Original Research Article

Impact of Early Remdesivir Treatment in Severe Covid-19 Pneumonia in ICU Patients

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Received: 06-10-2021 / Revised: 17-11-2021 / Accepted: 27-12-2021

Abstract

Background: This study was conducted with the main objective to study the effect of early treatment of patients tested COVID-19 positive with remdesivir and to study time to clinical improvement and recovery from clinical symptoms of severe Covid-19 infection. **Materials & Methods:** This is an institutional-based case-control study conducted on patients admitted at Bidar Institute of Medical Sciences for a period of 2 months. Hospitalized subjects who wereCOVID-19 pneumonia infection confirmed were included. Detailed history, physical examination and necessary investigations were conducted, and the data was collected using a pretested proforma. Subjects were evaluated by physical inspection as well as by documentation of concomitant medications, respiratory status & adverse events. On day 1, 3, 5, 8, 10, & 14, samples of blood were collected for the complete blood count analysis and also for creatinine as well as liver aminotransferase measurements. The subjects' clinical status was evaluated on a daily basis on a 6-point ordinal scale from day one through fourteen or until discharge.**Results:** The majority of the subjects treated with remdesivir did not have comorbidities. Median age and duration before remdesivir treatment were 6 days, with median ALT, AST and creatinine clearance was found to be IQR 7, 12 and 39. In our study, the commonest negative outcomes observed were (6%), deranged liver function (4%), hypotension (3%), hypokalaemia (3%), acute respiratory failure (2%), acute kidney injury (2%) and pneumothorax (1%). The most common morbidities observed in our study were diabetes (12%) asthmatic (10%), COPD and combination of diabetes and HTN (8%), diabetic COPD (5%), COPD and hypertension (2%) and diabetic COPD (1%). 25% of study subjects were died, while 75% of study subjects were discharged after recovery. **Conclusion:** Our study findings delineated the importance of early remdesivir treatment initiation and resulted in clear mortality benefit of ICU subjects suffering severely from COVID-19 pneumonia.

Keywords: COVID-19, Remdesivir, Pneumonia, Mortality, Adverse events.

Introduction

As the 1stcase noted in December 2019 in Wuhan, China, the world has witnessed the pandemic spread of the newly discovered beta coronavirus SARS-CoV-2 that holds accountable for COVID-19 (coronavirus disease-19)[1-3]. The SARS-CoV-2 infection's symptoms differ extensively from asymptomatic illness to pneumonia &life-threatening complications, comprising respiratory distress syndrome, multisystem failure of organ & eventually death.[4,5] Covid-19 has affected nearly 3crore population in India, 2.72 crore people recovered and accounting for 3.49 lakh deaths.SARS-CoV-2 is transmitted from person to person via direct contact or respiratory droplets and have a 5-day median incubation interval with 2.24 to 3.58 basic reproduction number[7,8]. COVID-19 has a wide clinical spectrum, ranging from mild illness (i.e., mild pneumonia or no pneumonia) in roughly eighty per cent of cases to life-threatening pneumonia in the form of ARDS (acute respiratory disease syndrome) needing critical care in six per cent cases[9-11].The CFR (case fatality rate) tends to differ, with estimates ranging from 1 to 7 per cent, but after surveillance studies confirm the number of patients that are infected, this will be more accurately identified[12,13]Since oxygen supplements, as well as supportive care, may always not be adequate, it is indeed critical to identify an efficient drug treatment due to the seriousness & projected high CFR of pneumonia induced by SARS-CoV-2.Remdesivir is an adenosine analogue monophosphoramidate prodrug with broad antiviral activity against a range of RNA viruses[14-17]. An expert panel constituted by the WHO R&D Blueprint recognized it as the most potential therapeutic agent for assessment in COVID-19 treatment.[18]The fundamental action mechanism is the intracellular incorporation of the pharmacologically active nucleoside triphosphate form into nascent RNA chains by the viral RNA-dependent RNA polymerase, initiating the termination of premature RNA chain[16-20]. Remdesivir has been shown to inhibit human pathogenic coronaviruses *viz.* COVID-1, SARS-CoV as well as MERS-CoV, endemic human coronavirus (229E,OC43) and bat coronaviruses as per in vitro studies.Remdesivir has been found to have both therapeutic as well as preventative benefits in a SARS-CoV mouse model[21]. Remdesivir, which is known to be therapeutic and prophylactic, helped in reducing severe lung pathological symptoms, enhanced functioning of the lung and reduced lung viral load in a mouse model of MERS-CoV[15].Remdesivir & its other parent compounds inhibited viruses from the Filoviridae, Paramyxoviridae and Coronaviridae families and exhibited broad antiviral activities. They also could inhibit alpha & beta-coronaviruses replication in human airway epithelial cell cultures as well as did show low in-vitro cytotoxicity in several human cell types[21-23].With these viewpoints, the current research was conducted to assess the impact of early treatment of patients tested COVID-19 positive with remdesivir and to study time to clinical improvement and recovery from clinical symptoms of severe Covid-19 infection.

