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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 chemokine receptor 5 (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).

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Kidney International (2021) 100, 1335–1337; https://doi.org/10.1016/j.kint.2021.09.015

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Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients

To the editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination has become the standard of care for the prevention of severe coronavirus disease 2019 (COVID-19), with a strongly positive impact in countries in which vaccination has been effectively promoted. 1 In kidney
transplant recipients (KTRs), SARS-CoV-2 vaccination has been recommended through international guidelines. Unfortunately, the data reported in KTRs are disappointing, with a low rate of seroconversion after 2 doses, whereas the occurrence of severe infection after vaccination is of concern. In this context, as of April 6, 2021, the French Administration recommends that solid organ transplant recipients receive a third mRNA vaccine dose at least 4 weeks after the second dose. Herein, we report the evaluation of humoral and cellular responses induced after the second and third doses of BNT162b2 (Pfizer–BioNTech) in 80 KTRs (see Supplementary Methods).

Baseline characteristics of the 80 KTRs are described in Table 1. After the second dose, 30 KTRs (37.5%) had anti-spike IgG antibodies; and 49 KTRs (61.2%) had these antibodies after the third injection (P < 0.0001) (Figure 1a). In patients already seropositive after the second dose (Figure 1b), median antibody titers increased from 217.1 arbitrary units (AU)/ml (interquartile range [IQR], 120.2–443.8 AU/ml) to 2238.3 AU/ml (IQR, 1934.4–7220.6 AU/ml; P < 0.0001). Forty-one KTRs (51.2%) displayed a significant number of IFN-γ–producing spike-reactive T cells after the second injection, and 56 (70%) displayed these cells after the third injection (P < 0.0001 compared with the second dose). No response to N, M, ORF3A, and ORF7A was evidenced, excluding a potential SARS-CoV-2 infection between the second and up to 1 month after the third dose. In these 41 patients, the median number of spike-reactive T cells increased from 225 spot-forming cells (SFCs)/10⁶ CD3⁺ T cells (IQR, 90–355 SFCs/10⁶ CD3⁺ T cells) to 330 SFCs/10⁶ CD3⁺ T cells (IQR, 187–610 SFCs/10⁶ CD3⁺ T cells; P < 0.0001) after the third dose (Figure 2b). Vaccination status after the third dose is summarized in Supplementary Figure S1.

Two KTRs presented with symptomatic COVID-19 67 and 72 days, respectively, after the third vaccine injection. One KTR was hospitalized but did not require intensive care. Both KTRs had a low number of spike-reactive T cells after the third dose (65 and 50 SFCs/10⁶ CD3⁺ T cells), and only the second KTR had a low titer of anti-spike antibodies (145 AU/ml).

Aza, azathioprine; E, enzyme-linked immunosorbent spot; eGFR, estimated glomerular filtration rate; f, female; IQR, interquartile range; IS, immunosuppressive; M, male; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; S, serology.

| Variable          | Entire cohort (n = 80) | S⁺/E⁺ (n = 43) | S⁺/E⁻ (n = 6) | S⁻/E⁺ (n = 13) | S⁻/E⁻ (n = 18) |
|-------------------|------------------------|----------------|--------------|---------------|---------------|
| Age, yr, mean ± SD| 63.6 ± 15.7            | 60.3 ± 14.9    | 66.7 ± 15.6  | 64.3 ± 18.1   | 70.2 ± 14.6   |
| Sex (M/F), n      | 48/32                  | 24/19          | 5/1          | 8/5           | 11/7          |
| Time from transplantation, yr, median (IQR) | 7.3 (3.4–14.1) | 10.3 (4.7–16) | 6.8 (3.5–17.5) | 6.6 (1.6–14.2) | 4.4 (1.7–6.8) |
| eGFR, ml/min per 1.73 m², mean ± SD | 44.8 ± 17.2 | 50.2 ± 14.2 | 46.6 ± 17.3 | 44.0 ± 21.6 | 32.0 ± 14.8 |
| IS regimen, n (%)  |                        |                |              |               |               |
| Tacrolimus        | 46 (57.5)              | 22 (51.2)      | 6 (100)      | 10 (76.9)     | 8 (44.4)      |
| Cyclosporine      | 14 (17.5)              | 13 (30.2)      | 0 (0)        | 1 (7.7)       | 0 (0)         |
| MMF               | 61 (76.2)              | 32 (74.4)      | 4 (66.7)     | 13 (100)      | 12 (66.7)     |
| AZA               | 9 (11.2)               | 6 (13.9)       | 0 (0)        | 0 (0)         | 3 (16.7)      |
| mTOR inhibitors   | 10 (12.5)              | 7 (16.3)       | 1 (16.7)     | 1 (7.7)       | 1 (5.6)       |
| Belatacept        | 12 (15)                | 1 (2.3)        | 0 (0)        | 1 (7.7)       | 10 (55.6)     |
| Steroids          | 32 (40)                | 16 (37.2)      | 3 (50)       | 4 (30.8)      | 9 (50)        |

AZA, azathioprine; E, enzyme-linked immunosorbent spot; eGFR, estimated glomerular filtration rate; f, female; IQR, interquartile range; IS, immunosuppressive; M, male; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; S, serology.
Our results suggest that the immune response to a third BNT262b2 dose is highly influenced by the intensity of the immunosuppressive regimen. As already reported, belatacept-treated patients were the worst responders, developing no antibodies and no or only few specific T cells. Mycophenolic acid by itself appears associated with a lower seroconversion rate. However, in our study, KTRs on cyclosporine were more likely to develop humoral and cellular responses than KTRs on tacrolimus (Supplementary Table S2), regardless of mycophenolate mofetil coadministration.

