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Predictive Factors for Humoral Response After 2-dose SARS-CoV-2 Vaccine in Solid Organ Transplant Patients

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Background. A weak immunogenicity has been reported in solid organ transplant (SOT) recipients after 2 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. The aim of this retrospective study was to identify the predictive factors for humoral response in SOT patients. **Methods.** Three hundred and ninety-three SOT patients from our center with at least 4 wk of follow-up after 2 doses of mRNA-based vaccine were included in this study. Anti-SARS-Cov-2 spike protein antibodies were assessed before and after vaccination. **Results.** Anti-SARS-CoV-2 antibodies were detected in 34% of the patients: 33.7% of kidney transplant patients, 47.7% of liver transplant patients, and 14.3% of thoracic transplant patients ($P = 0.005$). Independent predictive factors for humoral response after vaccination were male gender, a longer period between transplantation and vaccination, liver transplant recipients, a higher lymphocyte count at baseline, a higher estimated glomerular filtration rate and receiving the tacrolimus + everolimus ± steroids combination. Conversely, the nondevelopment of anti-SARS-CoV-2 antibodies after vaccination was associated with younger patients, thoracic organ recipients, induction therapy recipients, and tacrolimus + mycophenolic acid ± steroids recipients. **Conclusions.** The immunosuppressive regimen is a modifiable predictive factor for humoral response to SARS-CoV-2 vaccine.

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Several studies have shown that immunocompromised patients, especially solid organ transplant (SOT) patients, have an increased morbidity and mortality in coronavirus disease 19 (COVID- 19).[1-4] Lymphopenia was identified as a major risk factor for severe disease in this population.[1,4] Furthermore, in immunocompromised patients who have recovered from COVID-19, the duration of specific anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies is unknown but could be reduced.[5] Therefore, it is now widely recommended to offer a (SARS-CoV-2 vaccine to SOT patients.

However, the humoral response to the SARS-CoV-2 vaccine in this setting is weak, as was previously reported in SOT patients who received the influenza vaccine.[6] In fact, weak immunogenicity against SARS-CoV-2, ranging from 10.8% to 17%, 3 or 4 wk after the first mRNA vaccine dose has been observed.[7,8] In recent series with 23–658 transplant patients, the humoral response to 2 doses of mRNA vaccine ranged from 22% to 58.8%.[9-15] Our group recently examined the immunogenicity of the SARS-CoV-2 mRNA-based vaccine in a large cohort of 367 SOT recipients, including kidney, liver, and thoracic transplant patients. Overall, the humoral

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response at 4 wk after the second vaccine dose was 34%.[16] Our aim is to identify the risk factors for humoral response in our cohort of SOT patients.

MATERIALS AND METHODS

On April 26, 1024 out of 2666 SOT patients at our center had received at least 1 vaccine dose. Of these, 393 patients had at least 4 wk follow-up after the second dose (288 kidney transplant patients, 65 liver transplant patients, 35 thoracic transplant patients, and 5 isolated pancreas transplant patients). A comparison between patients with 4 wk of follow-up after the second dose and those with insufficient follow-up is presented in Table S1, SDC, http://links.lww.com/TXD/A382. All the patients received an mRNA-based vaccine (BNT162b2 vaccine, Pfizer-BioNTech, n = 391; mRNA-1273 vaccine, Moderna, n = 2). In accordance with the Francophone Transplantation Society's recommendation, patients were asked to participate in biological monitoring, including the anti–SARS-CoV-2 spike protein antibodies before and after vaccination, to assess the safety and efficacy of the vaccine. We also retrospectively collected clinical data such as demographic data, the period between transplantation and vaccination, immunosuppressive regimens, and any history of acute rejection. According to French law (Loi Jardé), anonymous retrospective studies do not require Institutional Review Board approval.

Virological Analyses

Anti–SARS-Cov-2 spike protein antibody detection was performed using the Wantai total antibody (IgG/IgM/IgA) microplate assay ELISA test (Beijing Wantai Biological Pharmacy Enterprise, Ltd, China) in 80% of the patients.[17] The remaining patients were tested with another anti-spike total or immunoglobulin G assay validated by the French National Reference Center.

