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Humoral Response After SARS-CoV-2 Vaccination in Kidney Transplant Recipients: Role of Immunosuppression Therapy

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ABSTRACT

Background. Messenger RNA vaccination against COVID-19 has been shown to produce an immune response with sufficient efficacy to prevent natural infection in immunocompetent recipients. However, the response in kidney transplant recipients is low. We aimed to evaluate the specific humoral response to SARS-CoV-2 after vaccination in a population of kidney transplant recipients and assess the main factors associated with a lack of response.

Methods. We undertook a prospective study of 105 kidney transplant recipients and 11 recipients of a combined kidney-pancreas transplant. We analyzed immunoglobulin G and immunoglobulin M antibodies after the patients received their second and third doses of the messenger RNA 1273 (Moderna) or BNT162b1 (BionTECH-Pfizer) vaccinations between February and November 2021.

Results. Mean (SD) age of the 116 patients was 50 (16) years, and 65% were men. They had their transplants for 40 months (IQR, 15-123 months), with 14% undergoing retransplant and 11% sensitized. The maintenance immunosuppression regimen was steroids + tacrolimus + mycophenolate (MMF) in 68% of the patients and any combination with mammalian target of rapamycin inhibitor (mTORi) in 28%. A humoral response developed in 40% of the patients 6 weeks (IQR, 4-10 weeks) after receiving the second dose of the vaccine. Of the 67 patients with no response to the second dose, 51 had an analysis of the humoral response after the third dose, which was positive in 16 (31%). A total of 80% received the Moderna vaccine and 20% the BionTECH-Pfizer. No patient experienced major adverse effects after the vaccination.

Factors associated with a lack of humoral response to the vaccine were recipient age (odds ratio [OR], 1.02; 95% CI, 1.001-1.05; $P = .04$), diabetes (OR, 2.8; 95% CI, 1.2-6.9; $P = .02$), and treatment with MMF (OR, 2.6; 95% CI, 1.08-6.8; $P = .03$). Treatment with mTORi was associated with a better response to vaccination (OR, 0.3; 95% CI, 0.1-0.9; $P = .04$).

Conclusions. The humoral response to the COVID-19 vaccine in kidney transplant recipients is poor. Factors related with this lack of immunity are recipient age and diabetes, plus MMF therapy, whereas mTORi therapy was associated with a better response to vaccination.

KIDNEY transplant (KT) recipients have a greater risk of developing severe disease if they become infected with SARS-CoV-2, as well as a higher likelihood of disease and death [1]. Although vaccination is recommended to protect this population from SARS-CoV-2, the humoral immune response in immunocompromised persons appears to be reduced or even absent in some patients [2]. This poor response to vaccination has been associated with the use of antimetabolite

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Table 1. Clinical and Laboratory Characteristics of the Patients Who Responded Compared With Those Who Failed to Respond

Characteristic	Responder (n = 62)	Nonresponder (n = 54)	*P* Value
Age, mean (SD), y	46 (17)	53 (15)	.03
Sex, % male	38	34	.7
Time after transplant, mean (SD), mo	80 (92)	58 (78)	.1
Creatinine, mean (SD), mg/dL	1.6 (0.8)	2.2 (1.1)	.005
Hypertension, %	88	89	.9
Diabetes mellitus, %	26	66	< .001
Ischemic heart disease, %	14	23	.2
Retransplant, %	13	15	.7
Hypersensitized, %	13	9	.5
Tacrolimus, %	85	100	.01
Mycophenolate mofetil, %	53	78	.004
mTOR inhibitors, %	40	19	.006
Bolus steroids 1 y before, %	37	42	.7
Thymoglobulin 1 y before, %	20	34	.1

mTOR, mammalian target of rapamycin.

immunosuppressive drugs, in addition to other specific transplant-associated risk factors [3].

MATERIALS AND METHODS

This prospective, observational study included 105 recipients of a KT and 11 recipients of a combined kidney-pancreas transplant. Analyses were made in all patients of immunoglobulin G and immunoglobulin M antibodies after receiving their second and third doses of a messenger RNA vaccination (Moderna 1273 or BionTECH-Pfizer BNT162b1) between February and November 2021.

The aim was to evaluate the specific humoral response against SARS-CoV-2 after vaccination in this population and determine the main factors associated with a lack of response.

Clinical and epidemiologic data were obtained from electronic clinical records. The main aspects considered were the clinical characteristics of the patients, the time from transplant to vaccination, and the type of immunosuppression, among others. The humoral serologic response was assessed between weeks 4 and 10 after the second and third doses of the vaccination. Major adverse effects were considered to be severe allergic reaction due to the vaccination.

