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SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question

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Since the onset of the COVID-19 pandemic, SARS-CoV-2 vaccine development has progressed at an unprecedented rate, with recent phase 3 trial data offering the tantalising prospect of achieving herd immunity.[1–3] Until now, researchers have focused on the contribution of specific liver disease phenotypes, including transplantation and immunosuppression, to COVID-19 susceptibility and outcome. However, the hepatology community must now urgently turn its attention to characterising SARS-CoV-2 vaccine responses in these vulnerable patient groups.

The Pfizer/BioNTech BNT162b2 mRNA, Moderna mRNA-1273, and the AstraZeneca/University of Oxford ChAdOx1-nCoV-19 chimpanzee adenovirus (ChAd) vector vaccines have each reported excellent safety profiles, marked efficacy in preventing symptomatic COVID-19 (62–95%), and have all gained rapid regulatory approval.[1–3] Currently, it remains unclear why a significant minority of those vaccinated appear susceptible to SARS-CoV-2, although both host factors (eg, underlying chronic diseases or genetic susceptibility) and viral factors (eg, high viral load exposure, specific viral variants) are likely to have a contributory role.

Despite the inclusion of nearly 100 000 participants in these trials, data for patients with liver disease are extremely limited (panel). In the Pfizer vaccination study, 217 (0·6%) of 37 706 participants had liver disease, and only three (<0·1%) had moderate to severe liver disease. A similarly low proportion of patients with liver disease were included in the Moderna trial (196 [0·6%] of 30 351). The ChAdOx1-nCoV-19 vaccine trial explicitly omitted patients with pre-existing liver pathology. Notably, in each study the criteria used to classify liver disease and its severity remain unclear. In addition, all trials listed systemic immunosuppression as an exclusion criterion, thus preventing extrapolation of the data to immunosuppressed liver transplant recipients or patients with autoimmune liver disease. Furthermore, granular detail regarding liver safety profiles remains largely unpublished, although abnormal liver biochemistry was reported in only one of 12 021 participants receiving ChAdOx1-nCoV-19. ChAd vaccines for hepatitis C virus (HCV) have previously been safely given to a small number of patients with non-cirrhotic chronic HCV infection.[4] However, a detailed understanding of SARS-CoV-2 vaccine safety and the immunological response in patients with liver disease

Panel: **Involvement of patients with liver disease in phase 3 SARS-CoV-2 vaccine trials and key outstanding questions**

Chronic liver disease and cirrhosis

Trial inclusion and exclusion criteria

- Pfizer/BioNTech: "liver disease" included but not defined
- Moderna: "liver disease" included but not defined
- Oxford/AstraZeneca: "liver disease" excluded (except Gilbert syndrome), "alcohol and drug dependency…injecting drug abuse in the 5 years preceding enrolment" excluded

Key outstanding questions

- Magnitude and duration of vaccine response
- Disease severity in predicting vaccine response
- Differential efficacies of single doses or additional booster doses
- Risk of liver injury unknown

Liver transplantation

Trial inclusion and exclusion criteria

- Pfizer/BioNTech: "Individuals who receive treatment with immunosuppressive therapy" excluded
- Moderna: "Immunosuppressive or immunodeficient state" or "systemic immunosuppressants or immune-modifying drugs for >14 days" excluded
- Oxford/AstraZeneca: "Any confirmed or suspected immunosuppressive or immunodeficient state" excluded

Key outstanding questions

- Magnitude and duration of vaccine response
- Durability of response post-transplantation; optimal timing of prime and boost vaccination in relation to transplantation
- Interactions with specific immunosuppression regimens
- Differential efficacies of single doses or additional booster doses
- Risk of liver injury unknown

Immunosuppressed autoimmune liver disease (eg, autoimmune hepatitis)

Trial inclusion and exclusion criteria

- Pfizer/BioNTech: "Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention" excluded
- Moderna: "Immunosuppressive or immunodeficient state" or "systemic immunosuppressants or immune-modifying drugs for >14 days" excluded
- Oxford/AstraZeneca: "Any autoimmune conditions" excluded

Key outstanding questions

- Magnitude and duration of vaccine response
- The effects of specific immunosuppression regimens of vaccine response
- Interactions with specific immunosuppression regimens
- Differential efficacies of single doses or additional booster doses
- Risk of liver injury unknown

will almost exclusively come from post-licensing, real-world investigation.

