.05 was considered significant to show the association of patients' outcomes with remdesivir treatment. To account for potential confounding variables such as age, sex, comorbidities, and disease severity at presentation, multivariable regression models (logistic regression) were used to assess the relationship between remdesivir treatment and mortality/morbidity outcomes.

Results

There were 62.7% males and 37.3% females in this study population. 28 out of 228 patients were single, and 12.7% came from a nuclear family system. The B+ve blood group was the most prevalent (29.8%). The frequencies of all the clinical characteristics are tabulated in Table 1. A total of 22.8% of the patients showed lung involvement on chest radiography. Out of the 228 patients, 155 (67.98%)

experienced symptoms of cough. Shortness of breath in 64.91% of patients with muscle ache was 22.37% and 7.02%, respectively (Table 1, Table 2 and Table 3).

Table 1: Demographic Characteristics of the study population

Variables		Frequency	Percent
Gender	Male	143	62.7
	Female	85	37.3
Marital Status	Single	28	12.3
	Married	200	87.7
Household	Joint Family	199	87.3
	Nuclear Family	29	12.7

Descriptive analysis of demographic characteristics

Table 2: Co-morbidities

Variables		Frequency	Percent
Hypertension	Non-hypertensive	113	49.6
	Hypertensive	115	50.4
Diabetes	Non-diabetic	175	76.8
	Diabetic	53	23.2
Ischemic Heart Disease	No	192	84.2
	Yes	36	15.8
COPD/Asthma	No	208	91.2
	Yes	20	8.8
Other Comorbid	No	191	83.8
	Yes	37	16.2
Smoking	Non-Smoker	181	79.4
	Smoker	47	20.6

COPD: Chronic Obstructive Pulmonary Disease

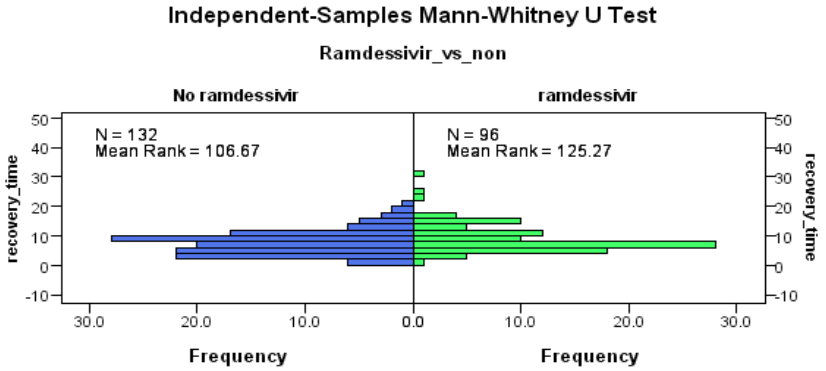

Figure 1: Non-parametric test to evaluate the impact of remdesivir administration (if the drug was given or not) on time taken to recover. It is significant (p value 0.035)

Table 3: Treatment of COVID-19 and ICU admission

Variables		Frequency	Percent
First Dose of 200mg	No	102	44.74
	Yes	126	55.26
Anti-Coagulant	Not Used	36	15.79
	Used	192	84.21
Steroids Used	Steroids not Used	51	22.37
	Steroids Used	177	77.63
ICU Admission	Not Admitted	77	33.8
	Admitted	151	66.2
Oxygen Therapy	Noninvasive	91	39.91
	Nasal Cannula	42	18.42
	Face Mask	19	8.33
	HFNC	4	1.75
	CPAP/BIPAP	61	26.75
	Ventilator	11	4.82

ICU: Intensive care unit
HFNC: High flow nasal cannula
CPAP/BIPAP: Continuous Positive Airway Pressure/Bi-level Positive Airway Pressure

Table 4: Symptoms of COVID-19 and Chest Involvement/ Chest x-ray findings and Blood Groups

