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KEYWORDS

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ABSTRACT

A low anti-spike antibody response of 28.6% was observed 28 days after BNT162b2 vaccine second dose among 133 solid organ transplant-recipients without previous COVID-19. No serious adverse events were recorded. Four severe COVID-19 cases were reported between or after the two doses. Our data suggests to change the vaccine strategy.

INTRODUCTION

Solid organ transplant (SOT)-recipients are at risk of infectious diseases with high morbidity and mortality rates. SARS-CoV-2 vaccination is then recommended in this population by international guidelines on Coronavirus disease 2019 (Covid-19) [1,2]. However, poor immune responses to vaccines have been reported among (SOT)-recipients.

Two SARS-CoV-2 mRNA-vaccines have been developed with reported efficacy reaching 94-95%. Nevertheless, immunocompromised patients including SOT-recipients were excluded from clinical trials [3,4]. Some authors have recently observed a poor anti-spike antibody response one month after a first dose of COVID-19 mRNA-vaccines in SOT-recipients [5,6]. Nevertheless, to our knowledge, limited data has been reported after two doses of vaccine [7–10]. Here we assessed vaccine immunogenicity and safety 28 days after two doses of mRNA-vaccine BNT162b2 (Pfizer/BioNTech) in a cohort of liver, kidney and heart transplant-recipients.

MATERIALS AND METHODS

The study was a single-centre cohort aiming to assess humoral response and safety of BNT162b2 (Pfizer/BioNTech) vaccine in SOT-recipients (Pitié-Salpêtrière hospital, Paris, France). The secondary outcome was to determine factors associated with negative serology test 28 days after the second vaccine injection among patients with negative SARS-CoV-2 serology at baseline. The study was approved by the “Bureau de la Protection des Données - APHP” (registration number: 20210329192434).

Patients

From January 2021 to April 2021**,** 143 SOT-recipients who received two doses (28 days apart) of BNT162b2 vaccine were retrospectively and consecutively included in our study, alongside a control group of healthcare workers (HCWs) with no major co-morbidities. All participants completed the full vaccination schedule. Exclusion criteria were: age <18 years, pregnancy, recent (less than 3 months) Sars-CoV-2 infection, active infection, previous vaccination (less than 3 weeks). Clinical data was obtained from patients’ medical records. Regarding

cardiovascular co-morbidities, arterial hypertension, ischemic heart disease, pulmonary embolism, acute stroke, arrhythmias, heart valvular disease, and venous thromboembolism were reported.

Immunogenicity

Chemiluminescent microparticle immunoassays (CMIA) were performed for the qualitative detection of IgG antibodies to the nucleocapsid protein of SARS-CoV-2 and the quantitative detection of IgG antibodies to the Receptor Binding Domain (RBD) of the S1 domain of the SARS-CoV-2 spike protein in sera at baseline, 28 days after the first and the second vaccine injection (Alinity i, Abbott Diagnostics, North Chicago, IL, USA; detection range 6.8-80 000 arbitrary units (AUs)/ml; positive agreement, 99.4%; negative agreement, 99.6%). Anti-spike response was defined as titers above 50.0 AU/ml, as recommended by the manufacturer. The correction factor between Abbott units and WHO binding antibody units (BAU) is of 0.142 (BAU/ml=0.142xAU/ml; established by Abbott with the WHO international standard NIBSC 20-136).

Safety assessment

Local reactions (mild-to- moderate injection-site pain) and systemic events (fever and chills, fatigue and headache, gastrointestinal disorders) systematically collected were reported. The side effects were recorded up to 7 days after the first dose injection and up to 1 month after the second dose injection.

Statistical analysis

Data is displayed as median (interquartile range (IQR)) for continuous variables and as number of patients and percentage in each group for categorical variables. A sub-group of 133 patients with negative SARS-CoV-2 serology at baseline was analyzed to evaluate the risk factors of negative serology test 28 days after the second dose. Mann-Whitney and Chi-Square statistic was used to assess statistical significance between groups for continuous and categorical variables, respectively. Binary logistic regression was performed on the significant variables found in univariate analysis (with p-value<0.1) to determine risk factors of negative serology test. P <0.05 was considered statistically significant for all analyses. IBM SPSS

Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses.

