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RESEARCH LETTER

Clinical Effectiveness and Safety of Remdesivir in Hemodialysis Patients with COVID-19

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INTRODUCTION

COVID-19, caused by SARS-CoV-2, has spread globally since December 2019. Remdesivir has been widely used for COVID-19 treatment since it received an Emergency Use Authorization by the US Food and Drug Administration in May 2020.[1] Nevertheless, the clinical trials that evaluated the effect of remdesivir did not include patients with an estimated glomerular filtration rate < 30 ml/min per 1.73 m^2; therefore, the safety and clinical effectiveness of remdesivir remain to be confirmed in patients with end-stage kidney disease.[2]

Patients undergoing in-center hemodialysis are more vulnerable to COVID-19 due to regular visits to medical institutions.[3] Moreover, drugs against SARS-CoV-2, such as remdesivir, are used restrictedly in patients on hemodialysis because of the lack of safety and efficacy data. Therefore, to improve the prognosis of patients with COVID-19 who are on hemodialysis, we aimed to provide information on the clinical efficacy and safety of remdesivir for COVID-19 treatment in hemodialysis patients.

METHODS

Study Participants

All hospitalized patients with COVID-19 who are on hemodialysis were analyzed from a retrospective cohort at the Kyungpook National University Chilgok Hospital between January 26, 2022, and March 31, 2022, when the Omicron variant had become the dominant species of SARS-CoV-2 in South Korea. The details of study methods are shown in the Supplementary Methods.

Outcome

The primary outcome was a composite of in-hospital mortality, use of a high-flow nasal cannula, or transfer to the intensive care unit. The secondary outcomes were aggravation of disease severity according to the National Institutes of Health COVID-19 severity criteria[4] and changes in the National Early Warning Score (NEWS) during hospitalization.

Definition

The NEWS is an early warning scoring system that facilitates early detection and response to clinical deterioration. It consists of 7 parameters, namely respiratory rate, peripheral oxygen saturation, supplemental oxygen use, body temperature, systolic blood pressure, heart rate, and neurological status; all parameters are assigned a score of 0 to 3.[5]

Clinical Management

All hospitalized patients received symptomatic care, including oxygen, antipyretics, and antitussive agents. Specialists in infectious diseases and nephrology prescribed remdesivir, antibiotics, and dexamethasone. Remdesivir was administered to patients with moderate severity within 7 days of symptom onset or to those with severe COVID-19. The attending physician explained the possible side effects of remdesivir, and only patients

Table 1. Information on the treatment administered and clinical outcomes

Outcome	All (n = 118)	Remdesivir (n = 44)	Nonremdesivir (n = 74)	P value
Treatment, n (%)				
Antibiotics	79 (66.9)	32 (72.7)	47 (63.5)	0.304
Regdanvimab	39 (33.1)	10 (22.7)	29 (39.2)	0.066
Dexamethasone	45 (38.1)	25 (56.8)	20 (27.0)	0.001
Oxygen therapy	27 (22.9)	11 (25.0)	16 (21.6)	0.673
HFNC	9 (7.6)	1 (2.3)	8 (10.8)	0.151
Mechanical ventilation	2 (1.7)	1 (2.3)	1 (1.4)	>0.999
CRRT	2 (1.7)	1 (2.3)	1 (1.4)	>0.999
ICU transfer	4 (3.4)	1 (2.3)	3 (4.1)	0.605
Clinical outcomes, n (%)				
In-hospital death	6 (5.1)	1 (2.3)	5 (6.8)	0.284
Composite outcome	11 (9.3)	1 (2.3)	10 (13.5)	0.042
Disease severity aggravation	18 (15.3)	3 (6.8)	15 (20.3)	0.049
Length of hospital stay, d	7.0 (6.0–8.0)	7.0 (6.0–9.0)	6.5 (6.0–8.0)	0.541

CRRT, continuous renal replacement therapy; HFNC, high-flow nasal cannula; ICU, intensive care unit.

who consented to use it were prescribed. Considering the risk of the side effects of remdesivir use, we reduced the dose to half the standard dose for a patient. The loading dose was 100 mg; the maintenance dose was 50 mg for the next 2 to 4 days depending on the patient's status, and it was injected after hemodialysis on the day of dialysis. Patients receiving remdesivir were monitored for adverse events by laboratory examination, including liver function tests, every 24 to 48 hours.

RESULTS

Baseline Characteristics

In total, 118 patients with COVID-19 who are on hemodialysis were included in the study, and 44 patients (37.3 %), were administered remdesivir during hospitalization. The mean age was 68.5 ± 12.8 years, and 66.1% were male (Supplementary Table S1). The remdesivir group had a tendency of more severe disease (P = 0.058), and the NEWS on the day of hospitalization was significantly higher in the remdesivir group (P = 0.026). The incidence of comorbid diseases did not differ between the 2 groups. The patients in the remdesivir group showed substantially higher lactate dehydrogenase levels and proportion of bilateral lung infiltration at admission.

