Analysis of Risk Factors for a Low Immune Response to Messenger RNA COVID-19 Vaccine in Kidney Transplant Recipients and Differences Between Second and Third Dose

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ABSTRACT

Background. The efficacy of the response to SARS-CoV-2 vaccination in kidney transplant recipients is low. The aim of our study was to evaluate the risk factors correlated with the low antibody response and whether there was an improvement between the second and the third dose.

Methods. A prospective study was conducted on 176 kidney transplant recipients who received the second and the third dose of the anti-SARS-CoV-2 mRNA Comirnaty vaccine. We evaluated the seroconversion process after administration of the second and the third dose and assessed a possible correlation with age, time between transplant and vaccination, and type of immunosuppressive therapy.

Results. A total of 98 of the 176 patients (55.7%) responded positively after the inoculation of the second dose and according to the multivariable logistic regression analysis the lack of seroconversion was independently associated with patient age ≥60 (P = .025; odds ratio [OR], 2.094), time since transplant of 1 to 3 months (P = .032; OR, 2.118), and triple therapy (P = .044; OR, 2.327). After the vaccine third dose, the seroconversion increased to 62.5%, and it was negatively influenced by calcineurin inhibitor use (12/21, 57.1% vs 71/78, 91.0%, P = .0006) and triple therapy (13/21, 61.9% vs 72/78, 92.3%, P = .0014). The median of anti-spike antibody response significantly increased from 18.5 IU/mL after the second dose to 316.9 IU after the third dose (P < .0001).

Conclusions. We demonstrated a correlation between older age and shorter distance from the transplant and triple immunosuppressive therapy with the lack of seroconversion. We noticed a significant improvement in antibody response by a third dose of messenger RNA vaccine.

BECAUSE of the global outbreak of the SARS-CoV-2 infection, new vaccine-based strategies have been gradually developed to control the spreading of the disease and reduce its fatality rate. December 27, 2020, a day referred to as "Vaccine Day," is commonly regarded as the date on which the vaccination campaign officially started across Europe; in Italy the campaign started on December 31 of the same year . The vaccine has been distributed for free all across Italy by adopting the scheme traced by the Italian Ministry of Health, Italian National Institute of Health, the Italian Medicines Agency and the National Agency for Regional Health Services agencies, which identified different priority categories. The first group that underwent vaccination was constituted by patients affected by various pathologies that may lead to a critical worsening of the health conditions in case of infection from SARS-CoV-2.

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Patients waiting for a transplant and those who already underwent a transplant belong to this first category.

The primary vaccination course for transplant recipients consisted of the administration of 2 doses plus an additional third dose at a distance of 21 to 28 days from each other to obtain a better immune response.

The mRNA vaccines, such as Comirnaty (Pfizer-BioNtech, Manhattan, NY) and Spikevax (Moderna, Cambridge, MA), have been used for transplant recipients as well as for the booster dose of vaccination. Both mRNA vaccines proved noteworthy (beyond 94% for Spikevax [1] and 95% for Comirnaty [2]) in preventing the SARS-CoV-2 symptomatic infection with respect to the placebo treatment after 14 days from the administration of the second dose.

Transplant recipients are, clearly, critical patients because of their pharmacologically induced immunosuppression. The lowered lymphocyte B activation leads to a reduced production of antibodies countering the action of SARS-CoV-2 viral agents.

In the transplant recipient, there also exists various risk factors that contribute, along with the drug-induced immunosuppression, to the definition of a high-risk patient. They are in fact affected by several comorbidities, such as cardiovascular disease, diabetes, or pulmonary fibrosis.

The major differences with respect from the rest of the population endowed with an efficient immune system mostly lie in the clinical manifestation of the pathology: transplant recipients are more frequently subject to a more severe manifestation, which may hence lead to a higher probability of hospitalization, even in the intensive care units (the percentage of hospitalization rises up to 25%-35% for transplant recipients [3], whereas the corresponding percentage for the rest of the population is about 14%) [4].

The most prominent statistical data that clearly demonstrate the relevance of vaccination in transplant recipients is the incidence of the infection in a sample of transplant recipients, some of whom were administered the vaccine doses, whereas the others were not. The incidence of infection was estimated at 0.2644 of 1000 in nonvaccinated individuals and to 0.0564 of 1000 in the vaccinated ones, namely a factor 4 lower than in the former case .

The aim of our study was to estimate, from a wide perspective, the impact of a solid-organ transplant, along with the related pharmacologic therapy, on the efficacy of the vaccination against SARS-CoV-2. Moreover, we also aimed at assessing quantitatively the increase of the immune response between the second dose and the first booster dose of the vaccine.

