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Modern Approaches to Vaccination of Patients with Chronic Liver Diseases and Inflammatory Bowel Diseases against a Novel Coronavirus Infection

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Aim. To analyze the literature data on the peculiarities of vaccination of patients with chronic liver diseases (CLD) and inflammatory bowel diseases (IBD) against COVID-19 infection.
Key findings. It has been shown that many patients with CLD (cirrhosis of the liver, non-alcoholic fatty liver disease) have a higher risk of severe course of a novel coronavirus infection, which necessitates their vaccination. IBD patients are also subject to vaccination, although the immunomodulatory drugs which they take may reduce its effectiveness. In addition, the correct timing of the vaccine administration is of great importance. Vaccination of patients with CLD and IBD is safe, and the frequency of side effects during its implementation does not differ from that in the general population.
Conclusion. Analysis of literature data shows that patients with CLD and IBD are subject to vaccination against COVID-19 infection, which is effective and safe.
Keywords: chronic liver disease, inflammatory bowel disease, novel coronavirus infection, vaccination
Conflict of interest: the authors declare no conflict of interest.

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Современные подходы к вакцинации против новой коронавирусной инфекции пациентов с хроническими заболеваниями печени и воспалительными заболеваниями кишечника

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Цель исследования: провести анализ данных литературы, посвященных особенностям вакцинации пациентов с хроническими заболеваниями печени (ХЗП) и воспалительными заболеваниями кишечника (ВЗК) против инфекции COVID-19
Основные положения. Показано, что многие больные с ХЗП (циррозом печени, неалкогольной жировой болезнью печени) имеют более высокий риск тяжелого течения новой коронавирусной инфекции, что обусловливает необходимость их вакцинации. Больные ВЗК также подлежат вакцинации, хотя принимаемые ими иммуномодулирующие препараты могут снижать ее эффективность. Кроме того, большое значение имеет правильный выбор времени введения вакцины. Вакцинация больных ХЗП и ВЗК безопасна, и частота побочных эффектов при ее проведении не отличается от таковой в общей популяции.
Заключение. Анализ данных литературы показывает, что пациенты с ХЗП и ВЗК подлежат вакцинации против инфекции COVID-19, которая является эффективной и безопасной.
Ключевые слова: хронические заболевания печени, воспалительные заболевания кишечника, новая коронавирусная инфекция, вакцинация
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Vaccination against SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] infection is currently considered the only effective intervention to manage the pandemic of COVID-19 [(COrona VIrus Disease 2019 (coronavirus infection 2019)] infection. When carrying out vaccination, it is necessary to take into account the concomitant diseases that can affect its effectiveness. In relation to diseases of the digestive system, these are **chronic liver diseases (CLD)** and **inflammatory bowel diseases (IBD).**

It has been shown that patients with advanced stages of CLD have a higher risk of SARS-CoV-2 infection due to immune disorders associated with the presence of cirrhosis. Thus, according to the European Association for the Study of the Liver (EASL), the death rate in patients with liver cirrhosis is 38 %, reaching 70 % in patients with Child-Pugh class C [1]. In addition, patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the presence of metabolic comorbidities (diabetes mellitus, hypertension and obesity) have increased risk of severe COVID-19 infection [2]. More severe COVID-19 is also observed in patients with non-cirrhotic alcoholic liver disease, hepatocellular carcinoma, awaiting and after liver transplantation [3]. Therefore, hepatologists believes that all patients with CLD should be vaccinated [4].

At the same time, according to the guidelines of the American Association for the Study of Liver Disease (AASLD), patients with CLD receiving antiviral therapy for viral hepatitis B and C, immunosuppressive therapy for autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis), as well as chemotherapy due to hepatocellular carcinoma, should not interrupt treatment during vaccination. Only patients with active hepatitis B and C and high fever should postpone vaccination until the condition stabilizes [5].

Patients awaiting liver transplantation should be vaccinated before the transplantation. The effectiveness of vaccination immediately after liver transplantation is reduced due to prescribed immunosuppressive therapy. Therefore, if the transplantation was performed before the vaccination, the vaccination should be carried out 3–6 months after the transplantation. It is not recommended to reduce the dose of immunosuppressive drugs due to the risk of possible graft rejection [1, 5]. The booster vaccination in liver transplant patients may increase their anti-SARS-CoV-2 antibody titer [6].

