DOI: https://doi.org/10.53350/pjmhs2115123230

ORIGINAL ARTICLE

Hepatic and Renal Safety of Remdesivir in COVID-19 patients Observational prospective study

MUHAMMMAD USMAN[1], SYEDA OMAMA ALI[2], MUHAMMAD IMRAN ASHRAF[3], AYESHA HAQUE[4], MUHAMMAD SHAHID JAVED[5], MUDASSAR ALI ROOMI[6], YASIR MEHMOOD[7]
[1]Faisalabad Institute of Cardiology hospital, Faisalabad
[2]Quaid-e-Azam Medical College, Bahawalpur
[3]Associate Professor Pharmacology, Allama Iqbal Medical College, Lahore.
[4]Associate Professor Anatomy, Dental College, HITEC-IMS, Taxilla Cantt.
[5]Assistant Professor Physiology, Sargodha Medical College Sargodha.
[6]Assistant Professor Physiology, Allama Iqbal Medical College, Lahore.
*[7]**Saffron Pharmaceuticals** (Pvt.) Ltd, Faisalabad, Pakistan.*
Corresponding to Dr. Yasir Mehmood, Email: Yasir_dpharm@hotmail.com

ABSTRACT

Background: SARS-CoV-2 has been demonstrated to be inhibited by Remdesivir, a broad-spectrum antiviral medication. Remdesivir has been tried for a compassionate use in severe COVID-19 in the absence of any viable treatment for SARS-CoV-2 infection (COVID-19).
Methods: In 50 patients with SARSCoV-2 infection who were given Remdesivir as part of their institutional treatment plan, we conducted an observational prospective analysis. Remdesivir 100 mg was given daily for7 days during the therapy period. The results of liver and kidney function tests were compared before and after Remdesivir administration.
Results: With the administration of Re%) exhibited an improvement in their oxygen needs. Patients reported only a few minor side effects. Serious side effects, on the other hand, were rare.
Conclusion: Remdesivir seems to have an excellent safety profile, while its efficacy in the treatment of COVID-19 is currently inconclusive. Remdesivir use in patients was shown to be safe, with no serious side effects or significant changes in normal test results for liver and kidney functions.
Keywords: Adverse events, Covid-19, liver function, remdesivir, renal function

INTRODUCTION

Coronavirus infection has been a global epidemic since last year, and it has the potential to cause major respiratory illnesses and death[1].. There is currently no prescribed prescription for coronavirus-2, however Remdesivir trials have yielded mixed results when compared to other trial-based COVID-19 treatments[2]. Remdesivir has antiviral properties against coronaviruses *in-vitro,* and early treatment reduced lung damage in monkeys that were infected with COVID-19[3]. Remdesivir got an Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) on May 1, 2020, and was approved for use on October 22, 2020[4]. We looked at all of the human studies that evaluated Remdesivir's efficacy and safety in the treatment of COVID-19. Coronavirus Disease 2019 (COVID-19) has infected over 50 million patients worldwide, resulting in over 1.2 million deaths[5]. When infected, older people with obesity, hypertension, diabetes, and chronic renal disease have a worse prognosis. Corticosteroid therapy has been found to prolong survival in the most severely ill COVID-19 patients, but no other medications have shown efficacy in randomized controlled trials (RCTs) with a suitable safety profile.

Biopharmaceutical, Gilead-USA produced Remdesivir (adenosine analog- GS-443902), a broad-spectrum antiviral medication metabolized by the host cell[6]. Remdesivir is a ribonucleic acid polymerase inhibitor that inhibits virus replication, such as Ebola virus, SARS-CoV, and MERS-CoV[7,8].. Remdesivir was advertised as a concentrated solution for IV administration[9], which was practically insoluble in water even after adding a solubility enhancer, such as sulfobutyl ether-beta-cyclodextrin practically not soluble in water even after adding solubility enhancer i.e. sulfobutyl ether-beta-cyclodextrin[10] and could not create sufficient high levels of pro-drug[9].

Mechanism of action: After three extra bases have been added, Remdesivir triphosphate causes chain termination to be delayed.

