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Strategy for the control of drug-induced liver injury due to investigational treatments/drugs for COVID-19

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Abstract

Investigational treatments/drugs for coronavirus disease 2019 (COVID-19) have been applied, with repurposed or newly developed drugs, and their effectiveness has been evaluated. Some of these drugs may be hepatotoxic, and each monotherapy or combination therapy may increase the risk of drug-induced liver injury (DILI). We should aim to control dysregulation of liver function, as well as the progression of COVID-19, as much as possible. We discussed the potential risks of investigational treatments/drugs and promising drugs for both COVID-19 and DILI due to investigational treatments/drugs.

Key Words: Coronavirus disease 2019; Drug-induced liver injury; Cytochrome P450; Drug-drug interaction; Drug-disease interaction; Cytokine

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Core Tip: To cope with dysregulation of liver function in coronavirus disease 2019 (COVID-19), drug-induced liver injury (DILI) due to investigational treatments/drugs or drug-drug or drug-disease interactions should be considered. We described useful information associated with clinical practice. We discussed the potential hepatotoxicity of dexamethasone or remdesivir as representative investigational treatments/drugs for COVID-19. These drugs are predicted to be used for a certain time in monotherapy or combination therapy. We also reported glycyrrhizic acid and ursodeoxycholic acid as therapeutic candidates for the control of DILI due to investigational treatments/drugs, as well as COVID-19.

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TO THE EDITOR

We read with great interest the review by Huang *et al*[1], which summarized the current understanding and perspectives on dysregulation of liver function in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We generally agree with the authors' comprehensive review. Additional information regarding the potential hepatotoxicity of investigational treatments/drugs for coronavirus disease 2019 (COVID-19) and the strategy for dealing with drug-induced liver injury (DILI) associated with investigational treatments/drugs is useful in clinical practice.

The investigators[1] cited that the synthetic corticosteroid dexamethasone worsens outcomes in patients with COVID-19 who show milder respiratory symptoms, which was reported in the RECOVERY trial[2]. However, to be technically accurate, dexamethasone therapy had several strengths in reducing the 28-d mortality rate, increasing the rate of patients who were discharged alive from hospital within 28 d, and reducing progression to invasive mechanical ventilation or death in comparison to those with usual care, while these merits were not observed in patients who did not receive oxygen[2]. The World Health Organization (WHO) announced guidelines regarding dexamethasone therapy for COVID-19[3]. Corticosteroids (*i.e.*, dexamethasone, hydrocortisone or prednisone) were recommended for the treatment of patients with severe and critical but not nonsevere COVID-19 on September 2, 2020[3]. The current situation has changed with the emergence of new genetic variants of SARS-CoV-2[4]. SARS-CoV-2 mutation may facilitate transmissibility or virulence, reduce neutralization by antibodies produced in response to natural infection or vaccination, promote the ability to evade detection, or decrease the effectiveness of therapeutics or vaccination[4]. They may affect the disease progression of COVID-19, and thus, we believe that the treatment strategy has a more important role in the control of COVID-19.

The role of dexamethasone is to ameliorate inflammatory organ injury in viral pneumonia[2]. However, dexamethasone is a cytochrome P450 (CYP3A4) inducer and has a high chance of drug-drug interactions with investigational treatments/drugs or agents used to treat comorbidities, especially CYP3A4 substrates. Importantly, CYP enzymes can be inhibited by an increase in infection-related cytokine levels and inflammation[5]. Both investigational treatments/drugs and agents used to treat comorbidities can be affected by compromised CYP-mediated hepatic metabolism, irrespective of the onset/Length of COVID-19 and the extent of liver dysfunction[5]. Subsequently, these drug-drug and drug-disease interactions and dysfunctional CYP-mediated hepatic metabolism might cause dysregulation of liver function, including drug-induced liver injury (DILI)[5]. In addition, dexamethasone therapy caused elevated liver enzymes, increased hepatic lipid peroxidation, and decreased antioxidant activities in rats[6]. On the other hand, dexamethasone is a type of corticosteroid that can be used to treat drug-induced cholestatic hepatitis[7]; in particular, corticosteroids are used for the treatment of DILI associated with hypersensitivity features[8]. The mechanism of dexamethasone against DILI might be involved in alleviation of tissue damage caused by inflammatory responses of the immune system within the liver[7]. Thus, dexamethasone has pros and cons in relation to liver injury. Dexamethasone could be used in combination with antiviral drugs, such as remdesivir (RDV), for COVID-19 patients, although the WHO announced a conditional recommendation against the use of RDV in hospitalized patients on November 20, 2020[9]. As a direct role of RDV in hepatocellular toxicity was suggested [10], combination therapy with dexamethasone and RDV is more likely to cause liver dysfunction, especially for patients with comorbidities, and we should perform careful observation during combination therapy or each monotherapy.

Regarding the treatment of DILI due to investigational treatments/drugs, glycyrrhizic acid was advocated as a treatment candidate for COVID-19 patients, especially those with complex liver injury[11]. In Japan, glycyrrhizic acid has been used for more than 40 years as a treatment for liver diseases[11]. It works as a hepatoprotective drug for a variety of liver diseases, including DILI[11], and has safe and economical features[11]. The possible mechanism of monoammonium glycyrrhizin, the main component of glycyrrhizin, against drug-induced hepatotoxicity involves

Table 1 Anti-coronavirus disease 2019 drugs and drugs for drug-induced liver injury

Name	Type	Mechanisms as anti-COVID-19 drugs and/or drugs for drug-induced liver injury	Mechanisms of hepatotoxicity	Ref.
Anti-COVID-19 drugs				
Dexamethasone	Anti-inflammatory drug	Amelioration of inflammatory organ injury in viral pneumonia. Alleviation of tissue damage caused by inflammatory responses of the immune system within the liver.	Drug-drug interactions due to cytochrome P450 induction. Elevation of liver enzyme levels, increase in hepatic lipid peroxidation, and decrease in antioxidant activities.	[2,6,7]
Remdesivir	Antiviral drug	Inhibition of RNA polymerase, as a nucleotide analog.	Hepatocellular toxicity.	[10]
Drugs for drug-induced liver injury				
Glycyrrhizic acid	Hepatoprotector	Regulation of the expression of hepatobiliary membrane transporters.		[12]
Ursodeoxycholic acid	Hepatoprotector	Anti-inflammatory, antioxidant, immunomodulatory and antiapoptotic profiles. Inhibition of proinflammatory cytokine production.		[14]

COVID-19: Coronavirus disease 2019.

regulating the expression of hepatobiliary membrane transporters[12].

Another therapeutic candidate for DILI due to investigational treatments/drugs is ursodeoxycholic acid (UDCA), which has been used in cholestatic DILI to reduce the time to resolution[13]. UDCA is a hydrophilic bile acid that has anti-inflammatory, antioxidant, immunomodulatory and antiapoptotic profiles[14] and inhibits proinflammatory cytokine production[14]. Thus, UDCA is also beneficial for cytokine storm syndrome, which is caused by a sudden, abnormal release of inflammatory cytokines due to overreaction of innate immunity[14], which is one of the critical pathogeneses of COVID-19. UDCA has been promoted as a candidate therapeutic agent for COVID-19[14,15]. Anti-COVID-19 drugs and drugs for DILI are summarized in Table 1.

We should manage dysregulation of liver function regardless of the association with treatment for COVID-19. We introduced the potential risks of investigational treatments/drugs and promising drugs for both COVID-19 and DILI due to investigational treatments/drugs. Further studies should confirm this hypothesis and may help to establish an effective strategy for the management of COVID-19 and DILI due to investigational treatments/drugs.

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