DOI: https://doi.org/10.53350/pjmhs20221611564

ORIGINAL ARTICLE

Remdesivir May Be Associated with Acute Kidney Injury in Covid-10 Patients: A Cohort Study

AMANI AMIR[1], SYED TAJAMMUL ALI[2], FARZANA ADNAN SHEIKH[3], MALEEHA SADAF[4], SADIQA ANWAR[5]
[1]*Senior Registrar Naimat Begum Hamdard University Hospital*
[2]*Senior Registrar Liaquat National Hospital and Medical College Karachi*
[3]*Assistant Professor Liaquat National Hospital and Medical College Karachi*
[4]*Specialist Pulmonologist Department Pulmonology, King Saud Hospital, Unaizah*
[5]*Resident Paediatrics Ziauddin University Hospital Karachi*
Corresponding author: Dr Syed Tajammul Ali, Email: syedtajammulali@yahoo.com, Cell: 03232283899

ABSTRACT

Objective: To assess the outcomes of coronavirus disease-2019 patients with acute renal damage who received remdesivir against placebo at a private hospital in Karachi, Pakistan.

Methodology: At the COVID-19 ICU of Hussain Lakhni Hospital, a cohort study was conducted from July 2021 to February 2022. Male and female study participants with COVID-19 and acute renal injury ranged in age from 40 to 80. Remdesivir-treated individuals with COVID-19 acute kidney injury were exposed, but placebo-treated patients with COVID-19 acute kidney injury were not exposed. In-hospital mortality, elevated serum creatinine levels, and prolonged hospital stays were the results. The data was analyzed using SPSS version 23.

Results: Patients who took remdesivir had a lower mortality rate than those who were placebo (32.2% vs 67.8%, OR=0.38, 95 percent CI=0.27-0.52), with a p-value of 0.001. Remdesivir was also associated with a shorter hospital stay (4.2% versus 95.8%, OR=0.005, 95 percent CI=.003-0.009) with a p-value of 0.001). However, increased serum creatinine revealed statistically insignificant differences between groups. The odds of in-hospital mortality were 0.376 times lower (AOR=0.376, 95 percent CI=0.275-0.514, p=0.0001) and the odds of a prolonged hospital stay were 0.030 times lower (AOR=0.030, 95 percent CI=0.012-0.074, p=0.001) in the remdesivir group than in the placebo group after controlling for covariates.

Practical implication: In literature Remdesvir was associated with acute kidney injury (rise in serum creatinine) and in many centres ,it was not used in patients with acute kidney injury although it has very beneficial effect in patients of severe covid pneumonia,many centres were not using it in patients of acute renal failure. in our study , rise in serum creatinine was not significant in remdesvir group in patient with acute kidney injury ,so remdesvir must not be withheld in this group of patients as it can decrease the severity of covid pneumonia and saves patients lives

Conclusion: Remdesivir is an effective medicine in COVID-19 patients with acute renal damage in terms of in-hospital mortality and duration of stay.

Keywords: Acute kidney injury, coronavirus, COVID-19, in-hospital mortality, kidney damage, remdesivir, renal function, serum creatinine

INTRODUCTION

Coronavirus disease 2019 (COVID-19) causes over 5,783,776 deaths by 11 February 2022 worldwide and influences a variety of human organs, comprising the kidneys [(1-3)]. While the cause of acute kidney injury (AKI) in COVID-19 patients is possibly multifactorial i.e. diabetes, heart disease, high blood pressure, and lung disease, the majority of cases display an acute tubular injury (ATI) trend [4]. Ischemic, inflammatory, or nephrotoxic stresses are the causes of ATI. The demand for nursing services increased along with the shortage of dialysis equipment and fluids as a result of the surge in AKI brought on by COVID-19 [(4,5)]. A recent report on patients with COVID-19 showed 63% had proteinuria, 27% had elevated urea nitrogen level, and 19% had an increased plasma creatinine level [(6)]. Another research revealed that 3.3% of the patients on dialysis were affected by COVID-19, which is significantly greater than non-dialysis patients (2.2%) [(7)]. Additionally, the rate of mortality among COVID-19 and hemodialysis patients is alarmingly higher than that of the general population [(8)].

Remdesivir is a prodrug that functions as an analog of ATP after being metabolized to remdesivir triphosphate, fighting for inclusion by RDRP and interfering with viral RNA replication [(9)]. Due to a shortage of effective therapeutic drugs, remdesivir has been given on a compassionate basis to COVID-19 patients [(9)]. Patients in the remdesivir group had a reduced mortality (8% vs. 11.6%) and lesser duration of hospitalization (11 vs. 15 days) than those in the placebo group, according to a multicenter study with 1063 patients [(10)]. The FDA has cleared the intravenous administration of this medication for use in COVID-19. Five days of therapy is just as beneficial as ten days, according to a paper by the same group of experts [(11)]. The goal of this study was to compare in-hospital mortality, raised serum creatinine level, and longer hospital stay in AKI and COVID-19 patients who were given remdesivir versus placebo, because there is a paucity of evidence on the use of remdesivir in Pakistan, and the cause-effect relationship between remdesivir and AKI has yet to be investigated. This study will help to enhance regulatory intervention and treatment recommendations for COVID-19 patients with AKI.

