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Position Paper

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EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients

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Summary

According to a recent World Health Organization estimate, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which originated in China in 2019, has spread globally, infecting nearly 100 million people worldwide by January 2021. Patients with chronic liver diseases (CLD), particularly cirrhosis, hepatobiliary malignancies, candidates for liver transplantation, and immunosuppressed individuals after liver transplantation appear to be at increased risk of infections in general, which in turn translates into increased mortality. This is also the case for SARS-CoV-2 infection, where patients with cirrhosis, in particular, are at high risk of a severe COVID-19 course. Therefore, vaccination against various pathogens including SARS-CoV-2, administered as early as possible in patients with CLD, is an important protective measure. However, due to impaired immune responses in these patients, the immediate and long-term protective response through immunisation may be incomplete. The current SARS-CoV-2 pandemic has led to the exceptionally fast development of several vaccine candidates. A small number of these SARS-CoV-2 vaccine candidates have already undergone phase III, placebo-controlled, clinical trials in healthy individuals with proof of short-term safety, immunogenicity and efficacy. However, although regulatory agencies in the US and Europe have already approved some of these vaccines for clinical use, information on immunogenicity, duration of protection and long-term safety in patients with CLD, cirrhosis, hepatobiliary cancer and liver transplant recipients has yet to be generated. This review summarises the data on vaccine safety, immunogenicity, and efficacy in this patient population in general and discusses the implications of this knowledge on the introduction of the new SARS-CoV-2 vaccines.

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Efficacy and safety of vaccines in patients with chronic liver diseases including patients with hepatobiliary cancer

Patients with chronic liver diseases (CLD) have *per se* an increased vulnerability to infections.[1] However, the individual risk depends on the aetiology of CLD, comorbidity, co-medication and stage of liver disease.

Furthermore, as CLD and age progress, immune responses to and immune memory against certain vaccine-delivered antigens decline.[2] Moreover, patients with alcohol-associated liver disease, CLD and cirrhosis (irrespective of aetiology) may have an impaired immune response to vaccination (Table 1), *e.g.* characterised by non or hypo-response to hepatitis B vaccination.[3,4] Co-medication may also be a reason for an impaired or altered immune response to vaccination, *e.g.* in patients with autoimmune hepatitis taking immunosuppressive agents, leading to reduced seroconversion rates to hepatitis B vaccination and lower anti-HBs titres.[5] An important factor affecting response to vaccination is the comorbidity of patients with CLD, *i.e.* metabolic diseases such as diabetes mellitus, steatohepatitis and obesity or chronic kidney disease (haemodialysis) as well as coeliac disease, which have been linked to declining vaccine response rates *i.e.* for standard hepatitis B vaccination.[3,4] In this particular case, new vaccine formulations through inclusion of Pre-S1/Pre-S2 epitopes or more stimulating adjuvants are now available to improve or bypass hypo-responsiveness to conventional HBV vaccines.[6–8]

One of the most important factors for the success of vaccination is the stage of CLD at the time of immunisation. On the one hand, patients with cirrhosis are more susceptible to infections and their sequelae,[1] and on the other hand the response to vaccination may be compromised, explained by cirrhosis-associated immune dysfunction (reviewed in[9]).

While data on safety and immunogenicity of hepatitis A, hepatitis B, seasonal influenza and *streptococcus pneumonia* vaccines in CLD are available (Table 1), there is insufficient data on vaccine

Table 1. Efficacy of vaccines in patients with chronic liver diseases (examples).