Variables				Frequency	Percent
Fever	No			63	27.6
	Yes			165	72.4
Cough	No			73	32.0
	Yes			155	68.0
Shortness of Breath	No			80	35.1
	Yes			148	64.9
Muscle ache	No			177	77.6
	Yes			51	22.4
Headache/Confusion	No			214	93.9
	Yes			14	6.1
Sore Throat	No			212	93.0
	Yes			16	7.0
Runny Nose	No			216	94.7
	Yes			12	5.3
Chest Pain	No			206	90.4
	Yes			22	9.6
Gastrointestinal tract upset	No			207	90.8
	Yes			21	9.2
Lethargy	No			199	87.3
	Yes			29	12.7
Chest X-Ray Findings	No-changes observed			220	96.49
	Unilateral Infiltration			1	0.44
	Bilateral Infiltration			5	2.19
	Atelectasis			1	0.44
	Bronchiectasis			1	0.44
Lung Involvement	None			176	77.19
	Unilateral			5	2.19
	Bilateral			47	20.61
Blood Groups	A+ve	46	20.2		
	B+ve	68	29.8		
	O+ve	56	24.6		
	AB+ve	18	7.9		
	A-ve	11	4.8		
	B-ve	7	3.1		
	AB-ve	14	6.1		
	O-ve	8	3.5		

The first dose (200 mg IV) was administered to 126 patients (Table 4). Mean number of doses of anti-viral was 2.0 (Table 5). The association of outcomes and administration of the Remdesivir is positive (Table 6).

Table 5: Clinical Characteristics of the patients, hospital stay, and disease severity

	Minimum	Maximum	Mean	Median	*SD
Respiratory rate	18	48	26.81	26	5.823
Systolic Pressure	100	180	126.97	121.5	17.150
Diastolic Pressure	50	130	78.9	80	11.279
Peripheral Capillary Oxygen Saturation	50	100	90.23	92.5	8.137
Body Mass Index	18.6	39.9	27.46	27.2	3.8789
Number of Antibiotic Doses Administered During Hospital Stay	0	15	4.75	5.0	3.509
Number of Anti-Coagulant Doses Administered During Hospital Stay	0	15	4.43	4.5	3.398
Number of Anti-Viral Doses Administered During Hospital Stay	0	10	2.0	1.0	2.451
Number of Steroid Doses Administered During Hospital Stay	0	22	4.91	5.0	4.01
Days Symptomatic Before Admission	1	6	3.12	3.0	1.536
Number of Days The Symptoms Persisted	0	33	9.03	9.0	5.421
Disease Severity	1	6	3.17	3.0	1.504
Days in Hospital	1	31	7.91	7.0	4.55

*SD: standard deviation

Table 6: Use of Remdesivir and COVID outcomes

		Remdesivir Not Used (102)	Remdesivir Used (126)	p-value
Recovered	176 (77.19%)	87	89	0.009
Not Recovered	52 (22.81%)	15	37	
When referral is also counted				
Death	39 (17.11%)	10	29	
Recovered	176 (77.2%)	87	89	0.023
Referred	13 (5.70%)	5	8	

Table 7: Regression analysis

	Sig.	OR	CI	Sig.	aOR	CI
Antiviral	0.009	0.414	0.212-0.809			
Antiviral adjusted with Anti-Coagulant				0.033	0.476	0.240-0.942
Antiviral adjusted with Steroid				0.073	0.53	0.265-1.063
Antiviral adjusted with Anti-Coagulant and Steroids				0.108	0.563	0.280-0.134
Anti-Coagulant	0.033	0.265	0.077-0.904	0.083	3.007	0.863-10.46
Steroid	0.007	0.228	0.078-0.669	0.027	3.472	1.152-10.46

The regression analysis to confirm association of Remdesivir drug treatment with outcomes given alone and in combination

