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Role of Remdesivir in the Clinical Outcomes Of Patients With Covid-19

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Abstract

Introduction: The severe acute respiratory syndrome coronavirus2, has been causing a global outbreak of COVID-19. Remdesivir is a novel drug which is under consideration for treating moderate and severe disease and this study aims to see the role it plays in improving the clinical outcomes of COVID-19 patients.

Materials And Methods: This is an observational retrospective cohort study with 240 patients who were segregated into Remdesivir and Non-Remdesivir arm and analysed for prognostic indicators like days on oxygen supplementation, NIV support, hospital stay and 30-day mortality.

Results: Patients with moderate disease had oxygen support for a mean of 3.17and 7.06(p=0.002) days respectively and patients with severe disease had an average of 5.87days and 11.2days respectively in the non-remdesivir and remdesivir arms(p=0.00). Patients in non-remdesivir arm were kept on NIV for an average of 1.24days and a mean of 5.9days in the remdesivir arm (p=0.008). Patients in category B had a mean hospital stay duration of 11days in the non-remdesivir arm and 11.1days in the remdesivir arm(p=0.91).Patients in category C had a mean duration of hospital stay for 9.6days and 14.3days in the non-remdesivir arm and remdesivir arm respectively(p=0.001). In the non-remdesivir group there was a 1.14day average and in the remdesivir group, there was an average of 2.73days in the 30-day mortality(p=0.128)

Conclusion: Patients with severe disease had a modest benefit from remdesivir in terms of 30-day mortality although not statistically significant. There was no significant benefit in patients with severe disease in terms of NIV requirement and in patients with moderate and severe disease in terms of oxygen requirement and days of hospital stay

Keywords: COVID-19, Remdesivir, Clinical outcome

Introduction

The COVID-19 disease caused by a novel coronavirus was first identified in December 2019 in Wuhan, China and spread rapidly throughout the world. The causative agent is an RNA beta coronavirus named severe acute respiratory syndrome coronavirus 2(SARS-CoV-2). It was declared to be a global pandemic on March 11, 2020. COVID-19 has a wide range of clinical spectrum which varies from asymptomatic to critical infection. The common clinical features of COVID-19 are fever, dry cough, shortness of breath, myalgia, anosmia, ageusia and fatigue. The understanding of the pathophysiology of COVID-19 has increased presently. The virus is transmitted via respiratory droplets and aerosols from person to person. In about 80% of patients, containment of infection occurs with viral clearance in 10-14 days. In the remaining 20% of patients, invasion and infection of the type 2 pneumocytes

occurs leading to the release of multiple inflammatory mediators known as the cytokine storm.[1]

Remdesivir is an antiviral nucleotide analogue used for therapy of severe novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection. Remdesivir therapy is given intravenously for 5 to 10 days.Remdesivir is a carboxylic ester. A broad-spectrum antiviral prodrug with potent in vitro antiviral activity against a diverse panel of RNA viruses such as Ebola virus, MERS-CoV and SARS-CoV. Remdesivir is a prodrug of an adenosine triphosphate (ATP) analog, with potential antiviral activity against a variety of RNA viruses. Upon administration, remdesivir, being a prodrug, is metabolized into its active form GS-441524. As an ATP analog, GS-441524 competes with ATP for incorporation into RNA and inhibits the action of viral RNA-dependent RNA polymerase. This results in the termination of RNA transcription and decreases viral RNA production.[2]

This study aims to evaluate the efficacy of remdesivir in improving the prognosis in COVID 19 patients.The Adaptive COVID-19 Treatment Trial (ACTT), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The randomized, controlled trial enrolled hospitalized adults with COVID-19 with evidence of lower respiratory tract involvement (generally moderate to severe disease). Investigators found that remdesivir was most beneficial for hospitalized patients with severe disease who required supplemental oxygen. Findings about benefits in other patient subgroups were less conclusive in this preliminary analysis.

