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SARS-CoV-2 antibody responses in infection-naive or previously infected peritoneal dialysis patients after 2 doses of the BNT162b2 vaccine

Rui Silva[1], Filipa Silva[1], Luís Mendonça[1], Luciano Pereira[1], Ana Oliveira[1], Angélica Ramos[2,3], Maria João Cardoso[2], Ana Malheiro[1], João Tiago Guimarães[1,2,3,4]

[1] Nephrology Department, Centro Hospitalar Universitário de São João, Porto, Portugal
[2] Clinical Pathology Department, Centro Hospitalar Universitário de São João, Porto, Portugal
[3] EPIUnit – Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal
[4] Biomedicine Department, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

Contributions of authors:
- RS: wrote the manuscript.
- RS, FS: designed and performed research.
- RS, LM: performed statistical analysis.
- LM, LP, AO, AR, MC, AM, TG: revised the manuscript for important intellectual content.

ABSTRACT

Dialysis-associated immune dysfunction makes chronic kidney disease patients both susceptible to severe Coronavirus disease 19 (Covid19) and to a weaker response to vaccination. Previously infected patients are thought to sustain stronger and more durable humoral responses than vaccinated patients. Four months after a two dose-regimen of the Pfizer/BioNTech SARS-CoV-2 mRNA vaccine (BNT162b2), we evaluated the SARS-CoV-2 spike immunoglobin G (IgG-S1) antibody levels in previously infected peritoneal dialysis patients and compared them with infection naïve PD patients. A total of 79 peritoneal dialysis patients were analyzed, of which 11 had a previous history of Covid19. We have verified that the median titer of the IgG-S1 in previously infected patients (14310 AU/mL) was significantly superior to that in infection naïve patients (760,05 AU/mL) ($p < 0,001$). Previous Covid19 was the only significant predictor of IgG-S1 levels in a multivariate linear regression model ($p < 0,001$). These results may impact vaccination strategies for peritoneal dialysis patients regarding the future administration of BNT162b2 booster doses. In conclusion, previously infected peritoneal dialysis patients who have completed a two-dose regimen of the BNT162b2 may be well suited without a third, booster dose for longer than infection naïve peritoneal dialysis patients. This strategy could make additional doses available around the world.

Keywords: antibodies, Covid-19, humoral immunity, peritoneal dialysis, vaccine

INTRODUCTION

A two-dose regimen of the Pfizer/BioNTech SARS-CoV-2 mRNA vaccine (BNT162b2) demonstrated 95% efficacy against Coronavirus disease 19 (Covid-19)[(1)], but end-stage kidney disease patients were not represented in this population. Dialysis patients are susceptible to severe Covid-19[(2,3)] making them a priority group for vaccination around the world[(4)]. However, as these patients are known for their weak humoral responses to vaccines, such as hepatitis B[(5)], concern has arisen on how well and for how long they might respond to BNT162b2. In the general population, the vaccine elicits high IgG and neutralizing antibodies responses within 15 days after the second dose, with titers peaking during the first month, but decaying afterwards[(6)]. This waning humoral response has led to booster doses being considered beyond the initially approved two-dose regimen[(7-9)], especially given that breakthrough infection in BNT162b2-vaccinated persons has been correlated with neutralizing antibody titers[(10, 11)]. However, a threshold titer that can predict breakthrough infection has not been defined and the duration of immunity is uncertain and probably heterogeneous. On the one hand, there are some groups of vaccinated infection-naïve individuals, including dialysis patients[(12)], who have been shown to develop lower antibody levels, suggesting that antibody titers in these populations may decrease earlier than others. On the other hand, both vaccinated and unvaccinated people previously infected with SARS-CoV-2 elicit much stronger and durable antibody responses[(13,14)]. After two BNT162b2 doses, we evaluated the SARS-CoV-2 spike immunoglobin G (IgG-S1) antibody levels in previously infected peritoneal dialysis (PD) patients and compared them with infection naïve PD patients.

