RESEARCH LETTER

Humoral response to COVID-19 vaccination in patients treated with peritoneal dialysis: the COViNEPH Project

Leszek Tylicki[1*], Magdalena Piotrowska[2], Bogdan Biedunkiewicz[1*], Maciej Zieliński[2], Małgorzata Dąbrowska[3], Piotr Tylicki[1], Karolina Polewska[1], Piotr Trzonkowski[2], Monika Lichodziejewska-Niemierko[1,4], Alicja Dębska-Ślizień[1]

1 Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdańsk, Poland
2 Department of Medical Immunology, Medical University of Gdansk, Gdańsk, Poland
3 Central Clinical Laboratory, University Clinical Center in Gdansk, Gdańsk, Poland
4 Department of Palliative Medicine, Medical University of Gdansk, Gdańsk, Poland

Correspondence to:
Prof. Leszek Tylicki, MD, PhD, Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland, phone: +48 58 349 25 05, email: leszek.tylicki@gumed.edu.pl
Received: May 31, 2021.
Revision accepted: July 17, 2021.
Published online: October 11, 2021.
Pol Arch Intern Med. 2021; 131 (10): 16091
doi:10.20452/pamw.16091

* LT and BB contributed equally to this work.

Introduction The need for COVID-19 vaccination is especially urgent in patients with impaired host defense and extensive comorbidity, such as those with end-stage kidney disease (ESKD) treated with maintenance dialysis. Previous studies have reported horrifyingly disproportionate age-adjusted rates of COVID-19 cases in dialysis patients, with fatality rates as high as 43.81% in individuals over 74 years old.[1] In many countries, the dialysis population is prioritized in vaccination programs. Serious obstacles that could inhibit the expected protective effects of the vaccines are the aberrations in the immune system in ESKD, consisting of immunodepression and immunoactivation.[2] Impaired antibody response after different vaccines (eg, those protecting against tetanus, influenza, hepatitis B, diphtheria, and pneumococcal disease) in hemodialysis patients is well known.[3] Some recent reports demonstrated decreased antibody response to COVID-19 vaccines in the hemodialysis population as compared with the general population, which leads to questions about the optimal vaccination schedule in this group of patients.[4] No data are yet available on the efficacy of COVID-19 vaccines in patients treated with peritoneal dialysis (PD). Given that PD seems to preserve the immune function better than hemodialysis, a higher vaccination efficacy can be expected among patients treated with this method.[5] This hypothesis is based on the less pronounced inflammation, preservation of residual renal function, or better removal of middle-molecular-weight uremic toxins during PD.[6] Accordingly, the purpose of this study was to compare the responsiveness to COVID-19 vaccination between patients on chronic PD and those on hemodialysis.

Patients and methods **Patient population** Adult patients treated with PD were considered eligible if they were on dialysis for at least 3 months and agreed to be vaccinated with the mRNA vaccine BNT162b2 (BionTech / Pfizer Comirnaty) as part of the national immunization program. The control group comprised hemodialysis patients who were to be vaccinated using the same regimen. Individuals with known previous SARS-CoV-2 infection were excluded from the study.

Study design We conducted a prospective, observational, exploratory study to elucidate the immune response to vaccination with BNT162b2 in PD patients as compared with those on hemodialysis. The main goal of the study was to analyze the seroconversion rate and titer magnitude of the neutralizing immunoglobulin G (IgG) antibodies directed against SARS-CoV-2 spike (S) protein antigen after the first and second doses of BNT162b2. The serostatus of nucleocapsid (N)-specific antibodies was measured in all patients to determine if they had evidence of prior asymptomatic infection with SARS-CoV-2. Ethics approval for the study was obtained at the Medical University of Gdansk (NKBBN/167/2021).

