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Research Article

AN EVALUATION OF ADVERSE DRUG REACTIONS WITH REMDESIVIR IN PATIENTS OF COVID-19

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ABSTRACT

Objectives: The aim of the study was to evaluate the adverse drug reactions (ADR) following Remdesivir therapy in patients of COVID-19.

Methods: All patients more than 18 years of age of any gender, diagnosed with COVID-19 infection receiving remdesivir therapy and fulfilling the selection criteria were included in the study after informed consent. They were monitored for ADRs till end of treatment and analyzed for characteristics of the ADRs: Causality, severity, and preventability.

Results: Out of 80 patients (mean age of 49.27±16.22 years) enrolled, 51 (63.75%) developed 84 ADRs. Most common ADRs included increased aspartate transaminases, (20.23%), increased bilirubin (19.04%), increased alanine transaminases (13.09%), increased creatinine (11.90%), and increased blood urea (9.52%). Causality assessment using WHO-UMC scale showed, 85.71% possible, 13.09% probable, and 1% certain causal association of the ADRs with remdesivir. A total 75% ADRs were mild in severity and 45% patients recovered from the event at the end of treatment.

Conclusion: Hepatic and Renal dysfunctions are observed with remdesivir in COVID-19 patients. Intensive monitoring of ADRs with newer drugs with EUA such as remdesivir is warranted to ensure safer use in patients.

Keywords: Remdesivir, Adverse drug reactions, COVID-19, Causality assessment.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a systemic thrombo-hyperinflammatory vasculitis caused by SARS-CoV2 virus, symptoms of which range from common cold to severe acute respiratory illness. By March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, since then 25.9 crore people have been infected and 51.7 lakh deaths have been recorded worldwide. In India, 3.45 crore people have been infected and 4.67 lakh deaths have been recorded till date [1].

Although most COVID-19 infections are self-limited, about 15% of infected adults develop severe pneumonia and additional 5% progress to critical illness with acute respiratory distress syndrome requiring ventilator support. As initially, there were no authorized treatments for patients infected with COVID-19; Azithromycin, Lopinavir/Ritonavir, and Hydroxychloroquine were repurposed and investigated for therapeutic efficacy [2].

In May 2020,the drug Remdesivir, a potential treatment for Ebola virus was granted an USFDA Emergency Use Authorization (EUA) for COVID-19 infection [3]. Remdesivir is an adenosine triphosphate analog which exhibits the antiviral activity in primary human airway epithelial cells. It inhibits the SARS-CoV-2 RNA-dependent RNA polymerase which results in delay in chain termination during replication of the viral RNA. The recommended dosage for adult patient is a single loading dose of 200mg on 1st day through intravenous infusion followed by once-daily maintenance doses of 100 mg from day 2 to a maximum duration of 10 days. Different studies across the world have shown variable clinical benefits of remdesivir in patients with moderate COVID-19 [4] The drug was, therefore, included in the COVID-19 treatment protocols in several countries, including India, Gujarat.

Incidence of adverse drug reactions (ADRs) following remdesivir therapy in clinical trials with patients of moderate COVID-19 was found to be 51% and the observed ADRs were hepatic impairment, renal impairment, gastrointestinal disturbances, electrolyte imbalance, anemia, thrombocytopenia, and allergic reactions [5]. Studies conducted before the marketing authorization of a drug usually cannot detect uncommon or rare adverse effects. Information available regarding safety of remdesivir in COVID-19 patients is limited. This study was, therefore, conducted to evaluate the ADRs following Remdesivir therapy in COVID-19 patients.

MATERIALS AND METHODS

This was an observational, prospective, and single-center study conducted at tertiary COVID care center for a duration of 3 months. The study was initiated after obtaining permission from the Institutional Ethics Committee.

