ORIGINAL ARTICLE

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

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KEY WORDS

COVID-19, hemodialysis, immunity, vaccine

ABSTRACT

INTRODUCTION There is an urgent need to check the efficacy of SARS-CoV-2 vaccination among hemodialysis patients who are known to have large abnormalities of acquired immunity and a catastrophic risk of death from COVID-19.

OBJECTIVES In this cross-sectional study, we aimed to assess the humoral response following vaccination with the BNT162b2 (BioNTech/Pfizer Comirnaty) vaccine.

PATIENTS AND METHODS We analyzed the titer magnitude of the IgG antibodies directed against SARS-CoV-2 spike antigen 14 to 21 days after the second dose of the BNT162b2 vaccine in a group of hemodialysis patients who have not been confirmed with SARS-CoV-2 infection yet, compared with HD patients with a history of COVID-19. A total of 126 hemodialysis patients were stratified based on evidence of a previous infection with SARS-CoV-2 confirmed by the detection of viral RNA or nucleocapsid-specific IgG antibodies.

RESULTS S-antigen immune response with a median (interquartile range) antibody titer of 366 (193–691) AU/ml was seen in 87 of 91 infection-naïve hemodialysis patients (95.6%), and in 68 (74.7%), a strong humoral response was observed with an anti-S antibodies titer greater than 200 AU/ml. Older patients were less likely to develop a response to S-antibodies ($P < 0.001$). The median (interquartile range) S-antigen antibody titer in 35 previously infected hemodialysis patients was over 12-fold higher than in infection--naïve hemodialysis patients: 4620 (1240–7820) AU/ml ($P < 0.001$). There were no significant differences in S-antibody titer between symptomatic and asymptomatic previously infected hemodialysis patients.

CONCLUSIONS Our study demonstrated that the majority of hemodialysis patients achieved a high immunization rate after vaccination with BNT162b2. Whether this translates into protecting this population from COVID-19 requires further research.

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Received: April 29, 2021.
Revision accepted: July 5, 2021.
Published online: August 5, 2021.
Pol Arch Intern Med. 2021;
131 (9): 797-801
doi:10.20452/pamw.16069

INTRODUCTION Patients on chronic hemodialysis have been identified as particularly susceptible to SARS-CoV-2 infection due to unavoidable exposure. This population is also characterized by high rates of comorbidities and varying degrees of immunosuppression, which puts them at risk of very severe forms of COVID-19 with fatality rates ranging from 16% to 32%.[1] In our recent study, we showed extremely high mortality rates in hemodialysis patients with COVID-19 with a fatality rate up to 43.81% in patients older than 74 years.[2] In such circumstances, vaccination is the only chance to improve the extremely poor prognosis in that patient population. However, as of now, there are very limited data on the response to vaccination in hemodialysis patients.[3,4] Furthermore, given the fact that hemodialysis patients have numerous and diverse disturbances of

WHAT'S NEW?

Chronically hemodialyzed patients have been identified as particularly susceptible to SARS-CoV-2 infection and to very severe forms of COVID-19 with fatality rates varying from 16% to 32%. Vaccination is the only chance to improve catastrophic prognosis in this patient population. Since hemodialysis patients have diverse disturbances of acquired immunity, it is uncertain whether vaccinating against SARS-CoV-2 will result in sufficient immune response, and as a consequence, protection against infection. This study is one of the first to show a very high rate of seroconversion following vaccination. Our results demonstrated that age was an important factor in the humoral response and young people showed an increased capacity to develop the humoral immune response compared with the older population. Thus, older patients may require more attention in a vaccine program, and possibly a different vaccination schedule.

acquired immunity, it is uncertain whether vaccinating against SARS-CoV-2 in this population will result in sufficient immune response and, consequently, protection against infection.[5] To shed more light on this issue, we performed a cross-sectional study on the magnitude of seroconversion of IgG antibodies against SARS-CoV-2 spike (S) protein in hemodialysis patients after vaccination with 2 doses of the mRNA vaccine from BioNTech / Pfizer.

