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EFFICACY AND SAFETY OF REMDESIVIR IN THE TREATMENT OF COVID 19: A RETROSPECTIVE STUDY

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ABSTRACT

Background: No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19).The aim of this study was to summarize the antiviral activities of remdesivir against SARS-CoV-2, the causative agent of COVID-19. We present our observations on remdesivir use.

Methods: In a retrospective case control study total 74 patients of moderate to severe covid 19 infection admitted to Dhiraj hospital were enrolled. Out of total 74 patients, 37 were given remdesivir assigned as group A and 37 patients were not given remdesivir assigned as group B. Data was collected from the case record form and analyzed with respect to inflammatory markers, mortality, length of ICU stay and days on ventilator support.

Results: Out of 74 moderate to severe RT PCR positive Covid 19 patients, 37 patients were in remdesivir group and others were in non remdesivir group. Mean age was 55.08 $\pm$ 8.98 years and 22 were male in remdesivir group. Statistically significant improvement was noted with ESR, CRP and Sr.LDH only. Other laboratory parameters (TLC, NLR, D-Dimer, and Sr.Ferrtin) showed minor improvement only (p value = >0.05).Less mortality was observed with remdesivir treatment, along with ICU stay and less days on ventilator therapy without any safety concerns.

Conclusion: Remdesivir use along with standard therapy had showed significant improvement in terms of clinical, laboratory parameters and recovery in patients with moderate to severe Covid 19 infection.

KEYWORDS : Remdesivir, Antiviral Drugs Inflammatory Markers, Covid 19 Infection

INTRODUCTION

The novel coronavirus 2019 (COVID-19) also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 is an enveloped, non-segmented positive-sense RNA virus belonging to the beta-coronaviridae family.[1] COVID-19 has been found to be the cause of severe pneumonia and acute respiratory distress syndrome (ARDS) with a significantly high mortality rate.[2] According to the World Health Organization, there are 42,053,710 confirmed cases and 11,43,709 deaths from COVID-19 as of Oct 23, 2020 and rapidly increasing.[3] Originating from bats like other virulent coronavirus (CoV) strains such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), COVID-19 has become the focus of the medical world and the pandemic of 2020.[1,4]

Remdesivir (GS-5734 is an antiviral drug that was developed by Gilead Sciences in 2014 as a possible treatment for Ebola Hemorrhagic Virus (EBV) and Marburg Virus infection. It is an adenosine analog, evidenced to have broad-spectrum activity against the single-stranded RNA viruses. [5] It binds to RdRp and acts as RNA chain terminator and exhibits effective in vitro activity against SARS-CoV-2 with an EC_{50} at 48 h of 0.77 μM in Vero E6 cells. [6] Few studies conducted have shown comparable activity against other zoonotic coronaviruses with EC_{50} values of 0.07 μM demonstrated for both SARS-CoV-1 and MERS-CoV. [7] Remdesivir is very discerning for viral polymerases, hence a low propensity to cause human toxicity. The drug also exhibits a high genetic hurdle to resistance in coronaviruses and has an extended intracellular half-life that permits for once-daily dosing.[8,9]

Remdesivir has become main stay of therapy for moderate to severe Covid 19 infection in many countries of world including India, many researchers and clinicians from different geographical area found it effective in covid 19 infections with good safety profile. [10] To generate more data related to effectiveness and safety of remdesivir in laboratory-confirmed Covid-19 infection, we conducted retrospective analysis at tertiary care center.

METHODOLOGY

A retrospective case control study was carried out at Covid unit, Department Of Medicine of tertiary care centre, Dhiraj Hospital, SBKS medical institute and research institute, Sumandeep Vidyapeeth after the approval from institutional Ethics Committee. Data of consecutive adult patients with RT-PCR confirmed Covid 19 infections having moderate to severe infection based on ICMR guidelines admitted from June to August 2020 were enrolled in this study. The decision to administer remdesivir was based on the presence of any or all three of the following: SPO2 of ≤94%, PaO2/FiO2 less than 300 on room air laboratory indication of CRS as indicated by markedly elevated inflammatory markers (CRP, Sr ferritin, D dimer, ESR) and worsening respiratory status or persistent high grade fever.

