Clinical Factors Associated With Lack of Serological Response to SARS-CoV-2 Messenger RNA Vaccine in Liver Transplantation Recipients

TO THE EDITOR:

Recent preliminary data report lower serological response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines in solid organ transplantation (SOT) recipients.[1,2] There are no data on factors associated with the lack of serological response in SOT recipients—information that could guide recommendations regarding booster dose and closer follow-up. We evaluated the serological response to SARS-CoV-2 vaccination in liver transplantation (LT) recipients.

Abbreviations: Ab, antibody; ALD, alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; EUA, Emergency Use Authorization; HBs, hepatitis B virus surface; HCC, hepatocellular carcinoma; IgG, immunoglobulin G; IQR, interquartile range; LT, liver transplantation; MMF, mycophenolate mofetil; mRNA, messenger RNA; NASH, nonalcoholic steatohepatitis; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplantation.

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Patients and Methods

In this prospective observational study, we recruited all consecutive adult LT recipients who received a SARS-CoV-2 vaccination at the Baylor St. Luke's Medical Center between January 8, 2021, and February 28, 2021. All patients received the Pfizer-BioNTech (New York, NY) BNT162b2 SARS-CoV-2 vaccine administered in 2 doses, 3 weeks apart. Serological response was evaluated 30 to 75 days after patients received their second vaccination dose. All patients were contacted and consented to the study, which was approved by the Baylor College of Medicine Institutional Review Board.

Clinical data were obtained through medical records and routine blood tests collected at the most recent clinic visit. Clinical characteristics included age, sex, race/ethnicity, indication for transplant, time from transplant, vaccination date, comorbidities, liver enzymes, immunosuppression therapy, and antibody (Ab) date. Laboratory and immunosuppression data were collected ±3 months from the first vaccine dose in recipients <1 year after LT and ±6 months in recipients >1 year after LT.

Participants were tested using laboratory-based immunoassays tests (Quest Diagnostics, Secaucus, NJ) for antibodies to the S1 domain SARS-CoV-2 spike protein and nucleocapsid protein. Semiquantitative spike immunoglobulin G (IgG) titers are interpreted as negative at a value <1 and positive at a value ≥1.00. The assay's positive semiquantitative reportable range is 1.00 to 20.00, and values above this were reported as >20.00. Qualitative nucleocapsid IgG test was checked to determine previous SARS-CoV-2 exposure. The sensitivity and specificity of the enzyme immunoassays for both the spike and nucleocapsid proteins were approximately 99.9% for the detection of

TABLE 1. Baseline Clinical Characteristics in LT Recipients Based on Serological Response to mRNA SARS-CoV-2 Vaccine

