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ORIGINAL ARTICLE

Use and Outcome of Remdesivir in patients with COVID 19 presenting to Mayo Hospital Lahore

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ABSTRACT

Aim: To assess the usage of Remdesivir in COVID 19 patients admitted to Mayo hospital Lahore
Methods: This Quasi experimental study was carried out in COVID-19 ward from July 2020 to September 2020 on patients presenting to Mayo Hospital with COVID-19.The sample size (n=150) was calculated through non-probability convenient sampling technique. We gave intravenous Remdesivir to hospitalized COVID-19 patients with proven SARS-CoV-2 infection with an oxygen saturation of ≤94% who were breathing ambient air or needed oxygen support and had an oxygen saturation of less than 94%. Remdesivir was administered to patients over the course of a 10-day course, starting with 200 mg intravenously (I/V) on day 1 and continuing with 100 mg per day for the following nine days.
Results: Among 150 participants in our study, 103 (69%) were male and 47(31.3%) were females. Mean age was 57.37±13.42years. Selected parameters were evaluated at day 1, 5 and 10. Significant improvement in fever, dyspnea score, serum C- Reactive proteins (CRP) and lactate dehydrogenase (LDH) was found on day 1 and 10 with a p value of 0.01 to 0.000 for CRP and 0.48 to 0.000 for LDH respectively. Serum ferritin also showed a statistical difference with a significant p value of 0.038 at day 10 as compared to day 1 and 5.
Conclusion: Among patients presenting with severe Covid-19, clinical improvement was noticed earlier in those who received Remdesivir than those who didn't receive this drug. Measurement of effectiveness will require ongoing randomized controlled trials of Remdesivir drug therapy.
Keywords: COVID-19, intravenous Remdesivir, earlier clinical improvement, outcome, oxygen support, breathlessness

INTRODUCTION

A new -corona virus known as SARS-CoV-2 is believed to be the cause of the coronavirus diseases of 2019 (COVID-19). The severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), both of which have caused significant outbreaks in China and Saudi Arabia since 2002 and 2012, respectively, share 79% RNA sequence similarity and 50% genome sequence similarity, respectively.[1,2] Despite international efforts to contain the epidemic, the pandemic continued to spread quickly, culminating in 496 million confirmed cases and 6.17 million fatalities globally as of 8 April 2022.[3] This COVID-19 epidemic posed a serious hazard to international economy along with psychological, physical and mental health stress.[4-5] Yet, in the initial days there were no proven treatment to halt the disease.[6-7] Many studies were conducted to find potential therapeutic drugs to combat this epidemic of COVID-19 illness.

COVID pandemic hit Pakistan but not as badly as in Europe and other countries. As per available data, we have 1.53 million confirmed cases with 30,361 expiries. As many as 3000 patients were critically ill at a particular point.[8] Mayo hospital Lahore, being the largest tertiary care center in Punjab, was dedicated and devoted for COVID-19 patients at early start of the epidemic. Since that day Mayo hospital has dealt with COVID-19 cases of all categories and treated all patients with various available trial treatment options to find the best possible therapeutic drug.

Tocilizumab, hydroxychloroquine, Arbidol, ritonavir+lopinavir, and remdesivir are among the medications being randomly tested in numerous nations to determine the most effective COVID-19 treatment options[9-10]. Remdesivir (GS-5734), one of the investigational drugs used to treat COVID-19 patients, had a few successful clinical trials[10,11]. Remdesivir was created by Gilead Sciences during the 2014 Ebola virus outbreak in Western Africa as a treatment for the disease. It is basically a nucleotide analogue pro-drug for intravenous usage and has broad-spectrum antiviral activity[12,13] against a number of RNA viruses including COVID-19. It acts by hindering RNA polymerase resulting in RNA transcription cessation. In China, researchers used Remdesivir as early treatment option during the first episode of COVID-19 outbreak. It also showed promising results in Italy and USA[14, 15].