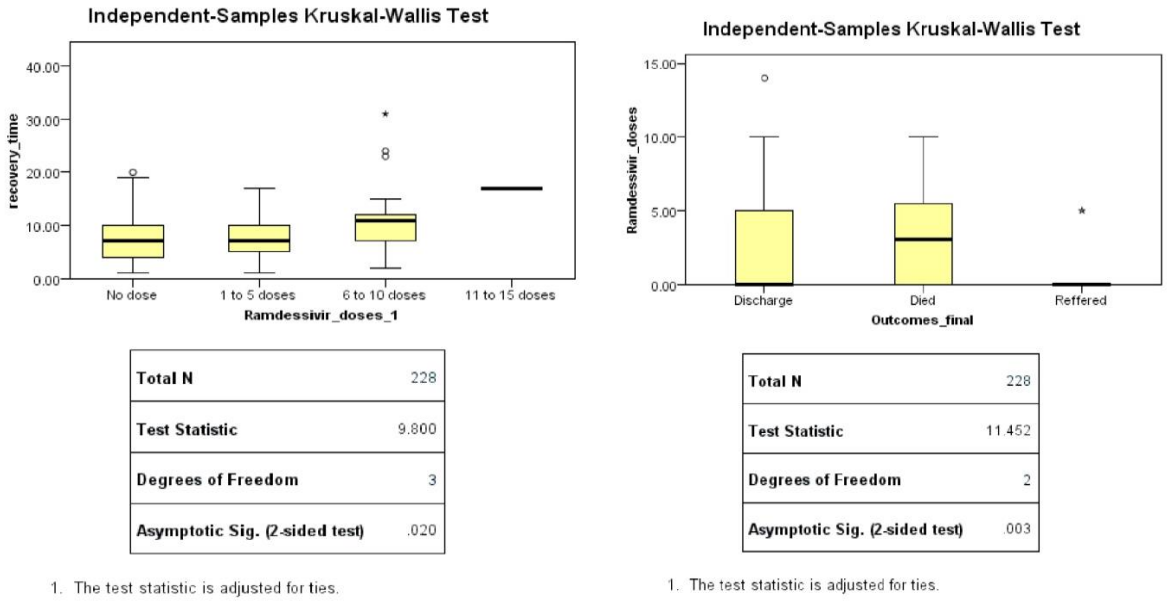

Figure 2: Recovery time and final outcome

Through Independent Samples Kruskal-Wallis test, two associations were measured.
(a): Association of time taken to recover with the time at which the first dose was administered. (b): Association of number of doses of the drug with the final outcomes

Discussion

SARS-CoV-2 spreads rapidly throughout China and the rest of the world. The novel coronavirus is 80% SARS-like. Researchers are focusing on the new coronavirus structures, immunogenicity, and pathogenesis (6). Researchers have tried COVID-19 unproven medicines for the management of disease. Clinical trials have examined chemotherapy, serotherapy, anticoagulation, and human recombinant soluble ACE2 treatment for COVID-19 (7). In individuals with severe COVID-19, corticosteroids, intereukin-6 receptor antagonists, and Janus kinase inhibitors are likely to lower mortality rates and provide other significant benefits. In individuals with non-severe COVID-19, the use of molutevir with nirmatrelvir/ritonavir is likely to reduce hospitalization (8).

Antiviral medications intended for other uses may provide a temporary response, and a combination of antivirals may be used to treat this illness (9). Remdesivir (1) and chloroquine were proven to be effective against COVID-19 in vitro, and chloroquine is a widely used drug (10). Remdesivir was suggested as a possible treatment option for COVID-19 based on laboratory tests and reports from compassionate usage, but its safety and impact on humans needed high-quality data; thus, many human trials started all over the world (11). Remdesivir trials yielded promising results (12). Remdesivir is a crucial COVID-19 therapeutic option at this time, although only for a few patients (13).