Statistical Analyses

Continuous variables are presented as means (±SEM). The proportion of patients who developed antibodies is reported with exact binomial 95% confidence interval (CI). Proportions were compared by the χ^2 test or Fisher exact test. Quantitative variables were compared by either the Student *t* test or the Mann-Whitney test. Independent factors associated with nonresponse to vaccine were examined with a multivariate logistic regression model that used initial inclusion criteria with a significance of $P < 0.05$. A P value of <0.05 was considered to be statistically significant. Data analysis was performed using GraphPad Prism version 9.0.2 (GraphPad Software, San Diego, CA) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Humoral Response According to the Transplanted Organ

Four weeks after the second vaccine dose, anti–SARS-Cov-2 antibodies were detected in 97 out of 288 kidney transplant patients (33.7%; 95% CI, 28.2%-39.5%), 31 out of 65 liver transplant patients (47.7%; 95% CI, 35.2%-60.5%), 5 out of 35 thoracic transplant patients (14.3%; 95% CI, 4.8%-30.3%), and 1 of the 5 pancreas transplant patients (20.0%; 95% CI, 0.5%-71.6%) ($P = 0.005$). Liver transplant patients were more likely to develop anti–SARS-CoV-2 antibodies compared to other transplant patients (odds ratio [OR] = 2.0; 95% CI, 1.1-3.5). Conversely, thoracic transplant patients developed anti–SARS-CoV-2 antibodies less frequently compared to other transplant patients (OR = 0.3; 95% CI, 0.1-0.8).

Comparison Between Patients With a Humoral Response to the Vaccine and Those Without

Compared with nonresponders, patients who developed anti–SARS-CoV-2 antibodies after vaccination were mainly male and younger with a longer period between transplantation and vaccination (Table 1). With respect to immunosuppression, those who received an induction therapy at transplantation significantly less frequently developed antibodies compared with those who did not (OR = 0.6; 95% CI, 0.4-1.0). However, no difference was observed between polyclonal antibodies and anti–interleukin-2 receptor blockers. Transplant patients who received mycophenolic acid (MPA) (OR = 0.5; 95% CI, 0.3-0.7), steroids (OR = 0.6; 95% CI, 0.3-1.0), or belatacept (OR = 0.3; 95% CI, 0.1-0.7) developed anti–SARS-CoV-2 antibodies significantly less often. Conversely, those who were treated with mammalian target of rapamycin (mTOR) inhibitors were more likely to develop a humoral response (OR = 1.8; 95% CI, 1.1-3.0).

Interestingly, patients who received tacrolimus + MPA with or without steroids developed significantly less antibodies than those treated with tacrolimus + everolimus with or without steroids (27% versus 47%, $P = 0.0004$). The characteristics of patients according to their immunosuppressive regimen are detailed in Table S2, SDC, http://links.lww.com/TXD/A382.

SOT recipients who developed anti–SARS-CoV-2 antibodies had a higher lymphocyte count before vaccination compared to nonrecipients. More precisely, when assessed, they had both a higher CD4+ and a higher CD19+ lymphocyte count. Conversely, CD8+ and natural killer cell counts were similar in both groups.

Finally, patients with anti–SARS-CoV-2 humoral response after vaccination had a higher estimated glomerular filtration rate (eGFR) compared with those who did not. This was observed in kidney transplant patients and in non-kidney transplant patients.

Predictive Factors for Humoral Response to SARS-CoV-2 Vaccines

The following variables were included in the multivariate analysis: gender (male versus female), age, the type of organ transplant (liver versus nonliver transplant and thoracic versus nonthoracic transplants), the period between transplantation and vaccination, induction therapy (induction versus no induction), the immunosuppressive regimen (use versus nonuse of MPA, steroids, mTOR inhibitors, or belatacept), the lymphocyte count, and the eGFR at baseline (Table 2).

Male gender, a longer period between transplantation and vaccination, and a higher eGFR level were independent predictive factors for humoral response after vaccination (Table 2). Conversely, younger patients, thoracic organ recipients, MPA, steroid, or belatacept recipients were associated with the nondevelopment of anti–SARS-CoV-2 antibodies after vaccination.