RESULTS

Patient characteristics

One hundred and forty-three patients and 25 HCWs were included. Median age of SOT-recipients was 61.0 years (IQR:55.0-67.0), and 71.3% (n=102) were male. Forty-point-five percent (n=58) were liver, 41.2 % (n=59) kidney and 18.1% (n=26) heart transplant-recipients. Diabetes and cardiovascular complications were the most common comorbidities, with a frequency of 39.9% (n= 57) and 53.8% (n=77) respectively. Median time from transplantation to the first BNT162b2 injection was 45.0 months (IQR:22.0-106.0). Calcineurin inhibitors-based immunosuppressive regimen was used in 62,2% (n=89), Mycophenolic acid in 72,0% (n=103), Steroids in 62,2% (n=89) and mTor-inhibitor in 18,9% (n=27) of the cases. Clinical characteristics of SOT-recipients according to the type of transplant are reported in Supplementary Table 1. The median age of HCWs was 55.0 years (IQR:38.0-62.0) and 72% (n=18) were female.

SARS-CoV-2 Spike-protein IgG

The seroconversion rate after the second dose was significantly lower among SOT-recipients than among HCWs (28.6% vs. 100.0%, p<0.0001), respectively. According to the type of transplant we reported a poor rate of seroconversion of 37.5%, 16.6% and 34.8% in liver, kidney and heart recipients, respectively. Among SOT-recipient responders, median titers of anti-S1 IgG were of 759 AU/mL (108 BAU/ml).

However, we observed positive anti-S1 IgG among all SOT-recipients with previous COVID-19 disease (8/143) even 28 days after the first dose with a median of anti-S1 IgG titers of 15 616 AU/ml (2 217 BAU/ml), and of 18 639 AU/ml (2 647 BAU/ml) 28 days after the second dose.

Safety

The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at injection site (25.7%, n=37), fatigue (14.2%, n=21), and headache (6.3%, n=9). Altogether, 44.2% (n=57/129) of patients developed side effects. No serious adverse events were reported.

Four patients have developed severe COVID-19 between (n=2) and after the two doses (n=2; one with positive anti-S1 IgG (476 UA/mL; 68 BAU/ml) and one with negative anti-S1 IgG at the time of the diagnostic). In details, the latter two developed Sars-Cov-2 infection 13 and 22 days after the second injection respectively and required hospitalization. One of the two patients was liver and kidney transplant-recipient, required admission to intensive care and eventually died from the disease.

Risk factors for negative serology 28 days after BNT162b2 second dose

Comparison of the clinical and serological data according to humoral response among the 133 SOT-recipients with negative SARS-CoV-2 IgG serology at baseline are shown in Table 1.

Recipients with negative serology 28 days after the second vaccine injection were more often over the age of 60 years (76.84% vs. 57.89%, *p*=0.029) compared with the recipients with positive serology. They were also more often kidney transplant-recipients (47.37% vs. 23.68%, *p*=0.012), treated with corticoids (67.37% vs. 42.10%, p=0.005) and by an immunosuppressive tritherapy (56.84% vs. 34.21%, p=0.018), transplanted <2 years (35.79% vs. 18.42, p=0.050) and diabetic patients (48.42% vs. 23.68%, p=0.010).

In our study, after adjustment for potential confounders, kidney transplantation [OR 4.01; 95% CI (1.56-10.28); *p*= 0.004], a time from transplantation to the first injection < 2 years [OR 2.87; 95% CI (1.06-7.75); *p*= 0.037] and diabetes [OR 3.49; 95% CI (1.39-8.54); *p*= 0.007] were the independent risk factors for negative SARS-CoV-2 anti-S1 IgG serology 28 days after the second vaccine injection.

DISCUSSION

We report here a low anti-spike antibody response 28 days after the second dose of the BNT162b2 vaccine among SOT-recipients, with 28.6% of seroconversion. Our results contrast with the vaccine trials but confirm the low immunogenicity response after one dose of mRNA vaccine in SOT-recipients previously reported [5,6]. They are slightly poorer than the recently published data on humoral response rate on SOT-recipients after two doses of mRNA SARS-CoV-2 vaccine [7–9]. Especially, the vaccine response seems to be dramatically low in kidney and heart transplant-recipients in our study (16.6% and 34.8%). Overall, an impaired immune response is generally expected in SOT-recipients as compared with the general population. In this work, kidney transplantation and time from transplantation to the first vaccination less than 2 years were risk factors related to a negative serological response (with OR of 4.01 and 2.87, respectively). Other studies have previously observed inadequate vaccine responses in transplant recipients depending on the age, type of organ, immunosuppressive regimens, time to transplant and vaccine composition [5–9].

