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Waning of SARS-CoV-2 Vaccine-Induced Immune Response over 6 Months in Peritoneal Dialysis Patients and the Role of a Booster Dose in Maintaining Seropositivity

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Keywords
Severe acute respiratory syndrome coronavirus 2 · Vaccine · Immunity · Peritoneal dialysis · Antibody

Abstract
Introduction: Although lower than general population, newly developed SARS-CoV-2 vaccines generate immune responses in end-stage kidney disease patients. However, the persistence of immune responses in the long term is not known yet. This study aimed to evaluate humoral immune responses in peritoneal dialysis (PD) patients over 6 months and to analyze the effects of the booster dose. ***Methods:*** Humoral immune responses of PD patients were measured after initial SARS-CoV-2 vaccinations and after 6 months following initial vaccinations. Immune responses were compared between patients who received and did not receive booster doses. PD patients were compared with 41 hemodialysis (HD) patients and 61 healthy controls. Humoral immune responses were measured by a commercial test that detects antibodies toward the receptor-binding domain of the spike protein of SARS-CoV-2. ***Results:*** Twenty PD patients were evaluated over 6 months. The initial seropositivity rate was 90.9% with inactivated vaccine and 100% with mRNA vaccine. Seropositivity decreased to 44.4% after 6 months, and a booster dose helped in maintaining the 100% of seropositivity ($p = 0.005$). Magnitude of humoral response at the 6th month was also higher in patients who received the third dose (1,132.8 ± 769.6 AU/mL vs. 400.0 ± 294.6 AU/mL; $p = 0.015$). Among patients who did not receive the third dose, those who got mRNA vaccine could maintain higher seropositivity than others who got inactivated vaccine (75% vs. 40% for PD, 81.8% vs. 50% for HD). Seropositivity and antibody levels were similar for PD and HD patients after 6 months ($p = 0.24$ and 0.56) but lower than healthy controls ($p = 0.0013$). ***Conclusion:*** SARS-CoV-2 vaccine-induced antibody levels and seropositivity of PD patients significantly fall after 6 months. A booster dose after around 3 months following initial immunization might help in maintaining seropositivity.

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Introduction

End-stage kidney disease (ESKD) is a bad prognostic factor for the disease course in COVID-19 [1]. Thus, prevention of transmission has a high degree of importance for these patients. Transmission control measures such as isolation, frequent hand hygiene, keeping social distance, and use of masks have been in place since the declaration of the pandemic [2]. However, none would be as effective as vaccines. Unfortunately, vaccine responses are generally diminished in ESKD patients [3]. Newly introduced SARS-CoV-2 vaccines were previously reported to generate antibodies, albeit lower than general population [4]. While achieving seroconversion is a marker of vaccine immonugenicity, seropositivity should also be maintained in the long term. There are different strategies for this maintenance in ESKD patients, like doubling the vaccine dose, using adjuvants, or application of additional doses [5]. Although peritoneal dialysis (PD) and hemodialysis (HD) patients might have different immune profiles, there is not a clear difference between them for vaccine responses [6]. In this study, we aimed to analyze humoral immune response to SARS-CoV-2 vaccines and the effect of booster dose in PD patients through a 6-month time frame and compare it with HD patients and healthy controls.

Materials and Methods

Patients and Setting

PD patients who were followed up at two tertiary healthcare centers (Cerrahpasa Medical Faculty and Dr. Lutfi Kirdar City Hospital) were investigated throughout 6 months after their initial vaccinations for SARS-CoV-2. The modality was either continuous ambulatory PD (1.6–2 L of exchanges four times a day) or automated PD (8–10 h with a volume of 1.6–2 L for 5–7 exchanges).

Exclusion Criteria

Patients who had documented COVID-19, who had malignancies, and those who received immune-suppressive treatment in the previous 12 months were excluded from the study. Additionally, patients who have missed at least one of their regular monthly visits and those who have reported any symptoms that may be related to upper or lower respiratory tract infections were also excluded.

Clinical Data

Demographic (age, gender) data and chronic kidney disease-related clinical data (etiology, time on dialysis, dialysis adequacy, albumin, complete blood count, ferritin, C-reactive protein, parathormone, mean arterial pressure) of the patients were collected from patient files and electronic health records. Dialysis adequacy for PD patients was evaluated by weekly Kt/V (urea), while single pool Kt/V (urea) was used for HD patients. Symptom inquiries and PCR control for SARS-CoV-2 were done at each monthly visit.

