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ORIGINAL RESEARCH

Clinical Outcomes of Remdesivir in COVID-19 Patients with Acute Kidney Injury or Chronic Kidney Disease: A Randomized Clinical Trial

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Abstract: **Background:** remdesivir is an RNA polymerase inhibitor approved to treat moderate to severe Coronavirus Disease 2019 (COVID-19); however, it has not yet been authenticated to apply to patients with acute kidney injury (AKI) or chronic kidney disease (CKD). Regarding some positive results obtained from previous studies, we aimed to evaluate the efficacy and safety of remdesivir in patients with COVID-19 with severe renal impairment.
Methods: In a randomized clinical trial, remdesivir was added to the standard regimen of treating patients with COVID-19 with AKI or CKD. 200 mg remdesivir was given on the first day of admission to 50 patients followed by 100 mg every other day until resolution of the symptoms. Clinical and paraclinical evaluation was performed daily and the findings were compared with the 50 patients on standard treatment regimen.
Results: the rates of intensive care unit (ICU) admission (P: 0.02), and mortality (P: 0.007) were significantly reduced in patients who received remdesivir. Moreover, a substantial decrease of aspartate transaminase (AST) (P: 0.004), lactate dehydrogenase (LDH) (P: 0.004), ferritin (P: 0.007), erythrocyte sedimentation rate (ESR) (P<0.0001), alkaline phosphatase (ALP) (P: 0.006) were observed in the patients receiving remdesivir compared to the baseline values which was absent in case of non-remdesivir group. No serious side effects were observed, except for one patient who showed elevated liver enzymes.
Conclusion: remdesivir appears to be well tolerated in patients with AKI and CKD. Administration of this drug resulted in reduced mortality and ICU admission as well as clinical and paraclinical improvement in these patients.

Keywords: COVID-19; Remdesivir; Chronic Kidney Disease; Acute Kidney Injury

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1. Introduction

In February 2019, severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) caused the pandemic of coronavirus disease 2019 (COVID-19) posing severe challenges to the health system. Given that at the beginning of the pandemic, there was no approved medication to treat the patients, high rates of mortality were recorded; however, by conducting several clinical trials many therapeutic options were introduced, including various anti-inflammatory and anti-viral agents as well as non-conventional methods such as serum therapy and cell therapy (1). Among different antiviral drugs, remdesivir has shown encouraging results, particularly in alleviating acute respiratory symptoms; therefore, it is widely used to treat patients with COVID-19 with moderate to severe symptoms. However, some adverse effects were reported, especially in patients with chronic kidney or hepatic diseases (2, 3).

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Remdesivir is a nucleotide analog, which inhibits SARS-Cov-2 by interfering with RNA-dependent RNA polymerase (RDRP). In a large-scale clinical trial recruiting 1062 patients from several sites, it was found that remdesivir reduced the recovery time from 15 to 11 days and the mortality rate from 11.6% to 8% in patients with COVID-19 (4). Nonetheless, because of the renal elimination of this drug, some doubts and controversies arose about the safety of administrating remdesivir in patients with impaired renal function. It is best avoided in treating patients with COVID-19 with a glomerular filtration rate (GFR) of less than 30 ml/min or those requiring renal replacement therapy. The potential renal toxicity of its carrier, sulfobutylether-β-cyclodextrin (SBECD), was the main reason to prohibit remdesivir to patients with chronic or acute kidney dysfunction. Moreover, the risk of developing acute kidney injury (AKI) in severe forms of COVID-19 complicated the issue (5). Nonetheless, treating patients with COVID-19 with renal insufficiency might fail if efficient medications are not administrated especially in the case of those in critical condition. For this reason, and because these patients are at a higher risk of SARS-Cov-2 infection with a considerable mortality rate, some centers tried remdesivir for treating patients with AKI and chronic kidney disease (CKD) weighing up the advantages and disadvantages of its administration. Overall findings suggest beneficial effects of remdesivir on admission duration and mortality rate; moreover, reported adverse effects were lower than expected (6, 7).

