1. Drug-induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors

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Abstract

We report a case of a male with COVID-19 who developed acute hepatotoxicity related to remdesivir with probable interaction of P-glycoprotein (P-gp) inhibitors. Until further details upon this interaction become available, we recommend physicians to be cautious with the prescription of P-gp inhibitors in patients receiving remdesivir therapy.

Keywords: Remdesivir, COVID-19, drug-drug interaction, hepatotoxicity

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged around the globe causing a pandemic of coronavirus infectious disease (COVID-19).

Clinicians worldwide are urgently looking for investigational antiviral agents for benefit over supportive care alone. Remdesivir is an investigational drug that shows in vitro anti-viral activity against SARS-CoV-2 and a shorter time to clinical recovery in clinical trials [1]. On May 1, 2020, the US Food and Drug Administration issued an emergency use authorization for remdesivir for the treatment of COVID-19. However, because of the limited experience with remdesivir, information about adverse drug reactions and possible drug-drug interactions is scarce.

We report a case of a critically ill patient with COVID-19 who developed hepatotoxicity following remdesivir therapy. We propose a relationship with a drug-drug interaction between remdesivir and P-glycoprotein inhibitors.

Case presentation

A 64-year-old male patient presented at our hospital with a 7-day history of fever, headache, cough and progressive dyspnea. He had a history of hypertension and hypercholesterolemia for which he used enalapril, amlodipine and simvastatin. He did not smoke or use illicit drugs. His blood pressure was 143/80 mmHg, with a pulse rate of 80/min, his body temperature was 38.8^{o}C, his respiratory rate 40/min and oxygen saturation 88% while breathing room air. The diagnosis of COVID-19 was confirmed by a positive SARS-CoV-2 PCR of the nasopharynx and consolidations in both lungs on radiology assessment. He was admitted to the hospital for oxygen therapy; a 5-day chloroquine course was started (loading dose 600 mg followed by 300mg b.i.d.), according to national guidelines at that time. Due to respiratory insufficiency on day three, he was transferred to the Intensive Care Unit (ICU) for mechanical ventilation. The ICU course was complicated by pulmonary embolism and ICU acquired weakness. On day 16, remdesivir was started as part of an extended access program

(GS-US-540-582) [2]. Because of new onset atrial fibrillation amiodarone was temporally given (700 mg on day 18) two days after initiation of remdesivir. Five days after start of remdesivir, an acute increase in alanine transaminase (ALT) and aspartate transaminase (AST) was seen. ALT was 1305 IU/L, AST 1461 U/L, alkaline phosphatase 269 U/L, total bilirubin 8 µmol/L, gamma-glutamyltransferase 227 U/L and creatine kinase 103 U/L. Remdesivir was immediately stopped, resulting in a rapid decrease of ALT and AST values to eventually normal levels (Figure 1). On day 48 the patient was discharged to a rehabilitation center. Two weeks hereafter, he returned home, and he was able to restart his normal daily activities.

Discussion

We presented a case of drug-induced liver injury most likely caused by remdesivir. Remdesivir toxicity was suspected based on the time-relation, the positive dechallenge, the known in vitro toxicity of remdesivir and the absence of alternative causes of hepatotoxicity. COVID-19 has also been found to be associated with elevated liver enzymes [3]. COVID-19 could therefore be the cause of elevated ALT seen in the period prior to remdesivir therapy (Figure 1) [4]. However, the sudden ALT peak occurred 27 days after the first onset of symptoms, making viral replication of SARS-CoV-2 as a cause of acute hepatotoxicity very unlikely. Amiodarone-induced liver toxicity was considered less likely, since acute amiodarone toxicity has an early onset (within 24 hours) and the given cumulative dose was low [5]. Furthermore, given amiodarone's very long half-life (26-107 days) the rapid resolution which was seen after the initial elevation of ALT makes a causative role of amiodarone unlikely.

