Potential Drug Induced Liver Injury (Dili) Event During Remdesivir Treatment in Covid-19 Patients

Ulvi Nur Rista[1,2], Desi Setyowati[2] and Julaeha[1]
[1]*Faculty of Pharmacy, Universitas 17 Agustus 1945 Jakarta, Jakarta, Indonesia*
[2]*Mitra Keluarga Kenjeran Hospital, Surabaya, Indonesia*

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Abstract: The global pandemic of COVID-19 has already caused about 1.4 million deaths, and liver injury was one of the foremost problems due to antiviral treatment besides mortality. Remdesivir was one of the antivirals approved for COVID-19 treatment. Nevertheless, some studies reported that remdesivir caused liver injury. This study aimed to identify the pattern and severity of liver toxicity during remdesivir treatment. The study adopted a retrospective cohort design conducted in Mitra Keluarga Kenjeran Hospital Indonesia. This study involved patients with COVID-19 on remdesivir treatment between June and August 2021. Patients with liver impairment or abnormal alanine aminotransferase (ALT) were excluded. We described the severity of liver toxicity based on the grading system and analyzed the comparison of baseline ALT and end-point ALT using the t-test/Wilcoxon test. The 83 patients were included in this study. Our study showed ALT elevation was observed in 21 patients (25.3%), including grade 1 in 14 patients (66.7%), grade 2 in 6 patients (28.6%), and grade 3 in 1 patient (4.7%). Median end-point ALT value was significantly higher than median baseline ALT (p-value < 0.001). The finding of this study suggests that monitoring of liver function tests must be considered before the start of remdesivir treatment.

1 INTRODUCTION

Since COVID-19 was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020, various studies have been conducted to improve understanding of the characteristics of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2). COVID-19 is a disease that predominantly attacks the respiratory tract, but some hypotheses suggest that COVID-19 disease can also attack the kidneys and liver (Sanders et al., 2020). Some mechanisms that can explain the pathogenesis of the occurrence of COVID-19-induced liver injury are direct cytotoxicity of liver cells due to viral replication, inflammatory responses mediated by the immune system, responses from hypoxia and ischemic due to severe sepsis, toxicity from COVID-19 therapeutic drugs (Aleem et al., 2021).

Drugs used to treat various symptoms are also increasingly being developed, one of which is remdesivir. Some research shows that remdesivir has the potential to cause Drug Induced Liver Injury (DILI) (Aleem et al., 2021). Remdesivir structurally belongs to the class of nucleoside drugs. It is well known that nucleoside analogues are an important class of antiviral drugs, which can cause liver disturbance through a variety of mechanisms. The most typical mechanism is a mitochondrial type of liver disturbance, which may be due to the incorporation of nucleoside analogues into or blocking mitochondrial DNA synthesis by mitochondrial gamma polymerase, leading to mitochondrial depletion (Zhai et al., 2021). This is in accordance with the cross-sectional study in Bangladesh in severe COVID-19 patients, the group who received supportive therapy with remdesivir showed a significant increase in AST (aspartate aminotransferase) and ALT (alanine aminotransferase) compared to the group who received supportive therapy without remdesivir (Ghosh et al., 2020). However, in the meta-analysis study, different results were obtained, the risk of increasing ALT and AST was significantly lower in the remdesivir group than placebo/control group (Angamo et al., 2022). There are differences in the results of existing studies, so we aimed to conduct a study to identify the pattern and severity of liver

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toxicity during remdesivir treatment in COVID-19 patients.

