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The SARS-CoV-2–neutralizing capacity of kidney transplant recipients 4 weeks after receiving a second dose of the BNT162b2 vaccine

To the editor: Coronavirus disease 2019 (COVID-19)–vaccinated kidney transplant recipients (KTRs) display a lower-than-normal antibody (Ab) response toward severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), indicating a reduced humoral immune response against the virus.[1] A remaining question is to which extent this translates into a lower ability of KTRs to combat SARS-CoV-2.[2] This capacity can be estimated by surrogate or pseudovirus neutralization assays or, optimally, the plaque reduction neutralization test (PRNT), in which live SARS-CoV-2 is challenged directly with patient blood plasma.[3,4]

Herein, we report results from PRNT performed on blood plasma from 58 KTRs and 20 age-matched controls, 4 weeks after the second BNT162b2 (Pfizer–BioNTech) vaccine dose. The neutralization results were compared with Ab levels, as measured by 2 widely used immunoassay platforms (Vitros and Liaison, respectively; see methods in Supplementary File S1).

Our results show that 31% (18 of 58 patients) of the KTRs display virus-neutralizing capacity compared with 100% (20 of 20 subjects) of healthy controls (Figure 1a). The virus

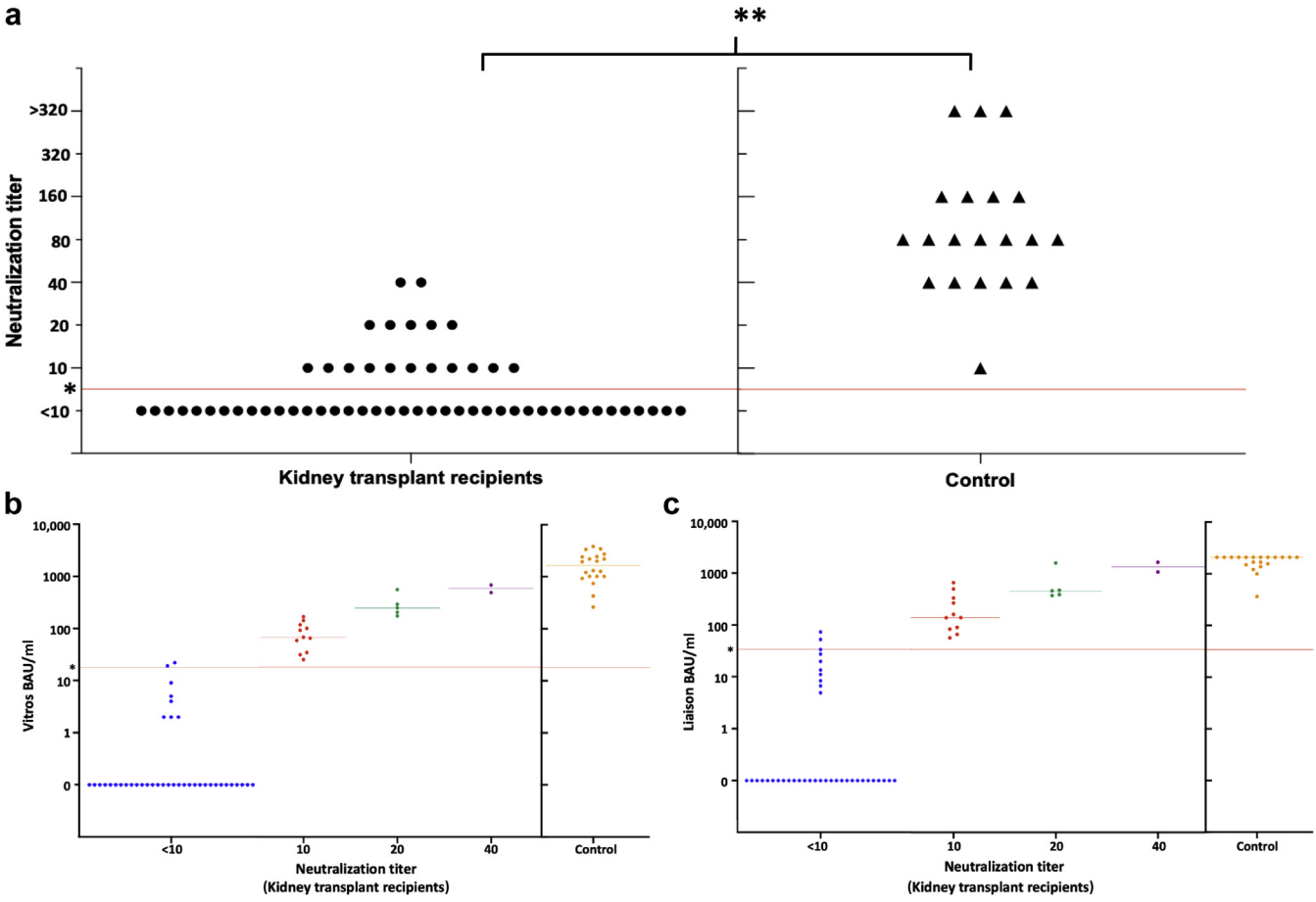

Figure 1 | Comparison of neutralization capacity and antibody (Ab) levels in coronavirus disease 2019 (COVID-19)–naïve kidney transplant recipients (KTRs) and healthy control subjects 4 weeks after the second BNT162b2 (Pfizer–BioNTech) vaccine. (**a**) Neutralization capacity of KTRs (n = 58) and control subjects (n = 20). *Threshold level of neutralization (PRNT90 titer ≥10 is defined as neutralizing). **Difference in neutralization response (+/–), $P < 0.001$ (Fischer exact test). (**b**) Ab levels measured by Ortho CD VITROS quantitative Anti–SARS-CoV-2 IgG immunoassay (Vitros) of KTRs (n = 58) and control subjects (n = 20). All groups are presented with medians. Comparing the Ab status (+/–) with the neutralization status (+/–), the sensitivity of Vitros was 100% (38 of 38; 95% confidence interval [CI], 91%–100%), and the specificity was 95% (40 of 42; 95% CI, 83%–99%). The results from Vitros correlated with the neutralizing titer $r_s = 0.894$ ($P < 0.0001$, Spearman correlation). *The threshold limit provided by the manufacturer of 17.8 binding antibody units (BAUs)/ml. (**c**) Performance of the Diasorin Liaison SARS-CoV-2 TrimericS IgG Quantitative immunoassay (Liaison) of KTRs (n = 57; missing data, n = 1) and control subjects (n = 20). All groups are presented with medians. Comparing the Ab status (+/–) with the neutralization status (+/–), the sensitivity of Liaison was 100% (38 of 38; 95% CI, 91%–100%), and the specificity was 95% (39 of 41; 95% CI, 82%–99%). The results from Liaison correlated with the neutralizing titer $r_s = 0.870$ ($P < 0.0001$, Spearman correlation). *The threshold limit provided by the manufacturer of 34.8 BAUs/ml.

Table 1 | Characteristics of the kidney transplant recipient cohort, according to neutralization response, 4 weeks after a 2-dose BNT162b2 (Pfizer–BioNTech) SARS-CoV-2 vaccine regimen

Characteristics	Responders	Nonresponders	*P* value
Total	18 (31)	40 (69)	NA
Age, yr	48.0 (42.3–61.4)	60.9 (53.0–67.4)	0.03
Female	9 (50)	25 (63)	0.40
BMI, kg/m^2	28.25 (25.1–31.6)	26.10 (22.4–29.6)	0.17
Time from TX, yr	9.40 (4.50–12.93)	5.65 (2.25–14.13)	0.21
First TX	16 (89)	30 (75)	0.41
Second TX	2 (11)	8 (20)	NA
Third TX	0 (0)	2 (5)	NA
Deceased donor	6 (33)	23 (58)	0.15
Induction			0.002
Rituximab	4 (22)	0 (0)	
Anti-CD25	13 (72)	23 (58)	
Anti-CD25 + rituximab	1 (6)	1 (3)	
Thymoglobuline	0 (0)	10 (25)	
Thymoglobuline + rituximab	0 (0)	6 (15)	
Maintenance			
Tacrolimus	17 (94)	28 (70)	0.05
Tacrolimus CO, ng/ml	5.2 (4.7–6.0)	5.4 (5.1–6.5)	0.26
Cyclosporin A	1 (6)	8 (20)	NA
Cyclosporin A CO, nmol/L	560	498 (372–653)	NA
Everolimus	0	1	NA
Everolimus CO, median, ng/ml	NA	10.6	NA
No CNI/mTORi	0 (0)	3 (8)	NA
MMF/MPA	15 (83)	39 (98)	0.09
MMF	9 (50)	31 (78)	0.07
MPA	6 (33)	8 (20)	0.33
MMF/MPA fraction of full dose, mean ± SD[a]	0.71 ± 0.33	0.80 ± 0.24	0.40
MMF/MPA, mean ± SD, fraction/kg ($\times 10^{-3}$)[b]	8.5 ± 3.8	10.9 ± 3.8	0.04
MMF/kg	10.8 (8.8–16.8)	19.1 (14.3–21.4)	0.001
MPA/kg	10.5 (7.3–13.6)	8.1 (5.6–12.7)	0.41
Azathioprine	3 (17)	1 (3)	NA
Azathioprine (individual dosings), mg	25-50-100	75	NA
Steroids	0 (0)	7 (18)	NA
Plasma creatinine, μmol/L	101 (84.5–145)	141 (100–200)	0.07
eGFR, ml/min	60.5 (42.3–80)	42 (29–68)	0.07
Underlying disease			0.84
Nonimmune disease	8 (44)	16 (40)	
Immune disease	7 (39)	12 (30)	
Diabetes mellitus	1 (6)	3 (8)	
Infection	1 (6)	3 (8)	
Unknown	1 (6)	6 (15)	

BMI, body mass index; CD, cluster of differentiation; CNI, calcineurin inhibitor; CO, concentration in plasma; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TX, transplant.