The report notes that patients who received remdesivir had a shorter time to recovery than those who received placebo. The study defined recovery as being discharged from the hospital or being medically stable enough to be discharged from the hospital. The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. The findings are statistically significant and are based on an analysis of 1059 participants (538 who received remdesivir and 521 who received placebo). Clinicians tracked patients' clinical status daily using an eight-point ordinal scale ranging from fully recovered to death. Investigators also compared clinical status between the study arms on day 15 and found that the odds of improvement in the ordinal scale were higher in the remdesivir arm than in the placebo arm. Trial results also suggested a survival benefit, with a 14-day mortality rate of 7.1% for the group receiving remdesivir versus 11.9% for the placebo group; however, the difference in mortality was not statistically significant[3].

Materials and Methods

Study design: This is an observational retrospective cohort study.

Study population:240 patients with lab confirmed COVID-19 admitted between June 2020 to November 2020 at Government Hospital for Chest and Communicable Diseases/ Andhra Medical College, Visakhapatnam.

Inclusion criteria:

1. Age > 18 years
2. Nasopharyngeal/ oropharyngeal swab for RTPCR or TrueNat positive for COVID-19

Exclusion criteria:

1. Age < 18 years
2. Pregnancy or breast feeding

Methodology: The subjects were selected from the population of patients by simple random sampling. After excluding data with missing values, 240 patients were selected for study who met the above criteria. Patients were grouped into COVID-19 categories based on guidelines by Ministry of Health and Family Welfare (MOHFW), India (Table 1). Clinical history of patients was noted, initial blood workup and radiological assessment and appropriate treatment as per the Government guidelines was provided. Patients were divided into Remdesivir and Non remdesivir arms. Patients were put on remdesivir only in cases in the later part of the study upon the implementation of the protocol in our institution eliminating the need for a clinical trial in which patients needed to be assigned to arms which receive treatment and which don't receive treatment. The prognosis of patients was assessed in terms of days of oxygen requirement, NIV(Non Invasive ventilation) requirement, hospital stay and 30 day mortality. Confounding factors were noted. Statistical

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analysis was done using Microsoft Excel and SPSS Version 21.

Results

The study included 240 patients of which 74(30.83%) were females and 166(69.16%) were males. The Remdesivir arm had 178 patients with 119 patients in category a, 18 in category B and 41 in category C. The Non Remdesivir arm had 62 patients with 6 patients in category A, 18 in category B and 38 in category C(Table 2) .

Oxygen support

None of the category a patients was on oxygen support in either arm. Category B patients were either managed without oxygen or kept on oxygen support for a maximum of 12 days in the non remdesivir arm and a maximum of 14 days in the remdesivir arm with a mean of 3.17 and 7.06(p=0.002) respectively(Table 3,4). In category C patients, patients in non remdesivir arm were kept on oxygen for at least 1 day upto a maximum of 33 days with an average of 5.87 days and the remdesivir arm had minimum, maximum and average of 5,27 and 11.2 days respectively.(p=0.00) (Table 5,6).

NIV support

None of the category A patients were on NIV support in either arm. Category B patients were managed without NIV in the non remdesivir arm and for 5 days in 1 patient in the remdesivir arm. In category C patients, patients in non remdesivir arm were kept on NIV for an average of 1.24 days and a mean of 5.9 days in the remdesivir arm(p=0.008)(Table 7,8). A lower usage of NIV was adopted because of risk of aerosolization and patients were maintained on high flow nasal cannula whenever possible. We also have to note that the peripheral oxygen saturation on admission was an average of 81.2% in the non remdesivir group and 75.5% in the remdesivir group which can be a confounding factor.

Hospital Stay

All patients in category A had a hospital stay for a duration less than or equal to 10days for the purpose of infection control unless for the management of comorbidities.

Patients in category B with had a mean hospital stay duration of 11 days in the non remdesivir arm and 11.1 days in the remdesivir arm(p=0.91). (Table 9,10)

Patients in category C had a mean duration of hospital stay for 9.6days and 14.3days in the non remdesivir arm and remdesivir arm respectively(p=0.001)(Table 11,12).

30-day mortality

None of the patients in category A or B expired within 30 days in either arm. In the non remdesivir group 31% of the Category C patients expired within 10 days of admission with 34% mortality within 30 days and there was a 1.14 day average. In the remdesivir group, 15.7% expired in the first 10 days of admission and 23.6% within 30 days with an average of 2.73 days(p=0.128)(Table 13,14). This is despite an average admission SpO2 of 81.2% % in the non remdesivir group and 75.5% in the remdesivir group.

