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RESEARCH ARTICLE

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Therapeutic interventions of remdesivir in diabetic and nondiabetic COVID-19 patients: A prospective observational study conducted on Pakistani population

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Abstract

We aimed to investigate the interventions of remdesivir in both diabetic and nondiabetic individuals who were suffering from a severe infection of novel coronavirus disease (COVID-19). In this study, we aimed to explore the relationship between therapeutic effectiveness of remdesivir and complications of diabetes mellitus by observing the recovery period among diabetic and nondiabetic patients associated with COVID-19 infection. A total of 850 COVID-19 patients were recruited for this study, out of which 48% were diabetic and 52% were nondiabetics. The results of this study indicated that nondiabetic individuals administered with remdesivir recovered from COVID-19 within 10 days showing a 95% confidence interval ($p < 0.01$), while the diabetic individuals recovered in 15 days. Nondiabetic patients administered with remdesivir exhibited higher chances of clinical improvement at 15th day than those who were associated with diabetes. Remdesivir administration improved the levels of various biochemical parameters, such as C-reactive protein, lactate dehydrogenase, D-Dimer, and ferritin both in diabetic and nondiabetic patients. However, a significant improvement ($p < 0.01$) was seen in the level of biochemical parameters among nondiabetic patients as compared to that of diabetic patients administered with remdesivir treatment. In the end, it was concluded that remdesivir could be considered as a possible therapeutic agent in the treatment of COVID-19 both in diabetic and nondiabetic situations. However, diabetic patients showed a delayed recovery as compared with that of nondiabetic patients, in which the recovery rate was high.

KEYWORDS

COVID-19, diabetic patients, nondiabetic patients, remdesivir

1 | INTRODUCTION

Remdesivir (initially named GS-5734) is an adenosine analog having a broad-spectrum antiviral activity against several viruses, such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome, and severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1).[1–3] Pharmacologically, remdesivir has been designed to deliver the monophosphate nucleoside analog GS-441524 to cells. Remdesivir is an adenosine simple nucleotide prodrug that is extensively utilized intravenously nowadays. Remdesivir combines with viral gene subordinate RNA polymerase and forestalls viral duplication by decreasing RNA production. It appears to be

hostile in SARS-CoV-2 activity *in vitro*. Remdesivir treatment was begun following vaccination in the SARS-CoV-2 model where the remdesivir-treated living subjects showed less viral invasion in lungs and proved to be less harmful as compared with the control living subjects.[4,5] Remdesivir has been approved by Food and Drug Authority (FDA) for the treatment of coronavirus disease 2019 (COVID-19) infection in hospitalized patients. Additionally, FDA supports the use of remdesivir for the treatment of COVID-19 symptoms in hospitalized pediatric patients having body weight 3.5–40 kg or 12 years old childrens. Remdesivir should be administered in an emergency clinic or a medical care environment providing care to inpatients. Previous research studies had depicted that coronavirus and glucose digestion are interlinked with each other in a way that the high level of glucose facilitates the replication of SARS-CoV-2 in human monocytes, resulting in the upregulation of glycolysis process, resulting in an increase in the replication of SARS-CoV-2. The replication of SARS-CoA-2 is accompanied by the delivery of responsive mitochondrial oxygen species and also by activating various factors that may lead to hypoxia. Subsequently, hyperglycemia may help in viral replication. Hyperglycemia or a background marked by type 1 diabetes mellitus and type 2 diabetes mellitus were as potential indicators of morbidity and mortality associated with SARS patients.[4,6,7]

Although COVID-19 has infected people of all ages, the average infected population was somewhere in the range of 47–59 years, with serious cases and nonsurvivors were of higher age comparatively. Male gender orientation seems to have a higher prevalence of cases. According to a Chinese investigational study, just 2% of infected patients were younger having an age of almost 20. The research studies had proved that the coronavirus has a wide clinical range. While most grown-ups and kids experience influenza-like manifestations, some foster acute respiratory distress syndrome, respiratory turbulence, arrhythmias, unexpected heart infarction, numerous organ failure, and deaths. Furthermore, fever, fatigue, the presence of sputum, and difficulty in breathing are the most well-known indications. In addition, migraines, upper respiratory infections (sore throat and rhinorrhea), and gastrointestinal manifestations (vomiting like sickness and diarrhea) all happen at a lower rate. Most of the patients, especially those with lymphocytopenia, have a diminished count of white blood cells. The patients with severe conditions exhibited higher neutrophil tallies accompanying provocative biomarkers of D-dimer, blood urea, and creatinine levels. However, various affirmed cases may have ordinary computed tomography scans where irregularities have been found in certain patients leading toward the beginning of manifestations.[4,7] SARS is a solitary abandoned RNA infection coated in a protein-enriched lipid bilayer with 82% resemblance of its DNA with human beings. The infection that causes the serious intense respiratory condition, that is, SARS will be SARS-CoV.[4,8,9] The angiotensin-converting enzyme-2, which is chiefly existed within lungs, heart, vessels, and few other cells acts as a chief passageway receptor for SARS-CoV-2 in human cells. The coronavirus patients showed symptoms within 5–6 days after infection. The patients with a higher risk of COVID-19 were associated with various characteristics and complications, including old age and male genders accompanying various clinic manifestations, such as cardiovascular diseases (CVD) and diabetic mellitus. A previous study had demonstrated that hidden CVD and diabetes mellitus proved as a basic complication in the progression of COVID-19 infection in patients admitted to emergency care units.[10]

