The COVID-19 pandemic: Clinical practice advice for gastroenterologists, hepatologists, and liver transplant specialists

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel acute infectious disease that has rapidly reached staggering pandemic proportions. This review addresses gastroenterologists, hepatologists, liver transplant (LT) specialists, and health-care professionals working in the field of liver diseases and liver transplantation. It has been written based on a limited number of publications, recommendations of national and international liver and organ transplantation societies, and experiences of patients with COVID-19 around the world. The purpose of this review is to provide information addressing questions and concerns about COVID-19, to reveal the effects of the novel disease on patients with chronic liver disease and LT recipients, and to share information about ways in which this pandemic will affect clinical practices. We, the Turkish Association for the Study of the Liver (TASL), would like to remind you that this text is actually not a practical guide. It is imperative to act according to the standards set by health-care institutions and the Ministry of Health, Republic of Turkey.

Keywords: *COVID-19, SARS-CoV-2, liver, liver transplantation*

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 virus, was recently declared a pandemic by the World Health Organization (WHO). SARS-CoV-2 is most similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) of the genus Betacoronavirus. These two viruses were the causative agents of the SARS outbreak in 2002 and the MERS outbreak in 2012, respectively (1, 2).

Respiratory viruses such as SARS-CoV-2 are transmitted from person to person via respiratory droplets (produced by talking, sneezing, or coughing), suspended droplet nuclei, and surface fomites (by touching a contaminated surface and then touching the mucous membrane in the eyes, nose, or mouth) (1, 2). Social distancing measures are based on the idea of interrupting these routes of transmission by separating infected and uninfected individuals. It is implemented to limit social mobility, thereby further preventing the dissemination of the virus. Physical distancing is the principal tool available to blunt the force of an epidemic (1). Therefore, outpatient clinics should be arranged and remodeled according to the new physical distancing regulations.

Fever and dry cough are the most common COVID-19 symptoms. However, only half of the patients are febrile at the time of admission (1). Some patients also present with shortness of breath, nasal congestion, sore throat, aches, and anosmia. Nausea, vomiting, and diarrhea have also been reported. It has been reported that the SARS-

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CoV-2 infection presents a broad-spectrum clinical aspect, ranging from asymptomatic, mildly symptomatic disease to rapidly progressive sepsis (1-3). Data suggested that approximately 80% of patients have mild disease, 20% require hospital admission, and 5% require intensive care unit (1, 3). The highest mortality rates have been reported in older individuals (>60 years) and individuals with chronic systemic diseases such as hypertension, diabetes, and coronary heart disease (1, 3). Lymphopenia, hypoalbuminemia, and raised D-dimer levels are the prognostic markers of severe-course COVID-19 (1-3). The first observations were made in China and then Italy, Spain, other European countries, and the USA. The international experience has shown that the health-care workers are the group with the highest risk of COVID-19-related morbidity and mortality (1-3).

In Turkey, the infection and death rates increased rapidly. The epidemic curve is now flattening. Unfortunately, several health-care workers were infected. It is therefore necessary to implement precautions to protect our patients and health-care staff, given that SARS-CoV-2 can also be transmitted through asymptomatic individuals. Furthermore, the virus can be detected in the stools even after having been cleaned from the respiratory tract, suggesting that the fecal–oral transmission might be possible (4). Moreover, it is imperative to maximize the bed capacity of intensive care units (ICUs), the number of ventilators and other equipment, and the nursing and assistant health-care staff in the centers and hospitals.

Effects of COVID-19 on Liver

SARS-CoV-2 is a single-stranded RNA-enveloped virus that enters the cell by binding to the "angiotensin-converting-enzyme 2" (ACE-2) receptor (1, 2). Hepatocytes and cholangiocytes are potentially targeted by SARS-CoV-2 because of the high expression of this receptor (1, 2).

MAIN POINTS

- *To provide information addressing questions and concerns about COVID-19.*
- *To reveal the effects of the novel disease on patients with chronic liver disease and LT recipients.*
- *To share information about ways in which this pandemic will affect clinical practices.*
- *The COVID-19 pandemic has negatively affected the daily lives of people, patients, and health-care workers.*

Data on the effect of SARS-CoV-2 infection in liver patients and liver transplant (LT) recipients are very limited, and most of the available information is based on specific cases (5-8). There is no specific clinical description regarding the COVID-19 in patients with advanced liver disease and LT recipients.