Since patients are treated with a combination of immunosuppressive drugs rather than a single immunosuppressant,

TABLE 1.

Clinical and biological characteristics of solid organ transplant recipients according to humoral response after mRNA-based vaccination

	Anti–SARS-CoV-2 positive patients (*N* = 134)	Anti–SARS-CoV-2 negative patients (*N* = 259)	*P*
Gender ratio % (M/F)	2.4 (95/39)	1.5 (156/103)	**0.037**
Age, mean ± SEM, y	56 ± 1	61 ± 1	**<0.001**
Type of organ transplant, n (%)			**0.005**
Kidney	97 (72)	191 (74)	0.773
Liver	31 (23)	34 (13)	**0.011**
Thoracic organs	5 (4)	30 (12)	**0.009**
Pancreas	1 (1)	4 (2)	0.665
History of rejection in the y preceding vaccination, n (%)	1 (1)	4 (2)	0.665
Time between vaccination and transplantation, mean ± SEM, mo	129 ± 8	101 ± 5	**0.004**
No induction therapy, n (%)	58 (43)	84 (32)	**0.034**
Induction therapy, n (%)	76 (57)	175 (68)	
Anti-IL2 receptor	46 (61)	98 (56)	0.601[a]
Thymoglobulin	30 (39)	74 (42)	
Other	–	3 (2)	
Type of immunosuppressive regimen, n (%)			0.532
Anticalcineurins	115 (86)	216 (83)	
Tacrolimus	102 (76)	202 (78)	
Ciclosporin A	13 (10)	14 (5)	
Antimetabolite	80 (60)	197 (76)	**<0.001**
MPA	77 (96)	193 (98)	**<0.001**
Azathioprine	3 (4)	4 (2)	0.694
mTOR inhibitors	45 (34)	56 (22)	**0.010**
Steroids	96 (72)	211 (81)	**0.026**
Belatacept	6 (4)	35 (14)	**0.005**
Immunosuppressive combination, n (%)			
Tacrolimus-MPA	56 (42)	155 (60)	**<0.001**
With steroids	39 (29)	131 (51)	**<0.001**
Without steroids	17 (13)	24 (9)	0.293
Tacrolimus-mTOR inhibitors	31 (23)	35 (14)	**0.016**
With steroids	27 (20)	31 (12)	**0.030**
Without steroids	4 (3)	4 (2)	0.453
Neutrophil count, mean ± SEM, /mm^3	5111 ± 162	5210 ± 145	0.838
Lymphocyte count, mean ± SEM, /mm^3	1827 ± 84	1602 ± 82	**0.004**
CD4+ T-cell count, mean ± SEM, /mm^3	n = 71; 570 ± 35	n = 124; 434 ± 26	**0.002**
CD8+ T-cell count, mean ± SEM, /mm^3	n = 71; 432 ± 40	n = 124; 431 ± 32	0.979
CD19+ lymphocyte count, mean ± SEM, /mm^3	n = 71; 188 ± 70	n = 124; 82 ± 10	**<0.001**
NK cell count, mean ± SEM, /mm^3	n = 71; 261 ± 19	n = 124; 219 ± 14	0.075
Baseline eGFR, mL/min/1.73 m2	62 ± 2	51 ± 1	**<0.001**
Kidney transplant eGFR	60 ± 3	49 ± 2	**<0.001**
Non-kidney transplant eGFR	67 ± 4	56 ± 3	**0.042**
Positive anti–SARS-CoV-2 antibodies before vaccination	n = 128; 1	n = 257; 5	0.668
History of COVID	n = 128; 1	n = 257; 5	0.668

Bold *P* values are significant.

[a]Comparison of the proportion of patients who received anti-IL2 receptor or thymoglobulin as induction therapy.