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Materials and Methods

An institutional-based case-control study was conducted on patients admitted at Bidar Institute of Medical Sciences (BRIMS), Bidar, for a period of 2 months. The present study was initiated after getting approval from the Scientific and Ethical Committee of the Institution. All the study subjects were also informed regarding the study procedure, &voluntary informed written consent was taken from the participants who were enrolled in the research study. The sample size of the study participants was 100, and the inclusion and exclusion criteria were as follows.

Inclusion criteria

- Subjects who were ≥ eighteen years of age at the time of signing of the informed consent form.
- Confirmed COVID-19 patients by laboratory RT-PCR (reverse transcription-polymerase chain reaction) method.
- With chest imaging, the indication of Pneumonia was confirmed.
- Hospitalized with SPO_2 ≤ 94% on room air or PaO2/FiO2 ≤ 300 mmHg
- ≤ 14 days since symptoms onset

Exclusion criteria

- Patients with known severe liver ailment (e.g., cirrhosis, ALT (Alanine aminotransferase) > 5 × ULN (upper limit of normal), or AST (Aspartate aminotransferase) > 5 × upper limit of normal)
- Subjects who are breastfeeding or pregnant or positive pregnancy test in women of childbearing age.
- Patients with known severe renal impairment (assessed rate of glomerular filtration ≤ 30 ml/min/1.73 m^2) or subjects undergoing continuous therapy of renal replacement, peritoneal or haemodialysis.
- Receipt of any investigational treatment for COVID-19 within thirty days before screening

Detailed history, physical examination and necessary investigations were conducted, and the data was collected using a pretested proforma. Physical assessments, as well as documentation of respiratory status, concomitant medications, and adverse events, were used to examine the subjects. On day one, three, five, eight, ten, &fourteen, samples of blood were collected for the analysis, as well as liver aminotransferases & creatinine measurement. The subjects' clinical status was evaluated on a daily basis on a 6-point ordinal scale from day one through fourteen or until discharge. Each day's worst (i.e., lowest) score was noted.

End Points: The primary efficiency endpoint was clinical status evaluated on day fourteen on a 6-point ordinal scale comprising of the following classifications:

1 - Death

2 - Hospitalized, receiving ECMO or invasive mechanical ventilation.

3 - Hospitalized, receiving high-flow oxygen devices or non-invasive ventilation.

4 - Hospitalized, needing low-flow supplemental oxygen.

5 - Hospitalized, receiving ongoing medical care (not related or related to COVID-19)
but not needing supplemental oxygen.

6 - Hospitalised, with no need for supplementary oxygen or ongoing medical care (other than what is mentioned in the remdesivir administration protocol).

The secondary endpoint of the study was the proportion of subjects who have adverse effects occurring on or after the initial remdesivir dose & lasting for thirty days after taking the final dose. Prespecified exploratory endpoints include the time to clinical improvement (defined as an improvement of at least two points from baseline on the 6-point ordinal scale), the time to recovery (defined by the NIAID [National Institute of Allergy and Infectious Diseases] as an improvement from a baseline score of 2-5 to a score of six) and death from any cause.

Data were entered, and computations were performed with the use of computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA).

Results

The majority of the study subjects, *i.e.*, 24%, were in a group of 36 to 45 yrs of age with male (62%) predominance as compared to females (38%). The most common co-morbidities observed among study subjects was diabetes & hypertension (12%), asthma (10%), COPD (8%). (Table 1)

Table 1: Distribution of the study participants on the basis of demographic details

Distribution of the study patients on the basis of demographic details			
Demographic details		**Frequency**	**Per cent**
Age	Less than 25 yrs	10	10.0
	26 to 35 yrs	12	12.0
	36 to 45 yrs	24	24.0
	46 to 55 yrs	10	10.0
Distribution of the study participants on the basis of gender			
Gender	Female	38	38.0
	Male	62	62.0
Distribution of the study participants on the basis of Co-morbidities			
Co-morbidities	Nil	42	42.0
	Asthma	10	10.0
	COPD	8	8.0
	COPD, HTN	2	2.0
	Diabetic	12	12.0
	Diabetic, COPD, HTN	5	5.0
	Diabetic COPD	1	1.0
	Diabetic, HTN	8	8.0
	HTN	12	12.0

