Original Article

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Remdesivir versus Standard of Care in Moderate to Severe COVID-19 Patients: A Retrospective Study

Internal Medicine Section

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ABSTRACT

Introduction: In December 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel coronavirus, was first identified as the cause of a respiratory illness designated Coronavirus Disease 2019 (COVID-19). Since then, several anti-viral drugs have been evaluated for the treatment of COVID-19, but none have shown any efficacy. The only drug which showed some efficacy was Remdesivir (RDV).

Aim: To assess the effect and efficacy of RDV and to compare the outcome of patients who are receiving RDV and those receiving standard treatment protocol without RDV.

Materials and Methods: A retrospective study was conducted. The data was collected from the case sheets of the case files of patients presenting to the Department of General Medicine Triage who were admitted from the month of July 2020 to December 2020 and analysis was done in January 2021. The method of sampling employed was a non-probability sequential sampling method.

Results: Age and sex distributions were comparable in both the groups. The percentage of the patients who expired was 10% and 9% (n=10 and 9, respectively) in Non-RDV and RDV groups respectively, this was statistically insignificant (p-value=0.809). However, the duration of hospital stay in those who received RDV was 10 (9-12) days while those receiving standard of care without RDV was 12 (10-15) days (p-value=0.0018) which was statistically significant. Also, after a comparison between the two groups it was evident that there was a significant difference in inflammatory markers D-dimer and Lactate Dehydrogenase (LDH) with p-value=0.001 and 0.029, respectively.

Conclusion: Study concludes that there was no significant difference in outcome of patients who received RDV. However, the duration of hospital stay was found to be decreased in patients receiving RDV and also there was a significant improvement in inflammatory markers like LDH and D-dimer.

Keywords: D-dimer, Lactate dehydrogenase, Neutrophil-lymphocyte ratio, Total leucocyte count

INTRODUCTION

A major global public health crisis, COVID-19, has claimed more than 2.2 million lives by December 2020 [1]. Thus, considerable efforts are underway to find effective treatments involving multiple possible mechanisms. An anti-viral drug, RDV that inhibits viral Ribonucleic Acid (RNA) dependent RNA polymerase [2], originally developed against Ebola virus, was recently granted emergency use authorisation by the US Food and Drug Administration. RDV has in-vitro activity against SARS-CoV-2 [3,4] and early clinical data suggest promise as a treatment for COVID-19 [5-7]. Preliminary reported findings from the randomised National Institute of Allergy and Infectious Diseases (NIAID).

Adaptive COVID-19 treatment trial indicated benefits of a 10-day course of RDV versus placebo, including significantly faster (32%) recovery time and numerically lower mortality [7]. Additionally, an open-label, randomised clinical trial (GS-US-540–5773) comparing two RDV courses demonstrated that outcomes of 5-day and 10-day regimens of RDV were not significantly different and had acceptable safety [6]. Although, a randomised study in China failed to demonstrate statistically significant clinical benefit of RDV [8], the study was underpowered because of lack of enrolment and early study closure due to local disease control [9]. Thus, in this study authors compared the mortality and hospital stay in patients of COVID-19 receiving RDV and those receiving standard treatment protocols without RDV.

MATERIALS AND METHODS

The present study was a retrospective study conducted in ESIC MC and PGIMSR Model Hospital, Bengaluru, Karnataka, India. Ethical clearance for the study was obtained from the Institutional Ethics Committee (reference no: 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol.IV).

Sample size estimation: Based on previous study by World Health Organisation (WHO), it was found that the time to recovery was higher among the patients who had received RDV as compared to those who received the placebo [10]. In the present study, the sample size was estimated considering a power of 80%, alpha error of 5%, Standard Deviation (SD) of 1.5 and 3 (RDV and Non-RDV group) and mean difference of 1, which was estimated to be 89 per group. As median values were considered for sample size estimation, additional 10% was added to the sample size considering skewed distribution and final sample size considered was 100 in each group [11].

Data was collected from a total of 200 patients presenting to the Department of General Medicine Triage and COVID Ward/Intensive Care Unit (ICU) at ESIC MC and PGIMSR Model Hospital Bengaluru during the period of July 2020 to December 2020 and analysis was done in January 2021, fulfilling the inclusion criteria and exclusion criteria. Patients were divided into two groups, one who received RDV and the other who did not.

Inclusion criteria: Adult patients (18 years and above) with either Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or rapid antigen test positive for COVID-19 (moderate to severe).

{COVID-19: Moderate-Oxygen Saturation (SpO_2) 90-94% at room air or Respiratory Rate (RR)=24-30 cycles per minute (cpm), Severe-SpO_2 <90% at room air or RR ≥30 cpm}

Exclusion criteria: COVID-19, mild cases i.e., SpO_2 >94% or RR <24 cpm [12].

