Significant Fade of Neutralizing Antibodies and Stable Cellular Immunity in 4 Times COVID-19 Vaccinated Noninfected Compared to COVID-19 Convalescent and 3 Times Vaccinated Hemodialysis Patients

To the Editor: COVID-19 breakthrough currently caused by the Omicron variant of concern (VOC) has been attributed to the antibody fade following SARS-CoV-2 vaccination and high number of mutations in the spike protein of Omicron VOC as compared with the spike protein of the wild-type vaccine. However, vaccination booster doses that highly increase wild-type–specific antibody titer can compensate the reduced specificity for at least 3 months.[1]

Therefore, regular boosters are recommended especially for the high-risk population such as hemodialysis patients. Our previous study in the general population demonstrated superior humoral and cellular immunity against alpha, beta, and delta VOCs in convalescent and vaccinated patients as compared with vaccinated and noninfected individuals.[2] The aim of this study was to explore humoral and cellular wild-type–specific and Omicron BA.4/5–specific immunity in hemodialysis patients after COVID-19 mRNA vaccination by comparing vaccinated COVID-19 noninfected (V+ C−) to vaccinated COVID-19 convalescent (V+ C+) hemodialysis patients.

To ensure that all patients had the same number of SARS-CoV-2 antigenic contacts, 22 noninfected hemodialysis patients who received 4 vaccinations of SARS-CoV-2 mRNA (4× V+ C−) were compared with 7 patients with COVID-19 caused by Omicron BA.1/2 who received 3 vaccinations (3× V+ C+) (Supplementary Table S1). We analyzed neutralizing antibodies against SARS-CoV-2 wild-type and Omicron BA.4/5 VOC by SARS-CoV-2 spike protein (S protein) pseudovirus assays. T-cell immunity reactive against SARS-CoV-2 wild-type and Omicron BA.4/5 overlapping peptide pools were analyzed by multiparameter flow cytometry (Supplementary Methods and Supplementary Figure S1).

In the vaccinated-only group (4× V+ C−), 21 of 22 patients (95.5%) showed a humoral immune response against SARS-CoV-2 wild-type, but only 8 of 22 patients (36.4%) against Omicron BA.4/5 VOC. In contrast, all 7 (100%) vaccinated and convalescent (3× V+ C+) patients showed a humoral immune response against wild-type, and 6 of 7 (85.7%) against BA.4/5. Although the incidence of patients with detectable wild-type–reactive and BA.4/5-reactive CD4 and CD8 T cells was similar in both groups (Figure 1a), the percentage of patients who had a combined humoral and cellular CD4 and CD8 T-cell response was significantly higher in the convalescent vaccinated group (62.5%) as compared with the vaccination-only group (25.0%) (Figure 1b). In line with it, the titer of neutralizing antibodies against Omicron BA.4/5 was significantly higher compared with vaccinated-only patients (Figure 1c). In contrast to the humoral immunity, there were no differences in the percentage of wild-type or Omicron BA.4/5–reactive CD4 and CD8 T cells and no significant differences in the production of proinflammatory cytokines interleukin-2 (IL-2) and tumor necrosisfactor (TNF) by these cells between the 2 patient groups (Figure 1d–f).

The high incidence of humoral nonresponders against the current Omicron VOC indicates the urgent need for adjusted COVID-19 mRNA vaccination in this vulnerable population. A better humoral immunity observed in convalescent and vaccinated group as compared with vaccinated-only patients can be explained by a stronger antigenic stimuli, a higher systemic inflammation, a better antigenic stimulation, and immune cell recruitment during the natural infection as compared with vaccination.[3]

DISCLOSURE

All the authors declared no competing interests.

