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Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—a prospective cohort study

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Emerging data has established end-stage renal disease (ESRD) as one of the highest risk comorbidities for severe coronavirus disease 2019 (COVID-19), with short-term mortality above 20% [1, 2]. Based on both a large clinical trial and real-life data from Israel in the general populations, the effectiveness of mRNA-based BNT162b2 vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was estimated at 95% [3, 4]. Nevertheless, dialysis patients present diminished immune response following immunization with various vaccines, and the efficacy of the available SARS-CoV-2 vaccine among this vulnerable group is unknown [5]. Therefore, we performed a prospective study, evaluating antibody response among hemodialysis and peritoneal dialysis (PD) patients 2–6 weeks after receiving the second dose of BNT162b2.

The study included hemodialysis and PD patients who were vaccinated with two doses of BNT162b2 vaccine, 21 days apart. Patients treated with current chemotherapy or immunosuppressive drugs, those who had only one vaccine dose, those who had been infected by COVID-19 before or those who were unable to give consent were excluded. To confirm sustained response, consenting participants were evaluated 2–6 weeks after receiving the second vaccine dose and were followed for up to 8 weeks. The study was approved by the ethics committee of Rabin Medical Center. Demographic data were collected by interview and medical records and blood samples for anti-spike (anti-S) SARS-CoV-2 antibodies were collected during the routine dialysis visits. SARS-CoV-2 immunoglobulin G (IgG) II Quant (Abbott©) assay was used for quantitative measurement of anti-S IgG antibodies of SARS-CoV-2. A test was considered as positive if IgG was above 50 AU/mL [6]. The primary outcome was the rate of seropositivity for anti-S antibodies. Univariate and multivariate linear regression analyses were performed to explore factors associated with higher log-transformed antibody titer. The results are presented as change of log-transformed antibody level per unit of explanatory variable (*B*).

Overall, 122 hemodialysis patients were included in the study (Supplementary data, Figure S1). Patients' characteristics are detailed in Table 1. At a median time of 36 days [interquartile range (IQR) 32–40, range 10–48 days] from the second immunization dose, 114 (93.4%) of the 122 hemodialysis patients were seropositive for anti-S IgG. The geometric mean of anti-S titer was 1190.8 AU/mL, median level was 1599 AU/mL (IQR 419.5–3976.9 AU/mL) and the mean log-transformed anti-S level was 3.08 ± 0.84 logAU/mL.

Factors associated with non-response (≥50 AU/mL) were lower serum albumin (3.41 ± 0.56 versus 3.99 ± 0.35, $P < 0.001$) and higher intravenous iron sucrose dose [median dose (IQR) 150 mg/week (62.5–300) versus 50 mg/week (0–100), $P = 0.003$] in non-responders and responders, respectively.

Younger age (*B* 0.021 per year decrease, 95% CI 0.011–0.031, $P < 0.001$), serum albumin above 3.5 g/dL (*B* 1.039, 95% CI 0.65–1.429, $P < 0.001$), lower intravenous iron dose (*B* 0.002 per mg/week decrease, 95% CI 0.00–0.004, $P = 0.009$) and body mass index (BMI) <30 kg/m^2 (*B* 0.394, 95% CI 0.107–0.681, $P = 0.008$) were associated with higher log-transformed antibody titer in a multivariate analysis (Supplementary data, Table S1).

Of the 23 PD patients, 22 (95.6%) were seropositive for anti-S IgG. The geometric mean of anti-S titer was 1515.14 AU/mL, median level was 1560 AU/mL (IQR 254.8–6423 AU/mL) and the mean log-transformed antibody level was 3.18 ± 0.83 logAU/mL. There was no significant difference between the mean antibody titer of PD and hemodialysis patients ($P = 0.58$). Younger age (*B* 0.034 per year decrease, 95% CI 0.009–0.06, $P = 0.011$) and serum albumin above 3.5 g/dL (*B* 1.147, 95% CI 0.536–1.758, $P < 0.001$) were associated with higher log-transformed antibody titer in a univariate analysis. Due to the small PD cohort, multivariate analysis was not performed.

Only two major adverse events following any vaccine dose were reported among 145 cohort participants. Major adverse events included: one syncope event, 1 day following the first vaccination dose (hemodialysis patient), and one pericarditis event 2 days following second vaccination dose (PD patient).

