Improved cellular and humoral immunity upon a second BNT162b2 and mRNA-1273 boost in prime-boost vaccination no/low responders with end-stage renal disease

To the editor: Patients with end-stage renal disease (ESRD) develop inefficient immune responses upon vaccination and have a high risk of developing severe coronavirus disease 2019 (COVID-19). The globally expanding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern (VOC), B.1.6.17.2/Delta, evades immune responses and might constitute a particular threat to these patients.1–3

Herein, we evaluated the efficacy of a third dose (second boost) by BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) mRNA vaccines (Supplementary Table S1 and Supplementary Figure S1) in ESRD patients with no response/low response (NR/LR) after prime-boost BNT162b2 vaccination and compared with ESRD with high response (HR) following the regular prime-boost vaccination. Enzyme-linked immunosorbent assay, pseudovirus neutralization assay, and flow cytometry were applied to assess humoral and cellular immunity against the spike (S) protein of SARS-CoV-2 wild type (WT-S) and the Delta-VOC (Delta-VOC-S) before and 3 to 5 weeks following the last booster vaccination.

In NR/LR, 20 of 23 patients developed high-binding WT-S antibody titers (Figure 1a and Supplementary Figure S2A), with neutralizing capacity in 19 of 22 patients. The third vaccination led to an increase in WT-S protein-reactive CD4+ T cells (Figure 1b) without differences between the applied vaccines (Supplementary Figure S2B and C). The higher frequency of S-reactive T follicular helper (Tfh) cells was the only difference observed in mRNA-1273–boosted patients (Supplementary Figure S2D).

Cellular immunity against WT-S and Delta-VOC-S was comparable irrespectively of helper or cytotoxic T cells or vaccine type (Figure 1e and Supplementary Figure S2E and F). In contrast, only 8 had neutralizing antibodies against Delta-VOC-S (Figure 1g). A clear association between cellular and humoral immunity was observed for each patient (Figure 1h). More important, when comparing the data obtained from NR/LR following the third dose with ESRD HR after the second dose, overall, superior results in cellular immunity and WT neutralizing capacity were observed. Although S-binding antibody titers and S-reactive CD4+ T cells were comparable between both cohorts (Figure 1i and j), WT neutralizing capacity and S-WT– and Delta-reactive CD8+ T cells and S-reactive Tfh cells were significantly higher in NR/LR after the second booster (third dose) compared with HR requiring only 1 booster (2 doses; Figure 1g, h, n, and o).

Our data demonstrate that patients with ESRD can benefit from a second vaccination boost by improving their cellular and humoral immunity not only to the vaccination-specific strain but also against the globally expanding Delta-VOC.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)

Supplementary Methods.

Figure S1. Comparison of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) adaptive immunity to the wild-type (WT) variant or Delta variant of concern (VOC) in hemodialysis patients requiring a second vaccine booster. Patients with no/low titers after a regular prime-boost SARS-CoV-2 mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost (2 boosts). (A) Antibody titers before and 3 to 5 weeks after the final SARS-CoV-2 mRNA vaccine boost. (B–D) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2 spike (S)-protein overlapping peptide pools. (B) Frequency of SARS-CoV-2 S-reactive CD4+ T cells. (C) Frequency of SARS-CoV-2 S-reactive CD8+ T cells. (D) Frequency of SARS-CoV-2 S-reactive Tfh cells as defined by CXCR3 expression. (E,F) Analysis of T-cell immunity following stimulation with Delta-VOC–S peptides (Delta) and corresponding peptides from WT-S (Wuhan-1 isolate). (E) The frequency of antigen (WT or Delta)–reactive CD4+ T cells. (F) Frequency of WT or Delta–reactive CD8+ T cells. The box plots indicate the 75th, 50th, and 25th quantiles, and the whiskers indicate 1.5× the interquartile range.

