Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 1173.e1–1173.e4

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Research note

Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study

Benaya Rozen-Zvi [1, 2, †], Dafna Yahav [2, 3, *, †], Timna Agur [1, 2], Boris Zingerman [1, 2], Haim Ben-Zvi [2, 4], Alaa Atamna [2, 3], Noam Tau [2, 5], Tiki Mashraki [1, 6], Eviatar Nesher [6], Ruth Rahamimov [1, 2, 6]

[1)] *Department of Nephrology and Hypertension, Rabin Medical Center, Petah-Tikva, Israel*
[2)] *Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3)] *Infectious Diseases Unit, Rabin Medical Center, Beilinson Campus, Petah-Tikva, Israel*
[4)] *Clinical Microbiology Laboratory, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel*
[5)] *Department of Diagnostic Imaging, Sheba Medical Center, Ramat Gan, Israel*
[6)] *Department of Transplantation, Rabin Medical Center, Beilinson Campus, Petah-Tikva, Israel*

ARTICLE INFO

Article history:
Received 29 March 2021
Received in revised form
23 April 2021
Accepted 24 April 2021
Available online 3 May 2021

Editor: J. Rodriguez-Baño

Keywords:
COVID-19
Immunogenicity
Immunosuppression
Kidney transplant recipients
Vaccine

ABSTRACT

Objectives: We aimed to evaluate the rates of antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine among kidney transplant recipients, and to identify factors associated with reduced immunogenicity.
Methods: This was a prospective cohort study including consecutive kidney transplant recipients in a single referral transplant centre. Participants were tested for anti-spike (anti-S) antibodies 2–4 weeks after a second vaccine dose. Primary outcome was rate of seropositivity. Univariate and multivariate analyses were conducted to identify factors associated with seropositivity.
Results: Of 308 kidney transplant recipients included, only 112 (36.4%) tested positive for anti-S antibodies 2–4 weeks after receiving the second dose of BNT162b2 vaccine. Median antibody titre was 15.5 AU/mL (interquartile range (IQR) 3.5–163.6). Factors associated with antibody response were higher estimated glomerular filtration rate (eGFR) (odds ratio (OR) 1.025 per mL/min/1.73 m^2, 95% confidence interval (CI) 1.014–1.037, $p < 0.001$), lower mycophenolic acid dose (OR 2.347 per 360 mg decrease, 95% CI 1.782–3.089, $p < 0.001$), younger age (OR 1.032 per year decrease, 95%CI 1.015–1.05, $p < 0.001$) and lower calcineurin inhibitor (CNI) blood level (OR 1.987, 95%CI 1.146–3.443, p 0.014). No serious adverse events resulting from the vaccine were reported.
Conclusions: Kidney transplant recipients demonstrated an inadequate antibody response to SARS-CoV-2 mRNA vaccination. Immunosuppression level was a significant factor in this response. Strategies to improve immunogenicity should be examined in future studies. **Benaya Rozen-Zvi, Clin Microbiol Infect 2021;27:1173.e1–1173.e4**

Introduction

High efficacy of the mRNA-based BNT162b2 vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been demonstrated in both a large clinical trial and real-life data in the general population [1]. Response to vaccination among solid-organ transplant recipients is expected to be diminished [2]; however, this has not yet been evaluated for the BNT162b2 vaccine. Current guidelines recommend vaccinating transplant candidates and recipients against SARS-CoV-2 despite the lack of data regarding its efficacy in these populations [3]. To assess immunogenicity to the vaccine among kidney transplant recipients, we prospectively evaluated the antibody response among recipients 2–4 weeks after they received the second dose of BNT162b2 in a single referral centre in Israel.

We hypothesized that transplant recipients will develop a suboptimal response to the vaccine, correlated with the degree of their immunosuppression.

* Corresponding author: Dafna Yahav, Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, 39 Jabotinsky Road, Petah-Tikva, 49100, Israel.
E-mail address: dafna.yahav@gmail.com (D. Yahav).
† BRZ and DY contributed equally to this work.

https://doi.org/10.1016/j.cmi.2021.04.028
1198-743X/

Methods

We included adult kidney transplant recipients who were vaccinated with two doses of BNT162b2 vaccine, 21 days apart, and followed at the Rabin Medical Center (RMC) kidney transplantation follow-up clinic between 8th and 28th February 2021. Consenting recipients were scheduled for a study visit 2–4 weeks after receiving the second vaccine dose and were followed for up to 6 weeks. The study was approved by the ethics committee of the RMC. Data collected included demographic data, adverse events following the vaccination, and immunosuppressive medication regimen. Blood samples for anti-spike (anti-S) SARS-CoV-2 antibodies were collected during the visit. The SARS-CoV-2 IgG II Quant (Abbott©) assay was used for quantitative measurement of IgG antibodies against the spike protein of SARS-CoV-2. A test was considered positive if IgG was ≥50 AU/mL [4]. Tacrolimus or cyclosporine blood levels and creatinine values were also collected. Renal function was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation. The primary outcome was rate of seropositivity for anti-S antibodies. Univariate and multivariate logistic regression analyses were performed to explore predictors of seropositivity. Statistically significant covariates were tested for co-linearity. Linear regression was conducted to evaluate factors associated with higher log transformed antibody titre.

