Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy

see commentary on page 1275

To the editor: Several of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines use a nucleoside-modified, purified mRNA lipid nanoparticle-encapsulated platform. Compared with traditional inactivated viral and adjuvanted protein vaccines, this RNA platform elicits far higher neutralizing antibody titers, stronger antigen-specific cluster of differentiation (CD) 4^+ and $CD8^+$ T-cell responses, and stronger germinal center B and T_{FH} cell activation in experimental animals.[1] The activated $CD4^+$ and $CD8^+$ T cells produce several proinflammatory cytokines, including interferon-γ and tumor necrosis factor-α. This led us to wonder if these vaccines may activate or exacerbate immune-mediated glomerular diseases. Two individuals with biopsy-proven IgA nephropathy (IgAN) developed gross hematuria shortly following the second dose of the Moderna vaccine. The patients are described in Table 1. At baseline, both had proteinuria of <1 g/d and well-preserved kidney function. Several hours after the second dose of vaccine was given, both developed systemic symptoms, ranging from body aches, headache, and fatigue to fever and chills. Between 8 and 24 hours after systemic symptoms appeared, the patients noticed gross hematuria that resolved after 3 days. Serum creatinine did not increase, but proteinuria increased in 1 patient (Table 1). Although we did not expect an exacerbation of IgAN after a nonmucosal immune challenge, IgAN patients have previously been reported to have a stronger IgA1 (albeit monomeric) response to intramuscular influenza vaccine than healthy subjects.[2] These episodes of apparent IgAN exacerbation should prompt the nephrology community to closely follow their patients with glomerular disease after SAR2-CoV-2 vaccination to determine the frequency and consequences of vaccine-induced disease activation.

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Weak anti–SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients

see commentary on page 1275

To the editor: International recommendations on coronavirus disease 2019 (COVID-19) vaccine distribution have given priority to immunocompromised patients, including kidney transplant recipients (KTRs).[1,2] Unfortunately, this guidance has been released without inclusion of this clinical population in vaccine clinical trials. In an effort to shed light on the efficacy and safety of an mRNA COVID-19 vaccine in KTRs, this preliminary study was undertaken to investigate

Table 1 | Patient demographics and clinical characteristics

Patient no.	Age, yr	Sex	Race	Year IgAN diagnosed	Treatment	Gross hematuria events during disease course	Persistent microscopic hematuria	Proteinuria in 2020, g/d	Proteinuria between SARS-Cov-2 vaccine doses, g/d	Proteinuria 3 weeks after last SARS-CoV-2 vaccine dose, g/d
1	38	F	W	2005	RAASi	At presentation; during 1 episode of gastroenteritis; occasionally after yearly influenza vaccine	Yes	0.63	0.82	1.40
2	38	F	W	2019	Cyc + Pred (6 mo), then RAASi	At presentation only	Yes	0.43	0.59	0.40

Cyc, cyclophosphamide; F, female; IgAN, IgA nephropathy; Pred, prednisone; RAASi, renin-angiotensin-aldosterone system inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; W, white.

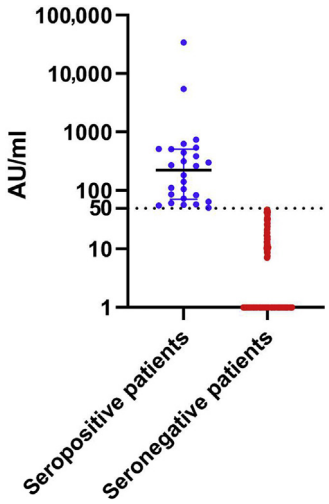

Figure 1 | Anti-spike IgG antibody titers measured at 28 days after vaccination in 215 seronegative kidney transplant recipients (median titer, <6.8 arbitrary units [AUs]/ml [interquartile range, <6.8−<6.8 AUs/ml]) and 26 seropositive kidney transplant recipients (median titer, 224 AUs/ml [interquartile range, 76−496 AUs/ml]). The dotted line indicates the cutoff for positivity (50 AUs/ml).

the anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody response after the first injection.

