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A study of clinical outcome and safety profile of Remdesivir in COVID-19 patients in a tertiary care centre

Fariha Fatima[1*], Fardan Qadeer[1], Afroz Abidi[1], Zeba Siddiqui[2], Dilshad A Rizvi[1] and Akhlaque Ahmad[1]

[1]Department of Pharmacology, Era's Lucknow Medical College and Hospital, Sarfarazganj, Hardoi Road, Lucknow-226003 Uttar Pradesh, India and [2]Department of General Medicine, Era's Lucknow Medical College and Hospital Sarfarazganj, Hardoi Road, Lucknow-226003 Uttar Pradesh, India

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Abstract: *Introduction:* COVID 19 disease has wrecked a havoc as pandemic in the entire world. It causes cardiac manifestations, digestive system disturbances, and adversely affecting other organs. As a result, ardent efforts are underway to find effective antiviral treatments targeting possible mechanisms to identify a specific medication for the disease to curb its progression and to prevent patients sufferings, one such therapy being injectable antiviral treatment namely, Remdesivir. *Objectives:* To evaluate the clinical outcomes and safety profile of Remdesivir in COVID-19 patients in a tertiary care center. *Methods:* An observational retrospective cohort study was planned with sample size of 210 patients suffering from active moderate to severe COVID 19 disease admitted in a single center tertiary care hospital requiring injectable anti-viral therapy that is Remdesivir. Patient data was collected from the case record forms. Primary outcomes in terms of length of hospital stay, duration of treatment with Remdesivir, survival rate in patients on Remdesivir and assessment of the days for the COVID 19 positive test to eventually become negative in patients and secondary outcome in terms of safety were evaluated. *Results:* There was a clinically significant improvement in the SPO2 levels from the time of admission till discharge. The appearance of adverse effects was taken as the secondary outcome. Hepatic and renal toxicity was observed after completion of treatment whereas no immunological abnormalities were observed. *Conclusion:* Until stronger evidences come to the fore, we cannot derive substantial inference that our injectable antiviral therapy drug namely, Remdesivir is efficacious for treating COVID-19.

Keywords: Retrospective, Cohort, COVID, Pandemic, Clinical Outcome, Anti-Viral Agents, Remdesivir, Spo2

Introduction

Coronavirus disease 2019 (COVID-19) in recent times has emerged as a major global public health and socioeconomic crisis, with approximately 168 million cases identified worldwide and more than 3.5 million deaths (as of 24th May 21, 2021). The total affected cases reported in India were over 27 million with approximately 300000 deaths (as of 24May 2021). The virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the family *Coronaviridae* and genus *Beta coronavirus*, together with SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV) [1]. The virus has 79.6% sequence similarity with SARS-CoV [2].

The rapid transmission of the virus is mainly owing to its high reproductive number (R_0), with a mean of 3.28 [3], implying that one infected person could transmit the virus to up to three unvaccinated individuals. Similar to other respiratory illnesses, it leads to symptoms which progress from fever, cough, dyspnoea, chest pain to pneumonia with ground-glass opacities being the most common finding as investigated by computed tomography imaging [4-5]. Apart from respiratory implications, the disease has been reported to cause cardiac manifestations [6], the digestive system disturbances [7] and adversely affecting other organs [8-9].

Consequently, ardent efforts internationally are underway to find effective antiviral

treatments targeting multiple possible mechanisms to identify a specific medication for COVID 19 disease to curb its progression and to prevent patients sufferings [10]. This lacunae in the treatment strategy has led to the proposal and application of many approaches such as the convalescent plasma and interferon (IFN) in addition to the interleukin 6 receptor inhibitors which are effective against the cytokine storm that poses another threat to the lives of the COVID 19 patients [11]. Remdesivir belonging to the group of nucleoside analogues inhibit reverse transcription and is the most potent antiviral agent available to combat the SARS-CoV-2 infection [12-13].

