Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

[IQR]: 612–3112 binding antibody units [BAU]/ml) than did patients vaccinated with BNT162b2 (median: 676; IQR: 197–1363 BAU/ml; $P < 0.0013$; Figure 1). After correction for age, sex, diabetes status, serum albumin, dialysis dose, previous kidney transplantation, ongoing immunosuppressive medication, and active malignancy, patients who were vaccinated with mRNA-1273 showed 2.98-fold higher anti-S-antibody titers than did patients vaccinated with BNT162b2 in a linear regression analysis ($P < 0.0003$). In a sensitivity analysis including only patients without ongoing immunosuppressive therapy (n = 102), anti-S-antibody titers of patients who were vaccinated with mRNA-1273 were 2.39-fold ($P < 0.005$) higher compared with patients who were vaccinated with BNT162b2.

In conclusion, patients on hemodialysis who were vaccinated with mRNA-1273 showed higher anti-S-antibody titers than did patients vaccinated with BNT162b2.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Patient flowchart.

Figure S2. Patients with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (N = 8; mRNA-1273: N = 5, BNT-162b2: N = 3) showed higher anti-S-antibody titers (median: 9418; interquartile range [IQR]: 6114–11,360 binding antibody units [BAU]/ml) than patients without prior SARS-CoV-2 infection (median: 1200; IQR: 447–2275 BAU/ml).

Figure S3. Beta-coefficients ± 1.96 SEs of the multivariate linear regression analysis with anti-S-antibody titers as the dependent variable.

Table S1. Patient demographics.

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Robert A. Kaiser[1], Maria C. Haller[1,2], Petra Apfalter[3], Heidrun Kerschner[3] and Daniel Cejka[1]

[1]Department of Medicine III—Nephrology, Hypertension, Transplantation, Rheumatology, Geriatrics, Ordensklinikum Linz–Elisabethinen Hospital, Linz, Austria; [2]Institute of Clinical Biometrics, Center for Medical Statistics, Informatics and Intelligent Systems (CEMSIIS), Medical University Vienna, Austria; and [3]Institute for Hygiene, Microbiology and Tropical Medicine, Ordensklinikum Linz–Elisabethinen Hospital, Linz, Austria

Correspondence: *Daniel Cejka, Department of Medicine III Nephrology, Transplantation, Rheumatology, Geriatrics, Ordensklinikum Linz–Elisabethinen, Fadinger Strasse 1, 4020 Linz, Austria. E-mail: daniel.cejka@ordensklinikum.at*

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Superior cellular and humoral immunity toward SARS-CoV-2 reference and alpha and beta VOC strains in COVID-19 convalescent as compared to the prime boost BNT162b2-vaccinated dialysis patients

To the editor: Patients undergoing maintenance dialysis (DP) have a high risk of fatal coronavirus disease 2019 (COVID-19).[1] Recent epidemiological data raise apprehension with respect to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOC) for DP.[2,3] Therefore, ensuring cellular and humoral immunity directed to SARS-CoV-2 including VOC isolates is essential for this population. There are no data on vaccine-induced nor on natural SARS-CoV-2 infection–induced long-term immunity and its responsiveness to VOC isolates in DP.

Here, we assessed cellular and humoral immunity to SARS-CoV-2 reference strain and alpha as well as beta VOC in 18 patients convalescing from mild or moderate COVID-19, which were compared to 22 age- and sex-matched DP after prime boost BNT162b2 vaccination (Supplementary Table S1). The great majority of infections occurred in November 2020 in Germany; therefore, contact of the convalescent subcohort with VOCs is unlikely. Appearance of the alpha and beta variants in Great Britain und South Africa, respectively, was first reported in December 2020.

Our data demonstrate a significantly higher number of humoral responders to VOCs and titers of neutralizing antibodies to both SARS-CoV-2 and VOCs in convalescent compared with vaccinated DPs (Figure 1a and b). Accordingly, cellular immune response also demonstrated significantly higher levels and functionality of T cells directed to the Spike (S)-protein of SARS-CoV-2 and VOCs in convalescent compared with vaccinated DPs. Frequencies of S-protein–reactive $CD4^+$ T cells (Figure 1c) including effector molecule-producing T cells (Supplementary Figure S1) as mono- or polyfunctional cells were significantly higher in convalescent DPs. Furthermore, frequencies of S-protein–reactive $CXCR5^+$ follicular T helper cells and effector memory T cells—phenotypes associated with T-cell functionality—were also significantly higher in convalescent patients (Figure 1f and g). For the employed gating strategy, see Supplementary Figure S2; representative dot plots of cytokine expression are shown in Supplementary Figure S3.

