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A third vaccine dose substantially improves humoral and cellular SARS-CoV-2 immunity in renal transplant recipients with primary humoral nonresponse

To the editor: Renal transplant recipients (RTRs) are at a high risk for fatal coronavirus disease 2019 (COVID-19).[1] Vaccinations are indispensable to protect this vulnerable population. Unfortunately, >50% of solid organ recipients do not mount antibody responses after 2 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines.[2,3] We hypothesized that a third vaccine dose elicits protective humoral and cellular immune response in primary nonresponders. Ten RTRs under immunosuppression (Supplementary Table S1) without measurable SARS-CoV-2 spike antibodies 4 weeks after a second dose of BNT162b2 (Pfizer–

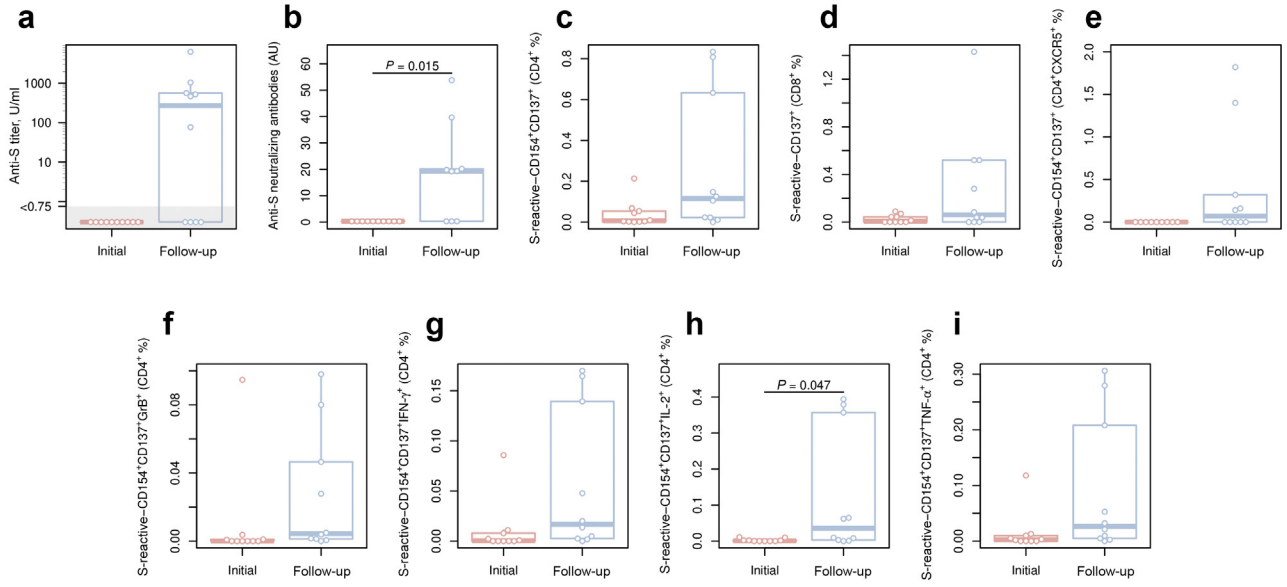

Figure 1 | Humoral and cellular response following the third vaccination in kidney transplant recipients in whom the primary vaccination failed. Renal transplant recipients with failed seroconversion after BNT162b2 (Pfizer–BioNTech) prime-boost vaccination were subjected to the third vaccination by mRNA-1273 (Moderna). Humoral and cellular immune responses before (red) and 2 weeks after (blue) the third vaccination are presented. Enzyme-linked immunosorbent assay (ELISA) was performed for the assessment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S)-protein–binding antibodies, and neutralizing antibody capacity was assessed by a pseudovirus system bearing the SARS-CoV-2 S-protein. S-protein–reactive T cells were analyzed by flow cytometry following an overnight stimulation of peripheral blood mononuclear cells with overlapping peptide pools (OPPs) spanning the S-protein of SARS-CoV-2. Activation markers CD154 and CD137 were used for the assessment and quantification of S-protein–reactive T cells within $CD3^+$ T cells. Expression levels of cytokines, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and interleukin 2 (IL-2), as well as the effector molecule granzyme B (GrB), were analyzed among activated $CD4^+$ T cells by intracellular staining and flow cytometry after stimulation with OPPs spanning the whole S-protein of SARS-CoV-2. Differences between the subcohorts were analyzed using the paired, 2-sided *t* test. The significance threshold was set at 0.05. Box plots depict the median and first and third quartiles of a variable; the maximum length of the whiskers corresponds to 1.5× the interquartile range. (**a**) Titers of anti–SARS-CoV-2 S-protein–binding antibodies assessed by ELISA. (**b**) Neutralizing antibody titers for the SARS-CoV-2 S-protein. (**c**) Frequencies of S-reactive $CD4^+$ T cells, as defined by $CD154^+CD137^+$ expression. (**d**) Frequencies of S-reactive $CD8^+$ T cells, as defined by CD137 expression and cytokine production. (**e**) Frequencies of S-reactive follicular $CD4^+$ T-helper cells, as defined by the expression of CXC chemokine receptor 5 (CXCR5). (**f–i**) Frequencies of S-reactive $CD4^+$ T cells producing (**f**) GrB, (**g**) IFNγ, (**h**) IL2, and (**i**) TNFα. AU, arbitrary unit.

BioNTech) received a third vaccine dose (mRNA-1273; Moderna), which was well-tolerated. For a description of the employed methods, see the Supplementary Methods. The third vaccination induced seroconversion in 6 subjects (60%) with a median antibody titer concentration of 542 (interquartile range, 478–923) U/ml and neutralizing capacity (Figure 1a and b). Correspondingly, a strong increase in the magnitude of SARS-CoV-2 spike (S)-protein–reactive T-cell immunity (median, 0.08%) was observed in 9 subjects (90%; Figure 1c and d and Supplementary Table S1) with T-cell frequencies comparable to healthy individuals.[2] Increased frequencies of cytokine-producing T cells and follicular T-helper cells indicated a gain of antiviral functionality (Figure 1e–i).

Compared with recent data showing increased SARS-CoV-2 S-protein antibody levels in transplant patients after 3-dose SARS-CoV-2 mRNA vaccination,[4,5] our study provides a deeper immunologic characterization of vaccination-specific immunity, as demonstrated by antibody neutralizing capacity and spike-reactive T-cell immunity.

In summary, a third dose of an mRNA vaccine elicits a humoral and cellular response in 60% and 90% of RTR patients, respectively, who failed the primary vaccination. Although larger cohort studies with longer observation time are needed to confirm our results, the exceptionally high risk of fatal COVID-19 in RTRs supports consideration of a third vaccination in clinical practice.

DATA STATEMENT

Data will be available on request.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Study population. Description of the demographic and clinical characteristics of the cohort, including information on the anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) humoral immune response after the first, second, and third doses and corresponding cellular immune response.

Supplementary Methods. Concise description of the employed methods.

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Anti–SARS-CoV-2 spike protein S1 receptor-binding domain antibody after vaccination with inactivated whole-virus SARS-CoV-2 in end-stage kidney disease patients: an initial report

To the editor: Patients with end-stage kidney disease (ESKD) are at greater risk for morbidity and mortality following coronavirus disease 2019 (COVID-19) than the general population.[1] Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for this vulnerable population is the main priority to prevent COVID-19 and mitigate unfavorable or severe complications. However, the immune responses to vaccination in patients with ESKD may be altered by accumulation of uremic toxins and comorbidities.[2] Currently, the effectiveness and safety