Statistical Analysis

The results were analyzed using SPSS version 15 for Windows (IBM, Armonk, NY). The descriptive results for continuous variables were expressed as mean (SD) unless they did not follow a normal distribution normal, in which case they were expressed as median and IQR. Qualitative variables were expressed as a percentage, number of cases of the total, and the 95% CI. Comparisons between groups were analyzed with the Student *t* test to compare 2 continuous variables and the nonparametric Mann-Whitney test when it was not considered suitable to use the normal distribution. The χ^2 test was used to compare qualitative variables, with Fisher exact test when necessary. In addition, we also undertook a multivariate logistic regression analysis to determine the risk factors associated with a lack of response to vaccination. A value of $P < .05$ was considered statistically significant for all analyses.

RESULTS

The mean (SD) age of the 116 patients was 50 (16) years, and 65% were men. The median time since transplant was 40 months (IQR, 15-123 months), with 14% being retransplants and 11% hypersensitized. The maintenance immunosuppression regimen received was steroids, tacrolimus, and mycophenolate mofetil (MMF) in 68% of the cases and any combination with mammalian target of rapamycin inhibitor (mTORi) in 28%. A humoral response developed in 40% of the patients 6 weeks (IQR, 4-10) weeks after receiving the second vaccine dose. Of the 67 patients who failed to respond to the second dose, 51 were evaluated after the third dose, with 16 (31%) showing a positive humoral response. A total of 80% received the Moderna vaccine and 20% the BionTECH-Pfizer vaccine.

The factors associated with a lack of humoral response to the vaccine were recipient age (odds ratio [OR], 1.02; 95% CI, 1.001-1.05; $P = .04$), the presence of diabetes mellitus (OR, 2.8; 95% CI, 1.2-6.9; $P = .02$), and treatment with MMF (OR, 2.6; 95% CI, 1.08-6.8; $P = .03$). Treatment with mTORi was associated with a better response to vaccination (OR, 0.3; 95% CI, 0.1-0.9; $P = .04$) (Tables 1 and 2). The response to the vaccination was 75% in the patients receiving mTORi vs 45% in the patients receiving MMF ($P = .004$) (Table 3). No patient presented major adverse effects after vaccination.

Table 2. Multivariate Logistic Regression Analyses of Factors Affecting Vaccine Response in Kidney Transplant Recipients

Variable	OR	95% CI	*P* Value
Model 1			
Recipient age	1.029	1.001-1.05	.04
Diabetes mellitus	2.8	1.2-6.9	.02
Mycophenolate mofetil	2.6	1.08-6.8	.03
Proteinuria	1.0	1.000-1.001	.2
Model 2			
Recipient age	1.028	1.001-1.005	.04
Diabetes mellitus	2.9	1.2-7.9	.01
mTOR inhibitors	0.3	0.1-0.9	.04
Proteinuria	1.0	1.0-1.001	.3

mTOR, mammalian target of rapamycin; OR, odds ratio.

Table 3. Clinical and Laboratory Characteristics of the Patients Who Received Mycophenolate Mofetil and mTORi

Characteristic	mTORi(n = 32)	MMF(n = 84)	*P* Value
Age, mean (SD), y	47 (15)	51 (17)	.2
Sex, % female	30	38	.3
Time on dialysis, mean (SD), mo	34 (64)	28 (16)	.5
Diabetes pretransplant, %	36	48	.2
Hypertension pretransplant, %	95	86	.09
Retransplant, %	16	13	.7
Hypersensitized, %	7	22	.03
Time posttransplant, mean (SD), mo	70 (80)	69 (88)	.5
Vaccine response, %	75	45	.004
Antibody titer second vaccine, U/mL	17 (34)	25 (59)	.5
Antibody titer third vaccine, U/mL	56 (61)	22 (49)	.01

MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor.

DISCUSSION

KT recipients have a greater risk of severe COVID-19 because of the immunosuppression needed to prevent graft rejection. Accordingly, vaccination is a crucial measure to prevent infection, with its resulting associated morbidity and mortality. This is why Western countries have given priority to these patients in vaccination campaigns against COVID-19. However, in immunocompromised persons, such as KT recipients, the humoral immune response seems to be reduced [4]. Among the factors shown to be associated with a poor response to the vaccine are patient age, immunosuppressive treatment with MMF, and high doses of corticoids [3].

Our study found that only 40% of the patients developed antibodies after receiving 2 doses of the COVID-19 vaccine, and of those who failed to respond after the second dose, just 30% responded after the third dose—data that coincide with those reported elsewhere [5]. Among the factors associated with a lack of humoral response were greater patient age, the presence of diabetes mellitus, and immunosuppression with MMF, which are factors also already described [3], whereas those patients who received mTORi had a better response [6].

DISCLOSURE

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 article.

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