COVID-19 vaccination in liver transplant recipients (Review)

AIKATERINI GKOUFA[1], MARIA SARIDAKI[2], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1], DEMETRIOS A. SPANDIDOS[3] and EVANGELOS CHOLONGITAS[2]

[1]Department of Infectious Diseases and COVID-19 Unit, and [2]First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 11527 Athens; [3]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion, Greece

Received March 3, 2023; Accepted April 26, 2023

DOI: 10.3892/etm.2023.11990

Abstract. Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) infection has significantly affected immunocompromised individuals and subsequently, liver transplant recipients (LTRs). Early in the course of pandemic, this vulnerable population was prioritized for vaccination, after obtaining encouraging data about the vaccination benefits on disease severity and mortality. As the published knowledge was mainly supported from studies which were limited to the healthy population, the present review summarizes the data from the literature on coronavirus disease 2019 (COVID-19) vaccination in LTRs and the available vaccination guidelines of international societies. The COVID-19 vaccination of LTRs is strongly recommended as a safe and effective measure in order to prevent severe disease and mortality.

Contents

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged as the most prominent public health concern. As a result, the medical community has been forced to confront extensive issues regarding protection against coronavirus disease 2019 (COVID-19), particularly in high-risk groups, such as solid organ transplant (SOT) recipients, including liver transplant recipients (LTRs) (1-3). Accordingly, since vaccination has become a principal tool with which to prevent the spread and severity of COVID-19, international and national health agencies have included transplant recipients in the priority groups for primary vaccination and booster doses. However, existing data on this field remain limited, as SOT recipients have been excluded from the approval trials for COVID-19 vaccines. Of note, recent studies have indicated that specific demographic and clinical characteristics of transplant recipients, such as an older age and the presence of renal disease, diabetes mellitus or other comorbidities, may have a greater adverse effect on the outcomes of patients with COVID-19, compared to the administration of immunosuppressants (4-7). The aim of the present review was to summarize the relevant literature on which, international health and scientific societies, such as the World Health Organization (WHO), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), based their recommendations regarding COVID-19 vaccination in the liver transplant setting.

2. Guidelines on COVID-19 vaccination from WHO, EASL and AASLD in immunocompromised patients and LTRs

Since December, 2020, following the first approval of the COVID-19 vaccine by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), ~50 vaccines have been approved worldwide, while >90 vaccines, based on different platforms (mRNA, recombinant DNA, protein subunits, nonreplicating viral vectors, inactivated viruses, viral-like particles, replicating viral vectors) are in phase III clinical trials (https://covid19.trackvaccines.org/vaccines/#approved). However, SOT recipients, as aforementioned, were excluded from the initial vaccine trials, leading to a knowledge gap concerning the efficacy and safety of COVID-19 vaccines in this specific population group (8). As a result, recommendations for SOT recipients and LTRs can only be based on the post-marketing data and considering the established risk of adverse outcomes of COVID-19 in individuals

Correspondence to: Professor Evangelos Cholongitas, First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: cholongitas@yahoo.gr

Key words: coronavirus disease 2019, coronavirus disease 2019 vaccine, liver transplant, vaccination

with significant comorbidities and/or immunosuppression (3). Table I presents the vaccines that have received WHO emergency use listing (EUL), and as no live replicating viral vector vaccines are available, all approved vaccines are acceptable for LTRs (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice). Table II summarizes the recommendations of EASL and AASLD for patients with chronic liver disease and LTRs (9,10).

