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TRANSPLANT INFECTIOUS DISEASE

CLINICAL CORRESPONDENCE

High rate of seroconversion after COVID-19 vaccination during the long term follow-up of heart transplant recipients

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Dear Editor,

Despite a third or fourth COVID-19 vaccine dose, rate of seroconversion remains usually lower in solid organ transplant recipients than in the community.[1–4] For instance, Peled et al. found a positive antibody response in 67% of the heart transplant recipient (HTR) 18 days after a third dose of BNT162b2 vaccine.[1] In contrast, we observed a very high seroconversion rate in our cohort of HTR vaccinated more than 3 years after transplantation. All these 50 patients received BNT162b2(Pfizer/BioNTech) vaccine. Vaccination protocol included the administration of two doses 1 month apart and of one third dose 3 months after the second dose. A fourth injection of vaccine was possible 3–6 months following the third dose according to serological status. The number of doses could be reduced in case of intercurrent SARS-CoV-2 infection. We measured immunoglobulin response using TrimericS Diasorin assay at the last visit in 2022. Using this assay, a level of antibodies <30 binding antibody unit (BAU)/ml is considered as a negative response to vaccination. A vaccine efficacy of 80% against symptomatic infection has previously been described with an antibody level >264 BAU/ml in the community.[5]

The first dose was given between February 2021 and September 2021. Two patients received one dose of vaccine, nine two doses, 21 three doses, and 18 four doses. The mean time between transplantation and the initiation of vaccination was 17.1 ± 7.2 years. At the time of vaccination, immunosuppressive therapy included a calcineurin inhibitor in 50 (100%), mycophenolate (MMF) in 25 (50%), azathioprine in 10 (20%), everolimus in 11 (22%), and corticosteroids in 12 (24%). Median dose of mycophenolate was 1500 mg/day among patients who received this antimetabolite. Immunosupressive regimen was not modified according to the pandemics. At baseline, significant comorbidities (diabetes, muscular dystrophy, heart failure, active neoplasia, chronic obstructive pulmonary disease, severe renal failure) were observed in 26 patients.

Among the 50 patients, we observed a seroconversion rate of 94% at last visit (three patients achieved an antibody level <30 BAU /ml, 3 a level 30 ≤ ≤ 264 BAU/ml, and 44 a level >264 BAU/ml). Twenty-four of the 50 patients had a symptomatic COVID-19 infection since the beginning of vaccination. All these infections were mild and did not result in hospitalization. The table gives baseline characteristics of patients according to the occurrence of COVID-19 infection after the beginning of vaccination. Mean number of vaccine injections was significantly lower in patients with intercurrent COVID-19 infection versus patients without. Median antibody level at last test was 1780 BAU in patients with intercurrent COVID-19 infection versus 1140 BAU in patients without (NS).

As the high seroconversion rate may signify an underpowered immunosuppressive therapy, we also examine anti-HLA antibodies levels. These antibodies were measured before and after vaccination in every patient using Luminex technology. At the time of vaccination, 10 patients (20%) had posttransplantation (post-Tx) persistent donor-specific antibodies (DSAs). No new DSA appeared after vaccination. Moreover, none of the 50 patients had acute graft rejection since the beginning of COVID-19 pandemics.

Several causes may explain this unusually high seroconversion rate. First, 78% of these HTR have received three or four doses of vaccine. However, this high number of vaccine injections does not fully explain this high seroconversion rate since recent studies using four injections of vaccine report lower levels of antibodies.[4] Second, 48% of the patients had COVID-19 infections after the beginning of the vaccination. Of note, none of these infections was severe despite a high rate of significant comorbidities. The third potential explanation

TABLE 1 Characteristics of the patients according to the occurrence of COVID-19 infection since the beginning of vaccination

	With COVID-19 infection	Without COVID-19 infection
N	24	26
Age (years) ± SD	53.0 ± 19.3	55.8 ± 18.3
Males	14	16
Patients with at least one significant comorbidity	16	10
Time since transplantation (years) ± SD	18.3 ± 8.0	15.9 ± 6.3
Mean number of vaccine doses ± SD	2.8 ± 0.9	3.3 ± 0.5*
On cyclosporine	13	11
Mean trough concentration of cyclosporine (ng/ml) ± SD	86.6 ± 25	92.0 ± 21
On tacrolimus	11	14
Mean trough concentration of tacrolimus (ng/ml) ± SD	6.7 ± 2.0	4.9 ± 1.9*
On MMF	12 (50%)	11 (42%)
On azathioprine	6	4
On corticosteroid	8	7
On everolimus	5	5

*$p < .05$ versus with COVID-19 infection.

is that the immunosuppressive treatment intensity was probably lower than in the previously published cohorts, since the mean time since transplantation was high (17.1 years). Plasma trough levels of cyclosporine and tacrolimus were relatively low as compared to previous cohorts (Table 1). [1–3] Moreover, the prevalence of mycophenolate treatment (50%) was lower than in most of the previously published HTR cohorts.[1–4] Accordingly, recent reports have shown that mycophenolate treatment predicts a lower humoral immune response to various anti-SARS-CoV-2 vaccines in HTR.[1–3] Finally, the prevalence of post-Tx persistent DSA observed in our patients (20%) was within the usual range (10%–30%).[6]

Thus, this series shows that a high level of seroconversion after COVID-19 vaccination may be reached among HTR receiving up to four vaccine doses and a relatively low intensity immunosuppressive treatment, without evidence of underpowered treatment. How this result can be generalized to patients with shorter time since transplantation requires further studies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Peled Y, Ram E, Lavee J, et al. Third dose of the BNT162b2 vaccine in heart transplant recipients: immunogenicity and clinical experience. *J Heart Lung Transplant*. 2022;41:148-157.
2. Marinaki S, Degiannis D, Roussos S, et al. Head-to-head comparison of response rates to the two mRNA SARS-CoV-2 vaccines in a large cohort of Solid Organ Transplant (SOT) recipients. *Vaccines*. 2022;10:190.
3. Tanner R, Starr N, Chan G, et al. Humoral response to SARS-CoV-2 adenovirus vector vaccination (ChAdOx1 nCoV-19 [AZD1222]) in heart transplant recipients aged 18 to 70 years of age. *J Heart Lung Transplant*. 2022;41(4):492-500.
4. Caillard S, Thaunat O, Benotmane I, et al. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. *Ann Inter Med*. 2022;75:455-456.
5. Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:2032-2040.
6. Barten MJ, Schulz U, Beiras-Fernandez A, et al. The clinical impact of donor-specific antibodies in heart transplantation. *Transplant Rev* 2018;32:207-217.

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