Low Immunoglobulin G Antibody Levels Against Severe Acute Respiratory Disease Coronavirus 2 After 2-Dose Vaccination Among Liver Transplantation Recipients

TO THE EDITOR:

Liver transplantation (LT) recipients (LTRs) were not included in severe acute respiratory disease coronavirus 2 (SARS-CoV-2) vaccine registration trials, and therefore the clinical efficacy of the different vaccines for this group of patients who are immunosuppressed is not yet known. Recent work has demonstrated a reduced humoral immune response after administration of SARS-CoV-2 messenger RNA (mRNA)–based vaccines to solid organ transplantation recipients (SOTRs),[1-3] especially in kidney transplantation recipients. However, there is still not enough information regarding the use of different vaccine platforms in LTRs. Recently, Rabinowich et al.[4] reported that only 47.5% of LTRs vaccinated with BNT162b2 (Pfizer-BioNTech, New York, NY, USA) developed specific anti-SARS-CoV-2 antibodies 2 or 3 weeks after the second dose administration. However, Strauss et al.[5] reported that LTRs vaccinated with 2 doses of SARS-CoV-2 mRNA-based vaccines developed a much more robust humoral response compared with other SOTRs.

Development of a robust humoral response against different vaccine platforms in LTRs remains an open question. In this work, we compared anti-SARS-CoV-2 antibody response in a study group of LTRs and a healthy control group after the 2-dose series of either inactivated virus CoronaVac (Sinovac Life Sciences Co., Beijing, China) or BNT162b2 vaccines.

Patients and Methods

We conducted a cross-sectional study to analyze the specific immunoglobulin G (IgG) response directed against the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein after full vaccination with BNT162b or CoronaVac.

A total of 85 LTRs registered in the National Liver Transplantation Programme of Uruguay were included with the following criteria: aged >18 years, no clinical criteria of previous disease or polymerase chain reaction confirmation for SARS-CoV-2 infection, and fully vaccinated with either the BNT162b2 (n = 11) or CoronaVac (n = 74) vaccines. The median time between LT and vaccine administration was 4 years (interquartile range [IQR], 2-8 years; range, 1 month-24 years). The distribution by type of vaccine was based on the guidelines defined by the national health authority, according to age groups, risk groups, and vaccine availability at the beginning of the vaccination program. A total of 44 healthy individuals belonging to the staff of a research institution were included in the control group with the following criteria: aged >18 years, no clinical history of coronavirus disease

Abbreviations: BAU, binding antibody units; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; IQR, interquartile range; LT, liver transplantation; LTR, liver transplantation recipient; mRNA, messenger RNA; NIBSC, National Institute for Biological Standards and Control; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory disease coronavirus 2; SOTR, solid organ transplantation recipient; WHO, World Health Organization.

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2019 (COVID-19), prevaccination negative serology, and 2 doses of either the BNT162b2 (n = 22) or CoronaVac (n = 21) vaccines. The ethical review institutional board approved the study, and all participants were included after signing the informed consent form.

Serum samples were obtained at least 15 days after the second dose from the LTR group (median, 45 days; IQR, 40-55 days) and from the healthy group (median, 45 days; IQR, 30-60 days). Specific RBD-IgG levels were determined by using the COVID-19 IgG QUANT ELISA Kit (ATGen SRL, Montevideo, Uruguay). Results are expressed in binding antibody units (BAU)/mL by using the World Health Organization (WHO) International Standard for anti-SARS-CoV-2 immunoglobulin (National Institute for Biological Standards and Control, NIBSC code 20/136, https://www.nibsc.org/documents/ifu/20-136.pdf) for assay calibration.

Results and Discussion

We report the results of the first 85 LTRs enrolled in this study (median age, 56 years; IQR, 45-65 years; 62.3% men). A total of 11 LTRs (13%) received the BNT162b2 vaccine, and 74 received (87%) the CoronaVac vaccine. The overall LTR seroconversion rate after second-dose vaccination with both platforms was 41.2% (35 of 85). However, a significantly higher seroconversion rate ($P = 0.045$) was found among LTRs who received BNT162b2 (72.7%; 8 of 11) versus CoronaVac (36.5%; 27 of 74). The control group included 43 healthy volunteers (median age, 41 years; IQR, 35-44 years; 35% men). The seroconversion rate for the healthy control group after the second dose with both vaccine platforms was 100%.

Significantly higher antibody levels ($P = 0.005$) were found among LTRs fully vaccinated with BNT162b2 (median, 66 BAU/mL; IQR, 5-321 BAU/mL) versus CoronaVac (median, 2 BAU/mL; IQR, 1-18.5 BAU/mL). Similarly, the antibody response was also significantly higher ($P < 0.001$) in healthy control individuals fully vaccinated with BNT162b2 (median, 1355 BAU/mL; IQR, 968.3-2495 BAU/mL) compared with CoronaVac (median, 190 BAU/mL; IQR, 96.5-328.5 BAU/mL). However, significantly lower IgG levels ($P < 0.001$) were found when comparing LTRs (median, 2 BAU/mL) with the healthy group (median, 190 BAU/mL) vaccinated with CoronaVac. Similarly, significantly lower specific antibody levels ($P < 0.001$) were also found when comparing LTRs (median, 66 BAU/mL) with the healthy group (median, 1355 BAU/mL) fully vaccinated with BNT162b2 (Fig. 1).

