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Fourth dose of the SARS-CoV-2 vaccine in kidney transplant recipients with previously impaired humoral antibody response

To the Editor:

Following three doses of the SARS-CoV-2 vaccines 30%–40% of kidney transplant (KTx) recipients remain without relevant antibody response.[1] Here, we report the effect of a fourth booster dose in 188 KTx recipients with no or low anti-SARS-CoV-2 antibody response following dose 3. The majority (171/188, 91%) had received three doses of Comirnaty, Pfizer BioNtech prior to dose 4 (the rest three doses Spikevax, Moderna).

We invited recipients with no serological response (<5 binding antibody units [BAU]/ml, $n = 102$) or low response (5–200 BAU/ml, $n = 86$) 1 month after three mRNA vaccine doses to receive the fourth vaccination with Spikevax, Moderna. The study was approved according to the research regulations in Norway, performed according to the Helsinki declaration, and all patients provided written informed consent.

At dose 4 none had a history of coronavirus disease 2019 (COVID-19). The median time between doses 3 and 4 was 18.0 weeks (interquartile range [IQR]: 9.7–18.3). Seropositive low-responders 1 month after the third dose ($n = 86$) decreased from a median 103 [IQR: 19–119] to 38 [IQR: 11–104] BAU/ml. Nine turned negative and 15 initial non-responders were slow responders i.e. 92 were seropositive at the time of the fourth dose (Table 1).

After the fourth dose 42% (79/188) developed above 200 BAU/ml, with a median of 1553 [IQR: 356–3703] BAU/ml versus 4.6 [IQR: 2.5–32] BAU/ml at vaccination. In the 96 recipients, who were

TABLE 1 Demographic data by status at dose 4

	All *N* = 188	IgG <200 BAU/ml after dose 4 *N* = 109	IgG >200 BAU/ml after dose 4 *N* = 79	*p*-values[a]
Age (year)	60 ± 12	61 ± 13	60 ± 11	.53
Male sex	109 (58%)	64 (59%)	45 (57%)	.87
Years since last Tx	8.3 ± 7.0	7.9 ± 6.4	8.9 ± 7.7	.37
Median (IQR) antispike IgG at dose 4, BAU/ml	4.6 (2.5–32)	2.6 (2.4–4.3)	38 (9.2–104)	<.001
Immunosuppression				
Basiliximab induction	188 (100%)	109 (100%)	79 (100%)	1.00
CNI, MPA and prednisolone	162 (86%)	100 (92%)	62 (78%)	.03
CNI and prednisolone	5 (3%)	3 (3%)	2 (3%)	.67
Other combinations	21 (11%)	6 (5%)	15 (19%)	.05
CNI	171 (91%)	103 (94%)	68 (86%)	.02
MPA	177 (94%)	105 (96%)	72 (91%)	.40
Prednisolone	185 (98%)	106 (97%)	79 (100%)	1.00
mTOR inhibitor	19 (10%)	5 (5%)	14 (18%)	.01
Azathioprine	1 (0.5%)	0 (0%)	1 (1%)	.87
Belatacept	0	0	0	1.00
eGFR (ml/min/1.73 m^2)	50 ± 16	47 ± 17	56 ± 14	<.001

Note: Data are presented as mean ± SD or numbers (%), if nothing else is mentioned, and groups are divided in dose 4 responders and non-responders using an anti-SARS-CoV-2 IgG antibody cut-off of 200 BAU/ml 1 month after the fourth vaccine dose.

Abbreviations: CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate (MDRD-4 formula); IQR, interquartile range; MPA, mycophenolate; mTOR, mammalian target of rapamycin; Tx; transplantation.

[a] Comparing responders and non-responders with Student's *t*-test or chi-squared test.