Based on these guidelines, LTRs are strongly advised to complete the primary series of regionally available COVID-19 vaccines (three doses of mRNA vaccines, a single dose of adenovirus vector-based vaccines followed by a mRNA vaccine at least 28 days later, or two doses of protein subunit vaccines) (11) [https://www.aasld.org/covid-19-and-liver]. Moreover, due to the decline in the protective effects of the vaccines over time, the administration of booster doses is recommended to maintain immunity (12). In that case, a bivalent mRNA booster dose at least 2 months after the final vaccine dose is currently preferred (13). For LTRs with a recent SARS-CoV-2 infection, the time to receive the vaccine for COVID-19 is not restrictive, and current guidelines recommend a complete series of COVID-19 vaccines, either following a full recovery or 3 months following infection (11) (https://www.aasld.org/covid-19-and-liver).

Recommendations regarding LTR candidates are based on the general guidelines, which indicate that all vaccinations should be completed prior to transplantation (10) and, in the case that this is not feasible, vaccination should be performed 3-6 months following transplantation, when immunosuppression has been minimized, increasing the rates of sufficient seroconversion (13). In addition, based on the general recommendations regarding immunization, all close contacts of LTRs should complete a full vaccination schedule (3), and reasonably, this should include vaccination against SARS-CoV-2, contributing to herd immunity and providing an additional layer of protection for LTRs (13).

3. Clinical efficacy: Humoral and cellular responses

Humoral response. Based on the available systematic reviews and meta-analyses, the humoral response rates in LTRs have been found to range from 22.4 to 29.5% after the first dose and from 47.5 to 86.4% after the second dose of the COVID-19 vaccine (14-20) (Table III). Only one meta-analysis was found to focus exclusively on LTRs and measured anti-spike or neutralizing antibodies; the authors of that study confirmed that LTRs had lower seroconversion rates compared to healthy controls [risk ratio (RR), 0.80; 95% confidence interval (CI), 0.69-0.92, P<0.01], while the overall humoral immune response was 70% (95% CI, 0.68-0.77) after the second dose of the COVID-19 vaccine (mRNA, adenovirus vector-based, or inactivated) (14). As regards the efficacy of the third dose of the COVID-19 vaccine in the liver transplant setting, to the best of our knowledge, there is only one meta-analysis available including only three observational studies with 151 LTRs, which revealed a pooled seroconversion rate of 88% (95% CI, 58-98%) (15) (Table III).

The currently available studies evaluating serological response rates in LTRs after the third dose of COVID-19 vaccines (21-28) are summarized in Table IV. Notably, in all but two studies (27,28), it was found that >90% of the LTRs were seropositive after the third dose (Table IV). Nevertheless, data from the literature suggest that fully-vaccinated SOT recipients have more favorable outcomes with a milder course of COVID-19 infection and a reduced mortality rate, compared to unvaccinated or partially vaccinated SOT recipients (29-31), while only one study focused on LTRs found lower rates of severe COVID-19 infection and mortality in fully-vaccinated LTRs compared to unvaccinated control subjects (32). Based on these findings, the COVID-19 vaccination of LTRs is strongly recommended. As regards the preferable type of vaccine (mRNA, adenovirus vector-based, or protein subunit vaccines), although the optimal combination of primary series vaccine and booster doses has not yet been clarified, it has been suggested that mRNA vaccines may induce a stronger humoral immunity than inactivated vaccines (18,33). In addition, it appears that SOT recipients boosted with mRNA vaccines may achieve a higher specific humoral immune response than combining different types of SARS-CoV-2 vaccines (18,33). However, to the best of our knowledge, no study to date has evaluated this issue in the liver transplant setting.

A variety of factors have been found to be associated with the reduced responses of LTRs to COVID-19 vaccination, possibly reflecting differences in the baseline characteristics of the included cohorts. Nevertheless, the aforementioned meta-analysis assessing the efficacy of two doses of COVID-19 vaccines (14), indicated that the male sex, an older age, chronic kidney disease, obesity, the use of multiple immunosuppressants, high doses of steroids or mycophenolate mofetil (MMF), as well as vaccination during the first year following transplantation, were risk factors for a reduced immunogenicity. However, Luo *et al* (20) confirmed that MMF, the use of more than two immunosuppressants and diabetes mellitus were associated with a poor response to antibodies. These results suggest that the intensity of immunosuppression, as well as the presence of comorbidities, such as diabetes mellitus and chronic kidney disease, are risk factors associated with a lower immune response to vaccination in the liver transplant setting.

