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Review Article

Current and New Drugs for COVID-19 Treatment and Its Effects on the Liver

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Abstract

Corona virus disease (COVID)-19 is caused by the novel severe acute respiratory syndrome coronavirus-2 (commonly referred to as SARS-CoV-2). In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. Though the target organ for the virus is primarily the lungs, with the recent understanding of the pathobiology of this disease and the immune dysregulation associated with it, it is now clear that COVID-19 affects multiple organ systems. Several drugs and therapies have been tried or repurposed to combat the wrath posed by this disease. On October 22, 2020, the USA Food and Drug Administration approved remdesivir for use in adults and pediatric patients (12 years of age and older). Several of the drugs being tried against COVID-19 have hepatotoxicity as their potential side effect. This review aims to provide the latest insights on various drugs being used in the treatment of COVID-19 and their effects on the liver.

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Introduction

Coronavirus disease (COVID)-19 caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected millions worldwide and the numbers of cases are consistently rising.[1] The ongoing COVID-19 caused by SARS-CoV-2 poses a serious threat to healthcare systems globally. As the virus continues to create havoc across the globe, it is eminent that the knowledge about the impact of this virus and its potential impact on different organs will evolve. Pulmonary and extra-pulmonary manifestations of COVID-19 are increasingly being recognized.[2]

Information on how COVID-19 affects the liver and how the drugs used for its treatment can affect the liver are slowly emerging. Although the real burden of this is currently unknown, as our understanding of the disease is constantly evolving, hepatic manifestations are being increasingly recognized. Various management strategies and research on drugs for COVID-19 are currently under study, many of which may have significant impact on liver.[3] In the present review we aim to provide updated information regarding interplay of liver and COVID-19 in the face of this pandemic and to promote understanding of the role of drugs used for COVID-19 treatment and their effects on the liver.

Virology: key aspects

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus classified as the newest member of the family of β coronaviruses.[4] The life cycle of this spiked virus typically involves attachment, penetration, biosynthesis, maturation, and release. Angiotensin converting enzyme 2 (ACE2) has been identified as an important functional receptor, to which the virus attaches and continues its lifecycle. The spike protein of the virus binds to the ACE2 receptors of the cell, which enables the virus to enter and subsequently replicate within the cells.[5] The receptor is not only present in the lungs but is also present in many extra-pulmonary sites like the kidney and gastrointestinal tract.[6] This may explain the extra-pulmonary symptoms associated with COVID-19. The virus, after its entry, induces an inflammatory response and virus-specific T cells are attracted to the site of infection.[7] The disease manifestations are primarily the result of direct viral-mediated damage and immune-mediated injury.[8]

Clinical manifestations

The symptoms of patients infected with SARS-CoV-2 can range from none or minimal to severe respiratory failure

Keywords: COVID-19; Drugs; Liver; Drug-induced liver injury.

Abbreviations: AAK1, adaptor-associated protein kinase 1; ACE2, angiotensin converting enzyme 2; AKR, anakinra; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZT, azithromycin; COVID, coronavirus disease; CP, convalescent plasma; CYP, cytochrome; DILI, drug-induced liver injury; DXA, dexamethasone; FDA, Food and Drug Administration; FPR, favipiravir; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICU, intensive care unit; IL, interleukin; IVN, ivermectin; JAK, Janus kinase; LPV/r, lopinavir/ritonavir; NAK, numb associated kinase; NIAID, National Institute of Allergy and Infectious Diseases; PCR, polymerase chain reaction; RdRp, RNA-dependent RNA polymerase inhibitor; RDV, remdesivir; REFHEPS, Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOC, standard of care; SOFA, sequential organ failure assessment; TCZ, tocilizumab; ULN, upper limit of normal; VTE, venous thromboembolism.

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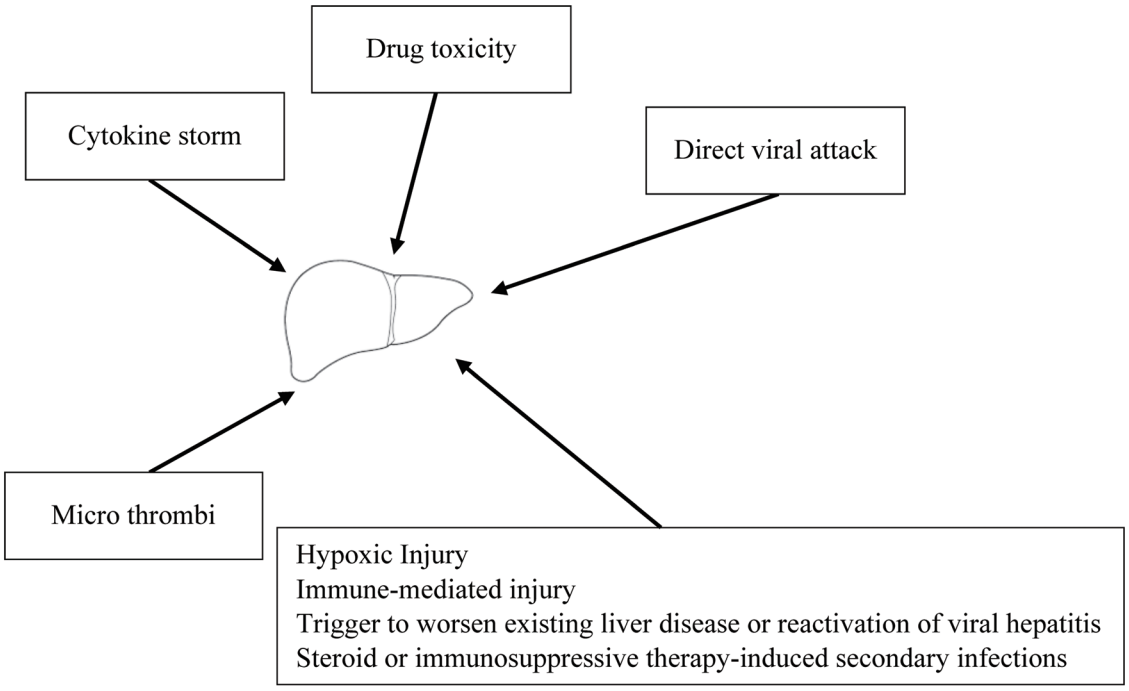