The most common comorbidity in our cohort was diabetes (39.9%), which was associated with a negative serological response as well. Diabetes is common among patients that have received transplants, notably as a complication of the transplant immunosuppressive therapy (steroids, calcineurin inhibitors). This is also in line with reports suggesting that seasonal influenza vaccination uptake remains suboptimal in patients with diabetes in most countries probably due to immune dysfunction in patients with diabetes mellitus [11,12], and, regarding SARS-CoV-2 vaccine, with a recently published study about the antibody response after two doses of mRNA-1273 among kidney transplant recipients [10].

We reported no major adverse events to the vaccine.

Finally, our data suggests that SOT-recipients remain at high risk for COVID-19 disease during the outbreak, as seen in our cohort. Indeed, we reported four cases of COVID-19 disease among patients, of which two received two doses of vaccine. One of them died from respiratory failure syndrome.

We then advise to reconsider the vaccine strategy in favor of a reinforced or changed vaccine scheme or a new prophylactic treatment in this special population. Moreover, we would recommend a vaccination strategy including family and friendship circles.

Unfortunately, our study has several limitations including the small simple size, the absence of cellular response investigation and short follow-up period. Future multicenter studies including a large number of patients and assessing the clinical outcomes of COVID-19 according to the immunogenicity following the vaccination are needed.

In conclusions, our study showed a poor humoral response to BNT162b2 in vaccine SOT-recipients, and defined kidney transplant-recipients, transplantation time and diabetes as risk factors for negative response to the vaccine. We advise to reconsider the vaccine strategy and we would recommend to promote family and friendship circles vaccination.

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Conflict of Interest

None.

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Table 1. Humoral response in SOT recipients without anti-SARS-CoV-2 Antibody at baseline.

	Overall N=133	**Responders N=38**	**Non-Responders N=95**	**Univariable analysis *p*-value**	**Multivariable analysis *p*-value** [a]
Age ≥60 years, n (%)	95 (71.4)	22 (57.9)	73 (76.8)	0,029	
Male gender, n (%)	92 (69.2)	28 (73.7)	64 (67.4)	0.476	
BMI, median (IQR)	25.0 (22.5-28.4)	25.8 (22.3-28.2)	24.8 (22.6-28.5)	0.543	
Liver transplant recipients, n (%)	56 (42.1)	21 (55.3)	35 (36.8)	0.052	
Kidney transplant recipients, n (%)	54 (40.6)	9 (23.7)	45 (47.4)	0.012	**0.004**
Heart transplant recipients, n (%)	23 (17.3)	8 (21.0)	15 (15.8)	0.468	
Comorbidities					
Diabetes, n (%)	55 (41.3)	9 (23.7)	46 (48.4)	0.010	**0.007**
Cardiovascular complications, n (%)	71 (53.4)	17 (44.7)	54 (56.8)	0.234	
Time since transplant, <2 years, n (%)	41 (30.8)	7 (18.4)	34 (35.8)	0.050	**0.037**
Immunosuppressive regimen					
Corticoids, n (%)	80 (60.1)	16 (42.1)	64 (67.4)	0.005	
Calcineurin inhibitors, n (%)	109 (81.9)	31 (81.6)	78 (82.1)	0.887	
MMF, n (%)	95 (71.4)	24 (63.2)	71 (74.7)	0.151	
mTor inhibitor, n (%)	26 (19.5)	8 (21.0)	18 (18.9)	0.792	
Tritherapy, n (%)	67 (50.4)	13 (34.2)	54 (56.8)	0.018	
Humoral response 28 days after 1st dose					
Ab response, n/total number (%)	9/125 (7.2)				
Anti-spike Ab titers among responders, median AU/ml; BAU/ml (IQR)	153; 22 (129-860; 18-122)				

Humoral response 28 days after 2[d] dose				
Ab response, n/total number (%)	38/133 (28.6)			
Anti-spike Ab titers among responders, median AU/ml; BAU/ml (IQR)	759; 108 (257-3 269 ; 36-464)			
Side effects, n (%)	57 (44.2)	19/36 (52.8)	38/93 (40.9)	0.221

[a]

Significative *p*-value reported in bold.
Ab: antibodies; AU/ml: arbitrary units per milliliter; BMI: body mass index; IQR: interquartile range (25[th] and 75[th] percentile); MMF: mycophenolic acid.