Remdesivir has an emergency use authorization (EUA) from the US Food and Drug Administration (FDA) for COVID-19 patients. Results from different regions of the world were fairly polarizing, even though certain clinical trials demonstrated the efficacy of remdesivir in COVID-19, which made it necessary to perform a clinical trial in our region of the world to determine its efficacy in patients with Covid-19.

Remdesivir, which had never been used in a public sector hospital in Punjab before, was approved by CEAG Punjab (Corona Expert Advisory Group in Punjab) for COVID patients in Mayo Hospital at the beginning of the outbreak, in Pakistan. This made it possible for us to evaluate the efficacy of this medication in COVID-19 patients presenting to Mayo Hospital, Lahore.

Early treatment with Remdesivir may lead to better outcomes. It can reduce hospital stay and reduce the need for mechanical ventilation. It can improve mortality rates. It may be more effective in combination with other treatments. Aims of the study was to have better understanding of COVID-19, development of effective treatment options, improved preparedness for future outbreaks and increased collaboration and sharing of information.

METHODS

This Quasi experimental study was conducted in COVID-19 ward (isolation/HDU/ICU) at Mayo hospital Lahore which included all patients with confirmed COVID-19, of both gender and in all the age groups, at any clinical stage of the disease requiring supplemental oxygen. Data was collected over 3 months. The sample size (n=150) was calculated through non-probability convenient sampling technique. The study was conducted after approval from the institutional review board on July 18, 2020 via reference no. 483/RC/KEMU.

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Patients were categorized, by lottery method, into two groups: Group A patients had Remdesivir drug in addition to conventional treatment and Group B comprised of patients having conventional drug therapy only. After Informed consent from patients/ their attendants, demographic data like name, age and gender was obtained. Necessary laboratory investigations like Complete blood count, Liver Function Tests, Renal function tests, Arterial blood gases, C-reactive protein, Lactate dehydrogenase, D-Dimers, Serum Ferritin and Chest X-ray were done before starting treatment on Day1, Day 5and then at the end of the treatment which is day 10. Patients were closely monitored and followed over a span of 10 days especially at day 1, 5 and 10. All the information was recorded on predesigned proformas

All collected data was analyzed by SPSS version 24. Quantitative variables e.g. Age and oxygen saturation were measured in the form of Mean±SD. Frequencies and percentages were calculated for gender. Independent T test was applied to find the variance between two groups with P value ≤0.05 was considered as significant.

RESULTS

Among 150 participants in our study, 103(69%) were male and 47(31.3%) were females. Mean age was 57.37 with ±SD 13.421. Among them 55% patients had diabetes mellitus, 55% patients had hypertension while 25% patients were smokers. Selected parameters were evaluated at day1, 5 and 10. Statistical analysis of fever parameter in remdesivir group showed MEAN± SD of 1.27±0.445 while in non-remdesivir group MEAN± SD was of 1.19±0.392 with a P value of 0.245 on day1, and 0.634 at day 10. P value for Dyspnea on day 5 was 0.004 And 0.000 on day 10 with a significant difference. P value for oxygen saturation was 0.691 on day 1, 0.015 on day 5 and 0.08 on day 10.Significant improvement in serum CRP and LDH was found on day 1 and 10 with a p value of 0.01 to 0.000 for CRP and 0.48 to 0.000 for LDH respectively. Serum ferritin also showed a statistical difference with a significant P value of 0.038 at day 10 as compared to day 1 and 5. However there wasn't any difference on Chest X-RAY changes and level of D-Dimers with a non-significant P value at day 5 and 10.

Table l shows the baseline characteristics of the patients

Comparison of routine investigations of patients at day 1, 5 and 10 are shown in Table ll. Evaluation of different disease severity parameters at day 1, 5 and 10 are mentioned in Table lll.