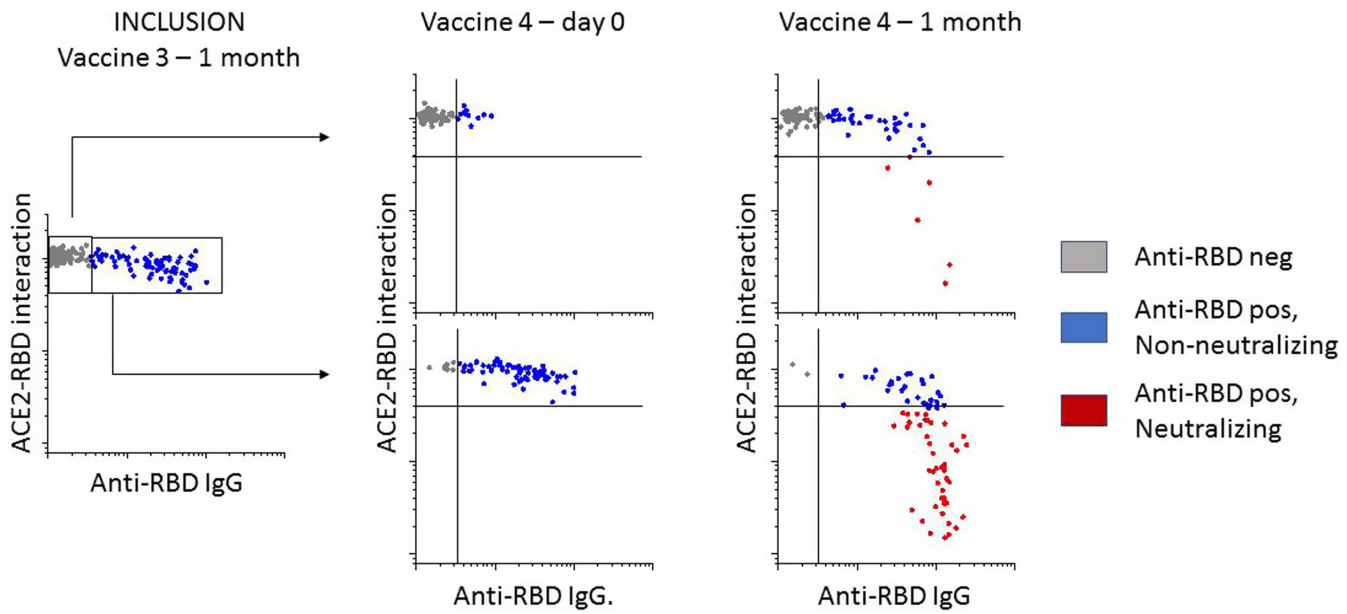

FIGURE 1 Anti-SARS-CoV-2 (Wuhan) receptor-binding domain (RBD) binding- (x-axis) and neutralizing-antibodies at selection time-point for receiving the fourth dose (INCLUSION; 1 month after dose 3, left panel), at time of dose 4 (middle panel), and 1 month after dose 4 (right panel). Dot-color represents the anti-RBD and neutralizing activity of each individual serum. The dot plots show accumulated data for 188 patients, and each dot corresponds to a different serum. Bead-based arrays were incubated with sera diluted at 1:100 and then labeled with fluorochrome-conjugated anti-human IgG or recombinant ACE2 (Tran et al.[2]).

sero-negative before dose 4, 27 (28%) showed detectable antibodies 3–4 weeks after dose 4 (median 53 [IQR: 12–407] BAU/ml). Only a minority (8/96, 8%) reached antibody levels that are considered to correlate with protection (2% >2000 BAU/ml, 6% between 200 and 2000 BAU/ml). Logistic regression analyses show that both antibody level and renal function at the time of vaccination are associated with response (Data S1).

No serious adverse events or acute rejections were detected after dose 4.

Following dose 3 we registered a decay of anti-SARS-CoV-2 antibody concentrations indicating that a majority will be in need of a fourth booster dose.[1] The antibody concentrations required for protection against severe COVID-19 in KTx recipients have not been accurately defined. Based on in vitro neutralizing assays in our lab, and in line with Dimeglio et al., we have defined 200 BAU/ml as a cut-off for neutralizing activity against ancestral SARS-CoV-2 and 11 000 BAU/ml as a cut-off for neutralization against the Omicron-variant.[2,3] Observational data after dose 3 registered in the Norwegian Renal Registry indicate >200 BAU/ml as clinically "protective" against the delta variant of concern. Neutralizing effect following dose 4 is presented in Figure 1.

A fourth mRNA vaccine dose in KTx recipients is safe and boosts antibody concentrations to potentially neutralizing levels in a relevant part of previous low-responders. Only a marginal number of previously seronegative recipients show a humoral response following dose 4, in line with the previous publications.[4,5] Analysis of cell-mediated immunity is needed to further understand vaccine immunogenicity in this population. Our result should inspire transplant-centers to monitor anti-SARS-CoV-2 antibody concentrations following dose 3 and to offer a fourth vaccination dose to low-responders. In recipients without vaccine response after dose 3, other protective alternatives are urgently warranted.

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