PATIENTS AND METHODS

Patient population

The cross-sectional study was performed in all 179 hemodialysis patients in the Hemodialysis Unit of the Nonpublic Healthcare Center Diaverum in Gdynia, Poland. Patients were considered eligible if they were on chronic dialysis for at least 1 month and had received vaccination with the mRNA BNT162b2 vaccine (BioNTech / Pfizer Comirnaty) with a 3-week interval between the first and the second dose from January 25 to March 15, 2021. Patients with a known history of SARS-CoV-2 infection were also vaccinated according to the rules of the national immunization program. Dialysis patients' medical histories were extracted from their medical records. Serum samples were obtained at 14 to 21 days following the second BNT162b2 vaccine dose. By the time the study was completed, 24 (13.4%) patients had refused to vaccinate due to fear of side-effects, 22 (12.3%) have not completed the full course of vaccination for medical reasons. A total of 133 (74.3%) patients were vaccinated with 2 doses of BNT162b2. Among them 7 people refused to participate in the study. Finally, we enrolled 126 patients (79 men [62.7%]) at a median (interquartile range [IQR]) age of 69 (59–75) years, with a median (IQR) duration of dialysis treatment of 36 (14–67) months, and a median comorbidity index of 7 (4–8). A total of 113 (89.7%) patients were treated with high-flux hemodialysis and 13 (10.3%) with online hemodiafiltration. The most common cause of end-stage renal disease was diabetes. Twenty-three patients had a history of polymerase chain reaction–confirmed symptomatic COVID-19 at least 3 months prior to the vaccination.

Study protocol

The first aim of our study was to analyze the titer magnitude of the IgG antibodies directed against the SARS-CoV-2 S antigen 14 to 21 days after the second dose of BNT162b2 vaccine in a group of hemodialysis patients who had not been previously confirmed with SARS-CoV-2 infection, compared with the magnitude of the same humoral response in hemodialysis patients with a history of COVID-19. Moreover, we analyzed the magnitude of association of the S-antibody titer with age, gender, BMI, comorbidities (ie, diabetes, connective tissue disease, active neoplastic disease, and the Charlson comorbidity index), the method and duration of renal replacement therapy, and response to hepatitis B vaccination. To check the relationship between the response to the hepatitis B vaccination with the humoral response after the BNT162b2 vaccine, we defined the following cutoffs: hepatitis B vaccine nonresponders were defined as having anti-HBs antibody titer lower than 10 IU/ml after at least one completed hepatitis-B vaccination cycle; low-responders titer was 10 to 100 IU/ml; and high-responders titer was greater than 100 IU/ml. A total of 32 patients with natural anti-HBs immunity and those who had not completed the vaccination cycle were not included into this analysis. Ethics approval for the study was obtained at the Medical University of Gdansk (NKBBN/167/2021). The study is part of the COVID-19 in Nephrology (COViNEPH) project focusing on the nephrological aspects of COVID-19, in particular epidemiology, prevention, disease course, and treatment.

Laboratory analyses

The serostatus of nucleocapsid (N)-specific antibodies was used in all patients to determine if hemodialysis patients had evidence of a prior asymptomatic infection with SARS-CoV-2. The presence of IgG anti-N antibodies was assessed with the commercially available Abbott Architect SARS-CoV-2 IgG 2 step chemiluminescent immunoassay according to the manufacturer's instructions. The assay presents a sensitivity / positive percentage agreement of 100.0% and specificity / negative percentage agreement of 99.63%. Samples were interpreted as positive (seroconversion) or negative with a cutoff specimen / calibrator index value of 1.4. Quantitative measurement of specific IgG antibodies against the trimeric S-protein was performed with a new-generation commercial chemiluminescent immunoassay (the LIAISON SARS-CoV-2 Trimetric-S IgG test, DiaSorin, Saluggia, Italy) according to the manufacturer's instructions. The assay presents a sensitivity of 98.7% and specificity of 99.5%, and agreement with neutralization in microneutralization tests: positive percentage agreement of

TABLE 1 Characteristics of previously infected hemodialysis patients and infection-naïve hemodialysis patients