The main aspect that may raise doubts about the efficacy of the vaccination campaign concerns the immunosuppressive regimen that transplant recipients typically adhere to.

Relying on the data provided by previous international works that studied the efficacy of the first vaccination cycle in giving rise to an adequate immune response, the attention has thus shifted on the serologic comparison between the second and the third dose, with the aim of assessing the efficacy of a further immunization in inducing higher seroconversion rates as well as a larger immune response, thus guaranteeing an increased protection from the disease.

MATERIALS AND METHODS

A prospective study was conducted on 176 kidney transplant recipients who received the second and the third dose of the anti-SARS-CoV-2 mRNA Comirnaty vaccine (BNT162b2), developed by Pfizer/BionTech to from July 2021 to May 2022 at the Transplant Centre in L'Aquila, Italy. This group of patients was randomly enrolled. All participants provided written informed consent.

Patients who had already been infected from COVID-19, patients who received a transplant less than a year prior, patients who received treatments against rejection with rituximab and cortisone in the last 12 months, patients who received a vaccine dose right before the transplant, and patients who received a vaccine other than the mRNA-type of vaccine named Comirnaty (BNT162b2) were all excluded from the study.

We evaluated the seroconversion process at 1 month after administration of the second and after the third dose of the anti-SARS-CoV-2 mRNA Comirnaty vaccine (BNT162b2), developed by Pfizer/BionTech.

The parameter taken into consideration was the serum value of IgG antispike COVID-19 (SARS-CoV-2), evaluated 1 month after the administration of the vaccine, by means of blood sampling and enzyme-linked immunosorbent assay, and the value of 15 IU/mL was considered as a cutoff to define the failure or successful seroconversion.

The first analysis of the sample and of the results was carried out in relation to the age of the participants, which led to the identification of 3 different groups of patients: the first included participants aged between 18 and 49 years; the second, participants between 50 and 59 years; and the third, patients >60 years.

A possible correlation of the antibody response in function of the time elapsed between kidney transplant and vaccination was also evaluated. The patients were divided into 4 groups in relation to the date of the transplant: kidney transplant performed between 1 and 3 years before vaccination, kidney transplant performed between 4 and 5 years before vaccination, kidney transplant performed between 6 and 10 years before vaccination, and kidney transplant performed >10 years before vaccination.

The 176 participants in the sample were also classified according to the immunosuppressive therapy, taking into consideration cyclosporine (calcineurin inhibitor [CNI]), tacrolimus (CNI), antimetabolites (mycophenolate mofetil), and corticosteroids as drugs and everolimus (tyrosine kinase inhibitor). Once classified and categorized in the different subgroups, the clinical and demographic parameters in the cases of nonseroconversion were compared with the aim of searching for potential risk factors for a lower immune response to vaccine.

Statistical Analysis

The clinical and experimental data have been analyzed by means of standard statistical tools and are presented as mean (SD) or, in the presence of a skewed distribution, as median (IQR). Kurtosis has been measured to check whether the data follow a normal distribution.

To compare the characteristics of the groups, Fisher exact test or Pearson χ^2 (categorical variables) or the Mann-Whitney U test, as appropriate, was used. The characteristics of the groups with or without seroconversion and other clinical outcomes were calculated using the Wilcoxon signed rank analysis of variance for nonparametric paired continuous variables and with the χ^2 test for the categorical variables. Values were considered statistically significant with 2-tailed $P \leq .05$.

Binary logistic regression analyses were also performed to evaluate dichotomous differences in gene expression profiles between groups. Only the statistically significant variables in the univariate analysis ($P < .1$) were included in a multivariate logistic regression, and a backward conditional method was chosen to select significant independent covariates. All the

factors considered in the univariate analysis were derived from data in the literature or from clinical data. In the multivariate logistic regression for the risk factors of the antispike antibody response, in addition to significance < .05, we used the odds ratio (OR; risk index), Wald factor (which tells how the independent variable increases the risk of the dependent variable), 95% CI, and β coefficient (standardized regression coefficient). The Hosmer-Lemeshow test was calculated for the goodness of the regression model and to assert whether the observed events are compatible with those expected in the population subgroups.

The correlation between the variables was performed with Pearson or Spearman test, depending on the distribution of the data (parametric or nonparametric) by evaluating their significance ($P < .05$) and the correlation coefficient r (value from −1 to +1). The calculations were performed using SPSS v.13.0 software (IBM SPSS, Inc, Armonk, NY) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA).