Vaccine	Response in patients with chronic liver diseases	Ref.
Seasonal influenza vaccine	Patients with cirrhosis (n = 20) had a lower response rate (75–85% *vs.* 100%) than healthy controls (n = 8) to the adjuvanted trivalent influenza vaccine. No safety concerns.	19
	Meta-analysis of 12 studies: effective antibody response may reduce the risk of all-cause hospitalisation in patients with chronic liver diseases (most patients had chronic viral hepatitis).	20
Streptococcus pneumonia vaccine	Patients with cirrhosis (n = 45) had a significant increase of IgA and IgG antibodies against the 23-valent pneumococcal vaccine at 1 month compared to baseline, however, larger decline in IgA and IgM at 6 months compared to controls.	21
Hepatitis A vaccine	Serum anti-HAV concentrations were significantly lower in patients with decompensated cirrhosis (n = 35) than in patients with cirrhosis (n = 49). Patients with Child-Pugh A had adequate responses (71% after the first and 98% after the booster dose). Child-Pugh class was the only factor predicting response to vaccination.	22
Hepatitis B vaccine	Patients with chronic liver diseases (n = 166, 34% cirrhosis) had lower response rates. Nine (26%) of 34 cirrhotic patients who received Engerix-B and 10 (45%) of 22 cirrhotic patients who received HeplisavB achieved immunity.	23
	Systematic review of 11 studies: Lower rate of seroconversion in patients with chronic hepatitis C compared to healthy controls, both in cirrhotic and non-cirrhotic patients.	24
	Patients with cirrhosis on the waiting list for liver transplantation (n = 49) had low antibody responses (28%) compared to 97% for healthy controls (n = 113).	25
	Patients with cirrhosis on the waiting list (n = 62) had low antibody responses (44% after 1st vaccine schedule, 62% after 2nd schedule)	26

response in patients with hepatobiliary cancer. Considering that patients with hepatocellular carcinoma often have cirrhosis, response to vaccines is expected to be impaired. In addition, it is known from other cancer types that the response to the vaccine may be lower depending on age, comorbidities, the underlying cancer and the chemotherapy administered (reviewed in[10]). Importantly, influenza vaccines also appear to be safe in the setting of chemotherapy, and the benefit of vaccination outweighs the potential risk.[11] An emerging question is whether vaccines can be administered in patients receiving immune checkpoint inhibitors (ICI) because of concerns that vaccination could increase the incidence of immune-related adverse events.[12] However, recent studies investigating the safety of seasonal influenza vaccination in patients receiving ICI showed no safety concerns with comparable rates of immune-related adverse events to those seen in clinical trials.[13,14] In addition, therapeutic RNA cancer vaccines are being tested in early clinical trials in patients with various cancers, including patients treated with ICI, and no safety concerns have been raised to date.[15–17]

As a final note, there is no confirmed information yet on the tolerability, immunogenicity and safety of novel COVID-19 vaccines in patients with CLD, including patients with hepatobiliary cancer.[18]

Efficacy and safety of vaccines in solid organ transplant recipients

Solid organ transplant (SOT) recipients are at an increased risk of infection because of the immunosuppression required to prevent graft rejection. In addition, infections can be more severe in transplant recipients than in immunocompetent individuals.[27] Therefore, vaccination is an important measure to prevent infections and their sequelae. However, the immunogenicity of vaccines in SOT recipients is lower than in immunocompetent individuals because of their underlying chronic disease and the administration of immunosuppressive therapy after transplantation, which may reduce the immune response of these patients to immunisations (Table 2). The quality and dosing of immunosuppression is certainly an important factor influencing the response to vaccination. Therefore, the timing of vaccination is important and it is recommended that vaccination should be completed prior to transplantation, ideally very early in the course of CLD[28,29] and latest at the time of listing.

There is some uncertainty regarding administration of live attenuated vaccines to transplant recipients and consequently, live attenuated vaccines are usually avoided after transplantation. Yet, a meta-analysis documented relatively preserved safety and efficacy for some live attenuated vaccines in paediatric and adult SOT recipients.[30] Nevertheless, immunisation with live attenuated vaccines following transplantation is usually performed only after a careful risk-benefit assessment and not at the peak of immune suppression. This dilemma can be partially avoided through pre-transplant testing of antibody titres against measles, mumps and varicella and appropriate vaccination before transplantation.