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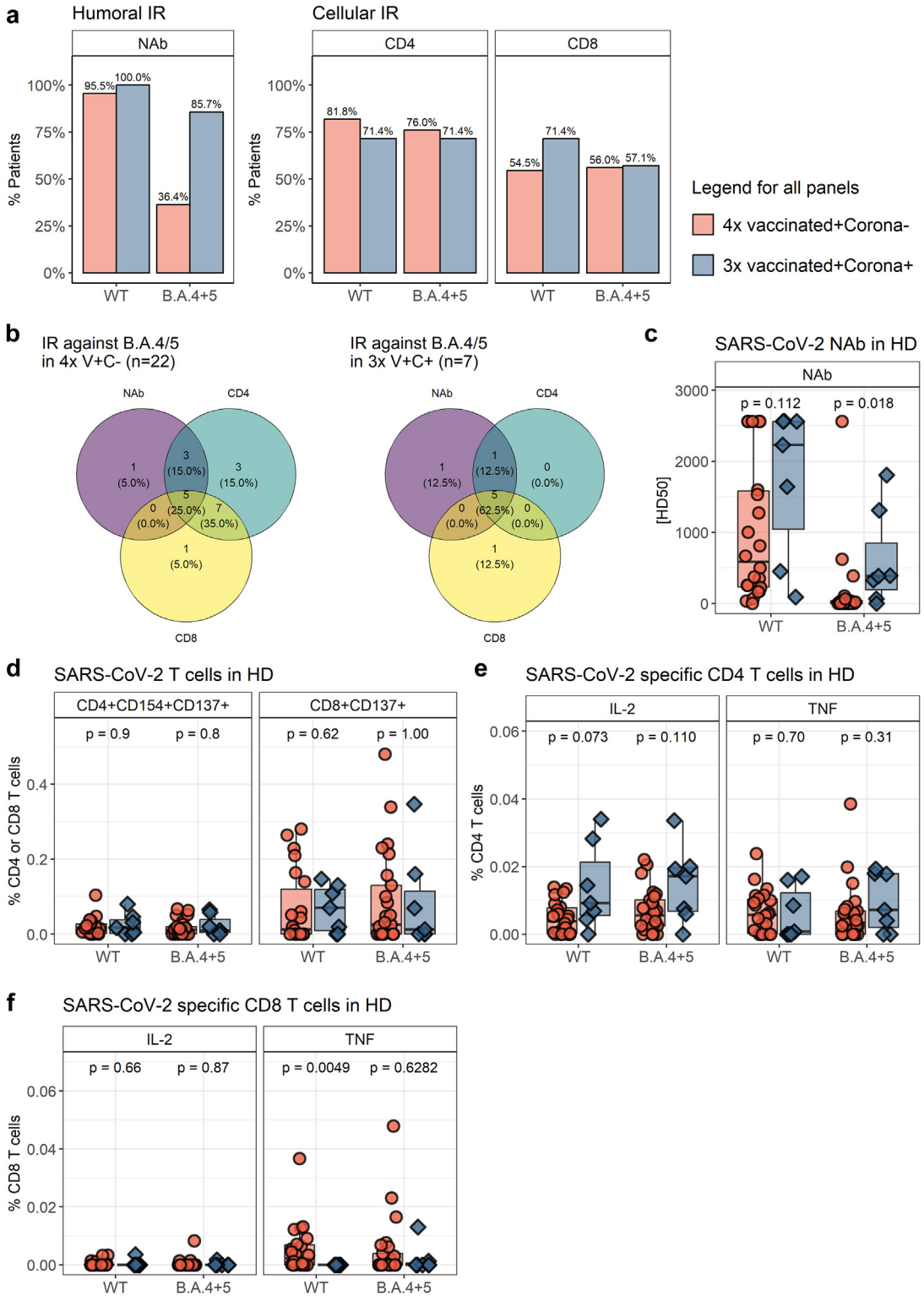

Figure 1. Humoral and cellular immune response of 4× vaccinated HD patients without receding SARS-CoV-2 infection (4× V+ C−, red, $n = 22$) and 3× vaccinated HD patients with receding SARS-CoV-2 infection (3× V+ C+, blue, $n = 7$). (a) Percentage of patients with a humoral and cellular immune response against SARS-CoV-2 wild-type and Omicron BA.4/5. (b) Venn diagram displaying the partial overlap of patients with neutralizing antibodies, CD4 or CD8 T-cell response against the Omicron BA.4/5 variant of concern. (c) Isolated serum from HD patients was analyzed for titers [HD50] of neutralizing antibodies against wild-type or BA.4/5 variant of concern. (d) Isolated peripheral blood mononuclear cells from HD patients were stimulated for 16 hours with 1 μg/ml SARS-CoV-2 wild-type or Omicron BA.4/5 overlapping peptide pools. SARS-CoV-2–reactive T-helper cells were identified as life/dead-marker-$CD3^+CD4^+CD137^+CD154^+$, and SARS-CoV-2–reactive cytotoxic T cells were identified as life/dead-marker-$CD3^+CD8^+CD137^+$. (e,f) Percentage of SARS-CoV-2–reactive (e) CD4 or (f) CD8 T cells producing the proinflammatory cytokines IL-2 or TNF. HD, hemodialysis; IL-2, interleukin-2; IR, immune response; NAb, neutralizing antibody; TNF, tumor necrosis factor; WT, wild-type.

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DATA AVAILABILITY STATEMENT

Data will be available upon request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Gating strategy.

Table S1. Study population.

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