Therefore, there is a need for further research on the safety and efficacy of remdesivir in patients with severe renal diseases. Accordingly, we aimed to compare the outcomes of patients with AKI or CKD who received remdesivir in addition to the standard treatment and the patients under the standard protocol.

2. Materials and methods

2.1. Study design

This randomized clinical trial (IRCT20210709051824N1) with the ethics code of IR.SBMU.RETECH.REC.1400.379 approved by the Research Ethics Committee of Vice-Chancellor in Research Affairs-Shahid Beheshti University of Medical Sciences was conducted between September 2021 and March 2022 at a single center. The patients were randomized to receive remdesivir or not by randomization software. One hundred adult patients (mean age: 67.10±14 years old) with AKI or CKD who were admitted to a single center with a definitive diagnosis of COVID-19 confirmed with nucleic acid amplification tests (reverse-transcription polymerase chain reaction (RT-PCR)) plus lung involvement of more than 30%, and oxygen saturation of less than 93% were recruited to the study. Accordingly, all patients were categorized as severe COVID-19. After obtaining informed consent, the patients were randomized into two groups. Fifty patients received the standard coronavirus treatment for patients with renal insufficiency, including supportive care and dexamethasone 8mg daily or methylprednisolone 250 mg for three days, while 50 patients in the intervention group received remdesivir in addition to the standard treatment. The patients took 200 mg of remdesivir on the first day and 100 mg every other day until either disease alleviation or the emergence of complications (Figure 1).

AKI was defined as the increase in serum creatinine by ≥0.3 mg/dL within 48 hours, or an increase in serum creatinine to ≥1.5 times baseline, which has occurred within the prior seven days, or urine volume <0.5 mL/kg/hour for six hours (8). CKD patients were diagnosed with decreased GFR (<60 mg/mi/1.73 m2), albuminuria, urine sediment abnormalities, electrolyte abnormalities, histologic findings, imaging clues, or history of kidney transplantation(9).

Remdesivir-related complications were defined as increased levels of aspartate transaminase (AST) or alanine transaminase (ALT) more than 5 times, ALT, AST, alkaline phosphatase (ALP) rise more than 3 times accompanied by hepatitis symptoms (abdominal pain, nausea, vomiting, jaundice), INR rise more than 2 times, or bilirubin rise more than 3 times accompanied by hepatitis symptoms, or creatinine rise more than 25% of baseline.

Results of the clinical and paraclinical evaluations were recorded daily. Blood tests including liver and renal function tests, complete blood tests, electrolytes, and oxygen saturation were regularly assessed. Moreover, the two groups were compared in terms of the progression of pulmonary injury, the need for intubation, the need for ICU admission, the total number of hospitalization days, and the disease outcome. Demographic, clinical, and paraclinical findings have been presented in Table 1.

2.2. Statistical analysis

Statistical analysis was performed using SPSS software (version 28; IBM Corp., Chicago, USA). Qualitative variables are presented as absolute numbers and percentages. Quantitative variables are expressed as mean ± standard deviation. Paired T-test for parametric and the Wilcoxon test for non-parametric data were used to make a comparison between the initial and final values. Independent sample T-test and Mann–Whitney U test were used to compare the outcomes of the two groups. Fisher's exact test was used for the analysis of the qualitative data. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

This clinical trial included 100 patients with AKI admitted with severe COVID-19 in two groups of 50 patients receiving

