COVID-19 vaccination in patients with liver cirrhosis: immune and clinical responses

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SUMMARY

Significance and background. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the novel coronavirus disease 2019 (COVID-19). It has become a global pandemic motivating major efforts in the development of SARS-CoV-2 vaccines, but data is lacking regarding their effect in patients with chronic liver disease (CLD), since these have been excluded from most of the trials. CLD patients have dysregulated innate and adaptive immune system responses, making certain types of infections more frequent and severe in this population, especially in certain subgroups under immunosuppressant drugs. Patients with liver cirrhosis are advised to be vaccinated against certain types of bacteria and viruses, however, the durability of humoral immunity after influenza and pneumococcal vaccination is reduced and they have lower rates of seroconversion in HAV and HBV vaccination. Similarly, in the case of **SARS-CoV-2 infection, patients with liver cirrhosis do not only have a more severe course of disease, but also are expected to have an attenuated response to vaccination against COVID-19**. First practical experiences with COVID-19 vaccination in Israeli patients with liver disease by Safadi R. (unpublished data) have reported lower antibody titers in males, older patients, patients with more advanced fibrosis and immunosuppressed. To conclude, **currently available data regarding safety and efficacy of COVID-19 vaccination in patients with liver cirrhosis is lacking and may differ among subgroups**. Concerns regarding lower immunological and therefore clinical responses raise attention to the **possible need for a booster injection** in this specific population.

Aims and hypotheses. Our goal is **to evaluate the safety, immunological and clinical response of patients with liver cirrhosis to COVID-19 vaccination and assess group differences** regarding gender, age, cause and stage of cirrhosis, use of immunosuppressant drugs, comorbidities and type of vaccine given. **We believe that our study will contribute to a better understanding of the immunological and clinical response to COVID-19 vaccination in patients with liver cirrhosis** and might help to **detect risk groups which may benefit from an additional inoculation to reach immunization**.

Methods. We propose to conduct a **multicentric observational prospective study in adult patients with liver cirrhosis** regularly followed in Portuguese hospitals, eligible for vaccination against COVID-19. Exclusion criteria include patients contraindicated for the COVID-19 vaccination program; completed vaccination before recruitment; history of previously documented COVID-19 infection; infection with Human Immunodeficiency Virus (HIV) and the use of immunosuppressant drugs for conditions other than autoimmune liver disease. Patients will be characterized at baseline according to demographic information (e.g., age, gender); cause of liver cirrhosis; previous history of cirrhosis decompensation; Model for End-stage Liver Disease and Child-Pugh scores; presence and features of portal hypertension; important medical and surgical comorbidities and current medication.

Patients meeting inclusion criteria who consent to participate will be characterized at baseline and asked to contact the hospital immediately after being vaccinated. They will be enquired about self-reported adverse events following vaccination and be given a personal code to present at the closest laboratory facility of *Centro de Medicina Laboratorial Germano de Sousa.* The laboratory will collect blood samples to quantify IgM and IgG antibody titers for SARS-CoV-2 at **three different time-points** of the study: the **first timepoint** taking place 2 weeks after completing vaccination; the **second timepoint** 3 months after completing vaccination and the **last timepoint** at 6 months after completing vaccination. During a 12-month follow-up period, data related to post-vaccination SARS-CoV-2 symptomatic infection and severe disease requiring hospital admission will be asked and registered. Interim analysis will be made every two months after the first patient's recruitment. Statistical analysis will be performed by the main investigator using Stata® 15 and a p-value <0.05 will be considered statistically significant.

Anticipated results and future perspectives. We anticipate that some subgroups of patients with liver cirrhosis, probably those with decompensated disease and under immunosuppressive treatment, will have lower antibody titers than the remaining ones. The results of this study may contribute to the **identification of the patients who might benefit from an additional injection in order to achieve adequate immunity.**

We plan to **present the preliminary results of the second timepoint analysis at the International Liver Congress 2022 by the European Society for the Study of the Liver** and to complete the study by the second semester of 2022, along with the publication of the study results in an indexed medical journal.

INFORMATION FOR COLLABORATING INSTITUTIONS

Participation in the study. Portuguese hospitals all over the country with dedicated physicians to the treatment and follow-up of patients with liver cirrhosis are invited to participate in this study. The **study protocol will be sent** to the collaborating investigators once they agree to participate.

Patient inclusion. We plan to conduct a **multicentric national observational study** including up to 300 adult patients with liver cirrhosis eligible for COVID-19 vaccination and without previously known SARS-Cov-2 infection. We would like to appeal to the recruitment of balanced groups in terms of compensated and decompensated cirrhosis and other clinical characteristics for effects of subgroup analysis.

Authorship criteria. Each center should **nominate one local Principal Investigator** responsible for the study. Further authors will be included according to the **number of patients vaccinated against SARS-CoV-2 recruited** by the institution: if less than 10 patients are recruited, there will be only one author, corresponding to the local Principal Investigator; if 10 to 19 patients are included, one additional author can be nominated; if 20 to 49 patients are recruited, two additional authors can be selected; if 50 or more patients are recruited, three additional authors can be attributed by the collaborating institution.