Fig. 1. Possible mechanisms of effects of SARS-CoV-2 on liver.

with multiple organ involvement.[9] The majority of patients experience mild symptoms, like fever, cough, myalgia, fatigue and less commonly headache, hemoptysis and diarrhea. The clinical severity in the largest published registry to date (i.e. Chinese Center for Disease Control and Prevention) reported disease being mild in 81.4%, severe in 13.9%, and critical in 4.7%.[10] The severe clinical manifestations have typically been described as severe pneumonia, acute respiratory distress syndrome and respiratory failure.[11] However, the recent literature has shed light on the extra-pulmonary manifestations of the virus. Although the major manifestations involve the respiratory system, owing to its attachment to the ACE2 receptors, the cardiac, vascular, neurological, renal, and hepatic manifestations have also been described.[12]

Liver involvement in COVID-19

Liver injury in patients with COVID-19 might be due to a direct viral infection of the liver cells or due to multiple indirect pathways (Fig. 1). Given the higher expression of ACE2 receptors in cholangiocytes, the liver forms a potential target for SARS-CoV-2. Studies from biopsy of liver tissues of SARS-CoV-2-infected patients have shown liver cell apoptosis, which supports the direct hit hypothesis for this virus.[13] In an elegant study by Lagana SM *et al*,[14] histopathologic analysis of liver sections in a cohort of 40 COVID-19 autopsies was performed. Histologically, the most frequently encountered findings were macrovesicular steatosis, minimal-to-mild portal inflammation, and mild acute hepatitis. Thirty eight percent of cases had lobular cholestasis. Two cases had pale ovoid sinusoidal inclusions, which at low power resembled apoptotic hepatocytes. Vascular findings were focal in nature, with sinusoidal microthrombi being present in six cases. Polymerase chain reaction (commonly known as PCR) was performed on 20 autopsied livers and was positive in eleven (55%); however, there were no significant correlations between PCR positivity and any histologic findings.[14] Other reports have described a significant cluster or scattered apoptotic hepatocytes, which are characterized by condensed nuclear or formed apoptotic bodies. There was no eosinophil infiltration, granuloma formation, centrilobular necrosis, or evidence of interface hepatitis.[15] The virus may bind to cholangiocytes and cause bile duct dysfunction, thereby impairing liver regeneration and immune responses.[16]

SARS-CoV-2 can affect the liver directly but also indirectly, via several mechanisms.[17] Indirect effects may be multifactorial, as depicted in Figure 1. Liver injury in patients with COVID-19 may be accounted for by a systemic inflammation induced by the cytokine storm or secondary to hypoxia or acute respiratory distress syndrome. The cytokine storm secondary to the virus infection can trigger extra-pulmonary systemic hyperinflammation syndrome. The cytokine surge (including interleukin (IL)-1, IL-6, and IL-10), inflammation and sepsis-related factors can damage the liver directly or indirectly.[18] The possibility of hypoxia-induced damage, microthrombi, immune dysfunction or drug toxicities are other important mechanisms which can impact the liver.[19]

To battle this new enigmatic virus, a plethora of drugs and therapies have been tried or repurposed. Newer drugs or drug combinations may have concerns of exacerbating liver diseases or causing drug-induced hepatotoxicity, or can interact with other drugs to exacerbate their hepatotoxic potential. Some drugs may also reactivate a latent virus, which might lead to liver damage. In patients with pre-existing liver disease, COVID-19 infection could trigger a potentially fatal acute-on chronic liver failure.[20]

Several case reports, series and studies have shed light on the hepatobiliary manifestations of the disease. Transaminitis has been found to be associated in up to 14% to 53% of COVID-19 cases.[21,22] Recent studies have reported abnormal liver function tests in as many as 76.3% of patients admitted with COVID-19. The authors also noted that liver test abnormalities became more pronounced during hospi-

talization. This can be explained in part by disease progression and super-added drug-induced liver injury (DILI). Hyperbilirubinemia has been documented in 11–18% of cases in some series.[23] One series from New York, USA showed 46.5% of the patients had aspartate aminotransferase (AST) >40 U/L, 32% had alanine aminotransferase (ALT) >40 U/L, and 9.1% had total bilirubin >17.1 μmol/L.[24] Cases of acute liver injury (ALI) have been reported and are associated with higher mortality.[22] Most of the transaminitis may be self-resolving; however, more studies are needed to determine the significance of mildly deranged liver enzymes with the outcome of the disease. An extensive meta-analysis including 21 studies concluded that altered liver and kidney function and increased coagulation parameters are seen in severe and fatal cases of COVID-19.[25]

Patients with chronic medical comorbidities have been clearly shown to have severe COVID-19 disease and worse outcomes. A systematic review including 1,527 patients reported the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17.1%, 16.4%, and 9.7%, respectively.[26] However, there is growing evidence to predict worse outcomes in patients with underlying liver disease.[27] Literature has suggested patients who have a second 'hit', that is liver injury on the background of underlying liver disease, have poor outcomes.[27] The first author of the manuscript has also noted a higher mortality in patients with acute-on chronic liver failure, in whom the acute precipitant was linked to COVID-19 infection.

Drugs used in the management of COVID-19

Several drugs have been tried in the prophylaxis and treatment of COVID-19 (Fig. 2); however, only one drug (remdesivir, RDV) has recently been approved by the USA FDA. Supplementary Table 1 depicts the current treatment protocol for COVID-19. The following section describes the various drugs used for COVID-19 and their implications on liver.