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METHODS

In February 2021 we vaccinated 81 PD patients with the BNT162b2, twenty-one days apart. At close to four months post-vaccination, we tested these patients for seroconversion using the *BioPlex 2200 SARS-CoV-2 IgG Panel* (BIO-RAD, Hercules, California, USA) and the *SARS-CoV-2 IgG II Quant assay* (Abbott Laboratories, Chicago, Illinois, USA). The former is a multiplex immunoassay for the qualitative detection and semi-quantitative differentiation of IgG antibodies against the following targeted viral antigen: receptor binding domain of SARS-CoV-2 spike protein, S1 domain of the SARS-CoV-2 spike protein, S2 domain of the SARS-CoV-2 spike protein and nucleocapsid (N) protein of SARS-CoV-2. A positivity cutoff is ≥ 10U/mL. The latter is a chemiluminescent microparticle immunoassay (CMIA). It is used for the semi-qualitative and quantitative determination of IgG antibodies to the receptor binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2 in human serum and plasma. A positivity cutoff is ≥ 50 AU/mL.

Infection naïve patients were considered those without a history of PCR confirmed Covid19 and negative BioPlex result for the anti-N IgG. Previously infected patients were those with a history of PCR confirmed Covid19. Due the lack of baseline serologies, patients without a history of Covid19, but with a positive anti-N IgG were excluded since we could not ascertain if the infection occurred before or after vaccination.

We analyzed both cohorts for gender, age, PD modality, dialysis vintage, weekly Kt/V, body mass index, previous immunosuppression, leucocytes, lymphocytes, albumin and comorbidities included in the Charlson Comorbidity Index. Continuous variables were expressed as mean ± standard deviation (SD) or median (range) if normally or non-normally distributed, respectively. Categorical variables were represented by absolute and relative frequencies. Comparisons between infected and non-infected groups were performed using Chi-squared test for categorical variables and Student's *t*-test or Mann-Whitney *U* test for continuous variables if normally or non-normally distributed, respectively. We used multivariable linear regression to study the association between IgG-S1 levels and baseline characteristics. Statistical analysis was performed using IBM SPSS Statistics 25.

Table I

Baseline characteristics by the state of previous COVID19 infection.

	COVID19-naive n=68	Previous COVID19 n=11	*P* value
Male	31 (45.6%)	5 (45.5%)	0.99
Age (years)	56.5 ± 13.3	55.5 ± 13.7	0.83
BMI (kg/m2)	25.9 ± 3.6	27.6 ± 2.7	0.14
Dialysis vintage (months)	34.9 ± 30.5	46.0 ± 37.4	0.28
Automated PD	29 (42.6%)	4 (36.4%)	0.70
Weekly Kt/V	2.3 ± 0.6	2.1 ± 0.3	0.19
Diabetes	9 (13.2%)	0 (0.0 %)	0.20
Rheumatologic disease	1 (1.5 %)	0 (0.0 %)	0.69
Immunosuppressive treatment	2 (2.9 %)	0 (0.0 %)	0.57
Transplant waiting list	39 (57.4%)	5 (45.5%)	0.47
Charlson Index[a]	4.0 [2.0, 5.0]	3.0 [2.0, 5.0]	0.86
Albumin (g/L)	36.7 ± 3.6	34.8 ± 4.7	0.13
Leukocytes (x10^9/L)	7.7 ± 2.0	7.5 ± 3.4	0.81
Lymphocytes (x10^9/L)[a]	1.5 [1.2, 1.9]	1.5 [1.2, 2.2]	0.69
COVID19 after vaccine	2 (2.9 %)	0 (0.0 %)	0.57

Values are presented as n (%) or mean ± standard deviation, unless otherwise noted.
BMI – body mass index; CI – comorbidity index; PD – peritoneal dialysis.
[a] Median [interquartile range]

RESULTS

Eighty-one PD patients were given the BNT162b2, of which two were excluded because of a positive anti-N IgG without a history of Covid-19. Of the remaining 79, there were 68 infection naïve PD patients and 11 PD with previous Covid-19 (Table I). We found no statistically significant differences between groups. All patients were