Vaccines

Patients initially received two doses of either inactivated vaccine (3 μg of CoronaVac® developed by Sinovac Life Sciences (Beijing, China) or mRNA vaccine (30 μg of BNT162b2 developed by Pfizer-BioNTech) 28 days apart. Vaccine selection was based on patient preferences. Patients had the opportunity to get a booster dose with either of the vaccines 3 months following the initial vaccinations.

Control Groups

PD patients were compared with HD patients of similar age who had similar vaccination and follow-up schemes. Three times weekly, 4-h HD sessions were resumed for these patients. Healthy controls initially received two doses of CoronaVac® in a similar protocol as study subjects, but they did not receive any booster doses.

Antibody Measurement

Antibody responses in the sera of vaccinated patients or controls were analyzed after the initial vaccinations and at the end of 6th-month postvaccination. Initial antibody responses were controlled on 21st–28th day following initial vaccinations, and 6th-month controls were done between 170th and 190th days. The analysis was carried out by Abbott SARS-CoV-2 IgG II Quant (Chicago, IL, USA), which is a chemiluminescent microparticle immunoassay that measures IgG antibodies toward the spike receptor-binding domain of SARS-CoV-2. Quantitative IgG level determination was performed on Abbott ARCHITECT i1000 (Chicago, IL, USA) equipment. All sera were diluted by 1:2 (75 μL serum + 75 μL diluent) and studied in full-automated mode, and 50 AU/mL was accepted as the cutoff value for positivity according to manufacturer's instructions.

Statistical Analysis

Continuous parametric data were presented as average ± standard deviation, and *t* test was used for comparisons. Categorical data were presented as percentages and compared by Fisher's exact or χ^2 test. Correlations of continuous parameters were computed by Pearson's test. SPSS Statistics software version 22.0 (Chicago, IL, USA) was used to carry out statistical analysis, and $p < 0.05$ (two sided) was accepted as the statistical significance.

Results

A total of 20 PD patients met the inclusion criteria. They were 67.8 ± 12.9 years old. They were on PD for 51.4 ± 39.8 months. Etiologies of chronic kidney disease were diabetes (6 patients), hypertension (6 patients), glomerulonephritis (3 patients), cystic kidney disease (1 patient), congenital urinary tract anomaly (1 patient), Fabry disease (1 patient), and unknown etiology (2 patients). Eleven patients received inactivated vaccine, and 9 patients

got mRNA vaccine with 90.9% and 100% of initial seropositivity rates, respectively. There was no statistically significant difference between two groups. Eleven patients received booster doses on 99.1 ± 4.2nd day. All patients (100%) who received a booster dose could maintain seropositivity at the end of 6th month. However, seropositivity rate decreased to 44.4% in patients who did not receive a booster dose. Administration of the booster dose was related to preservation of seropositivity (p = 0.005). Magnitude of humoral response was also higher in patients who received the third dose (1,132.8 ± 769.6 AU/mL vs. 400.0 ± 294.6 AU/mL; p = 0.015). Among patients who did not receive the booster dose, mRNA vaccine was more effective in maintaining seropositivity than inactivated vaccine at the end of sixth month (75% vs. 40%). Antibody levels were also higher in patients who got mRNA vaccine (454.5 ± 424.7 AU/mL vs. 44.0 ± 27.1 AU/mL; p = 0.06).

Among 41 HD patients who were analyzed for comparison with PD patients, 19 got inactivated vaccine, and 22 got mRNA vaccine with 73.6% and 95.4% of initial seropositivity rates, respectively. When a booster was not applied, 6th-month seropositivity decreased to 50% and 81.8% for inactivated and mRNA vaccines, respectively. The difference between inactivated and mRNA vaccine was also evident for antibody levels (71.1 ± 92.4 AU/mL vs. 445.0 ± 422.9 AU/mL; p = 0.007). On the other hand, HD patients who received the third dose could maintain 88.8% of seropositivity. Antibody titers at the 6th month were also higher for patients with a booster dose (1,120.8 ± 983.3 vs. 313.3 ± 435.3; $p < 0.001$). The rate of seropositivity as well as antibody titers after 6 months for patients with and without a booster dose were similar for PD and HD groups (p = 0.24, 0.97 and 0.56, respectively). Clinical comparison of PD and HD patients with and without booster doses can be found in online supplementary Tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000524658).