MATERIAL AND METHODS

A six-month cohort study took place at Hussain Lakhni Hospital's COVID-19 ICU from July 2021 to February 2022. The size of study was estimated using the Open epi sample size calculator, using mortality rates of 6.7% in the Remdesivir group [10] and 11.9% in the placebo group [10], a power of test of 80%, and a 95% confidence level. In each group, the estimated sample size was 491. The research comprised patients aged 40 to 80 years old, including males and females, who had COVID-19 (confirmed by PCR testing from nasal samples) and AKI (eGFR less than 30 mL/min). Patients with admission of less than 24 hours, pregnant females, patients with chronic liver disease and cancer were excluded from the study. Non-probability consecutive sampling technique was applied. After receiving clearance from the hospital's ethical review committee, data collection began with the approval number ERC-HLT-2021-002. After receiving informed permission, all eligible individuals were separated into exposed and non-exposed groups. COVID-19 patients with AKI on remdesivir therapy (at least 5 days of remdesivir medication) were exposed; COVID-19 patients with AKI on placebo were not (who did not receive even single dose of remdesivir). The outcomes were in-hospital mortality, increased serum creatinine levels (serum creatinine>2 milligram's) and longer hospital stay (hospital stay of more than 11 days). Data regarding socio-demographic factors like age, BMI, gender, and comorbids (hypertension, diabetes) were also noted down on pre-designed proforma.

The data were analyzed using SPSS version 23. While frequency and percentage were used to report categorical data, mean and standard deviation were used to display numerical data.

Utilizing univariate logistic regression, the relationship between treatment and outcome was examined. An estimate of the odds ratio was calculated along with 95% confidence interval. For the significant outcomes in the univariate analysis with p-values less than 0.25, multiple logistic regression analysis was utilized. Covariate adjustment was made to the models. The adjusted odds ratio with 95% confidence interval was estimated. The p-value less than and equal to 0.05 was considered as statistically significant.

RESULTS

The trial recruited 982 individuals with COVID-19 and AKI. The Remdesivir medication was given to 491 patients, whereas the placebo group had 491 patients. Table 1 displays the baseline features of the two groups. The mean age was 54.17±11.12 years, and the majority of them were males (56.6 percent). The average BMI for the group was 26.67±5.38 kg/m^2. The most common comorbidities among the individuals studied were diabetes and hypertension. Table 2 shows the comparative analysis of primary and secondary outcomes between both groups. In remdesivir group, the morality rate was 32.2% (74 deaths) compared with 67.8% (156 deaths) for placebo, with statistically significant difference (p=0.001). Thus, odds of mortality were 0.38 times lesser in remdesivir group than placebo (OR=0.38, 95% CI=0.27-0.52).

The proportions of raised serum creatinine showed statistically insignificant differences between both groups with p-value=0.553. In remdesivir group, rate of prolonged hospital stay was significantly greater than placebo group (4.2% vs 95.8%) with p-value=0.001. Hence, odds of prolonged hospital stay were 0.032 times lesser in patients treated who received remdesivir than placebo (OR=0.038, 95% CI=0.013-0.079). Multiple logistic regression was performed for significant outcomes i.e. in-hospital mortality and prolonged hospital stay and displayed in table 3. After adjusting age, gender, BMI, diabetes, hypertension, raised serum creatinine and prolonged hospital stay, the odds of having in-hospital mortality were 0.376 times lesser in remdesivir group than placebo. After adjusting age, gender, BMI, diabetes, hypertension, raised serum creatinine and in-hospital mortality, the odds of having prolonged hospital stay were 0.030 times lesser in remdesivir group than placebo.

Table 1: COVID-19 With AKI Patients' Characteristics in The Remdesivir and Placebo Groups (n=982)

Characteristics	Remdesivir therapy (n=491)	Placebo (n=491)	Overall (n=982)
Age in years	53.44±11.21	54.89±11.08	54.17±11.12
Gender			
Male	272 (55.4)	284 (57.8)	556 (56.6)
Female	219 (44.6)	207 (42.2)	426 (43.4)
BMI in kg/m2	26.42±5.57	26.90±5.18	26.67±5.38
Comorbids			
Hypertension	292 (59.5)	249 (50.7)	441 (44.9)
Diabetes	199 (40.5)	242 (49.3)	541 (55.1)

Table 2: Outcomes Of COVID-19 Patients with AKI Treated with Remdesivir Compared To COVID-19 Patients Treated with A Placebo