Total of 74 COVID-19 patients were indicated to receive remdesivir. Out of 74 eligible patients, who received remdesivir (n = 37) assigned as Group A and who had not received remdesivir (n = 37) assigned as Group B. Group B patients were also eligible for remdesivir as per indication criteria and as per hospital protocol but could not able to receive it because of either non availability of drug or financial constrain of patients.

Data regarding the presenting history, comorbidities status, contact history, vital signs and clinical findings including O2 saturation at the time of admission were recorded. Protocol based investigations findings of Complete blood count, coagulation profile, LFT, RFT, LDH, PCT, CRP, ESR and D dimer along with radiological investigation like Chest X-ray and if needed CT thorax was noted. All patients received same treatment as per institutional protocol for standard of care. Along with the standard care of treatment, patients of Group A

were given remdesivir intravenously over 30 to 120 minutes at a single loading dose of 200 mg on Day 1 followed by once daily maintenance doses of 100 mg from Day 2 with the recommended total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for total treatment duration of up to 10 days based on treating physician opinion after evaluating the patient. Group B received only standard care of treatment. Data including clinical and laboratory parameters was collected and recorded on 1st and 7th day of admission in CRF.

Patients who had co-infection other than COVID-19; history of severe allergic reactions to antiviral agents; less than 500 per L neutrophils or less than 50,000 platelets; active diverticulitis, inflammatory bowel disease, or another symptomatic gastrointestinal tract condition that might predispose patients to bowel perforation; severe hematological, renal, or liver function impairment were excluded.

RESULTS

Total 74 patients admitted in our hospital with moderate to severe covid 19 infection having indication for remdesivir as describe in methodology were included in this study. Out of these patients, 37 patients were given remdesivir (Group A) and 37 patients who were not given remdesivir (Group B). Mean age in years of group A was 55.08 ± 8.98 and that of group B was 56.78 ± 13.6. Male predominance is noted in both groups with 22 were male and 15 were females in group A while 29 were male and 08 were females in group B. Majority of patients in both the group belongs to urban area. More than half of the patients are from age group of 50 to 60 years in group A (56.75 %) while more than 60 years in group B (51.35 %) (Table 1) More than half of the patients were of moderate category of illness in both the groups (Group A Vs Group B; 54.05 % vs 65 %) at presentation. (Figure 1)

Comorbidities were present in 22(59.4%) patients and 24(60%) patients in group A and group B respectively. Hypertension and diabetes mellitus II were the most common comorbidities found in both the group followed by ischemic heart disease, COPD and hypothyroidism. 27.02 % (n =10) in group A and 32.43 % (n =12) in group B were having multiple comorbidities, commonest being hypertension and diabetes mellitus II together.

Most common presenting symptom in our study was breathlessness (group A: group B – 70.33 %: 81.45 %) followed by fever and cough. Other symptoms noted were sore throat, Bodyache, diarrhoea, Anosmia and loss of taste which are considered highly specific clinical symptoms for COVID-19 were found in less number of patients in our study. (Figure 2) Average o2 saturation on admission measured by pulse oximeter in group A was 85 % while in group B was 88 %.

Efficacy of Remdesivir

Hyperinflammatory response has been a hallmark of COVID-19 infection and considered key mediators of morbidity and mortality. We have assessed inflammatory markers, total duration of ICU stay and mortality between two groups to evaluate efficacy and safety of remdesivir in moderate to severe covid 19 infective patients. Difference of Mean was calculated for all inflammatory parameters (Total leucocyte count, Neutrophils to lymphocyte ratio, ESR, CRP, Ferritin, D-dimer, LDH) between values on admission and 7 days after 1st dose of remdesivir given in group A while on 7th day of admission in group B and analysed for significance using appropriate statistical tests (Table 2 A And B).