Cellular response. Although the T-cell immune response induced by COVID-19 infection appears to be comparable between LTRs and non-immunocompromised individuals (34), further clarification regarding this issue following COVID-19 vaccination is required. In addition, the accurate evaluation of cellular-mediated immunity has difficulties, which are related to the high costs and the need for the calibration of complex laboratory techniques. In three systematic reviews/meta-analyses investigating the immunogenicity of COVID-19 vaccines in immunocompromised individuals, including SOT recipients, lower cellular immune responses after the second or third dose of the COVID-19 vaccine were reported, compared to healthy controls (17,35,36). However, the presence or absence of interconnection between humoral and cellular immunity could not be assessed, since different laboratory methods to assess immunogenicity were used in the included studies. Of note, a recent meta-analysis including SOT and hematopoietic transplant recipients demonstrated that the third dose of the COVID-19 vaccine was associated with an increased cellular response (37). However, it should be mentioned that in all these meta-analyses, only a small proportion of LTRs were included,

Table I. COVID-19 vaccines with WHO emergency use listing.

Type of vaccine	Vaccine	Doses	Efficacy phase III data	Booster dose	Population
mRNA-based; RNA (embedded in lipid nanoparticles) encodes a variant of the SARS-CoV-2 spike protein	mRNA-1273 (Moderna)	Two doses, 4-8 weeks apart	Efficacy, 95%	One booster dose 4-6 months after the primary series; the WHO recommends a second booster dose 4-6 months after the first booster dose for the highest priority groups	General population ≥6 months old; approved for immunocompromised individuals
	BNT162b2 (BioNTech and Pfizer) vaccine	Two doses, 4-8 weeks apart	Efficacy, 94.1%	One booster dose 4-6 months after the primary series; the WHO recommends a second booster dose 4-6 months after the first booster dose for the highest priority groups	General population ≥6 months old; approved for immunocompromised individuals
Adenovirus vector-based; replication-deficient chimpanzee adenovirus vector, containing the full-length codon-optimized coding sequence of the SARS-CoV-2 spike protein	ChAdOx1-nCoV-19 vaccine (AstraZeneca/ University of Oxford)	Two doses, 8 to 12 weeks apart	Efficacy, 72% against symptomatic infection (efficacy with two standard doses, 62.1%; efficacy with low dose/standard dose, 90.0%)	One booster dose 4-6 months after the primary series; SAGE considers using a different type of COVID-19 vaccine for a third dose a more favorable option	General population ≥18 years old; approved for immunocompromised individuals
	Ad26.COV2-S vaccine (Johnson & Johnson)	Single dose (two dose regimen recommended, 2-6 months apart)	Single dose efficacy, 72%; double dose efficacy, 94%		General population ≥18 years old; approved for immunocompromised individuals
	CanSino Biologics Ad5-nCoV-S (recombinant) vaccine	Single dose	Efficacy of 58% against symptomatic disease; 92% against severe infection	One booster dose for the highest and high priority-use groups 4-6 months after completion of the primary series	General population ≥18 years old; approved for immunocompromised individuals
Inactivated vaccines; whole virus SARS-CoV-2 antigen inactivated and adjuvanted	Valneva (VLA2001) vaccine	Two doses, at least 28 days apart	Pending; accepted on immunogenicity data	4-6 Months after completion of the primary series for high priority groups	Aged 18-50 years; approved for immunocompromised individuals
	Bharat Biotech BBV152 COVAXIN	Two doses, 4 weeks apart; immunocompromised individuals should be offered an additional dose	Efficacy against COVID-19, 78%; efficacy against severe disease, 93%; efficacy in adults <60 years of age, 79%; adults >60 years, 68%	4-6 Months after completion of the primary series for the highest-risk groups	General population ≥18 years old; approved for immunocompromised individuals

Table I. Continued.

