

Original Article

Clinical outcome of Remdesivir in treatment of severe and critically ill elderly patient with COVID 19 infection.

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ABSTRACT

Background: Antiviral effect of remdesivir against SARS-CoV-2 is still controversial, during COVID-19 pandemic, using antiviral drugs may be an efficient strategy as there is no proven effective treatment. Remdesivir was approved as a promising antiviral drug for the pandemic COVID-19 disease. There is a debate over its efficacy, with different studies considering various factors.

Objective: The aim of the study was to evaluate the clinical outcome of using Remdesivir in elderly patients with severe and critically ill COVID-19 infection who received standard of care treatment and Remdesivir in comparison to similar patients who have received standard of care treatment only.

Methods: This is a retrospective observational study of 330 cases admitted to Geriatrics Isolation Hospital at Ain Shams University classified into 2 groups, Group A: 165 patients received standard of care treatment plus Remdesivir, Group B :165 patients received standard of care treatment only. Data extracted included patient's medical history, oxygen demand on admission and on discharge. Laboratory investigations including C reactive protein, ferritin, complete blood count, kidney function test, liver function test on admission and on discharge. Outcome was reported as regard length of hospital stay, morbidity and mortality.

Results: results showed that percentage of mortality in cases who received remdesivir was 17.2% and who didn't receive it was 44.9%, In hospital mortality was less in cases who received remdesivir with significant difference statistically (P value<0.001).

Conclusion: Remdesivir plus standard of care treatment for severe and critically ill cases improves prognosis in comparison to standard of care treatment only.

Key words: Remdesivir , critically ill , Mortality , COVID 19.

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) , was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19.¹ Many infected people are asymptomatic or experience mild symptoms and recover without medical intervention². However, older people and those with comorbid hypertension, diabetes, obesity, and heart disease are at higher risk of life-threatening illness.³

The disease is characterized by an initial phase of viral replication that can be followed by a second phase driven by the host inflammatory response.⁴ Remdesivir - an inhibitor of the viral RNA-dependent RNA polymerase with in vitro inhibitory activity against severe acute respiratory syndrome corona virus 1 (SARS-CoV-1) and the Middle East respiratory syndrome (MERS-CoV) ⁵ - was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in vitro. ⁶

The active metabolite of Remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proof reading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.⁷

The Adaptive COVID-19 Treatment Trial (ACTT-1) found that remdesivir shortened the time to illness recovery from a median of 15 days to 10 days among patients hospitalized with COVID-19⁸ , In addition , in nonhuman primate studies , remdesivir initiated 12 hours after inoculation with Middle East Respiratory Syndrome Corona virus (MERS-CoV10,11) reduced lung virus levels and lung damage. ⁹ Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID- 19 in hospitalized adult and pediatric patients. ¹⁰ Since the designation of the Geriatric hospital in Ain Shams University as an isolation hospital for management of COVID-19 patients, standard protocols were used in different stages of the disease with the introduction of remdesivir to selected patients. The efficacy of remdesivir specifically in elderly was a great concern to hold this study.

The aim of the study is to evaluate the clinical outcome of using Remdesivir in elderly patients with severe and critically ill COVID-19 infection who have received standard of care treatment and Remdesivir in comparison with similar patients who have received standard of care

treatment only.

METHODS

A retrospective observational study, 330 patients older than 60 years with proof of acute respiratory syndrome covid virus 2 (SARS-CoV2) infection by PCR from nasopharyngeal swab. Patients were classified into 2 groups: Group A: 165 patients who received standard of care treatment plus remdesivir, Group B: 165 patients who received standard of care treatment only.

