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ORIGINAL ARTICLE

Antibody response to the messenger RNA-1273 vaccine (Moderna) in liver transplant recipients

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Abstract

Different reports have shown the clinical and serologic response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines in preventing coronavirus disease 2019 (COVID-19) in the general population, but few studies have examined these responses in transplant recipients. We assessed the vaccine immunogenicity of two doses (100 μg) of the mRNA-1273 vaccine (Moderna) administered with a 28-day interval in liver transplant recipients (LTRs) at follow-up at the Marques de Valdecilla University Hospital. LTRs without a history of COVID-19 infection were tested for SARS-CoV-2 immunoglobulin G (IgG) antibodies directed against the spike protein (S) a median of 43 days after receiving the second Moderna vaccine dose. Clinical data, including immunosuppressive regimen and routine laboratory data, were obtained from the medical record of each patient up to 3 months before the date of the first vaccination. Factors associated with serologic response were evaluated through logistic regression. In total, 129 LTRs who had anti-S results were included. Most patients were men (n = 99; 76.7%) with a median age of 63 years (interquartile range, 56–68). Alcohol (43.4%) and chronic hepatitis C (18.6%) were the most frequent causes of liver transplantation. A positive anti-S IgG response was observed in 113 LTRs (87.6%; 95% confidence interval [CI], 80.8–92.2). A strong inverse relationship between mycophenolate mofetil use and serologic response was found (odds ratio, 0.07; 95% CI, 0.02–0.26; $p = 0.001$). *Conclusion:* Most LTRs develop an immunological response to the Moderna SARS-CoV-2 mRNA-based vaccine. An immunosuppressive regimen that includes mycophenolate predicts a weak serologic response.

INTRODUCTION

Several vaccines have been designed against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, with different mechanisms of action. The major target for most vaccines is the viral spike protein and its receptor-binding domain interaction with human angiotensin-converting enzyme 2 receptor, which is the mechanism of viral entry into human epithelial cells.[1] In the specific case of the messenger RNA (mRNA) SARS-CoV-2 vaccines, they are based on synthetic mRNA that encodes a variant of the spike glycoprotein, which is encapsulated in lipid nanoparticles for efficient delivery. The safety and efficacy of the mRNA SARS-CoV-2 vaccines (Moderna and Pfizer/BioNTech) among the general population has been demonstrated in several clinical trials, with protection rates as high as 95%.[2–4]

Solid organ transplant recipients (SOTRs) were excluded from these clinical trials, and therefore efficacy, durability, and safety data are scarce for this population. The occurrence of severe and fatal cases of corona virus disease 2019 (COVID-19) in some vaccinated transplant recipients suggests a suboptimal humoral response.[5–7] In fact, recent published data showed markedly attenuated antibody responses and low antibody titers in SOTRs after two doses of an mRNA vaccine against SARS-CoV-2 (18%-59%), with a relative difference in responses between the Pfizer/BioNTech and Moderna vaccines that resulted in less frequent antibody responses in SOTRs receiving the Pfizer/BioNTech vaccine.[8–13]

Recently, results of Pfizer/BioNTech vaccination in liver transplant recipients (LTRs) have been reported. In this Israeli study,[14] 80 LTRs and 25 healthy controls were included. Results showed that only 47.5% of the LTRs had a positive serology 10–20 days after receiving the second dose and that antibody titers were significantly lower than in healthy subjects.[14]

In Cantabria (northern Spain), the LTR vaccination campaign was started in April 2021. Most LTRs received the Moderna vaccine at the Preventive Medicine Department of the Marqués de Valdecilla University Hospital. The aim of the present study was to evaluate the antibody response following two doses (100 μg) of the mRNA-1273 vaccine (Moderna) with a 28-day interval in LTRs.

MATERIALS AND METHODS

Study design and population

We retrospectively included all LTRs undergoing regular follow-up at the Liver Transplant unit of our hospital (Marqués de Valdecilla University Hospital) and who had received two doses of the mRNA-1273 COVID-19 vaccine (Moderna) administered in the deltoid region following the standard protocol, between April 14 and May 18, 2021.

Combined liver and renal transplantation, prior or current diagnosis of COVID-19, having received a different vaccine against SARS-CoV-2, and not having the antibody quantification test result before August 1, 2021, were considered criteria for exclusion.

Clinical data, including comorbidities and the immunosuppressive regimen, were obtained from the medical records of each LTR as were routine blood tests up to 3 months before the date of the first vaccination. Definition and classification of chronic kidney disease were performed according to Kidney Disease: Improving Global Outcomes (KDIGO) recommendations.[15]

The study was approved by the Institutional Ethics Committee of Cantabria (internal code, 2021.272) and complied with the provisions of the Good Clinical Practice guidelines and Declaration of Helsinki.