Data was collected from case files of patients admitted in COVID ward and ICU. History, Laboratory investigations {Total Leucocyte Count (TLC), Neutrophil:Lymphcyte (N:L), D-dimer, Ferritin, C-Reactive Protein (CRP) and LDH} and radiological investigations were collected. The patients in both the groups were monitored and the outcome was measured either as improved (clinical improvement, decreasing trend of inflammatory markers and discharge) or deteriorated (clinically worsening, increasing trend of inflammatory markers and death of the patient).

The patients were discharged according to the discharge policy of the Government of Karnataka after 10 days of onset of symptoms when the following criteria were met:

1) No fever/symptoms for the last three consecutive days before discharge (without antipyretics).
2) Maintains oxygen saturation above 95% for the last four consecutive days (without oxygen support).
3) Resolution of clinical signs/symptoms (based on the report of investigations).
4) Resolution of breathlessness.
5) Repeat inflammatory markers (Serum Ferritin, LDH, D-dimer, CRP) at the time of discharge should be in normal range/ decreasing trend.
6) One RT-PCR/Cartridge Based Nucleic Acid Amplification Test (CBNAAT)/Truenat test shall be done after three days after complete clinical recovery and the patient has to be discharged if the report is negative. If the report is positive, the swab test shall be repeated after 72 hours [13].

STATISTICAL ANALYSIS

Data were entered into Microsoft excel data sheet and was analysed using Statistical Package for the Social Sciences (SPSS) version 18.0 (Chicago SPSS, Inc). Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as test of significance for categorical data. The continuous data was checked for normality assumption using Kolmogrov-Smirnoff test. The non-parametric test namely Willcoxon signed rank test was used to compare the before and after changes in the Pulse Rate (PR), RR, TLC etc., which was followed by a Mann-Whitney U test for group differences. The p-value <0.05 was considered as statistically significant.

RESULTS

Age and gender distribution: Age of the patients in Non-RDV group ranged from 22 to 82 years with an average of 55.6 (±14.2). While RDV group ranged from 17 to 90 years, with a mean age of 55 (±14.36) as shown in [Table/Fig-1]. On comparison the age distribution was similar in both groups with a p-value of 0.260 and hence statistically not significant. Therefore, age distribution was comparable in both the groups.

Age group (years)	Group		Total
	Non-RDV N (%)	RDV N (%)	
≤30	5 (5%)	5 (5%)	10
31-40	10 (10%)	8 (8%)	18
41-50	26 (26%)	22 (22%)	48
51-60	23 (23%)	32 (32%)	55
61-70	17 (17%)	22 (22%)	39
71-80	16 (16%)	6 (6%)	22
Above 81	3 (3%)	5 (5%)	8
Total	100 (100%)	100 (100%)	200

[Table/Fig-1]: Age distribution.
The difference was statistically insignificant using Chi-square test
p-value: 0.260

As outlined in [Table/Fig-2], the percentage of male in Non-RDV group was 67% as compared to 66% in RDV group with a p-value of 0.881 which was again statistically insignificant. Therefore, gender distribution was similar in both the groups.

Gender	Group		Total
	Non-RDV N (%)	RDV N (%)	
Female	33 (33%)	34 (34%)	67
Male	67 (67%)	66 (66%)	133
Total	100 (100%)	100 (100%)	200

[Table/Fig-2]: Gender distribution.
The difference was statistically insignificant using Chi-square test
p-value: 0.881

Co-morbidities (Hypertension, Diabetes Mellitus, Ischaemic Heart Disease, Thyroid disorders, Chronic Obstructive Pulmonary Disease):

In [Table/Fig-3], it is seen that the percentage distribution of co-morbidities was similar in both groups i.e., 70% in Non-RDV vs. 66% RDV with a p-value of 0.544 and this was statistically insignificant.

Co-morbidities	Group		Total
	Non-RDV N (%)	RDV N (%)	
No	30 (30%)	34 (34%)	64
Yes	70 (70%)	66 (66%)	136
Total	100 (100%)	100 (100%)	200

[Table/Fig-3]: Comparing co-morbidities between the two groups.
The difference was statistically insignificant using Chi-square test
p-value: 0.544

Patient's condition: Both groups, Non-RDV and RDV, when compared in terms of improvement in patient condition (both with and without co-morbidities as shown in [Table/Fig-4-6], respectively) had similar results and was statistically not significant.