Antibody titers at the end of the 6th month for healthy controls (n = 61, 31 males, 30 females, age: 56.5 ± 55) who were initially immunized by CoronaVac® were 188 ± 171 AU/mL. Healthy subjects could maintain 88% of seropositivity without a booster dose, which was significantly higher than HD and PD patients (p = 0.002 and p = 0.0013, respectively). As mentioned above, when a booster dose was not applied, antibody levels generated by inactivated vaccine decreased to 44.0 ± 27.1 AU/mL for PD and 71.1 ± 92.4 AU/mL for HD patients.

Antibody responses following initial vaccinations were inversely proportional to patients' age (r = −0.465, p = 0.000). While antibody levels at the end of the 6th month was proportional with the magnitude of initial humoral response (r = 0.310, p = 0.019), they did not show a statistically significant relation with age.

Discussion/Conclusion

Immune response in ESKD patients is generally diminished, and this may lead to poor vaccine immunogenicity [7]. While newly developed SARS-CoV-2 vaccines were reported to induce seroconversion in ESKD patients, the maintenance rate of seropositivity is still not very well known. With this study, we had the opportunity to analyze changes in humoral immunity of PD patients over a time frame of 6 months and compare it with both HD patients and healthy controls.

Unity of efforts to immunize vulnerable population should be sustained across the globe, and different vaccines might be available in different regions [8]. Our results show that initial seroconversion rates of PD patients with inactivated or mRNA vaccines were similar. On the other hand, mRNA vaccine tended to be more effective than inactivated vaccine in the maintenance of humoral immune response, but the difference near-missed statistical significance in PD patients, most probably due to the small sample size. The seropositivity rate and antibody levels significantly fell after 6 months in patients who did not receive a booster dose. Thus, planning additional vaccine doses in ESKD patients might be more important than preferring a vaccine type.

Initial SARS-CoV-2 vaccination regimes generally include two doses. There have been reports for waning of immune responses after initial immunization in ESKD patients [9]. This necessitates proper planning of additional doses. Exact timing of the third vaccine dose is another uncertain topic. In a recent report, antibody levels remained high in both PD (85%) and HD (79%) patients in 3 months after BNT162Bb2 vaccine [10]. In another study again with BNT162Bb2 vaccine, seropositivity was around 80% after 6 months [11]. There has been an example of 3rd dose application 4 weeks after the 2nd dose [12], but the same report also highlighted greater increase in antibody titers when interval between 2nd and 3rd doses were longer. A third dose was applied around the 100th day of initial vaccinations in our study and maintained high seropositivity at the 6th month.

In a previous study, the initial seroconversion rate of PD patients with inactivated vaccine was not different from healthy controls [13]. However, in this comparison over 6 months of time without a booster dose, we found that maintenance of seropositivity was significantly lower in PD patients than healthy controls (44% vs. 88%).

PD and HD patients might have different immune profiles. Some previous SARS-CoV-2 vaccine studies showed higher initial immunogenicity in PD patients [10, 13]. However, with this study, we found similar antibody levels and seropositivity rates for PD and HD patients 6 months after initial vaccinations. Older age and diabetes have been reported to negatively affect humoral immune response to SARS-CoV-2 vaccines [14]. Initial antibody responses of our patients were negatively correlated with age; however, such negative correlation was not significant for 6th-month responses. It is still not very well known if there is a relation between antibody levels and protection capacity of the vaccines. Antibody titers higher than the declared threshold (>50 AU/mL for the test kit used here) are generally accepted to provide protection. Nevertheless, initial antibody levels were correlated with 6th-month antibody titers in this study.

This study has some limitations. First, sample size of PD patients is relatively small. We have not studied B-cell subpopulations but have taken antibody measurement as the marker of humoral immune response. Responses of T cells were not studied which might have provided more information about the immunogenicity of the vaccines. We have not checked antibodies to the nucleocapsid protein, which could have been an early marker of some COVID-19 cases. However, we did a rigorous follow-up of our patients with monthly PCR tests and symptom inquiries. We excluded all who had confirmed COVID-19 or any symptoms of infection. Thus, our study sample is composed of asymptomatic individuals who never had any signs of COVID-19. Anti-nucleocapsid antibody test might not be ideal for such samples as it may miss half of the asymptomatic carriers [15]. Lastly, we could not recruit healthy controls who got mRNA vaccine due to the later introduction of mRNA vaccine for healthy population in our country.