After transplantation, vaccination is usually not recommended in the first 3–6 months during the period of intense immunosuppression, as immune responses are expected to be decreased.[28] Since transplant recipients may not have adequate protection against vaccine-preventable diseases in the early post-transplant period due to impaired immune responses or incomplete vaccination status, it is advised that household contacts of organ transplant recipients and candidates, as well as healthcare workers at transplant centres, if lacking specific immunity, are vaccinated against

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Table 2. Efficacy and safety of vaccines in transplant recipients (examples).

Vaccine	Type of study/population	Response in transplant recipients	Ref.
Seasonal influenza vaccine	Systematic review of 36 studies SOT patients	High variability of the response. Overall a 10% to 16% lower response rate in SOT recipients *vs.* controls. Calcineurin-inhibitors and azathioprine were associated with a slightly better response compared to sirolimus and MMF.	32
	Meta-analysis with 8 studies (SOT patients):	Transplant recipients receiving MMF had a significantly lower response rate.	33
	Systematic review of 7 studies (SOT patients)	Heterogenous responses. Despite alternative influenza vaccination strategies, seroconversion and seroprotection rates for influenza antigens were lower in SOT patients.	34
	Systematic review of 9 studies	A booster dose of the influenza vaccine did not effectively enhance immunogenicity in renal transplant recipients.	35
	Systematic review and meta-analysis	15 studies reported influenza-like illness with comparable rates between vaccinated transplant patients and immunocompetent controls. 55 studies reported on the serologic response to influenza vaccination. A weaker response to influenza vaccination was observed compared with immunocompetent controls, although some studies showed a comparable or increased response for some influenza subtypes. 25 studies described adverse events at rates comparable to healthy or placebo-vaccinated controls. 30 studies investigated rejection reactions or allograft function in transplant recipients vaccinated against influenza; however, no consistent evidence of an association with these outcomes or serious adverse events was found.	36
Mumps, measles, and rubella vaccine	Systematic review of 4 studies (SOT patients):	Heterogenous responses. Overall, the observed positive response rates were above 70% in all but 1 study.	32
Adjuvanted subunit varicella zoster vaccine	Systematic review of 6 studies (immunocompromised adults aged 18-49 years):	Significant humoral and cellular immune responses even in patients with the highest level of immunosuppression (sustained for at least 24 weeks); no safety concern, no evidence of graft rejection compared to placebo groups.	37
Hepatitis A vaccine	Systematic review of 17 studies (immunosuppressed patients	Heterogenous responses; lowest immune response in transplanted patients using multiple immunosuppressive drugs, especially after only 1 dose of vaccine.	38
Hepatitis B vaccine	Systematic review of 7 studies (SOT patients):	Low response rates in adult SOT recipients (6.7% to 36%) but higher response rate in the paediatric trials (63.6% to 100%)	32
Streptococcus pneumonia vaccine	Systematic review of 9 studies (SOT patients):	Overall response ranged from 32% to 100% with comparable responses in the control group, if included.	32
Tetanus vaccine	Systematic review of 6 studies (SOT patients):	High rate of responders in SOT recipients with conventional immunosuppression with no significant difference to healthy controls. Lower response in patients with anti-CD20 treatment.	32
Diphteria vaccine	Systematic review of 4 studies (SOT patients):	Comparable response rates in SOT recipients and controls.	32

SOT, solid organ transplantation; MMF, mycophenolate mofetil.

transmittable diseases, such as influenza, measles, mumps, pertussis, chickenpox and hepatitis B.[28,29] The same precaution applies to available COVID-19 vaccines.

Immune memory to various vaccine-preventable disease wanes over time in transplant recipients and additional vaccine doses should be considered depending on the serological follow-up. Another aspect of vaccine safety is the hypothesis that immune response to vaccination could stimulate immunologic rejection reactions. However, to the best of our knowledge, there is currently no solid evidence that the recommended standard vaccines lead to allograft rejection in SOT recipients.[31] While data are available for most of the recommended vaccines in SOT (Table 2), there is so far no confirmed information on the tolerability, reactogenicity, immunogenicity and overall safety of COVID-19 vaccines in SOT patients given the design of the phase III trials.[18]

COVID-19 vaccines

According to a continuously updated report by the World Health Organization (WHO), more than 200 vaccine candidates have been evaluated in preclinical animal models and in human clinical trials worldwide (published on January 26, 2021, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines).

