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Correspondence

Clinical update on the efficacy of anti-SARS-CoV-2 mRNA vaccines in patients on the waiting list for liver transplantation and in liver transplant recipients

Dear Editor,

The efficacy of full course of anti-SARS-CoV-2 mRNA vaccines (BNT162b2 e mRNA-1273) in protecting immunocompetent patients from symptomatic-severe Coronavirus disease-2019 (COVID19) is documented in more than 95% of cases [1,2]. However, in patients on the waiting list for liver transplantation and in liver transplant recipients, the efficacy of anti-SARS-CoV-2 vaccination seems to be inadequate in a consistent proportion of cases. This document, drafted by the expert panel of transplant hepatologists appointed by the Italian Association for the Study of the Liver (AISF), aims to present the updated scientific data on the efficacy of anti-SARS-CoV-2 mRNA vaccines in patients on the waiting list or after liver transplantation. Furthermore, the panel's expert opinion about several critical questions regarding the timing of administration of the second dose of vaccine after liver transplantation in subjects who received the first dose during the waiting list period, the vaccination of patients undergoing liver transplantation with a previous recovered COVID-19, and the possible option to administer a third "booster" vaccination dose in patients without antibody response at the end of the full vaccination course will be presented. At the time of preparation of this report, 5 research articles exploring the antibody response to a full schedule (two-doses) of anti-SARS-CoV-2 vaccination in patients undergoing solid organ transplantation have been published [3–7]. However, only two of them evaluated the antibody response at the end of the full course of BNT162b2 or mRNA-1273 antiSARS-CoV-2 vaccines, in a total of 158 liver transplant recipients [3,4] (Table 1). The cumulative data derived from these studies, showed that a reduced antibody response following the full course of vaccination, ranging from 31% to 47.5%, was observed in liver transplant recipients. In the study by Boyarsky et al. [3], the antibody response was significantly higher following the mRNA-1273 vaccine compared to the BNT162b2 vaccine (22% vs 8%, $p < 0.001$), although the data were not available for single types of solid organ transplantation. In the recent study [4] that enrolled 80 liver transplant recipients, who received the BNT162b2 vaccine, the antibody response was detectable in only 47.5% of cases. Older age, impaired renal function, and immunosuppressive therapy with three drugs and/or containing mycophenolate, were associated with a significantly reduced antibody response. No data regarding the timing of the administration of the second dose of anti-SARS-CoV-2 vaccine in liver transplant patients, in whom the first dose was administered during the waiting time on the list, are available yet. The American Society for the Study of the Liver [8] recommends administering the second vaccine dose as soon as possible after liver transplant (starting from the sixth post-transplant week). This recommendation is based on the empirical presumption that within this time the drug-induced immunosuppression may be not yet complete, therefore the immunological response to vaccination may be more efficient. In the absence of solid data on the clinical significance of the anti-SARS-CoV-2 antibodies in immunocompromised patients recovered from COVID-19, the optimal timing to carry out vaccination in these patients is the result of expert opinions and government provisions. It is recommended that patients on liver transplant waiting list, with a documented COVID-19 recovered, should be vaccinate with two doses of anti-SARS-CoV-2 mRNA vaccines, only after the complete disappearance of the clinical manifestations of the disease and after the end of the isolation period [9]. If the COVID-19 has been treated with monoclonal antibodies or plasma from convalescent patients, vaccination should be delayed for at least 90 days from the end of the above therapies [9].

It has been demonstrated that patients treated with azathioprine, methotrexate, or mycophenolate mofetil, developed a lower antibody response to the second vaccination dose of mRNA anti-SARS-CoV-2 vaccines, compared to patients on monotherapy with calcineurin or mammalian target rapamycin (mTOR) inhibitors. In the study by Boyarsky et al. [3], among the 473 patients treated with mycophenolate, 38 (8%) had antibody response after the first dose and 268 (57%) had no antibody response after the second dose of vaccine. Of the 185 participants who did not receive immunosuppression with mycophenolate or mTOR inhibitors, 60 patients (32%) had an antibody response after the first dose and 72% after the second dose of vaccine. Therefore, in transplanted patients receiving anti-SARS-CoV-2 vaccination, it can be assumed that for those treated with mycophenolate mofetil, azathioprine, high-dose of steroids (prednisone $>$ 40 mg/daily for more than 15 days) or treated with chemotherapy causing lymphopenia, a vaccination schedule based on three doses of vaccine rather than two standard doses may be advisable. Some European scientific societies have proposed a 4-week interval between the second and third dose of the BNT162b2 and mRNA-1273 vaccines [10]. In the Canadian clinical trial currently under enrollment (clinicalTrials.gov NCT04885907) a third dose of mRNA-1273 vaccine is planned 8 weeks after the second dose for all patients, regardless of the type of anti-rejection therapy. To date, there are no indications as to whether it is advisable or not to suspend/reduce the dose of immunosuppressive drugs, particularly mycophenolate, in the periods preceding and/or immediately following the administration of the booster dose of the vaccine, as this strategy may be potentially associated with an increased risk of graft rejection. A very recent report [11] evaluated the efficacy of the third administration of anti-SARS-CoV-2 vaccine on a series of 30 solid organ transplanted patients (3 liver transplanted), who had either a suboptimal or lack of antibody response to the previous vaccination course with two doses of mRNA vaccines. In 25/30 patients, immunosuppressive

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Table 1
Clinical studies evaluating the antibody response to a full course (two doses) of anti-SARS-CoV-2 vaccines in solid organ transplant recipients. Only reports that have been published in extenso in peer-reviewed scientific journals are cited.