CD, cluster of differentiation; COVID, coronavirus disease; eGFR, estimated glomerular filtration rate; F, female; IL2, interleukin 2; M, male; mycophenolic acid, ; mTOR, mammalian target of rapamycin; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

we performed a second multivariate analysis in which we included the most frequent combinations, that is, tacrolimus + MPA ± steroids and tacrolimus + mTOR inhibitors ± steroids, instead of considering each immunosuppressant separately (Table 3). Independent predictive factors for humoral response after vaccination were male gender, a longer period between transplantation and vaccination, liver transplant recipients, a higher eGFR, and receiving the combination of tacrolimus + everolimus ± steroids. Conversely, the non-development of anti–SARS-CoV-2 antibodies after vaccination was associated with younger patients, thoracic organ recipients, induction therapy recipients, and tacrolimus + MPA ± steroid recipients.

DISCUSSION

Several studies have reported weak immunogenicity in SOT patients who are at high risk for severe COVID-19 disease and the related mortality.[9-13,15] In this retrospective study, we aimed to determine the predictive factors for humoral response to mRNA-based anti–SARS-CoV-2 vaccine in a large cohort of SOT patients. Our findings were 3-fold: (1) anti–SAR-CoV-2

TABLE 2.

Predictive factors for humoral response after 2 doses of mRNA-based vaccination (model 1)

	Adjusted multivariable OR	95% CI	*P*
Male gender	1.964	[1.145-3.371]	**0.012**
Age	0.963	[0.944-0.982]	**<0.001**
Liver transplant (vs nonliver transplant)	1.469	[0.726-2.973]	0.275
Thoracic transplant (vs nonthoracic transplant)	0.204	[0.060-0.692]	**0.009**
Time between vaccination and transplantation	1.004	[1.001-1.007]	**0.005**
Induction therapy (vs no induction)	0.597	[0.351-1.015]	0.052
Immunosuppressive regimen including MPA	0.231	[0.113-0.473]	**<0.001**
Immunosuppressive regimen including steroids	0.463	[0.231-0.929]	**0.027**
Immunosuppressive regimen including mTOR inhibitors	1.072	[0.529-2.173]	0.845
Immunosuppressive regimen including belatacept	0.267	[0.092-0.775]	**0.013**
Baseline lymphocyte count	1.000	[1.000-1.000]	0.227
Baseline eGFR	1.024	[1.011-1.037]	**<0.001**

Bold *P* values are significant.
CI, confidence interval; eGFR, estimated glomerular filtration rate; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; OR, odds ratio.

TABLE 3.

Predictive factors for humoral response after 2-dose mRNA-based vaccination (model 2)

	Adjusted multivariable OR	95% CI	*P*
Male gender	1.691	[1.002-2.854]	**0.045**
Age	0.960	[0.941-0.980]	**<0.001**
Liver transplant (vs nonliver transplant)	2.291	[1.174-4.471]	**0.013**
Thoracic transplant (vs nonthoracic transplant)	0.196	[0.057-0.676]	**0.009**
Time between transplantation and vaccination	1.005	[1.002-1.008]	**<0.001**
Induction therapy (vs no induction therapy)	0.581	[0.345-0.977]	**0.037**
Tacrolimus + MPA ± steroids	0.462	[0.255-0.837]	**0.009**
Tacrolimus + mTORi ± steroids	2.463	[1.139-5.328]	**0.019**
Baseline lymphocytes count	1.000	[1.000-1.000]	0.107
Baseline eGFR	1.020	[1.008-1.031]	**<0.001**

Bold *P* values are significant.
CI, confidence interval; eGFR, estimated glomerular filtration rate; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; OR, odds ratio.

antibodies were detected in 34.0% of patients 4 wk after the second vaccine; (2) the humoral response differed significantly according to the grafted organ, that is, the best response was observed in liver transplant patients, and the weakest in thoracic organ transplant patients; and (3) patients receiving mTOR-based immunosuppression with calcineurin inhibitors were more likely to be responders than those on a mycophenolic based immunosuppressive regimen.