Mean values of total leucocyte count, neutrophils to lymphocyte ratio is increased in remdesivir group, though no clinically evident secondary infection was found in these patients. Among widely used inflammatory markers, ESR, CRP and S. LDH were reduced significantly (p value < 0.05) after remdesivir treatment. Mean S.ferritin and D-Dimer values were rather increased in Remdesivir group, though the result was statistically insignificant. (p value > 0.05)

Mortality Analysis

Group A patients who received remdesivir shows very less mortality (24. 32 %) compared to group B who didn't received remdesivir (48.64 %). Effects of confounding and risk factors on mortality were analyzed. Increasing age does not have effect on mortality in remdesivir group, while higher mortality rate is observed in young and elderly in non remdesivir group. Slightly less mortality observed in female in group A, while no gender difference in mortality rate is noted in group B. When the patient with various comorbidities received remdesivir, group A has shown quite less number of mortality compared to group B (table 4). Death rate is almost 50% more in non receiver group in both moderate and severe category of patients. Duration of ICU stay and days on ventilator theraphy were also taken as criteria for effectiveness of remdesivir in our study. Duration of ICU stay was quite less in remdesivir group as compared to non remdesivir group (group A 8.6 days compared to group B 11.9 days). Days on ventilator support is also quite reduced when remdesivir given (Group A 4.2 days compared to Group B 7.6 days) (Figure 3)

Table 1 Demographic data and disease profile

Characteristics	Group A (n =37)	Group B (n =37)
Age (Years)	55.08 ± 8.98	56.78 ± 13.6
Age Group (Years)		
< 50	08 (21.62%)	09 (24.32%)
50- 60	21 (56.75%)	09 (24.32%)
>60	08 (21.62%)	19 (51.35%)
Gender		
Male	22 (59.4%)	29 (78.38%)
Female	15 (40.6%)	08 (21.62%)
Locality		
Urban	24 (64.8%)	28 (70%)
Rural	13 (35.1%)	12 (30%)
Comorbidities		
Hypertension	18 (48.64%)	20 (54.05%)
Diabetes Mellitus II	14 (37.83%)	17 (46%)
IHD	10 (27.02%)	11 (30%)
COPD	09 (24.32%)	08 (22%)
Others	09 (24.32%)	06 (16.21%)