Confounding factors

Comorbidities

Diabetes mellitus(DM)

11.7% of patients in the non remdesivir arm and 38.7% patients in the remdesivir arm had a history of diabetes mellitus. Of these, in the non remdesivir arm, 2.8% patients of category A and B and 6.1% of category C had DM. In the remdesivir arm, 3.2% patients of category A, 12.9% of category B and 22.5% patients of category C had DM.(Table 15)

Systemic hypertension

14.6% of patients in the non remdesivir arm and 27.4% patients in the remdesivir arm had history of systemic hypertension. Of these, in the non remdesivir arm, 3.9% patients of category A, 3.3% of category B and 7.3% of category C had history of systemic hypertension. In the remdesivir arm, 1.6% patients of category A, 4.8% of category B and 20.9% patients of category C had history of systemic hypertension.(Table 16)

Steroid

26.4% of patients in the non remdesivir arm and 95.1% patients in the remdesivir arm used oral or parenteral steroids during their hospital stay. Of these, in the non remdesivir arm, 38.8% patients of category B and 92.6% of category C received steroids. In the remdesivir arm, 94.4% patients of category B and 100% patients of category C received steroids.(Table 17)

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Anticoagulants

7.3% of patients in the non remdesivir arm and 69.3% patients in the remdesivir arm used enoxaparin during their hospital stay. Of these, in the non remdesivir arm, 5.5% patients of category B and 29.2% of category C received enoxaparin. In the remdesivir arm, 66.6% patients of category B and 73.6% patients of category C received enoxaparin(Table 18).

Discussion

The current study showed a male preponderance in infection with COVID-19 .The ACTT trial had concluded that remdesivir was beneficial in shortening the hospital stay in patients with moderate and severe disease. In the present study,

Days on oxygen support had a statistically significant difference in moderate and severe disease with patients on remdesivir requiring more days on oxygen than the patients who were not on remdesivir. A decreased duration of oxygen support in the severe group can be attributed to the increased mortality of patients in this group although not statistically significant. It was also noted that days on NIV was less for severe patients who were not on remdesivir.

All patients were hospitalized to prevent the spread the pandemic in the beginning of the pandemic but as the number of patients drastically increased, only moderate and severe cases were admitted till they could maintain a normal room air saturation of at or above 95%. If patients in Category A had a hospital stay more than 10 days, it was for the management of their comorbidities..Also patients in my study with moderate disease had similar duration of hospital stay in both arms and patients with severe disease has a more prolonged stay in the remdesivir group and hence did not benefit from remdesivir. Also there was no statistically significant difference between 30 day mortality in patients on or off Remdesivir.

The confounding factors that may have affected the results are an increased percentage of comorbidities in the remdesivir group compared to the non remdesivir group although the patients in remdesivir arm had an added advantage of having increased percentage of concomitant steroids and anticoagulant treatment along with remdesivir.

Conclusions

To conclude patients with severe disease had a modest benefit from remdesivir in terms of 30 day mortality although not statistically significant. On the other hand, there was no significant benefit in patients with severe disease in terms of NIV requirement and in patients with moderate and severe disease in terms of oxygen requirement and days of hospital stay, from use of remdesivir in the treatment protocol.

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The correspondence author would like to guarantee that the manuscript is not, either in part or whole, under active consideration by any other journal, will not be submitted for review to another journal and has not been published in any other journal. Dr. Sneha Susan Jacob had full access to the data in the study and taken full responsibility for the integrity of the study. All co-authors (Dr. K V V Vijayakumar M.D., Dr. V Suryakumari M.D. and Dr. K Preethi M.D.) have made a substantial contribution to the design, data collection and analysis of the research and the drafting of the manuscript and have reviewed and accepted the contents of the manuscript before its submission. The authors are grateful to all participants who participated in this study.