RESULTS

In this study, a sample of 176 participants was considered, of which 121 were male, all aged between 28 and 80 years (median [IQR] age, 60.0 years [63-67 years]). All participants were regularly followed up at the Transplant Center of L'Aquila. They were classified into 4 categories based on the date of vaccination vs transplant: 60 transplant recipients between 1 and 3 years after transplant (34.1% of participants), 17 after 4 or 5 years (9.7%), 31 between 6 and 10 years (17.6% of the total), and 68 >10 years (38.6% of the total).

The patients in the sample were also classified according to the immunosuppressive therapy, taking into consideration as drugs cyclosporine, tacrolimus (CNIs), mycophenolate mofetil (antimetabolites), and corticosteroids and everolimus (tyrosine kinase inhibitors). The distribution of participants with different immunosuppressive therapy is shown in Table 1.

A total of 98 of the 176 patients (55.7%) evaluated for IgG antispike antibody titer after the second inoculum responded positively to the inoculation of the second dose, demonstrating seroconversion, in contrast to 78 (44.3% of the total) who reported IgG values <15 IU/mL and consequently a lack of seroconversion. Analyzing the characteristics of the patients, on the basis of the parameters described above (ie, sex, age, time from transplant, immunosuppressive therapy in progress), we found significant values in relation to some specific subgroups.

Table 1. Data of Patient Cohort

Variable	Cohort (N = 176), No. (%)
Age, y	
18-49	33 (18.8)
50-59	52 (29.5)
≥ 60	91 (51.7)
Male	121 (68.4)
Time since transplant, y	
1-3	60 (34.1)
4-5	17 (9.7)
6-10	30 (17.0)
>10	66 (37.5)
Immunosuppressive therapy	
Cyclosporine	22 (12.5)
CNIs	160 (90.9)
Antimetabolites (MMF)	145 (82.4)
Corticosteroids	151 (85.8)
Triple therapy (corticosteroid + CNI + MMF)	142 (80.7)
Everolimus (TKI)	13 (7.4)

CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; TKI, tyrosine kinase inhibitor.

In particular, we noted the worst immune response in the male group (male group: 62.2% vs 75.9%, $P = .054$) and a correlation with the time from the date of transplant and the administration of the vaccine. In participants who had undergone transplant in the last 3 years, a seroconversion rate of only 25.8% was found ($P = .011$), whereas in patients vaccinated with a time >10 years (66 of 176), a significantly higher seroconversion rate (45.9% vs 26.9%, $P = .015$) was evidenced.

Another parameter of great importance is the association between the possible occurrence of seroconversion and the pharmaceutical immunosuppression regimen in place. In participants administered with triple therapy (CNI, antimetabolites, steroids), there was a statistically significant low humoral response (92.3% vs 71.4%, $P = .001$).

After multivariable regression analysis of these factors, we confirmed the primary role as risk factors of triple therapy ($P = .044$; OR, 2.327), age >60 years ($P = .025$; OR, 2.094), and time since transplant 1 to 3 years ($P = .032$; OR, 2.118) after the second vaccination (Tables 2 and 3).

In the next phase of the study, data regarding the antibody response after administration of the third dose (booster) of Pfizer/BioNTech mRNA vaccine were considered, but because of the reduced availability of chemical reagents necessary for performing quantitative tests, the number of individuals subjected to antibody titer assessment 1 month after the third dose was reduced to 56 participants.

In the 56 participants examined, 62.5% responded positively by producing IgG for values above the cutoff of 15 IU/mL. In this sample we did not notice significant differences considering the different variables examined, but comparing the 2 patients groups (3rd vs 2nd dose) we evidenced an increased antibody production in participants vaccinated after 1 to 3 years since transplant (45.7% vs 25.8%, $P = .045$) and a reduction of patients without seroconversion depending on CNIs (57.1% vs 91.0%, $P = .0006$) or antimetabolite use (57.1% vs 87.2%, $P = .0053$) and triple therapy (61.9% vs 92.3%, $P = .0014$) (Table 4, Fig 1).

Given the small number of participants evaluated, we cannot assess with certainty whether the results obtained are actually because of the administration of the third dose, but certainly the width of the range of the 2 results corroborates significantly the efficacy and the usefulness of the third dose to be sustained after completion of the primary vaccination cycle.