In conclusion, vaccine-induced antibody levels and seropositivity of PD patients significantly fall after 6 months. A booster dose after around 3 months following initial immunization might help in maintaining seropositivity. Humoral immunity waned similarly in PD and HD patients. mRNA vaccines might be better than inactivated vaccine in long-term assurance of seropositivity.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All study subjects gave written informed consent to participate in the study. The study was approved both by the institutional review board of the medical faculty (approval nr: 09/04/2021 – A06) and by the COVID-19 research supervision committee of Ministry of Health (approval nr: 2021-03-08T10_50_25).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Ahmet Murt: literature search, data collection, formal analysis, interpretation of results, and writing. Harika Oyku Dinc: performing polymerase chain reaction and antibody tests and interpretation of results. Mehmet Riza Altiparmak: literature search, formal analysis, interpretation of results, and writing. Serkan Feyyaz Yalin: data collection, interpretation of results, and writing. Serap Yadigar and Ergun Parmaksiz: data collection and interpretation of results. Bekir Kocazeybek: recruitment and follow-up of the control group and critical review. Meltem Pekpak: literature search and interpretation of results. Muveddet Rezzan Ataman: conception, study design, and supervision.

Data Availability Statement

The dataset of this study is available from the corresponding author upon a reasonable request.

References

1 Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. Kidney Int. 2020;98(6):1530–9.

2 Caplin B, Ashby D, McCafferty K, Hull R, Asgari E, Ford ML, et al. Risk of COVID-19 disease, dialysis unit attributes, and infection control strategy among London in-center hemodialysis patients. Clin J Am Soc Nephrol. 2021;16(8):1237–46.

3 DaRoza G, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization, earlier is better. Am J Kidney Dis. 2003;42(6):1184–92.

4 Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol. 2021;16(7):1037–42.
5 Tong NKC, Beran J, Kee SA, Miguel JL, Sanchez C, Bayas JM, et al. Immunogenicity and safety of and adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. Kidney Int. 2005;68(5):2298–303.
6 Liu YL, Kao MT, Huang CC. A comparison of responsiveness to hepatitis B vaccination in patients on hemodialysis and peritoneal dialysis. Vaccine. 2005;23(30):3957–60.
7 Dinits Pensy M, Forrest GN, Cross AS, Hise MK. The use of vaccines in adult patients with renal disease. Am J Kidney Dis. 2005;46(6):997–1011.
8 World Health Organization. COVID-19 vaccines. (n.d). Available from: https://who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines (accessed February 1, 2022).
9 Berar-Yanay N, Freiman S, Shapira M, Saffoury A, Elemy A, Hamze M, et al. Waning humoral response 3 to 6 months after vaccination with the SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. J Clin Med. 2021;11(1):64.
10 Speer C, Schaier M, Nusshag C, Töllner M, Buylaert M, Kälble F, et al. Longitudinal humoral responses after COVID-19 vaccination in peritoneal and hemodialysis patients over twelve weeks. Vaccines. 2021;9:1130.
11 Nacasch N, Cohen-Hagai K, Benchetrit S, Zitman-Gal T, Einbinder Y, Erez D, et al. Comparison of long-term antibody response to mRNA SARS-CoV-2 vaccine among peritoneal dialysis and hemodialysis patients. Nephrol Dial Transplant. 2022 Feb 25;37(3):602–4.
12 Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, et al. SARS-CoV-2 antibody response after a third dose of the BNT162b2 vaccine in patients receiving maintenance hemodialysis or peritoneal dialysis. Am J Kid Dis. 2022 Feb;79(2):185–92.e1.
13 Murt A, Altiparmak MR, Ozbey D, Yalin SF, Sert-Yadigar S, Karaali R, et al. Antibody responses to inactivated SARS-CoV-2 vaccine in peritoneal dialysis patients. Semin Dial. 2022;35(3):264–8.
14 Chen JJ, Lee TH, Tian YC, Lee CC, Fan PC, Chang CH. Immunogenicity rates after SARS-CoV-2 vaccination in people with end-stage kidney disease: a systematic review and meta-analysis. JAMA Netw Open. 2021;4(10):e2131749.
15 Tutukina M, Kaznadzey A, Kireeva M, Mazo I. IgG antibodies develop to spike but not to the nucleocapsid viral protein in many asymptomatic and light COVID-19 cases. Viruses. 2021;13(10):1945.