Patient's condition	Group		Total
	Non-RDV N (%)	RDV N (%)	
Deteriorated	10 (10%)	10 (10%)	20
Improved	90 (90%)	90 (90%)	180
Total	100 (100%)	100 (100%)	200

[Table/Fig-4]: Comparing patient's condition in both the groups.
The difference was statistically not significant using Chi-square test.
p-value: 1.00

With co-morbidities (n=136)	Group		Total
	Non-RDV N (%)	RDV N (%)	
Deteriorated	5 (7%)	6 (9.01%)	11
Improved	66 (93%)	60 (90.9%)	125
Total	71	66	136

[Table/Fig-5]: Patient's condition in both groups, with co-morbidities.
Chi-square test p-value=0.659; not significant

Without co-morbidities (n=64)	Group		Total
	Non-RDV N (%)	RDV N (%)	
Deteriorated	3 (10%)	6 (17.6%)	9
Improved	27 (90%)	28 (82.4%)	55
Total	30	34	64

[Table/Fig-6]: Patient's condition in both groups, without co-morbidities.
Chi-square test, p-value=0.77; not significant

Patient's outcome: The percentage of the patients who expired were 10% and 9% in Non-RDV and RDV groups respectively. While the percentage of the patients who were discharged was 90% and 91% in Non-RDV and RDV groups respectively (as shown in [Table/Fig-7]). It was statistically insignificant as the p-value is 0.809.

Outcome	Group		Total
	Non-RDV N (%)	RDV N (%)	
Discharged	90 (90%)	91 (91%)	181
Expired	10 (10%)	9 (9%)	19
Total	100 (100%)	100 (100%)	200

[Table/Fig-7]: Comparing outcome in both the groups.
The difference was statistically insignificant using Chi-square test
p-value: 0.809

Duration of hospital stay: The duration of hospital stay (in days as shown in [Table/Fig-8]) for the patients who received RDV was 10 (9-12) and those receiving the standard of care was 12 (10-15) with a p-value of 0.0018 which was statistically significant using the Mann-Whiney U test.

Group	Duration of hospital stay in days median (IQR)	p-value
Non-RDV	12 (10-15)	0.0018
RDV	10 (9-12)	

[Table/Fig-8]: Comparing duration of hospital stay in both the groups.
The difference was statistically significant using Mann-Whiney U test

Comparing inflammatory markers in both the RDV and non-RDV groups: Various parameters have been compared from Day of admission (D1) to Day of Discharge (DD) in both groups and it was observed that in Non-RDV group there was significant difference in PR, RR, LDH and D-Dimer ($p<0.05$). In the RDV group, there was significant difference in PR, RR, TLC, Neutrophil count, Lymphocyte count ($p<0.05$). After a comparison between the two groups, it was evident that there was a significant difference in RR in Non-RDV group with a p-value of <0.001 and also in the RDV group, p-value 0.004. However, the p-value=0.085 in between the groups (not significant). There was significant difference in PR from D1 to DD for Non-RDV group (p=0.012) with mean difference of 2.79 and in the RDV group p=0.004 with mean difference of 7.09, the p-value being 0.463 in between the groups (not significant).

There was a decrease in NLR (1.49) among the RDV group and an increase of NLR (-3.37) in the Non-RDV group with p-value of 0.535 in between the groups. Also, the LDH among the Non-RDV showed a drop of 92.58 units with a p-value of <0.001 while the RDV group showed a drop of 69.62 with p-value of 0.796 and the p-value was 0.001 in between the two groups. The D-Dimer levels were also significantly decreased in both the RDV and Non-RDV groups with a p-value of 0.029 in between the groups [Table/Fig-9].

DISCUSSION

Remdesivir (RDV) (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with in-vitro inhibitory activity against SARS-CoV-1 and the Middle East Respiratory Syndrome (MERS-CoV), was identified early as a promising therapeutic candidate for COVID-19 because of its ability to inhibit SARS-CoV-2 in-vitro. On 15th October 2020, the Solidarity Trial published its interim results and found that the treatments using Hydroxychloroquine (HCQ), RDV, iopinavir/ritonavir, interferon and had negligible effect on overall duration of hospital stay and mortality in COVID-19 patients [10].

On November 20, 2020, WHO issued a conditional recommendation against the use of RDV as there was no evidence that the survival outcomes were improved by RDV [14]. In the study, conducted by National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial, the results showed that RDV was superior to placebo in shortening the time to recovery in patients of COVID-19 infection [7].

A study conducted by Olender SA et al., concluded that by Day 14 RDV was associated with significantly greater recovery and 62% reduced odds of death versus standard of care treatment in severe COVID-19 patients [15]. Spinner CD et al., concluded that among patients with moderate COVID-19, one group was randomised to a 10-day course of RDV and the other to a 5-day course of RDV, when compared, the group with 5-day course of RDV had a statistically significant difference in clinical status but the difference was of uncertain clinical importance [16]. In the recovery trial conducted on patients hospitalised with COVID-19, it was found that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen [17]. Kalil AC et al., studied the combination of Baricitinib with RDV and compared it with use of RDV alone and concluded that the combination was superior to RDV alone the outcome of COVID-19 patients. Also, the combination was associated with fewer serious adverse events [18].