Measurement of SARS-CoV-2 antibody levels Venous blood samples were collected at 3 time-points: before the first dose of the vaccine, 21 days after the first dose, and within 14 to 21 days of the second dose. The level of anti-N IgG

TABLE 1 Characteristics of patients treated with peritoneal dialysis and hemodialysis

Variable	PD patients (n = 21)	HD patients (n = 35)	*P* value
Male sex	14 (66.7)	24 (69)	0.88
Age, y	60.00 (40–69)	69.00 (53–75)	0.04
Body mass index, kg/m^2	25.93 (24.62–28.73)	24.97 (21.23–28.38)	0.42
Dialysis vintage, mo	26 (10–47)	49 (17–83)	0.08
History of kidney transplantation	6 (28.57)	6 (17.4)	0.31
Charlson Comorbidity Index	5 (3–7)	7 (4–9)	0.12
Diabetes	4 (19.05)	15 (42.8)	0.07
Residual diuresis >500 ml/day	14 (66.7)	13 (37)	0.03
Dialysis adequacy, Kt/V[a]	2.29 (1.84–2.7)	1.62 (1.33–1.75)	NA
Hemoglobin, g/dl	11.7 (103–13.30)	10.7 (10.0–11.6)	0.03
White blood cell count, × 10^9/l	7.75 (6.23–9.1)	6.67 (5.8–7.74)	0.14
Lymphocyte count, × 10^9/l	1.7 (1.49–1.93)	1.43 (1.18–1.73)	0.08
C-reactive protein, mg/l	2.38 (0.77–4.75)	4.0 (1.7–8.54)	0.06
Albumin, g/dl	3.7 (3.3–3.7)	3.5 (3.2–3.6)	0.06
Parathyroid hormone intact, pg/ml	576 (320–730)	685.66 (227–704)	0.29

Data are presented as number (percentage) or median (interquartile range).

SI conversion factors: to convert albumin to g/l, multiply by 10.0; hemoglobin to mmol/l, by 0.626; parathyroid hormone to ng/l, by 1.0

a Total weekly Kt/V for PD patients and single-pool Kt/V for HD session

Abbreviations: HD, hemodialysis; NA, not applicable; PD, peritoneal dialysis

antibodies was assessed using the Abbott Architect SARS-CoV-2 IgG assay (Abbott Laboratories, Chicago, Illinois, United States). The cutoff for a positive result was determined at a specimen / calibrator index value of 1.4. The DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG serology test (DiaSorin SpA, Saluggia, Italy) was used to detect the neutralizing anti-S (S1 and S2 subunits) antibody. The test range was up to 800 AU/ml. Samples equal to or above 15 AU/ml were interpreted as positive. To allow efficient comparisons between laboratories using BAU/ml, conversion factors standardizing the results of SARS-CoV-2 antibody assays were applied (0.142 and 2.6 for the Abbott and DiaSorin tests, respectively).

Statistical analysis Data were presented as number (percentage) for categorical variables and median (interquartile range [IQR]) for continuous variables. Multivariable stepwise bidirectional linear regression analysis of baseline characteristics (in 2 models) was performed to identify factors that had a significant impact on anti-S antibody titer after the second dose of BNT162b2. Detailed description of statistical analysis is presented in Supplementary material, *Statistical analysis*. A 2-tailed *P* value of less than 0.05 was considered significant. Data were evaluated using STATISTICA software package (version 12.0, Stat Soft Inc, Dell Software, Tulsa, Oklahoma, United States).

Results

Patients Among all 61 vaccine recipients, 5 individuals were excluded due to evidence of asymptomatic SARS-CoV-2 infection. Finally, 21 PD and 35 hemodialysis patients were analyzed. All PD patients (17 on continuous ambulatory PD and 4 on automated PD) were dialyzed with biocompatible fluids (Balance or Physioneal); icodextrin-based fluids (Extraneal) were used by 5 patients (23.8%). All hemodialysis patients were dialyzed using high-flux dialysers (High-flux FX or Revaclear). Detailed characteristics of both groups are presented in TABLE 1.