Clinical Characteristics	Overall, n = 69	Positive Spike Ab, n = 33	Negative spike Ab, n = 36	*P* Value
Age, years, median (IQR)	63 (51-68)	62 (50-66)	64 (52-69)	0.36
Sex, n (%)				0.29
Male	48 (70)	25 (76)	23 (64)	
Female	21 (30)	8 (24)	13 (36)	
Race/ethnicity, Asian, n (%)				0.35
White	45 (65)	25 (76)	20 (56)	
Black	8 (12)	3 (9)	5 (14)	
Hispanic	12 (17)	4 (12)	8 (22)	
Other	4 (6)	1 (3)	3 (8)	
Years after transplant, median (IQR)	3.3 (1.7-8.3)	5.0 (3.2-8.6)	2.2 (0.9-4.7)	0.29
Less than 1 year after transplant, n (%)	12 (17)	2 (6)	10 (28)	0.02
Time from first vaccine to antibody test, days, median (IQR)	81 (72-90)	77 (69-89)	83 (75-95)	0.34
Comorbidities, n (%)				
Obesity*	37 (54)	12 (36)	25 (64)	0.02
Diabetes mellitus†	33 (48)	16 (48)	17 (47)	0.92
Chronic kidney disease stage III/IV‡	36 (52)	16 (48)	20 (56)	0.56
Leucopenia§	9 (13)	2 (6)	7 (19)	0.09
Thrombocytopenia‖	23 (33)	9 (27)	14 (39)	0.31
Indication for transplant, n (%)				
ALD	24 (35)	11 (30)	14 (39)	0.46
NASH	13 (19)	5 (15)	8 (22)	0.44
HCC	21 (30)	12 (36)	9(25)	0.63
Immunosuppressive regimen				
Tacrolimus, n (%)	64 (90)	29 (88)	(94)	0.46
Tacrolimus daily dose, mg, mean (SD)	5.2 (3.4)	4.5 (2.7)	5.8 (3.8)	<0.001
Tacrolimus trough level,¶ ng/mL, mean (SD)	6.0 (2.2)	5.4 (2.0)	6.6 (2.2)	<0.001
MMF, n (%)	23 (36)	11 (33)	14 (39)	0.63
MMF daily dose, mg, mean (SD)	1150 (445)	1125 (490)	1150 (427)	0.06
Prednisone, n (%)	22 (37)	6 (18)	16 (45)	0.03
Prednisone daily dose, g, mean (SD)	11.0 (5.1)	10.8 (6.6)	11.3 (6.3)	0.01
Two agents, n (%)	24 (36)	9 (27)	15 (42)	0.32
Three agents, n (%)	8 (12)	3 (9)	5 (14)	0.53
Recent immunosuppression change,# n (%)	10 (14.5)	2 (6.1)	8 (22.2)	0.06
Laboratory findings				
Liver enzyme tests, mean (SD)				
AST, IU/L	20.1 (6.8)	19.8 (5.4)	20.3 (7.9)	0.18
ALT, IU/L	21.6 (6.8)	23.4 (11.2)	20.0 (10.2)	0.91
ALP, IU/L	98.0 (47.8)	104.9 (49.5)	91.9 (46.1)	0.81
Total bilirubin, mg/dL	0.7 (0.4)	0.7 (0.5)	0.7 (0.4)	0.52
Quantitative spike Ab titer, mean (SD)	—	8.3 (8.5)	—	
High spike Ab titer >20, n (%)		11 (33)	—	
White blood cells, cells/μL, mean (SD)	6.0 (2.2)	6.1 (1.9)	5.9 (2.4)	<0.001
Platelet count, cells/μL, mean (SD)	175 (65)	188 (72)	161 (59)	<0.001
Positive post-LT HBs Ab#	8 (22)	7 (41)	1 (5)	0.02

* Body mass index ≥30 kg/m^2 at time of first vaccine dose.
†History of diabetes mellitus or on antidiabetic medications.
‡ Defined as estimated GFR under 60 mL/min/1.73 m^2 during 2 separate outpatient visits within 1 year of first vaccine dose.
§White blood cell count (cells/μL) <4.0 at time of first vaccine dose.
‖Platelet count (cells/μL) <150 at time of first vaccine dose.
¶Mean tacrolimus trough levels calculated ±3 months from first vaccine dose for patients within 1 year after transplant and ±6 months for patients after 1 year from transplant.
#Of 69 recipients, 35 had a Hepatitis B surface antibody checked within 1 year after transplant. All patients had HBs Ab titer during pretransplant evaluation. Patients with negative HBs Ab reported receiving standard dose of hepatitis B vaccine series prior to transplant or within early peritransplant period.

humoral response to SARS-CoV-2 infection as well as cross-reactivity to other respiratory viruses.[3] Hepatitis B virus surface (HBs) Ab titers were interpreted as positive at ≥20.00.

Comparisons used χ^2 testing for categorical variables and the *t* test or Mann-Whitney U test for continuous variables. Forward stepwise multivariate logistic regression analyses were used to determine covariates associated with the negative spike Ab. Model assumptions were checked for multicollinearity using a variance inflation factor for immunosuppression characteristics, and the final model performance was summarized by a concordance index of 0.75.

Results

In total, 74 LT recipients were enrolled, of which 5 were excluded as a result of a positive nucleocapsid Ab. Baseline clinical characteristics for LT recipients and comparisons based on spike Ab are in Table 1. Median time from first dose was 81 days (interquartile range [IQR], 72-90 days) and most were male (70%) and White (65%) as described in Table 1. Of the recipients, 48% (n = 33) had a positive spike Ab, of which one-third (n = 11) had a high Ab titer (>20).