Clinical Course and Outcomes

The in-hospital course and outcome information is summarized in Table 1. The proportion of antibiotics used was similar, and the remdesivir group required more dexamethasone than the non-remdesivir group. The proportion of patients who received oxygen therapy, a high-flow nasal cannula, and mechanical ventilation did not differ between the 2 groups. Six deaths occurred during hospitalization (1 [2.3%] in the remdesivir group and 5 [6.8%] in the non-remdesivir group), and the mortality was not different between the 2 groups (P = 0.284). Nevertheless, the composite outcome of mortality, use of a high-flow nasal cannula, and transfer to the intensive care unit occurred less frequently in the remdesivir group (1 [2.3%] vs. 10 [13.5%], P = 0.042). Disease severity aggravation rate was also lower in the remdesivir group (3 [6.8%] vs. 15 [20.3%], P = 0.049).

Factors associated with the composite outcome and disease severity aggravation are shown in Supplementary

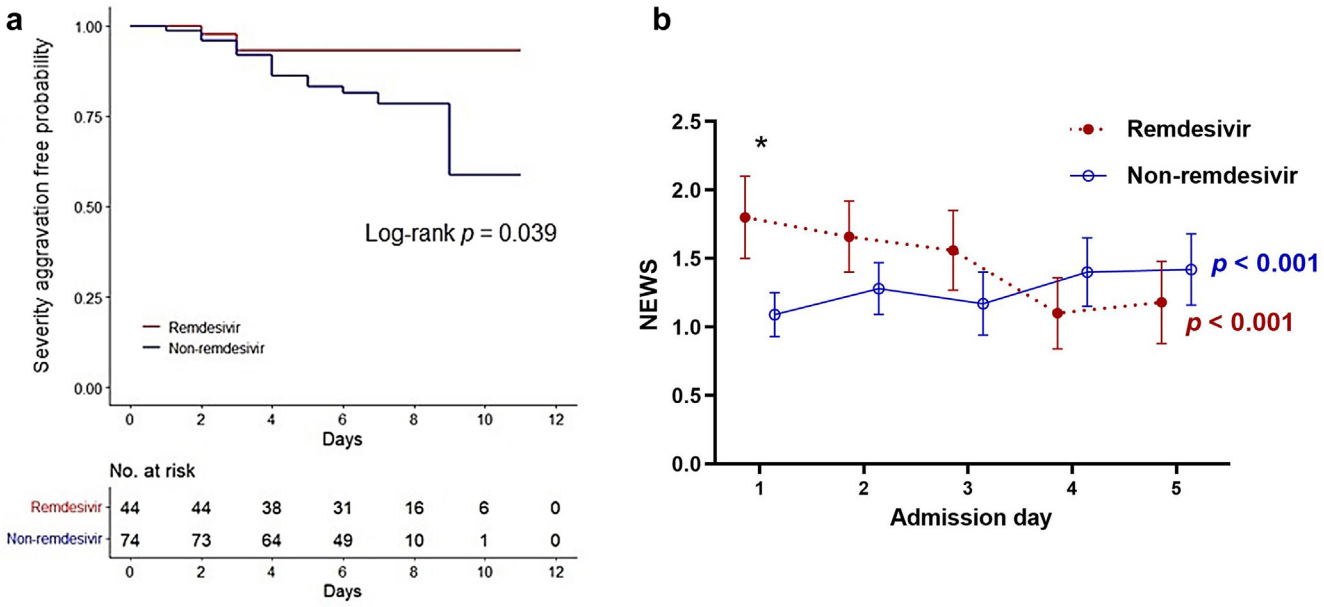

Figure 1. Clinical courses of hemodialysis patients with COVID-19. (a) Kaplan–Meier curve for disease severity aggravation according to remdesivir use. (b) Changes in the NEWS during hospitalization. On the day of hospitalization, the remdesivir group showed a higher NEWS than the non-remdesivir group (P = 0.026), but the difference in the NEWS was not found from the next day. *P < 0.05, between remdesivir and non-remdesivir groups on each admission day. NEWS, National Early Warning Score.

Table S2. In the multivariate logistic regression analyses, remdesivir use was independently associated with a lower occurrence of the composite outcome (adjusted odds ratio, 0.01, 95% confidence interval, 0.001–0.31, $P = 0.009$) and severity aggravation (adjusted odds ratio, 0.08, 95% confidence interval, 0.02–0.42, $P = 0.003$). In the Kaplan–Meier estimate of disease severity aggravation, the remdesivir group also showed a better prognosis with a lesser incidence of severity aggravation (Figure 1a, log-rank $P = 0.039$).

In the remdesivir group, dexamethasone was not associated with the aggravation of disease severity in the multivariate logistic regression model and Kaplan–Meier analysis (Supplementary Table S3 and Supplementary Figure S1).