Author	Organ	N. of patients	Median age (years)	Median transplant-to vaccination interval (months)	Vaccine type	Type of serological test employed———Days between the second vaccine dose and evaluation of the antibody response	Antibody response rate	Positive predictors of antibody response
Boyarsky et al. [3]	SOT	658	-	-	mRNA1273 BNT162b2	Euroimmun® Roche Elecsys® ——— 28 to 31	Overall: 54% LT: 32%	• Younger age • Liver transplantation • Longer time since transplantation • Immunosuppression without mycophenolate • mRNA1273 vaccine
Rabinowich et al. [4]	Liver	80	60	60	BNT162b2	Liason S1/S2 IgG® ——— 10 to 20	47.5%	• Younger age • Normal kidney function • Low dosage of steroids • Immunosuppression without mycophenolate
Peled et al. [5]	Heart	77	62	89	BNT162b2	IgG anti RBD (“*in house*” ELISA) ——— 21	57%	• Immunosuppression without mycophenolate
Shostak et al. [6]	Lung, heart	168	60.5	>12 in 90% of cases	BNT162b2	Abbott® ——— 14-21	18%	• Younger age • Immunosuppression without mycophenolate and/or mTOR
Grupper et al. [7]	Kidney	136	58.6	39.2	BNT162b2	Liason S1/S2 IgG® ——— 14-21	37.5%	• Younger age • Immunosuppression without mycophenolate and/or mTOR • Low dose of steroids

SOT: solid organ transplantations; LT: liver transplanted; S1/S2 IgG: immunoglobulin G antibodies against subunits S1 and S2 of the SARS-CoV-2 spike protein; IgG anti RBD: Immunoglobulin G antibodies against Receptor Binding Domain of the SARS-CoV-2 spike protein; ELISA: enzyme-linked immunosorbent assay; mTOR: mammalian target of rapamycin.

therapy was maintained with cyclosporine or tacrolimus in combination with mycophenolate, while steroids were maintained in 24/30 patients. The third dose of anti-SARS-CoV-2 vaccine (in 15 patients with Ad26.COV2.S viral vector vaccine, in 9 with mRNA-1273 vaccine and in 6 with BNT162b2 vaccine) was administered at a mean interval of 67 days after the second dose, and the evaluation of the antibody response was performed at a median interval of 14 days. In the 6 patients who presented a low antibody response to the previous two doses of vaccine, the administration of the third dose was associated with a significant increase of antibody response. On the contrary, the third dose of vaccine elicited an antibody response in only 6/24 (25%) of the patients in whom the two doses of vaccine did not induce the antibody response. In 2/24 (8%) patients, only a weak antibody response, and in 16/24 (67%) patients no antibody response was recorded. It should be noted that in this study the type of vaccines used was very heterogeneous, and the small number of patients enrolled did not allow to evaluate the independent predictors of the development of antibody response following the third dose of vaccine. Moreover, no clear indications to identify a potential higher efficacy of a vaccine over others can be deduced. The antibody response to three doses of an mRNA anti-SARS-CoV-2 vaccine has been also recently evaluated in a group of 101 solid organ transplant recipients (12 liver transplanted) [12]. The mean time interval between transplantation and vaccination was 97 months. In 87% of patients immunosuppression included steroids, in 79% calcineurin inhibitors, in 63% mycophenolic acid, in 30% mTOR inhibitors, and belatacept in 12% of cases. The antibody response was detectable in 40% of the patients before the third dose of vaccine and in 68% of the patients 4 weeks after the third dose. Among the 59 patients who had been seronegative before the third dose, 26 (44%) became seropositive 4 weeks after the third dose. Older recipient age, higher levels of immunosuppression, and a lower estimated glomerular filtration rate, were the independent factors associated with poor antibody response to the third dose of vaccine. The aforementioned studies demonstrated that the third dose of anti-SARS-CoV-2 vaccine in solid organ transplant recipients, who do not have a clinically significant antibody response to the full course of vaccination, may increase the percentage of patients developing a significant antibody response by approximately 44%. Mycophenolate therapy remains an independent predictor of failure to develop an antibody response after vaccination. This suggests that the modification of immunosuppressive therapy in the immediate pre and post vaccination period may be hypothesized in the future to increase the number of recipients who can benefit from anti-SARS-CoV-2 vaccination. At the present time, the available data justify the administration of a third dose of anti-SARS-CoV-2 vaccine, especially in liver transplant recipients who have had a weak or absent antibody response to the full two-doses of vaccination course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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