SARS-CoV-2 antibodies test

Antibody response was semiquantitatively assessed using serum samples analyzed on the Alinity i platform (Abbott Laboratories) using the SARS-CoV-2 anti-spike protein immunoglobulin G (IgG) II assay. Following manufacturer guidelines, titers >50 arbitrary units (AU)/mL were interpreted as positive (detection range, 6.8–80.000 AU/mL; positive agreement, 92.9%; negative agreement, 99.9%). Results of this assay have been shown to correlate with *in vitro* neutralization of SARS-CoV-2.[16]

Statistical analysis

Quantitative variables were expressed as mean (SD) or median (range or interquartile range [IQR]) according to data distribution and qualitative variables as absolute value and proportions. Comparisons between groups were performed with the unpaired Student *t* test, Mann-Whitney U test, or Fisher's exact test, as appropriate. Adjusted association with serologic response was investigated with logistic regression analysis by introducing variables that were related to the latter in a univariate analysis ($p < 0.1$) or that were considered clinically significant regardless of the *p* value. The maximum number of variables included in the multivariable analysis was one per 5–10 outcomes. The strength of the association of each variable with the response was estimated with the odds ratio (OR) with its 95% confidence interval (CI). Statistical significance was defined as $p < 0.05$. Statistical analysis was performed with IBM SPSS Statistics v22.0 for Apple Macintosh (IBM Corp, Armonk, NY).

RESULTS

Baseline characteristics

During the study period, 166 LTRs received two doses of the Moderna vaccine. A total of 37 patients were excluded from the analysis (7 patients with combined liver and renal transplantation; 3 patients with prior COVID-19 infection; and 27 patients without an antibody quantification result). Therefore, 129 LTRs were included in this study; their baseline characteristics are summarized in Table 1. All patients were Caucasian, and most patients were men (n = 99; 76.7%) with a median age of 63 years (IQR, 56–68). Alcohol (56; 43.4%) and chronic hepatitis C (24; 18.6%) were the most frequent etiologies, being the decompensation of cirrhosis (61; 47.3%), which is the main indication for liver transplantation, followed by hepatocellular carcinoma (52; 40.3%).

Comorbidities were common in LTRs, with 94.9% diagnosed with at least one comorbidity, such as arterial hypertension (78; 60.5%), diabetes (47; 36.4%), or chronic kidney disease (46; 35.9%).

Regarding immunosuppressive therapy before vaccination, calcineurin inhibitors (CNIs) were used as the backbone of the immunosuppressive regimen in 115 LTRs (89.1%). Everolimus was used in 10 LTRs (7.8%), and mycophenolate mofetil (MMF) was used in 32 LTRs (24.8%), 8 of whom received the latter as monotherapy. Mean CNIs and everolimus serum levels and mean daily MMF dose are presented in Table 1.

Antibody response and titers after SARS-CoV-2 vaccination

The median time between liver transplantation and vaccination was 7.0 years (IQR, 4–12). Serum samples for SARS-CoV-2 IgG antibodies were tested in a median of 43 days (IQR, 37–49) after the second intramuscular vaccination dose.

A positive antibody response was observed in 113 LTRs (87.6%; 95% CI, 80.8–92.2), while 16 patients remained negative (12.4%; 95% CI, 7.8–19.2). Among LTR responders, median titers of anti-spike 1 IgG were 4792.0 AU/mL (IQR, 1414.0–14,390.0 AU/mL). Comparison of the clinical and laboratory data of LTRs with positive and negative response to the Moderna vaccine is presented in Table 1. Age and sex distribution, cause of liver disease, and indication for liver transplantation were similar in both groups. No association was found between posttransplant time and serologic response. Patients who did not have an antibody response presented chronic kidney disease more frequently (68.8%; 95% CI, 44.4%–85.9% versus 31.0%; 95% CI, 23.2%–40.0%; p = 0.003) than responders and higher mean serum creatinine levels (1.4; 95% CI, 1.1–1.7 versus 1.1; 95% CI, 1.0–1.1 mg/dL; p = 0.005). Nonresponse was also associated with MMF treatment (75%; 95% CI, 50.5%–89.8% versus 17.7%; 95% CI, 11.8%–25.8%, p = 0.001) and a higher dose of MMF (Table 1). Moreover, the mean absolute count of leukocytes and lymphocytes was lower in nonresponders (leukocytes × 10^3/μL, 4.8; 95% CI, 4.0–5.7 versus 6.2; 95% CI, 5.8–6.5; p = 0.007 and lymphocytes × 10^3/μL, 1.3; 95% CI, 0.8–1.8 versus 1.8; 95% CI, 1.7–1.9; p = 0.001). Finally, the ratio of leukocytes to lymphocytes showed an inverse relationship with antibody response (nonresponders, 4.6; 95% CI, 3.3–5.8 versus responders, 3.7; 95% CI, 3.4–3.9; p = 0.04).

