Original Article

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Clinical Outcomes of Remdesivir in Moderate and Severe Cases of COVID-19: A Retrospective Cohort Study

Internal Medicine Section

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ABSTRACT

Introduction: Remdesivir is a nucleotide analogue prodrug that perturbs viral replication. Remdesivir has been used in various trials previously for the treatment of Coronavirus Disease 2019 (COVID-19). Some clinical trials found that remdesivir had a mortality benefit, while other studies did not. It was also seen that remdesivir shortened the duration of hospital stay among COVID-19 patients in some trials while in other trials remdesivir did not have any influence on the duration of hospital stay.

Aim: To study the clinical outcomes of remdesivir in moderate and severe cases of COVID-19.

Materials and Methods: The present retrospective, cohort study was conducted in the Department of General Medicine, SDM Medical College and Hospital, Dharwad, Karnataka, India, from September 2021 to May 2022, in which 400 case records of patients admitted with moderate to severe COVID-19 were studied. Among these 314 patients received remdesivir and 86 patients did not receive remdesivir. Categorical variables, nominal variables were represented as proportions and frequencies and continuous variables were represented as mean±SD. Statistical analysis was done using Chi-square test.

Results: A total of 400 COVID-19 patients were included in the study, among which 314 received remdesivir and 86 did not receive remedisivir. Those who received remdesivir had a mortality rate of 13.69% as compared to 11.63% among those who did not receive remdesivir (p-value=0.6170). In the remdesivir group, 36.62% had a hospital stay of >11 days, while it was 30.23% among the non remedisivir group (p-value=0.3060).

Conclusion: According to this study, remdesivir did not reduce mortality nor did it reduce the duration of hospital stay among moderate to severe COVID-19 patients.

Keywords: Coronavirus disease 2019, Mechanical support, Oxygen support

INTRODUCTION

Remdesivir is a nucleotide analogue prodrug that perturbs viral replication [1]. It is found to be effective against many Ribonucleic Acid (RNA) viruses like Ebolavirus (EBOV) and the respiratory pathogens, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory syndrome (SARS-CoV), and SARS-CoV-2 [2]. When the drug was first introduced by Gilead sciences, it was tested to check its effectiveness against Ebola virus in a trial and it was found to be inferior to the antibodies used in the trial [3]. The Food and Drug Administration (FDA) approved this drug on 22nd October 2020 as the first antiviral drug in the treatment of Coronavirus Disease 2019 (COVID-19) subsequent to an emergency use authorisation dated May 1, 2020; the approval of remdesivir was supported by the agency data analysis from three randomised controlled clinical trials that included adult patients and children >12 years hospitalised with mild-to-severe COVID-19 [4]. The Adaptive COVID-19 Treatment Trial 1 (ACTT1), a multicentre trial was conducted in various nations in which it was found that, the individuals who tested positive for COVID-19 and also who were on remdesivir treatment with oxygen support or on ventilator support fared well in comparison with those who did not receive remdesivir [5].

The ACCT1 study that was done among those with COVID-19 and who had lower respiratory tract infection it was found that, remdesivir was better than placebo as those who received remdesivir had a shorter time to recovery and lesser mortality when compared to those who received placebo. Those who received remdesivir had a median recovery time of 10 days as compared with 15 days among those who received placebo. The mortality rates were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 [5]. The second clinical trial was a randomised open labelled trial that was done among those with moderate COVID-19 disease in which it was found that, those randomised to a 10 day course of remdesivir did not have a better clinical status than those assigned to standard care at 11 days of treatment [6]. In the third clinical trial in which patients were assigned either to receive 5 days or 10 days of remdesivir it was found that there was no difference in the clinical status of individuals between the two groups at the end of 14 days [7]. In another study done among those with severe COVID-19 with clinical symptoms for lesser than 10 days it was found that, those who received remdesivir took a shorter time to clinically improve when compared to those who received placebo, but it was not statistically significant [8].

In a study done among COVID- 19 patients in which remdesivir was used on a compassionate-basis, 53 patients were treated with remdesivir and it was found that a significant number of them showed an improvement in oxygen support class and a good number of them who were on mechanical ventilation were extubated. Also mortality rate was low both among them who were not mechanically ventilated as well as those who were mechanically ventilated [9]. However, in the solidarity that is an international clinical trial that evaluated the effect of four drugs: remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon on COVID-19 outcomes, it was found that all 4 treatments did not influence mortality, initiation of ventilation or duration of hospital stay among those who were hospitalised [10]. In another study it was found that remdesivir had little or no difference to all cause mortality at upto 28 days [11].

