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Coronavirus Pandemic

Evaluation of Remdesivir to the outcomes of hospitalized patients with COVID-19 infection in a tertiary-care hospital in southern India

Hanna Alexander[1 #], Karthik Gunasekaran[2 #], Jisha Sara John[1], Naveena Gracelin Princy Zacchaeus[1], Prasanna Samuel[3], Sudha Jasmine[2], Devasahayam Jesudas Christopher[4], Kishore Pichamuthu[5], Priscilla Rupali[1]

[1] Department of Infectious Diseases, Christian Medical College, Vellore, Tamilnadu, India
[2] Department of Medicine, Christian Medical College, Vellore, Tamilnadu, India
[3] Department of Biostatistics, Christian Medical College, Vellore,Tamilnadu, India
[4] Department of Pulmonary Medicine, Christian Medical College,Vellore, Tamilnadu, India
[5] Department of Critical care Medicine, Christian Medical College, Vellore, Tamilnadu, India

# Authors contributed equally to this work

Abstract

Introduction: Remdesivir was the only antiviral used in the treatment of COVID-19 in the first wave of the COVID-19 pandemic, following the adaptive COVID-19 treatment trial-1 interim analysis report. However, its use in moderate to critical hospitalized COVID-19 patients continues to be controversial.

Methodology: In a cohort of 1,531 moderate to critical COVID-19 patients, we retrospectively performed a nested case-control study where 515 patients on Remdesivir were compared to 411 patients with no Remdesivir. Cases and controls were matched for age, sex and severity. The primary outcome was in-hospital mortality and secondary outcomes were duration of hospital stay, need for intensive care unit (ICU), progression to oxygen therapy, progression to non-invasive ventilation, progression to mechanical ventilation, and duration of ventilation.

Results: Mean age of the cohort was 57.05 + 13.5 years. 75.92% were males. Overall, in-hospital mortality was 22.46% (n = 208). There was no statistically significant difference in all-cause mortality among cases and controls (20.78% vs. 24.57%, $p = 0.17$). Progression to non-invasive ventilation was lower in the Remdesivir group (13.6% vs 23.7%, $p < 0.001$), however progression to mechanical ventilation was higher in the Remdesivir group (11.3% vs 2.7%, p value < 0.001*). In a subgroup analysis of critically ill patients, the use of Remdesivir lowered mortality (OR 0.32 95% CI: 0.13 - 0.75).

Conclusions: Remdesivir did not decrease the in-hospital mortality in moderate to severe COVID-19 but decreased progression to non-invasive ventilation. Its mortality benefit in critically ill patients needs further evaluation. Remdesivir may be useful if given early in the treatment of patients with moderate COVID-19.

Key words: Nested case-control study; Remdesivir; COVID-19.

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Introduction

As of 17th March 2022, the COVID-19 pandemic has affected more than 46 million people globally and contributed to more than 6 million deaths [1]. India has seen 4.2 million cases with more than 0.5 million deaths [2]. This new disease spawned many new clinical treatment trials, and non-peer-reviewed preprints of clinical trials, leading to confusion and anxiety regarding the treatment options. In addition, many irrational treatments were adopted in different parts of the world in national guidelines [3]. Remdesivir (RDV), a nucleotide prodrug, an inhibitor of viral RNA polymerase, the only antiviral drug approved in the early phase of the pandemic based on reduction in time to clinical recovery, clinical improvement, and faster symptom resolution in mild to severe COVID-19[4,7]. Both the United States Food and Drug Administration (FDA) and Drugs Controller General of India (DCGI) had also given emergency use authorization for use of many experimental drug regimens in the face of mounting mortality. Evidence revealed conflicting results with some trials revealing benefits [4] and others not [5]. With drugs like Chloroquine, Ivermectin, and Favipiravir falling out of favor, many hospitals over the world included RDV in the treatment protocols of COVID-19 despite its unimpressive results, in