Changes in the NEWS During Hospitalization

The changes in the NEWS during hospitalization are shown in Figure 1b. On the day of hospitalization, the remdesivir group showed a higher NEWS than the non-remdesivir group ($P = 0.026$), but there was no difference in the NEWS the next day. In addition, the NEWS significantly decreased over time in the remdesivir group ($P < 0.001$), whereas the non-remdesivir group showed an increase in the NEWS ($P < 0.001$).

Safety of Remdesivir

No anaphylaxis or hypersensitivity reaction was observed after the use of remdesivir. The incidence of elevation of liver enzymes during hospitalization did not differ between the remdesivir and non-remdesivir groups (22.7% vs. 17.6%, $P = 0.494$; Supplementary Table S4).

DISCUSSION

This study found an association between the clinical effectiveness and remdesivir use in SARS-CoV-2 infected patients on hemodialysis. The remdesivir group had a lower risk of the composite outcome and aggravation of disease severity, despite the higher disease severity at hospitalization than the non-remdesivir group. In addition, there were no serious side effects, such as hepatic failure; therefore, probably remdesivir could be safely used in patients on hemodialysis. The findings of the present study may provide evidence of safety and efficacy of remdesivir in the treatment of patients with COVID-19 who are on hemodialysis.

There are some studies that identified the effectiveness and safety of remdesivir use in SARS-CoV-2 infected patients on hemodialysis. In an Indian study, 48 patients with moderate to severe COVID-19 who are on hemodialysis were treated with remdesivir.[2] It was found to be safe and to reduce the recovery time if initiated within 48 hours of hospitalization. Another study from Pakistan reported the effects of remdesivir in 83 patients with COVID-19 who are on hemodialysis.[6] The overall mortality did not reduce, but the recovery time was shortened if remdesivir was administered within 48 hours. On the contrary, a Spanish study reported no beneficial effects of remdesivir on both mortality and hospital stay in 36 patients with COVID-19 who are on hemodialysis.[7] However, most patients (88.8%) had mild infection and only 58.3% of patients received remdesivir within the first 48 hours of diagnosis. Taken together, early initiation of remdesivir therapy may be necessary to improve outcomes in patients with COVID-19 who are on hemodialysis and severity of infection has to be considered before use. In our study, all patients had moderate or severe infection and most patients (36 out of 44 [81.8%]) received remdesivir within 48 hours of hospitalization, which might be responsible for the beneficial effects of remdesivir on the composite outcome and disease aggravation.

Accumulation of sulfobutylether-β-cyclodextrin, a vehicle for remdesivir, is a safety concern of remdesivir use in patients with end-stage kidney disease.[2,8,9] Nevertheless, considering that sulfobutylether-β-cyclodextrin is eliminated by dialysis,[S1] the risk of side effects might be low in hemodialysis patients. In previous studies involving patients with COVID-19 who are on hemodialysis, remdesivir did not cause severe liver function derangement, and only 1 of 131 patients (0.8%) discontinued remdesivir due to elevated liver enzyme levels.[2,6] Although our study patients were much older than those in previous studies, there were no significant side effects, and no patient discontinued remdesivir due to side effects. Therefore, the short-term use of remdesivir in patients with COVID-19 who are on hemodialysis may not result in a high risk of side effects, including hepatotoxicity.

The use of remdesivir in patients with COVID-19 who are on hemodialysis improved the NEWS during hospitalization and prevented progression to severe or critical disease. Moreover, the risk of side effects of remdesivir was not high; thus, it could be used as an additional treatment option based on the benefits and risks to patients. Further large-scale randomized controlled trials for patients with COVID-19 who are on hemodialysis are needed to corroborate the findings of this study.

This study has several limitations. First, this is a retrospective study; therefore, there was a chance of unaccounted bias. Second, the number of patients was too small to make a clear conclusion, and the long-term effect of remdesivir use could not be identified. Third, we enrolled patients after the Omicron variant became dominant but could not identify the individual subtypes of SARS-CoV-2.

In conclusion, remdesivir use in patients with COVID-19 who are on hemodialysis reduced the risk of composite of mortality, high-flow nasal cannula use, and intensive care unit transfer. In addition, the risk of severity aggravation decreased in patients treated with remdesivir. No significant side effects, including liver function test derangement, were observed after remdesivir use. Remdesivir may be used in patients with COVID-19 who are on hemodialysis after considering its benefits and risks.

DISCLOSURE

All the authors declared no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF).

Supplementary Methods.

Figure S1. Kaplan–Meier curve for severity aggravation according to dexamethasone use among the remdesivir group.

Table S1. Baseline characteristics.

Table S2. Factors associated with composite outcome and severity aggravation during hospitalization in the multivariate logistic regression analysis.

Table S3. Association between dexamethasone use and severity aggravation among the remdesivir group in the multivariate logistic regression analysis.

Table S4. Information on liver function tests during hospitalization.

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