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ANALYSIS OF RISK FACTORS FOR A LOW IMMUNE RESPONSE TO mRNA COVID-19 VACCINE IN KIDNEY TRANSPLANT RECIPIENTS AND DIFFERENCES BETWEEN SECOND AND THIRD DOSE

Panarese A , Canossi A , Fabiani R , Lupi D , Maccarone D , Pace P , Parzanese I , Martinez V , Lancione L , Savino V , Cacchioni C , Cervelli C , Papola F , Pisani F

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My manuscript is submitted as an original work

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ABSTRACT

INTRODUCTION: 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.

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. We evaluated the seroconversion process after administration of the second and the third dose and assessed a possible correlation with age, time between transplantation and vaccination and type of immunosuppressive therapy.

RESULTS: 98 out of the 176 (55.7%) patients 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=0.025, OR=2.094), time since transplantation of 1-3 months (p=0.032, OR=2.118) and triple therapy (p=0.044, OR=2.327). After the vaccine third dose the seroconversion increased to 62.5% and it was negatively influenced by Calcineurin inhibitors (CNI) use (12/21, 57.1% vs. 71/78, 91.0%, p=0.0006), and triple therapy (13/21, 61.9% vs. 72/78, 92.3%, p=0.0014). The median of anti-spike Ab response significantly increased from 18.5UI/ml after the 2nd dose to 316.9UI after the 3rd dose (p<0.0001).

DISCUSSION AND CONCLUSIONS: We demonstrated a correlation between older age, short 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 mRNA vaccine.

INTRODUCTION

Owing to the global outbreak of the SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2) coronavirus infection, new vaccine-based strategies have been gradually developed in order to control the spreading of the disease and reduce its fatality rate. December 27, 2020 - a day referred to as the 'Vaccine day' is commonly regarded as the date in which the vaccination campaign officially started across Europe; in Italy the campaign started on December 31 of the same year [1]. 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 (ISS) and by the AIFA e AGENAS Agencies, which identified different priority categories. The first group that underwent vaccination was constituted by fragile individuals, namely patients affected by various pathologies that may lead to a critical worsening of the health conditions in case of infection from SARS-CoV-2. Patients waiting for a transplant and those who already underwent a transplant belong to this first category.

The primary vaccination course for transplant patients consisted of the administration of two doses plus an additional third dose at a distance of 21-28 days from each other, in order to obtain a better immune response.

The mRNA vaccines, such as Comirnaty (Pfizer-BioNtech) and Spikevax (Moderna), have been used for transplanted patients as well as for the Booster dose of vaccination. Both mRNA vaccines proved noteworthy (beyond 94% for Spikevax [2] and 95% for Comirnaty [3]) in preventing the SARS-CoV-2 symptomatic infection with respect to the placebo treatment after 14 days from the administration of the second dose.

Transplanted subjects are, clearly, critical patients, due to their pharmacologically induced immunosuppression. The lowered lymphocite B activation leads, indeed, to a reduced production of antibodies countering the action of SARS-CoV-2 viral agents.

In the transplanted individual there also exist various risk factors which 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: transplanted patients 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 hospitalisation rises up to 25-35% for transplanted patients [4], while the corresponding percentage for the rest of the population is about 14%) [5].

The most prominent statistical data which clearly demonstrate the relevance of vaccination in transplanted patients is the incidence of the infection in a sample of transplanted subjects, some of which were administered the vaccine doses while the others were not. The incidence of infection was estimated equal to 0,2644 out of 1000 in non-vaccinated individuals and to 0,0564 out of 1000 in the vaccinated ones, namely a factor 4 lower than in the former case [6].

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

The main aspect which may raise doubts about the efficacy of the vaccination campaign concerns the immunosuppressive regimen which transplanted patients typically adhere to.

Relying on the data provided by previous international works which studied the efficacy of the first vaccination cycle in giving rise to an adequate immune response, the attention has thus shifted on the serological 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 the participants provided written informed consent.

Patients who have already been infected from Covid 19, as well as patients who received a transplant from less than a year, patients who received treatments against rejection with Rituximab and cortisone in the last 12 months, and also patients who received a vaccine dose right before the transplant or those 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 one 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 one month after the administration of the vaccine, by means of blood sampling and ELISA technique (Enzime-Linked ImmunoSorbent Essay) and the value of 15 IU/ml was considered as a cut-off 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 subjects, which lead to the identification of 3 different groups of patients: the first includes subjects aged between 18 and 49 years, the second subjects between 50 and 59 years whereas the third patients aged over 60 years old.

A possible correlation of the antibody response in function of the time elapsed between kidney transplantation and vaccination was also evaluated. The patients were divided into four 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; kidney transplant performed more than 10 years before vaccination.

The 176 subjects in the sample were also classified according to the immunosuppressive therapy, taking into consideration Ciclosporine (CyA - CNI), Tacrolimus (CNI), Antimetabolites (MMF), Corticosteroids as drugs and Everolimus (TKI). Once classified and categorized in the different subgroups, the clinical and demographic parameters in the cases of non-seroconversion 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 (interquartile range). Kurtosis has been measured to check whether the data follow a normal distribution.

