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A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients

To the editor: Solid organ transplant recipients have demonstrated a lower humoral immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination, leading transplant physicians to perform a third vaccine injection.[1] However, despite this early booster, about 35% of patients remained seronegative and, thus, inadequately protected against coronavirus disease 2019 (COVID-19).[2] Recently, a fourth mRNA injection has become available in France, as well as the possibility of monthly preventive preexposure monoclonal antibody therapy in low-responder or nonresponder patients.[3,4] On the basis of physicians' expertise and patients' choice, kidney transplant recipients from 2 French university hospitals with a strictly negative serologic assessment (i.e., binding antibody unit [BAU] <1/ml) 1 month after the third injection were proposed to receive a fourth mRNA vaccine as an alternative to preexposure monoclonal antibody prophylaxis.

We retrospectively evaluated 49 nonresponder kidney transplant recipients with a serologic assessment following a fourth mRNA vaccine (Table 1). The mean age was 63 years, and 47% were men. None of them had a history of COVID-19 infection nor anti-nucleocapsid IgG.

Table 1 | Characteristics of kidney transplant recipients strictly negative after 3 mRNA vaccines having received a fourth mRNA vaccine

	Negative (n = 28)			Positive (n = 21)			
Characteristic	NA	No.	%	NA	No.	%	*P* value
Male recipient	0	15	53.6	0	8	38.1	0.38
Transplant rank ≥2	0	4	14.3	0	2	9.5	0.68
Calcineurin inhibitor treatment	0	20	71.4	0	18	85.7	0.31
mTOR inhibitor treatment	0	0	0	0	1	4.7	0.43
Antimetabolite treatment	0	23	82.1	0	18	85.7	1
Steroid treatment	0	18	64.2	0	10	47.6	0.26
Belatacept treatment	0	0	0	0	1	4.7	0.43
BNT162b (Pfizer) mRNA vaccine	0	19	67.8	0	18	85.7	0.19
Lymphocytes <1500/mm^3	0	21	75.0	0	13	61.9	0.36
CMV seropositive status	0	17	60.7	1	8	40.0	0.15
Presence of donor-specific antibody	0	5	17.8	0	3	14.3	0.77
History of biopsy-proven acute rejection	0	6	21.4	0	1	4.8	0.21
	NA	Mean	SD	NA	Mean	SD	*P* value
Age, yr	0	63.4	11.1	0	62.4	12.8	0.87
Time from transplantation, yr	0	8.0	7.2	0	7.1	6.5	0.76
Time between third and fourth vaccine, d	0	82.6	25.7	0	93.4	31.7	0.30
Anti-spike IgG titer, BAU/ml	0	0.3	1.0	0	81.4	93.7	< 0.001
Allograft function by MDRD, ml/min	0	43.2	18.8	0	40.1	13.5	0.73

BAU, binding antibody unit; CMV, cytomegalovirus; MDRD, Modification of Diet in Renal Disease; NA, not available.

Maintenance therapy consisted of calcineurin inhibitors in 77%, antiproliferative drugs in 83%, and steroids in 57%. All of them had a strictly negative serology after the third injection (BAU, <1/ml, evaluated in different laboratories by ECLIA Roche, Architect Abbott, or Diasorin). Serologic screening was assessed in a median of 35 days following the fourth injection, and anti-spike IgG titers were expressed in BAU/ml after conversion, depending on the laboratory test. A total of 21 of 49 patients (42.8%) seroconverted (i.e., positive serology considered by laboratory thresholds) following the fourth injection, with a mean BAU titer of 82/ml (Figure 1). Of note, 4 of them had a high BAU titer (>264/ml), which can be considered as neutralizing,[5] and 3 patients without seroconversion had a slight increase in anti-spike IgG. SARS-CoV-2 infection occurred in 1 patient, who previously developed a low humoral response following 4 injections (BAU, 14.2/ml), presenting with mild symptoms and not requiring oxygen supportive care. Although no statistical differences were found between responders and nonresponders because of the small analyzed cohort, we noted lower steroid use (47% vs. 64%), less lymphopenia (62% vs. 75%), longer time between the third and fourth dose (93 vs. 82 days), and a larger utilization of the BNT162b vaccine (86% vs. 68%) in patients who developed a humoral response

