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BNT162B2 mRNA COVID-19 Vaccine in Heart and Lung Transplanted Young Adults: Is an Alternative SARS-CoV-2 Immune Response Surveillance Needed?

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In the present study, we report the safety profile and the immunogenicity of the BNT162B2 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Pfizer-Biontech) in a cohort of heart and lung transplanted recipients (solid organ transplant [SOT]), followed since childhood (mean age at transplantation = 14.65 [SD ± 7.24]) with no history of coronavirus disease 2019. Our data confirmed a good safety profile of the vaccine with no evidence of graft rejection in immunized patients.[1] Anti–SARS-CoV-2 S1 receptor-binding domain antibody (Ab) (Roche) and antitrimeric SARS-CoV-2 Ab (LIASION SARS-CoV-2 DiaSorin) along with the frequency of SARS-CoV-2–specific $CD4^+$ T cells, identified through flow cytometry by the surface expression of the inducible costimulatory molecule CD40L, were used to detect vaccine-induced SARS-CoV-2–specific responses, before vaccination, 21 d after priming (T21), and at 7 d after booster (T28) (Figure 1A) in 34 SOTs and 36 healthy controls (HCs). Local ethical committee approved the study and written informed consent was obtained from all participants or guardians. Overall, anti-S and antitrimeric Ab responses were significantly lower in SOTs versus HCs at T21 ($P < 0.0001$) and at T28 ($P < 0.0001$) (see Figure 1B–G). Ten out of 34 SOTs (29%) had undetectable SARS-CoV-2 immunoglobulin G at T28. The serologic test, performed in SOTs 120 d after vaccination (T120), showed a weak increase in anti-S SARS-CoV-2 Ab compared with T28 (Figure 1C). In addition to humoral response, we evaluated the frequency of SARS-CoV-2–specific T cell measured through the upregulation of CD40L after in vitro stimulation with SARS-CoV-2 peptides (representative gate in Figure 1H), as previously described.[2] HCs were able to significantly upregulate CD40L after in vitro stimulation ($P = 0.0034$) thus confirming that T-cell compartment is needed to mount specific antibody responses. Such increase was not observed in SOTs (Figure 1I) either showing Ab seroconversion after vaccination (responders [Rs]) or not (not responders [NRs]) (Figure 1 J). Baseline B-cell phenotype analysis (representative gate in Figure 1K), performed to investigate prediction markers of vaccine response, showed

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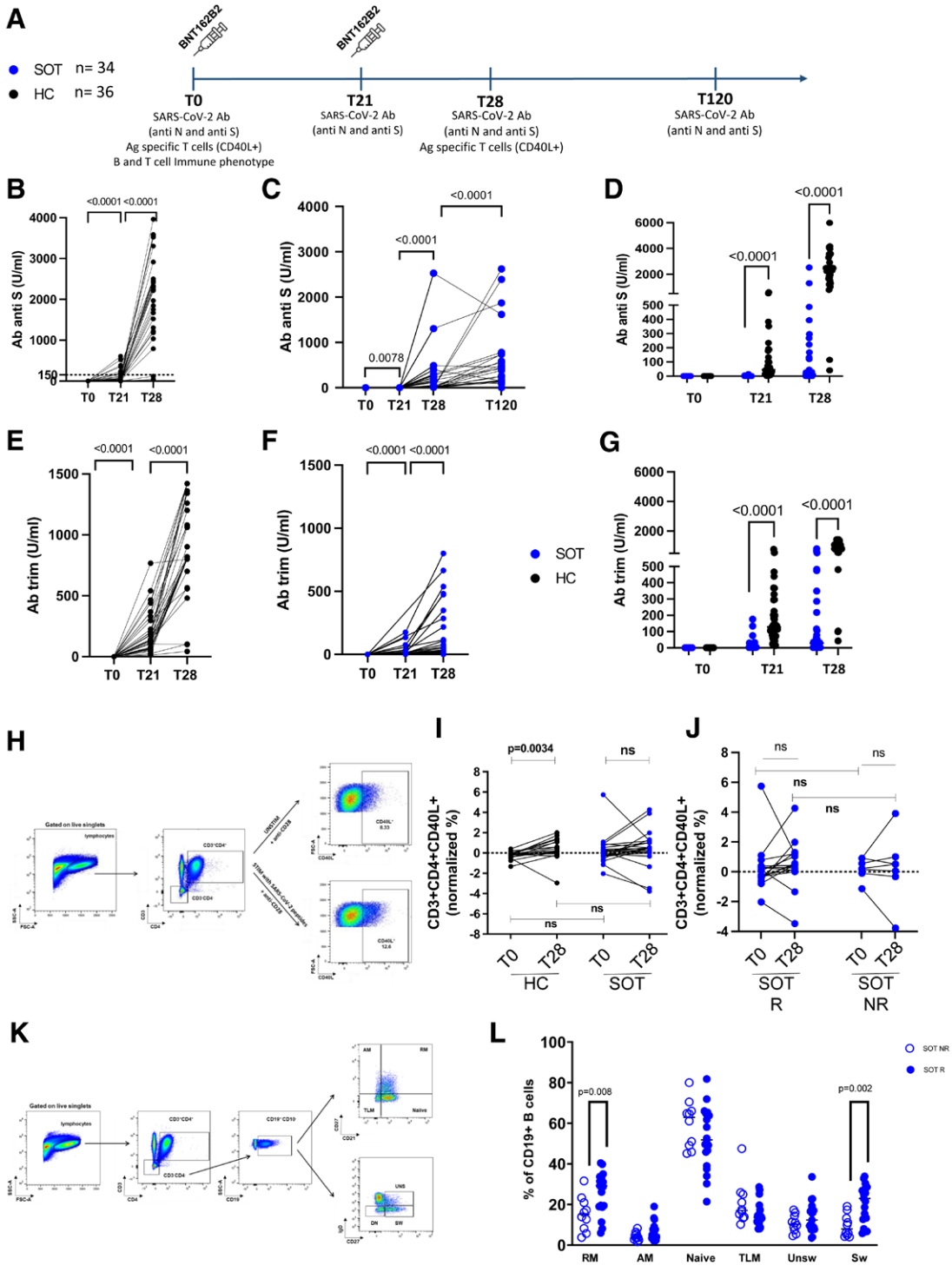