Variable		PI-HD patients (n = 35)	IN-HD patients (n = 91)
Male sex, n (%)		23 (65.7)	56 (61.5)
Age, y, median (IQR)		65.00 (58–74)	70.00 (62–76)
Body mass index, kg/m^2, median (IQR)		24.94 (22.22–28.09)	25.46 (22.32–29.41)
Dialysis vintage, mo, median (IQR)		39 (13–81)	34 (14–60)
HDF, n (%)		5 (14.3)	8 (8.8)
Past kidney transplantation, n (%)		5 (14.3)	8 (8.8)
Diabetic nephropathy, n (%)		7 (20.0)	17 (18.7)
Primary glomerulonephritis, n (%)		5 (14.3)	10 (11.0)
Charlson comorbidity index, median (IQR)		7 (4–8)	7 (4–8)
Diabetes, n (%)		5 (14.3)	34 (37.4)[a]
Malignancy, n (%)		4 (11.4)	13 (14.3)
Therapy with glucocorticosteroids, n (%)		2 (5.7)	6 (6.6)
Submitted for transplant, n (%)		4 (11.4)	5 (5.5)
Response to HBV vaccination	Total, n	26	68
	Low responders, n (%)	3 (11.5)	5 (7.35)
	Medium responders, n (%)	9 (34.61)	28 (41.17)
	High responders, n (%)	14 (53.85)	35 (51.47)

a $P = 0.012$

Abbreviations: HBV, hepatitis B virus; HDF, hemodiafiltration; IN-HD, infection-naïve hemodialysis; PI-HD, previously infected hemodialysis

100%, negative percentage agreement of 96.9%. Samples were interpreted as positive (seroconversion) or negative according to the manufacturer's instructions, with a cutoff index value of more than 12 AU/ml.

Statistical analyses Data were presented as numbers (percentages) for categorical variables and median (interquartile ranges [IQRs]) for continuous variables. The χ^2 or Fisher exact test was used for categorical variables. The Mann–Whitney test was used to compare continuous variables. The analysis of variance was used to compare the means of more than 2 independent variables. The Dunn multiple comparison test was used for post hoc analysis. Multivariable linear regression was used to determine the factors associated with the titer of the antibody directed against the SARS-CoV-2 S-antigen. A P value of less than 0.05 (2-tailed) was considered statistically significant. Data were evaluated using the STATISTICA software package, version 12.0 (Stat Soft Inc, Dell Software, Tulsa, Oklahoma, United States).

RESULTS A total of 126 hemodialysis patients were enrolled to the study and their characteristics are presented in TABLE 1. Stratification based on evidence of previous COVID-19 divided the cohort into 2 groups: the infection-naïve group of hemodialysis patients (IN-HD) with no history of COVID-19 and negative result for N-specific antibodies (91 [72.2%]), and the previously infected group of hemodialysis patients (PI-HD) (35 [27.8%]). The later included those with a history of COVID-19 (symptomatic, 23) and those with a positive result for N-specific antibodies but no COVID-19 history (asymptomatic, 12).

The previously infected group Anti-N domain antibodies were detectable in 31 of 35 PI-HD patients. N-specific seroconversion was not observed in 4 patients who were 5 months after SARS-CoV-2 infection, on average. S-specific antibodies were detectable in all PI-HD patients (35 [100%]). The median (IQR) S-antigen antibody titer of 4620 (1240–7820) AU/ml in PI-HD patients was over 12-fold higher than in IN-HD patients (P <0.001). There were no differences in the S-antibody titer between symptomatic and asymptomatic PI-HD patients (median [IQR], 4850 [2450–7820] AU/ml and 3055 [515–8940] AU/ml, respectively) (FIGURE 1).

The infection-naïve group S-specific immune response with a median (IQR) antibody titer of 366 (193–691) AU/ml was seen in 87 of 91 IN-HD vaccinated patients (95.6%). In 68 patients (74.7%), a strong humoral response was observed with the S-antibody titer greater than 200 AU/ml. In 4 patients (4 men) with a median (IQR) age of 70 (66.5–80.5) years and with median (IQR) comorbidity index of 8.5 (7.5–9.5), S-specific seroconversion was not found.