Outcomes	Remdesivir therapy (n=491)	Placebo (n=491)	p-value	OR (95% CI)
In-hospital mortality	74 (32.2)	156 (67.8)	0.001*	0.38 (0.27-0.52)
Raised serum creatinine	455 (50.3)	450 (49.7)	0.553	1.15 (0.72-1.83)
Prolonged hospital stay	19 (4.2)	432 (95.8)	0.001*	0.038 (0.013-0.079)

Table 3: Multiple Logistic Regression Models for In-Hospital Mortality and Prolonged Hospital Stay

Outcomes	Group	AOR (95% CI)	p-value
In-hospital mortality	Remdesivir therapy	0.376 (0.275-0.514)[a]	0.0001*
Prolonged hospital stay	Remdesivir therapy	0.030 (0.012-0.074)[b]	0.0001*

[a]. Model adjusted for age, gender, BMI, hypertension, diabetes, raised serum creatinine and prolonged hospital stay
[b]. Model adjusted for age, gender, BMI, hypertension, diabetes, raised serum creatinine and mortality

DISCUSSION

Data on the safety and effectiveness of remdesivir for COVID-19 patients with AKI are scarce in Pakistan. Patients with kidney problems were not included in the majority of earlier trials that examined remdesivir's effects in COVID-19 patients [(10-12)]. Therefore, in this study, we evaluated the effects of remdesivir treatment in COVID-19 patients with AKI in comparison to placebo. Even after adjusting for age, gender, BMI, diabetes, hypertension, raised serum creatinine, and prolonged hospital stay, we discovered that patients with COVID-19 and AKI who received remdesivir therapy had a significantly lower in-hospital mortality (32.2% versus 67.8%, p=0.001) than those who did not receive remdesivir therapy (AOR=0.376, 95 percent CI=0.275-0.514). In a prior observational research, Olender SA et al. also found that remdesivir was more effective than placebo in terms of morality benefit (7.6% vs 12.5%, p=0.001) in COVID-19 patients (AOR=0.38, 95% CI=0.22-0.68) [(13)]. Sullivan et al. reported improvements in the COVID-19 treatment with remdesivir and they concluded that remdesivir may not have directly contributed to the decline in AKI [(14)]. Ackley et al. discovered that people with an estimated creatinine clearance of ≥30 ml/min at the time of remdesivir administration had a 50% greater chance of dying within 30 days than those with an estimated creatinine clearance of 30 ml/min (p=0.001).

Furthermore, none of the two patients who had AKI while using remdesivir had an estimated creatinine clearance of less than 30 ml/min, according to the treating doctor [(15)]. Given the changing standard of care for COVID-19 patients with AKI during the study period and the known benefit in terms of in-hospital mortality over time among hospitalized COVID-19 patients, the findings of a significantly lower mortality rate in remdesivir-treated patients should be taken into consideration [(16)].

In the present study, we found prolonged hospital stay was significantly lesser in the patients treated with remdesivir therapy versus placebo (4.2% vs 95.8%, p=0.001). Even after adjusting for covariates i.e. age, gender, BMI, diabetes, hypertension, raised serum creatinine and in-hospital mortality, the odds for prolonged hospital stay remained significantly associated with remdesivir therapy (AOR=0.030, 95% CI=0.012-0.074). Buxeda et al. found that in kidney transplant patients with COVID-19, who were treated with remdesivir after 48 hours of admission had prolonged hospital stay (12.5 days versus 22.5 days from admission) as compared to early administration of remdesivir. This finding suggested that early initiation of remdesivir therapy could be resulted into improved clinical outcome [(17)]. Aiswaraya et al. also concluded that early treatment with remdesivir was significantly associated with a reduced hospital stay [(18)]. These findings are in agreement with what has been revealed in the general population [(10,19,20)] Megan et al. revealed that remdesivir significantly decreased the median to recovery as compared to placebo (11 days versus 15 days, p=0.001). They also found overall mortality rate in remdesivir was lower than placebo (8% vs 12%) [(21)].

One of the greatest unmet clinical needs is examining the care of COVID-19 patients with AKI, considering their increased risk of disease and fatality. The enormous scale and rapidity of the COVID-19 pandemic, as well as the vulnerability of these patients, need an urgent call to action for bigger studies that can help in clinical decision-making and enhance access to life-saving medicine for these patients [(4, 21-23)]. In our study, we found remdesivir did not affect the serum creatinine level of patients with COVID-19 and AKI. Similarly, Quratulain et al. did not find any significant change in serum creatinine level among patients treated with remdesivir [(23)]. Biancalana et al. also found that remdesivir had no effect on renal function in COVID-19 patients who have been hospitalized, and that eGFR has doubled with better outcomes [(24)].