Table 2: Median age and duration of days before remdesivir treatment, ALT, AST, creatinine clearance

	Minimum	**Maximum**	**Median**	**Interquartile (IQR)**
Age	19	89	54	28.8
Median duration before remdesivir (in days)	2	15	6	8

ALT (IU)	21	240	36	7
AST (IU)	28	140	40	12
Creatinine clearance (mL/min)	80	170	125	39

Table 3: Distribution of the study subjects based on ordinal scale and outcome

Distribution of the study subjects based on the ordinal score		
Ordinal score	**Frequency**	**Per cent**
Score 1	25	25.0
Score 2	23	23.0
Score 3	10	10.0
Score 4	16	16.0
Score 5	18	18.0
Score 6	8	8.0
Total	100	100.0
Distribution of the study participants on the basis of the outcome		
Outcome	**Frequency**	**Per cent**
Death	25	25.0
Discharged	75	75.0
Total	100	100.0

Table 4: Distribution of the study subjects based on clinical improvement and time of recovery

Time interval	Clinical improvement	Frequency	Per cent
Day 5	Death	25	25.0
	No	36	36.0
	Yes	39	39.0
Day 8	Death	25	25.0
	No	35	35.0
	Yes	40	40.0
Day 10	Death	25	25.0
	No	35	35.0
	Yes	40	40.0
Day 14	Death	25	25.0
	No	42	42.0
	Yes	33	33.0

Table 5: Distribution of the patients on the basis of adverse events and morbidity

Distribution of the patients on the basis of adverse events		
Adverse events	**Frequency**	**Per cent**
Acute kidney injury	2	2.0
Acute respiratory failure	2	2.0
Death	19	19.0
Deranged liver function	4	4.0
Hypokalaemia	3	3.0
Hypotension	3	3.0
Nausea, vomiting	6	6.0
Nil	60	60.0
Pneumothorax	1	1.0
Total	100	100.0
Distribution of the study subjects based on morbidity		
Morbidity	**Frequency**	**Per cent**
Nil	76	76.0
Depression	5	5.0
Embolism	1	1.0
Lung fibrosis	9	9.0
Palpitation	2	2.0
Respiratory failure	7	7.0
Total	100	100.0

Table 6: Comparison of the clinical parameters based on the clinical improvement at day 5

	Day 5	Minimum	Maximum	Median	IQR
Median duration before remdesivir (days)	Death	3	15	13	8.5
	No improvement	3	15	8	5.8

	Improvement seen	2	7	4	2
ALT	Death	21	240	36	10.5
	No improvement	23	46	36	8
	Improvement seen	23	140	36	7
AST	Death	29	140	43	22.5
	No improvement	28	56	39	9.5
	Improvement seen	30	70	41	12
Creatinine Clearance (mL/min)	Death	80	170	120	41
	No improvement	81	142	125	37
	Improvement seen	88	142	125	37

Table 7: Comparison of the clinical parameters based on clinical improvement at day 8

	Day 8	Minimum	Maximum	Median	IQR
Median duration before remdesivir (days)	Death	3	15	13	8.5
	No improvement	2	15	4	9
	Improvement seen	2	15	7	4
ALT	Death	21	240	36	10.5
	No improvement	23	45	34	13
	Improvement seen	23	140	36	4.8
AST	Death	29	140	43	22.5
	No improvement	29	58	39	9
	Improvement seen	28	70	41	11.3
Creatinine clearance (mL/min)	Death	80	170	120	41
	No improvement	82	142	128	35
	Improvement seen	81	142	124	39

Table 8: Comparison of the clinical parameters based on clinical improvement at day 10

	Day 10	Minimum	Maximum	Median	IQR
Median duration before remdesivir (days)	Death	3	15	13	8.5
	No improvement	2	7	4	3
	Improvement seen	2	15	8	7
ALT	Death	21	240	36	10.5
	No improvement	23	140	37	9
	Improvement seen	23	46	36	8
AST	Death	29	140	43	22.5
	No improvement	28	70	42	11
	Improvement seen	29	56	39	10.5
Creatinine clearance (mL/min)	Death	80	90	120	41
	No improvement	82	60	125	36
	Improvement seen	81	61	125	38.8