The aim of our study was to investigate the effectiveness of the antiviral drug, that is, remdesivir in the treatment of novel COVID-19 infection accompanying with and/or without diabetes mellitus manifestation. No doubt the discovery of the COVID-19 vaccine has eradicated various barriers coming in the way of treatment but still, we need an effective immediate response in the form of a specific therapeutic agent.

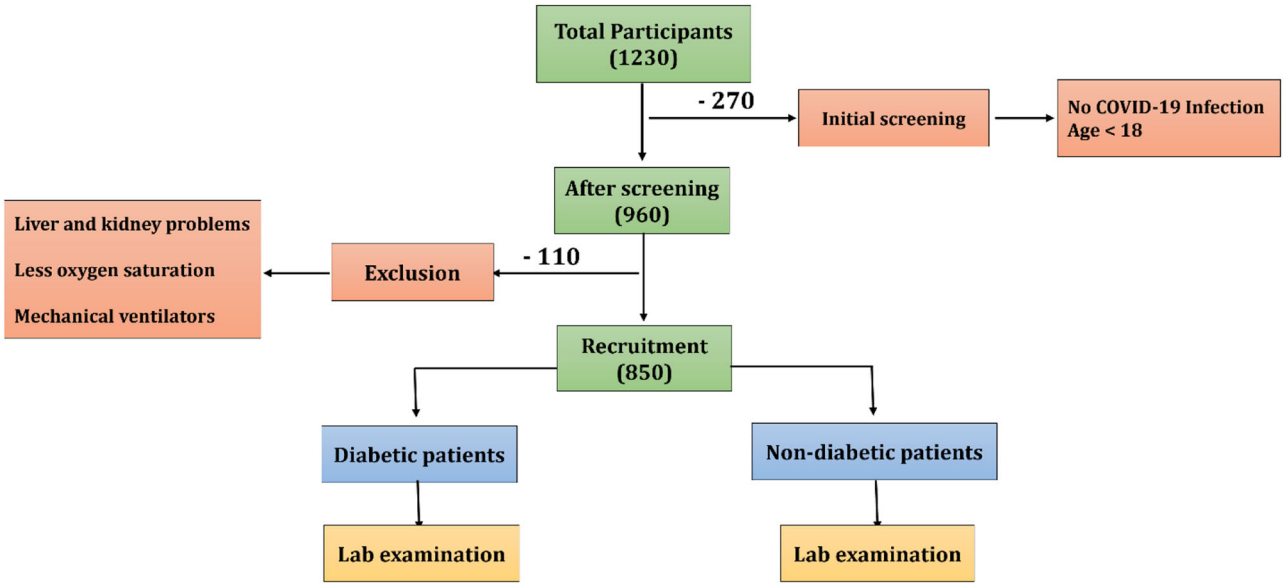

FIGURE 1 Flowchart for recruitment of study participants

2 | MATERIALS AND METHODS

2.1 | Sample collections

The blood samples were collected from both diabetic and nondiabetic COVID-19 patients living in Multan, Pakistan. Initially, 1230 participants took part in this study as shown in Figure 1. After screening, 850 samples were recruited in the current study. The remaining 380 participants were excluded because those participants were either in a critical COVID-19 situation or suffering from severe liver or kidney disorders. The samples were taken from both male and female COVID-19 patients without any gender discrimination.

2.2 | Ethical approval and study duration

This prospective observational study was ethically approved by the ethical research committee (26880-935/NMU&H) of Nishtar Medical University, Multan, Pakistan. This study was conducted from July 2020 to March 2021 in the Department of Medicine, Nishtar Medical University, Multan, Pakistan where the subjects complaining about respiratory symptoms were further assessed for COVID-19 laboratory examination. The patients with positive COVID-19 lab examination were included in this study.

2.3 | Inclusion criteria

In this study, we included only those participants with confirmed SARS-CoA-2 infection having an age of more than or equal to 18 years. The kidney and liver tests were also monitored while recruiting the patients in this study as prelaboratory examination and only those patients having creatinine clearance of more than 30 min/ml were included in this study.

