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Original Research Article

Effect of remdesivir on mortality rate, need of intubation and mechanical ventilation in COVID-19 positive patients: a retrospective observational study

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ABSTRACT

Background: The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ failure, and ultimately, death. Remdesivir has broad spectrum of activity against members of several virus families, including filoviruses and coronaviruses. Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial cells.
Methods: This is a prospective and observational study conducted in patients of either gender, age more than 18 years with confirmed diagnosis of COVID-19 by RT-PCR. A predesigned, pretested and semi structured questionnaire containing socio demographic details like age, sex, BMI, comorbidities, findings of systemic examination of the cases, dose and duration of Remdesivir received and adverse effect due to therapy was used to collect the data.
Results: Mean age of the patients were 56.19±10.93 years. Male patients were 66% and 34% patients were female. After receiving the remdesivir, 43% of the patients needed bag mask and 27% of the patients maintained on room air oxygen. Non-invasive ventilation required in 19% of the patients and 11% of the patient required mechanical ventilation. s14% of the patients needed admission in the ICU. 3.5% of the patients were died and 96.5% patients were discharged from the hospital.
Conclusions: Remdesivir reduces the need of non-invasive oxygenation and mechanical ventilation. Mortality was seen in 3.5% patients, henceforth remdesivir, is an effective drug for moderate to severe COVID-19, if given in early stages of infection.

Keywords: Mechanical ventilation, Remdesivir, SARS-CoV-2

INTRODUCTION

Severe acute respiratory coronavirus 2 (SARS-CoV-2) infection causes a worldwide pandemic and affecting the more than 674,538,489 individuals globally till December 2022 which results in death of 6,756,838 patients.[1-3] India remains the second most commonly affected country after USA. In India 44,682,532 individuals are infected with SARS-CoV-2 and 530,739 deaths occurred because of it.[1-2] Covid-19 illness affected the health care systems around the world.[3,4] The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ

failure, and ultimately, death.[5] Older patients and those with pre-existing comorbid condition like diabetes, hypertension, chronic kidney or respiratory or cardiovascular diseases having risk for severe complications.[6,7] Symptomatic patients with COVID-19 develop a clinical syndrome similar to the influenza. The majority of patients with clinical disease had fever (80%) and cough (60%) and myalgia/fatigue (40%). Other symptoms were less common and included dyspnea, sore throat, pharyngeal congestion, headache, diarrhoea, vomiting, anorexia and chest pain.[8-10] The majority of these symptoms appeared within 11 days post-infection but may vary depending on age and co-morbidities.[11]

Remdesivir is an antiviral prodrug that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad spectrum of activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV). It shown prophylactic and therapeutic efficacy in nonclinical models of coronaviruses.[12-15] Remdesivir have a favourable clinical safety profile in previously done studies.[16] Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial cells.[17-19] Remdesivir is currently FDA approved for emergency administration to COVID-19 patients. [20]

So because of the reported safety and efficacy of remdesivir against SARS-CoV-2 in clinical models, we planned this study to evaluate the effects of remdesivir on clinical recovery, need of mechanical ventilation and reduction in mortality in patients suffering from COVID-19.

METHODS

This is a prospective and observational study conducted from January 2021 to November 2022 in department of medicine in MGM Medical College and Hospital Aurangabad. Primary objective of the study was to assess the effect of remdesivir on mortality rate in COVID-19 positive patients. Secondary objectives were to assess the effect of remdesivir on need of intubation and to assess the adverse drug reaction of remdesivir in hospitalized patients. As the study period was during COVID pandemic, the sample size included in the study was time bound from January 2021 to November 2022 from the records of patients who were admitted in our hospital between June 2020 to November 2021for COVID-19 and received 5 days course of remdesevir. Hence a total of 200 cases were included in the study through records.

Patients of either gender, age more than 18 years had SARS-CoV-2 infection confirmed by reverse-transcriptase–polymerase-chain-reaction assay and/or rapid antigen test and received the 5-days course of remdesivir were included in the study. Patients with creatinine clearance less than 30 ml per minute and patients with serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) more than five times the upper limit of the normal range were excluded from the study.

Institutional ethics committee approval was taken prior to commencement of the study. Present study was conducted in medical intensive care unit and department of general medicine at tertiary care hospital. A predesigned, pretested and semi structured questionnaire containing following study variables were used to collect the data: Socio demographic details like age, sex, BMI, comorbidities like hypertension, diabetes mellitus, chronic kidney and respiratory diseases, findings of systemic examination of the cases, dose and duration of remdesivir received and adverse effect due to therapy was recorded.

Statistical analysis

The data was collected, entered in Microsoft Excel and analyzed using SPSS version 26. The values was expressed in mean, percentage and standard deviation.