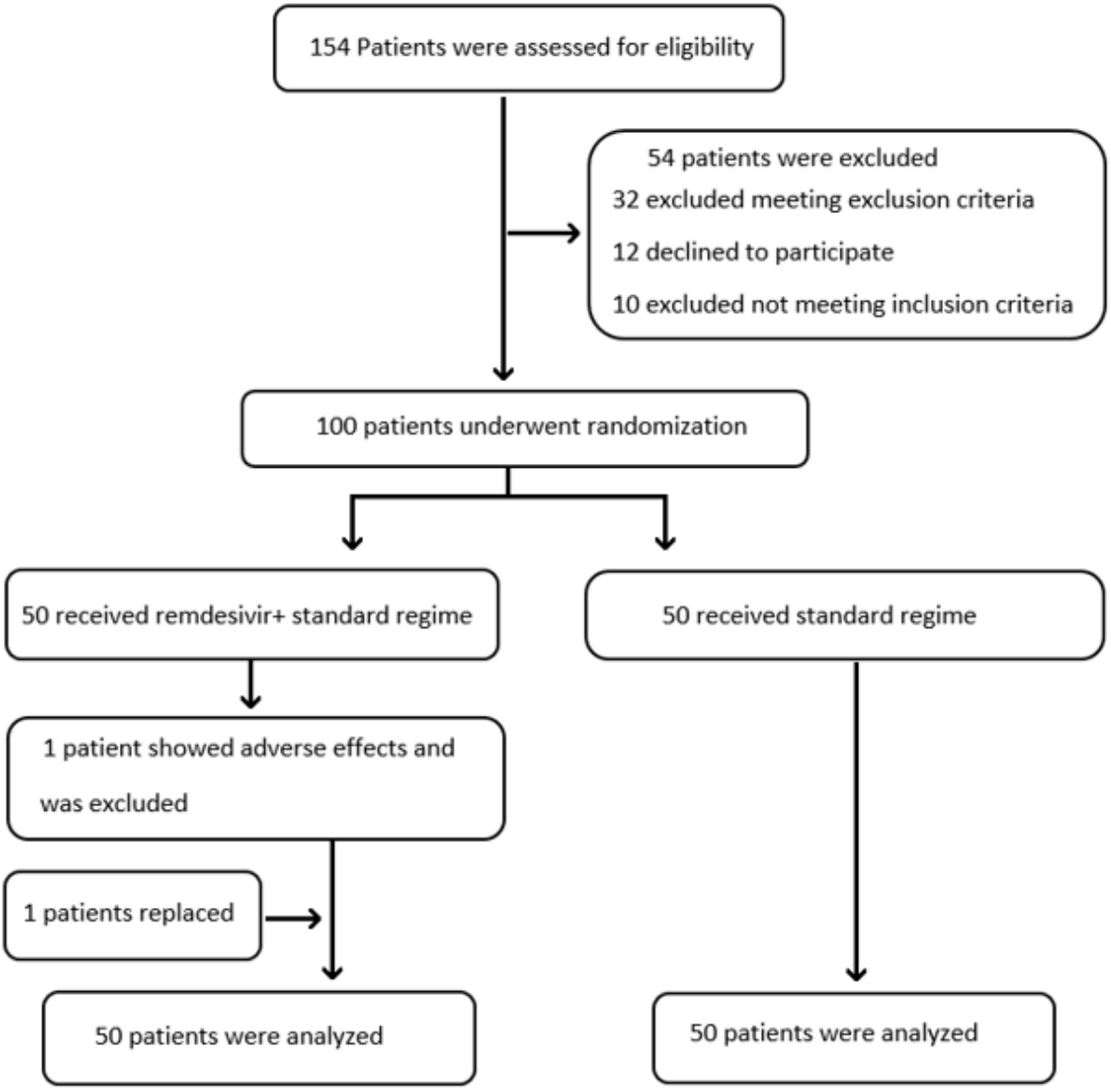

Figure 1: enrollment and randomization of the patients.

the standard treatment regimen (corticosteroids) and 50 taking remdesivir plus corticosteroids. The remdesivir group included 29 male/21 female participants, 15 (30%) diagnosed with AKI, and 35 (70%) known cases of CKD. The latter group included 32 male/18 female patients, 24 (48%) with AKI and 26 (52%) with CKD.

Our results showed that including remdesivir in the standard protocol of treating AKI/CKD patients with COVID-19 could improve the clinical situation of the patients significantly. The ICU admission rate of patients receiving remdesivir was lower than the control group (16% vs. 38%, P: 0.02). Moreover, the mortality rate decreased substantially by remdesivir (10% vs. 34%, P: 0.007). In addition, the mean O2 saturation at the end of the treatment period was higher in the remdesivir group compared to the others (91.32±2.2 vs. 89.6±2.9 P: 0.001).