2.4 | Exclusion criteria

The participants without SARS-CoA-2 infection were excluded from the study. Furthermore, the patients having severe kidney and liver problems were also excluded from this study. Furthermore, the patients who exhibited pneumonia in their radiographical images with an oxygen saturation of less than 94% thus requiring external oxygen support were also excluded from this study as they were suffering from severe COVID-19 infection.

2.5 | Grouping of patients

This study was conducted on two groups: (1) a diabetic category comprising of COVID-19 patients treated with remdesivir and (2) a nondiabetic category with positive COVID-19 treated with remdesivir. Coronavirus cannot be analyzed without microbiologic examination. The patients who met the accompanying rules ought to be tried for SARS-CoV-2 but notwithstanding with any other respiratory microorganisms' infection such as flu. However, while various lab tests have been grown for the diagnosis of COVID-19 infection, however, the constant reverse-transcription polymerase chain response has been recognized as the best quality diagnostic tool for the confirmation of COVID-19 infection having the ability to detect positive SARS-CoV-2 nucleic corrosive in sputum, throat swabs, and lower respiratory secretions.

2.6 | Biochemical parameters

To elaborate the effectiveness of remdesivir in diabetic and nondiabetic patients, a laboratory examination was performed to check the levels of ferritin, lactate dehydrogenase, C-reactive protein, and D-dimer in both diabetic and nondiabetic patients.

2.7 | Administration of remdesivir

The COVID-19 patients were administered with a 200 mg iv dose of remdesivir as a first dose followed by a dose of 100 mg iv for 5 days. The infectious diseases physician made a personalized decision for remdesivir dosage, followed by treatment extension up to 10 days depending on the patient's clinical condition or based on the patient's comfort with the medication or bacterial coinfection and ventilation duration. The remdesivir is accessible in two dosage forms, including fluid and powder. The powder should be blended in liquid and imbued (gradually infused) into a vein over by a specialist or medical caretaker in a clinic. It is commonly given once a day for a duration of 5–10 days. The duration of treatment depends on how the patient's body reacts upon the medication.[4,11]

2.8 | Statistical method

The results were given in the form of frequency, percentage, and median. The attributes of the study population were mentioned in frequency and percentage while the levels of biochemical parameters were elaborated in the form of the median. The level of significance was found by analysis of variance. The value of $p < 0.05$ was considered significant.

3 | RESULTS

The patients in two groups were balanced in disease characteristics. Diabetic individuals were 48%, out of which 42% were hypertensive, while nondiabetic patients were 52%, out of which 30% were hypertensive. Similarly, both groups had almost similar percentages of male and female participants. Furthermore, the division was also done on the basis of the patient's oxygen requirement, and it was clearly depicted from the results that both diabetic and nondiabetics had a similar ratio as shown in Table 1.

TABLE 1 Randomized studies of remdesivir in COVID-19 patients

Characteristics	Diabetic patients (48%)	Nondiabetic patients (52%)
Age	18–58	20–62
Gender (males)	64%	65%
Gender (females)	36%	35%
Hypertension	42%	30%
Hospitalized, not requiring oxygen	13%	12%
Hospitalized, requires oxygen	39%	41%
Median time from symptoms onset to randomization (days)	6–12	6–12

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 2 Results of biochemical parameters before and after treatment with remdesivir

		Nondiabetic COVID-19 patients		Diabetics COVID-19 patients	
Laboratory examinations	Reference ranges	Before median	After median	Before median	After median
BMI	18.5–24.9	22.2	–	27.8	–
Ferritin level	13–150 (mg/ml)	240	180	920	710
D-Dimer value	<0.5 (g/L)	0.7	0.6	0.9	0.85
CRP level	<5	115.7	90	118.2	102
LDH level	Up to 250 (μ/L)	740	450	920	680

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LDH, lactate dehydrogenase.

According to the results, nondiabetic patients treated with remdesivir showed a faster recovery ($p < 0.01$) than those placed in the diabetic category having COVID-19 complications. Furthermore, laboratory examinations were also performed for various parameters at the time when COVID-19 was detected. When the diabetic and nondiabetic patients recovered after treatment with remdesivir, lab tests were repeated for follow-up assessment (Table 2). The results of biochemical parameters that were measured during lab examination depicted that remdesivir showed therapeutic effectiveness in both diabetic and nondiabetic COVID-19 patients. Furthermore, the effectiveness of remdesivir was not associated with complications of diabetes mellitus. However, the recovery rate was slow in diabetic patients as compared with nondiabetic patients.