Even though there are conflicting reports regarding the efficacy of remdesivir in treatment of COVID-19 from various trials, remdesivir was prescribed extensively in the country from 2020 to 2021. Hence, the present retrospective study was aimed to study the clinical outcomes of remdesivir in the management of COVID-19.

MATERIALS AND METHODS

This retrospective cohort study was conducted in the Department of General Medicine, SDM Medical College and Hospital, Dharwad, Karnataka, India, from September 2021 to May 2022. COVID-19 cases admitted to the hospital during the years July 2020 to June 2021 were considered for the study. After obtaining Institutional Ethics Committee approval (SDMIEC/2021/113) the data collection was initiated.

Inclusion criteria: All diagnosed cases of moderate or severe COVID-19 based on Reverse Transcription Polymerase Chain Reaction (RT-PCR), aged ≥18 years were included in the study. The severity classification was based on the Government of India [12] and National Institutes of Health (NIH), guidelines [13].

Exclusion criteria: Pregnancy, presence of chronic kidney disease, chronic liver disease AST ≥5 times upper limit of normal, creatinine clearance ≤30 mL/min respectively), <18 years of age and duration of hospital stay <48 hours were excluded from the study.

Study Procedure

The records of patients admitted from July 2020 to June 2021 were identified by International Classification of Diseases-10 (ICD-10) code U07.1. Remdesivir was given as advised by the physician as 200 mg stat followed by 100 mg once a day for five days. The data was collected of age, gender, duration of hospital stay, death, co-morbidities, moderate and severe COVID, Acute Kidney Injury (AKI), exposed to remdesivir or not, administration of other drugs like glucocorticoids, anticoagulants, and whether mechanical ventilation, inotropic support and oxygen were given.

STATISTICAL ANALYSIS

Categorical variables, nominal variables were represented as proportions and frequencies. Continuous variables were represented as mean±SD. Chi-square test was done for significance and p-value <0.05 was considered statistically significant.

RESULTS

The severity of COVID-19, mean age and gender distribution were similar in both the groups. The age of >60 years was taken as a cut-off, above which people were considered to be elderly and this parameter was also analysed to depict how many were old aged among those who received remdesivir and those who did not. Among the co-morbidities, a majority of population in both groups had hypertension and diabetes mellitus. [Table/Fig-1]. The patients who received oxygen, anticoagulants and glucocorticoids were significantly more in the remdesivir group [Table/Fig-2].

There were more number of deaths recorded in the remdesivir group than the non remdesivir group, but it was not statistically significant (p-value=0.6170) [Table/Fig-3]. A cut-off of 11 days was considered for comparison of duration of hospitalisation because 11 days was the average duration of hospital stay. Although not significant, there was a longer duration of hospital stay among those who received remdesivir [Table/Fig-3].

Parameters	No remdesivir n (%)	Remdesivir n (%)	Chi-square value (p-value)
COVID-19 severity			
Moderate cases	52 (60.46%)	163 (51.91%)	1.9870 (0.15)
Severe cases	34 (39.53%)	151 (48.09%)	
Age in years (Mean±SD)	54.58±14.473	55.97±13.707	Mean difference-1.39 (p-value=0.410)
Age group (years)			
20-39	16 (18.60%)	45 (14.33%)	1.8920 (0.5950)
40-59	37 (43.02%)	126 (40.12%)	
60-79	30 (34.88%)	133 (42.35)	
≥80	3 (3.48%)	10 (3.18%)	
Age >60	33 (38.37%)	143 (45.54)	0.5140 (0.4730)
Gender			
Males	54 (62.79%)	227 (72.29%)	2.9170 (0.0880)
Females	32 (37.20 %)	87 (27.70%)	
Co-morbidities			
Hypertension	35 (40.69%)	138 (43.94%)	0.2910 (0.5900)
Diabetes	39 (45.34%)	140 (44.58%)	0.0160 (0.9000)
Immunocompromised (Human immunovirus disease)	7 (8.13 %)	11 (3.50%)	3.3770 (0.0660)
Cardiovascular disease	2 (2.32%)	21 (6.68%)	2.3710 (0.1240)
Cerebrovascular Disease	3 (3.48%)	5 (1.59%)	1.2380 (0.2660)
COAD+Asthma	2 (2.32%)	3 (0.95%)	1.0268 (0.310921)
Cancer	2 (2.32%)	2 (0.63%)	1.9440 (0.1630)
AKI	13 (15.11%)	56 (17.83%)	0.3490 (0.5540)

[Table/Fig-1]: Baseline characteristics of the patients in no remedisivir group (n=86) and remedisivir group (n=314).
COAD: Chronic obstructive airway disease; AKI: Acute kidney injury

