

OBSERVATIONS: CASE REPORTS

Antibody Response to a Fourth Messenger RNA COVID-19 Vaccine Dose in Kidney Transplant Recipients: A Case Series

Background: Kidney transplant recipients receiving immunosuppressive drugs have impaired immune responses to messenger RNA (mRNA) COVID-19 vaccines (1). Consequently, despite standard vaccination with mRNA vaccines, many of these patients remain at high risk for severe disease during the ongoing pandemic. The U.S. Food and Drug Administration has authorized immunocompromised people to receive a third dose of mRNA vaccine after the standard 2-dose regimen to further boost protection, and French health authorities approved a third dose on 11 April 2021. Subsequent studies found that approximately 50% of patients who did not respond after a second dose seroconverted after a third dose, which produced an overall seroconversion rate of about 65% (2, 3). Antispike IgG titers above 143 binding antibody units (BAU) per milliliter correlate with the presence of neutralizing antibodies (the most widely accepted marker of disease protection) against the wild-type virus and the Alpha, Beta, and Gamma variants, but neutralization of the Delta variant requires higher antispike IgG titers (4). Therefore, patients with low titers of antispike IgG may remain insufficiently protected. In June 2021, French health authorities approved offering a fourth vaccine dose to recipients of solid organ transplants who had a weak response after a third dose.

Objective: To investigate whether a fourth dose of an mRNA-based anti-SARS-CoV-2 vaccine would increase antispike

IgG titers in kidney transplant recipients who showed a weak serologic response after 3 doses.

Case Report: A fourth dose of mRNA vaccine (BNT162b2 [Pfizer], $n = 34$; mRNA-1273 [Moderna], $n = 58$) was given to 92 kidney transplant recipients from 3 independent French university hospitals (Strasbourg, Lyon, and Nantes) who had antispike IgG titers less than 143 BAU/mL 1 month after a third dose. All had measurements of antispike IgG titers 2 to 6 weeks later (median, 29 days [interquartile range, 26 to 34 days]). The Table shows the characteristics of these patients.

There were no safety concerns with the fourth vaccine dose. After a median of 29 days, median antispike IgG levels increased from 16.4 BAU/mL (interquartile range, 5.9 to 62.3 BAU/mL) to 145 BAU/mL (interquartile range, 27.6 to 243 BAU/mL) (Figure) and 50% of patients reached the threshold of 143 BAU/mL. Patients who reached this threshold had a longer interval between their transplant and fourth vaccine dose and were less frequently treated with steroids (Table). The percentage of patients who had antispike IgG titers above 143 BAU/mL after the fourth dose was 48% for the BNT162b2 vaccine and 52% for the mRNA-1273 vaccine, and patients who received the mRNA-1273 vaccine had higher IgG titers (median, 150 vs. 122 BAU/mL). Only 1 patient was subsequently diagnosed with mild COVID-19, and he had an antispike IgG level of 28 BAU/mL 1 month after his fourth vaccine dose.

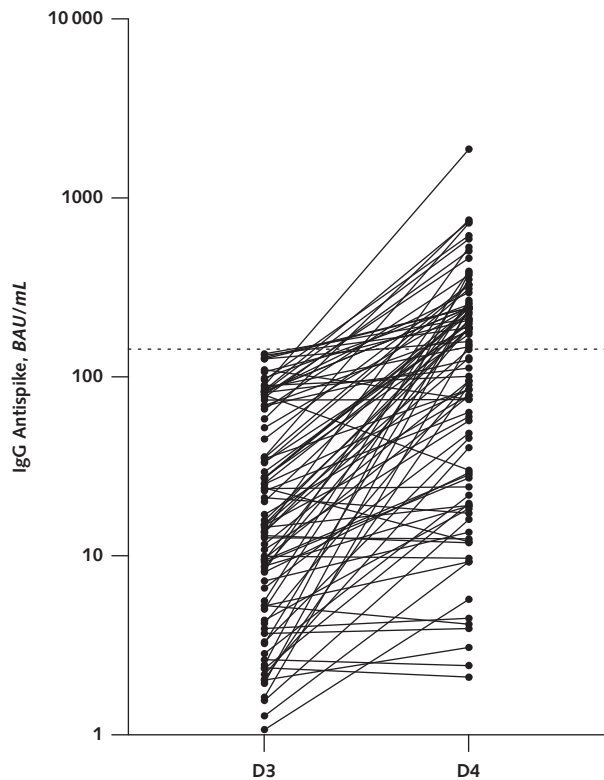
Discussion: Our study indicates that a fourth dose of an mRNA-based vaccine produces a satisfactory antibody response in some kidney transplant recipients who did not respond adequately after 3 previous doses, and it supports the