Elevation of serum aminotransferases levels and mild/moderate bilirubin levels have been reported in 14% to 53% of hospitalized patients with COVID-19 (2, 3, 5, 9). These rates are higher in severe cases. A meta-analysis study demonstrated that the pooled prevalence of abnormal serum aspartate aminotransferase (AST) levels was reported in 15% of the 2,514 patients with COVID-19, abnormal serum alanine aminotransferase (ALT) levels in 15% of the 2,711 patients with COVID-19, and abnormal bilirubin levels in 17% of the 1,841 patients with COVID-19 (10).

Liver test abnormalities may occur owing to a direct virus-induced cytopathic effect, resulting in systemic inflammatory response and/or the activation of an underlying liver disease (5, 10, 11). Viral hepatitis (caused by Hepatitis A, B, or C virus, the cytomegalovirus, or the herpes simplex virus) and other potential causes of elevated liver-enzyme levels should be investigated. Toxic hepatitis may occur in patients with COVID-19 treated with hydroxychloroquine/chloroquine, lopinavir/ritonavir, remdesivir, tocilizumab, or azithromycin. In mild cases, transaminitis is generally reversible, and no specific treatment is required.

Data on SARS-CoV-2-related histopathological damage are limited. The pathological features are non-specific and resemble those observed in SARS-CoV and MERS-CoV infections. Moderate microvesicular steatosis, mild lobular and portal inflammation, and focal necrosis have been reported (12).

The diagnostic tests of COVID-19 in patients with chronic liver disease and LT recipients are not different from those used in other individuals. The basic diagnostic test is the polymerase chain reaction (PCR)-based test. However, sensitivity and specificity of this test remains unknown. Viral RNA loads are substantially higher in sputum compared with those in throat swabs and are at the highest level in the early stages of the disease. Both upper (nasopharyngeal or oropharynx swab) and lower respiratory tracts (bronchoalveolar lavage [BAL]) samples are advised for diagnosis of the infection (1). Thorax computerized tomography (CT) is the most reliable test with a

high sensitivity and specificity in patients with COVID-19 pneumonia. Data indicated that RT-PCR has low probability of ruling out an infection, and repeat sampling and CT images may be required to guide the diagnosis in clinically high suspicious cases (1). Unnecessary imaging tests should be avoided.

Approximately 40% to 50% patients develop an antibody response to SARS-CoV-2 infection after 7 days (1).

Liver Diseases and COVID-19

It remains unclear whether patients with chronic liver disease are more susceptible to liver damage caused by SARS-CoV-2 infection (2, 3, 5, 6, 9). Moreover, there is no evidence that chronic liver disease affects the course of COVID-19. One study found that only 1% of severe COVID-19 cases had an underlying chronic liver disease (13). However, considering the information on previous similar viral infections, it should be assumed that patients suffering from organ failure (decompensated cirrhosis) and receiving immunosuppressive therapy (such as LT recipients and autoimmune hepatitis patients) are at risk of both exposure to SARS-CoV-2 and its infectiousness. The precise management of chronic liver disease and LT recipients greatly depends on the local COVID-19 burden. The priority should be to protect health-care professionals and patients from exposure to SARs-CoV-2. The benefits of maintaining care must be weighed against the risk of infection.

Both immunocompetent and immunosuppressed individuals can contribute to the spread of SARS-CoV-2 (1). Infected health-care workers may spread the virus to patients and to each other. Minimizing the contact between health-care workers and patients is critical for reducing the risk of transmission. Therefore, visit of the following patients if they are in stable condition, should be postponed:

- patients with chronic hepatitis,
- patients with compensated cirrhosis, and even
- LT recipients (5-8).

Telephone/telemedicine visits should be used instead. Patients should be kept away from the hospital. The Centers for Disease Control and Prevention has recommended to limit face-to-face visits, optimize supply of personal protective equipment (PPE), clean and disinfect rooms or waiting area, and monitor health-care workers for signs of the infection (13). Routine laboratory tests can be performed locally when necessary. Physical visits should be considered only for:

- patients with urgent issues and
- patients with abnormal liver injury tests (serum aminotransferases levels greater than 10 times the upper normal limit), jaundice, or a recent onset of hepatic encephalopathy (5-8).