Table II

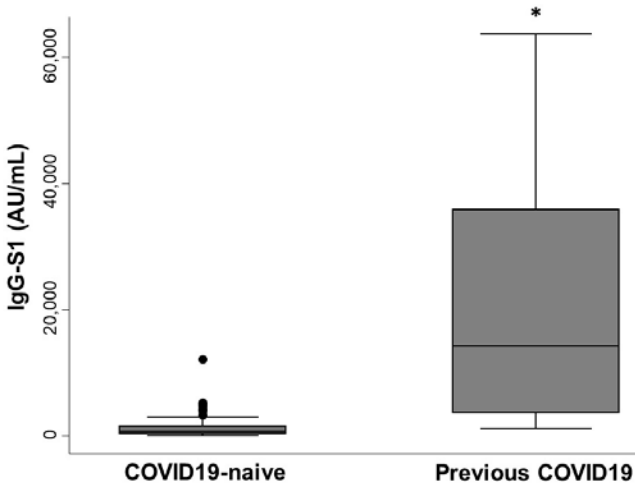
Multivariable linear regression for the association between IgG-S1 levels and baseline characteristics.

	Coefficient	95% CI	*P* value
Male	3410.5	-1526.5 – 8347.6	0.172
Age (years)	39.5	-138.1 – 217.1	0.657
BMI (kg/m2)	199.3	-365.1 – 763.7	0.482
Dialysis vintage (months)	-17.6	-83.9 – 48.7	0.597
Automated PD	3681.7	-335.1 – 7698.6	0.072
Weekly Kt/V	1722.1	-2219.0 – 5663.2	0.385
Diabetes	-4048.2	-10678.0 – 2581.6	0.226
Immunosuppressive treatment	-1974.8	-17627.5 – 13678.0	0.801
Charlson Index	-170.0	-718.3 – 378.3	0.537
Albumin (g/L)	-129.3	-1095.5 – 837.0	0.790
Previous COVID19	16600.9	10677.3 – 22524.4	< 0.001

BMI – body mass index; CI – confidence interval

Figure 1

Levels of IgG-S1 by the state of previous COVID19 infection. (* means p < 0.001)



positive for IgG-S1 at a median of 112 days after the second dose. Median IgG-S1 titers in previously infected PD patients (14310 AU/mL; maximum 63639 AU/mL, minimum 1207,7 AU/mL) was significantly superior to median IgG-S1 in the infection naïve group (760,05 AU/mL; maximum 12130,7 AU/mL; minimum 50,4 AU/mL) ($p < 0,001$) (Figure 1). After accounting for covariates in a multivariate linear regression model, previous Covid19 was the only significant predictor of IgG-S1 levels (Table II). To date, we have identified two cases of mild Covid19 breakthrough infection in the infection-naïve group (IgG-S1 of 368,7 AU/mL and 1541,6 AU/mL) and none in the previously infected group.

DISCUSSION

We aimed to determine one component of the immune response, the humoral response, of PD patients to *BNT162b2* four months after a two-dose regimen. We searched for differences in the level of antibodies directed against the SARS-CoV-2 spike protein between infection naïve and previously infected PD patients. Despite a 100% seroconversion rate, we observed significantly higher SARS-CoV-2 antibody levels in previously infected compared with infection-naive individuals. We did not specifically measure neutralizing antibody titers, but they have been strongly correlated to IgG-S1 before[6]. Given that breakthrough infections have been correlated to lower neutralizing antibody titers[10,11], the lower levels of IgG-S1 in the infection naïve group may result in a lower vaccine effectiveness and/or a shorter period of immune protection, whereas the higher levels of IgG-S1 amongst previously infected PD patients may imply just the opposite. In fact, studies in unvaccinated previously infected persons observed that both IgG and neutralizing antibody levels decrease only slightly at 8 to 10 months after the infection and that breakthrough infections are much less common[13-15]. Indeed, we experienced zero cases against two in the infection naïve group. This is in sharp contrast to antibody kinetics of vaccinated infection-naïve persons, who evidenced a significant decrease in antibody levels after 6 months[6]. Furthermore, previously infected individuals have been shown to exhibit higher antibody levels after only one dose of the BNT162b2 compared with infection-naive individuals after two doses[16], which is a reason why, after February 2021, previously infected patients in Portugal were recommended only one dose of a vaccine, irrespective of its standard regimen being of one or two doses. Additional doses beyond the first in the previously infected population came to be regarded as booster doses.