In the multivariate analysis, an immunosuppressive regimen containing mycophenolate (OR, 0.08; 95% CI, 0.02–0.29; p = 0.001) was the factor most strongly associated with an absence of a serologic response (Table 2). Although the absolute lymphocyte count was also associated with the immune response, the effect turned out to be practically neutral (OR, 1.0; 95% CI, 1.0–1.0; p = 0.046).

When we divided responders into low and high responders based on a more conservative threshold of >4160 AU/mL (that has been shown to have 95% concordance with the gold-standard plaque reduction neutralization test [PRNT]),[17,18] only the fact of having received MMF was (inversely) associated with the response (OR, 0.26; 95% CI, 0.09–0.8; p = 0.024).

At the time of writing this article, 3 patients who had received the complete vaccination schedule presented a SARS-Cov-2 infection during follow-up, a median of 235 days (range, 203–238 days) after the second dose. Only 1 patient required hospitalization because of concurrent cholangitis related to a biliary anastomosis stricture. None of these patients developed respiratory or other COVID-19-related symptoms.

DISCUSSION

This study evaluated the serologic response of LTRs to the mRNA SARS-CoV-2 Moderna vaccine in a real-life scenario. The Moderna vaccine induced a serologic response in 87.6% of LTRs.[8–13] In addition, the use of an immunosuppressive regimen containing MMF predicted a poor serologic response.

Recent data evaluating Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine immunogenicity in LTRs have shown protective levels of antibodies ranging between 47.5% and 79%.[14,19,20] The serologic response found in our study to the Moderna vaccine in LTRs (87.6%) indicates a good antibody response, and these results are in line with those recently published by Strauss et al.[21] in LTRs. Even so, response rate and antibody titers continue to be lower than those achieved in the general population.[2–4] This variable antibody response to different vaccines in LTRs may reflect

TABLE 1 Baseline characteristics of LTRs and comparison of LTRs with positive- and negative-SARS-CoV-2 IgG serology

Variables	All LTRs (n= 129)	Seropositive (n= 113)	Seronegative (n= 16)	*p*
Age, years; median (IQR)	63 (56–68)	63 (56–68)	63.5 (52.8–68)	0.71
Sex (male)	99 (76.7)	88 (77.8)	11 (68.8)	0.42
Race (Caucasian)	129 (100)	113 (100)	16 (100)	–
Etiology of liver disease				0.16
Alcohol	56 (43.4)	50 (44.2)	6 (37.5%)	
HCV	24 (18.6)	22 (19.5)	2 (12.5)	
Alcohol + HCV	12 (9.3)	12 (10.6)	0 (0)	
Other	37 (28.7)	29 (25.7)	8 (50)	
Transplant indication				0.37
Hepatocellular carcinoma	52 (40.3)	48 (42.5)	4 (25)	
Decompensated cirrhosis	61 (47.3)	52 (46)	9 (56.3)	
Other	16 (12.4)	13 (11.5)	3 (18.8)	
Interval since transplantation, years; n (%)				0.07
<1	8 (6.2)	5 (4.4)	3 (18.8)	
1–3	15 (11.6)	13 (11.5)	2 (12.5)	
3–6	30 (23.3)	28 (24.8)	2 (12.5)	
6–11	29 (22.5)	28 (24.8)	1 (6.3)	
>11	47 (36.4)	39 (34.5)	8 (50)	
ABO group				0.93
A	53 (51)	48 (50.5)	5 (55.6)	
B	8 (7.7)	7 (7.4)	1 (11.1)	
AB	2 (1.9)	2 (2.1)	0 (0)	
0	41 (39.4)	38 (40)	3 (33.3)	
Previous medical history				
Hypertension	78 (60.5)	68 (60.2)	10 (62.5)	0.86
Diabetes	47 (36.4)	39 (34.5)	8 (50)	0.23
Chronic kidney disease	46 (35.9)	35 (31.0)	11 (68.8)	0.003*
Cardiovascular disease	34 (26.4)	33 (29.2)	1 (6.3)	0.051
Chronic lung disease	12 (9.3)	12 (10.6)	0 (0)	0.17
Immunosuppressive regimen				0.001*
Without mycophenolate	97 (75.2)	93 (82.3)	4 (25)	
Monotherapy [CNI/imTOR]	91 [85/6] (70.5)	89 [83/6] (78.8)	2 [2/0] (12.5)	
Association with CNI[a]	6 (4.7)	4 (3.5)	2 (12.5)	
With mycophenolate	32 (24.8)	20 (17.7)	12 (75)	
Monotherapy	8 (6.2)	2 (1.8)	6 (37.5)	
Association with CNI	24 (18.6)	18 (15.9)	6 (37.5)	
Immunosuppression, dose in mg; mean (SD)				
Mycophenolate (n = 32)	1093.8 (482.6)	875.0 (222.1)	1458.3 (582.3)	0.003*
Prednisone (n = 3)	4.2 (2.9)	5 (3.5)	2.5	0.48
Immunosuppression, trough concentration µg/L; mean (SD)				
Cyclosporine (n = 12)	66.9 (33.9)	66.9 (33.9)	-	-
Tacrolimus (n = 103)	4.9 (1.4)	4.9 (1.4)	5.1 (2.1)	0.56
Everolimus (n = 10)	4.8 (1.6)	4.9 (1.24)	4.6 (3.7)	0.02*