Overall, we found that recipients with a negative spike Ab had a higher proportion with 2 or more immunosuppressive agents (56% to 36%), including prednisone (45% to 18%), within 1 year of LT (28% to 6%), leucopenia (19% to 6%), obesity (64% to 36%), and higher tacrolimus trough levels (6.6 versus 5.4 ng/mL) than those with positive spike Ab. In the multivariate model seen in Table 2, increase in tacrolimus trough levels, 2 or more immunosuppressive agents, and obesity were associated with negative spike Ab.

One recipient had mild biopsy-proven acute cellular rejection 2 months before first dose and had negative Ab. There were no significant differences in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) levels between groups. A total of 5 patients had ALT or ALP more than 2 times the normal level; 3 patients had negative spike Ab. Of the recipients, 36 (52%) had HBs Ab titer within 1 year after LT and received hepatitis B vaccination after LT if the pre-LT serology was negative; only 21% (n = 8) had positive HBs Ab with a higher proportion seen in those with a positive spike Ab (41% versus 5%).

TABLE 2. Multivariate Logistic Regression Model Evaluating Clinical Predictors for Negative Qualitative Spike IgG Serology in LT Recipients

	Negative Spike Antibody Titer	
Clinical Characteristics	Multivariate OR (95% CI)	*P* Value
Age, years	1.04 (0.98-1.10)	0.82
Immunosuppressant		
Single agent		
2+ agents	3.10 (1.30-12.50)	0.04
Time since transplant	1.02 (0.94-1.11)	0.63
Tacrolimus trough level, 1 ng/mL units	1.40 (1.06-1.87)	0.02
Obesity		
No		
Yes	4.40 (1.30-12.22)	0.02
Time from second vaccine to antibody testing	1.01 (0.96-1.04)	0.96

Discussion

We found that fewer than half of the LT recipients developed a serological response after receiving 2 doses of the mRNA SARS-CoV-2 vaccine, a concerning suboptimal response lower than previously reported.[2] These findings have several practical considerations for the management of LT recipients. Recipients within 1 year of LT are more likely to be on prednisone and are treated with multiple agents with frequent changes in immunosuppression; they represent a high-risk population that should be closely monitored for serologic response. Higher tacrolimus trough levels had lower responses, and reducing trough goals and avoiding supratherapeutic concentrations could be 1 potential strategy to improve the humoral response.

In recipients who received a hepatitis B virus vaccination series after LT based on pre-LT serology, only 33% had seropositivity within the first year after LT, further demonstrating the effect of high-intensity immunosuppression impairing the ability to develop a robust immune response to other vaccines as well. A recent report demonstrated that more than 90% of LT candidates were able to achieve a serologic response, which warrants further consideration for transplant centers to require those on the waiting list to complete a vaccination series prior to LT. In recipients who contract the SARS-CoV-2 infection, nearly one-quarter develop severe infection, with mortality rates of 17%. As the pandemic continues, LT

recipients are at an increased risk, with nearly one-quarter developing severe infection and with mortality rates of 17%.[4] Furthermore, the effects of severe SARS-CoV-2 infection on short-term and long-term allograft function is largely unknown. Because of this heightened risk and the low immune response after the second dose, a short delay for administering the third booster dose can improve the immune response in this vulnerable population.[5-7] Even with the recent Emergency Use Authorization (EUA) for a third dose in SOT recipients, there is a lack of data on its efficacy, optimal time between dosing, and long-term immunity. Given these unknown factors, optimizing immune response in waitlist candidates prior to LT can mitigate risk in the early post-LT period.

The limitations of this study include the small sample size, short follow-up period, lack of controls, and the inability to assess for T cell response. As vaccination strategies to improve humoral response in this population are being considered, including EUA approval for a third booster dose, we identified several risk factors related to higher levels of immunosuppression and laboratory markers that can aid clinicians in identifying patients at risk for a negative serological response.

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