Inclusion criteria were: All elderly patients (Both males and females) at the age 60 years old or more. Confirmed to have SARS-CoV-2 infection by swab Polymerase Chain Reaction (PCR). Severe cases (Respiratory rate > 30, blood oxygen saturation < 92 at room air, arterial oxygen partial pressure (PaO2 in mmHg) / fractional inspired oxygen (FiO2) ratio < 300, Chest radiology showing more than 50% lesion or progressive lesion within 24 to 48 hours) Critically ill cases (Respiratory Rate > 30, blood oxygen saturation < 92 at room air arterial oxygen partial pressure (PaO2 in mmHg) / fractional inspired oxygen (FiO2) ratio < 200 despite oxygen therapy). Onset of symptoms less than 12 days for group A (who received remdesivir)

Exclusion criteria: Liver injury or failure (aspartate transaminase (AST) / alanine transaminase (ALT) ≥ 5x upper normal level) , Onset of symptoms more than 12 days , Estimated Glomerular Filtration Rate (eGFR) <30 mL/minute

Data collected regarding these cases included demographic data and full medical history, oxygen saturation , C reactive protein (CRP), complete blood count (CBC), kidney function test (KFT), liver function test (LFT), lactate dehydrogenase (LDH), Ferritin, D dimer, on admission and on discharge, outcome of patient who received remdesivir plus standard of care treatment and who received remdesivir only.

Data obtained by retrospective review of medical records after approval of the study methodology by the Faculty of Medicine Ain Shams Research Institute (MASRI) ethical committee and Research Review Board of the Geriatrics and gerontology medicine department, Faculty of Medicine, Ain Shams University. Confidentiality and anonymity of participants was be ensured.

Data entry and statistical analysis were on a personal computer using Statistical Package for Social Science

(SPSS) (version 26) Quantitative variables were presented in the form of means and standard deviation. Qualitative variables were presented in the form of frequency tables (number and percent). A comparison between quantitative variables was carried out by t test for two variables or one way ANOVA for more than two variables. The statistical difference was accepted when $P < 0.05$.

RESULTS

A sample of 330 severe to critically ill COVID-19 patient was recruited from Geriatric isolation hospital at Ain Shams University. They were divided into two groups Group A: 165 patients who received standard of care treatment plus remdesivir and group B: 165 patients who received standard of care treatment only. Among those who received remdesivir. The mean age was 67.21 (SD 7.63) years, 58.3 % of them were males and 41.7 % were female, while among those who didn't receive remdesivir the mean age was 67.9 years, 49.1% were males and 50.9% were females. There is no significant difference statistically between the two groups regarding age or sex (p value for age 0.36 and p value for sex 0.1) as shown in Table 1 .

Table (2) shows there is a higher percentage of cases with hypertension (HTN), diabetes Mellitus (DM), chronic kidney disease (CKD), chronic liver disease (CLD) within the standard treatment group compared to remdesivir + standard treatment group and the difference was statistically significant. ($P=0.002, 0.03, 0.01, 0.01$ respectively)

Table (3) shows the percentage of all complications; acute respiratory distress syndrome (ARDS) , stroke , deep venous thrombosis (DVT), pulmonary embolism (PE), acute kidney injury (AKI), acute liver injury was higher in cases who didn't receive remdesivir with statistically significant difference ($P=<0.001 , < 0.001 , 0.03 , 0.03 , < 0.001 , 0.004$ respectively)

Percentage of in hospital mortality in cases who received remdesivir WAS 17.2% and who didn't receive it was (44.9%) (p value < 0.001).

By logistic regression analysis, older age, not taking remdesivir and development of complications are independent risk factors for mortality as shown in table (5).

Table (1): Table 1: Comparison between Group A (received remdesivir plus Standard care treatment) and Group B (standard care treatment only) as regard Demographic data:

		Total number (330) (mean ± SD)	Remdesivir plus standard care (165)		Standard care only (165)		t*	P value
			Mean	SD	Mean	SD		
Age		(67.60 ± 7.63)	67.21	6.58	67.98	8.53	0.91	0.36
		Total number (percentage)	N	%	N	%	X ^{2**}	P value
Sex	Male	178 (53.9%)	96	58.3%	82	49.1%	2.80	0.10
	Female	152 (46%)	69	41.7%	83	50.9%		

*Student t test **Chi square test.

