

Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study

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ABSTRACT

Background and Aims: When the world was frantically searching for a drug effective against the coronavirus disease (COVID)-19, remdesivir, a broad-spectrum anti-viral medication, became a part of the COVID treatment. We planned a study to evaluate improvement in clinical outcomes with remdesivir treatment for five days. **Methods:** Participants more than 40-years old and with moderate to severe COVID-19 but not on mechanical ventilation were randomly assigned into two groups-remdesivir group (34 cases) to receive the study drug intravenous (IV) remdesivir for five days plus the standard care (SC) and non-remdesivir group (36 cases) to receive the SC but not to receive the study drug. Follow-up was continued for 12 days after the beginning of treatment or until discharge/death. Patient's clinical status was assessed by laboratory investigations and physical examination (from day 1 to day 12 on a 4-point ordinal scale and from day 12 to 24 on a 6-point ordinal scale). Oxygen support requirements and adverse events were recorded. The data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 22.0. **Results:** High-flow oxygen support and non-invasive ventilation was required at baseline by lesser patients in the remdesivir group. In the end, both groups had similar outcomes after adjustment for baseline clinical status. There was no statistical difference in mortality between the two groups ($p = 0.749$). Patients in both groups had an equal time to recovery. There was no difference in the occurrence of adverse effects of remdesivir between the two groups. **Conclusion:** Remdesivir therapy for five days did not produce improvement in clinical outcomes in moderate to severe COVID-19 cases.

Key words: COVID-19, remdesivir, treatment outcome

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic of SARS-CoV-2 has produced a protracted medical, five days years old social, and economic crisis all over the world.^[1] The search for the 'right' drug to treat COVID-19 is not yet over. Many drug trials have taken place, but they have not provided any real-time therapeutic solutions.^[2] The search for different therapeutic strategies to combat COVID-19 is going on and is in different phases of completion.^[3] Mortality from COVID-19 is particularly high among patients with coexisting conditions, including hypertension, diabetes, and cardiovascular disease, and in those who reach the point of requiring

invasive mechanical ventilation. Safe and effective treatment options are needed to reduce the burden of COVID-19. The lungs are the organs most affected by COVID-19 because the virus accesses host cells via the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of the lungs. The virus uses a special surface glycoprotein

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called a “spike” (peplomer) to connect to ACE2 and enter the host cell. The density of ACE2 in each tissue correlates with the severity of the disease in that tissue. As the alveolar disease progresses, respiratory failure might develop and death may happen.

Remdesivir, a nucleotide prodrug of an adenosine analogue is a broad-spectrum antiviral medication administered intravenously. In 2020, during the COVID pandemic, remdesivir was approved for emergency use to treat COVID-19 in many countries. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against SARS-CoV-2.^[4] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.^[5] Given the preliminary results about remdesivir, the United States Food and Drug Administration issued Emergency Use Authorisation on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalised with suspected or laboratory-confirmed COVID-19.^[6]

There has always been a lack of consensus among societies and organisations on whether remdesivir should be used in the management of COVID-19. Its benefit in severe COVID-19 cases has been debated. Some clinical trials on remdesivir for the treatment of COVID-19 have used a 10-day course of treatment that was based on efficacy data in animal models of Middle East Respiratory Syndrome and supported by safety data in approximately 500 healthy volunteers and patients infected with Ebola virus.^[7] We hypothesised that a 5-day course of remdesivir treatment without potential adverse events and without a loss of efficacy could reduce hospital stays. Accordingly, we conducted a randomised clinical study in patients with moderate to severe COVID-19 to evaluate the clinical outcomes of treatment with remdesivir for 5 days. Our primary objective was to evaluate the improvement in clinical outcomes with remdesivir for 5 days and the secondary objectives were to assess the adverse effects that can occur with remdesivir treatment.

METHODS

Institutional Ethics Committee approval was obtained for the study. The study was conducted in a medical

college hospital in the period between June to December 2020. Written informed consent was obtained from each patient (or a close relative of the patient) participating in the study. We enrolled hospitalised patients who were between 18 and 60 years age group and had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay within the last 4 days.

