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Original Article

Assessment of Clinical Efficacy of Early Use of Remdesivir in The Patients of COVID-19 Pneumonia

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Abstract

Objective: Primary objective of the study is to evaluate the clinical efficacy of early use of Remdesivir in reducing the progression and severity of Covid-19 pneumonia.

Methods: This retrospective study was undertaken in Pulmonology department, Fatima Memorial Hospital, Lahore. After taking history and doing physical examination, loading dose of 200mg intravenous Remdesivir was given to the 350 patients of COVID-19 pneumonia followed by 100mg intravenous dose given once a day for five days. During treatment assessment of clinical efficacy of Remdesivir was evaluated along with viral clearance rate and evaluation of side effects of therapy. These were documented on preformed Performa.

Results: The results showed 99.9% efficacy in patients with Covid-19 pneumonia who were treated with early Remdesivir. Paired sample t-test showed statistical significant results in radiological findings and oxygen saturation pre and post Remdesivir therapy. Almost all the clinical symptoms got relieved after therapy. Drug related side effects were reported in 21 individuals (6%).

Conclusion: The early introduction of drug Remdesivir to the treatment of Covid-19 PCR positive patients has been suggested as a more efficacious strategy for treating Covid-19 pneumonia.

Keywords: Remdesivir, Covid-19, anti-viral

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Introduction

Coronavirus – SARS-CoV-2 was initially recognized in December 2019 as the virus accountable for respiratory disease,[1] Covid-19 disease. Despite trying out various anti-viral medications against Covid-19 treatment, none were showed any response. Morbidity was shown to be reduced by dexamethasone (morbidity remained 25.7% in control as compared to 22.9% in dexamethasone group; p 0.001), with the patients on invasive mechanical ventilation having the most pronounced benefit.

To consider the use of unapproved or unlicensed use of medications with potential anti-viral activity has brought regulatory authorities, researchers, clinicians and manufacturers together to find an effective therapeutic agent in the midst of the Coronavirus disease 2019 (Covid-19) pandemic.[1] Several therapeutic agents are currently being evaluated for Covid-19 management, with one of these being anti-viral agent Remdesevir.

Numerous studies on Remdesivir have been conducted, and the use of Remdesivir in the European Union has been approved by national regulatory authorities of Spain, Switzerland, Hungary, Slovenia, Greece, Iceland, Italy, Portugal, Netherland, Romania, Austria, Slovakia, Belgium, France, Germany, Cyprus and Estonia.[2] The food and Drug Administration (FDA) sanctioned first emergency drug named Remdesivir in the United States on 1st May 2020.

Remdesivir is a nucleotide pro-drug. It appears to work in various ways, however, the precise mechanism of action is unknown. It inhibits virus replication by blocking viral RNA-dependent RNA polymerases. In vitro studies, in the epithelial cells of the human airway, Remdesivir hindered SARS-CoV-2 replication. The active metabolite of Remdesivir adenosine nucleoside triphosphate analog doges proofreading by exoribonuclease. It can also synthesize an alternate substrate for the RNA-chain terminator that prevents active tri-

phosphates from entering coronavirus RNA. Remdesivir remains effective against coronavirus as it seems to have a genetic blockade to developing resistance. Remdesivir has activity against other coronaviruses, including Alpha-coronavirus NL63 and those causing SARS and MERS.[2,3]

Covid-19 has affected all age groups, median ages range between 47-59 years with elderly having a greater mortality risk. Higher incidence of cases was noted in male gender. According to a Chinese investigation, just 2% of those influenced were younger than 20.[3]

COVID-19 disease has variable clinical manifestations. While most adults and children experience fatigue, fever, catarrhal symptoms, some experience respiratory difficulty, arrhythmias, unexpected myocardial infarction, pancreatitis, ARDS, multi-organ failure and death. Fever, fatigue, cough and shortness of breath are the most well-known indicators. Headache, upper respiratory symptoms such as sore-throat and rhinorrhea and gastrointestinal manifestations such as nausea, vomiting and diarrhea occur at a lower rate.[4]