Overall, we conclude that the humoral response to a two-dose regimen of the BNT162b2 in previously infected PD patients at four months post-vaccination is higher and predictably longer than in infection-naïve PD patients. This study is confirmatory for the PD population that, as in the general population, previously infected patients elicit a much stronger humoral response to the BNT162b2. It may be useful for discussions surrounding vaccination strategies of PD patients, highlighting the potential to withhold a third, BNT162b2 booster dose in previously infected PD patients already with a two-dose regimen, making additional doses available around the world. Limitations of this study include the small sample, the lack of neutralization antibody measurements and the lack of T-cell response studies.

Disclosure of potential conflicts of interest: none declared.

References

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. The New England journal of medicine. 2020;383(27):2603-15.
2. Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J, et al. Presentation and Outcomes of Patients with ESKD and COVID-19. Journal of the American Society of Nephrology: JASN. 2020;31(7):1409-15.
3. 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 international. 2020;98(6):1530-9.
4. Francis A, Baigent C, Ikizler TA, Cockwell P, Jha V. The urgent need to vaccinate dialysis patients against severe acute respiratory syndrome coronavirus 2: a call to action. Kidney international. 2021;99(4):791-3.
5. Udomkarnjananun S, Takkavatakarn K, Praditpornsilpa K, Nader C, Eiam-Ong S, Jaber BL, et al. Hepatitis B virus vaccine immune response and mortality in dialysis patients: a meta-analysis. Journal of nephrology. 2020;33(2):343-54.
6. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. New England Journal of Medicine. 2021.
7. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. The New England journal of medicine. 2021;385(15):1393-400.
8. 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 Kidney Dis. 2021:S0272-6386(21)00833-7.
9. https://www.fda.gov/media/144413/download.
10. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. New England Journal of Medicine. 2021;385(16):1474-84.
11. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nature medicine. 2021;27(7):1205-11.
12. Yanay NB, Freiman S, Shapira Ma, Wishahi S, Hamze M, Elhaj M, et al. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. Kidney international. 2021;99(6):1496-8.
13. Vanshylla K, Di Cristanziano V, Kleipass F, Dewald F, Schommers P, Gieselmann L, et al. Kinetics and correlates of the neutralizing antibody response to SARS-CoV-2 infection in humans. Cell host & microbe. 2021;29(6):917-29.e4.
14. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science (New York, NY). 2021;371(6529).
15. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet (London, England). 2021;397(10283):1459-69.
16. Anderson M, Stec M, Rewane A, Landay A, Cloherty G, Moy J. SARS-CoV-2 Antibody Responses in Infection-Naive or Previously Infected Individuals After 1 and 2 Doses of the BNT162b2 Vaccine. JAMA network open. 2021;4(8):e2119741.

ORCID

Rui Silva 0000-0003-4244-2459
Filipa Silva 0000-0001-6308-5476
Luís Mendonça 0000-0003-1951-3941
Luciano Pereira 0000-0002-4576-3808
Ana Oliveira 0000-0002-5728-4572
Angélica Ramos 0000-0002-0763-7843
Maria João Cardoso 0000-0003-4190-4164
Ana Malheiro 0000-0002-0860-4648
João Tiago Guimarães 0000-0003-4836-6311

Correspondence to:
Rui Fernando Oliveira da Silva
Alameda Prof. Hernâni Monteiro
Serviço de Nefrologia do Centro Hospitalar de São João
4200-319 Porto
E-mail: ruinefro@gmail.com