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Journal of Infection 84 (2022) e98–e100

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

SARS-CoV2 antibody response after a third dose of heterologous ChAdOx1 nCoV-19 and Moderna vaccine in chronic dialysis patients

Dear Editor,

The battle against coronavirus disease 2019 (COVID-19) remains the biggest challenge in controlling the spread of the disease globally. In this Journal, the report by Li and colleagues highlighted the danger to renal dialysis patients in the COVID-19 pandemic (1). Using the whole-genome sequencing and epidemiological data, the author demonstrated that the risk of SARS-CoV-2 transmission was present in the community and the hospital setting. Among various strategies against the spread of infection, current evidence indicates that vaccines continue to offer substantial protection against COVID-19. However, immunogenicity reports that antibody titers wane relatively rapidly after receiving two doses of vaccine. Thus, a third dose has been recommended, especially in those with severely compromised immunity, including end-stage renal disease (ESRD) patients (2, 3). A recent systemic review has shown that dialysis patients had a significantly lower seroconversion rate following two doses of COVID-19 vaccination than in the control group (RR, 0.88; 95%CI, 0.82-0.93) (4). Moreover, a small prospective study had shown that four months following the second dose of the Pfizer-BioTech Comirnaty vaccine, 20% of dialysis patients became seronegative (SN) (5).

Cumulating evidence has been shown that heterologous vaccines have more immunogenicity than homologous prime-boost vaccination (6, 7). The question remains to be answered whether a

Table 1
Demographic characteristics of chronic dialysis patients.

	AZ/Moderna (n = 207)	Moderna/Moderna (n = 19)	p-Value
Age (years)	65.70±12.32	60.84±13.36	0.142
HD/PD	180/27	13/6	0.014*
Sex (M/F)	120/87	8/11	0.346
BW (kg)	62.66±13.19	62.93±15.72	0.932
BMI (kg/m^2)	23.94±4.18	23.46±4.06	0.628
Kt/V (HD/PD)	1.55±0.22/2.11±0.28	1.53±0.22/2.09±0.50	0.732/0.895
URR/WCC (HD/PD)	73.05±4.36/58.74±17.58	72.46±4.84/63.99±29.66	0.786/0.566
Alb (g/dL)	3.84±0.36	3.97±0.38	0.126
Dial vintage (Months)	83.04±75.32	57.53±32.93	0.145
Ferritin (ng/mL)	370.77±372.98	455.27±441.76	0.353
WBC ($10^3/\mu L$)	6.36±1.98	6.52±2.39	0.729
Hb (g/dL)	10.13±1.06	10.14±0.86	0.954
PLT($10^3/\mu L$)	179.40±61.90	192.84±79.20	0.378
Na (mmol/l)	136.31±4.05	135.21±4.28	0.259
K (mmol/l)	4.62±0.81	4.71±0.84	0.660
Ca (mg/dl)	9.28±0.85	9.10±0.63	0.382
Pi (mg/dl)	5.46±1.64	5.99±1.97	0.185
i-PTH (pg/ml)	305.12±326.21	358.59±224.46	0.486
TG (mg/dl)	171.31±112.23	128.47±69.11	0.104
Chol (mg/dl)	150.62±37.69	146.47±50.60	0.657
GOT (U/l)	16.38±9.55	23.68±29.39	0.052
GPT (U/l)	14.42±9.41	30.84±66.65	0.068
T-Bil (mg/dl)	0.49±0.27	0.49±0.14	0.982
D-Bil (mg/dl)	0.12±0.17	0.12±0.07	0.995
DM (%)	104 (47.83%)	11 (57.89%)	0.502
HTN(%)	189 (87.92%)	19 (100%)	0.913
CHF (%)	26(12.56%)	6(31.58%)	0.041*
Cancers (%)	16(7.73%)	1(5.26%)	0.657
Autoimmune (%)	1(0.48%)	2(10.53%)	0.052
Stroke (%)	21(10.14%)	0	0.998
Composite comorbidities	64(30.93%)	9(47.37%)	0.281

Abbreviations: Alb, albumin; BMI, body mass index; BW, body weight; DM, diabetes mellitus; Hb, hemoglobin; HD, hemodialysis; HTN, hypertension; GPT, Glutamic Pyruvic Transaminase; K, potassium; Kt/V, quantifying hemodialysis and peritoneal dialysis treatment adequacy, K, dialyzer clearance of urea; t, dialysis time; V, the volume of distribution of urea; PD, peritoneal dialysis; Pi, phosphorus; TG, triglyceride; URR, urea reduction ratio; WBC, white cell count; WCC, weekly creatinine clearance. * $p < 0.05$.

