BRIEF REPORT

Poor Antibody Response After Two Doses of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine in Transplant Recipients

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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 coronavirus disease 2019 (COVID-19). No serious adverse events were recorded. Four severe COVID-19 cases were reported between or after the 2 doses. Our data suggest to change the vaccine strategy.

Keywords.   SARS-CoV-2 vaccination; SOT recipients; humoral response; COVID-19 disease; anti-spike antibodies.

Solid organ transplant (SOT) recipients are at risk of infectious diseases with high morbidity and mortality rates. Severe acute respiratory syndrome coronavirus 2 (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 messenger RNA (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 1 month after the first dose of COVID-19 mRNA-vaccines in SOT recipients [5, 6]. Nevertheless, to our knowledge, limited data have been reported after 2 doses of vaccine [7–10]. Here we assessed vaccine immunogenicity and safety 28 days after

2 doses of mRNA-vaccine BNT162b2 (Pfizer/BioNTech) in a cohort of liver, kidney, and heart transplant recipients.

METHODS

The study was a single-center 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 2 doses (28 days apart) of BNT162b2 vaccine were retrospectively and consecutively included in our study, along with a control group of healthcare workers (HCWs) with no major comorbidities. All participants completed the full vaccination schedule. Exclusion criteria were age <18 years, pregnancy, recent (<3 months) SARS-CoV-2 infection, active infection, previous vaccination (<3 weeks). Clinical data were obtained from patients' medical records. Regarding cardiovascular comorbidities, 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 immunoglobulin G (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, Illinois, 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 World Health Organization (WHO) binding antibody units (BAU) is of 0.142 (BAU/mL = 0.142 AU/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) were systematically collected and 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 are displayed as median (interquartile range [IQR]) for continuous variables and as number of patients and percentage in each group for categorical variables. A subgroup 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 χ^2 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 < .1) to determine risk factors of negative serology test. P < .05 was considered statistically significant for all analyses. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, New York, USA) was used for all statistical analyses.

RESULTS

Patient Characteristics

In total, 143 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. In total, 40.5% (n = 58) were liver recipients, 41.2 % (n = 59) were kidney recipients, and 18.1% (n = 26) were 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 was used in 72.0% (n = 103), steroids were used in 62.2% (n = 89), and mTor inhibitor was used 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 < .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 developed severe COVID-19 between (n = 2) and after the 2 doses (n = 2; 1 with positive anti-S1 IgG [476 UA/mL; 68 BAU/mL] and 1 with negative anti-S1 IgG at the time of the diagnostic). In detail, the latter 2 developed SARS-CoV-2 infection 13 and 22 days after the second injection, respectively, and required hospitalization. One of the 2 patients was a 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 = .029) compared with the recipients with positive serology. They were also more often kidney transplant recipients (47.37% vs 23.68%, P = .012), treated with corticoids (67.37% vs 42.10%, P = .005) and by an immunosuppressive tritherapy (56.84% vs 34.21%, P = .018), transplanted <2 years (35.79% vs 18.42, P = .050), and were diabetic patients (48.42% vs 23.68%, P = .010).

In our study, after adjustment for potential confounders, kidney transplantation (odds ratio [OR] 4.01; 95% CI [1.56–10.28]; P = .004), a time from transplantation to the first injection <2 years (OR 2.87; 95% CI [1.06–7.75]; P = .037) and diabetes (OR 3.49; 95% CI [1.39–8.54]; P = .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 2 doses of mRNA SARS-CoV-2 vaccine [7–9]. Specifically, the vaccine response seems to be dramatically low in kidney and heart transplant recipients in our study (16.6% and 34.8%, respectively). 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 <2 years were risk factors related to a negative serological response (with OR of 4.01 and

Table 1. Humoral Response in Solid Organ Transplant (SOT) Recipients Without anti-Severe Acute Respiratory Syndrome Coronavirus 2 (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 y, n (%)	95 (71.4)	22 (57.9)	73 (76.8)	.029	
Male gender, n (%)	92 (69.2)	28 (73.7)	64 (67.4)	.476	
BMI, median (IQR)	25.0 (22.5–28.4)	25.8 (22.3–28.2)	24.8 (22.6–28.5)	.543	
Liver transplant recipients, n (%)	56 (42.1)	21 (55.3)	35 (36.8)	.052	
Kidney transplant recipients, n (%)	54 (40.6)	9 (23.7)	45 (47.4)	.012	**.004**
Heart transplant recipients, n (%)	23 (17.3)	8 (21.0)	15 (15.8)	.468	
Comorbidities					
Diabetes, n (%)	55 (41.3)	9 (23.7)	46 (48.4)	.010	**.007**
Cardiovascular complications, n (%)	71 (53.4)	17 (44.7)	54 (56.8)	.234	
Time since transplant, <2 y, n (%)	41 (30.8)	7 (18.4)	34 (35.8)	.050	**.037**
Immunosuppressive regimen					
Corticoids, n (%)	80 (60.1)	16 (42.1)	64 (67.4)	.005	
Calcineurin inhibitors, n (%)	109 (81.9)	31 (81.6)	78 (82.1)	.887	
MMF, n (%)	95 (71.4)	24 (63.2)	71 (74.7)	.151	
mTor inhibitor, n (%)	26 (19.5)	8 (21.0)	18 (18.9)	.792	
Tritherapy, n (%)	67 (50.4)	13 (34.2)	54 (56.8)	.018	
Humoral response 28 d 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 d after 2nd 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)	.221	

Abbreviations: Ab, antibodies; AU/mL, arbitrary units per milliliter; BAU/mL, binding antibody units per milliliter; BMI, body mass index; IQR, interquartile range (25th and 75th percentile); MMF; mycophenolic acid.
[a]Significant P values reported in bold.

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 2 doses of mRNA-1273 among kidney transplant recipients [10]. We reported no major adverse events to the vaccine.

Finally, our data suggest that SOT recipients remain at high risk for COVID-19 disease during the outbreak, as seen in our cohort. Indeed, we reported 4 cases of COVID-19 disease among patients, of which 2 received 2 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 larger 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 promoting family and friendship circles vaccination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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