FIGURE 1. Study design is shown in panel A. Longitudinal analysis of anti-S (B–D) and anti-trim Ab (E–G), respectively, in HCs and SOTs. Paired nonparametric *t* tests were performed to define longitudinal Ab increase (B, C, E, and F). Differences between HCs and SOTs were calculated for anti-S (D) and anti-trim Ab (G) at T0, T21, and T28. Unpaired nonparametric *t* tests were used for comparisons. SARS-CoV-2–specific T-cell responses are shown in panels H–L. Representative gating strategy for SARS-CoV-2–specific CD4 T cell after in vitro stimulation with SARS-CoV-2 peptides is shown in panel H. Normalized frequencies of $CD4^+$ $CD40L^+$ T cells (% stimulated – % unstimulated) are shown at both T0 and T28 in HCs and SOTs (panel I) and in SOT R or NR (panel J). Paired analysis showing delta of CD40L frequency between stimulated and unstimulated sample is shown in SOTs and HCs for T0 and T28 (panel I). The same analysis is shown for SOTs not presenting Ab seroconversion at T28 (NRs) and for patients with Ab serconversion (Rs) (panel J). Representative gating strategy for B-cell subsets is shown in panel K. Dot plot shows differences in B-cell subsets frequencies between SOT NRs and Rs (panel L). Ab, antibody; Ag, antigen; AM, activated memory; anti-trim, antitrimeric; DN, double negative; HC, healthy control; NR, not responder; ns, nonsignificant; R, responder; RM, resting memory; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; SW, switched memory; TLM, tissue like memory; UNSW, unswitched memory.

similar frequencies of total $CD19^+$ B cells between NRs and Rs (not shown). However, the analysis of maturational B-cell subsets showed a lower frequency of resting ($CD19^+$ $CD27^+$ $CD21^+$) ($P = 0.008$) and switched (immunoglobulinD^- $CD27^+$) ($P = 0.002$) memory B cells in NRs compared with Rs (Figure 1L). Overall, our results confirmed recent studies showing that SOTs have a suboptimal response following mRNA vaccination, which implies that additional information to identify an alternative and more effective approach is needed. A recent study showed that a third booster of the mRNA coronavirus disease 2019 vaccine, administered 2 mo after the second dose, can be considered in patients who failed to seroconvert.[3,4] Among other vaccination approaches, such as the heterologous (viral vectored + mRNA) or schedules with additional booster doses,[3,4] a promising strategy in SOTs could be the use of an adjuvanted protein vaccine, currently under investigation in human trials (National Clinical Trial 04904549).[5] It remains unknown whether these alternative strategies should be directed only to patients with a suboptimal serologic response or considered upon the use of additional cellular correlates,[5] hence suggesting that an alternative periodic longitudinal SARS-CoV-2 immune response surveillance may be needed in this population.

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APPENDIX

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