All patients more than 18 years of age of any gender diagnosed with COVID-19 infection receiving remdesivir and willing to provide written informed consent were included in the study. Pregnant and lactating women, patients with aspartate transaminases (AST), alanine transaminases (ALT) more than 5 times the upper normal limit (UNL), and patients with known renal impairment were excluded from the study. Three wards out of 20 were selected for this study from the tertiary COVID care center and 93 patients were screened. Thirteen patients were excluded from the study as they did not fulfill the inclusion criteria. Eighty patients were enrolled for the study. Patients were enrolled at the time of initiation of remdesivir treatment and were monitored daily till the end of the therapy for ADRs.

Information regarding demographic details, provisional diagnosis, vaccination history, baseline investigations, details of remdesivir therapy (dose, duration, and frequency), and details of the ADRs: Observed ARDs, onset, lag period, duration, seriousness, and outcome were recorded. All the data were entered in Microsoft Excel and analyzed using descriptive analysis, Chi-square test, and independent sample t test in GraphPad Prism 9.3.0. Observed ADRs were categorized under System Organ Classification (SOC) level and at the individual

preferred term (PT) level. SOC is a grouping of individual ADEs coded in pre fix PTs into the different headings based on etiology.

Causality assessment of the ADRs was done using WHO-UMC scale and Naranjo's algorithm [6], severity assessment was done using Hartwig and Siegel scale [7] and preventability assessment was done using Modified Schumock and Thornton criteria [8].

RESULTS

Of the total 80 patients enrolled in the study, 51 (63.75%) patients developed 84 ADRs during the treatment period. Death was reported in 4 (5%) patients. Mean age of patients developing ADRs was 49.47±16.12 (mean ± standard deviation) years. The number of ADRs was significantly higher in patients aged 61 years and more, as compared to patients of age groups ≤40 years and 41–60 years (Chi-square test: p<0.05) (Table 1).

It was observed that male patients had more chances of developing ADRs compared to female patients and this difference* was statistically significant using Chi-square test (p<0.05) (Fig. 1).

Comorbidities

Out of 80 patients, 51 patients had comorbidities, of which 66.67% patients developed ADRs following remdesivir therapy. From remaining 29 patients, 58.62% patients developed ADRs. The difference between the two groups was not statistically significant (p = 0.42).

Details of adverse drug reactions

Remdesivir therapy was for administered a duration of 5 days. Fifty-one patients developed 84 ADRs (Fig. 2). Average number of ADRs observed with remdesivir was 1.64±0.71. Mean duration for the development of ADRs following remdesivir therapy was 2.07±0.71 days. Out of 51 patients, 49% patients developed single ADR, 37.26% patients developed two ADRs. Three ADRs were observed in 13.73% patients.

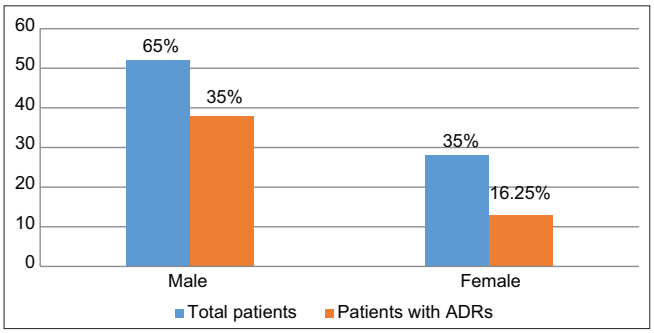

Fig. 1: Gender distribution of adverse drug reactions

Most observed ADRs were: Increased AST (20.23%), increased bilirubin (19.04%), increased ALT (13.09%), increased serum creatinine (11.90%), and increased urea (9.52%). Increased levels were defined as more than 3 times the UNL.

The ADRs were classified according to the SOC (Fig. 3). The majority of the ADRs were related to abnormal hepatic and renal functions, so they were classified under "Investigations."

Characteristics of ADRs such as causality, severity, and preventability associated with remdesivir therapy using different scales are listed (Table 2).

Outcome

Out of 51 patients who developed ADRs, 45% of the patients recovered from the ADRs and in 65% patients, recovery was unknown as patients were discharged and follow-up was not possible during the pandemic.