In the study by Beigel *et al.*,^[8] 957 severe disease stratum patients in the remdesivir group had a shorter time to recovery (median 11 days) than placebo group patients (median 18 days). Based on this, the estimated sample size was found to be 35 in each group at 80% power and 95% confidence interval as per the study by O'Keefe *et al.*^[9] We followed consecutive sampling for recruiting the patients, that is, all eligible patients as per the inclusion and exclusion criteria were enrolled in the study. For administering intervention, random number was generated in Excel to follow simple random sampling technique. The participants were randomly assigned in a 1:1 ratio, into two groups – Remdesivir group, who received intravenous (IV) remdesivir for 5 days in addition to the standard care (SC) and SC group, who did not receive remdesivir, but received SC. All participating patients in the study had radiographic evidence of pneumonia, respiratory rate >24/min and oxygen saturation of 94% or less. Patients receiving mechanical ventilation or patients with multi organ failure were not included in the study. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels were estimated in all participants and those with levels greater than three times the upper limit of the normal range were excluded. In addition, patients were required to have a creatinine clearance above 40 ml per minute.

Both groups received same treatment protocol except for no-remdesivir in SC group. Remdesivir group patients received IV 200 mg remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent four days. Both treatment groups continued supportive therapy throughout the duration of the study. Other drugs used for COVID treatment (off-label use and in the absence of written policy) were not allowed to be administered to the patients in the study period. Drugs like corticosteroids and heparin were given as per SC protocol. Follow-up was continued for 12 days after the beginning of treatment with remdesivir or until discharge or death.

Patients were assessed by physical examination and by documentation of respiratory status, adverse

events and concomitant medications. Blood samples were obtained every alternate day for complete blood count and measurement of creatinine, glucose, total bilirubin, and liver aminotransferases. The clinical status of patients was assessed daily on a 4-point ordinal scale (1, receiving low-flow oxygen supplementation; 2, receiving non-invasive ventilation or high-flow oxygen; 3, not receiving supplemental oxygen but requiring medical care; 4, receiving invasive mechanical ventilation) from day 1 to day 12 or until discharge. The clinical status was assessed from day 12 to day 24 on a 6-point ordinal scale (1, Do not require hospitalisation, 2, hospitalised, but not requiring supplemental oxygen, 3, hospitalised, requiring supplemental oxygen; 4, Patients requiring high-flow oxygen or non-invasive ventilation; 5, Requiring or receiving mechanical ventilation; 6, Death. If a patient was discharged before day 10, it was recorded as not hospitalised.) Oxygen-support requirements, adverse events and laboratory values, including serum creatinine, ALT and AST, were assessed in the routine follow-up. The incidence of key clinical events, including changes in oxygen-support requirements, administration of high-flow oxygen, institution of non-invasive positive pressure ventilation (NIPPV) and invasive mechanical ventilation, hospital discharge, and reported adverse events, including those leading to discontinuation of treatment and death were also recorded.

We calculated analysis out of a sample size of 70 patients. For time-to-recovery and time-to-improvement analyses, data for patients who did not recover and data for patients who died were collected at day 24. The data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 22.0. The continuous data like age, duration of symptom onset, and levels of biochemistry markers before and after drug administration were presented as means with standard deviation for both the intervention and control group. For categorical data like sex, pre-existing co-morbidity conditions and clinical outcomes like mortality, the data were expressed as numbers and percentages. Independent t-test was used to compare the mean distribution of age, biochemistry markers at baseline and after drug administration between the two groups. Chi-square test of association was used to compare the proportion distribution of categorical variables between the two groups. Yates correction was used whenever the cell value was below five. *P* value of less than 0.05 was used for statistical significance.

RESULTS

Of the 102 patients who were assessed for eligibility, 82 were enrolled and underwent randomisation and began treatment. Forty one of these were assigned to the remdesivir group and 41 to SC group. In remdesivir group, out of 41 patients, two were discharged when symptom-free, one patient died, two were withdrawn from treatment and remdesivir was stopped in three patients with deranged AST and ALT. Thus, 33 patients received the five-day remdesivir course. Of the 41 patients in the SC group, two were discharged, two died and one patient requested for remdesivir treatment after four days of admission. This patient was shifted to remdesivir group. Thus, one more patient was added to the remdesivir group and the total participants in that group increased to 34 while the number of cases in SC group came down to 36 [Figure 1].