Parameters	No remdesivir n (%)	Remdesivir n (%)	Chi-square (p-value)
Mechanical ventilation	7 (8.13%)	34 (10.82%)	0.5300 (0.4660)
Inotropic support	6 (6.98%)	28 (8.91%)	0.3270 (0.5680)
Oxygen support	43 (0.5%)	214 (68.15%)	9.6850 (0.0020*)
Anticoagulants	58 (67.44%)	300 (95.54%)	56.7220 (0.0001*)
Glucocorticoids	61 (70.93%)	299 (95.22%)	44.2670 (0.0001*)

[Table/Fig-2]: Treatment strategies influencing outcomes among no remedisivir group (n=86) and remedisivir group (n=314).
*p-value <0.05 was considered statistically significant

Parameters	No remdesivir n (%)	Remdesivir n (%)	Chi-square (p-value)
Number of patients who died (%)	10 (11.63%)	43 (13.69%)	0.2510 (0.6170)
Duration of hospital stay >11days	26 (30.23%)	115 (36.62%)	1.0470 (0.3060)

[Table/Fig-3]: Comparison of mortality rate and duration of hospital stay between no remedesivir (n=86) and remedesivir (n=314) groups.

DISCUSSION

The study found that there was no difference in the mortality rate among those who received remdesivir in comparison to those who did not. In a retrospective cohort study it was found that those who received remdesivir did not show any significant mortality benefit when compared to those who did not [14]. However, in a systematic review and meta-analysis it was found that remdesivir significantly reduced the mortality when compared to placebo [15]. The authors felt that remdesivir usage might have yielded a mortality benefit as remdesivir was only used in the less severe COVID-19 wave and not in the more severe wave.

In this study, it was found that there was a marginally longer duration of hospital stay in those who received remdesivir than those who did not. This might be because those who received remdesivir were also those who had a more severe disease. Ohl ME et al., found that the duration of hospital stay was longer in those who received remdesivir than those who did not. This was because those who received remdesivir required to receive it for a minimum of five days while those who did not were discharged on days 3 or 4 [14]. This is in contrast to the ACCT1 trial that demonstrated 10 days time to recovery among those who received remdesivir as against 15 days among those who received placebo [5].

Limitation(s)

A clinical trial could not be conducted, to assess the impact of remdesivir in the management of moderate to severe COVID-19

cases. The guidelines of classification of the severity of the disease and its management kept changing with time, this may have influenced the treatment and hence the results.

CONCLUSION(S)

According to this study, although mortality was marginally higher among those who received remdesivir it was not significant. Also, more number of patients in the remdesivir group had a long duration of hospital stay compared to those who did not receive remedesivir, which was not statistically significant. Hence, more clinical trials are required to study the clinical outcomes of remedesivir in COVID-19 patients.

REFERENCES

[1] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci. 2020;6(5):672-83.

[2] Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. Clin Microbiol Rev. 2020;34(1):e00162-20.

[3] Mulangu S, Dodd LE, Jr Davey RT, Mbaya OT, Proschan M, Mukadi D et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293-03. Doi: 10.1056/NEJMoa1910993.

[4] FDA. FDA approves first treatment for COVID-19. 2020. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.

[5] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. ACTT-1 study group members. Remdesivir for the treatment of Covid-19- Final report. N Engl J Med. 2020;383(19):1813-26.

[6] Spinner CD, Gottlieb RL, Criner GJ, Lopez JRA, Cattelan AM, Viladomiu AS, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical Trial. JAMA. 2020;324(11):1048-57.

[7] Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383(19):1827-37.

[8] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78.

[9] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327-36.

[10] WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19- Interim WHO solidarity trial results. N Engl J Med. 2021;384(6):497-11.

[11] Ansems K, Grundeis F, Dahms K, Mikolajewska A, Thieme V, Piechotta V, et al. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev. 2021;8(8):CD014962.

[12] Clinical Management Protocol: COVID-19 Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).https://covid19.india.gov.in/document/clinical-management-protocol-for-covid-19-2.15/10/2022.

[13] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/.

[14] Ohl ME, Miller DR, Lund BC, Kobayashi T, Richardson Miell K, Beck BF, et al. Association of remdesivir treatment with survival and length of hospital stay among US veterans hospitalized with COVID-19. JAMA Netw Open. 2021;4(7):e2114741.

[15] Bansal V, Mahapure KS, Bhurwal A, Gupta I, Hassanain S, Makadia J, et al. Mortality benefit of remdesivir in COVID-19: A systematic review and meta-analysis. Front Med (Lausanne). 2021;7:606429.

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