Patients should be forbidden from traveling to places with a high prevalence of COVID-19.

Patients with chronic viral hepatitis on antiviral treatment should continue their treatment and be followed up via telemedicine. Health-care professionals are advised to consult the HEP Drug Interactions website (https://www.hep-druginteractions.org) of the University of Liverpool for interactions between patients' existing antiviral treatments and treatments used for COVID-19. It is important to note that the initiation of antiviral treatment for chronic hepatitis B and C is not immediately warranted for patients with COVID-19. However, antiviral treatment should be started in patients with exacerbated hepatitis B or patients with hepatitis B who will receive immunosuppressive therapy (5, 6).

There is no evidence that COVID-19 induces cholestasis in patients with autoimmune liver diseases. In the case of abnormal liver injury tests, SARS-CoV-2 infection should be considered for patients with autoimmune hepatitis (AIH) on immunosuppressive therapy (5, 11). The effects of immunosuppression on COVID-19 are currently unknown. Reducing or discontinuing immunosuppressive treatment may result in a flare in patients with AIH. Therefore, discontinuation is not recommended, but patients with AIH should be considered a high-risk group for severe COVID-19. In the presence of COVID-19, reducing immunosuppression should only be considered after gastroenterology/hepatology consultation under special circumstances, such as lymphopenia, superinfection, and sepsis.

If immunosuppressive therapy is considered for autoimmune liver disease, the indication of the therapy should be strong as the potential benefit might be outweighed by the risks (5, 6).

Obesity, diabetes, hypertension, metabolic syndrome, and cardiovascular disease are commonly associated with nonalcoholic fatty liver (NAFLD) patients. It has been reported that SARS-CoV-2-infected NAFLD patients with metabolic disorders are at risk of severe COVID-19 (5, 14). NAFLD patients with concomitant metabolic disorders should be carefully monitored in this respect.

In patients with compensated cirrhosis, screening for varices should be delayed during the pandemic. Non-invasive approaches should be preferred for risk assessments. Endoscopic procedures should be performed in emergency situations. All endoscopic procedures should be aerosol generated. Endoscopists and other health-care professionals should wear full PPE to reduce the risk of being infected (5, 6, 10).

The effect of COVID-19 on hepatocellular carcinoma (HCC) is unknown. The approach to HCC should conform to guidelines (5, 6). HCC screening and, if possible, treatment may be delayed during the pandemic. Risk–benefit considerations regarding delaying screening and management should be discussed with the patients. In high-risk patients, sonography and other imaging modalities should be used while wearing PPE. In patients with COVID-19, HCC screening and surveillance should be deferred until after recovery (5, 6).

All elective endoscopic and other invasive procedures should be rescheduled (5, 6, 10). However, procedures such as the following may still need to be performed:

- Liver biopsies in patients with AST and ALT levels greater than five times the upper normal limit to rule out acute rejection,
- diagnostic percutaneous biopsies in patients with liver mass suspected of malignancy,
- endoscopic retrograde cholangiopancreatography in patients with biliary symptoms, such as cholangitis-related symptoms,
- therapeutic paracentesis or transjugular intrahepatic portosytemic shunt in patients with refractory ascites, and
- endoscopy in patients with variceal bleeding and band ligation in cases of recent variceal bleeding.

In the presence of COVID-19, these procedures may pose a risk of viral transmission.

The effect of COVID-19 in patients with decompensated cirrhosis is not well known. Patients should be treated and followed up according to national and international guidelines. Guidelines on the prophylaxis of variceal bleeding prophylaxis, spontaneous bacterial peritonitis, and hepatic encephalopathy should be strictly followed to prevent possible complications and to avoid hospitalization (5, 6, 8). To reduce the risk of transmission, visits should be limited, and health-care workers should take all necessary precautions during visits.