Antivirals

Hydroxychloroquine (HCQ)

HCQ is an oral drug which has both antimalarial and anti-inflammatory properties. It is commonly used in the management of rheumatological diseases. It is increasingly being used for management of COVID-19 based on *in vitro* data and initial reports.[28] HCQ is supposed to act by preventing ACE2-mediated or endosomal-mediated viral entry (Fig. 2).[29] Although it is considered as a relatively safe drug, reports of adverse cardiac effects in patients with COVID-19 is concerning (Supplementary Table 1).[30] Despite retrospective observational studies showing mixed results, randomized controlled trials have not shown any benefit in COVID-19 patients irrespective of severity (Supplementary Table 2).[31] HCQ has also been tried for the prophylaxis to prevent COVID-19. In an elegant randomized, double-blind, placebo-controlled trial, HCQ was used in people within 4 days of exposure to someone with confirmed COVID-19. After a high-risk or moderate-risk exposure to COVID-19, HCQ was not found to be effective in preventing illness compatible with COVID-19 (Supplementary Table 2).[32] In a study by Cavalcanti *et al*.,[33] the use of HCQ with or without azithromycin (AZT) in patients with mild to moderate COVID-19 did not improve clinical status at 15 days, as compared with standard care. In another randomized, controlled, open-label platform trial, the investigators noted that among patients hospitalized with COVID-19, HCQ usage did not result in a lower incidence of death at 28 days than those who received the usual care.[34]

HCQ is metabolized in the liver and may alter the metabolism of other drugs. HCQ has not been associated with significant elevations of liver enzymes and is not usually incriminated as a cause of DILI. ALI with jaundice due to usage of HCQ is very rare, with only few reports in the literature.[35] An exception to this is when HCQ is used in patients with porphyria cutanea tarda. Its usage in high doses can trigger ALI, which is associated with sudden onset of fever and marked serum enzyme elevations. This reaction appears to be caused by the sudden mobilization of porphyrins and can be avoided when HCQ is started at lower doses.[36] There have been scattered case reports in literature regarding DILI with the usage of HCQ in patients with COVID-19; however, it is to be noted that this is extremely rare.[37]

With recent data pointing at ineffectiveness of HCQ in altering the course of COVID-19 infection, the authors of this manuscript are not in favor of its clinical usage in patients with COVID-19.

Azithromycin (AZT)

AZT is commonly used in the treatment of bacterial infections and might also have antiviral activity against certain RNA viruses.[38] AZT has also been shown to be effective *in vitro* against viruses such as Zika and rhinovirus, in addition to SARS-CoV-2,[39] depicts immunomodulatory properties and can reduce exacerbations in chronic airway diseases.[40] The COALITION II is an open-label randomized trial evaluating AZT in addition to standard of care (SOC), which included HCQ, compared with SOC alone in patients admitted to hospital with severe COVID-19. The investigators however found no benefit of AZT on clinical outcomes, including clinical status or mortality when added to SOC (odds ratio 1.36 [95% confidence interval: 0.94–1.97]; p=0.11).[41]

AZT may lead to idiosyncratic ALI. The clinical presentation of AZT-related DILI is usually of a cholestatic hepatitis arising within 1–3 weeks after start of treatment. It occasionally arises after AZT is stopped, and can occur even after a short 2 to 3 day course. This form of DILI due to AZT usually follows a benign course, but in some instances is associated with a prolonged jaundice and persistence of liver test abnormalities for 6 months or more.[42] Case reports of vanishing bile duct syndrome with AZT usage have also been reported.[43] AZT can occasionally be associated with hepatocellular injury as well. In these instances, the period of latency is typically short. Serum aminotransferase levels are markedly elevated and alkaline phosphatase (ALP) and gamma glutamyl transpeptidase is usually less than twice the upper limit of normal (ULN). The hepatocellular forms of DILI can be severe and lead to acute liver failure, mandating the need for an urgent liver transplant (LT) in certain patients. AZT has also been linked to the development of cutaneous reactions, such as erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrosis. These cutaneous reactions are often associated with a certain degree of liver injury.[44] HCQ and AZT are known to induce QT prolongation via a human Ether-à-go-go–related gene potassium channel blockade.[45] In certain instances, this can trigger ventricular arrhythmias.

Lopinavir/ritonavir (LPV/r)

LPV/r is a protease inhibitor used in the treatment of human immunodeficiency virus (commonly known as HIV) infection. In the initial part of the COVID-19 pandemic, LPV/r was one of the first antivirals to be used in an attempt to