hospitalized patients with moderate to critical COVID-19 illness. Subsequent trials like WHO SOLIDARITY [5] and DISCOVERY [6] failed to show any mortality benefit, leading to recommendations against the use of RDV. However, many observational studies showed some evidence of efficacy, i.e., early fever defervescence, early clinical recovery, and weaning off oxygen supports with decreased need for ventilation and intensive care[5–7]. Our hospital adopted RDV in July 2020 for the treatment of mild to moderate COVID-19 infection after the initial results from the Adaptive COVID-19 treatment trial-1 (ACTT-1) interim analysis report[4], based on a shorter time to recovery and possible prevention of progression to severe disease. However, this adoption was not uniform across many clinical units due to the lack of convincing evidence of efficacy. Hence the use of RDV was audited and monitored by the Hospital Infection Control Committee during the COVID-19 pandemic in order to inform our treatment guidelines. This nested case-control study in a cohort of hospitalized COVID-19 patients aimed to evaluate the benefit of RDV in the treatment of moderate to severe COVID-19.

Methodology

This retrospective cohort study was carried out to evaluate if RDV improved outcomes in patients infected with COVID-19 in a 2800-bed tertiary-care hospital in southern India that cares for up to 8,800 outpatients daily and 500,000 inpatients on an annual basis. The institutional review board of Christian Medical College, Vellore approved this analysis of RDV in the treatment of hospitalized COVID-19 infection (IRB no: 13600, dated 25.11.20). The study period was 5 months, between June and October 2020.

Study samples and data collection

Patients were included if they were ≥ 18 years of age and had COVID-19 infection as confirmed by an RTPCR (RealStar® SARS-CoV-2 RT-PCR Kit RUO) from a nasopharyngeal swab. The severity of the disease as defined by the World Health Organization's severity criteria. Moderate covid defined as with Pneumonia - clinical or radiological, or hypoxia and resp rate ≤ 30/minutes, SpO_2 ≥ 90% on room air & no respiratory distress. Severe COVID-19 was defined as pneumonia and ≥ 1 of: resp rate > 30/minutes; severe respiratory distress; or SpO_2 < 90% on room air.

Between June 2020 and October 2020, a total of 6,374 patients were admitted in Christian Medical College, Vellore, with confirmed COVID-19 of which 4,843 patients were asymptomatic and 1,531 were symptomatic. Among 1,531 patients, 926 who were moderate to critically ill and had adequate documentation, were enrolled in the study. Those who received intravenous (IV) RDV loading dose 200mg single dose on day 1 followed by maintenance dose 100mg once daily for five days plus standard of care were considered as cases and those who received standard of care without RDV were controls. RDV was administered to patients in accordance with the hospital guidelines for COVID-19; 200mg on day 1 followed by 100mg once daily for subsequent 4 days. The patients received RDV on the day of admission or on the next day. Baseline data includes age, gender, comorbidities, signs and symptoms related to COVID-19 like fever, breathlessness and cough, laboratory parameters like WBC, creatinine, ferritin, neutrophils, lymphocytes, etc D-Dimer, baseline oxygen saturation and oxygen requirements were recorded until death or discharge. Clinical worsening was determined by admission to intensive care unit, progression to supplemental oxygen, noninvasive ventilation (NIV), and mechanical ventilation (MV) while on treatment. The incidence of COVID-19 related complications like secondary infections, pneumothorax, myocarditis and acute respiratory distress syndrome (ARDS) were also studied. Data were collected from electronic medical records and entered into data entry software for analysis.

Outcome measures

This study aims to evaluate the safety and efficacy of RDV in COVID-19. The primary outcome was in-hospital mortality. Secondary outcomes were duration of hospital stay, need for intensive care, progression to oxygen, non-invasive or invasive ventilation and total duration of ventilation.

Statistical approach

Quantitative variables were summarized using descriptive statistics. Baseline data for both the groups were represented in frequencies and percentages. All data was entered into an excel spreadsheet for analysis. Categorical and continuous variables were compared for outcome using the Fisher's exact test and student t-test respectively. Subgroup analysis was performed for the primary outcome, all-cause-mortality, in patients admitted to intensive care unit vs. those who were not. A p value of < 0.001 was considered statistically significant. Statistical analysis was done using Statistical Package for Social Sciences for Windows (SPSS Inc., version 21.0. Chicago).