Predictors of S-antibody titer in the infection-naïve group Older patients were less likely to develop a higher S-antibody response (Spearman correlation coefficient, −0.21; P = 0.04) in univariable analysis. Age remained the only factor associated with the titer of S-antigen antibody on multivariable linear regression (P <0.001).

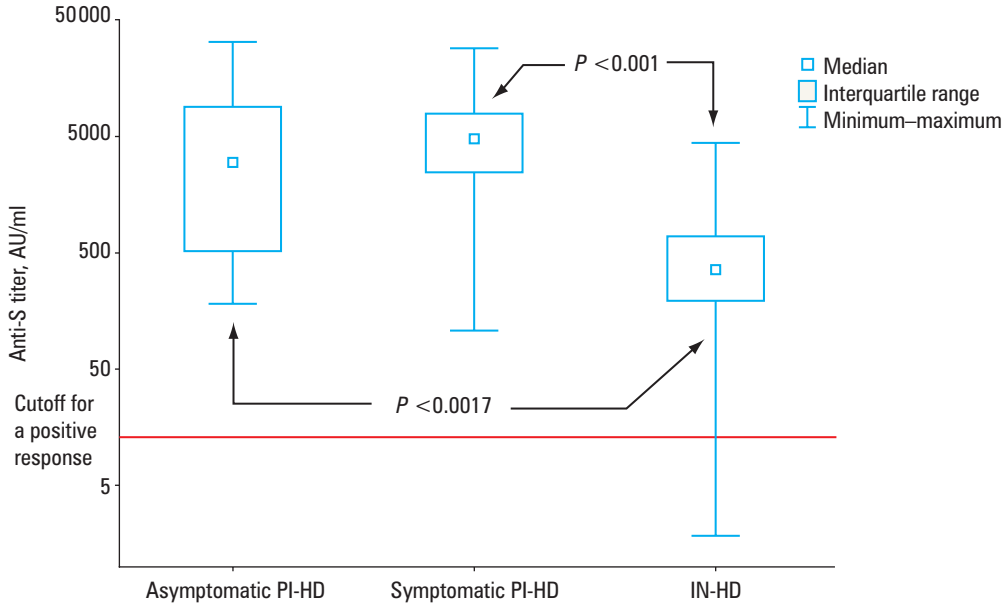

FIGURE 1 Anti-S IgG antibody titer after 2 doses of vaccination with BNT162b2 in infection--naïve and previously--infected symptomatic and asymptomatic hemodialysis patients. The Dunn Multiple Comparison test was used for post hoc analysis. Abbreviations: see **TABLE 1**

DISCUSSION The rationale for our study was the low serological response of hemodialysis patients to many vaccinations, for example, against tetanus,[6] influenza,[7] hepatitis B,[8] diphtheria,[9] and pneumococcal disease.[10] The often disappointing results of vaccinations may be due to the impaired function of the immune system involving mainly T lymphocytes and antigen presenting cells. It may be caused by uremia per se, the hemodialysis procedure, complications of chronic kidney disease, and therapeutic interventions for their treatment.[5] The pivotal trial that demonstrated 95% protection against COVID-19 infection following a 2-dose regimen of the BNT162b2 vaccine did not include hemodialysis patients.[11] Some weeks ago, Grupper et al[3] showed for the first time that most hemodialysis patients developed a substantial humoral response following the BNT162b2 vaccine, but it was significantly lower than that of controls from the general population. In a more recent study by Simon et al,[12] hemodialysis patients presented a substantially diminished SARS-CoV-2 S-antibody titer compared with a cohort of controls after the second dose of BNT162b2 with a median of 171 U/ml in hemodialysis patients and 2500 U/ml in controls. In both studies, however, the poorly adjusted control group was a significant limitation. There was a considerable age difference between dialysis and control patients and gender was unequally distributed: the majority of control subjects were younger women and the dialysis group included mainly older men.