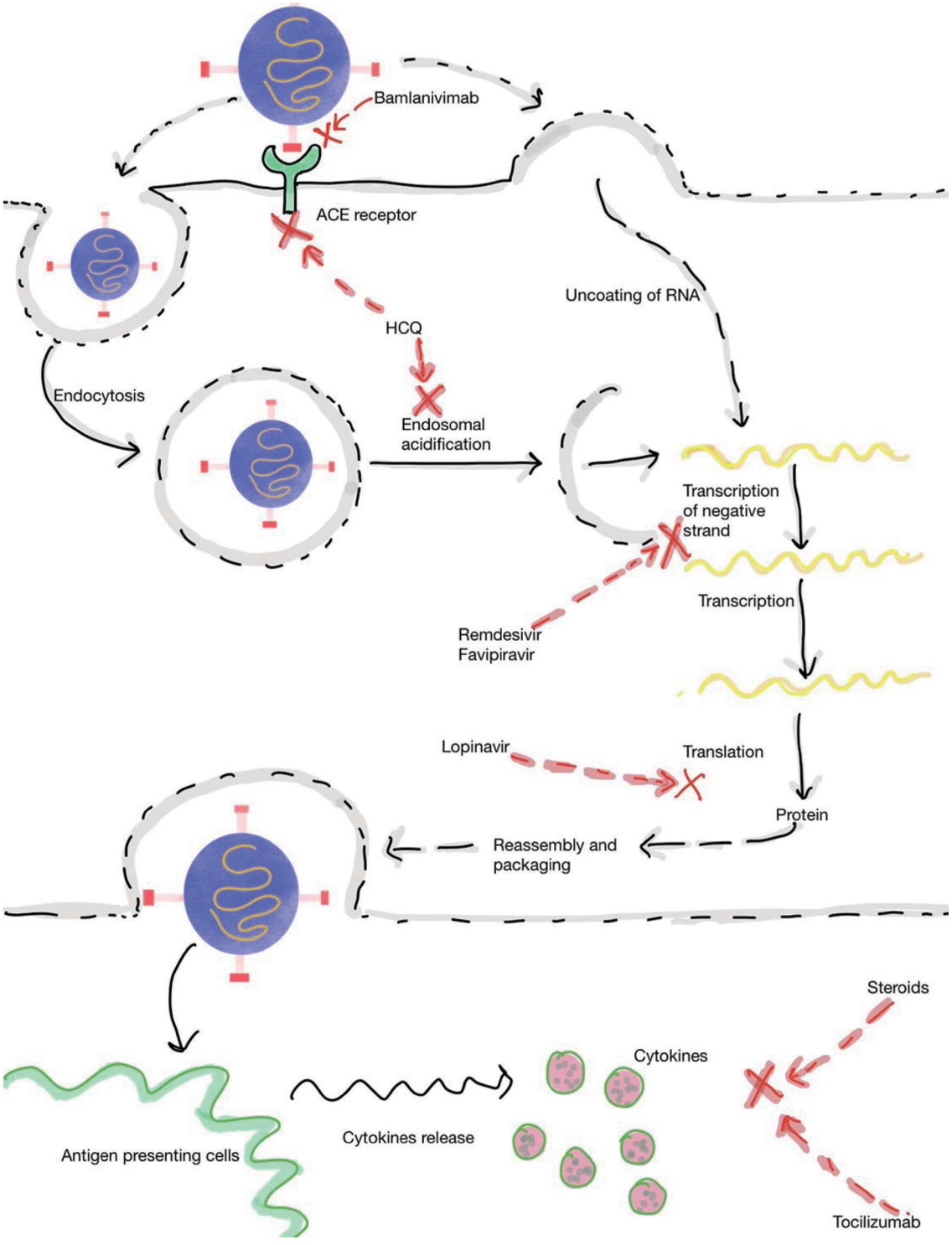

Fig. 2. Mechanism of action of drugs used in the treatment for COVID-19.

improve clinical outcomes. Except for minor gastrointestinal disturbances and potential for drug interactions, the short-term use of this drug is not associated with major side effects (Supplementary Table 1).[46] Although retrospective observational studies showed faster clearance with LPV/r, it was not associated with significantly better outcomes in randomized trials. In one of the pivotal randomized, controlled, open-label, platform trials of LPV/r conducted in patients admitted to the hospital with COVID-19, the investigators noted LPV/r not to be associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.[47] In

another key study in patients with severe COVID-19, no benefit was noted with LPV/r treatment beyond standard care.[48]

LPV/r is primarily metabolized in the liver, largely via the cytochrome (CYP) P450 pathway. This pathway can lead to the formation of a toxic intermediate, which can cause DILI.[49] Though mild elevation of liver enzymes can happen with LPV/r therapy, clinically apparent hepatotoxicities appear to be rare. The rate of DILI is higher in patients having underlying hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.[50] The latency to the onset of symptoms is usually 1 to 8 weeks, and the pattern of serum enzyme elevations varies from cholestatic to hepatocellular or mixed.[51] The injury is usually self-limited; however, fatal cases have been reported. Using LPV/r in patients with underlying HBV and HCV infection can also lead to exacerbation of underlying chronic liver disease, with associated rise in HBV DNA or HCV RNA levels.[52] In the context of LPV/r, the Réseau d'Étude Francophone de l'Hépatotoxicité des Produits de Santé (also known as REFHEPS), which is a European French-speaking study network, reported that within 2 weeks, four cases of LPV/r combination discontinuation occurred in patients with COVID-19 who were being treated with this drug.[53] As the LPV/r combination is falling out of practice to treat COVID-19, its potential to cause DILI in patients with COVID remains more of a theoretical problem.

Remdesivir (RDV)

RDV is an adenosine analogue that is an RNA-dependent RNA polymerase (RdRp) inhibitor. It was developed by Gilead Sciences and was initially used for the treatment of Ebola virus disease. It is a broad spectrum antiviral drug that has shown to inhibit SARS-CoV-2, *in vitro* and *in vivo*.[54,55] RDV has recently been approved by the USA FDA for use in patients who are older than 12 years of age and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization. In a recent double-blind, randomized, placebo-controlled trial of using intravenous RDV in patients who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection; the investigators noted that RDV was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 (Supplementary Table 2).[56] There have also been reports suggesting the use of RDV to not be associated with a difference in time to clinical improvement; however, it has been suggested that RDV is to be used early in the clinical course of COVID-19 infection, before the peak viral replication occurs.[57,58] The duration of therapy in most cases is 5 days.[59]

RDV is a prodrug and is metabolized in the cells into an alanine metabolite which is processed further into the monophosphate derivative and ultimately into the active nucleoside triphosphate.[60] Studies have shown RDV usage to be associated with elevations of AST and ALT.[61] In most instances, the enzyme elevations did not progress to severe liver damage, but cases of acute liver failure suspected as due to RDV usage have been reported.[62] In the report describing two patients with RDV-induced acute liver failure, significant increases in transaminases occurred between day 3 and day 10 of RDV usage. This was also associated with coagulopathy and hepatic encephalopathy. The authors utilized the Naranjo algorithm to determine the possibility of a drug-induced effect and both the cases scored as a 'probable' adverse drug reaction, with a score of 6 each. After discontinuing the drug and treatment with N-acetyl cysteine infusion, there was a marked improvement in transaminases and liver functions.[62] RDV is suggested to be stopped if the ALT >5-times ULN or ALP >2-times ULN, and total bilirubin >2-times ULN or in the presence of coagulopathy or clinical decompensation.[63] In view of its potential for hepatotoxicity, the authors of this manuscript have not used RDV in patients with decompensated cirrhosis who have COVID-19 infection.