Seropositivity rates following BNT162b2 vaccination in both hemodialysis and PD patients were high and comparable to the seropositivity rates reported in healthy volunteers [7]. Overall, 114 hemodialysis patients (93.4%) and 22 PD patients (95.6%)

Table 1. Baseline characteristics of the hemodialysis cohort according to antibody response

Variable name	All ($n = 122$)	Response ($n = 114$)[a]	No response ($n = 8$)	P
Age (years)	71.57 ± 12.87	71.1 ± 13.02	78.38 ± 8.47	0.123
Female gender	41 (33.6%)	38 (33.3%)	3 (37.5%)	0.809
Dialysis vintage (months)	39.73 ± 32.59	39.77 ± 33.06	39.07 ± 26.84	0.953
Primary kidney disease				0.105
Diabetic nephropathy	55 (45.1%)	54 (47.4%)	1 (12.5%)	
Hypertensive kidney disease	27 (22.1%)	25 (21.9%)	2 (25%)	
Glomerulonephritis	14 (11.5%)	13 (11.4%)	1 (12.5%)	
ADPKD	5 (4.1%)	3 (2.6%)	2 (25%)	
Other/unknown[b]	21 (17.2%)	19 (16.7%)	2 (25%)	
Diabetes mellitus	70 (57.4%)	66 (57.9%)	4 (50%)	0.662
Ischemic heart disease	64 (52.5%)	58 (50.9%)	6 (75%)	0.187
History of malignancy	24 (19.7%)	21 (18.4%)	3 (37.5%)	0.189
History of transplantation	8 (6.6%)	7 (6.1%)	1 (12.5%)	0.482
Jugular catheter as dialysis access	57 (46.7%)	54 (47.4%)	3 (37.5%)	0.589
KT/V	1.44 ± 0.28	1.45 ± 0.28	1.36 ± 0.32	0.395
nPCR (g/kg/day)	1.09 ± 0.27	1.1 ± 0.27	0.94 ± 0.22	0.113
Anuria	59 (48.4%)	56 (49.1%)	3 (37.5%)	0.525
BMI (kg/m^2)	26.69 ± 5.51	26.73 ± 5.51	26.16 ± 5.89	0.781
Obesity (BMI >30 kg/m^2)	31 (25.4%)	29 (25.4%)	2 (25%)	0.978
Serum albumin (per g/dL)	3.95 ± 0.39	3.99 ± 0.35	3.41 ± 0.56	<0.001
Hypoalbuminemia (albumin < 3.5 g/dL)	15 (12.3%)	11 (9.6%)	4 (50%)	0.001
Hemoglobin (g/dL)	10.63 ± 1.13	10.6 ± 1.12	11.05 ± 1.3	0.278
Transferrin saturation (%)	26.65 ± 10.98	26.65 ± 11.29	26.69 ± 5.6	0.993
Ferritin level (mg/dL)	610 (349–902)	713 (339–857)	579 (349–906)	0.905
Time from second vaccine dose (days)	34.94 ± 8	35.06 ± 7.96	33.25 ± 8.94	0.538
ESA dose (unit per week)	6000 (3000–13 000)	6000 (3000–12 250)	10 125 (2625–17 500)	0.566
Iron dose (mg/week)	50 (0–100)	50 (0–100)	150 (62.5–300)	0.003

[a]Response—above 50 AU/mL.

[b]Including: urinary tract obstruction (3), CACUT (3), cardio-renal syndrome (3), myeloma kidney (1), cholesterol emboli (1), obesity-related FSGS (2) and unknown (8). ADPKD, autosomal dominant polycystic kidney disease; nPCR, normalized protein catabolic rate; ESA, erythropoietin stimulating agents; CACUT, congenital anomaly of kidney and urinary tract; FSGS, focal segmental glomerulosclerosis.

Data are presented as *n* (%), mean ± SD or median (IQR).

were seropositive for SARS-CoV-2 anti-S IgG at 2–6 weeks following the second dose of BNT162b2 vaccination. Recently, similar high seropositivity rates were also reported by Grupper *et al.* [8] among 56 hemodialysis patients as well as in a control group of 95 health workers.

Factors associated with higher log-transformed S1-binding antibodies titers in hemodialysis patients included younger age, BMI <30 kg/m^2, serum albumin above 3.5 g/dL and reduced intravenous iron dose. In line with our findings, Grupper *et al.* [8] also demonstrated a significant inverse correlation between older age and antibodies levels in the hemodialysis group as well as in the control group. Nutritional status is a known risk factor for dampened antibody response to immunization in dialysis patients [5, 9]. Hypoalbuminemia as a marker of malnutrition and inflammatory state has been also shown to correlate with diminished seroconversion in response to hepatitis B (HBV) vaccine [10, 11]. However, higher BMI, which is often associated with improved nutritional state and outcome in dialysis patients, was previously reported to correlate with inferior response to HBV vaccine [10, 12]. Both iron deficiency and iron overload are associated with impaired immune reactivity. Intravenous iron supplementation was found to be associated with reduced antibody response in our study, as well as in a previous study which found that intravenous iron blunted the humoral response to HBV vaccination [13].