We examined 242 KTRs who received the first injection of the Moderna mRNA-1273 vaccine (100 μg) at the Strasbourg University Hospital (Strasbourg, France) between January 21 and 28, 2021. All had a negative history for COVID-19 and tested negative for anti–SARS-CoV-2 antibodies on the day of the first injection. The anti–SARS-CoV-2 antibody response against the spike protein was assessed at 28 days after injection using the ARCHITECT IgG II Quant test (Abbott, Abbott Park, IL), with titers >50 arbitrary units (AUs)/ml being considered as positive (detection range, 6.8–40,000 AUs/ml; positive agreement, 99.4%; negative agreement, 99.6%).

One patient developed mild symptomatic COVID-19 7 days after injection, and only 26 (10.8%) KTRs had a positive serology at 28 days after injection. The median IgG titer was 224 AUs/ml (interquartile range, 76−496 AUs/ml), whereas the median IgG titer in the seronegative group was <6.8 AUs/ml (Figure 1). Patients who seroconverted had longer time from transplantation, received less immunosuppression, and had a better kidney function (Table 1).

In summary, the burden of immunosuppression may induce a weak anti–SARS-CoV-2 antibody response in KTRs after the first injection of an mRNA COVID-19 vaccine. This finding is strikingly different compared with immunocompetent subjects, who invariably seroconverted after the first injection.[3,4] We highlight the need not to delay the second vaccine injection in immunocompromised patients. Close surveillance is also recommended to discuss the opportunity of a third dose in less responsive patients.

Table 1 | Characteristics of kidney transplant recipients, according to serologic response after the first dose of the Moderna mRNA-1273 vaccine

Characteristics	Entire cohort (n=241)[a]	SARS-CoV-2 seronegative patients (n=215)	SARS-CoV-2 seropositive patients (n=26)	*P* value	Missing data
Age, yr	57.7 (49.3–67.6)	57.7 (49.6–67.7)	58.4 (43.3–66.9)	0.51	0
Male sex	156 (64.7)	142 (66.1)	14 (53.9)	0.28	0
BMI, kg/m^2	25.7 (22.6–29.5)	25.7 (22.8–29.4)	26.4 (21.9–29.9)	0.73	2
Time from kidney transplantation, yr	6.4 (2.9–13)	5.8 (2.8–11.9)	15.4 (8.6–25.9)	<0.001	2
First transplantation	202 (83.8)	176 (81.8)	26 (100)	0.01	0
Deceased donor	192 (79.6)	172 (80)	20 (76.9)	0.8	0
ABO group				0.02	2
O	94 (39.3)	82 (38.5)	12 (46.2)		
A	101 (42.3)	93 (43.7)	8 (30.8)		
B	30 (12.6)	29 (13.6)	1 (3.9)		
AB	14 (5.9)	9 (4.2)	5 (19.2)		
Induction treatment				0.001	7
Anti-thymocyte globulin	138 (59.5)	127 (60.8)	11 (47.8)		9
Anti-CD25	88 (37.9)	80 (38.3)	8 (34.8)		
No induction	6 (2.6)	2 (1)	4 (17.4)		
CNI				0.06	0
Tacrolimus	133 (55.2)	124 (57.7)	9 (34.6)		
Ciclosporin	82 (34)	69 (32.1)	14 (50)		
No CNI	26 (10.8)	22 (10.2)	4 (15.4)		
MMF/MPA	191 (79.3)	177 (82.3)	14 (53.9)	0.002	0
Azathioprine	7 (2.9)	4 (1.86)	3 (11.5)	0.03	0
mTOR inhibitors	35 (14.5)	32 (14.9)	3 (11.6)	1	0
Steroids	142 (58.9)	133 (61.9)	9 (34.6)	0.01	0
Belatacept	9 (3.8)	9 (4.2)	0	0.26	0
eGFR, ml/min per 1.73 m^2	51.6 (38.1–68)	51 (37.9–66.5)	64.9 (39.9–72.2)	0.08	0
Serum creatinine, μmol/L	118 (99–158)	120 (101–159)	104 (85–134)	0.05	0

BMI, body mass index; CD, cluster of differentiation; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mechanistic target of rapamycin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]The patient who developed coronavirus disease 2019 after the first injection was excluded from the analysis.
Continuous variables are presented as medians (interquartile ranges), whereas categorical variables are given as n (%).

