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Remdesivir Induced Liver Injury and Severe COVID-19 Infection

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Abstract: *Background and Aims*: Remdesivir is identified as an effective therapeutic option in COVID-19, but its' hepatic safety has not been well studied. So, we aimed to identify the pattern and severity of hepatotoxicity in remdesivir treated COVID-19 patients. *Methods*: This cross-sectional study was carried out at a dedicated COVID-19 unit of a university hospital in Dhaka, Bangladesh among severe COVID-19 cases. Alterations of liver functions were compared between the remdesivir and the non-remdesivir treated patients. *Results*: Out of 50 severe COVID-19 cases 25 had received remdesivir and 25 had received other supportive care without remdesivir. Median serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were significantly higher in the remdesivir treated arm (p-value for AST <0.0001 and ALT <0.001). Grade-2 elevation of AST and ALT and grade-3 elevation of AST levels were significantly higher among the remdesivir treated group. No patients had significant bilirubin elevation (≥2.5 mg/dl) and only 1 patient had INR >1.5 in the remdesivir treated arm. *Conclusion*: Many of the patients with severe COVID-19 had mild to moderate aminotransferases elevation. If the elevation of liver enzymes occurs after the initiation of remdesivir, adverse drug reactions need to be considered and drug discontinuation may require if severe elevation occurs.

Keywords: Remdesivir, COVID-19, Hepatotoxicity, Aminotransferase

1. Introduction

At the end of 2019, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan city, China results in a respiratory illness designated as coronavirus disease 2019 (Covid-19) [1]. It was initially viewed as primarily a respiratory disease, but is now considered as a complex multisystem disease [2]. SARS-CoV-2-induced hepatic injury has been well described [3, 4]. So, to evaluate the hepatic safety of drugs administered and to monitor the liver function of COVID-19 patients is very important. Remdesivir, a nucleoside analog, an inhibitor of the viral RNA-dependent, RNA polymerase [5, 6] has been identified as a promising therapeutic option for Covid-19 because it inhibits SARS-CoV-2 in vitro [7]. Available data suggest remdesivir has some clinical benefit, although the overall evidence is low [8]. However, the hepatic safety of remdesivir in COVID-19 has not been well studied. So, we aimed to conduct a study to find out the patterns and severity of liver injury in COVID-19 patients treated with remdesivir.

2. Methods

This is a cross-sectional study carried out at a dedicated COVID-19 unit of a university hospital in Dhaka, Bangladesh. The study period was July 2020 to September 2020. Fifty RT-PCR positive severe COVID-19 cases aged ≥18 years were recruited according to case definition. Severe COVID-19 was defined as radiological findings of pneumonia in the chest x-ray or HRCT of the chest and any one of the following criteria – a) respiratory rate ≥30 breaths/min, b) O_2 saturation (SpO_2) ≤93% at rest on the pulse oximeter, c) arterial partial pressure of oxygen (PaO_2)/fraction of inspires oxygen (FiO_2) ≤300 mmHg in ABG or SpO_2/FiO_2 <315 mmHg [9]. Severe COVID-19 cases were grouped into two groups according to those who had received at least 5 days of i.v remdesivir (200

mg loading dose on day 1, followed by 100 mg daily for up 4 additional days). Impairments of hepatic functions were compared between the remdesivir and the non-remdesivir treated group.

Patients were assessed clinically and with laboratory parameters. Aminotransferase elevation was graded as grade-1 (1.25 to 3-fold elevation), grade-2 (3 to 5-fold elevation) and grade-3 (more than 5-fold elevation). Patients with preexisting liver disease, positive serology for the viral marker, and known exposure to indigenous drugs were excluded from the study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean and SD, while categorical variables were presented as frequency and percentage. Chi-square test, independent samples t-test, and Mann Whitney U test was conducted for categorical, normal, and skewed continuous variables respectively. A P-value of <0.05 was considered to be statistically significant.

The study was approved by the University Institutional Ethical Review Board. Informed consent was obtained from each patient in the study.