SARS-CoV-2 spike antigen antibodies The seroconversion rate (anti-S IgG titer ≥39 BAU/ml) after the first dose of BNT162b2 was 86% (PD patients) compared with 57% (hemodialysis patients) (P = 0.004). The proportions of seroconversion after the second dose were 100% and 97%, respectively. The median (IQR) levels of anti-S IgG antibodies in PD patients were 93.0 (67.9–160.9) BAU/ml after the first dose and 1623.7 (1202.5–2096.9) BAU/ml after the second dose (analysis of variance; P <0.001). In hemodialysis patients, the median (IQR) levels of anti-S IgG antibodies were 48.1 (15.6–114.9) BAU/ml and 925.6 (460.2–1908.4) BAU/ml after the first and second doses, respectively (analysis of variance; P <0.001). When comparing the anti-S IgG titers between patients treated with PD and hemodialysis, significant differences were found both after the first (P = 0.034) and second doses of the vaccine (P = 0.008) (Supplementary material, *Figure S1A*). In multivariable stepwise linear regression models, dialysis modality was the only independent predictor of anti-S IgG titer (P <0.05)

(Supplementary material, *Table S1*). We found an interesting trend (P = 0.038) in the antibody response, which indicated that 2 subpopulations could be distinguished in the hemodialysis group (very poor vs high response; cutoff, 1000 BAU/ml) (Supplementary material, *Figure S1B*). In the strata analysis, we found no factors determining this difference.

Discussion The study showed that PD patients had a better humoral response after COVID-19 vaccination compared with individuals treated with hemodialysis. The levels of anti-S antibodies were higher after both the first and second vaccination. Moreover, a higher percentage of PD patients seroconverted, after the first vaccination. To the best of our knowledge, this is the first report in this regard. Previous experiences with vaccinations protecting against other viruses show contradictory results in terms of the response to vaccination in patients treated with different dialysis modalities. For instance, some studies show a higher seroconversion rate after hepatitis B vaccine in PD patients compared with hemodialysis patients,[7] some show a worse response,[8] and others do not report any differences.[9] In the case of the H1N1 influenza vaccination, a better response was reported in PD patients.[10]

To date, COVID-19 has affected millions of patients worldwide and became a serious health threat, leading to almost 4 million deaths. Vaccination seems to be the most effective long-term strategy for prevention of this disease. Messenger RNA vaccines, such as BNT162b2, work by introducing an mRNA sequence which is coded for a SARS-CoV-2–specific S antigen. The cells use this genetic information to produce the S antigen. It is then displayed on the cell surface, where it is recognized by the immune system.[11]

There are several explanations for the potentially better immunogenicity of BTN162b2 in PD patients. End-stage kidney disease is associated with both immune activation (marked by systemic inflammation) and immune deficiency.[2] A defect in the co-stimulatory function of antigen-presenting cells is pathogenetically linked to the uremic state. In addition, during each hemodialysis session, blood contact with a foreign complement-activating dialytic membrane promotes a variety of complex and interrelated events, leading to an acute inflammatory response. Hemodialysis patients have a higher inflammatory monocyte count as well as a higher frequency of CD8 T cells and a reduced CD4/CD8 ratio.[12] In addition, the inflammatory changes involve the release of cytokines—for example, interleukin (IL)-12—that shift the globally-reduced activation of T-helper cells towards the T-helper 1 cell function, which may cause further deterioration of the antibody response to vaccination antigens.[5] In PD, where the natural membrane is utilized, the use of biocompatible solutions has been associated with better peritoneal host immune defense. It may well be that less pronounced inflammation, together with the better-preserved capacity to upregulate the counter-regulatory IL-10, which at least in part determines immune competence, is responsible for the higher antibody response to the COVID-19 vaccine in PD patients.[13,14] Importantly, the hemodialysis patients in our study had significantly fewer lymphocytes.

It cannot be ruled out that better removal of middle-molecular-weight uremic toxins during PD, residual diuresis persisting in a large part of PD patients, as well as comorbidities and the age of patients are also important in this context.[6] Of note, our group of PD patients had higher residual diuresis and shorter dialysis vintage. On the other hand, hemodialysis patients were older and more often had diabetes. Age is a well-known intrinsic factor that influences the humoral response after various vaccines, so young people have an increased capacity to mount humoral immune responses compared with older individuals, both in the general and dialysis populations. Observations carried out in patients vaccinated for hepatitis B and influenza indicate that people with diabetes show an impaired humoral response as well. Furthermore, residual renal function as expressed by residual diuresis in patients dependent on dialysis may decrease the degree of inflammation and, consequently, improve immune function.[15] Although we found no effects of these variables on S-antigen antibody titer in the regression analyses, the combined effect of these factors should be taken into account, as it is likely to affect the immune response after BNT162b2 in our PD patients. We were also unable to find the factors determining the subpopulations of hemodialysis patients with a very poor and high responses to vaccination. Studies in a larger group of patients will help explain all these relationships.