Figure S2. Gating strategy to identify spike (S)-protein reactive T cells. Peripheral blood mononuclear cells (PBMCs) were incubated for 16 hours with overlapping peptide pools (OPPs) of the complete severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) wild-type (WT) S-protein. Brefeldin A was added after 2 hours. The reactivity to the Delta variant of concern (VOC) mutations was evaluated using OPP peptides covering the Delta VOC mutations and the corresponding WT peptides. Stimulation with peptide diluent and Staphylococcus aureus enterotoxin B (SEB) as polyclonal stimulus served as negative and positive controls, respectively. Cells were acquired using a Cytoflex flow cytometer.

Table S1. Patient characteristics. Patients with no/low titers after a regular prime-boost severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost. Patients not requiring this additional boost (binding antibody titers > 250 IU/ml) serve as a control group (1 boost).

Supplementary References.


Figure 1 | The effect of a third severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination boost. Patients with no response/low response (NR/LR) after a regular prime-boost SARS-CoV-2 mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost (3 doses). Patients with antibody titres >250 IU/ml after the first boost served as control group (high response [HR], 2 doses). (a–h) Comparison within NR/LR. (a) Antibody titers before and 3 to 5 weeks after the second SARS-CoV-2 mRNA vaccine boost. (b–d) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2 Spike (S)-protein overlapping peptide pools. (b) The frequency of antigen-specific CD4+ T cells. (c) The frequency of antigen-specific CD8+ T cells. (d) The frequency of activated T follicular helper (Tfh) cells, as defined by CXC chemokine receptor 5 (CXCR5) expression. (e,f) Analysis of T-cell immunity following stimulation with (Delta-variant of concern [VOC])–S peptides (Delta) and corresponding peptides from wild type (WT-S; Wuhan-1 isolate). (e) The frequency of antigen-specific CD4+ T cells. (f) The frequency of antigen-specific CD8+ T cells. (g) A comparison of neutralizing antibodies against pseudoviruses bearing WT-S or Delta-VOC-S. (h) The comparison between the activation of CD4+ T cells and neutralization. White indicates no detection of humoral (antibody) or cellular (T-cell) immunity. (i–o) A comparison between HR (2 doses) and NR/LR (3 doses). (i) Antibody titers 3 to 5 weeks after the second SARS-CoV-2 mRNA vaccine boost. (j,k) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2–S-protein overlapping peptide pools. (j) The frequency of antigen-specific CD4+ T cells. (k) The frequency of antigen-specific CD8+ T cells. (l) The frequency of activated Tfh cells, as defined by CXCR5 expression. (m–o) The analysis of T-cell immunity following 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. (o) Neutralizing antibodies against pseudoviruses bearing WT-S or Delta-VOC-S. The box plots indicate the 75th, 50th, and 25th quantiles, and the whiskers indicate 1.5× the interquartile range. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001, ****P ≤ 0.0001. D0, day 0; D14, day 14; ND50, 50% neutralization dose; NS, not significant.

1Center for Translational Medicine and Immune Diagnostics Laboratory, Medical Department I, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Herne, Germany; 2Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Center for Advanced Therapies, Berlin, Germany; 3Department of Molecular and Medical Virology, Ruhr-University Bochum, Bochum, Germany; 4Department of Infectious Diseases, West German Centre of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany; 5Institut für Virologie und Immunologie, Abteilung Virologie, Bern, Switzerland; 6Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern, Bern, Switzerland; 7Dialyse Schwerte, Schwerte, Germany; 8Infection Biology Unit, German Primate Center—Leibniz Institute for Primate Research, Göttingen, Germany; and 9Faculty of Biology and Psychology, Georg-August-University Göttingen, Göttingen, Germany

Correspondence: Nina Babel, Center for Translational Medicine, Medical Department I, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Hölkeskamp 40, 44625 Herne, Germany. and Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin-Brandenburg Center for Regenerative Therapies, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: nina.babel@elisabethgruppe.de or nina.babel@charite.de

10THW, OC, and NB contributed equally.

Copyright © 2021, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.