Regarding in-patients, to reduce the risk of SARS-CoV-2 transmission (5, 6, 8),

- patients should be isolated,
- the number of health-care workers entering a patient's room and the number of rounds should be limited,
- consultations in other departments should be reduced,
- in-hospital transportation should be limited,
- visitor's access should be restricted or prohibited, and
- hospital stay should be shortened.

Cirrhotic patients should be vaccinated against influenza and *Streptococcus pneumoniae* (5, 6, 8). SARS-CoV-2 tests should be performed in patients with new-onset acute liver failure or acute-on-chronic liver disease (5, 6, 8).

Liver Transplantation and COVID-19

It is inevitable that the COVID-19 pandemic will prolong the patient waiting time. It is therefore important to identify patients who need to be evaluated for liver transplantation (LT) during the pandemic. Listing for LT should be limited on the basis of urgent cases (acute liver failure, acute on chronic liver failure, high Model for End-Stage Liver Disease [MELD] score, HCC progression, and pediatric cases) (5, 6, 8, 15, 16). For transplant evaluations, the number of patients visiting LT centers should be limited, and laboratory tests and imaging should be performed only when necessary. Telemedicine, telephone consultations, or videoconferences should be used for communication, and only patients at risk of liver disease progression should be advised to visit clinics (5, 6, 8, 15, 16).

It is essential that *organ transplantation* centers assess their situation in terms of ICU beds, ventilators, and other equipment to decide whether to proceed with transplantations during the pandemic. Living-donor LT should be considered on a case-by-case basis and performed only in emergency cases (5, 6, 8, 16). It is advisable that organ transplant programs be suspended if a transplantation center has a high prevalence of COVID-19 (5, 6, 8, 16).

The possibility of SARS-CoV-2 transmission from infected donated organs is currently unclear. However, most organizations are testing potential donors for SARS-CoV-2 RNA, and in the event of positive test, the donor is considered medically ineligible (5, 15, 17, 18). The American Society of Transplantation recommends postponing donation from symptomatic donors for 28 days and test-positive donors for 14 days and test them for SARS-CoV-2 by PCR at the end of these periods (16). Testing

should be performed in all living donors and recipients before LT. LT is not recommended for SARS-CoV-2-positive recipients. Screening for clinical symptoms, such as fever, cough, and dyspnea, and investigating possible history of exposure to COVID-19 and performing a PCR test on a nasopharyngeal swab 72 hours prior to LT are recommended (5, 6, 8, 16). Posteroanterior chest radiography and lung CT are also recommended (5, 6).

Besides all necessary precautions, risk factors such as the recipient's and donor's age and gender, smoking, and comorbidities, such as hypertension and chronic lung disease, should be assessed prior to organ acceptance (5, 6, 16).

Informed consent forms for COVID-19 should be signed before all procedures.

Although it has been suggested that LT programs be suspended in regions where the pandemic is severe, there is no scale to measure the severity. Liver transplant programs in Wuhan, northern Italy, Spain, and South Korea have not been completely stopped. In the United States, there has been a significant decrease in the number of solid organ transplants since the beginning of 2020 (Figure 1a, b) (15). In Turkey, a significant decrease in the number of solid organ transplants from January to April 2020 has been reported (Figure 2).

Transmission of SARS-CoV-2 through blood transfusion has not been reported. A significant reduction in blood donations is expected owing to social isolation and concerns regarding possible SARS-CoV-2 infection. The reduction in blood and blood product supply is expected to affect LTs, where these products are in high demand.

The effect of post-transplant immunosuppressive therapy on COVID-19 is not well known. Post-transplant immunosuppression has not been associated with SARS- or MERS-related mortality (5, 6, 19). In the case of SARS-CoV-2, there is no clear evidence that recipients are at greater risk of severe COVID-19. Therefore, immunosuppressive therapy should not be reduced in recipients without COVID-19 (5, 16, 20). In the event of fever, lymphopenia, or deterioration of the clinical status, dose reduction or discontinuation should be considered (5, 16, 20).

Post-transplant patients should know prevention measures against SARS-CoV-2 infection. Telephone/telemedicine communication should be preferred, and patients should not travel during the pandemic. International guidelines recommend the PCR-based testing for COVID-19 for donors while discharging.