Limitations of this exploratory study include a small sample size and mismatched groups. Secondly, we only tested humoral immune response. The cellular part of the adaptive immune system plays an important role in protection against COVID-19, which is not reflected in our investigation. Thirdly, due to the observational design of the study, any differences in the findings among the groups cannot be assumed to be causal.

In conclusion, we demonstrated that responsiveness to the mRNA BTN162b2TN vaccination in PD patients may be better than in individuals treated with hemodialysis. Whether this translates into better protection against COVID-19 requires further research.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS We would like to thank the hospital management for prioritizing the vaccination of dialysis patients from our center. In particular, we thank Adam Sudoł, MD and Anna Lignowska, MSN for their personal engagement. We sincerely thank all the patients who participated in the study. The study is part of the "COVID-19 in Nephrology" (COViNEPH)

multicenter project registered on ClinicalTrials.gov, identifier NCT04 905 862; https://clinicaltrials.gov/ct2/show/NCT04905862.

CONFLICT OF INTEREST None declared.

HOW TO CITE Tylicki L, Piotrowska M, Biedunkiewicz B, et al. Humoral response to COVID-19 vaccination in patients treated with peritoneal dialysis: the COViNEPH Project. Pol Arch Intern Med. 2021; 131: 16091. doi:10.20452/pamw.16091

REFERENCES

1 Puchalska-Reglińska E, Dębska-Ślizień A, Biedunkiewicz B, et al. Extremely high mortality rates among hemodialysis patients with COVID-19 before the era of SARS-CoV-2 vaccination: results from a large database from the North of Poland. Pol Arch Intern Med. 2021; 131: 643-648.

2 Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol. 2008; 3: 1526-1533.

3 Litjens NH, Huisman M, van den Dorpel M, et al. Impaired immune responses and antigen-specific memory $CD4^+$ T cells in hemodialysis patients. J Am Soc Nephrol. 2008; 19: 1483-1490.

4 Tylicki L, Biedunkiewicz B, Dąbrowska M, et al. Humoral response to SARS-CoV-2 vaccination promises to improve the catastrophic prognosis of hemodialysis patients as a result of COVID-19: the COViNEPH Project. Pol Arch Intern Med. 2021; 131: 797-801.

5 Girndt M, Sester M, Sester U, et al. Molecular aspects of T- and B-cell function in uremia. Kidney Int Suppl. 2001; 78: S206-S211.

6 Dhondt A, Vanholder R, Van Biesen W, et al. The removal of uremic toxins. Kidney Int Suppl. 2000; 76: S47-S59.

7 Mitwalli A. Responsiveness to hepatitis B vaccine in immunocompromised patients by doubling the dose scheduling. Nephron. 1996; 73: 417-420.

8 Khan AN, Bernardini J, Rault RM, et al. Low seroconversion with hepatitis B vaccination in peritoneal dialysis patients. Perit Dial Int. 1996; 16: 370-373.

9 Krediet RT. Similar clinical results of influenza vaccination in peritoneal dialysis and haemodialysis patients. Nephrol Dial Transplant. 2016; 31: 175-176.

10 Azak A, Huddam B, Kocak G, et al. Antibody response after single H1N1 influenza vaccine in chronic dialysis patients. Ther Apher Dial. 2013; 17: 55-59.

11 Wang C, Wang Z, Wang G, et al. COVID-19 in early 2021: current status and looking forward. Signal Transduct Target Ther. 2021; 6: 114.

12 Ducloux D, Legendre M, Bamoulid J, et al. ESRD-associated immune phenotype depends on dialysis modality and iron status: clinical implications. Immun Ageing. 2018; 15: 16.

13 Stenvinkel P, Ketteler M, Johnson RJ, et al. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia – the good, the bad, and the ugly. Kidney Int. 2005; 67: 1216-1233.

14 Bartosova M, Schmitt CP. Biocompatible peritoneal dialysis: the target is still way off. Front Physiol. 2018; 9: 1853.

15 Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. Clin Microbiol Rev. 2019; 32: e00084-18.