RESULTS

In the present study, patients with age more than 50 years were most commonly affected. Mean age of the patients were 56.19±10.93 years. Male patients were more common and 86% of the patients had BMI more than 23 and 14% of the patients had normal values of BMI. Majority of the patients were pre-obese (52.5%) followed by overweight (22%) (Table 1).

Table 1: Demographic details of the patients.

Variables	Number	Percentage
Age in years		
18-30	6	3
31-40	14	7
41-50	35	17.5
51-60	66	33
61-70	61	30.5
>70	18	9
Mean ± SD	56.19±10.93	
Gender		
Male	132	66
Female	68	34
BMI (Kg/m^2)		
<18.5 (underweight)	0	0
18.5-22.9 (normal)	28	14
23-24.9 (overweight)	44	22
25-29.9 (pre-obese)	105	52.5
30-40 (obese)	23	11.5

Fever (82%) was most common presenting symptom in the patients followed by dyspnea (62%). Cough and fatigue were other important symptoms present in 60% and 57% of the patients (Table 2). Diabetes and

hypertension were the most prevalent comorbid conditions in the patients (Table 2). In the present study, blood group A and O were more commonly found in the patients. 36.5% patients had blood group O and 33% patients had blood group A.

DISCUSSION

Remdesivir received Emergency Use Authorization (EUA) on 1 May 2020 by US FDA. In India on 21 June 2020, the CDSCO approved restricted emergency use of remdesivir for treating patients with severe COVID-19 infection, later expanded its indication to moderate and severe disease. So, we performed this study to assess the effect of remdesivir on mechanical ventilation and mortality of the patients.

In the present study, patients with age >50 years constituted >70% of the study population. Mean age of the patients were 56.19±10.93 years. 66% patients were male and 34% patients were female. Majority of the patients were pre-obese (52.5%) followed by overweight (22%) and 11.5% patients were obese (Table 1). In the studies of Beigel et al, Wang et al and Spinner et al mean age of the patients were 58.9±15.0, 65.2±13.2 and 57.1±11.0 years respectively.[21-23] In the studies of Beigel et al, Wang et al and Spinner et al male patients were more common than female and their percentage were 65%, 60% and 61% respectively.[21-23] Fever (82%) was most common presenting symptom in the patients followed by dyspnea (62%). Cough and fatigue were other important symptoms present in 60% and 57% of the patients respectively. Other less common presenting symptoms were sore throat, headache and chest pain (Table 2). In the study of Elsalam et al, 77% patients presented with fever, 64% presented with cough, 38% with headache, and 66% with fatigue.[24] Dai et al found the common symptoms at onset of illness was fever 75%, cough 75%, and shortness of breath 52.78% and less common symptom was diarrhea 5.56%.[25] In the study of Wajekar et al, the common clinical symptoms were fever (84.74%), cough (77.97%) and breathlessness (72.88%).[26] Herzog et al also found similar common symptoms such as dyspnea (21.9%), coughing (68.6%), fever (88.5%), myalgia (35.8%), and anosmia (47%).[27] Glowacka et al in their systematic review observed that mild or moderate symptoms include cough, fever, fatigue, dyspnea and smell and taste loss.[28] The observations in the present study are similar to the findings of these studies.

Diabetes and hypertension were the most prevalent comorbid conditions in the patients. Hypertension alone present in 13% patients but hypertension also present along with diabetes (10%), with DM and CKD (2%) and with IHD (3%). It means hypertension was present in 28% of the patients. Likewise, diabetes alone present in 9% patients but diabetes also present along with other comorbidities like hypertension, CKD and IHD and totally diabetes was present in 23% of the patients. Asthma (8%) and COPD (6%) were other important comorbidities present in the patients. 13% of the patients had history of smoking (Table 2).

In the study of Beigel et al, the most common comorbidities were, hypertension (50.7%), diabetes (30.6%) and obesity (45.4%).[21] Similarly in the study of Ismail et al, the common comorbidities were hypertension (30%), diabetes (22%) CKD (5%), COPD (4%), asthma (3%) and IHD (3%).[29] In the study of Balasubramanian et al, the common comorbidities were hypertension (14%), diabetes (19%) CKD (1%) and IHD (1%).[30] Sharma et al, the common comorbidities were hypertension (42.61%), diabetes (16.26%) and COPD (7%).[31] Wang et al, the most common comorbidities were, hypertension (46%), diabetes (25%) and IHD (9%).[22] In the study of Ader et al, the common comorbidities were hypertension (28%), diabetes (26%), obesity (34%) CKD (6%) and chronic pulmonary disease (18%).[32]

In almost all the studies the most prevalent comorbidities are hypertension, diabetes, ischemic heart disease, CKD and chronic pulmonary diseases. These findings are similar to present study.

Table 3: Distribution of patients according to mode of oxygenation, ICU admission, hospital stay and prognosis.