In addition, the BNT262b2 vaccine appears safe with regard to acute rejection and de novo donor-specific antibodies, a potent risk factors for antibody-mediated rejection and graft loss, up to 1 month after the third dose.

In conclusion, a third dose of the SARS-CoV-2 mRNA BNT162b2 vaccine in KTRs increases the rate of positive antibody and T-cell responses in nonresponsive patients after the second dose and improves the magnitude of these responses in already seropositive patients. In patients without significant response after a third dose, anti–SARS-CoV-2 monoclonal antibodies could be proposed in prophylaxis as recommended by the French Administration since August 6, 2021.

DATA STATEMENT
All relevant data are within the article.

ACKNOWLEDGMENTS
The authors wish to thank the health care professionals of the University Hospital of Rouen, who were involved in the care of the patients, and the nurse from the kidney transplant team Manuel Etienne for his help.

AUTHOR CONTRIBUTIONS
SC and DB designed the study; JL performed enzyme-linked immunosorbent spot assays; SC and DB collected data; MHam, SC, and DB analyzed the data; SC and DB wrote the article; and all authors provided feedback and critical review.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Methods.
Figure S1. Flowchart of the humoral and cellular response to the third dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA BNT162b2 (Pfizer–BioNTech) vaccine in kidney transplant recipients (KTRs).
Figure S2. Anti-spike antibody and T-cell responses in kidney transplant recipients (KTRs) following the second and third injections of the BNT162b2 vaccine (Pfizer–BioNTech), according to the immunosuppressive regimen.
Table S1. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen.
Table S2. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen tacrolimus (Tac) + mycophenolate mofetil (MMF; n = 32) or cyclosporine + MMF (n = 10).
Supplementary References.
New-onset systemic lupus erythematosus beginning as class V lupus nephritis after COVID-19 vaccination

To the editor: We read the report by Tuschen et al. of a 42-year-old woman with a previous diagnosis of systemic lupus erythematosus (SLE) and class V lupus nephritis (LN) that developed a flare 1 week after vaccination with the mRNA coronavirus disease 2019 (COVID-19) vaccine BNT162b2 (Pfizer–BioNTech). Here, we report a case of a 23-year-old woman who presented with nephrotic syndrome 1 week after vaccination with the first dose of the AZD1222 (ChAdOx1-S) nCoV-19 vaccine (AstraZeneca).

She had no previous medical history of disease and was taking no medications. She had not been previously infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Her family history was negative for autoimmune diseases. On July 21, 2021, she was vaccinated, without major adverse events. One week later, she developed abrupt eyelid edema and foamy urine that progressed to anasarca within days. She also experienced hair loss. Physical examination showed normal blood pressure and pitting edema up to the thighs. Her laboratory tests showed lymphopenia (1000 × 10^3/ml), a serum creatinine level of 0.8 mg/dl (estimated glomerular filtration rate of 104 ml/min per 1.73 m²), a serum albumin level of 1.57 g/dl, a total cholesterol level of 351 mg/dl, proteinuria of 12.6 g/24 h (protein-to-creatinine ratio of 11.0 mg/mg), a complement C3 level of 85 mg/dl (reference, 87–200 mg/dl), and a C4 level of 12 mg/dl (reference, 19–52 mg/dl). Antinuclear antibody (ANA) titer was 1:1280 homogeneous pattern; the anti-dsDNA-IgG level was 17.1 IU/ml; and antiphospholipid antibody panel was negative. Serology for SARS-CoV-2 demonstrated negative IgM and IgG antibodies to the nucleocapsid antigen (NCP), suggesting no previous infection by this virus. Anti–SARS-CoV-2–Spike IgG antibodies in response to vaccination were quantified at 32.8 UI/ml (reference, <1 UI/ml), suggesting an appropriate response to vaccination.

The kidney biopsy performed 1 week after the start of symptoms (2 weeks post-vaccination) demonstrated secondary membranous nephropathy, with diffuse thickening of the basement glomerular membrane and mild mesangial expansion. One of 13 glomeruli had sclerosis, and interstitial fibrosis was less than 10%, with no tubular atrophy, and normal vessels. Direct immunofluorescence revealed deposits of IgG, IgM, C1q, C3c, kappa, and lambda chains in the subepithelial and mesangial space. Electron microscopy showed mesangial and subepithelial electron-dense deposits (Figure 1). A diagnosis of SLE with class V LN was established. We started treatment with mycophenolate mofetil, high-dose glucocorticoids, hydroxychloroquine, and diuretics. After 3 weeks of follow-up, edema has improved and the patient continues follow-up.

Diverse glomerular diseases have been reported in association with COVID-19 vaccination, particularly podocytopathies, IgA nephropathy, and anti-neutrophil cytoplasmic antibody (ANCA) vasculitis. For SLE, the Vaccination Against COVID in Systemic Lupus (VACOLUP) study reported 2 renal flares (with no specification of the type of LN), and the report by Tuschen et al. also corresponded to a class V LN flare. In animal models, the loss of the Th1 response, with increased interleukin-4, and the development of a disease resembling human membranous nephropathy with IgG1-dominant electro-dense deposits in the subepithelial space. Moreover, the Th1 response has been associated with the development of LN proliferative variants. T cells are key to stimulating the immune response to vaccination. From phase 1 and 2 trials of the AZD1222 nCoV-19 vaccine, it has been shown that the spike-specific effector T-cell response presents early, from day 8 post-vaccination through day 56. There is a robust Th1 response with an expansion of CD8+ T cells, with increases in cytokines such as tumor necrosis factor, interleukin-2, and interferon gamma. However, no Th2 response has been found after AZD1222 nCoV-19 vaccination.