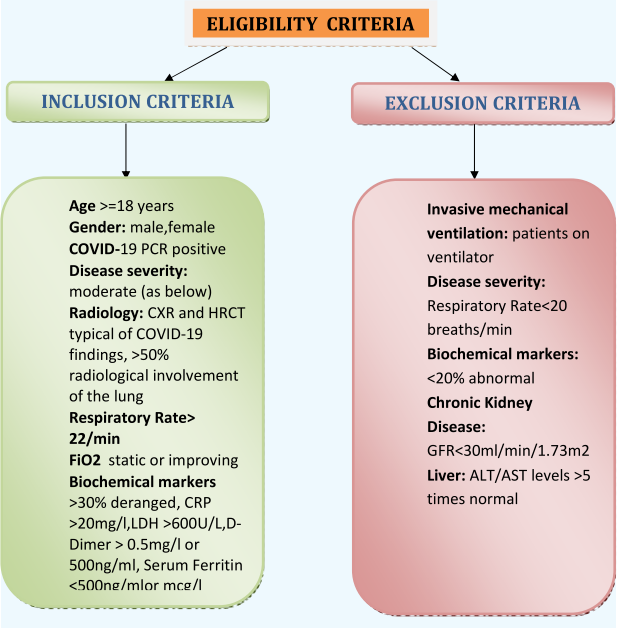
Blood picture displayed lymphocytopenia, with reduced lymphocyte count and white cell count. Severe Covid-19 disease correlated with higher inflammatory markers such as CRP, serum ferritin, serum LDH, D-dimers, deranged liver function tests and serum creatinine levels. Radiology shows peripheral consolidations. While certain affirmed cases may have ordinary high resolution CT scan of chest, irregularities have been found in certain patients preceding the beginning of manifestations.[5]

On 26th May 2020, the Medicine and Healthcare products Regulatory Agency (MHRA) approved a primary approach mechanism for Remdesivir for the patients over 12 years of age either requiring or not requiring invasive mechanical ventilation.[4] On 25th of June 2020, a positive recommendation was issued for Remdesivir by European Medicine Agency which had conditional approval from European Union, despite the fact that its safety and efficacy profile was unknown at the time.[6]

In Pakistan, there is limited data, evaluating the effect of Remdesivir in Covid-19 patients with studies limited to small numbers of patients and not evaluating its use early in disease process. Therefore, in order to assess its potential for use in the early stages of the disease and to avoid complications and hospitalization, the clinical efficacy of Remdesivir will be evaluated in our observational study, in our local population.[7,8]

Methods

Study Design & Sampling Technique: This was a retrospective study used convenient non-probability sampling frame.



Data Collection Procedure: After the approval of ethical committee, informed consent was taken from 350 patients full filling the criteria. After taking history and doing physical examination, loading I/V dose of 200mg Remdesivire and was injected to the COVID-19 Patients following a 100mg I/V daily dose was introduced for 5-10 days. Decision of customized doses of Remdesivire was taken by the attending physician keeping comfort usage in mind in terms of duration of ventilation, bacterial co-infection and doses were extended accordingly for no more than 10 days depending upon clinical condition of each COVID-19 Patient. Nasopharyngeal swabs were obtained after treatment to find the viral load and viral clearance rate of SARS-CoV-2 by rRT-PCR. Chest X-ray or HRCT chest were performed to assess the radiological improvement. During treatment assessment of clinical efficacy of Remdesivir, viral clearance rate and evaluation of side effects of therapy were done and information added on preformed Performa.

Data was processed by entering and analysis through statistical package for social studies software (SPSS) version 25.0. The variables like gender and presence of side effects are presented in frequency and percentages while other variables associated with efficacy of Remdesivir are compared to each other in paired sample t test. P Value <0.05 and confidence interval of 95% is considered as significant.

Results

The frequencies of lab findings and viral load check, after the Remdesivir therapy, showed 100% efficacy of the drug. The signs and symptoms were relieved in all the 350 individuals who participated in the study after induction of Remdesivir therapy. Shown in Table 1.

Table 1: *Sign and Symptoms of study subjects*

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Fever	350	1.00	1.00	1.0000	.00000
Cough	350	1.00	1.00	1.0000	.00000
SOB	350	1.00	1.00	1.0000	.00000
Sore_Throat	350	1.00	1.00	1.0000	.00000
Respiratory_Rate	350	1.00	1.00	1.0000	.00000
Pulse	350	1.00	1.00	1.0000	.00000
BP	350	1.00	1.00	1.0000	.00000

The paired sample t test was conducted to evaluate the two variables pre and post Remdesivir therapy, namely, oxygen saturation and radiological findings. The result concludes that the test is significant statistically as the p value is less than 0.05.