Favipiravir (FPR)

FPR is a prodrug with excellent bioavailability and has been approved in Japan for the treatment of influenza. FPR undergoes phosphoribosylation to favipiravir-RTP, which is the active form of this drug. It acts via inhibition of RdRp and also gets incorporated into the viral RNA strand, preventing its further extension.[64] As the SARS-CoV-2-RdRp complex is at least 10-fold more active than any other viral RdRp known, the adequate dose of FPR for COVID-19 needs to be ascertained.[65] The dose usually used in clinical practice is 1,800 mg twice a day on day 1, followed by 800 mg twice a day on days 2–14. An open-label, nonrandomized study conducted in China compared the effect of FPR vs. LPV/r in the treatment of COVID-19. Both groups had also received interferon-alpha (5 million units twice daily) by nasal inhalation. Compared with the LPV/r arm, patients in the FPR arm showed a statistically significant shorter median length of time to viral clearance (4 days vs. 11 days, $p<0.001$), improvement in chest computed tomography findings at day 14 (91.4% vs. 62.2%, $p=0.004$) and lower incidence of adverse effects (11.43% vs. 55.56% $p<0.001$).[66] A phase 3 Russian trial (COVIDFPR 01) using FPR (ClinicalTrials.gov Identifier: NCT04434248) is currently ongoing and includes 330 patients from 30 medical centers across 9 Russian regions. A randomized, multicenter, open-labeled clinical trial in Indian patients has just been completed and the results are expected to be published soon.[64]

Though FPR usage can lead to increases in AST, ALP, ALT and total bilirubin, clinically apparent DILI seems rare. Less than 10% of patients with COVID-19 might experience ALT elevation with the use of FPR.[63] Patients with severe liver dysfunction (Child-Pugh C) showed an increase in area under curve (6.3-fold) and C_{max} (2.1-fold). It is thus suggested that FPR dosage should be reduced in patients with COVID-19 who have severe liver function impairment.[67]

Ivermectin (IVN)

IVN is well known for its antiparasitic activity. This drug has shown an *in vitro* reduction of viral RNA in Vero-hSLAM cells at 2 h post-infection with the SARS-CoV-2 clinical isolate Australia/VIC01/2020.[68] IVN has demonstrated a broad spectrum of antiviral properties and acts as an inhibitor of the nuclear transport, which is mediated by the importin α/β1 heterodimer, itself which is pivotal for the translocation of viral species proteins (i.e. HIV-1 and SV40).[69] The Ivermectin in COVID-19 trial is a retrospective cohort study ($n=280$) which enrolled patients with COVID-19 infection admitted at four Florida hospitals. This study documented a significantly lower mortality rate in the IVN ($n=173$) arm compared with the usual care ($n=107$) arm (15% vs. 25.2%; $p=0.03$).[70] More data are needed to assess pulmonary tissue levels in humans and to assess its efficacy in the prophylaxis and treatment of COVID-19.

IVN is usually considered a safe drug and reports of IVN-related DILI are rare. In a case report where IVN was used for the treatment of Loa loa, IVN resulted in DILI that manifested 1 month later with aminotransferase elevation, showing a hepatocellular type of DILI. Liver biopsy depicted acute hepatocellular necrosis, lymphocytic lobular infiltrates and no fibrosis. The patient improved clinically within days

and serum aminotransferase levels fell rapidly, becoming normal 3 months later.[71]

Immunomodulators

Steroids

In patients with severe COVID-19, the pathogenesis has been described in two phases, namely the viremic phase and the hyper-inflammatory phase. The use of steroids has been proposed in the hyper-inflammatory phase based on the observations of trials, including the RECOVERY trial (Supplementary Table 2). In the UK-based RECOVERY trial, 6,425 patients [2,104 randomized to receive dexamethasone (DXA) and 4,321 randomized to receive SOC], treatment with DXA lead to a reduction in mortality by one-third in patients receiving mechanical ventilation and by one-fifth in patients receiving supplemental oxygen compared to usual care alone.[72] The recommended dose of DXA was 6 mg for a duration of 10 days. The CoDEX multicenter, open-label trial enrolled 299 patients in Brazil with COVID-19 and moderate to severe acute respiratory distress syndrome to 20 mg DXA daily (intravenous) treatment for 5 days, then 10 mg daily for 5 days or until intensive care unit (ICU) discharge atop SOC, or to SOC alone. DXA increased days alive and days free from mechanical ventilation during the first 28 days to a mean of 6.6 vs. 4.0 among controls (p=0.04) and also reduced the acute morbidity of the disease, with lower mean sequential organ failure assessment (commonly referred to as SOFA) scores at day 7 than with usual care (6.1 vs. 7.5, p=0.004).[73] In a recent meta-analysis by the World Health Organization's Rapid Evidence Appraisal for COVID-19 Therapies (otherwise known as REACT) working group, a total of 1,703 critically ill patients with COVID-19 were analyzed. The studies analyzed in the meta-analysis enrolled patients who were randomized to receive systemic DXA, hydrocortisone, or methylprednisolone, or to receive usual care or placebo. The use of steroids reduced 28-day mortality by a relative 34% compared with controls and the mortality effect size appeared similar between drugs used.[74]

Studies have also evaluated pulse steroid therapy in the treatment of COVID-19. In a single-blind, randomized, controlled, clinical trial involving hospitalized patients with severe COVID-19 who were in the early pulmonary phase of the illness were enrolled. Patients were randomized to either the steroid arm or the SOC arm. Methylprednisolone pulse was given as an intravenous injection of 250 mg daily for 3 days in the steroid arm. Patients with clinical improvement were higher in the methylprednisolone group than in the SOC group (94.1% vs. 57.1%), and the mortality rate was numerically lower in the methylprednisolone group (5.9% vs. 42.9%; p<0.001).[75]

Though steroids are generally considered safe, they can lead to worsening of liver functions in certain specific clinical conditions. Of special interest is HBV reactivation and consequent liver involvement. It is well known that steroid treatment can lead to viral flare and HBV reactivation, and there exist specific guidelines to address this issue.[76] In hepatitis B surface antigen (HBsAg)-positive patients, HBV reactivation is defined as a sudden and rapid increase in HBV DNA levels in patients with previously detectable DNA or reappearance of HBV DNA viremia in individuals who did not have viremia before the initiation of immunosuppressive therapy. In individuals who are initially negative for HBsAg and are hepatitis B core antibody (anti-HBc)-positive, HBV reactivation is defined by appearance of HBsAg and/or HBV DNA. In patients who are HBsAg-positive or patients who are HBsAg-negative but positive for anti-HBc, the doses of steroids which place the patient at risk of reactivation are reported as follows below.[76]

High risk (>10% risk): Prednisone therapy at either medium dose (10–20 mg orally daily) or high dose (>20 mg orally daily) for more than 4-week duration increases the reactivation in patients who are HBsAg-positive.