Results

Patient Demographics

A total of 926 consecutive patients with COVID-19 were included in this analysis, among which 515 patients were cases and 411 controls. The cohort's mean age was 57.05 + 13.5 years, with a male preponderance (75.92%). The baseline parameters with regard to comorbidities, vitals, laboratory parameters, and oxygen requirements were similar in both groups (Table 1).

Clinical Characteristics

Overall, 710 (77%) patients included in the analysis had at least one co-morbidity. Diabetes (58%) followed by hypertension (47%), ischemic heart disease (IHD) (8%), Chronic Kidney Disease (CKD) (7%) and Chronic Obstructive Pulmonary Disease (COPD) (6%) were common with 23% having more than one co-morbidity. At admission 86% of the patients were on supplemental oxygen, 13% were intubated and 0.43% did not require any form of oxygen (Figure 1). Most patients reported COVID-19-related signs and symptoms like fever (71%), cough (61%), and breathlessness (65%). The majority of the patients received steroids (96%) during the course of their hospital stay. ICU admission was required in 140/411 (34%) patients in the control group and 235/515 (45.6%) patients in the RDV group. Median (IQR)

Table 1. Baseline characteristics.

Parameters	Total (N = 926)	Remdesivir		*p*-value
		No (n = 411)	Yes (n = 515)	
Age Mean ± SD	57.05 (13.54)	56.84 (14.19)	57.22 (13.02)	0.676
Gender				
Female	223 (24.08)	109 (26.52)	114 (22.14)	
Male	703 (75.92)	302 (73.48)	401 (77.86)	0.121
Comorbidities	710 (76.67)	316 (76.89)	394 (76.50)	0.892
Hypertension	432 (46.65)	201 (48.91)	231 (44.85)	0.22
Diabetes	538 (58.10)	247 (60.10)	291 (56.50)	0.271
COPD/Bronchial Asthma	60 (6.49)	24 (5.84)	36 (7.02)	0.47
Chronic kidney disease	61 (6.59)	39 (9.49)	22 (4.27)	**0.001**
Ischemic heart disease	76 (8.23)	43 (10.46)	33 (6.43)	**0.027**
Chronic liver disease	8 (0.86)	7 (1.70)	1 (0.19)	**0.016**
Human Immuno deficiency Virus (HIV/Tuberculosis)	11 (1.19)	7 (1.70)	4 (0.78)	0.162
Others	280 (30.24)	93 (22.63)	187 (36.31)	**< 0.0001**
Vitals				
Temperature Mean (SD)	98.85 (1.49)	98.92 (1.56)	98.80 (1.43)	0.214
SPO_2 Mean ± SD	89.38 (11.83)	89.27 (12.49)	89.46 (11.36)	0.805
Blood Pressure Systolic, Mean ± SD	124.54 (20.66)	125.14 (22.28)	124.06 (19.29)	0.43
Blood Pressure Diastolic Mean ± SD	76.70 (12.39)	75.98 (11.70)	77.28 (12.90)	0.114
Pulse Rate Mean ± SD	98.30 (17.34)	99.92 (18.72)	97.02 (16.07)	**0.011**
Respiratory Rate Mean ± SD	30.79 (10.08)	30.51 (9.13)	31.01 (10.78)	0.463
Signs and Symptoms related to COVID-19				
Fever	660 (71.27)	271 (65.94)	389 (75.53)	**0.001**
Cough	562 (60.69)	234 (56.93)	328 (63.69)	**0.037**
Breathlessness	600 (64.76)	268 (65.21)	332 (64.47)	0.815
Laboratory parameters				
Creatinine Median (IQR)	0.9 (0.73, 1.14)	0.94 (0.76, 1.2)	0.86 (0.72, 1.07)	**0.0002**
Ferritin Median (IQR)	466.9 (207.8, 851.6)	443.9 (174.3, 953)	500 (235, 792)	0.4
White Blood Cells (WBC) Median (IQR)	8800 (6400, 12200)	8800 (6300, 12600)	8700 (6400, 12000)	0.898
Neutrophils (Mean ± SD)	80 (70, 86)	78 (61, 86)	80.5 (73, 87)	**< 0.0001**
Lymphocytes Median (IQR)	11 (6, 18)	9 (4, 16)	12 (8, 18)	**< 0.0001**
D-DIMER	717 (430, 1303)	766 (448, 1503)	684 (424, 1204)	**0.034**
Oxygen Requirement at admission				
None	271 (29.3)	223(54.2)	48(9.3)	< 0.001
Low flow oxygen	536(57.8)	204(49.6)	317(61.5)	< 0.001
Non-Invasive ventilation (NIV)	147(15.8)	14(3.4)	133(25.8)	< 0.001
Invasive Mechanical Ventilation (IMV)	23(2)	1(0.2)	22(4.2)	< 0.001
Steroids	890 (96.11)	381 (92.70)	509 (98.83)	**< 0.0001**
Anticoagulation	643 (69.44)	381 (92.70)	262 (50.87)	**< 0.0001**
Day of admission to Day of Remdesivir administration, median (IQR)			1 (1,3)	
Day of Admission to Day of initiation of NIV/IMV, median (IQR)		2 (0,5)	2 (1,3)	0.905