To compare the characteristics of the groups, Fisher's exact test or Pearson's X2 (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 Wilkoxon signed rank analysis of variance for non-parametric paired continuous variables and with the Chi2 test for categorical variables. Values were considered statistically significant with two-tailed $p \leq 0.05$.

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 ($p < 0.1$) 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 anti-spike

antibody response, in addition to significance <0.05, the odds ratio (risk index), the Wald factor (which tells how the independent variable increases the risk of the dependent variable), CI 95% and the Beta 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 non-parametric) by evaluating their significance ($p < 0.05$) and the correlation coefficient rs (value from -1 to +1). Calculations were performed using SPSS v.13.0 software (IBM Corporation, Somers, NY, USA) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA).

RESULTS

In this study, a sample of 176 subjects was considered, of which 121 were male, all aged between 28 and 80 years (median age: 60.0 years, IQR:63-67). All subjects were regularly followed at the Transplant Center of L'Aquila. They were classified into four categories based on the date of vaccination versus transplant: 60 transplanted patients between 1 and 3 years after transplantation (34.1% of subjects), 17 after 4 or 5 years (9.7%), 31 between 6 and 10 years (17.6% of the total) and 68 over 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 (CyA), Tacrolimus - Calcineurin inhibitors (CNI), Mycophenolate Mofetil (Antimetabolites), Corticosteroids and Everolimus - tyrosine kinase inhibitor (TKI). The distribution of subjects with different immunosuppressive therapy is shown in Table 1.

98 out of the 176 (55.7%) patients subjected to evaluation of the IgG Anti-Spike antibody titer after the 2nd 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 lower than 15 IU / ml and consequently a lack of seroconversion. Analyzing the characteristics of the patients, on the basis of the parameters described above

(gender, age, distance from transplantation, sex and immunosuppressive therapy in progress), significant values were found in relation to some specific subgroups.

In particular, we noted a worst immune response in the male group (male group: 62.2% vs. 75.9%, p=0.054) and a correlation with the distance from the date of transplantation and the administration of the vaccine. In subjects who had undergone transplantation in the last 3 years a seroconversion rate of only 25.8% was found (p = 0.011), while in patients vaccinated with a distance over 10 years (66 out of 176), a significantly higher seroconversion rate (45.9% vs. 26.9%, p=0.015) was evidenced.

Another parameter that was found to be of great importance is the association between the possible occurrence of seroconversion and the pharmaceutical immunosuppression regimen in place. In fact, it has been shown that in subjects administered with Triple Therapy (CNI, Antimetabolites and Steroids) there was a statistically significant low humoral response (92.3% vs. 71.4%, p= 0.001).

After multivariable regression analysis of these factors, we confirmed the primary role as risk factors of triple therapy (p=0.044, OR=2.327), the age over 60 years (p=0.025, OR=2.094) and time since transplantation 1-3 years (p=0.032, OR=2.118), after the 2nd vaccination (Table 2-3).

In the next phase of the study, data regarding the antibody response following administration of the 3rd 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 titre assessment one month after the third dose was reduced to 56 subjects.

In the 56 subjects examined, 62.5% responded positively by producing IgG for values above the cut-off of 15 IU/ml. In this sample we didn't notice significant differences considering the different variables examined but comparing the two patients groups (3rd vs. 2nd dose) we evidenced an increased antibody production in subjects vaccinated after 1-3 years since transplant (45.7% vs. 25.8%, p=0.045) and a reduction of patients without seroconversion depending on calcineurin inhibitors (CNI, 57.1% vs. 91.0%, p=0.0006) or anti-metabolite usage (57.1% vs. 87.2%, p=0.0053) and triple therapy (61.9% vs. 92.3%, p=0.0014) (Table 4. Graph 1).

Given the small number of subjects evaluated, we cannot assess with certainty whether the results obtained are actually due to the administration of the third dose, but certainly the width of the range of the two 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 anti-spike response estimated in patients treated up to the booster dose significantly increased from 18.5UI/ml after the 2nd dose to 316.9UI to the third dose (Wilcoxon signed rank test $p<0.0001$). These subjects were evaluated with ELISA tests, obtaining minimum values of 4 IU / ml and maximum values of over 2500 IU / ml in both the first and second measurement. The results of this survey are displayed in Graph 2.

DISCUSSION

The main aspect that may raise doubts regarding the effectiveness of the vaccination campaign is certainly the immunosuppressive regimen to which subjects who receives a solid organ transplant are subjected [7,8,9].

Several studies have shown a reduced immune response to the primary vaccination course among transplant recipients in association with more severe clinical manifestations when compared with the general population [10,11].

In the study published by Boyarsky et al., in fact, a very low immune response has been demonstrated among transplant recipients, showing how after the first dose 98 subjects out of 658 presented a measurable antibody response (15% of the sample), 259 responded positively only after the second (39% of the sample) and 301 they did not develop antibodies after either dose (46% of the sample) [12].

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 two doses [13,14,15,16].