Table I: Baseline Charateristics of the Patients

		Frequency	Percentage
Gender	Male	103	69%
	Female	47	31.3%
	Total	150	100%
Diabetes Mellitus	Yes	82	55%
	No	68	45%
	Total	150	100%
Hypertension	Yes	82	55%
	No	68	45%
	Total	150	100%
Smoking	Yes	37	25%
	No	113	75%
	Total	150	100%

Table ll :Comparison of Routine investigations at Day 01, 05 and 10 betweenGroup A (Remdevisir) & Group B (Non-Remdevisir)

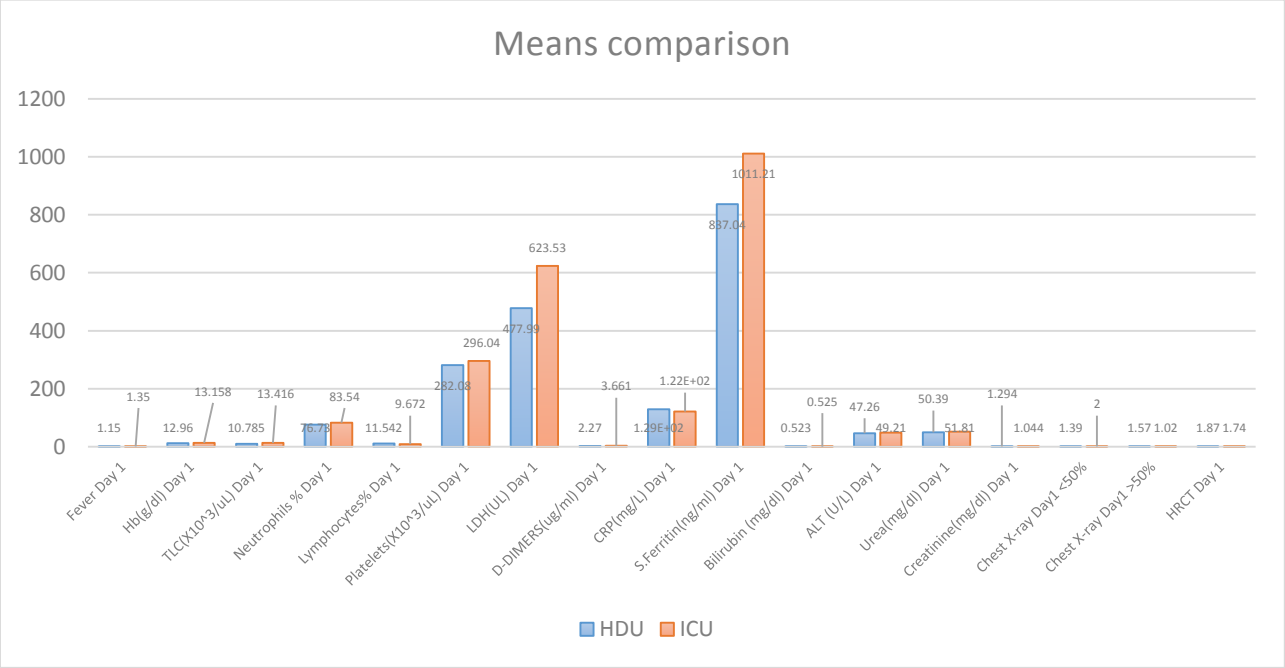
	Group	n	Day 01 (Mean ± SD)	Day 05(Mean ± SD)	Day 10 (Mean ± SD)
Hemoglobin (Hb) (g/dl)	Group A	75	13.291 ± 1.5159	13.123±1.3206	13.236±1.3073
	Group B	75	13.291 ± 1.5159	12.879±1.6471	12.749±1.5995
	P value		0.039	0.318	0.043
Total Leukocyte Count (TLC) (X10^3/uL)	Group A	75	9.898±4.6079	8.845±3.5385	8.591±2.2850
	Group B	75	13.671±7.3438	14.279±5.6181	13.867±4.4847
	P value		0.000	0.000	0.000
Neutrophils %	Group A	75	78.45±8.343	76.44±7.444	72.53±5.905
	Group B	75	80.19±9.104	81.37±8.671	79.33±8.475
	P value		0.226	0.000	0.000
Lymphocytes%	Group A	75	13.096±7.756	17.5067±6.376	22.453±5.4009
	Group B	75	8.567±8.2604	10.8075±7.733	11.689±7.9892
	P value		0.001	0.000	0.000
Platelets(X10^3/uL)	Group A	75	289.07±79.48	303.76±84.924	302.77±68.933
	Group B	75	285.69±76.52	284.36±97.877	286.79±77.056
	P value		0.792	0.197	0.183
Bilirubin (mg/dl)	Group A	75	0.499 ±0.1712	0.6120±0.5344	0.5547±0.13881
	Group B	75	0.549 ±0.16 59	0.6253±0.2175	0.5960±0.17967
	P value		0.071	0.842	0.117
Alanine Aminotransferase (ALT) (U/L)	Group A	75	49.73±41.913	48.13±28.382	50.39±28.912
	Group B	75	46.27±15.754	46.97±21.556	41.97±14.018
	P value		0.504	0.778	0.025
Urea(mg/dl)	Group A	75	42.61±26.277	38.89±23.559	37.19±12.999
	Group B	75	59.24±30.944	48.92±26.749	53.00±35.662
	P value		0.001	0.016	0.000
Creatinine(mg/dl	Group A	75	0.949±0.2830	0.9093±0.2422	0.8693±0.21932
	Group B	75	1.448±1.6459	1.3893±1.2254	1.3880±1.18925
	P value		0.011	0.001	0.000