Type of vaccine	Vaccine	Doses	Efficacy phase III data	Booster dose	Population
	BBIBP-CoV (Sinopharm)	Two doses, 3-4 weeks apart (three doses for those aged >60 years)	Efficacy of 79% against symptomatic infection and hospitalization	4-6 Months after completion of the primary series	General population ≥18 years old; approved for immunocompromised individuals
	CoronaVac (Sinovac)	Two doses, 2-4 weeks apart (three doses for those aged >60 years)	Efficacy of 51% against symptomatic infection (100% against severe COVID-19, and 100% against hospitalization)	4-6 Months after completion of the primary series	General population ≥18 years old; approved for immunocompromised individuals
Protein subunit vaccines; recombinant SARS-CoV-2 spike protein nanoparticle administered as a coformulation with the adjuvant Matrix-M	Novavax (NVX-CoV2373)	Two doses, 8 weeks apart	Efficacy, 90%	One booster dose 4-6 months after the primary series; the WHO recommends a second booster dose 4-6 months after the first booster dose for the highest priority groups	Aged ≥12 years; approved for immunocompromised individuals

COVID-19, coronavirus disease 2019; WHO, World Health Organization; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table II. AASLD and EASL recommendations regarding COVID-19 vaccination for patients with chronic liver disease and liver transplant recipients.

Type of vaccine	Vaccine	Administration	Booster dose	Population
mRNA-based	mRNA-1273 (Moderna)	Three doses	Bivalent ≥2 months after primary series	Age, ≥6 months (Pfizer-BioNTech bivalent booster recommended for ages 12-17 years; Moderna or Pfizer-BioNTech bivalent booster recommended for ages ≥18 years)
	BNT162b2 (BioNTech and Pfizer) vaccine	Three doses	Bivalent ≥2 months after primary series	Age, ≥6 months (Pfizer-BioNTech bivalent booster recommended for ages 12-17 years; Moderna or Pfizer-BioNTech bivalent booster recommended for ages ≥18 years)
Adenovirus vector-based	Ad26.COV2-S vaccine (Johnson & Johnson)	Single dose followed by mRNA vaccine	Bivalent ≥2 months after primary series	Age, ≥18 years (mRNA primary vaccine series preferred whenever possible)
Protein subunit vaccines	Novavax (NVX-CoV2373)	Two doses	Bivalent ≥2 months after primary series	Age, ≥12 years

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; COVID-19, coronavirus disease 2019.

and no separate data regarding this subgroup were provided. Nevertheless, in the liver transplant setting, it appeears that there is a coordination between B- and T-cell-mediated immunity following vaccination (38), while a recent study indicated an adequate T-cell protection against severe COVID-19 infection, even in the absence of a sufficient humoral response (39).

4. Safety

Data on the safety of COVID-19 vaccines in the liver transplant setting had not been thoroughly examined prior to their approval, since LTRs were excluded from the approval trials for COVID-19 vaccines, while there was an urgent need to protect this group of patients against COVID-19-associated devastating outcomes. A main concern was the risk of graft rejection due to the potential vaccine-mediated immune system stimulation. Although pre-COVID-19 literature data had not revealed any association between the risk of graft rejection and the administration of various types of vaccines (40), hesitation regarding this issue may be reasonable for COVID-19 mRNA-based vaccines, since they represent a new technology platform. Of note, Bailey *et al* (37), in their meta-analysis, including 101 LTRs, reported no graft rejection, while generally mild adverse events (local pain at the injection site, fatigue, headache and myalgias) were recorded. Similarly, Efros *et al* (36), analyzing 913 SOT recipients, found no vaccine-related graft rejection episodes or other severe adverse events (36), apart from one biopsy-proven antibody mediated rejection episode in a heart transplant recipient, 7 days after the third dose of the mRNA vaccine, although no clear association with the administration of the vaccine was established. Nevertheless, the scenario of a possible graft rejection, triggered by COVID-19 infection, could further strengthen the consideration of vaccination as a protective measure against graft rejection (41). Finally, based on the available studies focused on LTRs, it appears that vaccination-attributable side-effects did not outweigh their tremendous benefits in reducing the risk of COVID-19 severity and mortality, while severe adverse events (i.e., grade 3 or 4), requiring medication or hospitalization, were very rare (including Bell's palsy, joint pain, fever, fatigue with headache and muscle pain) (14,15,29). These data are summarized in Tables and IV.