P-value > 0.05: non-significant, P-value <0.05: significant , P-value<0.01 highly significant

Table (2) Comparison between Group A (received remdesivir plus Standard care treatment) and Group B (standard care treatment only) as regards medical history:

		Total number (percentage)	Remdesivir (165)		No (165)		X ^{2*}	P value
			Yes (165)	No (165)	N	%		
DM	No	162 (49%)	91	54.6%	71	42.5%	4.82	0.03
	Yes	168 (50.9%)	74	45.4%	94	57.5%		
HTN	No (33%)	109 (33%)	68	40.5%	41	24.6%	9.57	0.002
	Yes (66.9%)	221 (66.9%)	97	59.5%	124	75.4%		
ISHD	No (79.3%)	262 (79.3%)	129	79.1%	133	80.8%	0.15	0.70
	Yes (20.6%)	68 (20.6%)	36	20.9%	32	19.2%		
AF	No (93%)	307 (93%)	152	92.0%	155	94.0%	0.50	0.48
	Yes (6.9%)	23 (6.9%)	13	8.0%	10	6.0%		
Lung disease	No (93.9%)	310 (93.9%)	151	91.4%	159	96.4%	3.62	0.06
	Yes (6%)	20 (6%)	14	8.6%	6	3.6%		
CLD	No (90.3%)	298 (90.3%)	156	94.5%	142	86.2%	6.41	0.01
	Yes (9.6%)	32 (9.6%)	9	5.5%	23	13.8%		
CKD	No (84.2%)	278 (84.2%)	148	89.6%	130	79.0%	6.89	0.01
	Yes (15.7%)	52 (15.7%)	17	10.4%	35	21.0%		
HF	No (86.9%)	287 (86.9%)	146	88.3%	141	85.6%	0.54	0.46
	Yes (13%)	43 (13%)	19	11.7%	24	14.4%		
Stroke	No (95.4%)	315 (95.4%)	159	96.3%	156	94.6%	0.36	0.46
	Yes (4.5%)	15 (4.5%)	6	3.7%	9	5.4%		

*Chi square test. P-value > 0.05: non-significant, P-value <0.05: significant, P-value<0.01 highly significant

Table 3: Comparison between Group A (received remdesivir plus Standard care treatment) and Group B (standard care treatment only) as regard Complications:

		Total number (percentage)	Remdesivir				X ^{2*}	P value
			Yes (165)		No (165)			
			N	%	N	%		
ARDS	No	266 (80.6%)	147	89.0%	119	72.5%	14.37	<0.001
	Yes	64 (19.4%)	18	11.0%	46	27.5%		
Stroke	No	300 (90.9%)	161	97.5%	139	84.4%	17.17	<0.001
	Yes	30 (9.1%)	4	2.5%	26	15.6%		
MI	No	328 (99.3%)	164	99.4%	164	99.4%	0.00 FE	1.00
	Yes	2 (0.7%)	1	0.6%	1	0.6%		
DVT	No	325 (98.4%)	165	100.0%	160	97.0%	4.96 FE	0.03
	Yes	5 (1.6%)	0	0.0%	5	3.0%		
PE	No	325 (98.4%)	165	100.0%	160	97.0%	4.96 FE	0.03
	Yes	5 (1.6%)	0	0.0%	5	3.0%		
AKI	No	292 (88.4%)	159	96.3%	133	80.8%	19.40	<0.001
	Yes	38 (11.6%)	6	3.7%	32	19.2%		
Acute liver injury	No	318 (96.3%)	164	99.4%	154	93.4%	8.40	0.004
	Yes	12 (3.6%)	1	0.6%	11	6.6%		

*Chi square test (FE: Fisher Exact). P-value > 0.05: non-significant, P-value <0.05: significant, P-value<0.01 highly significant

Table (4) Comparison between Group A (received remdesivir plus Standard care treatment) and Group B (standard care treatment only) as regard Outcome:

		Total number (330)	Remdesivir				t*	P value
			Yes (165)		No (165)			
			Mean	SD	Mean	SD		
Length of hospital stay (days)		(mean ± SD) (13.95 ± 7.18)	14.50	6.94	13.42	7.39	1.37	0.17
		Total number (percentage)	N	%	N	%	X ^{2**}	P value
In hospital mortality	No	227 (68.7%)	137	82.8%	90	55.1%	29.55	<0.001
	Yes	103 (31.3%)	28	17.2%	75	44.9%		