It is a nucleoside prodrug whose active metabolite inhibits viral RNA-dependent RNA polymerases, structurally conserved enzymes that play a key role in the replication of a broad range of viruses, including Coronaviridae [14-15]. A first randomized, placebo-controlled trial of Remdesivir among patients with COVID-19 conducted in Wuhan, China, could not complete enrolment to assess efficacy [16]. In a larger randomized, double-blind clinical trial, including the patients with severe COVID-19 disease treated with a 10-day course of Remdesivir had a significantly shorter time to recovery and hospital stay than those receiving placebo (11 days vs 15 days) [17].

Also, a randomized, open-label trial in patients with severe COVID-19 showed a decline in spO2 on oxygen support and its use retarded the progress of the disease averting the need of ventilatory support with 5- and 10-day courses of Remdesivir but the results were not statistically significant [18]. These results prompted the US Food and Drug Administration to grant Emergency Use Authorization of Remdesivir for patients with severe COVID-19 and the European Medicines Agency to grant conditional marketing authorization to Remdesivir for treatment of COVID-19 in patients 12 years of age or older with respiratory complication such as pneumonia who require supplemental oxygen [19].

This retrospective single centred study was conducted parallel to the above mentioned studies to evaluate the clinical outcome and adverse events associated with Remdesivir administered for 5 or 10 days in hospitalized patients with COVID-19 infection. The aim of the study was to evaluate the clinical outcomes and safety profile of Remdesivir in COVID-19 patients in a tertiary care center.

Material and Methods

The protocol was approved by the institutional review board or independent ethics committee from each site and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements.

We performed a retrospective review of the electronic medical records for a convenience sample of consecutive adults (18 years of age or older) with confirmed severe COVID-19 infection who were hospitalized and given injection Remdesivir between April 15th 2021 till May 15th, 2021. All cases of COVID-19 were confirmed by positive result on polymerase chain reaction testof a nasopharyngeal sample. Severe COVID-19 infection was defined as any patient requiring oxygen therapy while hospitalized and changes in HRCT thorax with CT scoring ranging between 15-20.

All patients were randomized to a Remdesivir group receiving 200 mg intravenously on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 4 days, infused over 30 to 60 minutes. Remdesivir treatment was to be discontinued in any patient experiencing severe elevations in liver enzymes or decreases in estimated creatinine clearance to less than 30 mL/min during the course of the therapy.

- *Study design:* An observational retrospective cohort study was planned with sample size of 210 patients suffering from active moderate to severe COVID 19 disease admitted in a single center tertiary care hospital requiring injectable anti-viral therapy that is Remdesivir.
- *Data collection tool:*
    1. Patient data was collected from the case record forms available in electronic form in the Hospital Information System of a tertiary care hospital in Lucknow.

2. Patients matching the inclusion criteria were selected through this data base.
3. The patient data was tabulated in Microsoft Excel software, the data collection and storage were maintained under confidentiality by the Principal Investigator.

- *Inclusion criteria:*
  - *Age:* >18years
  - *Gender:* both male and female
  - *Study population:* 210 patients admitted in a tertiary care hospital diagnosed with COVID 19 moderate to severe infection with respiratory involvement.

- *Exclusion criteria:*
  - Patients with pre-existing renal disease
  - Patients with deranged liver function test
  - Mild asymptomatic COVID 19 positive cases

- *Primary outcome measures:*
  - Length of hospital stay in days
  - Duration of treatment with Remdesivir
  - Survival rate in patients on Remdesivir
  - Assessment of the days for the COVID 19 positive test to eventually become negative in patients

- *Secondary outcome measures:*
  - To evaluate the safety of Remdesivir given to patients of COVID 19 infection in terms of adverse drug reactions.

Statistical analysis: Results were expressed as mean and percentage. Statistical analysis was done using Microsoft excel software applying paired t test to determine the difference in between the groups. $p<0.05$ was taken to be statistically significant.

Results

The patient data was retrieved from the online Hospital Information System (HIS) and was electronically stored in the Microsoft excel software. The data confidentiality was maintained by the investigators.