The data obtained from DPs (who were convalescent for >5 months), compared with data from vaccinated DPs, suggest superiority of adaptive immunity directed to SARS-CoV-2 and VOCs. This is remarkable, due to the longer time since infection compared with time from vaccination. The data on

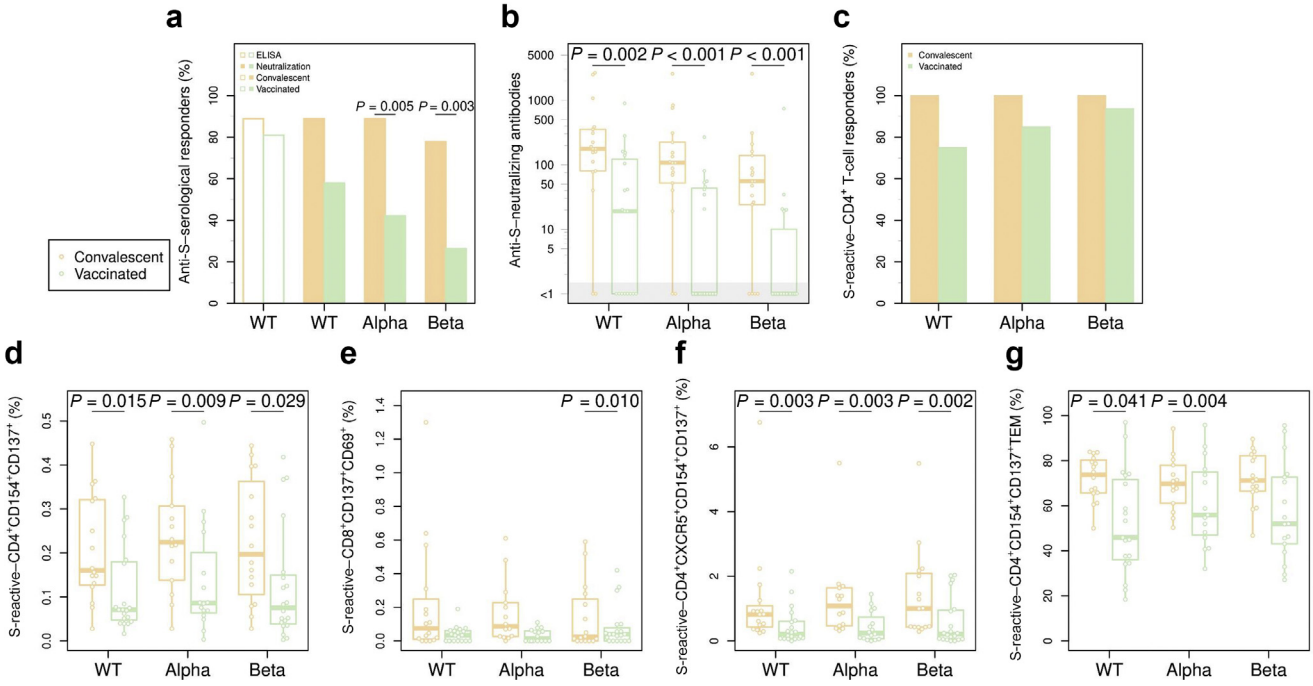

Figure 1 | A stronger humoral and cellular immune response in dialysis patients who were convalescent for coronavirus disease 2019 compared with vaccinated dialysis patients. Humoral response was assessed by neutralization assay for the reference strain and for variants of concern alpha and beta strains; and by conventional enzyme-linked immunosorbent assay (ELISA) for the reference strain; T-cell response was evaluated after stimulation with S-protein overlapping peptide pools of corresponding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains and subtracting background activation levels (dimethylsulfoxide). (**a**) Percentage of patients with a detectable (neutralization) serological response, for Spike (S) protein wild type (WT), alpha, and beta. (**b**) Neutralization antibody titers for the 3 SARS-CoV-2 strains. The gray area shows donors with a titer below the detection limit. (**c**) Percentage of patients with a $CD4^+$ T-cell response for reference, alpha, and beta SARS-CoV-2 strains, as defined by a stimulation index >3. (**d–f**) Percentage of activated $CD4^+$ T cells (**d**), $CD8^+$ T cells (**e**), and $CD4^+CXCR5^+$ T cells (**f**) for each of the 3 SARS-CoV-2 strain–derived S-protein overlapping peptide pools. (**g**) Percentage of effector memory T cells among S-protein–reactive $CD4^+$ T cells.

humoral immunity are in contrast to most available data in healthy cohorts.[4–8] Thus, mRNA vaccines have been repeatedly found to elicit stronger humoral neutralizing responses against the reference strain and VOCs.[4–8] The results are even more striking when considering that a drop of >50% in neutralizing antibody titers has been observed after the third month after infection.[6] We are not aware of any study directly comparing cellular immunity in the general population, although robust T-cell responses in convalescent and mRNA-vaccinated immunocompetent patients have already been reported.[9,10]

The reason for a significantly stronger humoral and cellular immune response found in DP after natural COVID-19 infection is unknown. We hypothesize that the high inflammation level observed in DPs during COVID-19 contributes to a stronger antigenic challenge and lymphocyte recruitment, generating superior cellular and humoral immunity as compared to prime boost vaccination in DPs. Although further studies are required, our preliminary data might have important implications for vaccination recommendation in patients who are convalescing.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Characteristics of convalescent and vaccinated hemodialysis patients.

Figure S1. Frequency of IFN-γ–, IL-2–, and TNF-α–producing cells among S-protein reactive $CD4^+CD154^+CD137^+$ T cells in convalescent and vaccinated hemodialysis patients.