Table. Characteristics of 92 Kidney Transplant Recipients Who Received a Fourth Dose of mRNA Vaccine Against SARS-CoV-2, According to Their Subsequent Levels of IgG Antibody Against the Spike Protein

Characteristic	Entire Cohort ($n = 92$)	IgG >143 BAU/mL After 4 Doses ($n = 46$)	IgG <143 BAU/mL After 4 Doses ($n = 46$)
Median age (IQR), y	55.9 (47.1–64.2)	57.5 (49.9–64.6)	53 (45.6–61.9)
Male sex, n (%)	64 (69.5)	35 (76)	29 (63)
Median BMI (IQR), kg/m^2	26.3 (22.8–30.2)	26.6 (22.2–29.1)	25.3 (22.8–30.6)
Comorbid conditions, n (%)			
Cardiovascular disease	28 (30.4)	13 (28.3)	15 (32.6)
Diabetes	30 (32.6)	16 (34.8)	14 (30.4)
Hypertension	76 (82.6)	37 (80.3)	38 (82.6)
History of cancer	20 (21.7)	9 (19.6)	11 (23.6)
Median time from kidney transplant (IQR), y	5.5 (2.3–11.4)	7.2 (3–11.7)	4.5 (1.6–11.1)
First transplant, n (%)	79 (85.8)	37 (80.4)	42 (91.4)
Deceased donor, n (%)	77 (83.6)	37 (80.4)	40 (86.9)
Medication use, n (%)			
Calcineurin inhibitors			
Tacrolimus	70 (76)	32 (69.6)	38 (82.6)
Cyclosporine	17 (18.5)	11 (23.9)	6 (13)
None	5 (5.4)	3 (6.5)	2 (4.3)
MMF/MPA	74 (80.4)	36 (78.3)	38 (82.6)
mTOR inhibitors	16 (17.4)	9 (19.6)	7 (15.2)
Steroids	59 (64.1)	23 (50)	36 (78.3)
Median serum creatinine level (IQR)			
$\mu mol/L$	132 (113.3–162.7)	136.2 (121.9–164.5)	131.5 (100.7–159.3)
mg/dL	1.49 (1.28–1.84)	1.54 (1.38–1.86)	1.49 (1.14–1.80)
Type of vaccine, n			
mRNA-1273 (Moderna)	58	30	28
BNT162b2 (Pfizer)	34	16	18
Median delay between third and fourth vaccine dose (IQR), d	68 (61–74.7)	68 (63–76)	63 (56.7–73.2)
Median antispike IgG titer after the third dose (IQR), BAU/mL	16.4 (5.9–62.3)	35.6 (14.7–83.3)	9.5 (3.6–21.7)

BAU = binding antibody units; BMI = body mass index; IQR = interquartile range; MMF = mycophenolate mofetil; MPA = mycophenolic acid; mRNA = messenger RNA; mTOR = mammalian target of rapamycin.

Figure. Antispikes IgG titers measured 2–6 wk after the third and fourth vaccine doses in 92 kidney transplant recipients.



Titers are expressed in BAU after calibration to the World Health Organization standard. The dotted line indicates the threshold of 143 BAU/mL. BAU = binding antibody units; D3 = third dose; D4 = fourth dose.

use of a fourth vaccine dose for these patients. We have shown in an unpublished study that kidney transplant recipients with previous COVID-19 had higher antispikes IgG titers than uninfected recipients who were vaccinated. Assuming that the difference can be attributed to a higher antigen dose with infection than with vaccination, those results also support the use of additional, repeated doses of vaccine for kidney transplant recipients who do not respond adequately to standard vaccination. Prophylactic infusion of monoclonal anti-SARS-CoV-2 antibodies can be offered to patients who do not respond adequately to additional vaccine doses (5). For example, in our experience, only 10% of patients who did not respond (<1 BAU/mL) after the third dose were able to reach antispikes IgG titers above 143 BAU/mL after a fourth dose. It would have been interesting to examine T-cell immunity after repeated vaccine doses in these patients, but the assays are time-consuming, which makes it challenging to implement them during routine practice. Finally, we recognize that an increase in antispikes IgG titers does not invariably provide protection from

infection and disease, which is why we encourage longitudinal studies with a sufficient duration of follow-up to evaluate the risk for COVID-19 in patients like these after additional vaccine doses.

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