duration from the day of admission to institution of NIV/IMV were 2 (0,5) days in the RDV and 2 (1,3) in the non-RDV group ($p = 0.905$).

Most patients received RDV (200mg loading dose on day 1 followed by 100mg) at a median duration of 1 day (IQR: 1-3) from admission to hospital and continued to receive the drug for 5 days.

Clinical outcomes

The mortality rate in the RDV vs. non-RDV group was 21% vs. 24% (p value: 0.169) and the length of stay median (IQR) of in the RDV group was similar to that in the non-RDV group 12 (9, 17) days vs. 11 (8, 15) days ($p = 0.001$). The Median (IQR) duration of ventilation requirement was 7 days (4, 13) in the RDV vs. 6 days (3, 10) in non-RDV groups. A lower number of patients progressed to oxygen in the RDV group (4%) was observed compared to the non-RDV group (31%). Similarly, progression from oxygen to NIV was lesser in the RDV group 13.6% vs 23.7% in the non-RDV group. However, the progression from NIV to mechanical ventilation, was higher in the RDV group 11.3% vs 2.7% in the non-RDV group ($p < 0.001$) (Figure 2). Similarly, COVID-19-related complications like secondary infections, pneumothorax and myocarditis were higher in the RDV group 2.92% vs. non-RDV group 0.98% ($p = 0.013$) (Table 2).

Discussion

In this nested case-control study, we evaluated the effect of RDV in improving clinical outcomes and reducing progression to severe disease in patients hospitalized with COVID-19 infection. There is conflicting evidence regarding the utility of RDV in the treatment of moderate to severe COVID-19 infection as seen in randomized controlled trials like ACTT-1[4], WHO Solidarity [5] and SIMPLE [7] and various other prospective and retrospective study data published from all around the world. Though recent data suggests that RDV when given early in outpatients has a beneficial effect in reducing the need for hospitalization and medically attended visits, [8] the utility in hospitalized patients continues to be unclear. A similar retrospective

Figure 1. Oxygen requirement at admission.

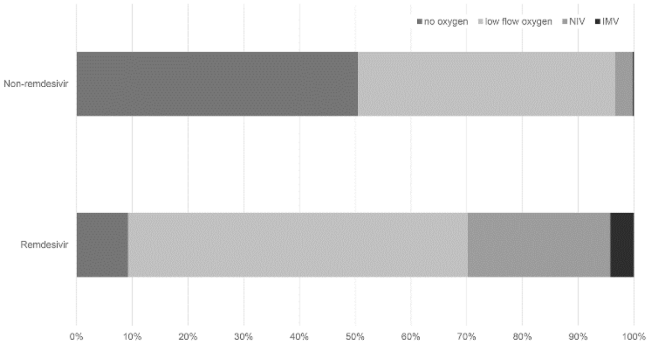

Figure 2. Progression in Oxygen requirement.

