

Safety of Remdesivir in COVID-19-Infected Patients with End-Stage Renal Disease on Haemodialysis: An Observational Study at a Tertiary Care Hospital, 2021-2022

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ABSTRACT

Background: The COVID-19 pandemic, caused by SARS-CoV-2, presents a global health crisis. Patients with End-Stage Renal Disease (ESRD) on haemodialysis are particularly vulnerable to severe COVID-19. This study evaluates the safety of remdesivir, a potential treatment for COVID-19, in this high-risk population.

Methods: This retrospective observational study was conducted over five months (March-July 2021) at a tertiary care hospital. It included 140 adult patients with ESRD on haemodialysis who were infected with COVID-19; 94 received remdesivir, and 46 did not. Data was collected from patient records, and liver function tests and adverse drug reaction reports were the primary parameters assessed. Secondary parameters included oxygen requirement and length of hospital stay.

Results: Remdesivir was generally well-tolerated. The mean age of the patients was 46.7 years. Hypertension was the most common comorbidity. The mean length of

hospital stay was 5.75 days for the remdesivir group and 2.56 days for the non-remdesivir group. The 30-day mortality rate in the remdesivir group was 4.25%, and 4.34% in the non-remdesivir group. Significant differences post-treatment were observed in lymphocytes, D-dimer, and serum creatinine levels.

Conclusion: Remdesivir demonstrates a potential for safe administration in COVID-19-infected ESRD patients undergoing haemodialysis. Further research is needed to establish its efficacy and long-term outcomes in this population.

Keywords: COVID-19, Remdesivir, End-Stage Renal Disease, Haemodialysis, Safety, Retrospective Study

INTRODUCTION

The emergence of the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented a global health crisis. ¹ The World Health Organization (WHO) declared COVID-19 a

pandemic on March 11, 2020, marking its rapid spread across the globe and resulting in millions of confirmed cases and fatalities.¹ SARS-CoV-2, a single-stranded RNA virus, primarily infects human lung cells.² Transmission occurs through respiratory droplets and aerosols produced during coughing, sneezing, speaking, singing, and breathing.³ While COVID-19 can affect individuals of any age, those over 65 and those with comorbidities like cardiovascular disease, chronic respiratory disease, diabetes, chronic renal disease, or cancer are more prone to acquire severe illnesses.³ The median incubation period for SARS-CoV-2 is approximately 5.1 days, with the majority of patients displaying symptoms within 11.5 days.⁴

COVID-19 presents with a range of clinical manifestations, from asymptomatic infection to critical illness.⁴ The National Institutes of Health (NIH) classify the disease into categories including mild, moderate, severe, and critical illness, characterised by varying degrees of respiratory dysfunction, sepsis, or multiple organ dysfunction.⁴ Symptoms can include fever, cough, sore throat, headache, and nausea.²

While there is no known cure for COVID-19, several potential treatments have been explored, including antiviral drugs like remdesivir.⁵ Remdesivir has received FDA approval for the treatment of hospitalised COVID-19 patients.⁶ It functions as a viral RNA-dependent RNA polymerase inhibitor, thereby inhibiting viral genome replication.⁷ Remdesivir is a nucleoside analogue prodrug.⁷ After being metabolised into its active form, it competes with ATP for incorporation into the viral RNA strand, leading to the termination of RNA synthesis and the limitation of viral replication.⁷ Remdesivir is administered intravenously.⁸

Chronic kidney disease (CKD), characterised by the gradual loss of kidney function, affects a significant portion of the population.⁹ Diabetes and high blood pressure are the most common causes of CKD.⁹ CKD is classified into five stages based on the estimated glomerular filtration rate (eGFR),

ranging from Stage 1 to Stage 5, which signifies kidney failure.^{10,11} End-stage renal disease (ESRD), the final and irreversible stage of CKD, necessitates dialysis or kidney transplantation for ESRD, kidney function is severely impaired.¹³ Haemodialysis, a life-sustaining treatment for ESRD, involves removing blood from the body, filtering it, and returning the purified blood.¹⁴

Patients with ESRD, particularly those undergoing treatment, are especially vulnerable to infections, including COVID-19. This vulnerability is compounded by factors such as immune dysregulation and frequent exposure to healthcare settings.¹⁵ While remdesivir has shown promise in treating COVID-19, its use in ESRD patients on haemodialysis presents a complex challenge.¹⁶ Limited data exist regarding its safety and efficacy in this population, especially considering that the drug and/or its metabolites are partially renally excreted.¹⁶ This observational study, which involves the collection of retrospective data, aims to address this critical gap by evaluating the safety of Remdesivir in COVID-19-infected patients with ESRD undergoing hemodialysis in a tertiary care hospital.