In present study, the outcome of the treatment given to the patient was measured in terms of either deterioration of patients condition resulting in demise of the patient or improvement in the

Group	Non-RDV					p-value for pre and post difference	RDV					p-value for pre and post difference	p-value between groups
	Mean	SD	Quartiles				Mean	SD	Quartiles				
			Q1	Q2	Q3				Q1	Q2	Q3		
PR-D1	94.65	18.53	88	92	101.75	0.012*	93.50	15.78	86	90	102	0.004*	0.463
PR-DD	91.86	16.64	82	91	98		86.41	12.54	78	87	94		
RR-D1	22.64	5.60	20	22	25.25	<0.001*	22.82	12.79	14	22	24	0.004*	0.085
RR-DD	19.95	3.79	18	20	22		19.73	8.73	16	18	22		
TLC-D1	10247	10540.21	6667.5	8150	10770	0.829	8380.67	4409.93	4800	8210	11160	<0.001*	0.119
TLC-DD	10374	8414.90	6700	8700	11900		9910.71	4114.69	7312.5	10000	12050		
L-D1	14.41	13.27	5.25	10.5	18	0.464	15.76	10.24	7	13	22	<0.001*	0.002*
L-DD	13.10	9.35	7	11	16.75		9.33	5.96	5	8	13.5		
NLR-D1	9.55	7.52	3.9	8.2	12	0.381	12.96	10.38	3	9.15	22.125	0.673	0.535
NLR-DD	12.92	13.38	4	6.66	22.5		11.47	8.66	7	10	11.25		
LDH-D1	414.74	341.17	248	366	452	<0.001*	511.93	256.37	334.5	468.5	682.5	0.796	0.001*
LDH-DD	322.16	209.36	213	282	358		442.31	274.39	321	403	604.75		
D-DIMER D1	1.20	1.91	0.3	0.5	1.06	<0.001*	1.56	1.79	0.276	0.7	2.465	0.971	0.029*
D-DIMER DD	0.65	1.25	0.19	0.3	0.7		1.48	2.15	0.3	0.5	1.705		
N-D1	77.68	15.39	71	82	89	0.732	76.57	13.06	70	79	88	<0.001*	0.001*
N-DD	79.31	11.05	73	81	88		84.87	7.37	81	85	91		

[Table/Fig-9]: Inflammatory markers comparison in the Non-RDV and RDV groups respectively.
*p-values obtained, indicates statistical significance; within group comparisons done by Wilcoxons signed rank test and between group comparisons using Mann-Whitney U test
D1: Day of admission; DD: Day of discharge; RR: Respiratory rate; TLC: Total leucocyte count; L: Lymphocyte; NLR: Neutrophil-lymphocyte ratio; LDH: Lactate dehydrogenase, N: Neutrophils

patients health resulting in discharge of the patient. The percentage of the patients who expired was 10% and 9% in Non-RDV and RDV groups, respectively. While the percentage of the patients who were discharged was 90% and 91% in Non-RDV and RDV groups respectively. Also, the duration of hospital stay in patients who received RDV was shorter compared to those who received standard of care without RDV i.e., 10 and 12 days respectively.

In the RDV group, there was significant difference in PR, RR, Neutrophil count, Lymphocyte count, TLC. After a comparison between the two groups it was evident that there was a significant difference in LDH and D-Dimer levels.

Comparing different studies made regarding the use of RDV for COVID-19, Food and Drug Administration (FDA) issued an Emergency Use Authorisation on May 1, 2020 (modified on August 28, 2020) to permit the use of RDV for treatment of COVID-19 patients. However, despite the use of RDV, the mortality rate of patients was high. It is thus clear antiviral drug alone is not likely to be sufficient for treatment of COVID-19 in all patients. Current strategies are evaluating other drugs like the Janus Kinase (JAK) inhibitor baricitinib in ACTT-2 [18], and interferon beta-1a in Adaptive COVID-19 Treatment Trial (ACTT)-3 [19]. Anyway, a variety of therapeutic approaches including novel antivirals, immuno-modulators and combination approaches have to be studied in detail to continue to improve outcomes in patients with COVID-19 and to successfully help tackle this pandemic.

Limitation(s)

The study is however not without limitations. First limitation is that the sample size was small and it being a single centre study and the other one is that it was a retrospective study.

CONCLUSION(S)

Present study concludes that there was no significant difference in outcome of patients who had received RDV. However, the duration of hospital stay was found to be decreased in patients receiving RDV and also, there is a significant improvement in inflammatory markers (LDH and D-Dimer).

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