Reducing the number of days spent in the ICU by using dexamethasone instead of the standard treatment for ventilated patients and remdesivir for non-ventilated patients is anticipated to result in cost savings (14). Prophylactic and therapeutic RDV enhances lung function, viral load, and severe lung disease in mice. Prophylactic LPV/RTV/IFNb significantly lowered viral loads without affecting illness parameters. LPV/RTV-IFNb improves pulmonary function but not viral replication or severe lung damage. Researches demonstrated RDV's ability of RDV to treat MERS-CoV infection in vivo (15). Remdesivir, which kills Ebolavirus and other RNA viruses in vitro, accelerates COVID-19 recovery in severe cases (16). While one study has shown it to be effective against SARS-CoV-2 and speed up recovery, others have linked it to ineffectiveness and unwanted side effects of the medication (17).

Remdesivir trials in hospitalized COVID-19 patients showed conflicting results, probably due to treatment heterogeneity among the standard care groups. In one such study, Cox proportional hazards regression models were corrected for research time, supplementary oxygen consumption, vaccination status, and other confounders. The remdesivir group (n=14,509) had lower inpatient mortality, 90-day post-discharge mortality, 30-day readmission, and longer hospital stays than the non-remdesivir group (n=4,364) (18).

When remdesivir and dexamethasone were used to treat moderate-to-severe COVID-19 from June through December, compared to treatment from February through May, there was a decrease in 30-day mortality and the requirement for MV (18) (Table 7). In another study the statistical association scored a "null" evaluation (-3 points), along with a "doubtful" p of interaction (p=0.0650) among subgroups, and mortality failed to attain statistical significance for the entire population (19). Clinical improvement was noted in 36 of 53 (68%) hospitalized patients with severe Covid-19 who received compassionate-use-remdesivir (20). At eleven days after therapy, moderate COVID-19 patients randomized to a 10-day remdesivir course had no statistically significant difference in clinical status compared to usual care. Patients randomized to a 5-day treatment with remdesivir had a statistically significant difference in clinical status compared with usual therapy; however, the difference was of questionable clinical value (21). Remdesivir can treat SARS-CoV-2, even if it starts late (22). Severe COVID-19 pneumonia is fatal, especially in resource-constrained settings. Remdesivir may need to be used early to reduce COVID-19 related death (23). In the present study, early first dose administration resulted in speedy recovery (Figure 1).

Remdesivir has shown mixed results in patients with COVID-19, with acceptable side effects. Remdesivir's initial compassionate use has yielded promising results, but it is difficult to measure without a control arm (24). Limited intensive care unit (ICU) capacity prevents certain nations, such as South Africa, from providing ICU care for the anticipated number of COVID-19 patients. Remdesivir can minimize fatalities in nations such as South Africa by reducing the number of days patients stay in the ICU and freeing up ICU bed space. Time to recovery-hospital discharge of infection-control hospitalization was the main outcome. In people hospitalized with COVID-19 and lower respiratory tract infection, remdesivir shortened the recovery time compared to placebo (25).

Same trend was seen in our study (Figure 2). There is a contrast difference in recovery time when the antiviral is used and when it is not used.

Patients in the initial group were administered a combination of remdesivir and standard corticosteroid therapy (SCT). The second cohort of patients was administered a combination of remdesivir and high-dose corticosteroid pulse therapy (HDCPT). The latter group had a lower incidence of invasive mechanical ventilation and admission to the critical care unit (7.3% vs. 29.8%), as well as a higher incidence of noninvasive ventilation (36.4% vs. 61.7%). The combination of Remdesivir and HDCPT demonstrated a notable enhancement in the rate of improvement of the SpO2/FiO2 index (26). The present study also demonstrated use of combination of drugs and their effectiveness alone and in combination (Table 7).