Several clinical studies described amino transaminase elevations following remdesivir therapy. In healthy individuals grade 1 and 2 transaminase elevations were seen [6]. In the prevail-IV study using remdesivir as treatment in 38 patients with Ebola, the remdesivir dose was reduced in one patient because of amino transaminase elevations [6]. In contrast, hepatotoxicity was not documented as a serious adverse event in 175 Ebola patients receiving remdesivir in the Palm study [7]. In the ACTT-1

study hepatotoxicity, defined as transaminase elevations of grade 1 or higher, was seen less in COVID-19 patients receiving remdesivir as compared to placebo (4.1% versus 5.9%) [1]. In a study by *Wang et al*. one out of 155 patients experienced grade 3 or 4 AST elevations and in a study by Goldman et al. remdesivir was discontinued because of ALT elevations in 3.0% of the patients [8, 9], which according to the authors could also have been caused by COVID-19 itself [9].

On a cellular level, it has been shown that remdesivir is toxic to human hepatocytes [6]. The in vitro threshold concentration for remdesivir toxicity is 10 uM, which is only 1.1 times the maximal targeted therapeutic concentration [10]. As such, the upper limit of toxicity could be exceeded with a minor increase in hepatocellular concentration.

A possible cause for an increase in hepatocellular concentration and thereby an explanation for remdesivir toxicity, could be an interaction between P-glycoprotein (P-gp) inhibitors and remdesivir. P-gp is an efflux transporter located on the membrane of several humane cells including the hepatocytes. In the hepatocyte P-gp transports xenobiotics out of the cell into the bile duct (Figure 2). Remdesivir has been identified to as a substrate for P-gp in vitro [6]. A reduced efflux rate of remdesivir was observed in vitro in P-gp overexpressing cells in the presence of the P-gp inhibitor cyclosporine [10]. Therefore, P-gp inhibitors could decrease the remdesivir efflux out of the hepatocyte, resulting in a hepatocellular concentration above the toxic threshold.

The patient we described was treated with the P-gp inhibitors chloroquine (last gift nine days before remdesivir, half-life approximately two weeks) and amiodarone (concomitantly with remdesivir)[11, 12]. The combination of these two agents with remdesivir could have increased the intrahepatocellular concentration above the toxicity threshold which caused the hepatocellular toxicity. No studies investigating the influence of P-gp inhibition on remdesivir mediated hepatotoxicity have been performed yet.

To summarize, we presented a case of hepatotoxicity most likely related to remdesivir. Therefore, we urge the need for consistent monitoring for hepatotoxicity in patients receiving remdesivir. Additionally, we proposed a mechanism for a drug-drug interaction between remdesivir and P-gp inhibitors. More research is needed to verify this mechanism, but we recommend physicians to be cautious with the prescription of P-gp inhibitors in patients receiving remdesivir therapy.

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Conflict of interest

The authors declare no conflict of interest.

References:

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. New England Journal of Medicine **2020**.
2. Agency EM. EMA provides recommendations on compassionate use of remdesivir for COVID-19. Available at: https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19.
3. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol **2020**; (2468-1253 (Electronic)).
4. Schaefer EAK, Arvind A, Bloom PP, Chung RT. Interrelationship Between Coronavirus Infection and Liver Disease. Clinical Liver Disease **2020**; 15(5): 175-80.
5. Chen CC, Wu CC. Acute Hepatotoxicity of Intravenous Amiodarone: Case Report and Review of the Literature. **2016**; (1536-3686 (Electronic)).
6. Gilead. Summary on compassionate use. Available at: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed 04-06.
7. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. New England Journal of Medicine **2019**; 381(24): 2293-303.
8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet **2020**; (1474-547X (Electronic)).
9. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New England Journal of Medicine **2020**.
10. Gilead. INVESTIGATOR'S BROCHURE REMDESIVIR (GS-5734TM) 21-02-2020.
11. EMC. Amiodarone 150 mg/3 ml Concentrate for Solution for Injection/Infusion. Available at: https://www.medicines.org.uk/emc/product/8739/smpc. Accessed 04-06.
12. Crowe A, Ilett KF, Karunajeewa HA, Batty KT, Davis TME. Role of P Glycoprotein in Absorption of Novel Antimalarial Drugs. Antimicrobial Agents and Chemotherapy **2006**; 50(10): 3504-6.