Furthermore, at quantitative level, the median of antibody antispike response estimated in patients treated up to the booster dose significantly increased from 18.5 IU/mL after the second dose to 316.9 IU to the third dose (Wilcoxon signed rank test $P < .0001$). These participants were evaluated with enzyme-linked immunosorbent assay tests, obtaining minimum values of 4 IU/mL and maximum values >2500 IU/mL in both the first and second measurement. The results of this survey are displayed in Fig 2.

Table 2. Demographic and Clinical Parameters in the 2 Groups of Patients With or Without Seroconversion After Second Dose−Graft Antibody Response.

Variable	Cohort (n = 176), No. (%)	2nd Dose−Antibody Response (N = 176)		*P* Value
		Seroconversion (n = 98, 55.7%), No. (%)	No Seroconversion (n = 78, 44.3%), No. (%)	
Age, y				
18-49	33 (18.8)	20 (20.4)	13 (16.7)	
50-59	52 (29.5)	33 (33.7)	19 (24.4)	.238
≥ 60	91 (51.7)	45 (45.9)	46 (59.0)	.116
Male sex	121 (68.4)	61 (62.2)	60 (75.9)	.054
Time since Tx, y				
1-3	60 (34.1)	25 (25.8)	35 (43.8)	.011
4-5	17 (9.7)	9 (9.3)	8 (10.1)	NS
6-10	31 (17.6)	18 (18.4)	13 (16.5)	NS
>10	68 (38.6)	45 (45.9)	21 (26.9)	.015
Cyclosporine	22 (12.5)	13 (13.3)	9 (11.5)	NS
CNI use	160 (90.9)	89 (90.8)	71 (91.0)	NS
Antimetabolite	145 (82.4)	77 (78.6)	68 (87.2)	.197
Steroid use	151 (85.8)	78 (51.7)	73 (48.3)	NS
Triple therapy	142 (80.7)	70 (71.4)	72 (92.3)	.0010
Everolimus	13 (7.4)	8 (8.2)	5 (6.4)	.775

CNI, calcineurin inhibitor; NS, not significant; Tx, transplant.

Table 3. Multivariable Analysis for the Risk Factors of Undetectable Antispike Antibody Response After the Second SARS-CoV2 Vaccination in Kidney Transplant Recipients (Backward Conditional Method)

Variables	β	SE	Wald	OR	95% CI Lower/Upper		*P* Value
Age ≥60, y	0.739	0.329	5.05	2.094	1.099	3.990	.025
Time since transplant, y	0.751	0.351	4.574	2.118	1.065	4.213	.032
Triple therapy (corticosteroid + CNI + MMF)	0.845	0.420	4.05	2.327	1.022	5.299	.044

Hosmer-Lemeshow test: 0.734.
CNI, calcineurin inhibitor; MMF, mycophenolate mofetil.

Table 4. Demographic and Clinical Parameters in the 2 Groups of Patients With or Without Seroconversion After Third Dose−Graft Antibody Response

Variables	Cohort (n = 56), No. (%)	3rd Dose−Antibody Response (n = 56)		*P* Value
		Seroconversion (n = 35, 62.5%), No. (%)	No seroconversion (n = 21, 37.5%), No. (%)	
Age, y				
18-49	9 (16.1)	5 (14.3)	4 (19.0)	NS
50-59	22 (39.3)	17 (48.6)	5 (23.8)	.092
≥ 60	25 (44.6)	13 (37.1)	12 (57.1)	.23
Male sex	38 (67.9)	23 (65.7)	15 (71.4)	NS
Time since Tx, y				
1-3	24 (42.9)	16 (45.7)	8 (38.1)	NS
4-5	5 (8.9)	3 (8.6)	2 (9.5)	NS
6-10	10 (17.9)	5 (14.3)	5 (23.8)	NS
> 10	16 (28.6)	11 (31.4)	5 (23.8)	NS
Cyclosporine	2 (3.6)	2 (5.7)	0 (0)	NS
CNI use	36 (64.3)	24 (68.6)	12 (57.1)	NS
Anti-metabolite	35 (62.5)	23 (65.7)	12 (57.1)	NS
Steroid use	35 (62.5)	23 (65.7)	12 (57.1)	NS
Triple therapy	39 (69.6)	26 (74.3)	13 (61.9)	NS
Everolimus	5 (8.9)	3 (8.6)	2 (9.5)	NS

CNI, calcineurin inhibitor; Tx, transplant; NS, not significant.