*Student t test **Chi square test. P-value > 0.05: non-significant, P-value <0.05: significant, P-value<0.01 highly significant

Table (5) Logistic regression analysis for risk factors of mortality:

	B	S.E.	P value	Odds ratio	95% C.I. for odds ratio	
					Lower	Upper
Age	.080	.019	<0.001	1.083	1.044	1.124
Female sex	.178	.284	0.529	1.195	.685	2.085
Taking Remdesivir	-.734	.308	0.017	.480	.263	.877
Presence of Comorbidity	-.452	.410	0.270	.636	.285	1.421
Development of Complications	1.912	.303	<0.001	6.768	3.737	12.260
Constant	-6.059	1.279	<0.001	.002		

DISCUSSION

Remdesivir (RDV) is an adenosine analogue with broad-spectrum antiviral activity against several single-stranded RNA viruses. It was originally developed for treating patients with Ebola virus infection. After recording the potential benefits of remdesivir against SARS-CoV-2 in vitro, pre-clinical, and human cell line studies, its efficacy was evaluated in patients with COVID-19. On 1 May 2020, remdesivir received the Emergency Use Authorization (EUA) status based on a preliminary report from an interim analysis of an ongoing double-blind randomized controlled trial by the United States Food Drug Administration (US FDA).¹¹

The main aim of this study was to evaluate the clinical outcome of using Remdesivir in elderly patients with severe and critical COVID-19 infection who have received standard of care treatment and Remdesivir in comparison to similar patients who have received standard of care treatment only.

As regard sociodemographic data; there is no significant difference statistically regarding age and sex between the two groups. The mean age of the studied group was 67.60 ± 7.63 years. Most of them were males.

The present study showed that as regard medical history; there is higher percentage of cases who had HTN, DM, CKD, CLD in those who didn't receive remdesivir and the difference is significant statistically while in study of Terkes et al 2022¹², they reported that the most frequent coexistent disease in patients received remdesivir was hypertension (80; 58.4%), followed by diabetes mellitus (44; 32.1%) and oncological disorders (14; 10.2%), this may be attributed to the fact that our study population is elderly patients > 60 years with multiple comorbidities as DM, HTN and CKD and these disease lead to decreased creatinine clearance so be excluded from receiving remdesivir also our study population have atypical and may be delayed presentation of the disease excluding them from receiving remdesivir if presented after 12 days of symptoms while in Terkes study the study population was more wide for adult patients > 18 years old.

The current study showed that the percentage of acute respiratory distress syndrome (ARDS) was significantly lower in cases who receive remdesivir. in Beigel et al⁸ 2020 it was showed that patients in the remdesivir group experienced a lower proportion of major adverse events related to respiratory failure, as well as a lower incidence of new oxygen usage among patients who were not using oxygen at enrolment and a lower proportion of patients requiring higher levels of respiratory support throughout the study, suggests that receiving remdesivir may avoided the progression to more severe respiratory disease. Remdesivir therapy was linked to a reduction in the number of days of subsequent oxygen use for patients receiving oxygen at enrollment as well as a reduction in the length of later mechanical ventilation.

The current study also showed that cases who received remdesivir have their mean survival time more than those who didn't receive it with significant difference statistically, also older age, not taking remdesivir and development of complications are independent risk factors for mortality.

Our results showed that in hospital mortality was less in cases who received remdesivir with significant difference statistically. this was supported by study of Elsawah et al (2020)¹³, a study that analyzed 5 studies (4 clinical trials and 1observational study) , reported that Remdesivir treatment for ten days was associated with a 36% reduction in 14-day mortality among moderate and severe Covid-19 patients pooled from three clinical trials (RR = 0.64, 95% CI = 0.45-0.92), and after removing the study of moderate cases pooled from two trials, it was associated with the same reduction among severe case

Also, our result agreed with Mariko et al (2022)¹⁴ study which showed that Compared to the control group, remdesivir usage (interval ≤ 9 days) was associated with a lower risk of in-hospital mortality (HR: 0.10; 95% CI: 0.025-0.428 , P<0.001). On the other hand, the association between remdesivir use (interval 10+ days) and lowering in-hospital mortality was insignificant (HR: 0.42; 95% CI: 0.117-1.524)

