Impaired Humoral Response to Third Dose of BNT162b2 mRNA COVID-19 Vaccine Despite Detectable Spike Protein–specific T cells in Lung Transplant Recipients

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The immunogenicity of the mRNA coronavirus disease 2019 vaccine in thoracic organ transplant recipients is poor.[1,2] Early reports provided evidence of increased immunogenicity after the third mRNA vaccine dose in solid organ transplant recipients.[3,4] However, the antibody and cellular responses after the third dose of the BNT162b2 vaccine (Pfizer-BioNTech) and its safety in lung transplant recipients (LTRs) are unknown to date.

We included 15 LTRs without a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who received 2 doses of the BNT162b2 vaccine 21 d apart with no antibody response. In this cohort, we assessed the antibody and cellular responses immediately before and 3 wk after the third dose administered 3 mo after the second dose. Anti–SARS-CoV-2 immunoglobulin (Ig) G levels were tested by Microblot-Array coronavirus disease 2019 IgG against a mix of recombinant antigens (TestLine Clinical Diagnostics, Brno, Czech Republic). SARS-CoV-2–specific T cells were assessed by detecting intracellular cytokines after a 4-h stimulation of patients' peripheral blood mononuclear cells with 51 overlapping 11mer peptides of the spike receptor–binding domain protein (JPT Peptide Technologies, Berlin, Germany) as we described previously.[2]

The study was approved by the Motol University Hospital institutional review board and the participants provided written informed consent.

The median age was 56.2 y (interquartile range [IQR], 54–60), 87% were male, the median time from transplant to the first dose was 1277 d (IQR, 889–2496), the median time from the second to third dose was 96 d (IQR, 95–97), and the median time from the third dose to SARS-CoV-2 IgG and specific T-cell detection was 21 d (IQR, 20–21). The maintenance immunosuppression included calcineurin inhibitors (100%), mycophenolate (93%), and corticosteroids (100%).

Before the third vaccine dose, we detected cellular response in 2 out of 15 patients (13%), albeit at low frequency. SARS-CoV-2–specific IgG levels were not detected in any of the vaccinated LTRs. Three weeks after the third dose, we detected cellular response in 7 patients (47%) and humoral response in 2 patients (13%). The frequencies of the SARS-CoV-2–specific T cells were above 0.1% in 4 of the 7 responders; levels never achieved after the second dose in our previous cohort (Figure 1).[2]

The significantly lower antibody response in LTRs as compared to patients after other organ transplantations is probably related to higher immunosuppression in this group, specifically to the dose of mycophenolate.[3,5] One of the 2 patients with humoral response was the only one without mycophenolate, and the second one had the lowest dose of mycophenolate of all patients.

We did not observe any systemic adverse events, rejection episodes, or decline in allograft function in any patient within 3 mo after the third dose.

In conclusion, in the absence of humoral response, we detected emergence of cellular response in 47% of

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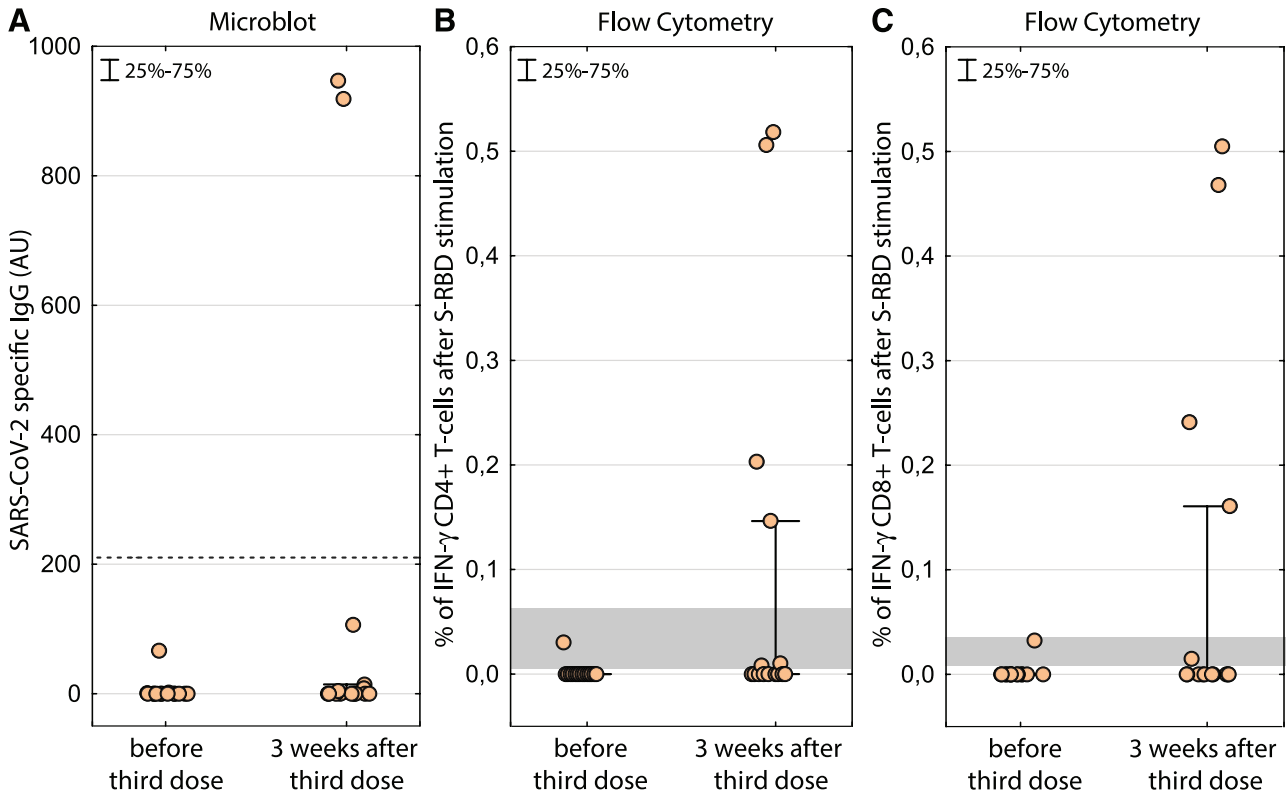

FIGURE 1. SARS-CoV-2–specific IgG response before and after the third BNT162b2 mRNA vaccine. The dotted line shows the positivity threshold (A). SARS-CoV-2 S-RBD–specific response of $CD4^+$ (B) and $CD8^+$ T cells (C). The magnitude of the response is calculated as percent of interferon-γ–responding T cells after S-RBD stimulation less percent of interferon-γ without any stimulation. The gray area depicts the levels of positive response measured after second dose in a previous cohort by the same technique.[2] IFN-γ, interferon-γ; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, spike receptor–binding domain.

LTRs after the third vaccine dose, which might have a clinical benefit; however, the measurable response is low, dominantly cellular, and only detectable in half of the patients. Together with no evidence of rejection episodes, the third dose should be recommended in LTRs but with the caution that protection by the vaccine may not be more than partial.

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