Oxygenation	Number	Percentage
Room air	54	27
Bag mask	86	43
Non-invasive ventilation	38	19
Mechanical ventilation	22	11
ICU admission		
Yes	28	14
No	172	86
Hospital stay		
14 or less days	165	82.5
More than 14 days	35	17.5
Prognosis		
Died	7	3.5
Discharge	193	96.5

In the present study, after receiving the remdesivir, 43% of the patients needed bag mask and 27% of the patients maintained on room air oxygen. Non-invasive ventilation required in 19% of the patients and 11% of the patient required mechanical ventilation. Out of 200 patients, 14% of the patients needed admission in the ICU. 82.5% patients required hospital stay of 14 or less days and 17.5% patients required hospital stay of more than 14 days. So, majority of the patients were discharged within 14 days after the treatment with remdesivir (Table 3). Beigel et al, in Adaptive COVID-19 Treatment Trial (ACTT-1) found that remdesivir was superior to standard treatment in shortening the time to recovery in hospitalized adults with COVID-19 and lower respiratory

tract infection.[21] The median time to recovery was 10 days in the remdesivir group compared to 15 days in the standard treatment group. ('P' less than 0.001). Olender et al, done a multicenter study compared efficacy of remdesivir and standard of care in patients with severe COVID-19.[33] They found that at day 14, 74.4% of remdesivir patients had recovered and 59% of patients receiving standard of care recovered. Spinner et al, conducted a randomized, open-label, multicenter study compared efficacy of remdesivir 5-day and 10-day therapy vs. standard care alone in patients hospitalized with moderate COVID-19 pneumonia.[23] The 5-day remdesivir group had statistically significant better clinical status compared to standard care. Wang et al, performed a randomized, double-blind, placebo-controlled, multicenter trial evaluating efficacy and safety of remdesivir in SARS-CoV-2 infected hospitalized adults.[22] They found that no difference between remdesivir and placebo in the time to clinical improvement. Goldman et al, conducted a randomized, open-label, phase 3 trial comparing 5-day and 10-day courses of remdesivir in hospitalized patients with severe COVID-19.[34] They found that no significant difference between the 5-day and 10-day courses was observed in patients with severe COVID-19. WHO Solidarity trial remdesivir did not reduce the initiation of ventilation in those not already ventilated (295 for remdesivir vs. 284 for the control group).[35] Remdesivir did not reduce the duration of hospitalization, with 69% of remdesivir and 59% of the control group still hospitalized at day 7.

Table 4: Frequency distribution of adverse drug reaction.

Adverse drug reaction	Number	Percentage
Nausea	17	8.5
Vomiting	11	5.5
Diarrhea	10	5
Headache	13	6.5
Rashes	15	7.5
Increased liver enzymes	13	6.5
Anemia	14	7
Thrombocytopenia	16	8
Increased blood glucose	10	5
Hypokalemia	9	4.5

In the present study, most common adverse drug reaction associated with remdesivir was nausea (8.5%) followed by thrombocytopenia (8%). Other common ADR were rashes, anemia, headache, increased liver enzymes, vomiting, diarrhea, increased blood glucose and hypokalemia (Table 4). Not a single serious type of ADR was reported in the study. In the study of Wang et al, the common ADRs were nausea, thrombocytopenia, rashes, anemia, headache, increased liver enzymes, vomiting, diarrhea, increased blood glucose, hyponatremia, hyperkalemia and hypokalemia.[22] Spinner et al reported that the common ADRs associated with remdesivir were nausea, vomiting, diarrhea, headache and hypokalemia.[23] These findings are in accordance with the present study.

In the present study, 3.5% of the patients were died and 96.5% patients were discharged from the hospital. In the study of Beigel et al, Kaplan-Meier estimates of mortality by day 29 were 11.4% for remdesivir and 15.2% for placebo.[21] In the study of Wang et al, 28-day mortality was similar between remdesivir (14%) and placebo (13%).[22] In the study of Goldman et al, mortality was lower (8%) in remdesivir group and (11%) in the patients received standard treatment.[34] In the study of Olender et al, at day 14, 7.6% of patients in remdesivir group had died as compared to 12.5% of patients receiving standard of care.[33]

This study has some limitations. Data was collected only in the period of pandemic so limited number of patients were included and they were not followed up for longer period. Hence study was unable to comment on long term complications of COVID-19 and long term adverse effect of remdesevir. Randomized clinical trials and large sample size are required to confirm the efficacy and safety of remdesevir for the treatment of COVID-19.

CONCLUSION

Remdesivir reduces the need of non-invasive oxygenation and mechanical ventilation. It also decreases the duration of hospital stay in significant number of patients and only non-serious ADRs were reported in patients. Mortality was seen in 3.5% patients. So, Remdesivir, is an effective and safe drug for the treatment of moderate to severe COVID-19, if given in the early stages of infection.

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