The clinical range of COVID-19 is wide, going from gentle flu-like manifestations to intense respiratory conditions, organ dysfunction, and demise. Old age, diabetes, and other comorbidities are generally critical indicators of mortality. Constant irritation, expanded coagulation action, compromised immunity, and direct pancreatic harm brought about by SARS-CoV-2 are on the whole potential components underlying the diabetes-COVID-19 affiliation. There is insufficient evidence to justify discontinuing angiotensin-converting enzyme inhibitors, or blockers, thiazolidinediones in people with diabetes who have been exposed to COVID-19. Care must be taken when administering the chloroquine as there may be a possibility of occurance of hypoglycemic events. Adverse events can be minimized by employing patient-specific therapeutic strategies, strict glucose monitoring, and careful consideration of drug interactions.

4 | DISCUSSION

This study clearly depicted that remdesivir was therapeutically active in both diabetic and nondiabetic COVID-19 patients; however, diabetic patients showed a delayed recovery but nondiabetic patients recovered quickly. Due to dramatic expansion in new COVID-19 cases, it has been speculated that this pandemic will proceed for the following months and may even repeat occasionally. The concurrence of two worldwide pandemics, such as COVID-19 and diabetes mellitus, have major threatful clinical outcomes and ramifications for bleakness and mortality.[4,11] It is mandatory for clinicians that they should focus and draw their concentration on people suffering from diabetes mellitus accompanying with COVID-19 infection to increase the understanding about the metabolic factors related to disease severity and to be aware of disease progression, precautionary measures on the antidiabetic regimen, RAAS inhibitors, and potential COVID-19 medication therapies. Finally, and most importantly, we accentuate the significance of ideal inoculations for people with diabetes mellitus where the end goal leads toward COVID-19 vaccination, which is the topmost priority to jeopardize the chances of viral infection.[12]

Patients with diabetes mellitus are more susceptible to COVID-19 infection, resulting in an intense respiratory condition. The coronavirus can increase the chances of hyperglycemia in individuals infected with this infection. The coronavirus can increase the risk of hyperglycemia in diabetic individuals. Hyperglycemia, in association with other harmful factors, may change immunological and provocative reactions, leading toward lethal outcomes.[4,6] During the treatment with remdesivir, it is mandatory that health care personal should regularly monitor the patient. During the administration of remdesivir the patients have to tell the physician or medical caretaker about any adverse reaction that they may experience, including chills or shuddering, sickness, spewing, exorbitant perspiring, difficulty in standing, rash, wheezing or difficulty in breathing, abnormal heartbeat, inflammation or expanding of the face, throat, tongue, lips, or eyes. If any of these effects persist, the physician should immediately diminish or cease the treatment.[13] However, up

till now, very limited data is available to compare the results of our study with the previous study. According to our knowledge, this was the first prospective observational study in Pakistan. However, according to our knowledge, no data or few literature studies may be available about this fact.

4.1 | Limitations of study

The current observational randomized study did not consider adults or young people. Furthermore, this study also did not provide discrimination about the effectiveness of remdesivir in different types of diabetes. The lack of such information will surely enhance the area for further research.

4.2 | Strength of study

To the best of our knowledge, this was the first study conducted in Pakistan. No doubt, research studies are being conducted on the therapeutic effectiveness of remdesivir, but those studies lack the data about diabetic complications. Few studies in this domain exist but still have limited data.

5 | CONCLUSION

This is the comprehensive research data that will be helpful in the current COVID-19 situation. The remdesivir is still being studied as a therapeutic agent for the treatment of COVID-19. Although it has a quick recovery period and also decreases the length of hospitalization, still no evidence regarding mortality benefit has been found. These findings do not establish the efficiency of remdesivir in the treatment of COVID-19. The inducement of the drug remdesivir through pulmonary and intravenous routes has been proposed as a more effective strategy for treating COVID-19. However, the bigger multicenter randomized controlled trials with a placebo treatment control category are needed to affirm the viability and wellbeing of remdesivir before it tends to be considered a standard antiviral treatment for COVID-19 infection. To explain the remdesivir a part across the COVID-19 clinical range, we require contrasting of different treatment systems as well as organization courses in case of extreme COVID-19 infection.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Qiadat Hasnain Qureshi: Recruitment of study participants, initial screening, data curation, experimental analysis, investigation, and writing the original draft. **Taimoor Ashraf**: Literature search, monitoring of study participants, dose preparation and administration, writing the original draft, and statistical analysis. **Muhammad Kaleem Khosa**: Literature search, data curation and investigation, conceptualization, writing the original draft, and editing. **Muhammad Sajid Hamid Akash**: Project administration, supervision, conceptualization, methodology, writing the final draft, and editing.

DATA AVAILABILITY STATEMENT

All data generated and/or analyzed during this study are included in this published article.

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