It has been noted that local or systemic reactions (fever, headache, myalgia) may occur within the first 48 hours after vaccination in patients with CLD [5]. In a multicenter study including 381 patients with non-alcoholic fatty liver disease, it was shown that the frequency of adverse effects within 7 days after vaccination was 24.9 %, within 28 days — 29.4 %. The most common of them were: pain at the injection site (18.4 %), myalgia (5.5 %), and headache (5.2 %). All adverse effects were mild. At the same time, antibodies that neutralize the virus were found in 95.5 % of patients who were vaccinated [7].

Since the immune response to the SARS-CoV-2 vaccine in patients with CLD may not be high enough, vaccination of their family members, as well as healthcare workers who manage these patients, is recommended. In addition, after vaccination, the need to comply with the mask regimen, hand washing, and social distancing remains [1, 5].

The work that studied the features of the COVID-19 course in vaccinated patients with CLD is interesting. The authors used data from 2 major international registries: SECURE-Liver (supported by the American Association for the Study of the Liver) and COVID-Hep.net (supported by the European Association for the Study of the Liver). Authors analyzed the results of a survey of 21 CLD patients and 19 liver-transplanted patients, who received at least one vaccination against SARS-CoV-2 and who subsequently had laboratory-confirmed COVID-19. Twelve of them received a full vaccination and were diagnosed with COVID-19 more than 2 weeks after the second vaccination. Among 21 patients with CLD, 90 % of patients had cirrhosis, 33 % were hospitalized, and 1 patient (5 %) was admitted to the intensive care unit (ICU). There were no fatal cases in this group of patients. In the group of patients who underwent liver transplantation, 6 patients (32 %) were hospitalized, three patients (16 %) required a mechanical ventilation and 2 patients (11 %) died. All 3 cases of severe COVID-19 infection occurred in patients who received only the first dose of the vaccine. In unvaccinated patients with CLD, the incidence of a severe course of infection, as well as the frequency of hospitalization (including in the ICU) and transfer to mechanical ventilation, as well as the frequency of deaths, were significantly higher. Thus, among all non-vaccinated patients with CLD (225 people), the need for hospitalization was in 72 % of cases (including 9 % admitted in the ICU), mechanical ventilation was required in 5 % of patients, 8 % of patients were died. The authors concluded that vaccination of patients with CLD leads to a milder course of COVID-19 and a favorable outcome [8].

Recently, an article was published proving the clinical efficacy and safety of vaccination against COVID-19 with Sputnik V in patients with cirrhosis. The study included 89 vaccinated patients and 148 unvaccinated ones. There were 4 cases of COVID-19 in the vaccinated group and 24 cases in the unvaccinated group ($p = 0.035$). Moreover, among the unvaccinated persons there were 12 severe cases, 10 of which ended in death. All the cases of COVID-19 among vaccinated patients with cirrhosis were mild or moderate, and there were no deaths ($p = 0.012$). The vaccine efficacy was 69.5 % [95 % CI 18.5–94.4 %] against symptomatic cases of COVID-19,

100 % [95 % CI 25.1–100.0 %] against severe cases, and 100 % [95 % CI 1.6–100.0 %] against death associated with COVID-19. The efficacy of full vaccination with revaccination against symptomatic cases of COVID-19 was 88.3 % [95 % CI 48.0–99.6 %]. The overall mortality rate was higher in the unvaccinated group than in the vaccinated group (17.1 % vs. 3.0 %; p = 0.001). There was no significant difference in liver-related mortality, the incidence of liver decompensation, bleeding esophageal varices, and vascular events between groups of patients [9].

A number of publications are devoted to the specifics of vaccination against SARS-CoV-2 in patients with **inflammatory bowel diseases (IBD)**. IBD in itself does not increase the risk of developing COVID-19 infection and does not affect its course, although immunosuppressive drugs used in their treatment (in particular, corticosteroid and derivatives of the thiopurine series) can aggravate it [10–12]. According to the guidelines of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) consensus meeting, patients with IBD should be vaccinated against a new coronavirus infection, as early as possible and with the same dosing regimen as when vaccinating patients without IBD [13]. Consensus meeting of the Korean Association for the Study of Intestinal Diseases (KASID), the Inflammatory Bowel Disease Section of British Society of Gastroenterology and IBD Clinical Research Group concluded that vaccination against SARS-CoV-2 is strictly indicated for patients with IBD and that it is safe when patients receive immunomodulatory therapy. Full vaccination is also necessary for patients with IBD who have had a new coronavirus infection [14, 15]. The last opinion is shared by the majority of experts, although among practitioners treating patients with IBD, only 50 % are convinced of this [11].

