A Vector-Based Vaccine Dose After 3 Doses of mRNA-Based COVID-19 Vaccination Does Not Substantially Improve Humoral SARS-CoV-2 Immunity in Renal Transplant Recipients

To the Editor: COVID-19–related mortality in kidney transplant recipients (KTX) is significantly higher when compared with nontransplant patients.[1] Vaccination against SARS-CoV-2 is the most efficient measure to protect this vulnerable population. Nevertheless, after the application of 2 doses of mRNA-based vaccine, more than 50% of kidney transplant recipients have seronegative results.[2] A third dose of the mRNA-based vaccination induced seroconversion in 60% of the primary nonresponders, which however still leaves approximately 25% of all KTX without protection.[3] Because heterologous mRNA and vector-based COVID-19 vaccine regimens were found to be superior compared with homologous regimens,[4] we hypothesized that a fourth vaccination with a vector-based vaccine can improve humoral SARS-CoV-2 immunity in KTX who received 3 doses of COVID-19 vaccination without having a humoral response. A cohort of 20 KTX under immunosuppression (Supplementary Table S1) with low or no SARS-CoV-2–specific IgG 4 weeks after mRNA-based vaccinations received a fourth dose of the vector-based vaccine Ad26.COV2.S, which was well tolerated. The vaccination induced seroconversion in only 2 of 13 seronegative KTX. In KTX with increasing antibody titers, the median titer developed from 3.7 [0.6–35.9] to 50.0 [11.3–342.9]. Of the 9 KTX with detectable IgG titers, a borderline neutralizing capacity against the WT SARS-CoV-2 strain and the delta VOC could be observed in 3 and 4 KTX, respectively (Figure 1a and b). The functional SARS-CoV-2–reactive CD4 and CD8 T-cell response could be enhanced in approximately 30% to 60% of the KTX (Figure 1c–i). T-cell immunity against WT-S and Delta-VOC-S was comparable (Figure 1m and n). The CD4 T-cell response did correlate neither with the antibody titers nor with the neutralization capacity (Supplementary Figure S2).

In summary, the heterologous vaccination regime consisting of mRNA- and vector-based vaccine is enhancing the cellular immunity in a substantial fraction of KTX, whereas effects of humoral immunity are neglectable. A limitation of the study is the low number of KTX included. Although a fourth vaccination with Ad26.COV2.S was rather disappointing, a fourth vaccination with an mRNA-based vaccine seems to be more appropriate.[S1] Our data also highlight the need for the development of alternative vaccines that are efficient in KTX.

DISCLOSURE

All the authors declared no competing interests.

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DATA STATEMENT

The data will be available on request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Study population.

Figure S1. Flow cytometry gating strategy.

Figure S2. Correlation analysis of T-cell response versus titer and neutralization.

Supplementary Methods. Concise methods.

Supplementary References.

1. Caillard S, Chavarot N, Francois H, et al. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant.* 2021;21:1295–1303. https://doi.org/10.1111/ajt.16424
2. Stumpf J, Siepmann T, Lindner T, et al. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur.* 2021;9:100178. https://doi.org/10.1016/j.lanepe.2021.100178
3. Westhoff TH, Seibert FS, Anft M, et al. A third vaccine dose substantially improves humoral and cellular SARS-CoV-2 immunity in renal transplant recipients with primary humoral