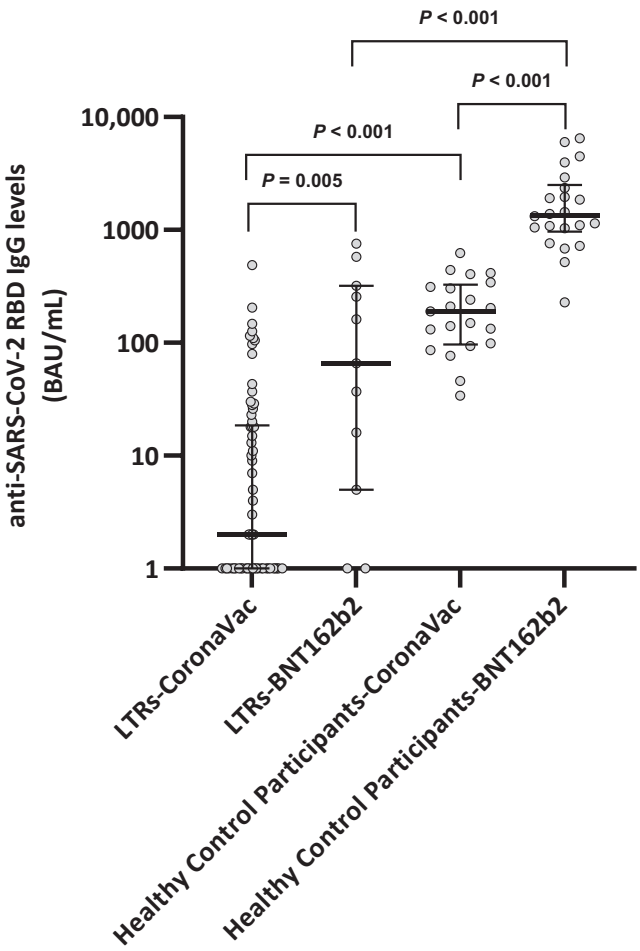

FIG. 1. Specific anti-RBD SARS-CoV-2 IgG levels in LTRs and healthy control participants fully vaccinated with 2 doses of either the BNT162b2 or CoronaVac vaccines. IgG levels are expressed in BAU/mL, by using the WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136) for assay calibration. Medians and IQRs are indicated by horizontal bars. Differences between independent-group continuous data were analyzed by Mann-Whitney U test.

No major adverse events or rejection episodes associated with vaccination were identified in this LTR cohort.

During the development of this study, 2 fully vaccinated LTRs developed a mild form of COVID-19 without the need for therapeutic intervention: 1 vaccinated with CoronaVac and the other with BNT162b2.

A reduction in glomerular filtration (cutoff point <60 mg/dL) was statistically associated with the LTR

TABLE 1. Demographic and Clinical Characteristics of LTRs Fully Vaccinated With BNT162b2 or CoronaVac Associated With Seroconversion Status

Variable	LTR Nonresponders	LTR Responders	LTR Total	*P* Value
Number (%)	50 (58.8)	35 (41.2)	85 (100)	
Age in years, median (IQR)	54.6 (48-65)	49.4 (31-62)	56 (45-65)	0.102
Male sex, n (%)	33 (66)	20 (57)	53 (62.3)	0.306
Type of vaccine, n (%)				
Inactivated SARS-CoV-2, CoronaVac	47 (63.5)	27 (36.5)	74 (87)	0.045
mRNA BNT162b2, Pfizer/BioNTech	3 (27.3)	8 (72.7)	11 (13)	
Immunosuppression treatment, n (%)				
Tacrolimus	45 (90)	31 (88.5)	76 (89.4)	1
Mycophenolate	32 (64)	16 (45.7)	48 (56.5)	0.094
Corticosteroids	26 (52)	16 (45.7)	42 (49,4)	0.568
Everolimus	12 (24)	11 (31.4)	23 (27)	0.584
LTRs in the first year after transplant	7 (14)	1 (2.8)	8 (9.4)	0.133
Glomerular filtration <60 mg/dL, n (%)	33 (66)	2 (5.7)	35 (41.2)	<0.001

group that did not elicit a measurable antibody response against the vaccine ($P < 0.001$; 95% confidence interval, 1511-2767). Although nonstatistically significant ($P = 0.133$), patients fully vaccinated during the first year after LT showed a low seroconversion rate, in line with the major pharmacological immunosuppression period. Fisher's exact, chi-square, and Student *t* tests were used in the statistical analysis (Table 1).

In this work, we show significantly lower anti-RBD-IgG levels in the LTR fully vaccinated group (2 doses 28 days apart) either with CoronaVac or with BNT162b2 when compared with the healthy control group. These results are in agreement with previous reports showing low levels of specific IgG after the 2-dose administration of mRNA-based vaccines in LTRs (Fig. 1). Furthermore, our work provides original evidence on the significant low immunogenicity of CoronaVac in this special risk group.

To our knowledge, this is the first study that reports the seroconversion rate in LTRs vaccinated with CoronaVac. Our results also provide information about the low incidence of major adverse events or rejection episodes associated with vaccination in this LTR cohort.

Taking into account the international evidence and the results presented in this work, the Uruguayan Ministry of Public Health decided to reinforce the primary scheme of vaccination in the transplant recipient group. After 1 month of the second dose, those who have received BNT162b2 may receive a third dose of the same vaccine, whereas those who have received the complete vaccination schedule with CoronaVac may receive the complete vaccination schedule with BNT162b2 (2 doses). The effects of this intervention in reinforcing the recipient immune response will be analyzed by following this cohort over time.

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