As per basal observations, all patients in both groups were in the state of highest disease-severity. There was no significant difference in the distribution of sex and mean age among the two groups ($P > 0.05$) [Table 1]. There was no significant difference in the baseline characteristics of intervention and control groups for past medical history like proportion of diabetes, hypertension, hypothyroidism, hypoglycaemia, coronary artery disease (CAD), chronic kidney disease (CKD) or asthma. Similarly, there was no statistically significant difference for levels of AST, ALT, and serum creatinine

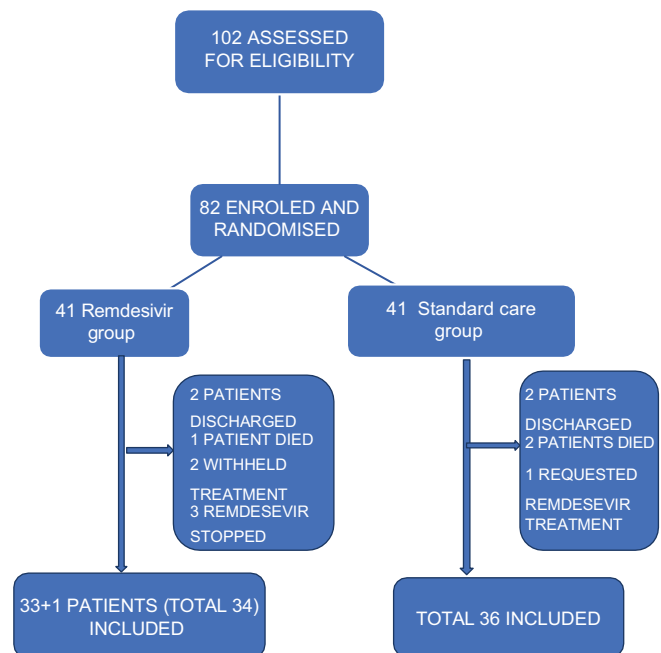


Figure 1: CONSORT diagram

between the two groups at baseline. However, the mean duration of appearance of symptoms before enrolment in the trial was significantly more in the SCgroup (7.38 ± 0.99 days) as compared to remdesivir group (6.26 ± 2.49 days) [Table 2]. The percentage of patients receiving low-flow supplemental oxygen and non-invasive ventilation or high-flow oxygen were equally distributed between the two groups, indicating, no statistically significant difference in the management of patients belonging to either remdesivir group or SC group.[Table 2] Also we could not find any significant difference in the mean number of hospital admission days between patients belonging to either group ($P = 0.472$) [Table 3]. The

initial length of hospital stay was almost equal in both remdesivir group and the SC groups [Table 3], but two of the patients in remdesivir group were readmitted to the hospital as compared to one patient in the SC group.

No statistically significant difference was found in the final treatment outcome of patients in the two groups as measured by the six point scale. There was an almost equal proportion of patients requiring hospitalisation in the two groups. Similarly, there was no difference in the mortality proportion in the two groups (14.7% vs 8.3%, $P = 0.749$) [Table 4]. Four patients received invasive mechanical ventilation

Table 1: Demographic profile of study participants

Variable	Remdesivir group (n=34) n (%)	SCgroup (n=36) n (%)	Total (n=70) n (%)	P
Sex				
Male	21 (61.7)	27 (75.0)	48 (65.5)	0.233
Female	13 (38.3)	9 (25.0)	22 (34.5)	
Age (years)[mean±SD]	58.08±12.1	57.41±14.1	57.74±13.1	0.832