https://doi.org/10.1016/j.jinf.2022.04.011

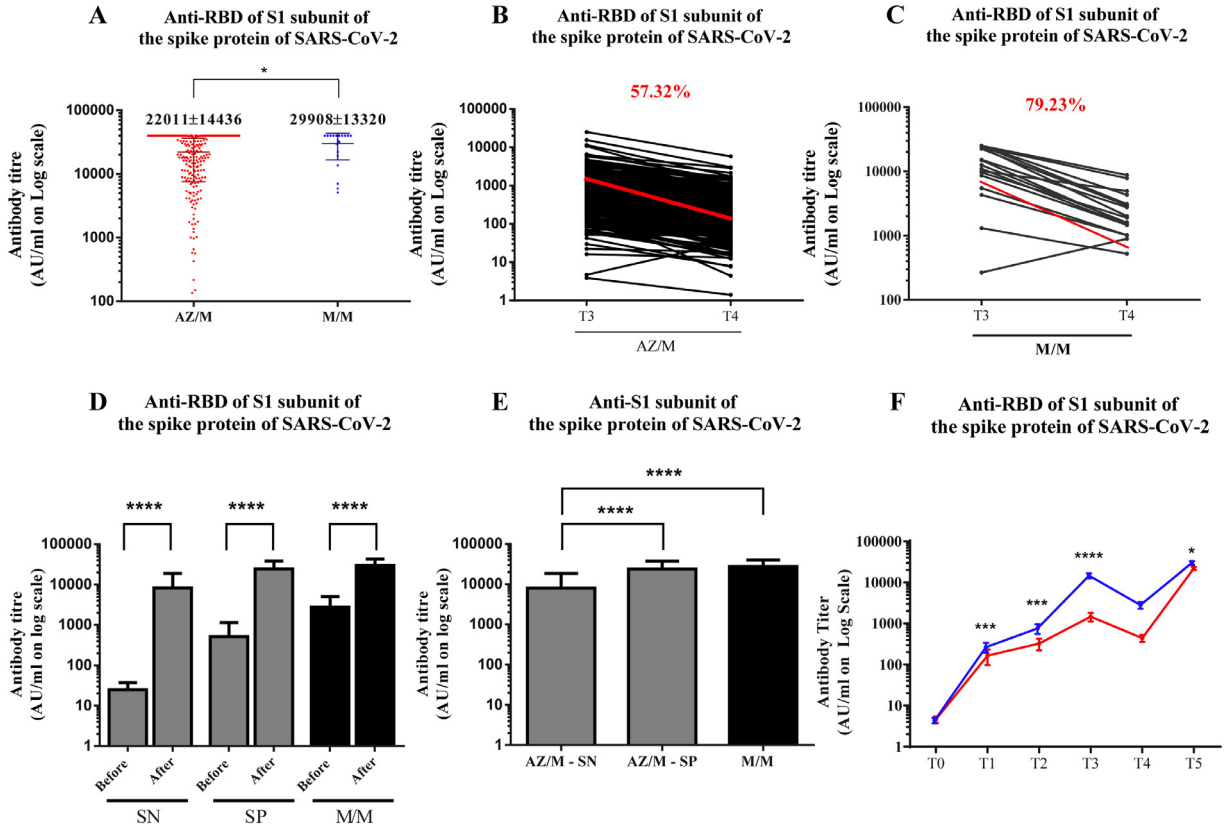

Fig. 1. (A). Anti-RBD antibody levels of patients receiving heterologous AZ/Moderna versus Moderna/Moderna on a log scale. (B,C). Changes in anti-RBD levels after the second and before the third vaccine in AZ/Moderna group and in Moderna/Moderna group. The red arrow indicates the percentage of average reduction of antibody levels from T3 to T4. (D) Anti-RBD levels before and after the third vaccine in the SN patients, the SP patients, and the Moderna group. (E) Anti-RBD levels after the third Moderna vaccine in both AZ and Moderna groups. (F) The average anti-RBD antibody levels in both groups of patients before and after vaccines at the six designed blood test points (T0-T5). Abbreviations: AZ/M, heterologous ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca) and Moderna group; M/M, Moderna/Moderna group; SN, patients who received two doses of AZ vaccines and became seronegative; SP, patients who received two doses of AZ vaccines remained seropositive; T3, 21-35 days after the second vaccine; T4, 20 weeks after the second vaccine, 0-7 days before the third dose of vaccine. * $p < 0.05$, *** $p < 0.005$, **** $p < 0.0001$.

third heterologous vaccine offers a better immunogenicity response than a homologous regimen in dialysis patients. In the present study, we administered the third messenger RNA-based (Moderna) vaccine to the dialysis patients, the humoral response of the additional vaccine was examined.