Table III :Comparison of Severity Indicesat Day 01, 05 and 10 betweenGroup A (Remdevisir) & Group B (Non-Remdevisir)

	Group	n	Day 01(Mean ± SD)	Day 05 (Mean ± SD)	Day 10 (Mean ± SD)
LDH (UL)	Group A	75	564.0±228.1	490.2±208.6	380.3±184.4
	Group B	75	502.5±137.6	510.5±136.2	422.6±166.9
	P value		0.048	0.480	0.000
D-DIMERS(ug/ml)	Group A	75	1.72±2.19	1.28±0.97	1.20±1.08
	Group B	75	3.87±4.99	2.49±3.18	1.42±0.66
	P value		0.001	0.002	0.137
CRP(mg/L)	Group A	75	1.51±102.37	132.4±74.2	69.01±53.42
	Group B	75	1.01±82.67	128.2±71.05	1.22±60.05
	P value		0.001	0.721	0.000
Serum Ferritin(ng/ml)	Group A	75	1067.1±485.5	1039.6±468.8	739.8±400.8
	Group B	75	739.3±604.3	964.3±584.9	906.19±561.15
	P value		0.001	0.382	0.038
Improvement on HRCT	Group A	75	1.79±0.41	1.79±0.41	1.80±0.40
	Group B	75	1.85±0.35	1.88±0.32	1.93±0.25
	P value		0.034	0.002	0.000

LDH= Lactate dehydrogenase, CRP= C-Reactive protein, HRCT: High Resolution computed tomography

Fig l: Baseline Investigations of COVID-19 patients admitted in High dependency Unit (HDU) and Intensive care Unit (ICU) at presentation



DISCUSSION

Our study was the first randomized controlled trial of an experimental therapeutic drug, Remdesivir, for COVID-19 in Mayo hospital Lahore, which was a dedicated tertiary care facility for COVID-19 patients.

Results of our study revealed that Remdesivir reduced the duration of illness and in-hospital stay of mild/moderate severity illness patients who didn't require high flow/invasive oxygenation while it had no effect on patients with invasive ventilation. These findings are consistent with ACTT, Adaptive Covid-19 Treatment Trial (ACTT-1)[16]which was a controlled randomized double-blind clinical trial of remdesivir of 1062 patients having COVID pneumonia. Data showed that those patients who got remdesivir had an average recovery time of 10 days compared to a15 days recovery time in patients who got a placebo. Data showed that remdesivir was better than placebo in reducing the recovery time in patients with Covid-19 pneumonia.