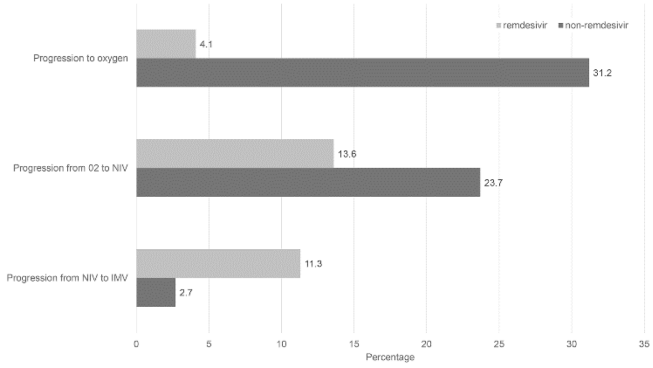

Table 2. Primary and secondary outcomes.

Parameters	Total (N = 926)	Remdesivir		*p*-value
		No (n = 411)	Yes (n = 515)	
Length of stay Median (IQR)	11 (9, 16)	11 (8, 15)	12 (9, 17)	**0.001**
Admission to Intensive care Unit (ICU)	375 (40.50)	140 (34.06)	235 (45.63)	**< 0.0001**
Progression from O_2 to Non-Invasive Ventilation	168(18.1)	98 (23.7)	70 (13.6)	< 0.001
Progression from Non-Invasive Ventilation (NIV) to Invasive Mechanical Ventilation (IMV)	69(7.4)	11 (2.7)	58 (11.3)	< 0.001
Total days of ventilation (O_2 + invasive) Median (IQR)	7 (4, 12)	6 (3, 10)	7 (4, 13)	**0.0007**
Oxygen at discharge	16 (1.73)	12 (2.92)	4 (0.98)	**0.013**
Outcome				
Mortality	208 (22.46)	101 (24.57)	107 (20.78)	0.16
Alive	718 (77.54)	310 (75.43)	408 (79.22)	0.169
Complications	66 (7.13)	9 (2.19)	57 (11.07)	**< 0.0001**
Infections	51 (5.51)	5 (1.22)	46 (8.93)	**< 0.0001**
Pneumothorax	13 (1.40)	1 (0.24)	12 (2.33)	**0.005**
Myocarditis	9 (0.97)	3 (0.73)	6 (1.17)	0.374
Acute Respiratory Distress Syndrome (ARDS)	318 (34.34)	147 (35.77)	171 (33.20)	0.415

study in the Indian subcontinent; the SORT trial also found that early initiation of RDV (within 9 days of symptom onset) corresponded to lower mortality rates when compared to those who were treated later supporting the hypothesis that antivirals are most effective when given in the earlier stages of the disease [9].

Similar to the reports from randomized controlled studies like ACTT-1 [4] and WHO solidarity [5], we observed in our study that RDV did not have any effect in reducing mortality when data were pooled across varying levels of severity from moderate to critical categories, but when the critically ill group requiring Intensive care admission 34.06 % vs. 45.63% ($p < 0.0001$) were evaluated it seemed to confer a mortality benefit (OR = 0.32; $p = 0.009$) (Table 3). The main criticism with various trials that evaluated the role of RDV in the treatment of COVID-19 infection has been that it was not administered early enough in the course of illness, which is likely the period when an antiviral like RDV would be efficacious, before the hyperinflammatory phase has set in. It has been suggested that the rapid deterioration of COVID-19 may be related to massive replication, leading to viremia and injury to multiple organs [10,11]. SARS-CoV-2 viremia and longer duration of the same have also been correlated with increasing mortality and hyperinflammation. RDV inhibits RdRp and thus exerts antiviral activity by inhibiting the replication of SARS-CoV-2, with an EC50 of 23.15 μM. [12] and has been shown to decrease viral load and improve pulmonary lesions without long-lasting damage *in vivo* when given to Rhesus macaques infected with SARS-Co-V2 for 7 days. In most of the randomized controlled trials thus far, RDV was generally found to be given later in the disease at an average of greater than 6 days [6,7,13-15], suggesting perhaps that it was probably administered too late to change the course of the disease.