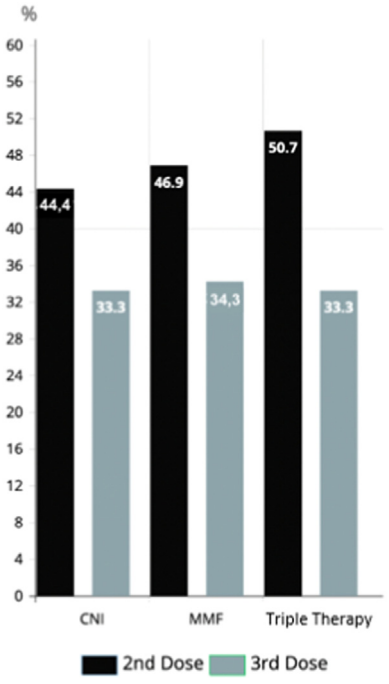

Fig 1. Percentage variations between second and third dose in relation to immunosuppressive therapy in participants with non-seroconversion.

DISCUSSION

The main aspect that may raise doubts regarding the effectiveness of the vaccination campaign is certainly the immunosuppressive regimen to which participants who receives a solid-organ transplant are subjected [5−7].

Several studies have shown a reduced immune response to the primary vaccination course among transplant recipients in association with more severe clinical manifestations compared with the general population [8,9].

In the study published by Boyarsky et al, a very low immune response has been demonstrated among transplant recipients, showing how after the first dose 98 of 658 participants presented a measurable antibody response (15% of the sample), 259 responded positively only after the second (39% of the sample) and 301 did not develop antibodies after either dose (46% of the sample) [10].

In the most relevant studies regarding the efficacy of the third dose in transplant recipients, the results point to the administration of the third dose to improve or even trigger an immune response that would otherwise be deficient or even absent after the first 2 doses [11−14].

In the literature, several studies conducted after the first 2 vaccination doses [15−19] confirmed age, short period from transplant, and triple therapy are risk factors for the lack of immune response to vaccination.

The results of our study confirmed that more advanced age, adoption of a triple immunosuppressive therapy, and greater proximity between the transplant date and the vaccine administration date can be considered risk factors for a lack of seroconversion in kidney transplant recipients after the second dose of SARS-COV-2 vaccination but also an improvement in antibody response after the third dose depending on inhibitory calcineurin, antimetabolite, and triple therapy use.

On the one hand, our investigation is based on a relatively small cohort of patients with a nonmatched control group. Our quantitative investigation will certainly benefit from useful comparisons with data obtained from other research groups. On the other hand, the strength of our study was to have prospectively assessed the response to the second and third dose in the same group of patients.

The results of this study could help evaluate, in the future, the advantage of modifying immunosuppressive therapy at the turn of vaccination. A further future goal is to correlate the humoral response with the clinical symptoms and cellular response in patients who have fallen ill with COVID-19 after vaccination.

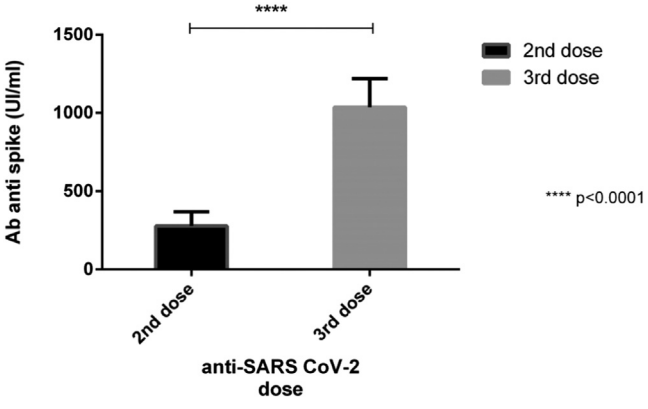

Fig 2. Antispike IgG antibody titer after the second and third dose of vaccine in the reference subpopulation.

CONCLUSIONS

According to the data obtained from this study, compared with similar studies and with comparable endpoints, we can argue that a third dose of mRNA vaccine in transplant recipients leads to a significant improvement in antibody response compared with a primary vaccination course. Indeed, in some cases, the third dose induces an immune reaction that was completely absent after the second dose.

We can also confirm the existence of a close correlation between various risk factors such as older age, greater proximity between the date of transplant and the date of vaccine administration, triple pharmacologic immunosuppressive therapy, and the lack of seroconversion in transplant recipients.

Finally, we can thus consider the administration of the third dose of vaccine in transplant recipients to be of crucial importance to reduce the incidence of SARS-CoV-2 infection, but also to avoid serious manifestations of disease and its unfortunate outcomes.

DATA AVAILABILITY

The data that has been used is confidential.

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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