Health-care workers and other hospital staff are at risk of contracting SARS-CoV-2. It is therefore imperative that they follow personal protection rules. They must protect patients and donors from potential nosocomial transmission. To this end, interactions between health-care workers and patients should be minimalized. Moreover, all staff should be monitored for COVID-19 symptoms.

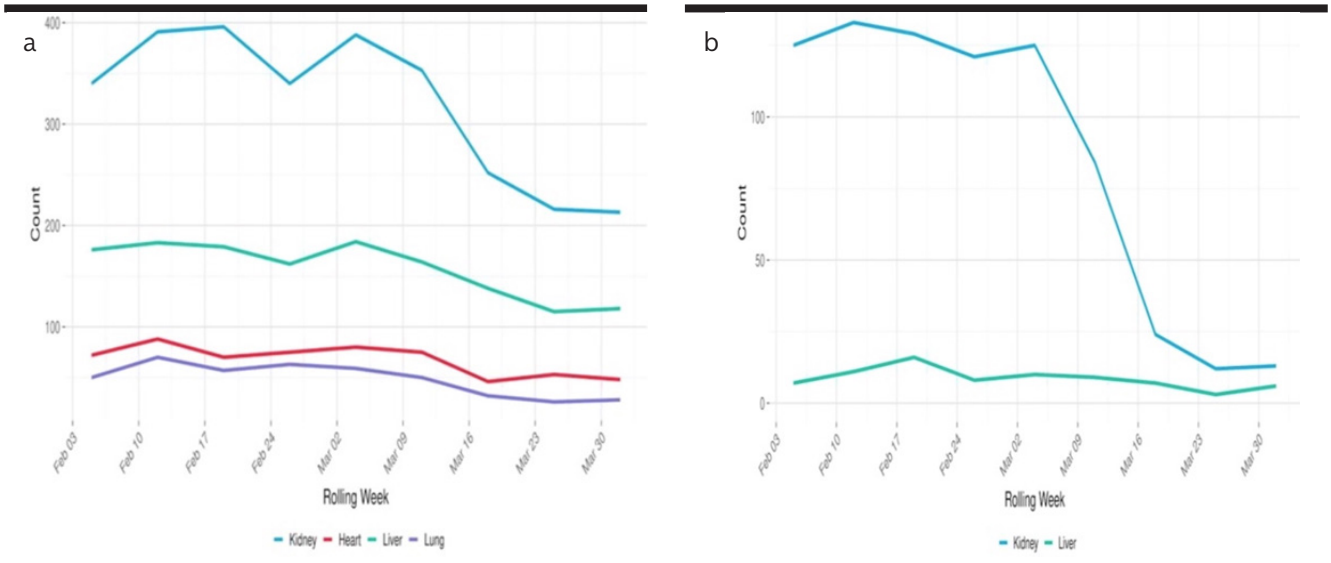

Figure 1. a, b. The UNOS organ transplant data. (a) Deceased donor and (b) living donor. UNOS, United Network for Organ Sharing.