In the literature several studies conducted after the first two vaccination doses [17,18,19, 20,21] confirmed as the age, short period from transplantation and triple therapy are risk factors for the lack of immune response to vaccination.

The results of our study confirm that a more advanced age, the adoption of a triple immunosuppressive therapy and the 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, anti-metabolite and triple therapy use.

On the one hand, our investigation is based on a relative small cohort of patients with a non-matched control group. Our quantitative investigation will certainly benefit from useful comparisons with data obtained from other research groups. On the other hand, the point of strength of our study is 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.

CONCLUSIONS

According to the data obtained from this study, compared with similar studies and with comparable end-points [22], we can argue that a third dose of mRNA vaccine in transplant recipients leads to a significant improvement in antibody response compared to 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 an older age, the greater proximity between the date of transplant and the date of vaccine administration, a triple pharmacological 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 in order to reduce the incidence of SARS-CoV-2 infection but also to avoid serious manifestations of disease and its unfortunate outcomes.

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Table 1 – Data of patient cohort

VARIABLES	**COHORT (n=176)**
Age (years)	
18-49	33 (18.8%)
50-59	52 (29.5%)
≥60	91 (51.7%)
Male	121 (68.4%)
Time since transplant (years)	
1-3	60 (34.1%)
4-5	17 (9.7%)
6-10	30 (17.0%)
>10	66 (37.5%)
Immunosuppressive therapy	
Ciclosporin (CyA)	22 (12.5%)
Calcineurin Inhibitors (CNI)	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%)

Table 2- Demographic and clinical parameters in the two groups of patients with or without seroconversion after 2nd dose-graft antibody response.

				P value
VARIABLES		**2nd dose- Antibody response (n=176)**		
	Cohort (n=176)	**Seroconversion** (n=98, 55.7%)	**No seroconversion** (n=78, 44.3%)	
Age, year				
18-49	33 (18.8%)	20 (20.4%)	13 (16.7%)	
50-59	52 (29.5%)	33 (33.7%)	19 (24.4%)	0.238
≥60	91 (51.7%)	45 (45.9%)	46 (59.0%)	0.116
Male sex	121 (68.4%)	61 (62.2%)	60 (75.9%)	**0.054**
Time since Tx, ys				
1-3	60 (34.1%)	25 (25.8%)	35 (43.8%)	**0.011**
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 %)	**0.015**
Cyclosporine	22 (12.5%)	13 (13.3%)	9 (11.5%)	NS
CNI use	160 (90.9%)	89 (90.8%)	71 (91.0%)	NS
Anti-metabolite	145 (82.4%)	77 (78.6%)	68 (87.2%)	0.197
Steroid use	151 (85.8%)	78 (51.7%)	73 (48.3%)	NS
Triple therapy	142 (80.7%)	70 (71.4%)	72 (92.3%)	**0.0010**
Everolimus	13 (7.4%)	8 (8.2%)	5 (6.4%)	0.775

Table 3- Multivariable analysis for the risk factors of undetectable anti-spike antibody response after the 2nd SARS-CoV2 vaccination in kidney transplant patients (Backward conditional method)

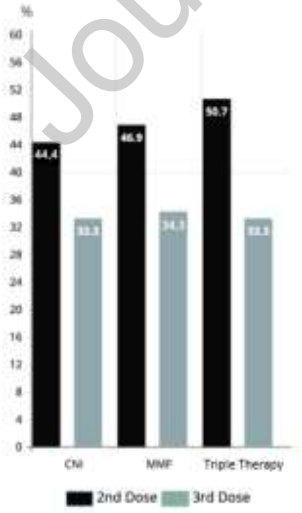
Variables	***Beta***	***S.E.***	***Wald***	***OR=***	***IC 95%*** ***Lower / Upper***		***P-Value***
Age ≥ 60 years	0.739	0.329	5.05	**2.094**	1.099	3.990	**0.025**
Time since transplant (years)	0.751	0.351	4.574	**2.118**	1.065	4.213	**0.032**
Triple Therapy (Corticosteroid+CNI+MMF)	0.845	0.420	4.05	**2.327**	1.022	5.299	**0.044**

Hosmer-Lemeshow test: 0.734

Table 4- Demographic and clinical parameters in the two groups of patients with or without seroconversion after 3rd dose-graft antibody response.

				P value
VARIABLES		**3nd dose- Antibody response (n=56)**		
	Cohort (n=56)	**Seroconversion** (n=35, 62.5%)	**No seroconversion** (n=21, 37.5%)	
Age, year				
18-49	9 (16.1%)	5 (14.3%)	4 (19.0%)	NS
50-59	22 (39.3%)	17 (48.6%)	5 (23.8%)	0.092
≥60	25 (44.6%)	13 (37.1%)	12 (57.1%)	0.23
Male sex	38 (67.9%)	23 (65.7%)	15 (71.4%)	NS
Time since Tx, ys				
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

Graph 1 – Percentage variations between second and third dose in relation to immunosuppressive therapy in subjects with non-seroconversion



Graph 2 – Anti Spike IgG antibody titer after the second and third dose of vaccine in the reference subpopulation