3. Result

A total of 50 severe COVID-19 cases was included in this study. Of them, 25 had received remdesivir along with other supportive care and 25 had received other supportive care without remdesivir. The mean age was 57.3±13.3 and 55.6±12.7 years among remdesivir and non-remdesivir groups respectively. Male (68%) were predominant in both groups. There was no significant difference in mean body mass index (BMI) and Oxygen saturation (SpO_2) level among both groups. Baseline characteristics are shown in table 1.

Table 1. *Baseline characteristics of the study population.*

	Remdesivir treated group (n=25)	Non-remdesivir treated group (n=25)	P-value
Age (mean±SD)	57.3±13.2	55.6±12.7	0.641
Gender (Male)	17 (68.0%)	17 (68.0%)	1.000
BMI (mean±SD)	23.4±3.9	23.6±2.8	0.794
Obesity	2 (8.0%)	1 (4.0%)	1.000
O_2 saturation (mean±SD)	87.0±3.8	87.1±5.7	0.907

Values are presented as mean±SD and number (percentage).

Median serum bilirubin, prothrombin time, INR, and serum albumin values were similar in both groups. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were significantly higher in the remdesivir treated arm (p-value for AST <0.0001 and ALT <0.001). Median serum alkaline phosphatase (ALP) value was also significantly higher in the remdesivir treated group (p-value 0.005) but within the upper limit of the normal range. No patients had bilirubin elevation of ≥2.5 mg/dl and only 1 patient had INR >1.5 in the remdesivir treated arm. Laboratory parameters of the study participants are shown in table 2.

Table 2. *Laboratory parameters of the study population.*

	Remdesivir treated group (n=25)	Non-remdesivir treated group (n=25)	P-value
S. Bilirubin (mg/dl)	0.6 (0.15 – 2.4)	0.6 (0.3 – 2.3)	0.907
AST (u/L)	120 (35 – 275)	46 (17 – 149)	<0.0001
ALT (u/L)	104 (27 – 276)	38 (14 – 243)	0.001
Alkaline phosphatase (u/L)	129 (51 – 371)	88 (57 – 230)	0.005
Prothrombin time (sec)	13.1 (12.0 – 22.0)	13.4 (12.0 – 17.2)	0.586
INR	1.10 (1.0 – 1.9)	1.03 (1.0 – 1.4)	0.411
S. Albumin	35.6±5.8	35.1±3.5	0.747

Values are presented as median (range) and mean±SD. AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; INR, International normalization ratio.

Though higher numbers of grade-1 elevation of AST and ALT were observed in remdesivir treated arm in comparison to non-remdesivir treated arm (44.0% vs. 32% and 40.0% vs. 24.0% respectively), the difference is not statistically significant. Remdesivir treated group had a significantly higher frequency of grade-2 AST and ALT elevation in comparison to the non-remdesivir treated group (36.0% vs. 12% and 40.0% vs. 8.0% respectively). The odds ratio for the grade-2 elevation of AST level in the remdesivir treated group was 1.78 with a 95% confidence interval (CI) 1.09 to 2.92. The odds ratio for the grade-2 elevation of ALT level in the remdesivir treated group was 2.11 with a 95% CI 1.32 to 3.37. All patients with grade-3 elevation of AST (16.0%) were in the remdesivir treated group, the odds ratio was 2.19 with a 95% CI 1.60 to 3.00. Aminotransferase elevation in the remdesivir and the non-remdesivir treated group is shown in tables 3-4.

Table 3. *Aspartate aminotransferase (AST) elevation between remdesivir and non-remdesivir treated group.*

AST elevation	Treatment group	Number (%)	Odds ratio	95% CI	P-value
Grade-1	Remdesivir group	11 (44.0%)	1.28	0.74 – 2.21	0.382
	Non-remdesivir group	8 (32.0%)	0.77	0.41 – 1.42	
Grade-2	Remdesivir group	9 (36.0%)	1.78	1.09 – 2.92	0.047
	Non-remdesivir group	3 (12.0%)	0.43	0.16 – 1.19	
Grade-3	Remdesivir group	4 (16.0%)	2.19	1.60 – 3.00	0.05
	Non-remdesivir group	0 (0.0%)			

AST, Aspartate aminotransferase; CI, Confidence interval.