Moderate risk (1–10% risk): Low-dose steroid therapy equivalent to prednisone 10 mg administered orally daily over 4 weeks may increase the risk of reactivation up to 10% in HBsAg-positive individuals, and medium-dose steroids such as prednisone 10–20 mg administered orally (or equivalent) daily may increase the risk of seroconversion in HBsAg-negative and anti-HBc-positive individuals.

Low risk (<1% risk): Patients are administered intra-articular steroid injections or a low dose of prednisone < 10 mg orally daily.

Recently, a pivotal study was published which analyzed the risk of HBsAg seroconversion in 12,997 patients exposed to at least one dose of systemic corticosteroids in the period between 2001 and 2010. Among the patients analyzed, 1,800 were positive for anti-HBc. Among those, 830 were positive for anti-HBs, which served as a protective factor. It was noted that in the remaining group of 970 anti-HBc-positive/anti-HBs-negative patients, the annual risk of presenting with a hepatitis flare was 16.2%, independent of the time of corticosteroid treatment. Patients who were anti-HBc-positive only had a higher risk of HBsAg Seroreversion (1-year incidence was 1.8%) as well.[77]

Drugs used to treat the disproportionate immune response after SARS-CoV-2 infection (mainly IL-6 receptor antagonists or high dose corticosteroids) were considered to be associated with moderate risk for HBV reactivation in HBsAg-negative/anti-HBc-positive individuals. However, a recent study enrolling 600 patients with severe COVID-19, who were treated with immune-modulator therapy, demonstrated that the risk of HBV reactivation while undergoing immunosuppressive treatment was low.[78] This study was not randomized and had a small sample size, which is why more data is needed in this area to make strong recommendations.

In patients who merit HBV prophylaxis (HBV is otherwise inactive, but antiviral therapy is started to prevent HBV reactivation), it should ideally be started 2–4 weeks before the initiation of immunosuppressive therapy and maintained for at least 6 months after the last dose of immunosuppressive therapy. In patients where a decision to monitor (antiviral therapy not being initiated) has been made, the strategy should be monitoring of viral reactivation with determination of aminotransferases and HBV DNA levels conducted every 3 months.[76]

Figure 3 describes an algorithm for COVID-19-positive patients who are candidates for treatment with steroid therapy according to serological findings of an HBV screening.[76,79]

IL-6 receptor antagonists

Tocilizumab (TCZ): TCZ is a humanized IgG1 recombinant monoclonal antibody used for the treatment of cytokine release syndrome associated with rheumatological conditions. It inhibits the inflammatory action of IL-6 by inhibiting the IL-6 receptor (Fig. 2). Since IL-6 is one of the prominent cytokines responsible for the hyper-inflammatory phase of COVID-19, it was postulated to have some role in patients with a severe or life-threatening disease. In a recent randomized, double-blind, placebo-controlled trial involving patients with confirmed SARS-CoV-2 infection having features of hyperinflammation, patients were randomized to receive a single dose of either TCZ (8 mg/kg of body weight) or placebo. The hazard ratio for intubation or death in the TCZ

