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Editorial

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Protected or not protected, that is the question - First data on COVID-19 vaccine responses in patients with NAFLD and liver transplant recipients

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Immunocompromised patients and those with cancer were excluded from the phase III trials of current COVID-19 vaccines and limited data are available on patients with chronic liver disease (CLD). This led the European Association for the Study of the Liver (EASL) to publish a position paper guiding COVID-19 vaccination in patients with CLD, hepatobiliary cancer, and liver transplant recipients (LTRs).[1] In this issue, Wang *et al.*[2] and Rabinowich *et al.*[3] report initial data on COVID-19 vaccination in patients with non-alcoholic fatty liver disease (NAFLD) and in LTRs, respectively.

In a multicenter study in China, Wang *et al.* assessed antibody responses in 381 patients with NAFLD at least 14 days after the second dose of the alum-adjuvanted inactivated COVID-19 vaccine (Beijing Institute). Similar to phase I/II studies in healthy individuals, 95.5% of patients elicited detectable antibody responses[4] and rates of adverse events were comparable. However, detailed characterization of the CLD in terms of liver function tests and fibrosis stages is not described and it is uncertain whether patients with advanced CLD and cirrhosis, who are most at risk of severe COVID-19 outcomes, were included. Their cohort was rather young (median age 39 years) and only 3.7% had diabetes mellitus, a major risk factor for steatohepatitis and disease progression. This suggests that study participants did not have advanced CLD and might explain why these findings are different to what is seen with other vaccines, such as those for influenza, where patients with advanced CLD elicit lower humoral immune responses.[1] More data on COVID-19 vaccination in patients with advanced CLD and with different vaccine types are eagerly awaited.

The second study from Tel-Aviv Sourasky Medical Center, Israel, evaluated humoral antibody responses in 80 LTRs and 25 healthy volunteers after vaccination with the mRNA vaccine BNT162b2 (BioNTech/Pfizer). This study confirmed concerns regarding lower immunogenicity of vaccination in transplant recipients (reviewed in[1]); antibodies were detectable in only 47.5% of patients compared to all 25 healthy controls and antibody titers were significantly lower in LTRs (95.41 AU/ml *vs.* 200.5 AU/ml, p <0.001).[3] Importantly, the authors reported no serious adverse events associated with the vaccine, and no event of graft rejection was observed. This is consistent with other early real-world reports in transplant recipients vaccinated with Moderna or BioNTech/Pfizer mRNA vaccines, wherein no graft rejections were observed during the early follow-up period.[5,6]

The same group evaluated vaccine responses in 136 kidney transplant recipients (KTRs) and reported even lower antibody responses following vaccination with BNT162b2; only 37.5% of KTRs had detectable SARS-CoV-2 specific antibodies.[5] Compared to LTRs, seropositivity rates and mean antibody titers were lower in KTRs,[5] matching previous reports that transplant recipients other than LTRs generally have a lower humoral response to vaccination.[7] This may be due to distinct immunosuppressive treatments used in different transplant groups. Indeed, predictors of absence of humoral vaccine responses in both LTRs[3] and KTRs[5] were treatment with high-dose steroids and antimetabolites (*i.e.* mycophenolate mofetil), in addition to older age and, for LTRs, lower estimated glomerular filtration rate.

In summary, the 2 studies published in this issue indicate that the humoral response to COVID-19 vaccination does not appear to be impaired in patients with hepatic steatosis when vaccinated with an inactivated vaccine, but is lower in immunosuppressed LTRs vaccinated with an mRNA vaccine. As expected, the quality and extent of immunosuppression is an important factor contributing to vaccine responses. However, many questions remain open.

Most importantly, there is no correlate of protection for COVID-19 to date, and therefore it is difficult to interpret antibody levels. Phase I/II trails have shown that especially mRNA

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and viral vector COVID-19 vaccines elicit T cell responses that might – in addition to humoral responses – play a role in protection.[8,9] Vaccine efficacy in preventing symptomatic COVID-19 even in healthy individuals ranges between around 70% and 95%, depending on the type of vaccine (reviewed in[1]). Thus, it is expected that SARS-CoV-2 infection and cases of COVID-19 pneumonia will also occur in CLD or transplant recipients, as has been reported in KTRs, who were fully vaccinated with the BNT162b2 mRNA vaccine.[10] However, a more severe COVID-19 course may have been prevented by vaccination. A *post hoc* subgroup analysis of vaccine efficacy in 1,674 immunocompromised vaccinated individuals from Israel showed that more than 80% of these vaccinated individuals were protected from symptomatic COVID-19.[11] These data need cautious interpretation given the sample size (solid-organ recipients constituted only a small minority of the subgroup) and design as an effectiveness study, but they shed hope that immunized immunocompromised patients might still be protected, especially from severe COVID-19.

Therefore, it is of utmost importance that registries are established to document the clinical outcome following COVID-19 vaccination in the patient populations mentioned here. This will help provide valuable information for optimal patient management and provide insights into whether additional vaccine doses are needed or whether specific vaccines are more effective in this setting. In addition, the best timing for vaccination after transplantation needs to be determined to elicit a protective response without unnecessarily delaying vaccination.

Furthermore, studies now demonstrate that mRNA or viral vector COVID-19 vaccination decreases the risk of being an asymptomatic carrier[12] or of transmission within the household.[13] This highlights the importance of vaccinating close contacts and healthcare professionals to reduce the risk of exposure for immunocompromised individuals. Finally, we would like to reiterate our strong recommendation to vaccinate patients with CLD and LTRs. Even if immunocompromised patients may experience a decreased response to vaccination, such as seen for influenza vaccination, where it still reduces morbidity and mortality in vaccinated compared to unvaccinated transplant recipients,[14] COVID-19 vaccination may still confer some benefit and reduce the risk or severity of COVID-19. It is therefore encouraging to see that the acceptance rate for COVID-19 vaccination in LTRs in Genoa is over 95%.[15]

It is paramount that healthcare professionals provide the necessary counsel to help patients make informed decisions and to increase COVID-19 vaccination adherence in vulnerable patients, their close contacts and among healthcare professionals.

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Authors' contributions

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Supplementary data

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