Patients with advanced liver disease have well recognised deficiencies in innate and humoral immunity, termed cirrhosis-associated immune dysfunction (CAID). Although attention has mostly focused on mechanisms leading to severe bacterial infections, CAID has also been shown to predispose to a variety of viral or fungal related diseases.[5] This same immune dysfunction might partly explain the severe complications of COVID-19 observed in patients with decompensated cirrhosis[6] and contribute to the impaired immunological responses seen with existing vaccinations. For example, rates of seroconversion after hepatitis B virus (HBV) immunisation, and the durability of humoral immunity after pneumococcal and influenza vaccination are all markedly reduced in patients with cirrhosis.[7–9] It is therefore likely that patients with cirrhosis will have attenuated immune responses to SARS-CoV-2 vaccination. Nonetheless, given the high COVID-19-related mortality in patients with decompensated cirrhosis, it remains of utmost importance to prioritise vaccination in this subgroup.[6] Patient education regarding the benefit of SARS-CoV-2 vaccination programmes will also be essential, particularly given that routine immunisation uptake in patients with cirrhosis is often suboptimal.[10]

The value of routine immunisation in liver transplant recipients is well established, with vaccine immunogenicity greatest in the pre-transplantation rather than the post-transplantation setting, even in the context of advanced liver disease. Current guidelines therefore recommend pre-transplant vaccination where possible, with any subsequent immunisation deferred until doses of immunosuppression have been reduced to maintenance levels.[11] The optimal timing of SARS-CoV-2 vaccine delivery within the transplantation pathway is undetermined, but currently due to the high global burden of COVID-19 should most likely be administered as soon clinically available. Blunting of the response in immunosuppressed liver transplant recipients is well recognised, with lower antibody titres reported following influenza, hepatitis A virus, HBV, and pneumococcal vaccinations.[12]

At present, the product information for the mRNA vaccines recommends against their use in those with immunosuppressive conditions or when receiving immunosuppressive medications. This is presumably related to the lack of specific efficacy and safety data in these subpopulations. However, neither the ChAdOx1-nCoV-19 or the mRNA vaccine platforms contain live or attenuated virus and it therefore seems unlikely that immunisation represents a particular safety concern for these patients. Although historically there have been anxieties that vaccination in transplant recipients may lead to the development of alloimmunity and graft rejection, no clinical evidence has emerged to support this.[12] Although liver transplant recipients have comparable rates of COVID-19-related mortality to the matched general population,[13] they do have higher rates of admission to intensive care and may have been relatively more protected throughout the pandemic due to enhanced social distancing or shielding. Therefore, we still believe this group remains a vulnerable population and should be prioritised for vaccination, with the likely benefits far outweighing the potential risks. However, until it is established whether patients with liver disease and transplantation achieve optimal protection after immunisation, clinicians should remain vigilant for post-vaccination COVID-19 in these cohorts.

More work is needed to define the precise laboratory correlates of vaccine protection following delivery of the mRNA and ChAdOx1-nCoV-19 platforms. Both vaccine types induce high concentrations of anti-spike IgG antibodies as measured ex-vivo[14,15] and also generate high levels of spike-specific CD4+ and CD8+ T cells,[14,15] which might improve durability of B-cell responses and help protect against future infection. In evaluating patient responsiveness it is therefore vital to assess for the magnitude and durability of both humoral and cellular responses.

Finally, despite the frequency of post-vaccination SARS-CoV-2 infection in liver disease cohorts being unknown, it is likely to be rare in absolute terms. Therefore, large scale case reporting through platforms such as the COVID-Hep and SECURE-Cirrhosis registries may be the only mechanism through which to draw meaningful conclusions. Furthermore, disentangling the relative contributions of vaccine type, liver disease phenotype, and host factors to the immunisation response will require wide collaborative efforts to pool clinical and laboratory data. Currently, advice regarding vaccine delivery in disease subpopulations is inconsistent and subject to geographical variation.

For the **COVID-Hep registry** see https://www.COVID-hep.net

For the **SECURE-Cirrhosis registry** see https://covidcirrhosis.web.unc.edu

Detailed investigation of immune responses is therefore vital to ultimately allow the standardisation of vaccination guidelines. As we usher in the new era of SARS-CoV-2 immunisation, it is now of fundamental importance to examine the effect of new vaccines on patients with liver disease, for whom evidence is thin yet clinical consequences profound.

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