MATERIALS & METHODS

This retrospective observational study was conducted over a 5-month period, from March to July 2021, during the second wave of the coronavirus pandemic. The study site was the nephrology dialysis unit at Krishna Institute of Medical Sciences (KIMS) hospital in Secunderabad. Based on the prevalence of COVID-19 and ESRD, a total of 140 subjects were included in the study. Patients were included if they were adults infected with Covid-19, undergoing regular haemodialysis and administered with remdesivir. Pregnant and lactating women were excluded.

Data was collected from patients' records, laboratory reports, and prescriptions, and through communication with healthcare professionals and patients. The primary parameters assessed were liver function test results and ADR reports. Secondary

parameters included oxygen requirement and length of hospital stay.

Demographic details were collected from case sheets, and objective data was obtained from the dialysis unit. Variables included in the study were age, sex, smoking and alcohol status, side effects of remdesivir, past medical history (including diabetes and hypertension), duration of hospitalisation, day of remdesivir initiation, and laboratory investigation results (CRP, LDL, IL-6, ferritin, ALT, AST, ALP, NLR, ESR, D-dimer, BNP, fibrinogen, and CBP) before and after remdesivir administration. All data was collected in a structured proforma and analysed at the end of the study.

This study was conducted at Krishna Institute of Medical Sciences (KIMS) Hospital, Secunderabad, after obtaining ethical approval from the KIMS ethical committee. The confidentiality of the study participants was maintained. All patients were monitored for adverse events throughout the study period and were specifically questioned about any adverse events at the time of remdesivir administration.

Statistical Analysis

Results were presented as mean $\pm$ S.D. The demographic and other biochemical parameters of the patients (e.g., age, gender, etc.) are summarised in the table. Mean was used to compare the pre- and post-treatment values for each variable. Paired t-test was used to test if the means of two paired measurements are significantly different. A P-value of less than 0.05 was considered significant ($\alpha = 0.05$ and a confidence interval of 95%).

RESULT

This retrospective observational study included 140 patients with End-Stage Renal Disease (ESRD) on haemodialysis who were infected with COVID-19. Of these, 94 (67%) received remdesivir, and 46 (39%) did not. The age of the patients ranged from 24 to 87 years, with a mean

age of 46.7 years (SD: 20.03). The majority of patients were over 60 years of age. In the remdesivir group, 10% of patients were aged 20–40 years, 27.1% were aged 41–60 years, and 30% were over 60 years. In the non-remdesivir group, 7.14% were aged 20–40 years, 27.14% were aged 41–60 years, and 14.3% were over 60 years. The distribution of males and females in the remdesivir group was 50% and 17.14%, respectively, whereas in the non-remdesivir group, it was 22.8% and 10%, respectively, indicating a male predominance in the study population. Hypertension was the most common comorbidity, reported in 55% of patients in the remdesivir group and 21% of those in the non-remdesivir group. Overall, 34% of the 140 patients required oxygen support during their COVID-19 infection, while 66% did not. Long-term oxygen support was required by 14.2% of patients. In addition to remdesivir, which was administered to 94 patients at a loading dose of 200 mg followed by 100 mg on alternate days for three doses, concomitant medications among patients receiving remdesivir included heparin (11%), cefoperazone+sulbactam (41.42%), doxycycline (4.2%), ticarcillin (2.9%), azithromycin (32.8%), antiplatelets (2.9%), steroids (74%), hydroxychloroquine (3.8%), proton-pump inhibitors (90%), multivitamins (61.42%), and ivermectin (2.8%). The most common symptom in the Remdesivir group (n=94) was fever (76.5%), followed by shortness of breath (57.4%) and cough (51%). As evident from Table 1, the mean duration of hospitalisation was longer among patients in the remdesivir group than in the non-remdesivir group (5.75 vs. 2.56 days). The 30-day mortality and survival rates were comparable between the two groups.

Table 1. Clinical Outcomes of Patients According to Remdesivir Use

Outcome	Remdesivir group	Non-Remdesivir group
Mean of the length of hospital stay	5.75	2.56
Need for Hospitalization (%)	94 (100%)	36 (78.2%)
30-day mortality (%)	4 (4.25%)	2 (4.34%)
Survival rate	90 (95.74%)	44 (95.65%)

As evident from Table 2, significant changes in laboratory parameters following COVID-19 infection were observed for lymphocyte count, D-dimer, and serum creatinine ($p=0.013$, $p=0.017$, and $p=0.020$, respectively). Lymphocyte levels decreased,

whereas D-dimer levels increased in the post-COVID period. Changes in alanine transaminase and aspartate transaminase levels were not statistically significant ($p=0.053$ and $p=0.060$, respectively).