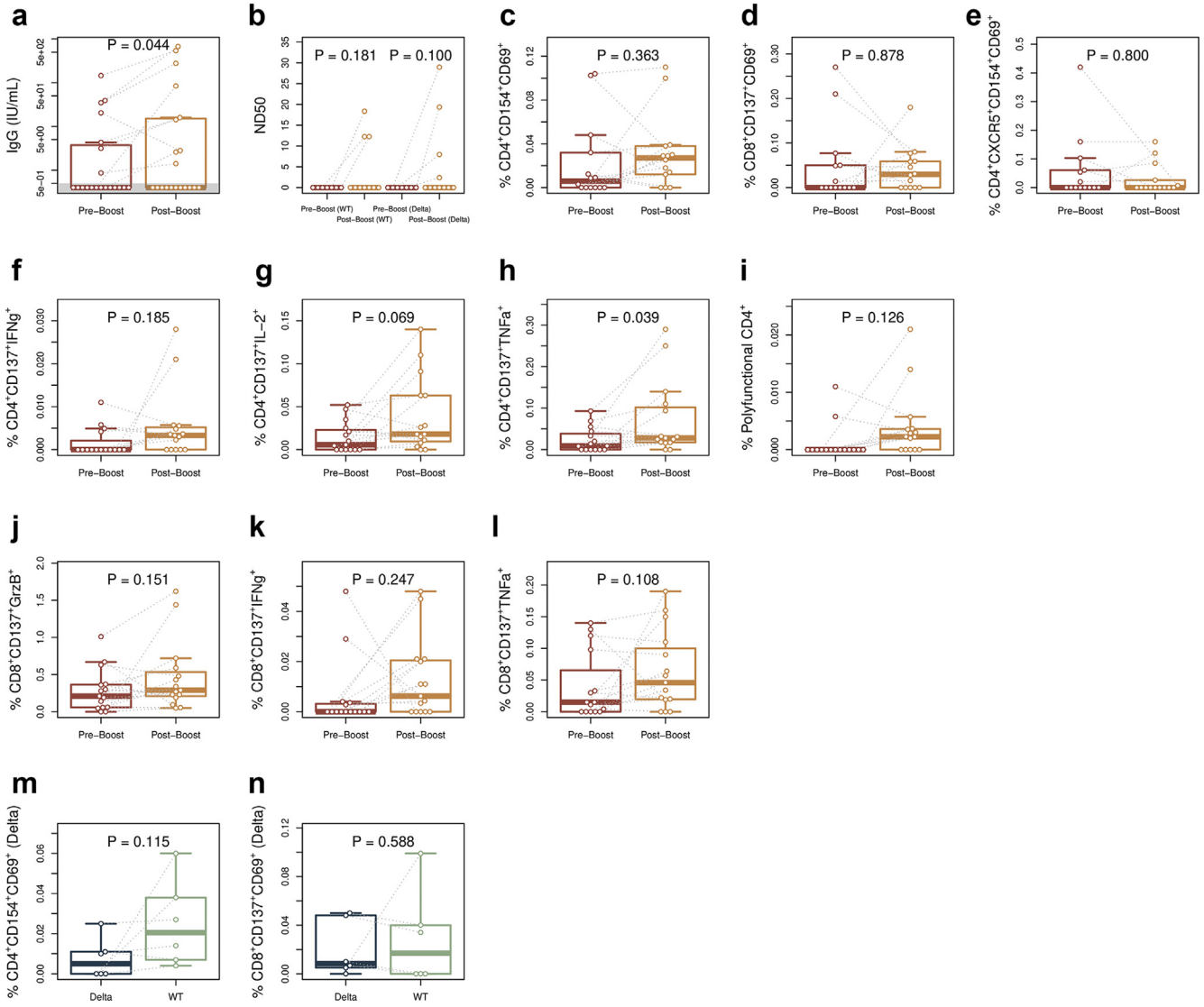

Figure 1. Humoral and cellular immune responses after a vector-based vaccination in kidney transplant recipient who failed the vaccination with 3 mRNA-based vaccines. KTX with failed or low seroconversion after 3 BNT162b2 (Pfizer–BioNTech) prime-boost vaccinations were subjected to a fourth vaccination with Ad26.COV2.S (Johnson & Johnson). Humoral and cellular immune responses before (red) and after 35 days in median with an interquartile range of 15.25 days (orange) of the fourth vaccination are found. (a) ELISA was performed to quantify the level of SARS-CoV-2 S-protein–binding antibodies. (b) Neutralizing capacity of the serum was evaluated by a pseudovirus system bearing the SARS-CoV-2 WT or the delta-VOC-S-protein. The assay detection range for ND50 is 20 to 2560. Values below 20 were extrapolated. (c–l) S-protein–reactive T-cells were analyzed by flow cytometry after an overnight stimulation of PBMC with OPPs spanning the S-protein of SARS-CoV-2 (Supplementary Figure S1). (c) CD154 and CD69 expression was used for quantification of S-protein–reactive $CD4^+$ T-cells. (d) CD137 and CD69 expression was used for quantification of S-protein–reactive $CD8^+$ T-cells. (e) Quantification of S-protein–reactive Tfh cells, as defined by CXCR5 expression (Supplementary Figure S1). Expression of (f) IFNγ, (g) IL-2, and TNFα by CD4+CD137+ T-cells. Expression of (j) the effector molecule GrB, (k) IFNγ, and (l) TNFα among activated CD8+CD137+ T-cells. (m, n) Analysis of T-cell immunity after stimulation with Delta-VOC-S peptides (Delta) and the corresponding peptides from WT-S (Wuhan-1 isolate). (m) The frequency of antigen-specific CD4+ T-cells. (n) The frequency of antigen-specific CD8+ T-cells. The box plots indicate the 75th, 50th, and 25th quantiles, and the whiskers indicate 1.5× the interquartile range. Statistical differences were analyzed using the paired *t* test. CXCR5, CXC chemokine receptor 5; ELISA, enzyme-linked immunosorbent assay; GrB; granzyme B; IFNγ, interferon gamma; IL-2, interleukin 2; OPP, overlapping peptide pool; PBMC, peripheral blood mononuclear cell; Tfh, T follicular helper; TNFα, tumor necrosis factor alpha.

nonresponse. *Kidney Int.* 2021;100:1135–1136. https://doi.org/10.1016/j.kint.2021.09.001

4. Schmidt T, Klemis V, Schub D, et al. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients. *Am J Transplant.* 2021;21:3990–4002. https://doi.org/10.1111/ajt.16818

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