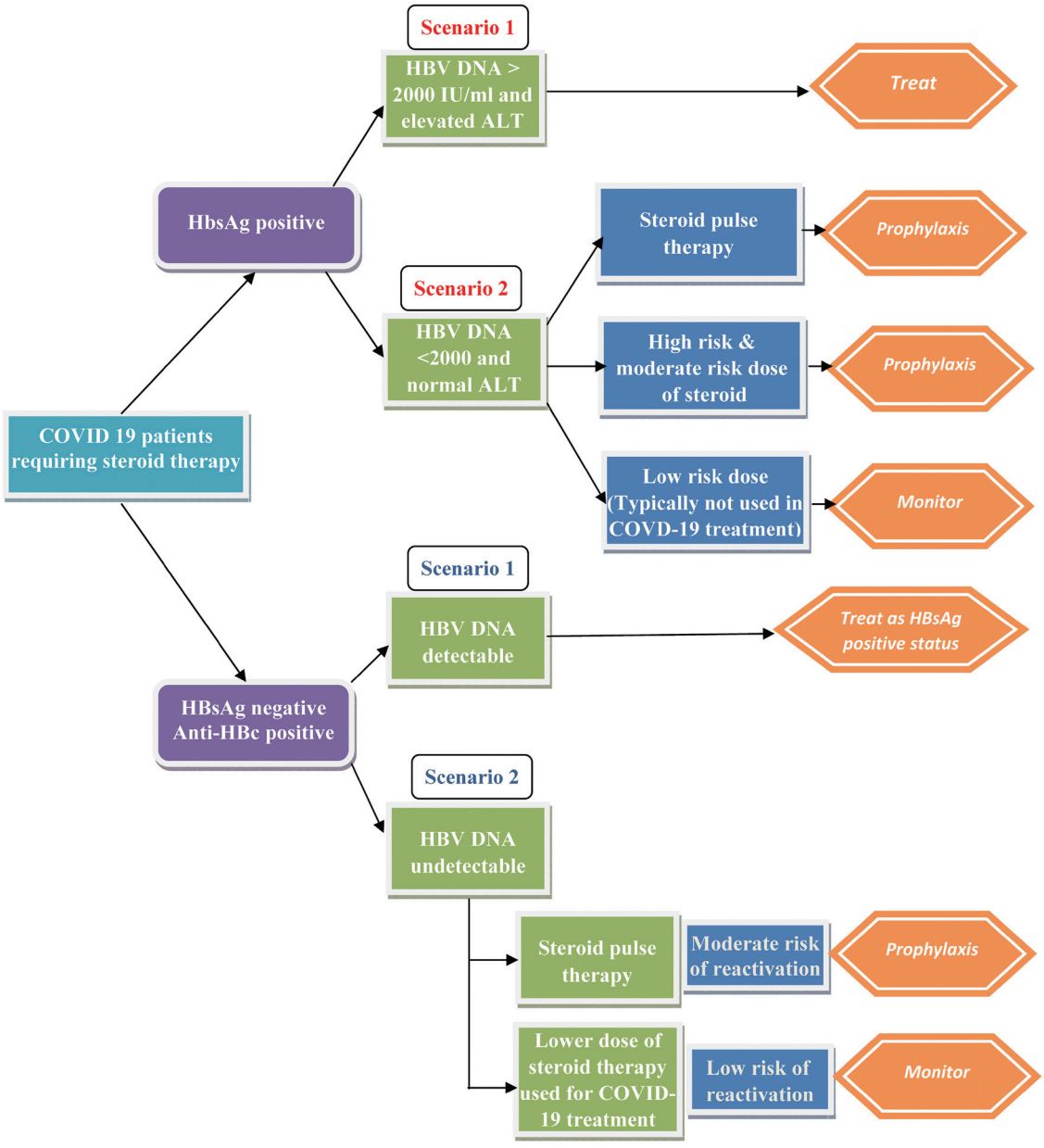

Fig. 3. Antiviral treatment strategy in patients with COVID-19 at risk for HBV reactivation receiving steroid therapy.

group, as compared with the placebo group, was 0.83 (95% confidence interval: 0.38–1.81; p=0.64), and the hazard ratio for disease worsening was 1.11 (95% confidence interval: 0.59–2.10; p=0.73). It was thus inferred that TCZ was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19.[80] The EMPACTA trial is the first global phase III trial to demonstrate patients with COVID-19 pneumonia who received TCZ in the first 2 days of ICU admission to have a lower risk of in-hospital mortality compared with those not treated with TCZ. Patients randomized to the TCZ group were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus SOC.[81]

The most common side effects of TCZ are headache, upper respiratory symptoms and hypertension. TCZ has minimal hepatic metabolism, and early registration trials of the usage of TCZ in rheumatologic conditions have shown mild serum aminotransferase elevations to occur in a high proportion (10% to 50%) of patients receiving TCZ. In a minority of patients (1–2%) levels rose above 5-times the ULN, which triggered discontinuation of treatment. The liver injury with TCZ is predominantly hepatocellular in nature, with no immunoallergic or autoimmune features. While the liver injury was severe, it was usually self-limited, with complete recovery occurring in 2 to 3 months. The mechanism by which it causes DILI is unknown, but may be the result of its effects on the immune system or on the IL-6 pathway, which is important in liver regeneration. TCZ being an immunosuppressive medication might also cause liver injury indirectly by reactivation of HBV.

Data of TCZ-related DILI when being used in the management of COVID-19 is scarce and limited to case reports.

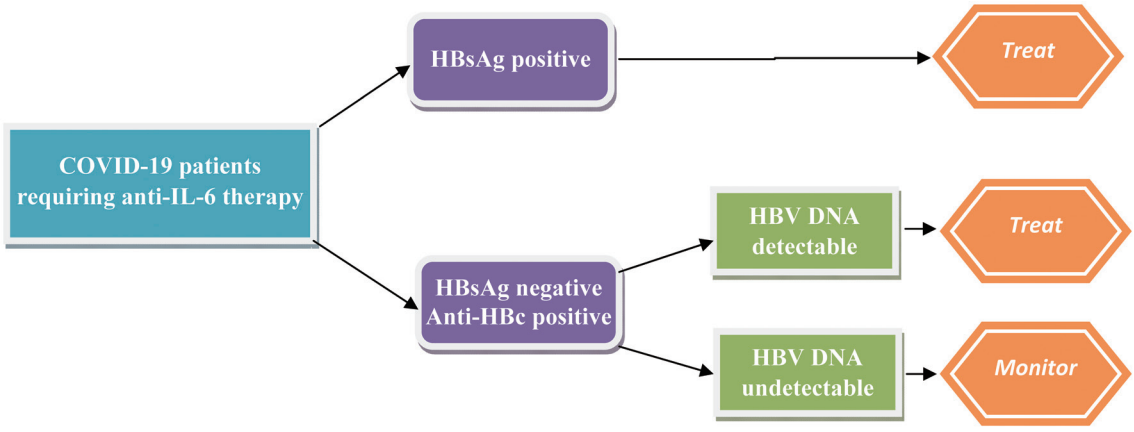

Fig. 4. Antiviral treatment strategy in patients with COVID-19 at risk for HBV reactivation receiving anti-IL-6 therapy.

Case reports also exist on the usage of TCZ in patients with elevated liver enzymes. In one of the case series using TCZ for patients with severe COVID-19 and having elevated liver enzymes (up to 5-times the ULN), it was noted that after TCZ administration, the clinical condition of patients rapidly improved and liver function test normalized within 3 weeks of treatment.[82]

TCZ, being an immunosuppressive agent, is associated with the risk of hepatitis B reactivation. There have been reports of HBV reactivation and flare in patients with rheumatoid arthritis who have chronic hepatitis B and receive a short course of TCZ therapy, which in severe cases has also led to liver failure.[83]

In patients with past resolved infection, the risk of HBV reactivation seems low with the use of TCZ therapy. In a key study, which enrolled 152 patients with resolved hepatitis B infection managed with disease-modifying anti-rheumatic drugs (including 25 patients with TCZ), the risk of HBV reactivation was very low (<5%).[84] In a study enrolling patients with COVID-19 who received TCZ, the risk of HBV reactivation was reported to be low in patients with markers of past HBV infection.[78] Though concrete guidelines on using antiviral prophylaxis to prevent HBV reactivation in patients with COVID-19 being treated with TCZ are lacking, we suggest using antiviral prophylaxis in patients with chronic hepatitis B infection and serial monitoring in patients with past HBV infection with undetectable HBV DNA levels (Fig. 4).

Other IL-6 receptor antagonists being tried for COVID-19-related cytokine release syndrome are siltuximab and sarilumab.