DISCUSSION

Remdesivir is a potential drug for COVID-19 infection. It is included in protocols for the treatment of mild-to-moderate COVID-19 infection. Data from controlled clinical trials illustrated a pattern of ADRs following the remdesivir therapy, but the actual quantum and type of ADRs may vary when the drug is used in a larger, variegated population scenario, duration of drug therapy, and disease severity. Hence, in this study, we aimed to evaluate the ADRs following remdesivir therapy in patients of COVID-19 in a tertiary care hospital. Remdesivir was given for the duration of 5 days and all the ADRs were noted.

Out of 80 patients enrolled, 63.75% patients developed ADRs which was similar with a study conducted by Spinner *et al*. 2020 where 51% of patients developed ADRs following remdesivir therapy for 5 days [5]. In our study, four patients succumbed during the course of treatment due to disease progression. ADRs observed were higher in the age group of more than 61 years (89.5%), which suggests that incidence of ADRs increases with age.

In this study, ADRs occurred more frequently in males (73.08%) with Male: Female ratio being 3.6:1. It was similar with the study conducted

Table 1: Age-wise distribution of adverse drug reactions in patients treated with remdesivir

Age group (years)	Number of patients (*n*=80), *n* (%)	Number of patients developed ADRs (*n*=51), *n* (%)	Number of ADRs (*n*=84), *n* (%)	Mean number of ADRs (mean±SD)
≤40	27 (33.8)	13 (48.1)	20 (23.8)	1.53±0.51
41–60	34 (42.4)	21 (61.7)	31 (36.9)	1.47±0.60
≥61	19 (23.8)	17 (89.5)*	33 (39.3)	1.94±0.89#

*Statistical significance was observed using Chi-square test. *P*<0.05 considered statistically significant as compared to patients of age group ≤40 years and 41–60 years, #Statistical significance was observed using independent sample *t*-test. *P*<0.05 considered statistically significant as compared to patients of age group 41–60 years and >61 years. ADRs: Adverse drug reactions, SD: Standard deviation

Table 2: Causality, severity, and preventability assessment of adverse drug reactions with remdesivir (*n*=51)

Causality assessment	Certain, *n* (%)	Probable, *n* (%)	Possible, *n* (%)
WHO-UMC Scale	1 (1.19)	11 (13.09)	72 (85.71)
Naranjo's algorithm	1 (1.19)	38 (45.23)	45 (53.57)
Severity assessment	**Mild, n (%)**	**Moderate, n (%)**	**Severe, n (%)**
Modified Hartwig and Siegel Scale	63 (75)	19 (22.62)	2 (2.38)
Preventability assessment	**Probably preventable, *n* (%)**	**Not preventable, *n* (%)**	
Modified Schumock and Thronton criteria	82 (97.6)	2 (2.4)	

