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Remdesivir induced Liver Injury in a Patient with Coronavirus Disease 2019

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Abstract Remdesivir, is a broad-spectrum antiviral medication that has been used recently for COVID-19 patients. Herein, we report a case of COVID-19 who developed liver injury following administration of remdesivir.

Keywords: *COVID-19, liver injury*

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1. Introduction

A new rapidly spreading virus strain of coronavirus was discovered as the cause of fatal pneumonia in China At the end of 2019. Many therapeutic agents have been tried to manage the COVID-19 virus including remdesivir which was approved by the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19 in October 2020 [1]. However, information regarding adverse drug reactions and possible drug-drug interactions are scarce. Nevertheless, few case reports documented hepatotoxicity following remdesivir administration. Herein, we report a case of a critically ill patient with COVID-19 who developed hepatotoxicity following remdesivir therapy.

2. Case Presentation

A 59-year-old male with past medical history of hyperlipidemia and type 2 diabetes mellitus who presented at our hospital with a 4-day history of worsening shortness of breath associated fever. Patient is an active smoker with 2-3 cigerrate per day over the last 40 years. Upon presentation, His blood pressure was 140/88 mm Hg, with a pulse rate of 123 beats per minute, his body temperature was 36.0°C, his respiratory rate was 29 breaths per minute, and oxygen saturation was 86% on non-rebreather mask. The diagnosis of COVID-19 was confirmed by a positive SARS-CoV-2 polymerase chain reaction test of the nasopharynx and consolidations in both lungs on radiology assessment. Due to respiratory insufficiency on day 2, patient required intubation and connected to mechanical ventilator; a 10-day dexamethasone course was started (loading dose 10 mg Intravenous followed by 6 mg IV daily). On day 2, remdesivir was started (loading dose 200 mg Intravenous followed by 100 mg IV daily). Because of suspected pneumonia-, doxycycline was started (100 mg on day 1) 1 day before initiation of remdesivir and discontinued on day two. Patient developed acute kidney injury requiring continuous renal replacement therapy (CRRT) on day 14. Twelve days after start of remdesivir, patient noticed to be jaundiced and an acute increase in total was noticed alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was seen. Total bilirubin was 19.4 µmol/L, ALT 166 IU/L, AST 194 U/L, alkaline phosphatase 403 U/L. Furthermore, patient liver function conditioned to deteriorate. On day 16, Patient passed away.

3. Discussion

Remdesivir is nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication by termination of RNA transcription [2,3]. Also, it has demonstrated in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir resurfaced lately upon the emergence of the COVID-19 pandemic, years after its creation back in 2009 [2,3].

We report a case of remdesivir induced Liver Injury in a patient with COVID-19. The causative agent fell into suspicion due to the strong time relation, the well-established knowledge of in vitro toxicity of remdesivir, and the absence of alternative causes of hepatotoxicity. Although COVID-19 was found to raise ALT levels in some cases, the sudden surge that occurred 12 days after the already established infection in our patient precluded away from believing that the viral replication of SARS-Co V-2 was the cause behind this patient's hepatotoxicity. Other drugs were excluded as inducive agents since their intake was initiated as early as the time of diagnosis, and no

evidence-based direct drug interactions were reported. Moreover, Remdesivir is a substrate of cytochrome P450 (CYP) 3A4 and of the drug transporters organic anion-transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1 [4]. To our knowledge, no clinical drug-drug interaction studies of remdesivir have been conducted. The reported case did not receive medication that could lead to interaction between P-glycoprotein (P-gp) inhibitors and remdesivir.

Few previous literatures have extensively addressed the association of remdesivir and liver toxicity. The Partnership for Research on Ebola Virus in Liberia IV (PREVAIL IV) study which used remdesvir in the treatment of 38 Ebola-infected patients, has found an elevation of aminotransferase, and the dose was reduced in one of the patients [5]. In another study by Mulangu for Ebola patients who received remdesivir treatment, hepatotoxicity was not reported as a significant side effect [6]. In contrast, in a study by Goldman et al [7], remdesivir was discontinued because of ALT elevations in around 3.0% of the patients. Also, studies have shown a direct toxic effect of remdesivir to human hepatocytes [5], particularly with an increase in liver enzymes which could have been induced by COVID-19 itself as in the reported case. It should be noted that the drug should be discontinued if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed [4].

4. Conclusion

In summary, we present a case of hepatotoxicity most likely related to remdesivir. Having a baseline liver function and monitoring for hepatotoxicity in patients receiving remdesivir is recommended to obtain before starting the treatment.

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