A wide variety of technologies/platforms have been used, such as mRNA, viral vectors, recombinant DNA, inactivated viruses, protein subunits and live attenuated viruses. Several comprehensive reviews are available that discuss the different vaccine candidates in more detail.[39–41] The high speed of COVID-19 vaccine development is unprecedented and exceptional, with several vaccines already approved by regulatory authorities within a year of the start of the pandemic. We will discuss 3 vaccines that have been approved by the EMA and FDA by February 2021 (Table 3).

Two of these vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), are based on mRNAs that encode variants of the SARS-CoV-2 spike glycoprotein and are encapsulated into lipid nanoparticles.[42,43] Both mRNA vaccines must be administered twice, 21–28 days apart according to the product information. The efficacy of both

Table 3. Summary of data for COVID-19 vaccines approved* to date (as of February 2021).

Vaccine	Phase III data	Special features	Ref
BNT162b2 (Tozinameran; Comirnaty) (BioNTech and Pfizer) RNA (embedded in lipid nanoparticles) encodes a variant of the SARS-CoV-2 spike protein	N = 43,548 (randomised 1:1 vaccine *vs.* placebo) Efficacy 95% (9 vaccinated *vs.* 169 controls with COVID-19) 10 cases of severe COVID-19; 9 in the placebo group Safety: Injection site reactions and systemic AEs (headache, fever, fatigue) most mild to moderate. SAE rates were below 4%.	2 doses (30 μg) 21 days apart Storage at a temperature of -90 to -60°C for 6 months, storage at 2 to 8°C for up to 5 days and for up to 2 hours at room temperature (up to 30°C).	42
mRNA-1273 (Moderna) RNA (embedded in lipid nanoparticles) encodes a variant of the SARS-CoV-2 spike protein	N = 30,420 (randomised 1:1 vaccine *vs.* placebo) Efficacy 94.1% (11 vaccinated *vs.* 185 controls with COVID-19) 30 cases of severe COVID-19 only in the placebo group Safety: Injection site reactions and systemic AEs (headache, fever, fatigue) most mild to moderate. SAE rates were low after the first dose and increased to around 16% after the second dose.	2 doses (100 μg) 28 days apart Storage at a temperature of -25 to -15 °C for 7 months, storage at 2 to 8°C for up to 30 days and at 8–25°C for up to 12 hours, 6 hours after first dose was taken.	43
ChAdOx1 nCoV-19 (AZD122) (AstraZenenca and University of Oxford) replication-deficient chimpanzee adenovirus vector, containing the full-length codon-optimised coding sequence of SARS-CoV-2 spike protein.	Interim analysis (N = 11,636 from Brazil, South Africa, UK) Vaccine *vs.* MenACWY Efficacy 70.4% (30 [0.5%] of 5,807 vaccine recipients *vs.* 101 [1.7%] of 5,829 controls with COVID-19) Efficacy with 2 standard doses 62.1% Efficacy low dose/standard dose 90.0% Efficacy after 1 standard dose 64.1% Safety: 175 SAEs in 168 participants, 84 SAEs in the vaccine group and 91 in the control group.	2 doses. A second dose could be given between 4 and 12 weeks after the first dose. Detailed storage information pending but expected to be less complex (stable at 2–8°C). The number of patients aged ≥70 years was low (3.8%).	44

AE, adverse event; SAE, serious adverse event (grade 3); MenACWY, meningococcal group A, C, W, and Y conjugate vaccine. *by EMA or FDA (AZD122 so far only authorised in the UK, EMA/FDA approval was pending at submission of the manuscript).