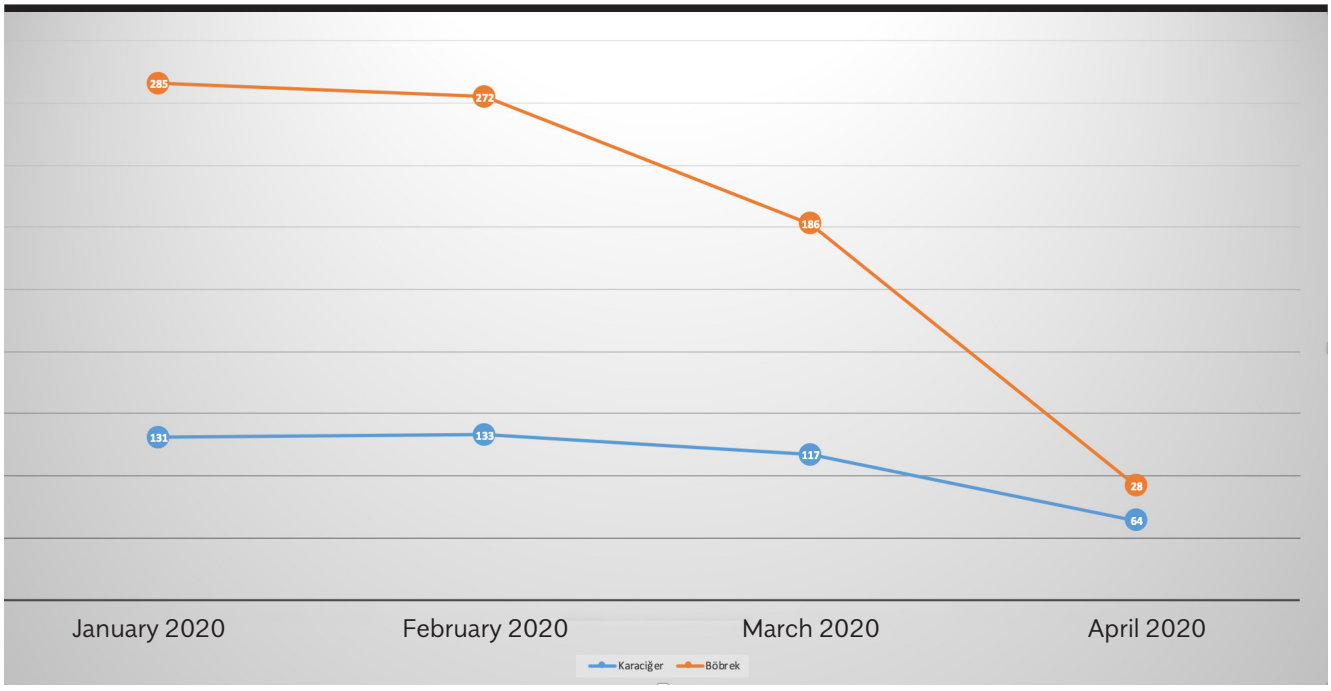

Figure 2. The National kidney and liver transplant data.

According to mathematical epidemic modeling (21), after the end of the first wave of the pandemic, if there is no vaccine or effective treatment modality, low-intensity waves similar to seasonal-flu outbreaks are expected. This is projected to last until 2024. Thus, it has been suggested that social distancing measures not only be maintained for as long as possible to overcome the first wave with the least possible damage but also be implanted during future waves.

After the pandemic, the number of LTs will increase, and massive hospital admission of patients whose treatment and follow-ups have been postponed is expected. This will inevitably place an additional burden on the health-care system, and some patients will unfortunately miss the chance of treatment/transplantation. The risk faced by health-care personnel, the disruption of the work and home environments, uncertainty, financial losses, loss of control, and the instinct to protect their patients and relatives are causing increasing anxiety. To ameliorate these, efforts are required at the levels of authorities, health institutions, non-governmental organizations, and health-care professionals.

Drugs Used in COVID-19 Treatment

The SARS-CoV-2 lifecycle stages provide potential targets for drug therapy. Nonstructural proteins, such as 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase, and viral entry and immune regulation pathways are potential targets. However, no existing drugs have been proven effective against COVID-19. There is no clear evidence from clinical trials that any therapy improves the disease outcomes or that any medication can be used for prophylaxis (22, 23). Several agents are being investigated; many of them have hepatotoxic effects.

Hydroxychloroquine and chloroquine are antimalarial agents. They have been reported to block viral entry into cells by inhibiting glycosylation of cell receptors (22, 23). They exert immunomodulatory effects by reducing cytokine production and inhibiting autophagy and lysosomal activity in host cells (22, 23). Chloroquine inhibits SARS-CoV-2 *in vitro* (24). However, its effectiveness and safety in the treatment of COVID-19 is unclear. Potential side effects, including fatality, have been reported in these patients during COVID-19 treatment (23, 24). Although hydroxychloroquine and chloroquine are relatively tolerable drugs, in rare cases, they can cause serious adverse effects. Abdominal pain, loss of appetite, diarrhea, nausea and vomiting, hypoglycemia, QTc prolongation, retinal toxicity, and hemolysis can be seen during the therapy. Although there are insufficient data on dose-related hepatotoxicity in the treatment of COVID-19, a correlation

between hydroxychloroquine dose and serum ALT elevation has been reported (24). Dose adjustment is not necessary in chronic liver disease, but this drug should be used with caution. Caution should also be exercised in cases of alcohol dependence and when the drug is combined with other potentially hepatotoxic agents. Use of hydroxychloroquine and chloroquine in pregnant women is generally considered safe (23). An interaction of hydroxychloroquine and chloroquine with immunosuppressive drugs has been reported. Dosages of immunosuppressive drugs should be closely monitored in LT recipients (22, 23).