The present study is a successive cohort of our recently published study (8). The Abbott IgG II method was used to quantify antibodies against the spike protein's receptor-binding domain (RBD). A value ≥ 50 AU/ml was defined as seropositive (SP), < 50 AU/ml was defined as seronegative (SN). Two time points blood tests, T4 and T5, evaluated the post-vaccination anti-RBD response. T4, 20 weeks after the second vaccine (or 0-7 days before the third vaccine). T5, 14-20 days after the third vaccine. Dialysis patients' demographic details were obtained from their medical records. All data were summarized and displayed as mean ± standard deviation for the continuous variables. A p-value < 0.05 was considered statistically significant for all analyses. IBM SPSS Statistics for Windows, version 25, was used for all statistical analyses.

Overall, 226 patients participated in the study (207 patients AZ+Moderna group (AZ/M) and 19 patients Moderna/Moderna group (M/M)). The AZ/M group has more HD, peritoneal dialysis (PD), and congestive heart failure patients than the M/M group (Table 1). The anti-RBD levels were significantly higher in the M/M group than in the AZ/M group (29908±13320 vs. 22011±14436 AU/ml, $p = 0.023$) (Fig. 1A). At T4, 57.32% reduction of anti-RBD levels in the AZ/M group compared to 79.23% decrease in the M/M group (Fig. 1B and 1C). At T3 (21-35 days after the second vaccine), only five patients had antibodies < 50 AU/ml. However, at T4, 30 patients became seronegative. Fig. 1D shows a significant difference in the SN, SP, and M/M groups' anti-RBD levels before and after the third vaccine. Fig. 1E shows significant differences in anti-RBD levels in the SN patients after the third vaccine compared to the SP and M/M patients. The M/M group had significantly higher mean anti-RBD levels before and after all three vaccines than the AZ/M group (Fig. 1F) except at T0 (before the first vaccine). However, these differences became less prominent after the third vaccine (p = 0.023).

Univariable analysis identified age, body weight (BW), serum calcium, platelet counts, and composite comorbidities as significant factors associated with reducing antibodies in the AZ group. Using multivariable logistic regression analysis, we found that age and platelet counts were significantly correlated with reducing the AZ group's anti-RBD levels (supplementary Table S1).

This study followed the IgG antibody response to the RBD of the spike protein in maintenance dialysis patients who received an extended primary series of Moderna vaccines. Before the third dose, the Moderna group had a higher antibody reduction rate than the AZ group (79.23% vs. 57.32%, respectively). However, the AZ group had less sustainable antibody levels than the Moderna group (30 patients seronegative). The third vaccine, Moderna, induced a dramatic humoral response in both AZ and Moderna groups (22011±1016 and 29908±3056 AU/ml, respectively).

Age is the critical factor in the humoral response to the SARS-CoV-2 vaccine. Older patients tend to wane off anti-RBD antibodies earlier than younger patients (supplementary Table S1). The BW of SN and SP patients was 57.62±11.55kg and 63.51±13.29 kg, re-

spectively. Current evidence regarding vaccine antibodies and the body mass index (BMI) is conflicting and scanty, perhaps partly because of differences in the distribution and physiology of fatty tissue in men compared to women. Yamamoto et al. observed that a higher BMI was associated with lower titers of spike IgG antibodies against SARS-CoV-2 in men but not women (9). We found that BW positively correlated with antibody levels but not sex. Patients with lower BW have less sustainable antibody levels than patients with greater BW.

Dialysis patients with lower platelet counts tend to have earlier wane-off anti-RBD response than the higher platelet counts counterpart. A recent study indicated that circulating platelets of rapid responders to the BNT162b2 vaccine expressed lower surface levels of the immunoreceptor tyrosine-based inhibitory motif (ITIM)-coupled receptor CD31 (PECAM-1) compared to slow responders. This result suggests that the platelet-immune crosstalk could be exploited as early biomarkers of vaccine efficacy (10).

In summary, the present study demonstrated the beneficial effect of the third Moderna vaccine in dialysis patients. We found that 14.5% of patients became seronegative 20 weeks after the second AZ vaccine, but all patients had a positive anti-RBD response after the additional Moderna vaccine. Monologous M/M group had higher anti-RBD levels from T1 to T5 than the heterologous AZ/M group. However, these differences had become less prominent after the third dose (Fig. 1F). Older patients with lower platelet counts and higher calcium and GPT levels tend to have less sustainable antibody responses. A third heterologous Moderna vaccine provided a comparable anti-RBD response. The sustainability of this effect would need a further longitudinal study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.04.011.

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