TABLE 1 (Continued)

Variables	All LTRs (n= 129)	Seropositive (n= 113)	Seronegative (n= 16)	*p*
Laboratory parameters, mean (SD)				
Hemoglobin (g/dL)	14.1 (1.8)	14.1 (1.8)	13.4 (1.9)	0.78
Platelets (×10^3/μL)	172.5 (56.9)	174.5 (57.3)	158.6 (54.4)	0.48
Leukocytes (×10^3/μL)	5.9 (1.8)	6.2 (1.8)	4.8 (1.6)	0.007*
Lymphocytes (×10^3/μL)	1.7 (0.7)	1.8 (0.7)	1.3 (0.9)	0.001*
Ratio Le/Ly	3.8 (1.5)	3.7 (1.3)	4.6 (2.4)	0.04*
eGFR (mL/minute/1.73 m^2)	70.1 (18.5)	71.9 (17.3)	58 (22.4)	0.02*
Serum creatinine (mg/dL)	1.1 (0.4)	1.1 (0.3)	1.4 (0.5)	0.005*
Serum albumin (g/dL)	4.4 (0.3)	4.4 (0.3)	4.5 (0.2)	0.13
Days between vaccine and serologic test, median (IQR)	43 (37–49)	43.0 (37.0–50.5)	42 (37.0–47.8)	0.48

Note: Qualitative variables are expressed as n (%).

Abbreviations: CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IgG, immunoglobulin G; imTOR, mammalian target of rapamycin inhibitors; IQR, interquartile range; Le/Ly, ratio leukocytes/lymphocytes; LTR, liver transplant recipient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]CNI was associated with prednisone, imTOR, or both.

*Levels are significant.

TABLE 2 Factors associated with the serologic response to the SARS-CoV-2 vaccine

	Univariant		Multivariant	
Variable	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (increase by year)	1.1 (0.9 –1.1)	0.16		
Time since transplantation (increase by year)	1.0 (0.9–1.1)	0.86		
Immunosuppressive regimen (reference, without mycophenolate)	0.07 (0.02–0.25)	0.001	0.08 (0.02–0.29)	0.001
Mycophenolate dose (increase by mg)	1.0 (1.0–1.0)	0.001		
Tacrolimus trough concentration (increase by μg/L)	0.9 (0.6–1.4)	0.71		
Everolimus trough concentration (increase by μg/L)	1.1 (0.4–3.1)	0.84		
Leukocyte count (increase by 1 × 10^3/μL)	1.0 (1.0–1.0)	0.009		
Lymphocyte count (increase by 1 × 10^3/μL)	1.0 (1.0–1.0)	0.010	1.0 (1.0–1.0)	0.046
Ratio Le/Ly (increase by unit)	0.7 (0.5–0.9)	0.04		
Serum creatinine (increase by mg/dL)	0.2 (0.1–0.6)	0.004		

Abbreviations: CI, confidence interval; Le/Ly, ratio leukocyte/lymphocyte; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

differences in serologic assay sensitivities and not necessarily a higher efficacy of the Moderna vaccine.[8,9,22] Nevertheless, it could be speculated that the higher Moderna vaccine immunogenicity may be due to its higher dose (100 μg) compared to Pfizer/BioNTech (30 μg) in addition to its better thermostability and handling. These differences, although insignificant for immunocompetent individuals, might be important in patients with impaired immunity in whom strong stimuli are required.[21] Longitudinal studies indicate delayed IgG seroconversion and lower titers when individuals who are immunosuppressed suffer COVID-19 illness.[23–25] Thus, another possible explanation for its higher success rate is that the response to vaccination may be delayed in patients who are immunosuppressed.[5] Indeed, while the median time from the second dose to the antibody assay was carried out in the first month in previous studies in SOTRs, in our case the median time was 43 days.[11,14,19,20,26]