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Tables

CATEGORY	PATIENT STATUS ON EVALUATION
GROUP A	Asymptomatic/ patients with mild symptoms RR94% at room air
GROUP B	Symptomatic patient with mild to moderate pneumonia with no signs of severe disease RR: 24-30/min (Or) SpO2: 90-94% at room air
GROUP C	Symptomatic patient with severe pneumonia with RR>30/ min (Or) SpO2

Table 1: Clinical severity categories of COVID-19 according to MOHFW India

GRADING OF SEVERITY		
CATEGORY	NON REMDESIVIR ARM-178	REMDESIVIR ARM-62
GROUP A	119	6
GROUP B	18	18
GROUP C	41	38

Table 2: Study participants according to grading of severity

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	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on oxygen	Non-Remdesivir	18	3.1667	3.39983	.80135
	Remdesivir	18	7.0556	3.68578	.86875

Table 3: Number of days on Oxygen support in moderate disease

Levene's Test for Equality of Variances		t-test for Equality of Means						
F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
							Lower	Upper
0.069	0.795	-3.29	34	0.002	-3.8889	1.1819	-6.2908	-1.487

Table 4: Statistical significance of number of days on Oxygen support in moderate disease

	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on oxygen	Non- Remdesivir	41	5.878	5.6533	0.8829
	Remdesivir	38	11.2368	4.66403	0.75661

Table 5: Number of days on Oxygen support in severe disease

	Levene's Test for Equality of Variances		t-test for Equality of Means							
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		

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								Lower	Upper		
Equal variances assumed	0.206	0.651	-4.575	77	0	-5.3588	1.17127	-7.6911	-3.0265		

Table 6: Statistical significance of number of days on Oxygen support in severe disease

	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on NIV	Non-Remdesivir	41	.7561	3.00650	.46954
	Remdesivir	38	3.4211	5.28451	.85726

Table 7: Number of days on NIV support in severe disease

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	18.764	.000	-2.781	77	.007	-2.66496	.95839	-4.57336	-.75655
Equal variances not assumed			-2.727	57.724	.008	-2.66496	.97742	-4.62168	-.70823

Table 8: Statistical significance of number of days on NIV support in severe disease

	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on NIV	Non-Remdesivir	18	11.0000	2.82843	.66667
	Remdesivir	18	11.1111	3.30577	.77918

Table 9: Number of days of hospital stay in moderate disease

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	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	1.064	.310	-.108	34	.914	-.11111	1.02546	-2.19509	1.97287

Table 10: Statistical significance of number of days of hospital stay in moderate disease

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	4.189	0.044	-3.414	77	0.001	-4.7606	1.3944	-7.5372	-1.984
Equal variances not assumed			-3.461	71.264	0.001	-4.7606	1.37543	-7.5029	-2.0182

Table 11: Number of days of hospital stay in severe disease

	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on NIV	Non-Remdesivir	41	1.1463	2.42447	.37864
	Remdesivir	38	2.7368	5.88486	.95465

Table 12: Statistical significance of number of days of hospital stay in severe disease

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	Treatment arm	N	Mean	Std. Deviation	Std. Error Mean
Number of days on NIV	Non-Remdesivir	41	1.1463	2.42447	.37864
	Remdesivir	38	2.7368	5.88486	.95465

Table 13: 30 day mortality in severe cases

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	13.864	.000	-1.592	77	.116	-1.59050	.99932	-3.58040	.39940
Equal variances not assumed			-1.549	48.448	.128	-1.59050	1.02700	-3.65493	.47392

Table 14: Statistical significance of 30 day mortality in severe cases

USE OF ANTICOAGULANTS		
CATEGORY	NON REMDESIVIR ARM	REMDESIVIR ARM
GROUP A	0(0%)	3(50%)
GROUP B	1(5.5%)	12(66.6%)
GROUP C	12(29.2%)	28(73.6%)

Table 15: Confounding factor of anticoagulation

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USE OF STEROIDS		
CATEGORY	NON REMDESIVIR ARM	REMDESIVIR ARM
GROUP A	2	4
GROUP B	7	17
GROUP C	38	38

Table 16: Confounding factor of steroids

PRESENCE OF COMORBIDITY-DIABETES MELLITUS		
CATEGORY	NON REMDESIVIR ARM	REMDESIVIR ARM
GROUP A	5	2
GROUP B	5	8
GROUP C	11	14

Table 17: Confounding factor of comorbidities: Diabetes mellitus

PRESENCE OF COMORBIDITY-SYSTEMIC HYPERTENSION		
CATEGORY	NON REMDESIVIR ARM	REMDESIVIR ARM
GROUP A	7	1
GROUP B	6	3
GROUP C	13	13

Table 18: Confounding factor of comorbidities: Systemic Hypertension

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