Table 9: Comparison of the clinical parameters based on the day of clinical improvement at day 14

	Day 14	Minimum	Maximum	Median	IQR
Median duration before remdesivir (days)	Death	3	15	13	8.5
	No improvement	2	15	4	3
	Improvement seen	2	15	8	7.5
ALT	Death	21	240	36	10.5
	No improvement	23	140	37	8.3
	Improvement seen	23	46	35	9
AST	Death	29	140	43	22.5
	No improvement	28	70	40	9.3
	Improvement seen	29	56	40	12
Creatinine clearance (mL/min)	Death	80	170	120	41
	No improvement	82	142	125	36.3
	Improvement seen	81	142	125	39

The median age and duration before initiation of remdesivir were 54 yrs and 6 days, respectively. Median ALT and AST levels estimated were 36and 40 IU, respectively and the median creatinine clearance (mL/min was 125, respectively. (Table 2)

The distribution of study subjects based on the ordinal score was as follows; score one (25%), score two (23%), Score three (10 per cent), score four (16%), score five (18%), and score six(8%). 25% of study subjects were died, while 75% of study subjects were discharged after recovery (Table 3). The results of the distribution of the study subjects based on clinical improvement and time of recovery were represented in Table 4. The results revealed that the recovery percentage was increased as the day progressed, i.e., On day 5, 8, and 10, the clinical improvement percentage recorded was 39%, 40%, & 40%, respectively. A total of 40 study subjects (40%) reported adverse events, whereas 60 (60%) of the subjects did not show any kind of adverse events. 19% of the study subjects had died, and the most common adverse events were nausea (6%), deranged liver function (4%), hypotension (3%), hypokalaemia (3%), acute

respiratory failure (2%), acute kidney injury (2%), and pneumothorax (1%). Morbidity was seen in 34% of the study subjects; among them, the majority of the subjects (9%) had lung fibrosis, followed by 7%, 5%, and 1% of the subjects had respiratory failure, depression and embolism (Table 5).On day 5, the median duration (13 days) of remdesivir treatment was longer for subjects who died, followed by subjects who showed no improvement (8 days). On day 8, the median duration (13 days) of remdesivir treatment was longer for subjects who died, followed by subjects who showed improvement (7 days). On day 5 and day 8, ALT (36) was similar for all the subjects with different clinical improvements. AST (43) was found high for the subjects who died. On day 5, Creatinine clearance (120) was low for subjects who died, whereas creatinine clearance (125) was similar for subjects who showed no improvement and for subjects where improvement was seen. However, the creatinine clearance (120) on day 8 was low for subjects who died. Improvement was seen in the subjects who had the creatinine clearance 124, whereas creatinine clearance was 128 for subjects who showed no improvement. The clinical parameters based on the day of clinical improvement on days 5 and 8 were represented in Tables 6 & 7.On day 10, the median duration (13 days) before initiation of remdesivir treatment was longer for subjects who died, followed by study subjects who showed improvement (8 days). ALT (36) was similar for subjects who showed improvement and subjects who died. AST (43) was high for subjects who died, followed by subjects who showed no improvement (42). Creatinine clearance was low for patients who died (120), whereas creatinine clearance (125) was the same for subjects who showed no improvement and improvement. (Table 8)

The comparison of the clinical parameters based on the clinical improvement on day 14 was represented in Table 9.On day 14, ALT (37) was slightly high for subjects who showed no improvement as compared to subjects who died (36). A slightly higher level of AST (43) was seen in subjects as compared to subjects who showed improvement and no improvement (40). Creatinine clearance (120) was low for subjects who died, whereas creatinine clearance (125) was similar for subjects who showed no improvement and improvement.

Discussion

In this research, we have assessed the effect of early treatment of patients tested COVID-19 positive with remdesivir and to study time to clinical improvement and recovery from clinical symptoms of severe infection of Covid-19. Our study's major results showed that the majority of the study subjects in our study were in the age group 36 to 45 years with male predominance. The majority of the subjects treated with remdesivir did not have comorbidities. Median age and duration before remdesivir treatment were 6 days, with median ALT, AST and creatinine clearance was found to be IQR 7, 12 and 39. The clinical status of the study subjects was evaluated using a 6-point ordinal score. The common ordinal score was found to be score 1, which included 25 subjects and score 2, which included 23 subjects. Overall, out of 100 subjects admitted, 75 subjects were discharged, and 25 subjects died. These findings were comparable with several other studies reported in the literature.

