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LETTER TO THE EDITOR

Should people with chronic liver diseases be vaccinated against COVID-19?

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Abstract

Hepatic impairment in coronavirus disease 2019 (COVID-19) may derive from cholangiocyte damage in the beginning, but not from direct infection of hepatocytes. Chronic liver disease patients co-infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibited overexpression of angiotensin-converting enzyme 2 receptors and overwhelming cytokine storm. Consensus has been reached that we should encourage as many people as possible to be vaccinated in order to achieve herd immunity. SARS-CoV-2 vaccines can prevent or alleviate severe infection and cytokine storm. It is recommended that all adult patients with chronic liver diseases and liver transplant recipients should receive COVID-19 vaccines using the standard dose and schedule. Data is not yet sufficient to compare the efficacy of different types of vaccines used in chronic liver disease patients.

Key Words: Chronic liver disease; Vaccine; COVID-19; SARS-CoV-2; Hepatic impairment

Core Tip: Chronic liver disease patients co-infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibited overexpression of angiotensin-converting enzyme 2 receptors and overwhelming cytokine storm. SARS-CoV-2 vaccines can prevent or alleviate severe infection, and cytokine storm. Recently, a question has been raised whether chronic liver disease patients should be vaccinated against coronavirus disease 2019 (COVID-19). The American Association for the

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Study of Liver Diseases and European Association for the Study of the Liver Expert Panel suggested that all adult patients with chronic liver disease and liver transplant recipients can receive the COVID-19 vaccines using the standard dose and schedule.

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TO THE EDITOR

Coronavirus disease 2019 (COVID-19) has become a global pandemic. It poses not only a huge threat to public health, but also a major impact on economic development and regional stability. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anchors host cells by binding to angiotensin-converting enzyme 2 (ACE2). ACE2 is not simply expressed in the respiratory tract, but also in the central nervous system, heart, liver, gastrointestinal tract, kidney, and skeletal muscle. Therefore, patients with severe COVID-19 may show multiple organ dysfunction.

Due to the lack of suitable experimental models, tissue or organ tropism of the virus has not been well established. The first autopsy with COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity in the liver, indicating that the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury[1]. Chai *et al*[2] found that distribution of ACE2 in the liver was unique. ACE2 showed higher expression level in cholangiocytes (59.7%), compared with hepatocytes (2.6%). The ACE2 expression level in cholangiocytes was comparable to that in type 2 alveolar cells of the lungs. Further research by Fudan University using human organoids showed that liver ductal organoids were susceptible to SARS-CoV-2, and viral replication was dramatic after infection. SARS-CoV-2 infection induced cell death of host cholangiocytes and impaired bile acid transporting functions of cholangiocytes[3]. These results indicated that hepatic impairment in COVID-19 may derive from injury to liver cholangiocytes in the beginning, but not from direct target to hepatocytes. Of course, hepatocyte impairment in severe cases can also be indirectly induced by the systemic inflammatory response and abnormal metabolism. According to previous meta-analysis, abnormal serum levels of alanine transaminase, aspartate transaminase and bilirubin were reported in 15.0%, 15.0%, and 16.7% of the patients[4, 5]. However, there are few reports on the severity of hepatic impairment, clinical outcome and mortality rate in patients with different chronic liver diseases co-infected with SARS-CoV-2. Ali *et al*[6] summarized the remarkable impact of SARS-CoV-2 on several types of liver diseases, including non-alcoholic fatty liver disease), liver cirrhosis, hepatocellular carcinoma, and hepatitis B and C virus infection. Furthermore, they reviewed the devastating cytokine storm in COVID-19 and concluded that in a similar pattern, hepatic impairment patients co-infected with SARS-CoV-2 could exhibit overexpression of ACE2 receptors and overwhelming cytokine storm, which might worsen the hepatic impairment and increases the mortality rate.