Table 4. *Alanine aminotransferase (ALT) elevation between remdesivir and non-remdesivir treated group.*

ALT elevation	Treatment group	Number (%)	Odds ratio	95% CI	P-value
Grade-1	Remdesivir group	10 (40.0%)	1.42	0.83 – 2.42	0.225
	Non-remdesivir group	6 (24.0%)	0.67	0.33 – 1.35	
Grade-2	Remdesivir group	10 (40.0%)	2.11	1.32 – 3.37	0.008
	Non-remdesivir group	2 (8.0%)	0.28	0.08 – 1.00	
Grade-3	Remdesivir group	1 (4.0%)	1.00	0.24 – 4.11	1.000
	Non-remdesivir group	1 (4.0%)	1.00	0.24 – 4.11	

ALT, Alanine aminotransferase; CI, Confidence interval.

4. Discussion

SARS-COV2 infection can cause an increase in liver enzymes in 14 – 53% of cases [4, 10-12]. The mechanisms are mostly unknown. It may be due to virus-induced inflammation, hypoxic liver injury, and/or drug-induced liver injury. Among several drugs used for the treatment of COVID-19, remdesivir is one of the promising drugs. Information on the safety profile of remdesivir is rapidly evolving. Several clinical studies reported aminotransferase elevations following remdesivir treatment [13-15], which is consistent with our findings. In our study, remdesivir caused frequent grade-1 and grade-2 elevation of aminotransferases which didn't require drug discontinuation. It is unclear if the liver function abnormalities observed in patients with COVID-19 treated with remdesivir are due to the infectious process or the drug itself. Although Wang et al, and the ACTT-1 study reported that, aminotransferases elevation were infrequent and occurred in similar proportions of remdesivir and placebo-treated patients [13, 16], we observed significantly higher numbers of grade-2 and grade-3 aminotransferases elevation in remdesivir treated arm compared to the non-remdesivir treated arm. Transient mild ALT elevations were reported in most subjects in the multi-dose PK studies, including one individual with ALT values more than 10 times from baseline [17]. All three patients out of the first 12 COVID-19 cases in the US who received remdesivir experienced transient aminotransferases elevations [18]. According to Grein et al.'s study on compassionate-use remdesivir against COVID-19, 23% of the patients reported increased hepatic enzymes, and two of them therefore discontinued remdesivir prematurely [17]. Lescure et al. also reported one COVID-19 patient discontinued remdesivir because of alanine aminotransferase elevation and rash, which then decreased within 3 days [19]. Except for 1 case of hyperbilirubinemia, all other cases were asymptomatic [17]. We found no cases of bilirubin elevation above 2.5mg/dl. The FDA reported grade 3 and 4 aminotransferase elevations occurred in 7% and bilirubin elevations were uncommon (1.3%) with 5- and 10-day courses of remdesivir in patients with COVID-19 [17]. At this time, it is also unclear how remdesivir causes hepatic impairment. It may cause liver injury like other nucleosides. Nucleoside analogs are known to cause liver injury by a variety of mechanisms [20]. Mitochondrial dysfunction caused by inhibition of mitochondrial DNA synthesis is the most commonly involved mechanism. This can affect various tissues, leading to neuropathy, myopathy, pancreatitis, marrow suppression, and/or liver injury [20]. To date, no extra-hepatic manifestations of mitochondrial dysfunction have been reported in patients treated with remdesivir. Other mechanisms may include acute hypersensitivity reactions or the production of toxic intermediates to cause liver injury [20].

5. Conclusion

Since many of the patients with severe COVID-19 had mild to moderate aminotransferases elevation, if the elevation of liver enzymes occurs after the initiation of remdesivir, adverse drug reactions need to be considered. Drug discontinuation may require if severe elevation occurs. Although it is reassuring that, most of the cases are non-severe and asymptomatic, it is unknown that asymptomatic abnormalities are harbingers of more serious liver injury. Remdesivir should not be used with other hepatotoxic drugs or in preexisting liver disease. The monitoring of the liver function is warranted during the treatment.

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