Of interest is the attitude of IBD patients themselves to vaccination against a new coronavirus infection. R.S. Dalai et al. [16] conducted an anonymous survey of IBD patients in order to determine their readiness to be vaccinated if possible. 80.9 % of respondents declared their intention to be vaccinated. The most frequently cited reasons for refusal were the lack of data on the long-term safety of the vaccine used.

Immunomodulatory therapy, which patients with IBD receive, should not be a cause for refusing vaccination, although this drugs may affect effectiveness of vaccination [13, 15], which causes some features regarding the timing of vaccine administration.

It has been shown that the intake of 5-aminosalicylic acid and sulfasalazine by patients with IBD does not reduce the severity of the immune response to vaccination against SARS-CoV-2. With regard to corticosteroids, vaccination against COVID-19 infection is effective if the patient receives these drugs at a dose equivalent to a dose of prednisolone <10 mg per day. In cases where treatment with higher doses of corticosteroids (>20 mg per day equivalent dose of prednisolone) is planned, vaccination should be considered 2 weeks before the expected start of therapy (if the course of the disease allows it). If the patient is already receiving high doses of corticosteroids, it is advisable to postpone vaccination until their dose become equivalent to a dose of prednisolone <20 mg per day [10].

In patients with IBD receiving immunomodulators such as methotrexate, thiopurines (azathioprine or 6-mercaptopurine), the immune response to the first injection of the vaccine may be insufficient, but it becomes adequate after the second dose of vaccine [10].

Therapy with antibodies to tumor necrotizing factor-alpha (infliximab) also reduces the immune response [10, 13, 17]. If it is planned, then vaccination is recommended 2 weeks before it starts. If the patient is already receiving infliximab, interrupting it during vaccination is considered inappropriate [10].

N.A. Kennedy et al. [18] compared the peak concentration of antibodies to SARS-CoV-2 in IBD patients treated with infliximab and the anti-integrin drug vedolizumab. The level of this marker was lower in the case of infliximab. Interrupting vedolizumab therapy during vaccination is also not recommended. Treatment with antibodies to interleukin 12/23p40 (ustekinumab) does not reduce the effectiveness of vaccination, although the available data are still very limited [10].

The use of the Janus kinase inhibitor tofacitinib may reduce the immune response to vaccination. If the patient is receiving treatment with this drug, then vaccination is recommended to be postponed until the patient is switched to a maintenance dose of 5 mg 2 times a day. The start of therapy with tofacitinib is possible 2 weeks after vaccination [10].

So far, a few studies have been published on the effectiveness of vaccination against COVID-19 in patients with IBD. N. Khan and N. Mahmud [19] observed 14,627 patients with IBD, of which 7,321 patients were vaccinated at least once. Over the next 4 months, coronavirus infection developed in 1.34 % of unvaccinated patients and only 0.11 % of those vaccinated. K. Cerna et al. [20] compared the incidence of anti-SARS-CoV-2 IgG antibodies after vaccination of 602 IBD patients (82.2 % of them received various immunomodulatory drugs at the time of vaccination) and 168 healthy healthcare workers. The frequency of detection of these antibodies 8 weeks after vaccination was 97.8 % and 100 %, respectively. A meta-analysis of 6 studies on the effectiveness of vaccination of 676 patients with IBD showed that within 90 days after the second vaccination, seroconversion was achieved in 96.4 % of patients [21].

The frequency of side effects of vaccination of patients with IBD corresponds to that in the population and includes general weakness, fever, headache [10, 15]. J.J. Botwin et al. [22] evaluated side

effects in 246 patients with IBD (vaccinated at least once) that occurred in the first 8 days after the first and second vaccines. At the same time, 80 % of patients at the time of vaccination received various immunomodulatory drugs (corticosteroids, antibodies to tumor necrotizing factor-alpha, vedolizumab, ustekinumab, etc.). The frequency of side effects after the first and second vaccinations was comparable to that in healthy individuals. Among patients with IBD, adverse reactions were more common in young patients, as well as in patients who had a new coronavirus infection.

Thus, an analysis of published works on the vaccination of patients with CLD and IBD shows that these patients should be vaccinated against SARS-CoV-2, which is quite effective and safe for them. Considering that patients with IBD usually receive immunosuppressive drugs, which will also be indicated for patients with CLD after liver transplantation, the correct timing of vaccination is of great importance.

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