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SARS-CoV-2–reactive cellular and humoral immunity in hemodialysis population

see commentary on page 1275

To the editor: The outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients receiving hemodialysis (HD) is significantly worse compared with the general population.[1–3] Whether the SARS-CoV-2–specific immunity in patients with coronavirus disease 2019 (COVID-19) receiving dialysis is impaired as a possible cause for the inferior outcome is not known so far.

We performed an observational case-control study comparing the frequencies and functionality of SARS-CoV-2–reactive T cells as well as antibody titers in 14 COVID-19 convalescent patients receiving HD with 14 age-, sex-, and COVID-19–presentation matched patients with normal renal function (Supplementary Table S1).

In general, the frequencies of SARS-CoV-2 spike, nucleocapsid, and membrane protein-reactive T cells in patients receiving HD and patients with normal renal function were similar (Table 1; Supplementary Figure S1A). Spike-specific antibody titers were also comparable in both groups (Supplementary Figure S1B). Frequencies of SARS-CoV-2–reactive $CD4^+$ and $CD8^+$ T cells producing effector cytokines granzyme B, interleukin-2, tumor necrosis factor, and interferon-γ were similar or, for certain cytokines, even significantly higher in patients receiving HD compared with patients with normal renal function (Table 1; Supplementary Figure S1C). Patients receiving dialysis demonstrated higher frequencies of memory SARS-CoV-2–reactive T cells (Supplementary Figure S2).

To our knowledge, this exploratory study suggests for the first time that patients receiving dialysis are able to generate efficient T-cell immunity, as demonstrated by their multiple cytokine production. The magnitude and functionality of SARS-CoV-2–reactive T cells was comparable or even higher than in patients with normal renal function. Further larger studies are required to confirm our observation.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Cohort characteristics.

Figure S1. Frequency of SARS-CoV-2–reactive T cells. Isolated PBMCs from dialysis (n = 14) and nondialysis patients with normal renal function (n = 14) after a SARS-CoV-2 infection were stimulated for 16 hours with 1 μg/ml of SARS-CoV-2 OPPs from the M (n = 13/14), N (n = 13/14), or S (n = 14/14) protein. 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$^+$. (**A**) Frequencies of total SARS-CoV-2–reactive CD4$^+$CD137$^+$CD154$^+$ and CD8$^+$CD137$^+$ T cells reactive to the M, N, or S protein combined are shown. (**B**) Comparison of the relative titers of SARS-CoV-2 Spike-protein–specific IgG antibodies of

Table 1 | Frequency of SARS-CoV-2–reactive T cells in dialysis and nondialysis patients

		$CD4^+CD154^+CD137^+$			
Group, %	$CD4^+CD154^+CD137^+$	+Granzyme B^+	+IFN-γ^+	+IL-2^+	+TNF^+
Dialysis	0.7745 (0.057–1.57)	0.02029 (0–0.134)	0.1538 (0.017–0.437)	0.42 (0.054–0.651)	0.282 (0.02–0.588)
Nondialysis	0.237 (0.031–0.734)	0 (0–0.025)	0.0255 (0–0.195)	0.1165 (0.023–0.3)	0.0705 (0.012–0.223)
		$CD8^+CD137^+$			
Group, %	$CD8^+CD137^+$	+Granzyme B^+	+IFN-γ^+	+IL-2^+	+TNF^+
Dialysis	0.355 (0.187–1.21)	0.2795 (0.08–0.61)	0.0225 (0–0.1665)	0.0225 (0–0.096)	0.085 (0–0.15)
Nondialysis	0.1325 (0–0.33)	0.0205 (0–0.107)	0 (0–0.06)	0 (0–0.018)	0 (0–0.045)

IFN-γ, interferon-γ; IL-2, interleukin-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.
Frequency of SARS-CoV-2–reactive $CD4^+$ or $CD8^+$ T cells among all $CD4^+$ or $CD8^+$ T cells. Data are given as median (95% confidence interval).