The other significant differences between the two groups were a substantial decrease in ferritin (P: 0.007), erythrocyte sedimentation rate (ESR) (P<0.0001), lactate dehydrogenase (LDH) (P: 0.004), AST (P: 0.004), and ALP (P: 0.006) levels in the patients receiving remdesivir, while despite a subtle decline, there was not any significant difference between before and after treatment values in the control group. Moreover, no unusual creatinine rise was observed in patients receiv-

Table 1: Demographic, clinical, and paraclinical data of the studied population before treatment in two groups of remdesivir and no-remdesivir

Variable		Mean± Std. Deviation	P-value
Gender(m/f)	with rem	50 (29/21)	NS
	no rem	50 (32/18)	
Age	with rem	65.10±14.7	NS
	no rem	70.2±13.8	
BMI	with rem	24±3.3	NS
	no rem	23.6±2.7	
AKI	with rem	15 (30%)	NS
	no rem	24 (48%)	
CKD	with rem	35 (70%)	NS
	no rem	26 (52%)	
Diabetes type 2	with rem	21 (42%)	
	no rem	12 (24%)	
Hypertension	with rem	39 (78%)	
	no rem	35 (70%)	
coronary artery disease	with rem	7 (14%)	
	no rem	9 (18%)	
GFR	with rem	19.2±6.8	NS
	no rem	21±7.2	
Days before treatment	with rem	4.7±1.3	0.03
	no rem	4±1.5	
Hospitalization days	with rem	8.2±2.6	0.01
	no rem	6.8±2.9	
Lung involvement percent	with rem	42.1±12.5	NS
	no rem	45.1±13.9	

Abbreviations: NS: not significant; rem: remdesivir; BMI: body mass index; AKI: acute kidney injury; CDK: chronic kidney disease; GFR: glomerular filtration rate.

ing remdesivir. Results of the comparison between before and after treatment amounts in two groups of remdesivir and non-remdesivir have been summarized in Table 2.

One 58-year-old male patient with CKD in the remdesivir group showed a two-fold rise of liver enzymes (AST/ALT) after receiving the third dose and discontinued participating.

4. Discussion

According to the encouraging results obtained from case studies (10, 11), some clinical trials have been conducted to reveal the advantages and disadvantages of administrating remdesivir to patients with severe renal impairment (SRI). A retrospective chart review comparing 115 normal patients with 30 SRI cases who received remdesivir following COVID-19 infection, showed a total incidence of 30% for adverse events (AEs) in SRI patients versus 11% in the control group. Liver function tests (LFT) more deteriorated in the SRI group but this was not significant (10% vs 4%). Creatinine rise occurred in 27% of SRI patients while 6% among controls. However, neither LFT nor creatinine elevation could be attributed to the remdesivir. Of note, the SRI patients were significantly older than the control group. Therefore, it was suggested that remdesivir is safe to be used for patients with SRI and its benefits may outweigh the adverse effects (12). Furthermore, another retrospective chart review of hospitalized 347 patients with SARS-CoV-2 infection compared the safety of remdesivir among the patients with creatinine clearance of <30and ≥30ml/min. The results showed that the frequency of acute kidney injury (5% versus 2.3%), and abnormal liver function tests (LFTs) (0% versus 3.9%) were statistically comparable between the two groups. Of the 5% of patients who developed AKI on remdesivir, no cases were attributable to remdesivir administration. Moreover, similar to the previous study, the patients with impaired renal function were significantly older than the control group. This study indicated that remdesivir use was not associated with increased rates of AKI in patients with creatinine clearance less than 30ml/min (7). In addition, in a single-center study, 56 patients with either AKI or CKD who have been admitted with COVID-19 were treated with remdesivir. Elevated AST/ALT levels were observed in 14 patients (13 grade 1 and 1 grade 2) but it was resolved in 12 of them by the end of therapy thus administration of remdesivir was not discontinued for this reason. In addition, no renal function abnormalities attributable to remdesivir were reported (13). Similarly, administration of remdesivir for forty-six AKI or CKD patients with COVID-19 as a total dose of 600 mg (200 mg on day 1, followed by 100 mg/day) was well tolerated and improved the clinical situa-