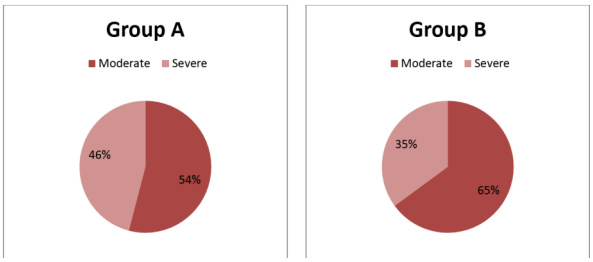

Figure 1: Severity Category of Covid- 19

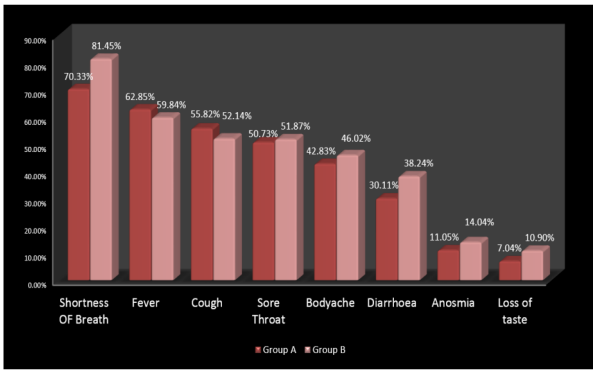

Figure 2: Frequency distribution of presenting symptoms in both the groups

Table 2 A: Difference of mean for inflammatory markers in remdesivir group A

	Investigations			
Group A (n=37)	On admission (Mean±SD)	7 days after remdesivir (Mean±SD)	Difference of mean	p value
TLC	9158.823 ± 5021.35	11418.78 ± 3518	-2259.957	.289
N/L Ratio	15.84 ± 13.11	19.05 ± 14.82	-3.2144	.480
ESR	80.06 ± 36.19	36.21 ± 16.02	43.85876	**.007**
CRP	94.55 ± 75.33	42.47 ± 73.91	52.08478	**.008**
Ferritin	322.46 ± 209.42	419.37 ± 259	-96.91231	.662
D-dimer	1195.38 ± 879.51	1570.18 ± 1278.75	-374.33212	.536
LDH	1140.85 ± 1324.76	689.26 ± 250.97	451.5967	**.041**
P/F Ratio	142.47 ± 101.59	254.97 ± 121.86	-112.522	.006

Table 2 B: Difference of mean for inflammatory markers in non remdesivir group B

Investigations				
Group B(n=37)	On admission (Mean±SD)	7th day of admission (Mean±SD)	Difference of mean	p value
TLC	9972.222 ± 3963.66	13550 ± 4876.132	-3577.778	**.008**
N/L Ratio	19.16 ± 14.27	16.98 ± 11.10	2.1800	.580
ESR	96.10 ± 34.53	60.12 ± 28..18	35.9833	.056
CRP	92.96 ± 88.79	73.92 ± 31.21	19.04147	.112
Ferritin	975.76 ± 259.02	1054.14 ± 379.2	-78.38667	.580
D-dimer	1237.56 ± 1046.55	1330.5 ± 127.9	-92.9466	**.004**
LDH	925.35 ± 493.41	1224.8 ± 302.65	-299.4583	.870
P/F Ratio	127.64 ± 96.16	150.4 ± 108.08	2.82333	.511

Figure 3: Subgroup Analysis of Comparative Mortality

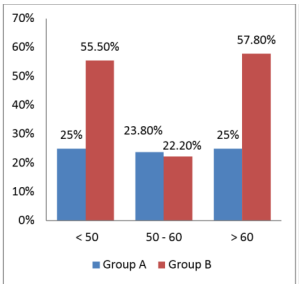

Figure 2 A: Age group wise mortality Analysis

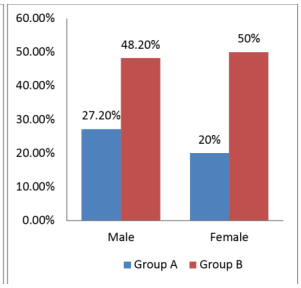

Figure 2 B: Gender wise mortality Analysis

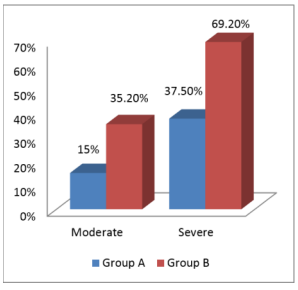

Figure 2 C: Severity wise mortality Analysis

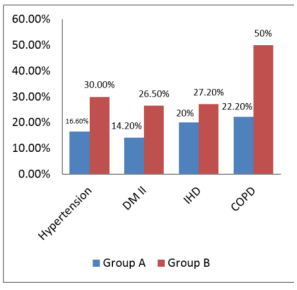

Figure 2 D: Comorbidities wise mortality Analysis

DISCUSSION

The ongoing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has led to more than 11, 43, 709 deaths globally as of Oct 23, 2020.[11] Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxemic respiratory failure, acute respiratory distress syndrome, and multiorgan failure that necessitates ventilatory support, often for several weeks.[12, 13, 14] The associated burden on health-care systems, especially intensive care units, has been overwhelming in several affected countries. Although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 in vitro [15], at present there are no therapies of proven effectiveness in treating moderate to severely ill patients with COVID-19 and current management consists of supportive care including invasive and non invasive oxygen supports, steroids, low molecular weight heparin. Remdesivir, an antiviral drug was found to be most promising treatment among number of off label therapies including antiretroviral, antiparasitic, anti-inflammatory drugs and convalescent plasma.