5. Future prospects

Since the COVID-19 pandemic is probably far from becoming endemic, and previous exposure to COVID-19 or vaccination do not offer long-term immunity, scientific societies need to continue to search for strategies with which to deal with COVID-19-related issues Further research is required, with consideration for immunocompromised individuals, as they have a more severe course of the disease and an increased risk of mortality. In fact, studies are required to target both prevention and treatment strategies for this specific population group. In line with this, it may be useful to include LTRs in clinical trials with novel vaccines, as well as in studies evaluating the efficacy and safety of the vaccines already on the market, as they were inadequately represented in the approval clinical trials. This strategy may improve the current knowledge regarding the immunogenicity of COVID-19 vaccines, facilitate the design of more effective vaccines, and at the same time, reduce the reluctance to vaccination. Similarly, observational bias was met in the field of antivirals, monoclonal antibodies and anti-inflammatory regimens, where most effectiveness and safety data were derived mainly from studies that recruited healthy individuals (42,43). By contrast,

Table III. Published meta-analyses providing data for COVID-19 vaccination in LTRs.

First author	Country	No. of SOTs	No. of LTRs	Type of vaccine	%, Seroconversion rate after 1st dose in LTRs	%, Seroconversion rate after 2nd/3rd dose in LTRs	Cellular response rate in LTRs	Side-effects	(Refs.)
Yoo	Korea	-	2,416	mRNA	NA	70/-	NA	Overall incidence, 68%; 1 patient with Bell's palsy and 6 patients with joint pain/fever, fatigue/ headache/muscle pain requiring hospitalization	(14)
Cheung	China	-	2,147	mRNA (15 studies), inactivated vaccines (four studies)	NA	69/88	2nd dose, 65%	Pooled prevalence, 63%; 17 subjects with severe systemic side-effects or requiring medications (grade 3), one subject requiring hospitalization (grade 4)	(15)
Tang	China	15,328	2,734	mRNA	22.4	60.8/-	NA	No cases of acute rejection, allograft dysfunction or allograft; failure, pain (~47-63%) swelling (~9%) being the main local reactions, fatigue (~23%) and headache (~7%) being the main systemic reactions	(16)
Meshram	India	15,391	1,434	BNT162b2,	NA	67/-	NA	NA	(17)
Chen	China, Germany	11,886	1,946	mRNA-1723, ChAdOx1nCoV-19, inactivated whole virus vaccine	29.5	64.5/-	2nd dose, 66.3%	NA	(18)
Sakuraba	USA	6,158	NA	mRNA, inactivated vaccine, recombinant vector	NA	47.5 (from one study, 80 LTRs)/-	NA	NA	(19)
Luo	China, Germany	-	1,700	mRNA, AD26. COV2.S, ChAdOx1 nCoV-19	NA	66/-	2nd dose, 71%	NA	(20)

LTRs, liver transplant recipients; LT, liver transplantation; SOT, solid organ transplant; NA, not applicable.

Table IV. Published studies with available data on serological response after the third dose of the COVID-19 vaccine in LTRs.