Our study has several limitations. First, correlation between antibody response to vaccine and protection against SARS-CoV-2 infection has not yet been proven. Nevertheless, evidence is accumulating to support antibody response as a potential correlate of disease protection. Furthermore, we did not include neutralization antibodies and cellular immunity assays in our study. However, a strong correlation has been reported between anti-S antibody titers and neutralization antibody levels [7, 14, 15].

In conclusion, in our cohort, high seropositivity rates above 90% were demonstrated among 122 hemodialysis and 23 PD patients following BNT162b2 vaccination, with few serious adverse events. Younger age, BMI <30 kg/m^2, normal albumin level and reduced intravenous iron dose were associated with elevated anti-S antibody titers in hemodialysis patients. These findings strongly support the efficacy of the BNT162b2 vaccination among dialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

CONFLICT OF INTEREST STATEMENT

B.R.-Z. reports a consulting fee from Fresenius Medicare and a payment for a lecture from AstraZeneca plc. B.Z. reports a consulting fee from Fresenius Medicare. All remaining authors have nothing to disclose.

REFERENCES

1. ERA-EDTA Council, ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant* 2021; 36: 87–94
2. Francis A, Baigent C, Ikizler TA *et al.* The urgent need to vaccinate dialysis patients against SARS-CoV-2: A call to action. *Kidney Int* 2021; doi: 10.1016/j.kint.2021.02.003
3. Dagan N, Barda N, Kepten E *et al.* BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; doi: 10.1056/NEJMoa2101765
4. Polack FP, Thomas SJ, Kitchin N *et al.* Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383: 2603–2615
5. Krueger KM, Ison MG, Ghossein C. Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation. *Am J Kidney Dis* 2020; 75: 417–425
6. Abbott Core Laboratory. SARS-CoV-2 IgG II Quant (https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2)
7. Ugur S, Alexander M, Isabel V *et al.* BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. medRxiv 2020; doi: 10.1101/2020.12.09.20245175, preprint: not peer reviewed
8. Grupper A, Sharon N, Finn T *et al.* Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. *Clin J Am Soc Nephrol* 2021; doi: 10.2215/CJN.03500321
9. Janus N, Vacher LV, Karie S *et al.* Vaccination and chronic kidney disease. *Nephrol Dial Transplant* 2008; 23: 800–807
10. Udomkarnjananun S, Takkavatakarn K, Praditpornsilpa K *et al.* Hepatitis B virus vaccine immune response and mortality in dialysis patients: a meta-analysis. *J Nephrol* 2020; 33: 343–354
11. Ghamar-Chehreh ME, Agah S, Khedmat H *et al.* Serum albumin level as an indicator of response to Hepatitis B vaccination in dialysis patients: A systematic review and meta-analysis. *Caspian J Intern Med* 2017; 8: 250–257
12. Chazot C, Gassia JP, Di Benedetto A *et al.* Is there any survival advantage of obesity in Southern European haemodialysis patients? *Nephrol Dial Transplant* 2009; 24: 2871–2876
13. Liu JH, Liu YL, Lin HH *et al.* Intravenous iron attenuates postvaccination anti-HBsAg titres after quadruple hepatitis B vaccination in dialysis patients with erythropoietin therapy. *Int J Clin Pract* 2009; 63: 387–393
14. Jin P, Li J, Pan H *et al.* Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. *Signal Transduct Target Ther* 2021; 6: 48
15. Harvey RA, Rassen JA, Kabelac CA *et al.* Association of SARS-CoV-2 seropositive antibody test with risk of future infection. *JAMA Intern Med* 2021; doi: 10.1001/jamainternmed.2021.0366

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Younger children treated with rituximab for nephrotic syndrome are at higher risk of adverse events

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Rituximab is efficient to prevent relapse in pediatric steroid-dependent nephrotic syndrome (SDNS). Although rituximab tolerance is usually reported as good in clinical trials [1–7], the rate of severe adverse events (SAEs) differs considerably between studies, ranging from 3% to 33%, suggesting disparities in SAE reporting. One study has shown that the median age of patients presenting with agranulocytosis after rituximab treatment for nephrotic syndrome (NS) was younger than those who did not [8]. In this single-center retrospective study, we aimed to determine risk factors associated with occurrence of adverse events following rituximab in children with SDNS.

Detailed methods are provided in the Supplementary file. Briefly, we retrospectively reviewed the charts of all patients aged <18 years who had received rituximab for SDNS between November 2007 and September 2019 in our institution. Patients were seen in the Nephrology clinic at least once a month after their treatment. Our main objective was to assess rituximab safety in our cohort. Information on SAEs [Grade 3, severe but not immediately life-threatening; Grade 4, life-threatening; and Grade 5, death, according to the Common Terminology Criteria for Adverse Events (CTCAE)] [9] was collected in patients' charts. We performed a survival analysis to assess risk factors associated with SAEs and relapses.