Favipiravir is an agent that inhibits viral RNA-dependent RNA polymerase (25). Preclinical data are derived from its activity against influenza and Ebola viruses (22, 23). However, clinical experience in the treatment of COVID-19 is limited. A previous study found that favipiravir elicited better therapeutic responses in COVID-19 than lopinavir/ritonavir in terms of disease progression and viral clearance (26). It is a tolerable drug with a mild side effect profile (22, 23). Diarrhea, increased transaminase levels, hyperuricemia, and neutropenia may develop during treatment. As favipiravir is not metabolized by the CYP450 system, it is not affected by drugs metabolized by this pathway. It has shown teratogenic effects in animal experiments and is thus contraindicated during pregnancy.

Lopinavir/ritonavir is a combination of protease inhibitors approved for HIV treatment (22, 23). It has shown some *in vitro* antiviral effects on SARS-CoV-2 (23). A randomized controlled trial comparing lopinavir/ritonavir with standard treatments in severe COVID-19 cases demonstrated no clinical efficacy (27). Moreover, because of adverse effects, lopinavir/ritonavir treatment was terminated early in some patients (27).

Lopinavir is primarily metabolized in the liver. Gastrointestinal problems such as diarrhea, nausea, and hepatotoxicity are known adverse effects. Fatigue, headache, muscle pain, and rash (especially in children), hyperglycemia, hypertriglyceridemia, and hypercholesterolemia can also be seen. Moreover, pancreatitis and cardiac conduction disorders have been observed. Combination therapy for COVID-19 or viral infection may increase the risk of hepatotoxicity and adverse effects. Liver tests should be performed before initiating lopinavir/ritonavir treatment in patients with COVID-19, and it should not be used in cases of advanced chronic liver disease. Ritonavir is a potent CYP3A4 inhibitor (23). This enzyme plays a role in the metabolism of calcineurin, mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus). Therefore, dosages should be closely monitored when used together with calcineurin inhibitors or mTOR inhibitors. Lopinavir/ritonavir is considered safe to use during pregnancy (22, 23).

Tocilizumab is a monoclonal antagonist of the IL-6 receptor (23). Adverse effects include headache, upper respiratory tract infection, nasopharyngitis, and hypertension. Tocilizumab can also cause hypercholesterolemia, and sometimes skin and mucous reactions, such as mouth and gastric ulcers. Hepatotoxicity has also been reported during tocilizumab treatment (23). Transaminitis is usually asymptomatic. Liver failure is rare. Liver tests and viral marker assessments before initiating treatment are recommended. Tocilizumab is contraindicated when serum aminotransferase levels are greater than 1.5 times the upper normal limit (23). Hepatitis B virus (HBV) reactivation may also occur during tocilizumab treatment. Therefore, HBV treatment should be initiated in HBV-infected COVID-19 patients receiving tocilizumab. Tocilizumab should not be used in patients with decompensated cirrhosis (23).

Remdesivir is a nucleotide analog that acts as an RNA polymerase inhibitor (23). It has potential antimicrobial effects against flaviviruses, Ebola virus, and coronaviruses. Because of its broad-spectrum and its reported *in vitro* efficacy against SARS-CoV-2, it is considered a promising agent for the treatment of COVID-19 (23, 28). It has reversible hepatotoxicity and nephrotoxicity potential and may cause an increase in serum ALT and AST levels. No dose adjustments are required in patients with liver or kidney disease. No relevant drug interactions have been reported.

CONCLUSION

The COVID-19 pandemic has negatively affected the daily lives of people, patients, and health-care workers in Turkey and around the world. Protecting patients with liver disease, LT recipients, and health-care workers against SARS-CoV-2 infection by minimizing exposure is the most important mission of clinicians and other medical staff. At the same time, offering our patients with COVID-19 the most effective treatment with the available drugs is a priority.

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