Table 2: Comparison of clinical and paraclinical values before and after treatment in two groups of remdesivir and no-remdesivir

Variable	p-value	
	With rem	No rem
O2 before / O2 after	.000	.000
Creatinine before / Creatinine after	.000	NS
AST before / AST after	.004	NS
ALT before / ALT after	NS	NS
INR before / INR after	NS	NS
LDH before / LDH after	.004	NS
Ferritin before / Ferritin after	.007	NS
CRP before / CRP after	.000	.004
ESR before / ESR after	.000	NS
d-DIMER before / d-DIMER after	.003	.002
TIBC before / TIBC after	.004	.000
WBC before / WBC after	NS	NS
PMN(%) before / PMN(%) after	NS	NS
LYM(%)before / LYM(%) after	NS	NS
BUN before / BUN after	.000	.007
ALP before / ALP after	.006	NS
platelet before / platelet after	NS	NS
MVP before / MVP after	.000	.001
Calcium before / Calcium after	.000	.000
Albumin before / Albumin after	.003	.01
GFR before / GFR after	0.041	NS

Abbreviations: rem: remdesivir, AKI: acute kidney injury, CDK: chronic kidney disease, GFR: glomerular filtration rate, AST: aspartate transaminase, ALT: alanine transaminase, INR: international normalized ratio, LDH: lactate dehydrogenase, CRP: C - reactive protein, ESR: erythrocyte sedimentation rate, TIBC: total iron-binding capacity, WBC: white blood cell count, PMN: Polymorphonuclear, LYM: lymphocyte, BUN: Blood Urea Nitrogen, ALP: alkaline phosphatase, MPV: Mean platelet volume, GFR: glomerular filtration rate.

tion of the patients. This study proposed the safety of this drug for patients on hemodialysis (13). Moreover, adding 100 mg remdesivir to the standard protocol of treatment 4 hours before hemodialysis in 48 dialysis-dependent patients with SARS-CoV-2 infection resulted in a significant decrease in CRP levels and improvement in oxygen saturation of patients without any considerable adverse effects. It was also demonstrated that early administration of remdesivir (within 48 hours of hospitalization) could reduce the hospitalization days significantly (14).

Finally, a systematic review including 16,199 COVID-19 patients demonstrated that the pooled estimated incidence of AKI in all hospitalized COVID-19 patients was 10% with 4% needing continuous renal replacement therapy. The incidence of AKI could be associated with age, disease severity, and ethnicity. Of note, the incidence of AKI in hospitalized COVID-19 patients being treated with remdesivir was 7% suggesting a positive contribution of this drug in preventing AKI in COVID patients (15).

The results of the present study also showed positive outcomes of using this drug in patients with AKI or CKD, as the mortality rate and ICU admission were significantly lower in patients receiving remdesivir; O2 saturation was improved and many laboratory tests including ferritin, erythrocyte sedimentation rate, aspartate transaminase, lactate dehydrogenase, and alkaline phosphatase reduced significantly in these patients. Only one patient showed serious adverse effects (a two-fold rise in liver function test) who discontinued participation. Taken together, the application of remdesivir to patients with SRI appears to have considerable advantages.

5. Conclusion

The present study showed significant improvement in clinical and paraclinical criteria, decreased ICU admission, and lower mortality rates by administration of remdesivir for AKI and CKD patients with severe COVID-19 infection.

6. Appendix

6.1. Acknowledgment

All the techniques carried out in the present study involving human participants were by the standards of the institutional research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. It has the ethical approval of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1400.379). Informed consent was obtained from all participants after de-

scribing the process and goals of the study. The data that support the findings of this study are available from the corresponding author upon request.

6.2. Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

6.3. Funding support

None.

6.4. Author's contributions

MF : recruitment of patients, writing; TA: conceptualization, patients monitoring; MK: patients monitoring; SA: data analysis, writing

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