Risks of Remdesivir: Remdesivir triphosphate is thought to have a low risk of mitochondrial toxicity since it is a mild inhibitor of mammalian DNA and RNA polymerases[13]. Other nucleotide/nucleoside antivirals (e.g., tenofovir) can cause mitochondrial damage in epithelial cells of renal tubules, but renal toxicity only occurs after extended exposure, therefore it would be extremely unusual to occur during 5 to 10 day therapeutic course[14]. Significantly greater than the EUA dose, toxicological investigations in rhesus monkeys revealed renal damage and casts at doses of 5, 10, and 20 mg/kg for 14 days. A single randomized controlled trial in COVID-19 did not show an increased risk of renal toxicity among patients randomized to receive remdesivir, according to the available data. Furthermore, when Remdesivir was utilized in an Ebola clinical trial, no severe renal side effects were reported[15].

METHOD

In 48 patients with SARSCoV-2 infection who were given Remdesivir as part of their institutional treatment plan, we conducted an observational prospective analysis. Remdesivir, 100 mg, was given during the therapy period. Before and after Remdesivir treatment, liver and kidney function tests were compared.

Antiviral regimen: On the first day, all of the patients were given 200 mg of Remdesivir, followed by 100 mg once daily for the next 6 days. On the eighth day, team evaluated patients' clinical state.

RESULTS

The study involved fifty individuals who received a Remdesivir dosage in December 2020. The participants in the study ranged in age from 25 to 50 years old. The study's participants were mostly men (60 percent). The participants of study had been experiencing symptoms for a median of three days when they came to see us. The average length of stay in the hospital was 7 days. Seventeen individuals were diabetic (34%) and 12 were hypertensive (24%). The disease severity was moderate in 21(42%) individuals and severe in 29(58%) patients. All patients were given a 7-day regimen consisting of single and double doses on the first day. During the trial period, no patient died.

Received on 11-06-2021
Accepted on 21-11-2021

Table 1: Patient profile

Characteristic	n (%)
Age in years (Average)	
Mean $\pm SD$	39
Range	25-50
Gender	
Male	60
Female	40
Body Mass index	
Mean $\pm SD$	25
Diabetes as native disease	17
HIV	0
Hypertensive	0

Table 2 adverse events reported during the study period

Variable	n (%)
Discontinuation of treatment due to adverse effect	0
Adverse Events	
Fatigue	50
Nausea	18
Headache	17
Insomnia	43
Pruritus	21
Anemia	19
Cough	38
Arthralgia	19

*ALP, alkaline Phosphate, ALT alanine aminotransferase; AST, asparate aminotransferase; CRP, C-reactive protein; LDH, lactase dehydrogenase; LFT, liver function test, SD, standard deviation.

Table 3: Baseline Characteristic (n=50)

Parameters	Baseline Characteristics	*P* value
Age	25-50	
Male Sex, n (%)	30(60)	
Female Sex n (%)	20 (40)	
Diabetes, n (%)	17(34)	
Hypertension, n (%)	12(24)	
Median Laboratory values before Remdesivir		
ALT,U/l	Between 15-30	0.33
AST, U/l	Between 21-58	0.45
ALP, IU/l	Between 69-90	0.64
CPR, mg/l	Between 7-10	0.32
LDH. U/l	Between 147-208	0.66
eGFR, median mL/min/1.73 m_2	Between 100-112	0.40
Median Laboratory values after 7 days treatment		
ALT,U/l	Between 18-31	0.72
AST, U/l	Between 26-50	0.76
ALP, IU/l	Between 63-90	0.23
CPR, mg/l	Between 7-14	0.95
LDH. U/l	Between 137-210	0.43
eGFR, median mL/min/1.73 m_2	Between 90-108	0.32