It is widely accepted that herd immunity through vaccination is the ultimate weapon of controlling infectious diseases. Smallpox is the only human infectious disease that has been eradicated by widespread vaccination around the world. We have also eradicated poliovirus (poliomyelitis) type 2 and 3. In this point of view, countries around the world are working intensively to develop and produce SARS-CoV-2 vaccines. In June 2020, Kwok *et al*[7] calculated the threshold and the minimum proportion of total population required for herd immunity based on the number of new cases and the serial interval at that time. Given the mortality rate of 0.25%-3.0%, herd immunity may be difficult to achieve through natural infection. Furthermore, the threshold might be changed according to the transmissibility of variants (such as more transmissible variant B.1.617.2) and the measures taken to control the virus. So, the actual threshold in real life is still unknown, herd immunity can be observed with certainty only by retrospectively analyzing the data[8]. However, consensus has been reached that we should encourage as many people as possible to be vaccinated in order to achieve herd immunity. The estimated coverage rate must be achieved at least

72.9% in China[9]. Moreover, a recent study also estimated the neutralization level by vaccination for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level. The estimated neutralization level required for 50% protection from severe infection was significantly lower, only 3% of the mean convalescent level[10].

People with stable chronic liver disease status were included in clinical trials of mRNA BNT162b2[11] and mRNA-1273[12] vaccines and CoronaVac[13] and BBIBP-CorV[14] inactivated vaccines. Although only a small percentage of chronic liver disease patients were included, it has been proven to be safe and well tolerated. Considering the poor outcomes and high mortality rate of chronic liver disease co-infected with SARS-CoV-2, and the efficacy of vaccines against severe infection, the American Association for the Study of Liver Diseases[15] and European Association for the Study of the Liver[16] Expert Panel suggested that COVID-19 vaccines should be administered to all adult patients with chronic liver diseases and liver transplant recipients. Moreover, patients with chronic liver diseases who are receiving antiviral therapy for hepatitis B virus or hepatitis C virus should not withhold their medications while receiving the COVID-19 vaccines. Patients with hepatocellular carcinoma undergoing locoregional or systemic therapy should also be considered for vaccination without interruption of their treatment.

No large sample-size data is available on COVID-19 vaccines inoculated in immunosuppressed patients. According to the efficacy and safety of other vaccines (seasonal influenza vaccine, adjuvant subunit varicella zoster vaccine, *etc.*) used in solid organ transplant recipients, the immunogenicity of vaccines in these recipients is lower than in immunocompetent individuals. For patients with cancer, one dose of the BNT162b2 vaccine yielded poor efficacy. Immunogenicity increased significantly in cancer patients with a vaccine boost at day 21 after the first dose[17]. Another novel study from Albert Einstein Cancer Center showed that comparing to solid tumors, a significantly lower rate of seroconversion was observed in patients with hematological malignancies (98% *vs* 85%), particularly the recipients of highly immunosuppressive therapies such as anti-CD20 therapy (70%), and stem cell transplantation (73%). Patients receiving immune checkpoint inhibitor therapy (97%) or hormonal therapies (100%) demonstrated high seroconversion after vaccination. Relatively, lower immunogenicity was observed following vaccination with the adenoviral than mRNA-based vaccines[18]. Data is not sufficient to compare the efficacy of protein subunit vaccines or other vaccine types used in liver cancer patients or candidates for liver transplantation. So, COVID-19 can be administered using the standard dose and schedule in immunosuppressed patients in order to achieve a favorable efficacy.

Even for those vaccinated, personal precautions in moderate-high risk areas should still be used, including wearing a mask, washing hands frequently, and keeping a social distance, because the effectiveness of the vaccines cannot be 100%. Some people may still be infected with SARS-CoV-2 after receiving the vaccine, but will not present with any symptoms, which is often termed as asymptomatic infection. The asymptomatic person can spread the virus to family and friends around them. Due to the emerging vaccine-resistant mutations, fight against COVID-19 pandemic is a marathon, which will last a long time.

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