Patient demographics: A total of 210 patients data was retrieved from the hospital information system software (HIS). The patients demographic characteristics are mentioned in Table 1. The mean age of the patients was 57 years with the average age of 26 to 78 years. Total number of male patients were 121(57.60%) and total number of female patients were 89 (42.3%). Most patient belonged to the urban background (n=156) and few were from rural background (n=54). Three important comorbidities were taken into consideration. Diabetes, Hypertension and pre-existing lung disease. 131 patients had one or more of these comorbidities.

Table-1: Patient demographic characteristics

Characteristic	N	Percentage (%)
Gender		
Male	121	57.6%
Female	89	42.3%
Age		
20-30 years	12	5.71%
31-40 years	32	15.23%
41-50 years	44	20.95%
51-60 years	70	33.33%
61-70 years	52	24.7%
71-80 years	0	0
> 80 years	0	0
Background		
Urban	156	74.28%
Rural	54	25.71%

Comorbidities	Diabetes	Hypertension	Respiratory illness	More than one comorbidities
Patients with comorbidities (n=131)	52	34	21	24

Primary outcome: Remdesivir was prescribed to the patients both in the Intensive care setting (ICU) and in the high dependency unit (HDU). Remdesivir was given according to the standard protocol in a dose of 200 mg on Day 1 followed by 100 mg per day for the remaining 4 days. The median duration of treatment with Remdesivir was 5 days. In some patients (n=21) drug was stopped due to

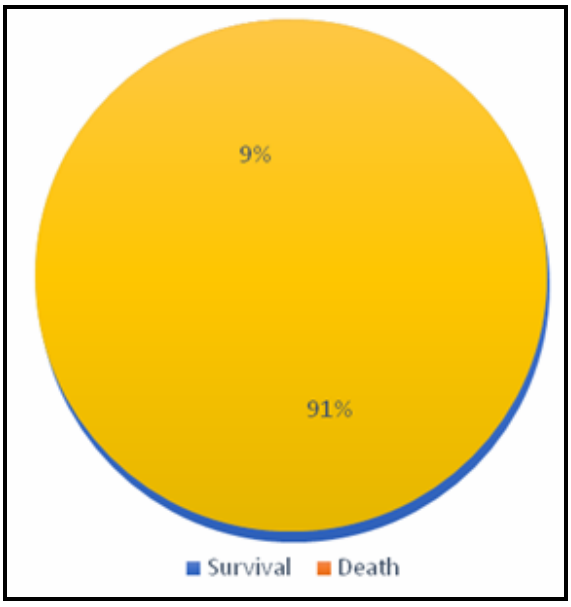
appearance of adverse effects and in certain individuals the drug was given for an extended period of time(n=14) [Table 2]

Table-2: Duration of treatment with Remdesivir

Number of days	Patients (n)	Percentage (%)
<5 days	21	10%
5 days	175	83.33%
>5 days	14	6.66%

The survival rates in the patients was 90.9%. (n=191). The mean length of hospital stay in the patients who survived was 17 days. Death was reported in 19 patients (9.04%) [Chart 1].

Chart-1: Survial Rates in patients of Remdesivir



There was no statistically significant difference in the SPO2 levels from the time of admission to the time of discharge. (P = 0.07) however clinically significant improvement in the SPO2 levels was observed. The mean SPO2 level at the time of admission was 88% and at the time of discharge was 97%.

Secondary outcome: The appearance of adverse effects was taken as the secondary outcome. The renal and hepatic adverse effects were evaluated by the biochemical investigations and other adverse effects like immunological adverse effects and gastrointestinal adverse effects were recorded from the patients symptoms [Table 3].