mRNA vaccines has been tested in large phase III trials with more than 70,000 participants, which showed that COVID-19 could be prevented in up to 95% of cases while the remaining cases were mostly not severe. Adverse events such as fatigue and fever – considered typical vaccination reactions – occurred more frequently in vaccinated than in placebo recipients. The incidence and severity of such adverse events appear to be somewhat higher compared to seasonal influenza vaccines (reviewed in[40]). Importantly, the incidence of serious adverse events was similar in the vaccine and placebo recipients[42,43]

The third approved vaccine (AZD1222), known as the Oxford–AstraZeneca vaccine, is a replication-deficient chimpanzee adenovirus vector, containing the full-length, codon-optimised gene encoding the SARS-CoV-2 spike protein. To date, only interim data from a phase II/III trial are available, showing efficacy of more than 70% without a serious safety signal. Of note, a subgroup of patients in the UK received a lower initial vaccine dose followed by booster vaccination with the standard dose and showed 90% efficacy, whereas the standard regimen resulted in vaccine efficacy of only 62%.[44]

Despite the high number of study participants, only few patients with mild to moderate liver disease were included in the trials and patients with immunosuppressive conditions were excluded (reviewed in[18]). However, in real life, a substantial number of individuals have already been vaccinated worldwide, including patients with liver disease; thus, data on safety and effectiveness are expected to be available soon.

A frequently asked question which still awaits an answer is whether individuals should be vaccinated against SARS-CoV-2 after they have resolved the natural infection. The level of protection someone acquires from infection (so called "natural immunity") varies depending on the underlying disease and differs from person to person. To date, there is still no information about the duration of post-infection “natural” immunity, and, more importantly, despite the availability of new serologic assays, there is no established correlate of protection. This means that there are currently no standardised and validated data on SARS-CoV-2-specific immunity and the definition of serologic protection. Therefore, positive serology, even if detected 6 months or more after infection,[45] does not yet confirm whether convalescent patients have acquired long-term protection. Hence, serological testing prior to COVID-19 vaccination is not recommended at present although it remains optional. Meanwhile, patients with a known history of SARS-CoV-2 infection are not suggested to be prioritised. Other issues to be determined in future studies include the duration of vaccine-induced protection, the requirement for booster vaccination(s) and the level of protection against emerging SARS-CoV-2 variants. Further research is also needed on the development of a diagnostic serological assay to differentiate between a past or vaccine-induced immunity and acute infection.

Evolving recommendations for the emerging COVID-19 vaccines for patients with chronic liver diseases including hepatobiliary cancer

Cumulative experience supports the perception that prevention of inflammation and infection in patients with CLD is essential for improving survival.[1,46–48] Indeed, such patients are at high risk of hepatic decompensation and increased mortality and, in the case of SARS-CoV-2 infection, of the extrahepatic sequalae of severe COVID-19.[49,50] Of note, in the international registries SECURE-cirrhosis and COVID-Hep.net, hospitalised COVID-19 patients with cirrhosis had an overall case fatality rate of 38%, which was as high as 70% in Child-Pugh C patients, compared to 8% in non-cirrhotic patients, while mortality was similar in all age groups.[50]

Patients with hepatobiliary cancer need special consideration because, on the one hand, these patients usually have concomitant CLD or cirrhosis and, on the other hand, curative treatment options may be delayed in the case of COVID-19. Therefore, cancer patients should also be prioritised for vaccination against SARS-CoV-2, considering the phase of the malignant disease and therapy, age and comorbidity (see ESMO guidelines:[10]).