Our study's main strength is that it generated local evidence for the utilization of remdesivir in patients with COVID-19 and AKI, where patients were prospectively monitored for in-hospital mortality, elevated serum creatinine levels, and longer hospital

stays. There are a few flaws in our research. Because of the observational nature of the study, we did not assign remdesivir to patients at random, which might contribute to selection bias. Furthermore, the confounding effects of other drugs such as anticoagulants, antibiotics, and steroids were not investigated. We were unable to analyze the long-term outcomes and side effects of remdesivir medication due to the short trial follow-up duration. Furthermore, we were unable to generalize the study findings since all data was obtained from a single institute. Despite the fact that our findings for the use of remdesivir were satisfactory, we believe that larger studies should be done in order to generalize the findings and expand the therapeutic implications.

CONCLUSION

In COVID-19 patients with acute renal injury, Remdesivir is an efficacious drug in terms of in-hospital mortality and length of stay.

REFERENCES

1. WHO. Weekly epidemiological update on COVID-19 - 30 March 2021: World Health Organization; 2021 [cited 2021 31 March]. Available from: file:///C:/Users/kabid.CPSP/Downloads/20210330_Weekly_Epi_Update_33.pdf.
2. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27.
3. WHO. WHO Coronavirus (COVID-19) Dashboard: World Health Organization; 2022 [cited 2022 11 Feb]. Available from: https://covid19.who.int/.
4. Raines NH, Ganatra S, Nissaisorakarn P, Pandit A, Morales A, Asnani A, et al. Niacinamide May Be Associated with Improved Outcomes in COVID-19-Related Acute Kidney Injury: An Observational Study. Kidney360. 2021;2(1):33-41.
5. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829-38.
6. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. medRxiv. 2020:2020.02.08.20021212.
7. Azghandi M, Kerachian MA. Detection of novel coronavirus (SARS-CoV-2) RNA in peripheral blood specimens. J Transl Med. 2020;18(1):412.
8. Aydin Bahat K, Parmaksiz E, Sert S. The clinical characteristics and course of COVID-19 in hemodialysis patients. Hemodial Int. 2020;24(4):534-40.
9. Hajjar LA, Costa IBSdS, Rizk SI, Biselli B, Gomes BR, Bittar CS, et al. Intensive care management of patients with COVID-19: a practical approach. Ann Intensive Care. 2021;11(1):36.
10. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-26.
11. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020;383(19):1827-37.
12. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78.
13. Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. Clin Infect Dis. 2021;73(11):e4166-e74.
14. Sullivan MK, Lees JS, Drake TM, Docherty AB, Oates G, Hardwick HE, et al. Acute kidney injury in patients hospitalized with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. Nephrol Dial Transplant. 2022;37(2):271-84.
15. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A Valid Warning or Clinical Lore: an Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort. Antimicrob Agents Chemother. 2021;65(2).
16. Asch DA, Sheils NE, Islam MN, Chen Y, Werner RM, Buresh J, et al. Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic. JAMA Intern Med. 2021;181(4):471-8.
17. Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, Cacho J, Cabello Pelegrin S, Melilli E, et al. Use and Safety of Remdesivir in Kidney Transplant Recipients With COVID-19. Kidney International Reports. 2021;6(9):2305-15.
18. Aiswarya D, Arumugam V, Dineshkumar T, Gopalakrishnan N, Lamech TM, Nithya G, et al. Use of Remdesivir in Patients With COVID-19 on Hemodialysis: A Study of Safety and Tolerance. Kidney Int Rep. 2021;6(3):586-93.
19. Bansal V, Mahapure KS, Bhurwal A, Gupta I, Hassanain S, Makadia J, et al. Mortality benefit of remdesivir in COVID-19: a systematic review and meta-analysis. Frontiers in medicine. 2021:1124.
20. Mehta RM, Bansal S, Bysani S, Kalpakam H. A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis. Int J Infect Dis. 2021;106:71-7.
21. Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, et al. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. J Am Soc Nephrol. 2020;31(7):1384-6.
22. Raza A, Estepa A, Chan V, Jafar MS. Acute Renal Failure in Critically Ill COVID-19 Patients With a Focus on the Role of Renal Replacement Therapy: A Review of What We Know So Far. Cureus. 2020;12(6):e8429.
23. Shaikh Q, Sarfaraz S, Rahim A, Hussain M, Shah R, Soomro S. Effect of Remdesivir on mortality and length of stay in hospitalized COVID-19 patients: A single center study. Pak J Med Sci. 2022;38(ICON-2022).
24. Biancalana E, Chiriacò M, Sciarrone P, Mengozzi A, Mechelli S, Taddei S, et al. Remdesivir, Renal Function and Short-Term Clinical Outcomes in Elderly COVID-19 Pneumonia Patients: A Single-Centre Study. Clin Interv Aging. 2021;16:1037-46.