Figure S2. Gating strategy to identify S-protein–reactive T cells among $CD4^+$ T cells, $CD4^+$ $CXCR5^+$ T cells, and $CD8^+$ T cells.

Figure S3. Representative dot plots illustrating expression of IL-2, TNF-α, and IFN-γ by activated $CD4^+CD154^+CD137^+$ T cells.

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Arturo Blazquez-Navarro[1,2,8], Lema Safi[2,8], Toni L. Meister[3,8], Constantin J. Thieme[1], Sviatlana Kaliszczyk[2], Krystallenia Paniskaki[4], Mara Stockhausen[2], Jan Hörstrup[5], Okan Cinkilic[6], Linus Flitsch-Kiefner[7], Corinna Marheinecke[3], Eike Steinmann[3], Felix S. Seibert[2], Ulrik Stervbo[2], Timm H. Westhoff[2,9], Stephanie Pfaender[3,9], Toralf Roch[1,2,9] and Nina Babel[1,2,9]

[1]Berlin Center for Advanced Therapies, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany; [2]Center for Translational Medicine and Immune Diagnostics Laboratory, Medical Department I, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Herne, Germany; [3]Department of Molecular and Medical Virology, Ruhr-University Bochum, Bochum, Germany; [4]Department of Infectious Diseases, West German Centre of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [5]Berlin Department, KfH Kuratorium für Dialyse und Nierentransplantation e.V., Berlin, Germany; [6]Dialyse Schwerte, Schwerte, Germany; and [7]Hagen Department, KfH Kuratorium für Dialyse und Nierentransplantation e.V., Hagen, Germany

Correspondence: *Nina Babel, Center for Translational Medicine, Medical Department I, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Hölkeskampring 40, 44625 Herne, Germany. E-mail: nina.babel@elisabethgruppe.de or nina.babel@charite.de; and Nina Babel, 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*

[8]AB-N, LS, and TLM contributed equally to this work.

[9]THW, SP, TR, and NB contributed equally to this work.

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Neutralizing antibody response against variants of concern after vaccination of dialysis patients with BNT162b2

To the editor: We and others showed high seroconversion rates after BNT162b2 mRNA vaccination in patients on hemodialysis, but still significantly lower rates as compared to those of healthy controls.[1–3] Variants of concern (VOCs) such as B.1.351 (beta variant) or B.1.617.2 (delta variant) partially escape from neutralizing antibodies (NAbs) and will probably replace wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or the B.1.1.7 (alpha) variant with increasing immunity in the population, induced by natural infection or vaccination. Wall *et al.*[4] recently revealed a 4- to 6-fold reduction in vaccine-induced peak NAbs against VOCs B.1.351 and B.1.617.2 in healthy controls compared with wild-type SARS-CoV-2 and the B.1.1.7 variant. Immune-compromised populations such as dialysis patients mounting lower NAbs might become most sensitive to VOCs.

We investigated the neutralization of variants B.1.1.7 and B.1.351 in SARS-CoV-2 infection–based experiments on VeroE6 cells using sera taken 3 weeks after the second BNT162b2 dose in a dual-center cohort of 30 patients receiving maintenance hemodialysis and 18 healthy controls. Only individuals with seroconversion, defined as detectable anti-spike(S)1 antibodies and >30% inhibition in a surrogate neutralization test, were included.

Seropositivity rate was 24 of 30 (80%) in dialysis patients having a median age of 78 years (interquartile range [IQR]: 69–88 years; Supplementary Table S1). The median S1-IgG index was 6 (IQR: 1–19) and the median inhibition in the surrogate neutralization test was 55% (IQR: 32%–78%; Figure 1a and b). All 24 seropositive dialysis patients had NAbs against the B.1.1.7 strain with a median ID_{50} (i.e., serum dilution that inhibits 50% of the infectivity) of 160 (IQR: 50–320; Figure 1c). However, NAbs against the VOC B.1.351 were only detected in 15 of 24 patients (63%). With a median of 15 (IQR: 0–20), the ID_{50} was significantly lower as compared to that of the B.1.1.7 strain ($P < 0.001$; Figure 1c). In contrast, all 18 healthy controls showed neutralizing activity against both B.1.1.7 and B.1.351, with significantly higher ID_{50} values compared with those of dialysis patients, respectively (Figure 1c). The S1-IgG index of dialysis patients correlated well with the ID_{50} of both B.1.1.7 and B.1.351 (Figure 1d). Of note, even dialysis patients with low anti-S1–IgG antibody levels had detectable neutralization against B.1.1.7, whereas this was not the case for B.1.351 in the same patients (Figure 1d).

Overall, this study suggests that a large proportion of dialysis patients may not be adequately protected against VOCs with vaccination regimens currently applied in the healthy general population. Even if SARS-CoV-2–specific antibodies are detectable by commercially available tests, neutralization of VOCs may be insufficient to protect against infection. Further immunization strategies of dialysis patients seem to be urgently indicated, especially in regions with rapidly increasing VOC prevalence.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.