It is also notable that in this context, influenza and pneumococcal vaccines are recommended in patients with advanced liver disease despite concerns regarding somewhat reduced immunogenicity in this population (Table 1). Furthermore, influenza vaccination is considered safe and may prevent liver decompensation[51] and has been reported to reduce the risk of hospitalisation in patients with liver disease.[20]

In the past, the development of new vaccines has repeatedly raised concerns regarding vaccine-induced adverse effects including unconfirmed reactivation of occult autoimmune phenomena.[52–54] This argument was often linked to the use of distinct adjuvants (*i.e.* aluminum hydroxide, Toll-like receptor agonists or lipid emulsions) in the formulation of subunit and inactivated vaccines.[55] However, no such causal link has been unequivocally established,[56,57] even for adjuvanted vaccines containing AS03[58,59] or aluminum hydroxide or aluminum phosphate.[60] Although long-term safety data on SARS-CoV-2 vaccination in patients with liver disease are not yet available, it is important to weigh the predicted benefit of vaccination against the potential risk of vaccination, especially given the already known serious consequences of SARS-CoV-2 infection in at-risk populations. It goes without saying that with the introduction of new vaccines, it will be crucial to carefully monitor the safety and immune response to vaccination in patients with liver disease. Ideally, national and international prospective registries (preferably without regulatory hurdles) should be initiated as soon as possible. Meanwhile in view of the satisfactory short-term safety records of the newly licensed vaccines, prevention of SARS-CoV-2 infection through vaccination should receive appropriate priority in patients at risk.

In summary, there is currently no specific evidence to contradict the safety and generation of protective immunity by vaccines against COVID-19 in patients with CLD. Given the high risk of serious health consequences of SARS-CoV-2 infection in patients with cirrhosis and hepatobiliary cancer, the potential benefits of the vaccine, both to patients and to healthcare systems, are likely to outweigh the risks associated with vaccination. Thus, it is the opinion of the authors of the present communication that patients with CLD should be immunised against SARS-CoV-2 and patients with advanced cirrhosis, liver decompensation, and hepatobiliary cancer should be prioritised for COVID-19 vaccination. Finally, since the effectiveness of vaccination may be lower in these patients, immunisation against SARS-CoV-2 should be recommended to household members and healthcare professionals caring for these patients to reduce exposure to SARS-CoV-2. Meanwhile, current protective measures including use of masks, appropriate hand washing, and social distancing remain of great importance since it is not yet known whether vaccination confers sterilising immunity and prevents transmission from asymptomatic individuals.

Evolving recommendations for the emerging COVID-19 vaccines for liver transplant recipients

As a general rule and based on the available experience on vaccination of organ transplant patients against other pathogens, it is advised that liver transplant candidates be vaccinated prior to transplantation whenever applicable. In addition, it is important to note that phase III trials of current vaccine candidates have excluded organ transplant recipients and patients receiving immunosuppressive drugs (reviewed in[18]). Therefore, further clinical trials should include such patient populations. Consequently, the current recommendations for this particular risk group can at present only be based on theoretical considerations taking into account that immunogenicity and protective efficacy could potentially be lower in transplanted patients, depending on the intensity of immunosuppression.[27]

At the time of writing this article, it is too early to reach a judgement regarding the use of one type of vaccine or another. The COVID-19 vaccine platforms described here are mRNA vaccines and viral vector vaccines (Table 3). Certainly, there are open questions regarding the potential side effects, safety and long-term immunogenicity of these new

vaccines in the transplant population. Viral vector vaccines can be replication competent (*e.g.*, VSV-ZEBOV vector) or replication incompetent. The COVID-19 (chimpanzee) adenoviral vector vaccine (ChAdOx1-nCoV-19) is replication incompetent, which is reassuring when considering vaccination of the immunocompromised transplant recipient, in whom live attenuated vaccines are generally not advised.