Few studies have assessed the humoral response to 2 doses of mRNA vaccine in SOT patients.[7,9-12,15] Most studies have included patients who received 1 type of transplant organ. Anti–SARS-CoV-2 antibodies were detected in 22% to 58.8%. We recently reported a 34% humoral response in 367 patients followed at our center who had a 4-wk follow-up after the second vaccine dose.[16] In this study, we included some additional patients who had sufficient follow-up. One hundred thirty-four out of 393 patients developed anti-SARS-CoV-2 antibodies (34.0%). We found that the vaccine immunogenicity was significantly higher in liver transplant patients (47.7%) compared with other organ transplant patients. This proportion of positive patients is in line with a recent study that reported antibody positivity in 48% of a cohort of 80 liver transplant patients.[12] Conversely, we found that thoracic transplant patients are less likely to develop anti–SARS-CoV-2 antibodies (14.3%), which is similar to the findings in previous reports.[18] This might be related to differences in immunosuppression, particularly to the use of induction therapy. In this study, we found that patients who received induction therapy with polyclonal antibodies or anti–interleukin-2 receptor blockers developed anti–SARS-CoV-2 antibodies less frequently. Currently, nearly all thoracic transplant patients receive induction therapy,[19] whereas this is not the case for liver transplant patients.[20] In addition, the type, dosage, and levels of immunosuppressants may significantly differ between these 2 populations.

With respect to maintenance immunosuppressive therapy, we had similar findings to those in previous reports; MPA and steroid recipients are less likely to develop anti–SARS-CoV-2 antibodies.[9-12,16] Patients who received belatacept also developed antibodies less frequently. In a group that included patients from our center and patients from Necker Hospital, we previously showed a very weak humoral and cellular response to anti–SARS-CoV-2 vaccination.[21] These findings were confirmed by other groups.[15,22,23] Conversely, we found that the use of mTOR inhibitors was associated with a higher rate of seroconversion after vaccination, which is similar to the findings by Benotmane et al[11] that included 204 kidney transplant patients. Interestingly, although the tacrolimus and MPA combination with or without steroids is associated with a decreased humoral response, the tacrolimus and mTOR inhibitor combination with or without steroids is associated with a better immunological response. These findings are of interest since the

latter regimen has been shown to be efficient and safe after kidney, liver, and heart transplantation.[24–26] Moreover, we observed that patients who developed anti–SARS-CoV-2 antibodies have both a higher CD4+ and CD19+ lymphocyte count. The presence of CD19+ peripheral B cells has been linked to anti–SARS-CoV-2 humoral immune response in nontransplanted patients.[27] Lymphopenia is a common side effect of MPA, and its use has been associated with the inhibition of the immune response after vaccination, in contrast to mTOR inhibitors.[28]

Finally, as previously reported, we found that patients who were younger, were male, had a longer period between transplantation and vaccination, and had a higher eGFR were more likely to develop antibodies.

Because of to the weak immunogenicity of the vaccine, COVID-19 cases have been reported among vaccinated transplant patients.[29,30] SOT recipients who received 2 doses of the vaccine remain at higher risk of developing COVID-19 with a higher risk of hospitalization and death compared with fully vaccinated immunocompetent patients.[31] Therefore, different strategies have been or are considered to enhance the immunological response and consequently the protection rate. One such strategy is a vaccine with a higher dose. Boyarsky et al[7] have shown that patients who receive an mRNA-1273 vaccine, which has a higher dose than the BNT162b2 vaccine, were more likely to develop an antibody response. Benotmane et al,[11] who vaccinated their kidney transplant patients with the mRNA-1273 vaccine, noted a higher humoral response (48%) compared with our kidney transplant patients who received the BNT162b2 vaccine (33.7%). However, no comparison between both mRNA-based vaccines was performed. Recently, monocentric reports and a randomized controlled trial have shown that a boost with a third dose can significantly increase the humoral response in up to 70% of patients.[32-36] The third dose is now approved in several countries. However, this should be done under biological monitoring since acute rejection episodes have been reported after anti–SARS-CoV-2 vaccination.[37] Finally, based on our results, it can be hypothesized that modifying immunosuppression and using the combination of low-dose tacrolimus and mTOR inhibitors during the vaccination period improves the immunogenicity of the vaccine.

In conclusion, our study, which included a relatively large number of patients, confirmed the weak humoral response to 2 doses of mRNA vaccines in transplant patients and identified predictive factors for humoral response. Among these are immunosuppressive regimens that can be modified to improve the humoral response, especially when access to a third dose is not possible.

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