First author, year of publication	Type of study	Country	N, LTRs	N, Responders LT 3rd dose, (%)	Time from LT, years	Time between 2nd and third dose, days	Type of vaccine	Safety	(Refs.)
Chauhan[a], 2022	Prospective	USA	45	41 (91.1%)	-	164	mRNA (Pfizer/Moderna) or Johnson & Johnson vaccine	No severe side-effects/ most common pain at the injection site (43%) and fatigue (11%)	(21)
Strauss, 2021	Prospective	USA	148	138 (93.2%)	6 (2-13)	169 (149-188)	Pfizer-BioNTech BNT162b2 mRNA or mRNA-1273; Moderna	-	(22)
Davidov, 2022	Prospective	Israel	61	60 (98.3%)	7 (4-18)	-	Pfizer-BioNTech BNT162b2 mRNA	Only mild side-effects (37% local pain, fatigue)	(23)
Odriozola, 2022	Prospective	Spain	129	125 (96.8%)	7 (4-12)	4 Months (133-139)	mRNA-1273; Moderna	-	(24)
Harberts A, 2022	Prospective	Germany	106	97 (91.5%)	8.8 (2.6-14.8)	157 (127-188)	Pfizer-BioNTech BNT162b2 mRNA or mRNA-1273; Moderna	Only mild side-effects; 60% local side-effects; 35% fatigue	(25)
Toniutto, 2023	Prospective	Italy	107	98 (91.5%)	91 (48-189) months	6 Months (165±4)	Pfizer-BioNTech BNT162b2 mRNA	No safety concerns, 11% local side-effects	(26)
Sriphoosanaphan, 2022	Prospective	Thailand	89	81.3-94.7%[b]	5.7 (2.5-11.8)	86 (81-94)	ChAdOx1 (AstraZeneca, Cambridge, UK)/ChAdOx1] or heterologous [ChAdOx1/ BNT162b2 (Pfizer Biotech, New York, NY, USA)] as primary vaccine protocol, booster dose of mRNA-1273 (Moderna, Cambridge, MA, USA) three months following the standard two-dose vaccine series	No graft rejection or severe AEs were noted	(27)
Perrier, 2022	Retrospective	France	291	89.1%	6.7 (3-11.2)	42 (31-74.3)	mRNA (BNT162b2)	-	(28)

Data are presented as the mean (± standard deviation), or median (interquartile range). [a]Three LTRs in the study received a viral vector vaccine as booster dose; [b]response rates were ranging depending on the different types of primary vaccine regimens. LTRs, liver transplant recipients; LT, liver transplantation; AE, adverse event.

evidence regarding LTRs remains limited and is based only on case reports and case series, indicating the need for future large-scale observational studies. Additionally, the antibody cut-off levels after vaccination for offering protection against severe forms of COVID-19 and the rates of the decline of antibody titers stress the need for further research in the form of well-designed studies. Finally, as regards the neglected, yet crucial component of T-cell immunity triggered by vaccination, a better understanding and accurate evaluation of the vaccine-induced cellular response and its interaction with humoral immunity may lead to the introduction of novel strategies for vaccine development.

6. Conclusion

Since the emergence of the COVID-19 pandemic, overwhelming scientific research has aimed to shed light on a previously unknown disease. Its therapeutic management has evolved from symptomatic treatment to the recently approved antiviral and immunomodulatory agents, while the protective measures of tracing, distancing, isolation, and contact precautions were reinforced with monoclonal antibodies and vaccines. However, as evolution concerns not only the scientific knowledge, but also the virus itself due to new and more contagious mutations, researchers have to face further challenges and perform further studies in order to develop effective tools and strategies, particularly for combating the severe forms of COVID-19 in the most fragile population of immunocompromised individuals, improving their survival and well-being.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AG and EC conceptualized the study. VEG, MS, AG, DAS and EC analyzed the data from the literature to be included in the review, and wrote and prepared the draft of the manuscript. EC and AG provided critical revisions. All authors contributed to manuscript revision and have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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