Table 2. Comparison of laboratory parameters before and after COVID-19 infection among patients receiving remdesivir

Variables	Pre-Covid	Post-Covid	P-value	
Alanine transaminase	20.81±20.45	60.52±200.19	0.053	NS
Aspartate transaminase	31.39 ± 28.53	98.55 ± 336.8	0.06	NS
Alkaline phosphatase	158.50 ± 84.35	156.9 ± 76.67	0.9	NS
Total bilirubin	0.62 ± 0.30	0.73 ± 0.42	0.109	NS
Lymphocyte	21.5±10.25	18.26±9.53	0.013	S
Platelet	1.66 ± 0.52	1.78 ± 0.97	0.177	NS
C-reactive protein	7.46 ± 6.24	5.98 ± 5.63	0.309	NS
D dimer	1373 ± 1799	3179 ± 3539.98	0.017	S
Sr Creatinine	6.19 ± 3.58	5.90 ± 1.89	0.02	S
GFR	11.11 ± 14.78	10.89 ± 4.054	0.87	NS

*NS- Non significant, S-Significant

DISCUSSION

This study investigated the efficacy and safety of remdesivir in COVID-19 patients with End-Stage Renal Disease (ESRD) on hemodialysis. Our study found a male predominance (50% Remdesivir group, 22.85% non-Remdesivir group) which aligns with other studies. John H. Beigel¹⁷ reported 64.4% male dominance in the Remdesivir group, and Carolina Garcia-Vidal (7) reported 61%. The mean age of patients receiving Remdesivir in our study was 46.7 years, lower than the 58.6 years reported by John H. Beigel¹⁷. The most common comorbidity in the Remdesivir group was hypertension (55%), followed by diabetes mellitus (18%), similar to Gabriel Stefan¹⁸ findings of hypertension (81%) and diabetes (32%). Remdesivir use was associated with a decreased length of hospital stay, with a mean duration of 5.75 days in the Remdesivir group compared to 2.56 days in the non-Remdesivir group. This is lower than the

median lengths of hospital stay reported by Jia H. Ng¹⁹ and Molly Fisher²⁰ (7.7 days & 9 days). The 30-day mortality rate in the Remdesivir group was 4.25%, and 4.34% in the non-Remdesivir group, which is lower than the 19% mortality rate reported by Gabriel Stefan¹⁸. The most common symptoms in our hemodialysis patients were fever (81.42%), cough (68%), and shortness of breath (52.85%), consistent with other studies that reported dyspnea (38%) & cough (35%) and fever (49%), cough (39%), dyspnea (36%), and chills (10%) (Anthony M. Valeri²¹). Biochemical parameters showed significant differences post-treatment in lymphocytes, ALP, and GFR, while pre-treatment differences were noted in ALT and total bilirubin. Yongwen Luo²² also reported significant differences in hemoglobin, WBC, neutrophils, D-dimer, AST, ALT, Sr. creatinine, and procalcitonin. Our study suggests Remdesivir has a good

tolerability profile with no serious adverse effects.

Several limitations warrant consideration when interpreting the findings of this study. The retrospective and observational nature of the design introduces the potential for selection bias and confounding factors. As the decision to administer remdesivir was based on clinical judgement rather than randomisation, imbalances in baseline characteristics between the treatment and non-treatment groups might exist, despite the presented demographic and comorbidity data. Furthermore, the study's conduct at a single tertiary care center in Secunderabad during a specific 5-month period (March to July 2021) of the pandemic's second wave limits the generalisability of the findings to other geographical locations. The study's primary focus on remdesivir's safety meant a limited exploration of its direct efficacy regarding viral clearance or the improvement of specific COVID-19 symptoms in this ESRD population. For instance, the observed longer mean hospital stay in the remdesivir group necessitates further investigation to ascertain if it correlated with the severity of their COVID-19 infection, underlying comorbidities, or other contributing elements. Lastly, the reliance on retrospective data from patient records and communication with healthcare professionals for the assessment of adverse drug reactions could have resulted in underreporting or incomplete documentation of all potential adverse events.

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CONCLUSION

This retrospective observational study provides valuable insights into the safety of remdesivir in COVID-19-infected patients with end-stage renal disease undergoing haemodialysis. The findings suggest that remdesivir was generally well-tolerated in this vulnerable population, with no serious adverse events directly attributable to the drug observed during the study period. While the study noted statistically significant changes in certain laboratory parameters (lymphocytes, D-dimer, and serum creatinine) following remdesivir administration, the clinical significance of these changes in the context of ESRD and COVID-19 warrants further investigation. Importantly, the 30-day mortality rate was similar between the remdesivir-treated and non-remdesivir-treated groups, suggesting that remdesivir did not negatively impact short-term survival in this cohort. Furthermore, the Remdesivir group experienced a numerically longer mean duration of hospitalisation compared to the non-Remdesivir group, a finding that requires further exploration to understand the contributing factors. Overall, this study contributes to the limited existing data on

remdesivir use in ESRD patients on haemodialysis, suggesting a potential for safe administration, although further research is needed to definitively establish its efficacy and long-term outcomes in this complex patient population.

Declaration by Authors

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