SD, standard deviation

Table 2: Baseline clinical characteristics of study participants

Characteristic	Remdesivir group (n=34) n (%)	SCgroup (n=36) n (%)	Total (n=70) n (%)	P
Coexisting conditions at baseline				
Diabetes				
Yes	21 (61.8)	21 (58.3)	42 (60)	0.811
No	13 (38.2)	15 (41.7)	28 (40)	
Hypothyroidism				
Yes	4 (11.8)	3 (8.3)	7 (10)	0.706
No	30 (88.2)	33 (91.7)	63 (90)	
Hyperlipidaemia				
Yes	4 (11.7)	3 (8.3)	7 (10)	0.705
No	30 (88.3)	33 (91.7)	63 (90)	
Hypertension				
Yes	15 (44.1)	17 (47.2)	32 (45.7)	0.815
No	19 (55.9)	19 (52.8)	38 (54.3)	
CAD				
Yes	4 (11.8)	5 (13.9)	9 (12.9)	1.000
No	30 (88.2)	31 (86.1)	61 (87.1)	
CKD				
Yes	2 (5.9)	1 (2.8)	3 (4.3)	0.609
No	32 (94.1)	35 (97.2)	67 (95.7)	
Asthma				
Yes	1 (2.9)	0	1 (1.4)	0.485
No	33 (97.1)	36 (100)	70 (98.6)	
Blood biochemistry				
AST level (U/litre) [Mean±SD]	37.09±11.4	38.03±12.2	37.57±11.7	0.741
ALT level (U/litre) [Mean±SD]	38.94±13.4	35.19±13.6	37.01±13.5	0.251
Serum creatinine level (mg/dl) [Mean±SD]	0.98±0.13	1.01±0.15	1.00±0.1	0.457
Duration of symptoms before involvement in trial (days) [Mean±SD]	6.26±2.49	7.38±0.99	6.84±1.9	0.015

AST, aspartate transaminase; ALT, alanine aminotransferase; IQR, interquartile range; SD, Standard deviation; CAD, coronary artery disease; CKD, chronic kidney disease

between 9th to 12th day of remdesivir treatment and died between the 16th to 24th day of treatment. In the SC group, two patients received invasive mechanical ventilation, and were later extubated and 22 required high-flow oxygen or non-invasive mechanical ventilation [Table 4].

Discharge rates were higher among patients who had had symptoms for less than 5 days before receiving treatment. Patients in the remdesivir group and SC group had an equal time to recovery between 10 and 20 days. For the 17 (24%) patients receiving non-invasive ventilation or high-flow oxygen at enrolment, the median duration of use of these interventions was 12 days in both the remdesivir and non-remdesivir groups and among the 53 patients receiving low-flow oxygen supplementation at enrolment, those in the remdesivir group continued to receive oxygen for almost equal days in comparison to patients in the SC group. Patients in the remdesivir group had a shorter time to improvement of one or two categories on the ordinal scale from baseline than patients in the SC group. After adjustment for baseline clinical status, the occurrence of adverse events like nausea, vomiting, increased liver enzymes, increase in

serum creatinine and others like seizures, skin rash, and hypersensitivity reactions was not much different between the two groups [Table 5].

DISCUSSION

We did not find a significant difference in efficacy between remdesivir course and non-remdesivir course. After adjustment for baseline imbalances in disease severity, outcomes were similar as measured by a number of end points: clinical status on day 14, time to clinical improvement, recovery and death from any cause. Subsequent oxygen use for patients receiving oxygen at enrolment was also similar in both remdesivir and SC groups. Four patients in remdesivir group received mechanical ventilation and did not recover in comparison with two patients in SC group who required invasive mechanical ventilation and got extubated in due course. All this shows that treatment with remdesivir did not prevent the need for higher levels of respiratory support and did not make any major difference in the progression to more severe respiratory disease.