In the presented study, we showed that 95% of IN-HD patients had an S-specific humoral response following BNT162b2. Longitudinal studies on the dynamics of anti-S–specific IgG antibodies after vaccination showed that their titer rapidly increases after the second dose, peaking around day 14, and starts gradually waning after the next few days. Therefore, determination of the postvaccination humoral response was performed between days 14 and 21 after the booster dose, during the short period of maintenance of the maximum S-antibody titer.[13] Although the titer of anti-S antibody was numerically much lower than that observed in the general population of the pivotal trial, almost three--quarters of our patients demonstrated an S-antibody titer above 200 AU/ml which corresponds to the high neutralizing antibody titer of 1:80 as stated earlier.[14] A direct comparison of the S-antibody titer to those reported in previous studies is difficult because all 3 analyzes were carried out with different kits and presented in different units.[3, 12] Nevertheless, there is no doubt that further studies are needed to validate the impact of a protective S-antibody titer in clinical settings.

In our cohort, 23 patients had a confirmed history of COVID-19 in the previous 5 months. The N-specific antibody serostatus was used to determine whether our cohort had evidence of prior asymptomatic infection with SARS-CoV-2.[15] N-specific immune response was seen in 12 patients which was 11.65% of the cohort considered to be infection-naïve, indicating a significant asymptomatic infection rate. A history of COVID-19 was associated with much stronger humoral immunity observed after vaccination. Indeed, previously infected patients had over 12-fold higher median S-specific antibody titer than infection-naïve patients, regardless of whether they presented symptoms of COVID-19 or were asymptomatic. The assessment of the humoral response after only a single dose of vaccine against SARS-CoV-2 in this group may be of particular interest. Perhaps a sufficient immunization level might be achieved with only a single dose of BNT162b2, as observed recently in the general population.[16]

As in other studies, age was found to be an important factor in the humoral response, that is, young people have an increased capacity to mount humoral immune responses compared

with the older population.[3] Many studies showed that women exhibit a greater immune response to foreign antigens that can facilitate vaccine efficacy.[17] Our results did not show any differences between men and women in this regard. One should note, however, that of the 4 patients who did not seroconvert in the infection-naïve group, there were only men. Perhaps older men may require more attention in a vaccine program, and possibly, a different vaccination schedule to increase the effectiveness of an mRNA vaccine, for example, using higher doses or repeated booster doses of vaccine. It is also worth checking the effectiveness of other types of vaccines against COVID-19, that is, viral vector, inactivated, attenuated, and protein-based types. Although some studies may have suggested a better immune response in lean people or in patients treated with hemodiafiltration, we did not confirm such an association.[18,19] Similarly to another study, no relationship was found between the hepatitis B vaccination response with the S-specific humoral response following BNT162b2. This could probably reflect different immune mechanisms and levels of reactogenicity in response to the 2 vaccines.[12] We were not able to identify other clinical clues that could help predict the serological response to SARS-CoV-2 vaccination in this population.

Our study is one of the first to show a very high rate of seroconversion following vaccination against COVID-19 among hemodialysis patients. The strength of our study is the use of a highly sensitive test using the S-trimer antigen demonstrating almost 100% compliance with neutralization tests.[20] One limitation is that we only tested humoral response. The cellular part of the adaptive immune system probably plays a role in protection from COVID-19 which is not reflected in our investigation. Also, because of the cross-sectional design, we could not obtain baseline antibody titers, and thus, despite N-antigen testing, we cannot exclude the possibility that the S-seroconversion may reflect infection versus vaccination in some IN-HD patients. A decrease in anti-N antibodies after infection has been observed and even 40% of asymptomatic individuals may become seronegative for IgG anti-N antibodies in the early convalescent phase. Given the fact that most infections in our unit occurred 4 or 5 months before blood was taken for analysis, this should also be taken into account.[21]

In conclusion, our study demonstrated that the majority of hemodialysis patients achieved a significant immunization level after vaccination with BNT162b2. Whether this translates into protecting this high-risk population requires further research.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT All authors conceived the idea for the study. LT, BB, WS, ADS, and MD contributed to the design of the research. SR, IR, WS, KP, and PT were involved in data collection and management. LT, MD, BB, amd ADS analyzed and interpreted the data. All authors edited, revised, and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE 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. doi:10.20452/pamw.16069

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