In a previous study, remdesivir treatment for two weeks did not significantly affect mortality. Remdesivir improved clinical outcomes on day 14 compared to the placebo/ control group (p=0.047). Additionally, remdesivir reduced the incidence of significant adverse events (27). Remdesivir reduced hospitalization time and mortality in oxygen-dependent patients. This is a big step in combatting COVID-19; however, it will not solve public health issues (28). In a real-world scenario, initiation of remdesivir within 24h of hospitalization in conjunction with standard of care was not associated with a benefit at 14 days, but supported clinical trial evidence of a potential reduction in 28 days mortality (29). RDV reduced mortality at 14 days and 28 days. COVID-19 patients with hospitalized RDV had better survival rates. Our data support RDV in hospitalized COVID-19 patients (30). Inflammatory makers and clinical outcomes were examined in 55 remdesivir-treated COVID-19 patients. CRP, D-dimer, and lactate dehydrogenase levels were considerably higher in patients who underwent intubation or death by 14 days compared to stable patients. Remdesivir significantly reduced CRP levels in non-intubated patients. This was the largest study on inflammatory markers before and after remdesivir treatment (31).Remdesivir may not affect hospital fatalities after 28, 60, or 150 days. This may somewhat improve patients and minimize the risk of worsening health outcomes. None of the outpatients died during the 28-day study period. Remdesivir treatment reduces hospitalization and adverse outcomes. Remdesivir has fewer significant side effects than placebos or usual care (32). According to a study, remdesivir may be beneficial for SARS-CoV-2 pneumonia patients who are hospitalized outside of an intensive care unit, where the clinical outcome is better and adverse events are less common (33). Remdesivir therapy dramatically reduced inpatient mortality in patients with COVID-19 (34). Remdesivir saves 8 lives per 1000 people compared with placebo or usual treatment (35). Age, comorbidities, C-reactive protein level, enrolment period, and anti-SARS-CoV-2 antibodies had no subgroup effect. Remdesivir did not have any serious side effects. In hospitalized COVID-19 patients without an oxygen aid, remdesivir lowered mortality, but not in ventilated patients (36). When mortality or progression to ventilation were combined, the remdesivir group outperformed the control group (37). Remdesivir reduced 30-day readmissions, particularly for mild illnesses. Remdesivir therapy reduced all-cause mortality and increased the length of hospital stay. In larger prospective studies, remdesivir may prevent severe COVID-19 with a high risk of infection progression and return to the hospital within 30 days (38). Remdesivir (RDSV)-treated hospitalized COVID-19 patients were studied for death, readmission, mean hospital stay, need for oxygen support, and adverse effect-induced desertion. After COVID-19 and respiratory failure hospitalization, all patients received RDSV within a week of symptom onset. Severe COVID-19 patients had a 20.3% mortality rate, but these individuals had 10.3% 1 in 3 RDSV patients requiring oxygen, the only fatality risk (39). Antiviral medication did not predict death or hospitalization, but did predict comorbidities, hematological disease, gastrointestinal symptoms, and each day after the onset of symptoms. Nirmatrelvir/ritonavir caused 49.2% of the adverse events (40). Remdesivir did not delay clinical improvement. Remdesivir improved clinically faster than placebo in patients with illness duration of ≤ 10 days. Adverse events occurred in 102 (66%) of the 155 remdesivir patients and 50 (64%) of the 78 placebo recipients. Eighteen (12%) remdesivir participants and four (5%) recipients

withdrew early owing to side effects. The numerical reduction in the time to clinical improvement in patients treated earlier requires confirmation in larger investigations. The efficacy and safety of remdesivir for defined key outcomes in COVID-19 studies should be examined in future trials, particularly for distinct demographic subgroups (41). Remdesivir works better early in the disease course. Due to the unpredictability of illness progression and demographic variance, selecting patients for therapy is difficult.

Conclusion:

Remdesivir is a good therapeutic choice for COVID-19 infection. It is effective in reducing mortality and also affects the recovery time. The time for first dose is important. Early administration can generate better outcomes and reduce disease severity.

Limitation: Retrospective study usually lemmatizes the extent to which the outcomes can be measured. We could only get a small data set from hospital records; the outpatients who used the drug could not be traced. Follow-up data is also missing.

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