Several randomised trials on the use of remdesivir in COVID-19 have been published. Wang *et al.* conducted

Table 3: Clinical management of study participants

Clinical status at enrolment	Remdesivir group (n=34)	SCgroup (n=36)	Total (n=70)	P
Variable	n (%)	n (%)	n (%)	
Management protocol				
Receiving low flow supplemental oxygen	27 (79.4)	26 (72.2)	53 (75.7)	0.097
Receiving non-invasive ventilation or high-flow oxygen	7 (20.6)	10 (27.8)	17 (24.3)	
Receiving invasive mechanical ventilation	0 (0)	0 (0)	0 (0)	
Admission days [Mean±SD]	11.55±4.3	12.38±5.2	11.9±4.7	0.472

Table 4: Clinical Outcomes of treatment among study participants

Outcome characteristic (Clinical status from day 12 to 24 on 6 -point ordinal scale)	Remdesivir group (n=34)	SCgroup (n=36)	Total (n=70)	P
	n (%)	n (%)	n (%)	
Did not require hospitalisation*	2 (5.9)	3 (8.3)	5 (7.1)	0.749
Hospitalised, but did not require supplemental oxygen	0 (0)	0 (0)	0 (0)	
Hospitalised, required supplemental oxygen	4 (11.8)	6 (16.7)	10 (14.3)	
Required high-flow oxygen or non-invasive ventilation	19 (55.9)	22 (61.1)	41 (58.6)	
Required or received mechanical ventilation	4 (11.8)	2 (5.6)	6 (8.6)	
Death	5 (14.7)	3 (8.3)	8 (11.4)	

* If a patient was discharged before or on day 10, it was recorded as not hospitalised

Table 5: Adverse events during remdesivir treatment

	Remdesivir group (n=34)		SC group (n=36)		Total		P
	Baseline	After treatment	Baseline	After treatment	Baseline	After treatment	
Nausea, vomiting	7	3	9	2	16	5	0.56
Increase in liver enzymes (ASTlevels)	37.09±11.4	38.06±10.9	38.03±12.2	39.01±11.2	37.57±11.7	38.21±11.3	0.768
Increase in liver enzymes (ALTlevels)	38.94±13.4	39.01±12.3	35.19±13.6	36.21±13.2	37.01±13.5	38.91±13.4	0.672
Increase in creatinine levels	0.98±0.13	1.12±0.15	1.01±0.15	1.56±0.67	1.00±0.1	1.09±0.7	0.284

AST, aspartate transaminase; ALT, alanine aminotransferase

the first randomised, double-blind, placebo-controlled clinical trial to assess the effect of IV remdesivir in adults admitted to hospital with severe COVID-19. 237 patients were enrolled in the Wang *et al.* study which showed a shorter time (21 days) to improvement with remdesivir compared to 23 days in the placebo group.^[10] In the study by Beigel *et al.*, 957 severe disease stratum patients in the remdesivir group had a shorter time to recovery (median 11 days) than placebo group patients (median 18 days). Also, 5% patients in remdesivir group were readmitted to hospital compared with 3% in placebo group.^[8] In our study, patients in the remdesivir group had a shorter time to improvement of one or two categories on the ordinal scale from baseline than patients in the non-remdesivir group and 5.88% patients in the remdesivir group were readmitted to the hospital, as compared to 2.78% in the non-remdesivir group. Spinner *et al.* too in their open-label randomised study of remdesivir in moderate severity COVID-19 hospitalised patients, found that those who received remdesivir for five days had higher odds of clinical improvement than those receiving SC.^[11] Goldman *et al.* in a randomised phase 3 trial, reported no significant difference between a 5 day and a 10 day course of remdesivir. The patients included in their trial were similar to our study cases. They were hospitalised patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less when on room air, and with radiological evidence of pneumonia. The dosage of remdesivir was the same as used by us in our cases, but they compared IV remdesivir for 5 days with 10 days and they used a 7-point ordinal scale.^[12] We used the ordinal scale which was proposed by the World Health Organisation (WHO) and is a standard scale for interventional COVID-19 studies.

Our study had some limitations. All our study cases were of moderate to severe disease category; however, the disease is progressive and there can be an overlap of symptoms between categories and the definitions of 'moderate' and 'severe' category are variable. We did not grade the adverse events. We did not give placebo injection in the no-remdesivir group and did not do blinding. This is because we conducted the study during COVID times with a shortage of supporting staff. Also, ours was a single-centre study with a small sample size.

To conclude, remdesivir therapy for five days did not produce improvement in clinical outcomes in moderate to severe COVID-19 cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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