Remdesivir seems to be well-tolerated as well as safe. In a combined evaluation by the European Medicines Association of 4 studies involved one hundred thirty eight healthy participants, adverse events that occurred in5or more subjects comprised(n = 8)phlebitis, (n = 7)constipation, (n=6)headache, (n = 5) ecchymosis, (n = 5)discomfort in extremities, and(n = 5) nausea. Transient treatment-emergent increase in AST (aspartate aminotransferase) & ALT (alanine aminotransferase) were all grade 1 or grade 2 in severity seen in healthy participants; the rates of incidence also were not recorded[24,25].In our study, the commonest adverse effects noticed were (6%), deranged liver function (4%), hypotension (3%), hypokalaemia (3%), acute respiratory failure (2%), acute kidney injury (2%) and pneumothorax (1%). Most of the global research has analysed remdesivir effects in COVID-19 through comparison of remdesivir to placebo or by examining different remdesivir treatment durations[21-26]. Nevertheless, neither of these studies examined the impact of early remdesivir treatment on mortality.Early treatment has been shown to provide clinical advantages in SARS-CoV-2infected rhesus macaques (a primate model).Antivirals are most efficient in the early phases of illness when viral replication is active; determining this treatment window is very critical. Furthermore, because the average latency between exposure to virus & clinical symptoms is of five days, reducing the time between symptom onset and initiation of treatment are very critical in terms of outcomes. In the present study, on days 5 and 8, the median duration before remdesivir treatment was longer for subjects who died, and all the subjects who died had higher levels of AST and lower levels of creatinine clearance. A study conducted within ten days of symptom onset by Wang et al. noticed that subjects treated with remdesivir had a lower twenty-eight-day death rate than those treated with placebo.Although, in remdesivir-treated subjects, no comparison was done between late& early treatment. Goldman et al. found that in subjects who did not require mechanical ventilation, the rate of hospital discharge was higher in those who had symptoms for more than or equal to ten days.In previous research, the median time from onset of symptom to treatment was 8 to 11 days, which was used to analyse several findings.[26,21] The discharge rates/recovery time& mortality indicated in the published research papers widely vary on the basis of factors like selection of patients, the severity of disease (defined differently in several studies), duration of treatment, & the pandemic stage (with different therapeutic procedures). In our research, the rate of mortality (25%) was higher compared to other studies reported in the literature and remained the same at all-time intervals. In the trial of ACTT-1 (overall deaths: 6.7percent at day fifteen; 11.4percent at day twenty-nine),[26] research by Wang et al. (overall deaths: 14percent at day twenty-eight),[21] research by Goldman et al. (overall death sat day 14: 8percent in five-day and 11percent in ten-day remdesivir treatment group correspond ingly),and the Solidarity trial (overall death sat day twenty-eight: 12.5percent). Mehta et al. (22%).[30] The increased rate of mortality observed in our research is possibly justified by greater illness severity since we involved severely infected COVID-19patientsonly.The most common morbidities observed in our study were diabetes (12%) asthmatic (10%), COPD and combination of diabetes and HTN (8%), diabetic COPD (5%), COPD and hypertension (2%) and diabetic COPD (1%). The randomised clinical trials conducted by Wang et al. reported that the commonest comorbidities observed were (49.6%)hypertension, (37.0%)obesity, &(29.7%)diabetes.Mehta et al. stated in their study that the majority of patients had ≥1 comorbidity (70.2%), including diabetes mellitus (50.0%), hypertension (47.1%), CHD (15.6%), CKD (5.2 per cent), & chronic respiratory illness (asthma/COPD (3.5%)[30].Due to rapidly evolving data, numerous aspects of COVID-19 therapies have been confounded by various treatment strategies that can have a considerable effect on the results. For e.g., moderate doses of steroids will be administered uniformly only when the outcomes of the Covid-19 treatment trial's randomised assessment are revealed, i.e., after July 2020.In comparison to studies with uniform use of steroids, trials are lacking steroids or a mixed populace without/with steroids are likely to produce various results. In addition, detailed collection of data& reporting was difficult in the earlier part of the pandemic as healthcare systems had to face an unprecedented burden. Our research mirrors real-world practises in the latter pandemic stage, which includes uniform remdesivir use along with a healthcare system that is well-prepared.

Conclusion

Study findings delineated the significance of early remdesivir treatment initiation and resulted in clear mortality benefit of ICU subjects suffering from severe COVID-19 pneumonia.

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Conflict of Interest: Nil
Source of support:Nil