[a]Full dose of MMF is 1000 mg twice daily, except in patients treated with tacrolimus, in whom full dose is 750 mg twice daily. Full dose of MPA is 720 mg twice daily, except in patients treated with tacrolimus, in whom full dose is 540 mg twice daily.

[b]The fraction of full dose of MMF/MPA per kg body weight.

Continuous variables are presented as median (IQR) and binomial variables are presented as n (%), unless otherwise noted. Differences have been analyzed with the Student *t* test and Fisher exact test, respectively. $P < 0.05$ is considered statistically significant.

neutralization capacity showed considerable concordance with the commercial immunoassays in that all KTRs with Ab levels below the assay-specified threshold were unable to neutralize the virus (Figure 1b and c). However, for both immunoassays, 10% of the KTRs with Ab levels above the threshold were nonneutralizing in the PRNT (Figure 1b and c). The clinical and demographic characteristics of the KTRs are shown in Table 1.

In conclusion, we found that less than one-third of BNT162b2-vaccinated KTRs display SARS-CoV-2–neutralizing capacity. Moreover, the KTRs who responded to the vaccines had a significantly lower median neutralizing titer (median, 10; interquartile range, 10–20) compared with the age-matched controls (median, 80; interquartile range, 40–160). Our findings emphasize the inadequate protection against SARS-CoV-2 in many KTRs despite COVID-19 vaccination.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary File S1. Patients, plaque reduction neutralization test (PRNT), serological immunoassays, statistics, supplementary references.

Figure S1. Stages in patient inclusion.

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Better late than never: eventual seroconversion against SARS-CoV-2 in a kidney transplant recipient after repeated immune challenge and monoclonal antibody therapy

To the editor: Kidney transplant recipients are disproportionately affected by coronavirus disease 2019 (COVID-19). In addition to limited therapeutic options, concerns have arisen regarding poor vaccine efficacy in this population.[1]

We report the case of a 64-year-old kidney transplant recipient treated with an association of tacrolimus, mycophenolate mofetil, and steroids who developed a second severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection 1 year after a first COVID-19 episode, and 55 days after receiving his second BNT162b2-mRNA vaccine injection (Pfizer–BioNTech). Three days after the onset of isolated fever, a high viral load of SARS-CoV-2 gamma variant was detected through reverse transcriptase polymerase chain reaction in a nasopharyngeal swab (Table 1). Mycophenolate mofetil was interrupted, and i.v. monoclonal antibody (casirivimab, 1200 mg, and imdevimab, 1200 mg; Regeneron) therapy was given. Clinical and virological evolutions were favorable: viral load decreased <1000 copies/ml on day 8 and was eventually negative on day 28 after perfusion (Table 1). Interestingly, an anti-N native antibody seroconversion was observed on day 28 (Table 1). Notably, 3 serologic tests had been performed before the second SARS-CoV-2 infection (including one 43 days after the second vaccine dose injection) and were all negative for both anti-N and anti–receptor-binding domain antibody.

Table 1 | Evolution of SARS-CoV-2 viral load and anti–SARS-CoV-2 antibody titers after monoclonal antibody therapy

Variable	Day 0	Day 8	Day 28
Viral load, copies/ml	10,264,225	570	0
Anti-N antibody (index)	0.083	0.221	7.74
Anti-RBD antibody titer, U/ml	0.701	57,753	40,135

RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Day 0 indicates day of monoclonal antibody perfusion. Positivity thresholds: anti-N antibody, ≥1; anti-RBD antibody, ≥0.8 U/ml (upper detection limit of the assay, 250 U/ml).

Anti–SARS-CoV-2 monoclonal antibodies have shown promising effects in COVID-19,[2] and preliminary results suggest efficacy in preventing severe disease after solid organ transplantation.[3] Our patient eventually mounted a natural immunity against SARS-CoV-2 in a context of repeated previous immune challenges and immunosuppression tapering. The effect of passive immunization on the development of protective immunity remains unknown.[4] Whether monoclonal antibody infusion has promoted the development of natural immunity against SARS-CoV-2 remains to be investigated.

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