2 METHODS

The study was a cohort retrospective design with purposively sampled. Ethical approval was obtained from the Health Research Ethics Committee of 17 August 1945 University, Jakarta with number 30/KEPK-UTA45JKT/EC/EXE/03/ 2022. This study was conducted at Mitra Keluarga Kenjeran Hospital. This study involved Inpatients with COVID-19 diagnosed who getting a minimum one dose of remdesivir in Mitra Keluarga Kenjeran Hospital between June and August 2021. Patients with liver impairment or abnormal alanine aminotransferase (ALT) and getting hepatoprotection treatment (glycyrrhizin and silymarin) before/during remdesivir treatment were excluded. All of the patient's data were collected from the electronic medical records, such as patient characteristics, medication treatment during hospitalized, duration of remdesivir treatment, baseline and end-point (during/after remdesivir therapy) ALT value, the clinical manifestation of COVID-19, co-existing condition, and other COVID-19 treatment. ALT value was used as a liver injury marker, because it is more specific for liver damage than aspartate aminotransferase (AST) (Kim et al., 2008). Descriptive analysis was performed for patient characteristics, medication treatment, and percentage of cases of ALT elevation based on the DILI grading system developed by the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (CTG). The grading system is used to assess the severity of liver test abnormality, with the value expressed as multiples of the upper limit of the normal range (ULN). The following grades are Grade 1 (1.25-2.5) indicating mild, Grade 2 (> 2.5-5) moderate, Grade 3 (> 5-10) severe, and Grade 4 (> 10) life-threatening (LiverTox, 2012). Furthermore, the IBM SPSS for windows version 24.0 was used for non-parametric analysis. Wilcoxon signed-rank test was performed to find out differences in ALT value between baseline and end-point measurement, p-value < 0.05 means statistical significantly.

3 RESULTS AND DISCUSSION

3.1 Results

In total, 159 patients received remdesivir treatment from June until August 2021. 76 of these patients were excluded because of missing end-point ALT, the elevation of ALT on pre-remdesivir, getting hepatoprotection treatment before/after the start of remdesivir, and getting double antivirals. Of the 83 remaining patients included in this study.

3.1.1 Baseline Characteristics of Patients

Table 1 shows the demographic and clinical characteristics of 83 patients in this study. A total of 43 patients (52%) were women, the mean age was 56 ± 16.35 years. The mean duration of remdesivir treatment was 6.5 ± 1.95 days. Most patients (58 patients (69.9%)) had moderate symptoms on admission. Of 3 patients (3.6%) had mild symptoms on admission, but they got remdesivir because of worsening symptoms during the in-hospital. The most of patients having co-existing conditions were hypertension (33 patients (39.8%)) and type 2 diabetes mellitus (25 patients (30.1%). More than 50% of patients got other drugs, which are levofloxacin and dexamethasone.

Table 1: Demographic and Clinical Characteristics of the Patients (N=83).

Patient characteristic	N (%)
Sex	
Men	40(48%)
Women	43(52%)
Age (years)	56 ± 16.35
Clinical manifestation of COVID-19	
Mild	3.6%
Moderate	69.9%
Severe	26.5%
Co-existing condition	
Hypertension	39.8%
Type 2 Diabetes Mellitus	30.1%
Chronic Kidney Disease	4.8%
Coronary Heart Disease	9.6%
Dyslipidemia	6.0%
Stroke	1.2%
Asthma	2.4%
Duration of remdesivir treatment (days)	6.5 ± 1.95
Other medication*	
Levofloxacin	68.67%
Azithromycin	4.82%
Moxifloxacin	12.05%
Dexamethasone	57.83%
Hydrocortisone	3.61%
Tocilizumab	26.51%

*Other medication belongs to standard of care of COVID-19 in Indonesia

3.1.2 An ALT Elevation during Remdesivir Treatment

Based on classification of DILI by AIDS CTG, ALT elevation was observed in 21 patients (25.3%), including grade 1 elevation in 14 patients, grade 2 elevation in 6 patients, and grade 3 in 1 patient. The majority of patients who having ALT elevation were men, having moderate symptoms and the mean duration of remdesivir treatment was approximately 5-9 days (shown in Table 2)

Table 2: The Characteristic of Patients Who Having ALT Elevation (N=21).

Characteristics	Grade 1 (N=14)	Grade 2 (N=6)	Grade 3 (N=1)
Age (years)	44.8 ± 10.8	43 ± 20	24
Sex			
Men	7	4	1
Women	7	2	0
Clinical Manifestation of COVID-19			
Mild	1	1	0
Moderate	8	3	0
Severe	5	2	1
Duration of Remdesivir Treatment (days)	6.9 ± 1.8	6.5 ± 2.0	5

Table 3: Statistic Result of The Difference in ALT Level.