Remdesivir is a prodrug of a nucleotide analogue, having in vitro activity against many virus families including SARS-COV and MERS-COV. Several randomized controlled trials are providing many crucial informative evidence regarding the safety and efficacy of remdesivir for COVID-19. In one of the retrospective cohort study published on 11 June 2020 by, Jonathan Grein *et al* in the New England Journal of Medicine shown that with compassionate use of remdesivir, clinical improvement was observed in 36 of 53 patients (68%).[16] and concluded measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. Pandya H at al reported a case report concluded that remdesivir might be crucial for ensuring an efficient treatment, decrease mortality and allow early discharge in relation to in treatment of severe category COVID 19 patient. [17] In recently published solidarity trial results of WHO, Remdesivir failed to show effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilator and duration of hospital stay. Similar results were noted for other drugs like hydroxychloroquine, lopinavir and interferon too.[18] Remdesivir has become the standard of care for patients hospitalized with severe COVID-19 after a major study led by the National Institutes of Health showed that it reduced hospital stays by five days. The US Food and Drug Administration approved Gilead Sciences Inc's antiviral drug remdesivir for treating patients hospitalized with COVID-19, making it the first and only drug approved for the disease. Yeming Wang at al observed in his study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies. [19] Remdesivir for the Treatment of Covid-19, Preliminary report by J.H. Beigel at al supports the use of remdesivir for patients who are hospitalized with Covid-19 and require supplemental oxygen therapy. However he stated that given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in Covid-19. [20]

We have analyzed clinical data retrospectively from tertiary care center to check for effectiveness of remdesivir in moderate to severe category of COVID-19 patients in our

geographical area. In this study, overall patients who received remdesivir show almost half mortality (24. 32 %) as compared to non remdesivir group (48.64 %). Secondary outcome end points like duration of ICU stay was reduced in remdesivir (8.6 days) group as compared to non remdesivir group (11.9 days) and days on ventilator support is also quite reduced when remdesivir given (Group A 4.2 days compared to Group B 7.6 days). Rather quite high mortality is observed in non receiver sub groups of genders, younger and elderly age groups, moderate and severe disease category as well as in patients with comorbidities. In fact, Remdesivir treatment was found to quite less effective in primary endpoint reduction, when given along with standard protocol and treatment.

No new safety signals were detected in remdesivir therapy during this study. Nonclinical toxicology studies have shown renal abnormalities, but no clear evidence of nephrotoxicity due to remdesivir therapy was observed. Remdesivir is considered as a safe drug, however some studies shows patients in the remdesivir group discontinued the study drug because of adverse events or serious adverse events (18 [12%] in the remdesivir group *vs* four [5%] in the placebo group), among whom seven (5%) were due to respiratory failure or acute respiratory distress syndrome in the remdesivir group. [19] Nevertheless, the safety and side effect profile of remdesivir in patients with Covid-19 require proper assessment in large trials.

Interpretation of the results of this study is limited by the small sample size and relatively shorter duration of follow. Unfortunately, we could not able to retrieve viral load data to confirm the antiviral effects of remdesivir on viral load and viral suppression. Because of high cost of the drug, non affordability of patients and severe scarcity of drug in our region, we could not give drugs to many patients having indications as per standard regional treatment protocol.

CONCLUSION:

Compassionate use of remdesivir along with standard treatment in COVID-19 patients showed significant improvement, thereby reducing mortality and hospital stay associated with the disease. Though it is early to conclude while monitoring the results of large ongoing trials, but our study may add to the existing literature on providing results of remdesivir.

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