WHO-UMC: World health Organisation - Uppsala monitoring Centre

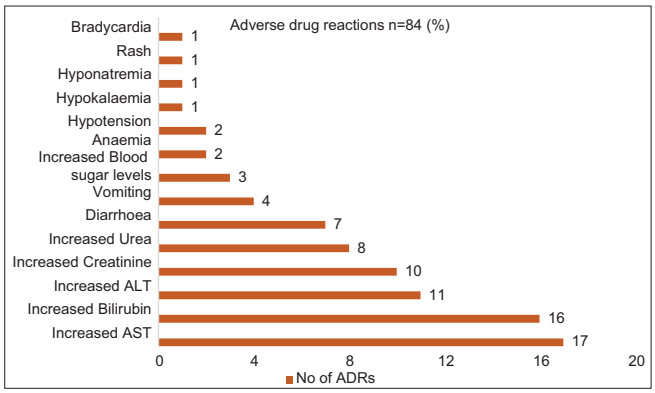

Fig. 2: List of adverse drug reactions

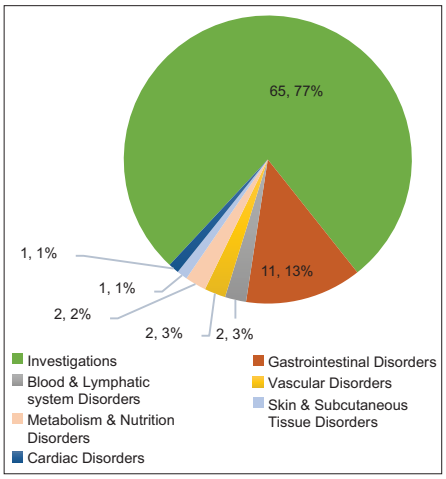

Fig. 3: System organ classification of adverse drug reactions

by Zekarias *et al.* 2020 [9], with males developing more ADRs. The reason here could be more male patients enrolment (65%) in our study and slightly higher incidence of COVID-19 in male patients.

Most frequently observed ADRs in this study were: Increased AST levels (20.23%), increased bilirubin levels (19.04%), and increased ALT levels (13.09%) which were similar to the study by Grein *et al.* 2020 where increased hepatic enzymes were reported in 24% of patients [10]. Hepatic enzyme increase may attribute due to COVID-19 disease itself or it may be due to the effect of the drug.

Increased creatinine (11.90%) and increased urea (9.52%) were observed which was also similar to the study conducted by Grein *et al.* 2020 with 12% of the patients experienced renal impairment [10]. The renal impairment might be due to the excipient of the remdesivir, *sulfobutylether β cyclodextrin* which was also present in the remdesivir formulation used in this study. It gets accumulated in the kidneys with low glomerular filtration rate. Remdesivir should not be given in patients with GFR< 30 ml/min [11]

In our study, bradycardia was observed in one patient. Pharmacovigilance Program of India also published monthly drug safety alert (Suspected ADR; December 2021) stating association of sinus bradycardia with use of remdesivir in patients with severe COVID-19 [12].

Hepatic and renal impairment are major concerns with remdesivir therapy; hence, vigilant monitoring of the hepatic and renal functions prior and during the drug therapy is recommended.

The majority of the ADRs had *"possible"* causal association with remdesivir; 85.71% according to the WHO-UMC scale and 53.57% in Naranjo's algorithm. This could be because of multiple drug therapy for COVID-19 patients, absence of de-challenge and re-challenge, and individual host and disease factors affecting the development of ADRs. According to Modified Hartwigand Siegel severity scale, 75% ADRs were mild in severity, 22.62% were moderate and two ADRs (2.38%) – Rash and increased creatinine levels were severe as it required intensive medical care for the patient. About 97.6% ADRs were probably preventable as per Modified Schumock and Thronton criteria. No serious ADRs were reported in this study and the deaths of four patients were not related to remdesivir therapy.

In our study apart from evaluation of the ADRs following remdesivir therapy, we also have done causality, severity, and preventability assessment of the ADRs. The limitation of the study was incomplete data regarding recovery of the ADRs (65% outcome was unknown), as patients were followed up only till discharge from the hospital.

CONCLUSION

This study evaluates the ADRs following remdesivir therapy in patients of COVID-19. The majority of the ADRs were *investigational abnormalities* related to hepatic and renal systems. COVID-19 has necessitated EUA of several drugs, including remdesivir. While the COVID-19 is on the decline, the data evaluated form this and similar studies will help the prescribers evaluate the drug better for its safety in patients, for COVID-19 and other similar infections. Hence, an active surveillance of ADRs with remdesivir is warranted, to ensure its rational and appropriate use, in the interest of safety of the patients.

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AUTHOR'S CONTRIBUTION

The study design and concept was done by Chetna Desai, Suchi Shah and MiruthuBashini.S; MiruthuBashini. S performed data collection, data analysis, wrote the paper and drafted the manuscript, and contributed to the final manuscript. Chetna Desai and Suchi Shah cowrote the paper, drafted the manuscript, and contributed to the final manuscript.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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