Table 2: *Paired Sample t-test for Pre and Post Treatment Comparison*

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Dev.	Std. Error Mean	95% CI of the Difference Lower	95% CI of the Difference Upper			
Pair 1	SPO2_CE1 - SPO2_CE2	91.54000	5.09986	.72123	90.09064	92.98936	126.922	49	.000
Pair 2	Radiological_Findings_CE1 - Radiological_Findings_CE2	.72000	.57286	.08101	.55720	.88280	8.887	49	.000

After getting the Remdesivir therapy done, 6% of individuals reported with the afore mentioned side effect.

Table 3: *Therapeutics Effects*

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Broadcarida	7	2.0	2.0	2.0
	Developed bradycandia with PR upto 35 / min	7	2.0	2.0	4.0
	Deveopped hemoptysis	7	2.0	2.0	6.0
	NA	329	94.0	94.0	100.0
	Total	350	100.0	100.0	

Discussion

Currently, proof from RCT's has opened up. Wang et al. led the first multicentre preliminary in Hubei, China that was randomized, double –blinded and placebo-controlled. A sum of 236 patients, were randomly allocated to get Remdisivir or a placebo treatment. Eight individuals in the Remdisivir category and two participants in the other group were barred from the study since they did not start or finish treatment within five days. The essential clinical result measure was the time needed to accomplish clinical improvement within 28 days of randomization, as controlled by international scale standards. Though not significant statistically, average time to clinical improvement was less in the Remdesivir-treated gathering.[6,7]

Another stage 3 randomized, open-mark preliminary

(SIMPLE-Severe) was led in numerous nations (i.e. Italy, United States, Germany, Spain, Singapore, Hong Kong, Taiwan and South Korea) to assess the safety, efficacy and adequacy of various Remdesivir doses (5 versus 10 days) in patients with serious COVID-19. 397 patients were arbitrarily relegated to get the medication intravenous during the treatment. On day 14, clinical status was assessed. At day 14, 64 patients treated with Remdesivir for five days showed clinical improvement, contrasted with 54% of patients treated with Remdesivir 10 days. Subsequently, by assessing clinical status, it was found that there was no additional benefit for giving Remdesivir for 14 days. The average length of hospital stay was the same (7 days for the 5-day treatment group versus 8 days for the 10-day therapy group) among patients discharged prior to day 14. There was no marked difference in mortality between the two groups.[9]

The investigation by Spinner et al. on this issue gives significant new data on the likely adequacy of Remdesivir in patients with moderate COVID-19, and recommends an unassuming clinical advantage for the 5-day course contrasted with standard consideration. Discrepancies in sample selection possibly contribute for some of the differences in Remdesivir RCT outcomes. To begin with, the optimum patient population is not defined. Secondly, the treatment period is not defined. Thirdly, there is no information on the effects on specific clinical outcomes. However, the costs of mass-producing and distributing Remdesivir are prohibitive, and it's unclear whether it is better than corticosteroids, which are readily available and in-expensive. As a result, additional Remdesivir studies in large-scale RCT's should be conducted as soon as possible to address remaining uncertainty and inform optimal use.[10]

Finally, this study evaluated the safe use of Remdesivir among COVID-19 patients. Though a prior research work showed Spartan communal adverse effects consisting raised liver enzymes among 32.1% cases, renal problem as 14.4%, ekevated creatinine levels among 11.2% and failure in respiration among 6.4%. This study found little evidence of elevated risks of adverse effects after treatment with Remdesivir such as bradycardia and haemoptysis in 21 individuals while other 329 individuals showed no side effects. Our findings suggest, Remdesivir may be considered a safe anti-viral medication for the treatment of patients infected with SARS-CoV-2. Furthermore, early administration of Remdesivir may aid to improve the clinical consequences of COVID-19 patients.

Comprehensive acknowledgment of the current data on Covid-19 is critical for pandemic containment. Remdesivir is still being studied as a Covid-19 treatment. Our findings suggest that length of illness was reduced and patients with early institution of Remdesivir progressed significantly less to severe disease requiring hospitalization. Further randomized control trials must be conducted to further establish the efficacy of early use of Remdesivir against Covid-19 infection. The introduction of Remdesivire drug through intravenous and pulmonary routes being suggested for more appropriate plan in treatment of COVID-19 patients.[11,12]

Conclusion

Given the shortage of compelling treatment alternatives accessible to date, testing Remdesivir in patients with serious Covid-19 pneumonia is sensible. Bigger multicenter RCT's considering placebo treatment and case control groups are required to confirm the benefits of early use of Remdesivir.

Conflict of Interest: *None*

Funding Source: *None*

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