IL-1 receptor antagonists

Endogenous IL-1 levels are elevated in patients with COVID-19 and high levels are associated with cytokine release syndrome.[85] Anakinra (AKR) is the prototype drug being studied for COVID-19. A study conducted in Paris, France compared the outcomes of 52 patients with COVID-19 who were given AKR with 44 historical cohort patients. Admission to the ICU for invasive mechanical ventilation or death occurred for 13 (25%) patients in the AKR group and 32 (73%) patients in the historical group [hazard ratio of 0.22 (95% confidence interval: 0.11–0.41; p<0.0001).[86] An increase in liver aminotransferases (>3-times the ULN) occurred in seven (13%) patients in the AKR group and four (9%) patients in the historical group.

In large registration trials enrolling patients with rheumatologic conditions, ALT elevations occurred in <1% of patients taking AKR, a rate not different from that in placebo recipients, and no cases of clinically apparent liver injury with jaundice were reported. AKR-related DILI usually follows a hepatocellular pattern. Liver biopsies have demonstrated an acute hepatocellular injury with prominence of eosinophils. Most patients with AKR-related DILI recovered within 2 to 8 weeks of stopping the drug, without evidence of residual injury. There have been cases reported where the DILI is severe, protracted and associated with transient features of hepatic failure.[87]

In patients with COVID-19 being treated with AKR, Cavalli *et al*.[88] discuss the observations of elevated liver aminotransferases in some patients receiving the drug. Three of the 29 patients with COVID-19 who received AKR had derangement of liver enzymes, while 5 of 16 similar patients who did not receive AKR also showed increased enzymes. The authors, however, chose to taper AKR in those with elevated liver enzymes and observed that the LFTs did respond to the reduction in the dose of AKR. AKR has not been linked to reactivation of hepatitis B or exacerbation of chronic hepatitis C.[89]

Janus kinase (i.e. JAK) and numb associated kinase (i.e. NAK) inhibitors

ACE2 receptors are a point of cellular entry for the COVID-19 virus, which is expressed in lung alveolar epithelial type 2 cells. A known regulator of endocytosis is the adaptor-associated protein kinase 1 (i.e. AAK1). Disruption of AAK1 may interrupt intracellular entry of the virus. Baricitinib is a JAK inhibitor and has been identified as a NAK inhibitor, with a particularly high affinity for AAK1.[90] Drugs which target NAK are likely mitigate alveolar and systemic inflammation in patients with COVID-19 pneumonia by inhibiting cytokine signaling.[91] The National Institute of Allergy and Infectious Diseases (commonly referred to as the NIAID) Adaptive COVID-19 Treatment Trial evaluated the combination of RDV (100 mg administered intravenously daily, up to 10 days) along with baricitinib (4 mg per once daily, up to 14 days) compared with RDV alone. In September 2020, the investigators reported a 1-day reduction in the median time to recovery for the overall population treated with RDV plus baricitinib compared with RDV alone.[92]

In the large prelicensure clinical trials evaluating baricitinib in patients with rheumatoid arthritis, serum aminotransferase derangements occurred in up to 17% of subjects treated with baricitinib compared to 11% in placebo recipients. The aminotransferase elevations were typically

mild and only in <1% of patients, and the values rose above 5-times the ULN. Less than 10% of the drug undergoes hepatic metabolism, which is primarily via the CYP 3A4 pathway. Serum aminotransferase elevations above 5-times the ULN should lead to temporary cessation of the drug. If liver enzyme elevations do not completely normalize or improve within a few weeks of drug cessation, or if symptoms of DILI worsen, baricitinib should be permanently discontinued.[93]

Convalescent plasma (CP)

Plasma from an individual who has recovered from COVID-19 with high titers of neutralizing antibodies has been proposed as a novel therapy for COVID-19. Although there is a theoretical risk of antibody enhancement and transfusion-related reactions, this therapy is otherwise considered safe. The FDA granted emergency use authorization on August 23, 2020 for use of CP in patients who are hospitalized with COVID-19. Early data indicated that the use of CP seemed to be effective for a better course of COVID-19 in critically ill patients.[94] However, the multicenter, randomized, controlled PLACID trial, published recently and which enrolled 464 adults (≥18 years) admitted to the hospital with confirmed moderate COVID-19, demonstrated that the use of CP was not associated with a reduction in progression to severe COVID-19 or all-cause mortality.[95] No serious adverse effects have been reported with use of CP; however, there exists a theoretical risk of transmission of infections like HBV and HCV.

Several other drugs being tried in the treatment of COVID-19 are mentioned in Supplementary Table 3.

Anticoagulants

The risk of venous thromboembolism (VTE) is increased in critically ill patients with COVID-19. A recent meta-analysis which analyzed 86 studies (33,970 patients) reported that VTE occurs in 22.7% of patients with COVID-19 who are admitted to the ICU. VTE risk was reported to be higher in non-ICU hospitalized patients as well.[96] Reports have shown that there is a substantial microthrombosis, or immunothrombosis, related to hypoxemia, endothelial injury, and inflammation.[97] Data is emerging on the discrepancy between the rate of pulmonary embolism and deep-vein thrombosis in patients with COVID-19 infection, and several cases are being reported where pulmonary embolism is occurring in the absence of deep-vein thrombosis and are located in the more peripheral pulmonary arteries. This leads to the hypothesis that immunothrombosis is probably much more prominent in patients with COVID-19 than originally recognized.[97,98] Most current guidelines thus recommend that standard doses of anticoagulants be used for thromboprophylaxis in patients hospitalized with COVID-19. VTE prophylaxis is also to be administered post-discharge in patients with known additional risk factors for VTE, such as thrombophilia, obesity, advanced age, and a prior history of VTE.[97]

The potential effects of anticoagulants on liver are displayed in Supplementary Table 4.

Conclusions

COVID-19 is a disease which causes multisystem involvement. The immune dysregulation and the cytokine release syndrome associated with the disease are primarily responsible for the worse outcomes in those affected with it. Several drugs have been tried and several others remain in the pipeline to combat the deadly effects of this virus. Hepatotoxicity, reactivation of underlying viral hepatitis and potential to cause DILI remains with several of the drugs being used to treat COVID-19. However, as the involvement of liver can be the result of various pathobiologic pathways, in many instances it becomes difficult to discern the accurate etiology of the same.

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Conflict of interest

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Author contributions

Manuscript writing and critical revision (SS, NG, PK), administration (SS).

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