DISCUSSION

Remdesivir is an antiviral medication that has proved to have a considerable inhibitory effect against SARS-CoV-2, putting it ahead of other repurposed drugs being tested for COVID-19 treatment. Early administration of Remdesivir, as in other acute viral infections, was clearly more efficacious in animal tests. Treating individuals who have already developed respiratory failure may not be the best usage of Remdesivir in this case. However, due to the longer duration of viral shedding in COVID-19 and intensive care hospitalization, even late treatment may be beneficial. Remdesivir is currently only approved by the FDA for severe COVID-19 in both adults and children. As far as discussing the outcome of Remdesivir in COVID-19, one RCT demonstrated no benefit with Remdesivir in COVID-19, preliminary results from another RCT indicated that it may be beneficial. Remdesivir's safety profile in COVID-19 is still not being characterized completely. While the safety evidence from COVID-19's past use during acute EVD suggests no cause for concern, COVID-19's clinical features are vastly different from those of EVD. Remdesivir was originally used to treat Ebola, but it is currently being used to treat COVID-19 in some countries, such as Pakistan. Remdesivir's specific effect in COVID-19 patients, however, must be determined. Because Remdesivir is supplied with a cyclodextrin carrier that filters primarily through the glomeruli, patients with impaired renal function are unable to clear it fast and as a result, Remdesivir might cause renal or hepatic damage during the COVID-19 treatment process. The evaluation of renal and hepatic function in COVID-19 patients is critical.

The study included 50 patients, all of whom had at least one of the laboratory measurements available, the majority of whom were male (60 percent), and their ages ranged from 25 to 50.

Table 3 illustrates the change in eGFR, AST, and ALT from baseline readings for each patient, as well as the mean change each day after starting Remdesivir. In 50 patients, the median baseline eGFR was between 100 and 112 mL/min/1.73m2, which is a normal number. The usual range of eGFR did not change appreciably after 7 days of Remdesivir administration. In 50 patients, the median AST was between 21- 58 U/L at the start. After starting Remdesivir, the AST levels of 50 patients (100%) returned to normal. Other test values, such as ALT, ALP, CPR, and LDH, remained unchanged before and after treatment.

CONCLUSION

Remdesivir seems to have an excellent safety profile, while its efficacy in the treatment of COVID-19 is currently inconclusive. Remdesivir use in patients was shown to be safe, with no serious side effects or significant changes in normal test results for liver and kidney functions. option for COVID-19 infection in the hepatic and renal systems.

Author Contribution: Co-authors helped with data analysis, drafting, and revising the manuscript, and they agree to take responsibility for all elements of the work.

Conflict of interest: No conflict of interest was found in this study.

REFERENCES

1. Wang, Y., et al., Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. 2020. **395**(10236): p. 1569-1578.
2. Wang, Y., et al., Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. 2020. **21**: p. 1-11.
3. Goldman, J.D., et al., Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine, 2020. **383**(19): p. 1827-1837.
4. Rizk, J.G., et al., Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic. Drug Discovery Today, 2020.
5. Sohrabi, C., et al., World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International journal of surgery, 2020. **76**: p. 71-76.
6. Konkolova, E., et al., Remdesivir triphosphate can efficiently inhibit the RNA-dependent RNA polymerase from various flaviviruses. 2020. **182**: p. 104899.
7. Kokic, G., et al., Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. 2021. **12**(1): p. 1-7.
8. Uddin M. et al., SARS-CoV-2/COVID-19: viral genomics, epidemiology, vaccines, & therapeutic interventions. 2020. **12**(5):526.
9. Maus, A., L. Strait, and D.J.E.R. Zhu, Nanoparticles as delivery vehicles for antiviral therapeutic drugs. 2021. **2**: p. 31-46.
10. Gurunathan, S., et al., Antiviral potential of nanoparticles—Can nanoparticles fight against coronaviruses? 2020. **10**(9): p. 1645.
11. Lamb, Y.N.J.D., Remdesivir: first approval. 2020: p. 1-9.
12. van Laar, S.A., et al., Liver and kidney function in patients with Covid-19 treated with remdesivir. British journal of clinical pharmacology, 2021.
13. Pranith, P., et al., A review on the role of remdesivir for the treatment of COVID 19. 2021.
14. Kohler, J.J., et al., Tenofovir renal toxicity targets mitochondria of renal proximal tubules. Laboratory investigation, 2009. **89**(5): p. 513-519.
15. Pardo, J., et al., The journey of remdesivir: from Ebola to COVID-19. Drugs in context, 2020. **9**.
16. Adamsick, M.L., et al., Remdesivir in patients with acute or chronic kidney disease and COVID-19. Journal of the American Society of Nephrology, 2020. **31**(7): p. 1384-1386.