Figure Legends:

Figure 1: ALT concentration versus time, the dotted line represents the upper limit of normal. CQ is chloroquine.

Figure 2: Schematic overview of the possible interaction between remdesivir and P-glycoprotein

Figure 1

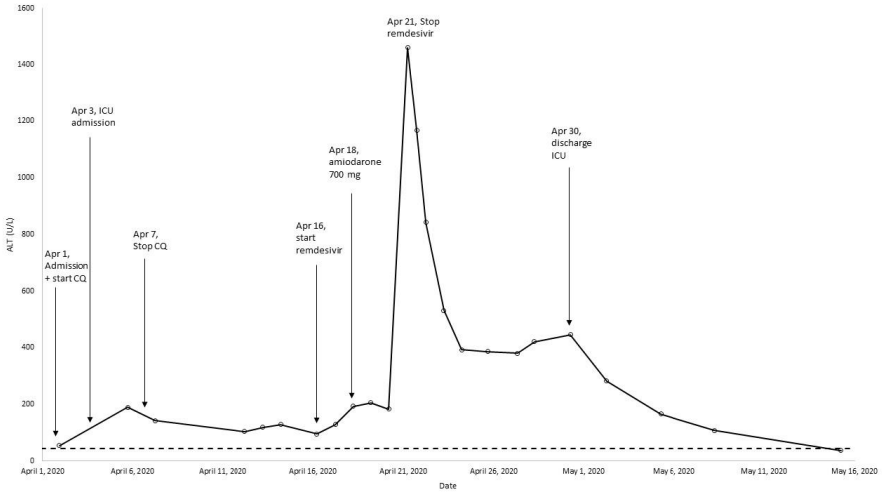
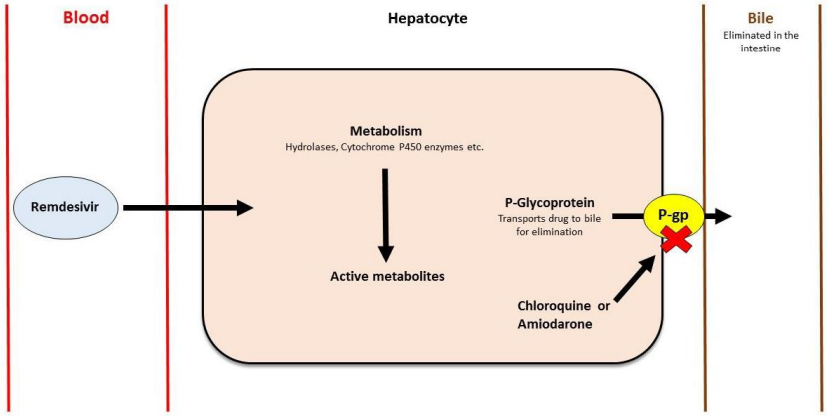

1600
1400
1200
1000
800
600
400
200
0
ALT IU/L)
Apr 1, Admission + start CQ
Apr 3, ICU admission
Apr 7, Stop CQ
Apr 16, start remdesivir
Apr 18, amiodarone 700 mg
Apr 21, Stop remdesivir
Apr 30, discharge ICU
April 1, 2020
April 6, 2020
April 11, 2020
April 16, 2020
April 21, 2020
April 26, 2020
May 1, 2020
May 6, 2020
May 11, 2020
May 16, 2020
Date

Figure 2


Blood
Hepatocyte
Bile
Eliminated in the intestine
Metabolism
Hydrolases, Cytochrome P450 enzymes etc.
Remdesivir
Active metabolites
P-Glycoprotein
Transports drug to bile for elimination
P-gp
Chloroquine or Amiodarone