Results

We included 308 consenting kidney transplant recipients. Table 1 shows the baseline characteristic of participants and immunosuppressive drugs used. Antibody levels were collected at a median time of 28 days (interquartile range (IQR) 22–34 days) from the second vaccine dose. Of 308 included kidney transplant recipients, only 112 (36.4%) tested seropositive for anti-S antibodies. Median antibody titre was 15.5 AU/mL (IQR 3.5–163.6). Factors associated with anti-S seropositivity in univariate and multivariate analysis are detailed in Table 2 and include higher estimated glomerular filtration rate (eGFR) (OR 1.025 per mL/min/1.73 m^2, 95%CI 1.014–1.037, p < 0.001), lower mycophenolic acid dose (OR 2.347, 95%CI 1.782–3.089, p < 0.001), younger age (OR 1.032 per year, 95%CI 1.015–1.05, p < 0.001) and lower blood levels of calcineurin inhibitors (CNIs) (OR 1.987, 95%CI 1.146–3.443, p 0.014). Treatment with mammalian target of rapamycin inhibitors (mTOR) was not associated with decreased odds of antibody response by univariate analysis but was significant after multivariate adjustment (OR 2.87 for no mTOR inhibitors treatment, 95%CI 1.058–7.781, p 0.038). Treatment with high-dose corticosteroids in the 6 months prior to the first vaccine dose was associated with decreased odds of response by univariate analysis (OR 0.293, 95%CI 0.098–0.873, p 0.028) but not by multivariate analysis (p 0.29). The same factors were also associated with higher log transformed antibody titre (Supplementary Material Table S1). No acute kidney injury or acute rejection cases were reported. During the follow-up period, four recipients had symptomatic COVID-19 disease; all were in the seronegative group. One had mild disease, two had severe disease, and one patient had critical illness and died in hospital.

Discussion

Seropositivity rates of kidney transplant recipients to current BNT162b2 vaccine schedules are low, <40% in our cohort of 308 fully vaccinated recipients. Factors associated with seropositivity included younger age, higher eGFR (representing better renal function), and reduced immunosuppression (including lower dose of antimetabolites, lower blood levels of CNI, and no use of mTOR). A similarly low antibody response to mRNA COVID-19 vaccines among kidney transplant recipients was recently reported following one vaccine dose in a cohort from the US. Older age and use of antimetabolite maintenance were significantly associated with seronegativity in this study, in line with our results [5]. Suboptimal antibody response to other vaccines has also been reported among

Table 1
Baseline characteristics according to response status

Variable	All (n = 308)	Response[a] (n = 112)	No response (n = 196)	p
Age (years)	57.51 ± 13.84	53.68 ± 14.45	59.7 ± 13.02	<0.001
Female gender	111 (36%)	36 (32.1%)	75 (38.3%)	0.282
Time from transplantation (years)	7.08 ± 7.54	7.05 ± 7.17	7.11 ± 7.77	0.393
Transplantation in the previous 3 months	12 (3.9%)	0 (0%)	12 (6.1%)	0.008
Living donor	234 (76%)	91 (81.3%)	143 (73%)	0.101
eGFR (mL/min/1.73 m^2)	62.74 ± 22.74	70.54 ± 24.66	58.28 ± 20.32	<0.001
eGFR <60 mL/min/1.73 m^2	149 (48.4%)	38 (33.9%)	111 (56.6%)	<0.001
Diabetes mellitus	53 (17.2%)	15 (13.4%)	38 (19.4%)	0.180
Time lapsed from second vaccine dose (days)	28.6 ± 9.49	28.2 ± 9.49	28.83 ± 9.51	0.576
BMI (per kg/m^2)	26.91 ± 4.62	26.84 ± 4.38	26.94 ± 4.77	0.852
No mycophenolic acid	82 (26.6%)	46 (41.1%)	36 (18.4%)	<0.001
Low-dose mycophenolic acid[b]	26 (8.4%)	13 (11.6%)	13 (6.6%)	
Medium-dose mycophenolic acid[b]	117 (38%)	38 (33.9%)	79 (40.3%)	
High-dose mycophenolic acid[b]	83 (26.9%)	15 (13.4%)	68 (34.7%)	
Tacrolimus yes/no	285 (92.5%)	104 (92.9%)	181 (92.3%)	0.870
Cyclosporine yes/no	23 (7.5%)	8 (7.1%)	15 (7.7%)	
Tacrolimus level (ng/mL)	7.76 ± 2.19	7.1 ± 1.61	8.14 ± 2.39	<0.001
Cyclosporine level (ng/mL)	129.13 ± 55.13	112.63 ± 39.54	137.93 ± 61.29	0.305
mTOR inhibitor	26 (8.4%)	10 (8.9%)	16 (8.2%)	0.816
High calcineurin inhibitor level[c]	181 (58.8%)	55 (49.1%)	126 (64.3%)	0.009
High-dose CS[c]	26 (8.4%)	4 (3.6%)	22 (11.2%)	0.02
Treatment with rituximab[c]	6 (1.9%)	0 (0%)	6 (3.1%)	0.149
Treatment with ATG[c]	14 (4.5%)	3 (2.7%)	11 (5.6%)	0.234