Similarly, there may be concerns that highly immunogenic vaccines could lead to immune-mediated rejection. However, a meta-analysis of 8 prospective controlled trials showed no increased risk of rejection with standard vaccination compared with non-vaccinated controls.[31] This finding was supported by data from registry analyses.[31] In this context it is also important to mention reports that the risk for allograft rejection may be increased in the case of systemic or graft infection which could be prevented, for example, by vaccination.[61]

Until more and robust safety data on COVID-19 vaccination in immunosuppressed patients are available, the benefits and potential risks of vaccination should be weighed individually. Based on current experience, it appears that in patients after liver transplantation, immunosuppression by itself is not an independent risk factor for an unfavourable course of COVID-19, but that age and comorbidities determine individual risk,[62] and these risk factors are particularly prevalent in these patients. In the early post-transplant period, when immunosuppression is at its peak, the immune response is likely to be attenuated. Thus, vaccination at a later time (3–6 months after transplantation), when immunosuppression can be reduced, should be considered. Hence, vaccination of patients at risk cannot always be accomplished in a timely manner and given the reduced effectiveness of vaccination in transplanted patients, vaccination of household members is important and should be prioritised to minimise exposure to SARS-CoV-2. In this context it is also important to prioritise vaccination among healthcare professionals caring for immunocompromised patients. To date, there is insufficient data to suggest that vaccination against SARS-CoV-2 confers sterilising immunity, and it is unclear whether vaccinated individuals may still transmit SARS-CoV-2. Still, so far, data from the Moderna vaccine trial suggest some level of protection by the vaccine against shedding of the virus in the absence of symptoms and thus a lower potential for transmission (reviewed in[40]). Nonetheless, it is critical to continue general protective measures such as social distancing, hand washing, and wearing a mask until the current outbreak is under control.

Once COVID-19 vaccines are introduced in immunocompromised patients, it will be important to monitor the humoral and cellular immune response to the different vaccines (following the first and second dose) as well as the infection rates in this population.

Conclusion

In conclusion, the rapid development of several vaccines against SARS-CoV-2 within the last year is indeed a remarkable achievement. The already licensed COVID-19 vaccines are immunogenic, and the short-term safety record appears excellent in healthy individuals aged ≥16. Thus, based on current knowledge, there is no evidence to contradict the safety and immunogenicity of currently approved vaccines in patients with CLD, hepatobiliary cancer or in immunocompromised patients after liver transplantation. Given the high risk of serious health consequences of SARS-CoV-2 infection in such patients, the potential benefits of the vaccine, both to higher-risk patients and to healthcare systems, are likely to outweigh the risks associated with vaccination. We therefore recommend SARS-CoV-2 vaccination in patients with CLD, hepatobiliary cancer and candidates for liver transplantation, with prioritisation in patients with risk factors for severe COVID-19. The optimal timing of vaccination in transplanted recipients is still unestablished but vaccination 3–6 months after transplantation is advisable.

Summary of key interim recommendations*

- We recommend vaccination against SARS-CoV-2 for patients with chronic liver diseases and hepatobiliary cancer, as well as for liver transplant recipients.
- Among these patients, vaccination should be prioritised in
  - patients with cirrhosis or liver decompensation
  - patients with hepatobiliary cancer
  - patients with chronic liver diseases and risk factors for severe COVID-19
  - liver transplant recipients with risk factors for severe COVID-19.
- Vaccination against SARS-CoV-2 should be prioritised in household members of patients with cirrhosis, hepatobiliary cancer and liver transplant recipients, and in healthcare professionals caring for these patients.
- Prospective registries should be established as soon as possible to monitor safety, immunogenicity and effectiveness of different SARS-CoV-2 vaccines in patients with chronic liver diseases and transplant recipients.

**These recommendations will be reviewed periodically as further information becomes available.*

Conflict of interest

MC reports personal fees from Abbvie, personal fees from Gilead Sciences, personal fees from Merck Sharp & Dohme (MSD), personal fees from GlaxoSmithKline (GSK), personal fees from Janssen-Cilag, personal fees from Spring Bank Pharmaceuticals, personal fees from Novartis, from Swedish Orphan Biovitrum (SOBI), personal fees from Falk Foundation, grants and personal fees from Roche, outside the submitted work. PAG reports personal fees from Merck, Sharp & Dohme, personal fees from Biotest, personal fees from

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Author contributions statement

All authors have contributed to the review.

Supplementary data

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