ALT level	Median (interquartile range)	p value*
Baseline	22 (14)	< 0.001
End-point	29 (33)	

*Wilcoxon test, the ALT level decreased in 29 patients, increased in 49 patients, and steady in 5 patients

Table 3 showed there was significantly differences ($p<0.001$) ALT value before and during/after (end-point) remdesivir treatment. There are several drugs of standard therapy in COVID-19 other than remdesivir, were used in this study, which may be caused liver toxicity according to the likelihood score of DILI LiverTox. These drugs have shown in Table 4, including the percentage of patients who received concomitant medications.

Table 4: Percentage of Patients with Concomitant Medications (N=83).

Medication	ALT elevation Group (N=21)	ALT non-elevation Group (N=62)
Levofloxacin	15 (71.43%)	42 (67.74%)
Azithromycin	2 (9.52%)	2 (3.23%)
Moxifloxacin	2 (9.52%)	8 (1.9%)
Dexamethasone	20 (95.2%)	28 (45.16%)
Hydrocortisone	1 (4.76%)	2 (3.23%)
Tocilizumab	8 (38.10%)	14 (22.58%)

3.2 Discussion

Liver injury associated COVID-19 has occurred in 14-53% of patients. Various mechanisms have been hypothesized to explain that pathogenesis, such as the the worsening of COVID-19 illness and drug toxicity. Several drugs in the management of COVID-19 are potential hepatotoxic (Aleem et al., 2021). Liver injury during remdesivir treatment was reported and registered in WHO vigibase pharmacovigilance. Increased liver transaminase (88%) was the most frequent adverse drug reaction of remdesivir (Montastruc et al., 2020). These reports are consistent with our result that ALT value increased significantly during/after remdesivir treatment ($p<0.001$). According to the AIDS CTG grading system, ALT elevation occurred in 21 patients (25.3%). Our result is contrary to a meta-analysis study which showed that treatment with remdesivir was associated with a lower risk of ALT elevation ($p=0.006$) (Angamo et al., 2022). However, the cut-off value of ALT to define ALT elevation in that study was unclear.

We also found that most of our patients had mild-moderate liver injury (grade 1-2), and only one had a severe liver injury (grade 3). All of our patients didn't require to stop remdesivir, some patients got hepatoprotection treatment. This finding was also reported by Ghosh, et al, that remdesivir caused frequent grade-1 (1.25 to 3-fold) and grade-2 (3 to 5-fold) elevation of ALT which didn't require drug discontinuation (Ghosh et al., 2020). In contrast to Wang et al., two patients with severe COVID-19 in the remdesivir group had increased ALT events (any grade) leading to drug discontinuation (Wang et al., 2020).

We observed liver injury in our study possibly occurred in patients with moderate COVID-19 illness. In most of the previous studies, liver injury following remdesivir treatment occurred in patients with severe-critical COVID-19 illness, due to subjects who included in that studies were only severe/critical illness (Ghosh et al., 2020; Grein et al., 2020; Wang et al., 2020).

According to the standard of therapy in the national guideline, our patients got other drugs than remdesivir such as dexamethasone, levofloxacin, and tocilizumab. All three were the most used concomitant with remdesivir. Based on the likelihood score of DILI LiverTox, dexamethasone and

levofloxacin are well-established causes of liver injury (Category A), and tocilizumab is a probable rare cause of liver injury (Category C) (LiverTox, 2012). Therefore, the possibility of another cause-induced liver injury could not be sorted.

A caution interpretation of the findings of this study is required due to several methodological limitations. Firstly, the sample size of the study might not reflect and represent overall liver injury condition due to remdesivir in Indonesia. Further study with multiple sites and large sample size is necessary. Secondly, this study did not observe a long-term period of the patient's clinical condition. Therefore, a longitudinal study is strongly recommended to observe the effect of remdesivir on liver injury. Despite several limitations, our study has superiority in milestone contribution on evidence-based providing of remdesivir safety and efficacy in COVID-19 treatment.

4 CONCLUSIONS

This study highlighted that ALT elevation is probably due to remdesivir. Mostly, this event occurred in moderate COVID-19 patients. However, there were other causes of induced liver injury that could not be sorted.

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