Unlike other studies that have found an influence of age[9,14,19,23] or time elapsed since transplantation[14,19] on the serologic response to the vaccine, we did not observe this in our cohort. Moreover, although renal dysfunction was associated with a worse serologic response, it did not reach statistical significance in the multivariate analysis. It is possible that our study did not have sufficient statistical power to show this. Certainly, chronic kidney disease is associated with a proinflammatory state and immune dysfunction, which encompasses both the innate system and acquired immunity

that could explain the worse serologic response observed in other studies.[8,14,27]

The influence of different immunosuppressive regimens on vaccination was explored in our study. In fact, the strongest predictive factor for the absence of serologic response, with an OR of 0.07 (95% CI, 0.02–0.26), was the use of MMF. This antimetabolite immunosuppressant has a well-known suppressive effect on the immune system, including the inhibition of antibody production.[28] Our finding is in line with previous reports and suggests that immune paresis perhaps promoted by antimetabolite therapy is the most likely explanation.[4,8,9,14,19,20,22,23] Moreover, the absolute lymphocyte blood count before vaccination tended to be higher in responders, and the association was statistically significant in the multivariate analysis. Although the effect was very weak, probably related to a low statistical power of the study, it is plausible and consistent with studies supporting its implication for establishing a response to vaccination[20] as it occurs with the vaccines against influenza virus.[29]

The current data suggest that SOTRs might be vulnerable to COVID-19 disease despite their vaccination status.[5–7] The correlation between antibody level after vaccination and clinical protection from COVID-19 has not been proven, and antibody levels are difficult to interpret.[30] Therefore, low antibody response may imply an inadequate protective response (and perhaps of shorter duration), and further studies are needed in order to determine whether these patients with positive, albeit low, antibody levels possess a higher risk of SARS-CoV-2 infection. Some studies have applied a more conservative threshold of >4160 AU/mL as this has been shown to have 95% concordance with the gold-standard PRNT.[17,18] A recent such study by Narasimhan et al.[13] observed that vaccinated patients with a lung transplant without prior infection that mounted an antibody response appeared to generate a response not comparable to that of a neutralizing antibody titer. Applying this cutoff to our study, only 63 patients (49.6%; 95% CI, 41.1%–58.2%) had shown neutralizing antibody titers. These data could mean that a greater number of LTRs are really unprotected. That said, antibody titers may not be a sufficient measure of protection against COVID-19 in patients with chronic liver diseases and LTRs. Although reports of cellular immunity in SOTRs are scarce, cellular immunity probably plays an important role in the control of SARS-CoV-2 infection, and a recent report suggests that heart and liver transplant recipients develop adequate humoral or cellular responses to an mRNA vaccine.[31] Taking all these considerations into account, on September 7, 2021, the Spanish National Health Authority decided to administer a third dose of booster vaccine to all SOTRs and other patients who were immunocompromised, regardless of serologic evaluation, at least 4 weeks after the second dose. All LTRs included in the study received a third homologous dose of the mRNA-1273 SARS-CoV-2 vaccine between September 27 and October 10, 2021.

Although it was not an objective of our study, only 3 patients who had received the complete vaccination schedule presented a SARS-Cov-2 infection during follow-up, and only 1 of these patients required hospitalization because of a concurrent cholangitis related to a biliary anastomosis stricture. None of these patients developed respiratory or other COVID-19-related symptoms. These findings appear to be consistent with a recently published paper reporting that SARS-CoV-2 vaccination reduces severe disease in patients with cirrhosis and SOTRs.[32]

Some of the limitations of our study are related to the retrospective design and the absence of a control group. However, there are extensive and consistent data in large clinical trials regarding efficacy of vaccine in healthy individuals.[2–4] Other limitations are the absence of serial measurements after vaccination, short time of follow-up, and lack of exploration of neutralizing antibody and/or cellular responses.

In conclusion, our data reveal a high response rate to the administration of the Moderna vaccine in LTRs. Immunosuppressive treatment, including MMF, was the strongest factor associated with a poor serologic response.

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CONFLICT OF INTEREST

The authors declare no personal or financial conflict of interest pertaining to this work.

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