We also noted in our study that similar to the ACTT-1 trial [4], the incidence of new oxygen requirement or progression from oxygen to non-invasive ventilation (NIV) was lower in the group given RDV group compared to that in the standard of care group (Figure 2). A higher number of patients progressed from NIV to IMV in the RDV group, possibly as a higher number of patients required oxygen support at baseline. RDV was administered in our cohort at a median of 1 day, however since we are a tertiary referral care hospital, it is possible that the patients sought help at a later date, at which point it is unlikely that RDV had little influence on the progression of the disease. Additionally, it was noted that in the RDV group, there was a lesser need for oxygen at discharge when compared to the non-RDV group which was clinically significant. This signaled the possibility that RDV when administered at the optimal therapeutic window i.e., early stages of the disease, when the viral load was high and only mild symptoms were present without the activation of the inflammatory cascade[16] (which usually happens in the later stage of the disease) it may have a definite benefit as has been demonstrated recently[8]. This beneficial effect was not evident in previous RCTs as the median duration from admission/symptoms to administration of RDV was 11 days in older studies like Wang *et al.* [15] and 8 days in Spinner *et al.* [14]; 6 and 9 days in Mahajan *et al.* [13] and Ader *et al.* [6], respectively. In addition, the earlier studies did not have concomitant steroid administration as part of their protocols e.g., in ACTT-1[4] steroid administration was

Table 3. Subgroup analysis for mortality stratified by ICU admission.

Parameters	Odds Ratio (OR)	*p*-value	95 % Confidence Interval	
ICU ADMISSION-YES				
Remdesivir/mortality	0.32	0.009	0.134	0.751
Do not intubate//Do not Resuscitate (DNI/DNR)	13.48	< 0.0001	3.676	49.435
Other	2.60	0.008	1.282	5.258
Non- Invasive Ventilation	15.52	0.050	1.001	240.656
Progression from O_2 to Non- Invasive Ventilation	0.06	0.039	0.004	0.861
Progression from Non-Invasive Ventilation to Mechanical Ventilation	6.68	**< 0.0001**	2.898	15.382
Total days of ventilation O_2/ Invasive Ventilation	1.07	0.013	1.014	1.128
Complications	3.73	0.017	1.262	11.017
ICU ADMISSION-NO				
Length of stay (LOS)	0.67	< 0.0001	0.587	0.760
Do not intubate / Do not Resuscitate (DNI/DNR)	94.14	< 0.0001	25.067	353.552
Chronic kidney disease	5.01	0.022	1.261	19.862
Cough	0.39	0.022	0.175	0.875
Total days of ventilation O_2/ Invasive Ventilation	1.34	< 0.0001	1.163	1.538
Nasal prongs	0.21	0.001	0.080	0.540

22%; Wang *et al.* it was 65% [15]; WHO Solidarity it was 48% [5] which could have affected the outcomes such as mortality and progression to invasive mechanical ventilation.

Considering resource-limited settings in developing countries like India, with high patient load leading to constraints with oxygen and beds, clinical endpoints like early recovery times, lesser times on ventilation and lesser progression to oxygen therapy may be meaningful clinical and research endpoints that cannot be dismissed. [17] Hence, RDV does show some promise as an antiviral, and optimal timing along with optimal administration of concomitant therapies proven to prevent progression will need further exploration.

Our study has a few limitations. Data were obtained concurrently from the hospital's electronic medical records due to the challenges with onsite data collection. We did not perform any analysis about clinical improvement as measured by WHO ordinal scale or WHO progression scale. Data were collected only at one-time point i.e., at death or discharge. However, our analysis presents findings of a large cohort of patients admitted to a tertiary care setting catering to the treatment of COVID-19.

Conclusions

To recapitulate, it is uncertain if RDV has any significant effect in patients with moderate to severe COVID-19 in terms of mortality benefit but may prevent progression of moderate to severe and severe to critical disease. It decreases in-hospital mortality of patients with a critical illness.

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Corresponding author

Prof. Priscilla Rupali, MD, DTM&H, CTH, FRCP
Department of Infectious Diseases,
SP Complex 4th Floor, Ida Scudder Road,
Vellore,Tamilnadu, India
Tel: 0416-2282804
Email: priscillarupali@yahoo.com

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