Many studies are under-process for finding the effectiveness of remdesivir as a remedy for COVID-19. The largest one is SOLIDARITY TRIAL of World Health Organization (WHO)[17]encompassing more than 30 countries, which evaluated the effectiveness of these treatments on mortality, commencement of ventilation, and length of hospital stay in admitted patients. Interim outcome of the Solidarity Trial revealed that remdesivir, interferon, lopinavir/ritonavir and hydroxychloroquine didn't have any effect on mortality or duration of in hospital stay in COVID-19 patients. However, these results were contradictory to another trail done in china.[18]

In another multicenter double-blinded controlled trial conducted at ten hospitals Hubei, China[18], all those patients having remdesivir with symptoms duration of ≤10 days had an earlier clinical improvement compared to those getting placebo only. There was no little or no difference in patients with severe COVID-19pneumonia; however, the reduction in duration of illness in terms of days in those treated at an early stage required further endorsement inlarger studies.

Another open-label Randomized clinical trial[19] of admitted patients with severe COVID-19 and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation

>94%) enrolled from March 15 to April 18, 2020, at 105 hospitals in the United States, Europe, and Asia and published in AMERICAN JOURNAL OF MEDICAL ASSOCIATION[20] and New England Journal of Medicine[21] compared a 5- and 10-day course of remdesivir with conventional treatment. Among patients with moderate COVID-19 illness, there was no significant numerical difference in clinical outcome in those who were given a 10-day course of remdesivir compared to standard conventional treatment at 11th day of treatment. But notable difference was found in Patients randomized to a 5-day course of remdesivir compared to conventional treatment, though the difference was of undetermined numerical significance. These findings were consistent with our study.

The WHO guidelines count on the resultsobtained from the Solidarity trial data[17]. Statistics obtained from the interim results of this trial had not been made available or peer-reviewed. The data disclosed to date is at variance with more strong substantiation obtained from the NIAID and Gilead's open-label trials, whose results have showed the clinical advantage of remdesivir.

Curing fatal ailment with drugs that combat the pathogen had been the mainstay for treating any disease. Being an antiviral, remdesivir hampers SARS CoV-2 virus hence halting its replication and infectivity burden. Different combinations of remdesivir and other anti-inflammatory agents are being used in order to find a potential therapeutic regimen for COVID-19 patients.

Compared with an earlier study about the use of remdesivir, our study sample size is smaller with patients at variable stage of the disease and less patients on invasive ventilation as in first wave of COVID. Some were treated at an early stage of their disease course. Such dissimilarity might favor remdesivir, providing much benefit to study group. For the patients referred from other hospitals, we were unable to assess properly whether earlier remdesivir therapy provided a better clinical response. However, remdesivir was found to limit the duration of clinical illness in patients treated within 10 days of symptom outset. Ongoing clinical trials are anticipated to support our findings.

Our study established that there were no serious safety concerns regarding remdesivir and it was well tolerated. Limitations of our study were quite late start of treatment in some patients presenting at a late stage and little or no data about factors minimizing the receptiveness to remdesivir. The periodic use of steroids in our study patients might have contributed to rapid viral duplication, as observed in SARS27 and MERS, although these studies only outline the lengthening of the time of detection of non-infectious viral RNA. Moreover, our study didn't support whether higher doses and a long course of remdesivir might be of any help in severe COVID-19 patients. However, numerical improvement was observed in few clinical parameters which was more marked in moderate and severe illness group of COVID-19. Ongoing studies with large group of people will continue to strengthen our perception of the effect of remdesivir onCOVID-19. Further strategies to boost the antiviral activity of remdesivir (e.g., high-dose regimen, combination with other antivirals, or SARS-CoV-2 neutralizing antibodies) and to alleviate immune-pathological host responses which add to severity of COVID-19 (e.g., IL-6, IL-1 inhibitors, or TNF α inhibitor) require meticulous research in patients with severe COVID-19.

This study has certain limitations. First of all, it is not a multicenter trial and the sample size was somehow, limited depending upon the study design and prerequisites. To support the findings of the current study, more interventional research is needed.

CONCLUSION

Our study data showed that remdesivir is helpful in reducing the hospital stay and in improving some clinical parameters in moderate severity disease group but not in severe disease group. Further multi-central trials are the need of the hour to explore whether the use of Remdesivir earlier in the course of disease is more beneficial than when more severe symptoms of COVID-19 are there.

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