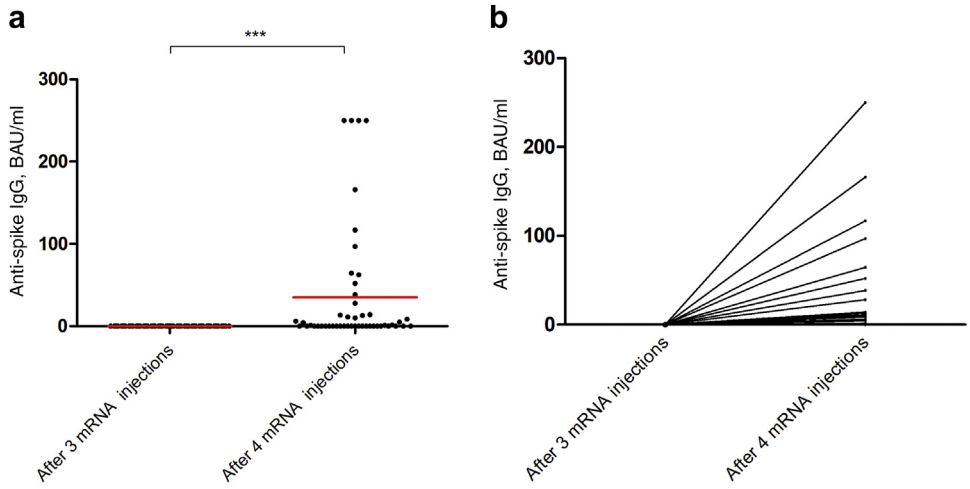

Figure 1 | (a) Anti-spike IgG titers (binding antibody unit [BAU]/ml) following the third and fourth mRNA injection in kidney transplant recipients. (**b**) Evolution of IgG anti-spike titers in strictly seronegative patients after 3 injections, having received a fourth mRNA vaccine. ***$P < 0.001$.

after the fourth injection. History of biopsy-proven acute rejection seemed more frequent in seronegative patients, but the clinical significance of these data may be hard to assess as most cases in this group (4 of 6) occurred >5 years ago.

Our report highlights the results of a fourth mRNA vaccine in strictly nonresponder kidney transplant recipients, resulting in seroconversion in 43% of them. Only 4 patients developed a strong humoral response that can be considered as protective from SARS-CoV-2 infection; other patients may benefit from another booster dose to improve their antibody titer.[6] Further studies are required to clearly determine risk factors of nonresponse after a fourth mRNA vaccine in this selected population. A fourth mRNA vaccine in strictly nonresponder kidney transplant recipients induced a humoral response in 43%; however, this response remained globally weak and was probably not protective enough against COVID-19. Monoclonal antibody provides a quicker and higher protection for these patients, and thus may be considered, especially during a high-incidence SARS-CoV-2 infection period when risk of contamination is higher.

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New-onset class III lupus nephritis with multi-organ involvement after COVID-19 vaccination

To the editor: Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger an autoimmune response. Two cases of lupus nephritis after the administration of the mRNA vaccine (BNT162b2, Pfizer–BioNTech) and the adenoviral vector vaccine (AZD1222 [ChAdOx1-S], AstraZeneca) have been reported.[1,2] We present a case of lupus nephritis with multi-organ involvement after the administration of the AZD1222 vaccine.

In 2015, a 60-year-old woman was treated with oral corticosteroids for a skin rash at a private dermatologic clinic. The rash was an itchy, brownish skin lesion with erythematous