Table-3: Adverse effects associated with the use of Remdesivir

Adverse effects	Pre-treatment	Post treatment	P value
Renal			
S. creatinine	1.1462	2.2956	P=0.03
S. Urea	50.4	77.94	P<0.001
Hepatic			
SGOT	105.6	164.42	P=0.087
SGPT	231.52	418.62	P=0.0405

Serum creatinine levels were significantly increased (P= 0.03). The mean serum creatinine levels at the time of admission was 1.14 mg/dl whereas serum creatinine levels at the time of discharge was 2. 29 mg/dl. Serum urea was also increased significantly (P<0.001). The mean serum urea levels was 50.4 mg/dl at the time of admission and the mean serum urea levels at the time of discharge was 77.94 mg/dl.

Hepatic profile was seen to be deranged. SGPT was significantly elevated post treatment (p=0.04) where as other parameters were not elevated significantly. No patient reported hypersensitivity reaction to the drug. Nausea and abdominal discomfort and loose stools was reported by minority of patients (n=15) [Table 4].

Table-4: Other adverse effects associated with Remdesivir

Type	N	Percentage (%)
Immunological	0	0
Gastrointestinal including nausea, vomiting and loose stools	15	7.14%

Discussion

This study offers its contribution to the current literature on the efficacy of Remdesivir for the treatment of severe COVID-19 by evaluating the clinical outcomes and its safety profile in a tertiary care centre. In our sample population, the mean length of hospital stay of patients on Remdesivir was 17 days which was longer than the previously-reported median of 7 days following a 5-day course of Remdesivir for

the treatment of COVID-19 [20]. Survival rates in the patient was 90.9% which was comparable with the rates reported in the previous literature when patients were treated with a 5-day course of Remdesivir [20].

Death was reported in 19 patients which summed up to 9.04%. The exact reason for these increased hospital stay and mortality can be attributed to the fact that 131 patients in the study population had several comorbities like Diabetes, Hypertension, respiratory illnesses and more than one of these conditions in a patient [21]. Previous literature has also shown that comorbid conditions are strongly related to COVID-19 disease associated severity and mortality [22].

Several published reports have also depicted that men were more likely to get infected with COVID-19 and also experience worse clinical outcomes than women [23] as reported in our study where 57.6% men specifically have higher rates of hospitalization, intensive care admission, and mortality as compared to severity experienced by 42.3% women. Clinical improvement in spO2 levels was noted in the patients but the results were not statistically significant.

Despite similar incidence of comorbid conditions in both the genders, the men in our study had higher rates of poor clinical outcomes, in terms of mortality, intensive care admission, mean duration of oxygen therapy, and mean length of stay as compared to women [20].

With regards to the safety profile of this drug, it caused significant alteration in hepatic and renal function tests. There was a statistically significant increase in the levels of serum urea and SGPT whereas a clinically significant rise in serum creatinine and SGOT was also observed which further emphasises against its use in patients with compromised renal and hepatic functions. These results were in sync with a randomised controlled clinical trial which (n = 236) was stopped early due to adverse effects and also with the other three clinical trials which reported reported outcomes between 11 and 15 days [24].

In addition to the above adverse effects 7.14% patients in our study population also reported gastrointestinal disturbances for instance nausea, loose stools, vomiting, etc.

Hence, some more randomized controlled trials with large sample size are needed to further establish the effect of Remdesivir in moderate to severe COVID-19 infection in the community setting. As there is a paucity of adequately powered and fully reported RCTs evaluating effects of Remdesivir in hospitalized COVID-19 patients. Until stronger evidences come to the fore we cannot derive substantial inference that our injectable antiviral therapy drug namely, Remdesivir is efficacious for treating COVID-19.

Conclusion

It has been observed that Remdesivir has shown statistically significant clinical improvement in patients of COVID-19 without any significant adverse effects, however larger community randomised controlled trials are required to establish the clinical efficacy and safety of the drug.

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Conflicts of interest: There are no conflicts of interest.

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*All correspondences to: Dr. Fariha Fatima, Assistant Professor, Department of Pharmacology, Era's Lucknow Medical College and Hospital, Sarfarazganj, Hardoi Road, Lucknow-226003, Uttar Pradesh, India. Email: drfarihafshikoh@gmail.com