Similarly, in the study of Marx et al (2022)¹⁵, a total of 839 patients were fully evaluated, 68% of whom received specific COVID-19 drug therapy. Remdesivir, corticosteroids, and monoclonal antibodies were utilized by 31.3%, 61.7%, and 2.3% of the patients, respectively. While dexamethasone administration predominated during the second pandemic wave, remdesivir and corticosteroids were most frequently used in combination therapy during the third wave. Combination therapy was not linked to a faster rate of clinical improvement, according to Cox regression analysis (median: 13 days in both matched groups, HR 0.97 [95% CI 0.77-1.21], P = 0.762). In contrast, in the low-care setting, the corticosteroid-remdesivir group saw significantly lower 28-day mortality (14.8% versus 22.2% in the corticosteroid group, HR 0.60 [95% CI 0.39-0.95], P = 0.03). A subgroup analysis of individuals receiving remdesivir monotherapy (n = 44) in comparison to standard of care further supported this impact.

In Aboelsaad et al(2022)¹⁶ as they reported that death, MV, and transfer to a higher level were the primary composite outcomes in 17.7% of the RDV group and 22% of the non-RDV group, the effect of remdesivir was statistically insignificant (p-value 0.289), even after stratification into moderate and severe cases (p = 0.684 and 0.291, respectively). However, they performed a series of univariate and multivariate Cox proportional hazard regression models for each outcome constituting their composite outcome separately (mortality, mechanical ventilation, or transfer to a higher level) to include the time factor in the analysis. The use of RDV was associated with an insignificant reduction in the MV and escalation of care, and an insignificant increase in mortality. In Aboelsaad et al , sample size for remdesivir group and non-remdesivir group was not equal (175 in RDV group and 334 in non RDV group) so cases are less in RDV group and that may made affect comparison for its effect , also they didn't mention the onset of starting remedisivir related to symptoms , that may affect the outcome in our study there was significant decrease in mortality in cases who received remdesivir compared to who didn't receive it as cases in

our study received remdesivir in an appropriate time (within 12 days of onset of symptoms), also our population is different and by regular follow up avoidance of complications sometimes happened , also the comparison was of matched group regarding age and sex, and they were equal in patients numbers.

Another study Trial Consortium, (2020)¹⁷ showed that remdesivir did not statistically improve mortality rates compared to placebo or standard care only, the onset of starting remdesivir related to symptoms was not considered, also in this study cases who received remdesivir had more comorbidities than control , number of smokers in remdesivir group was more which may worsen condition despite of drugs given , also numbers of cases already ventilated at initiation of treatment was more in remdesivir group and all these factors may contribute to decreased effect of remdesivir on mortality

Our study showed that Length of hospital stay in cases who received remdesivir was more than cases who didn't receive it with no significant difference statistically and the Percentage of cases discharged on oxygen is less in cases who didn't receive remdesivir, this could be due to that the percentage of mortality was higher among cases who did not receive remdesivir than cases who received it our results agree with Beigel et al (2020)⁸ Remdesivir was more effective than a placebo throughout a 10-day duration

in treating Covid-19-positive hospitalised patients, Remdesivir-treated patients recovered more quickly than placebo-treated patients, with a 31% shorter recovery time compared to placebo (median recovery time, 10 days vs. 15 days; rate ratio for recovery, 1.29 [95% CI, 1.12 to 1.49] P<0.001)

According to Hsu et al 2020¹⁸ Remdesivir treated patients had a 33% (95% CI 28– 38%) increased odds of discharge than the control group and had a shorter hospital stay, also the severity of COVID-19 was directly associated with a longer recovery time. The shortest recovery time was noted were within 48 h of administration of Remdesivir, the clinical condition of the patients improved remarkably.

CONCLUSION

Our data revealed that treatment with RDV within 12 days of symptoms influenced elderly patient outcomes over standard care treatment, including ARDS and the need for MV, and in hospital mortality.

No Conflict of Interest

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