Categorical variables are presented as numbers (percentage); continuous variables are presented as mean + -standard deviation. eGFR, estimated glomerular filtration rate; BMI, body mass index; mTOR, mammalian target of rapamycin; CNI, calcineurin inhibitors; ATG, antithymocyte globulin; CS, corticosteroids.

[a] Adequate antibody response was defined as IgG ≥50 AU/mL using the SARS-CoV-2 IgG II Quant (Abbott©) assay.

[b] Low-dose mycophenolic acid was defined as ≤360 mg/day, medium dose as 361–1079 mg/day, and high dose as ≥1080 mg/day.

[c] High CNI level was defined as >7 ng/mL for tacrolimus and >150 ng/mL for cyclosporine; high-dose CS was defined as intravenous methyl prednisolone (at least 250 mg dose) in the previous 6 months before the first vaccine dose; treatment with rituximab or ATG was defined as any dosage in the last year before the first vaccine dose.

Table 2
Factors associated with adequate antibody response[a] by univariate and multivariate analyses

Variable	Univariate				Multivariate			
	Odds ratio (OR)	95%CI for OR		p	OR	95%CI for OR		p
Younger age (per year decrease)	1.032	1.015	1.050	<0.001	1.038	1.018	1.059	<0.001
Female gender	0.764	0.468	1.248	0.282	—	—	—	—
Time from transplantation (per year)	0.999	0.969	1.030	0.949	—	—	—	—
Living donor	1.606	0.909	2.839	0.103	—	—	—	—
eGFR (per mL/min/1.73 m^2 increase)	1.025	1.014	1.037	<0.001	1.032	1.018	1.045	<0.001
eGFR <60 mL/min/1.73 m^2	0.393	0.243	0.637	<0.001	—	—	—	—
Diabetes mellitus	0.643	0.336	1.230	0.182	—	—	—	—
Time from second vaccine dose (per day)	0.993	0.969	1.018	0.575	—	—	—	—
BMI (per kg/m^2)	0.995	0.946	1.047	0.852	—	—	—	—
Lower mycophenolic acid dose (per 360 mg decrease)	1.763	1.422	2.187	<0.001	2.347	1.782	3.089	<0.001
Cyclosporine yes/no	0.928	0.381	2.263	0.870	—	—	—	—
No mTOR inhibitor	0.907	0.397	2.072	0.816	2.870	1.058	7.781	0.038
Low CNI level[b]	1.865	1.164	2.990	0.010	1.987	1.146	3.443	0.014
High-dose CS[b]	0.293	0.098	0.873	0.028	—	—	—	—
Treatment with ATG[b]	0.463	0.126	1.696	0.245	—	—	—	—

Odds ration > 1 indicates adequate association with antibody response. eGFR, estimated glomerular filtration rate; BMI, body mass index; mTOR, mammalian target of rapamycin; CNI, calcineurin inhibitors; ATG, antithymocyte globulin; CS, corticosteroids.

[a] Adequate antibody response was defined as IgG ≥50 AU/mL using the SARS-CoV-2 IgG II Quant (Abbott©) assay.

[b] Low CNI level was defined as ≤7 ng/mL for tacrolimus and ≤150 ng/mL for cyclosporine; high-dose CS was defined as intravenous methyl prednisolone (dose at least 250 mg) in the previous 6 months before the first vaccine dose; treatment with ATG was defined as any dosage in the last year before the first vaccine dose.

solid-organ transplant recipients compared to healthy subjects [2,6,7]. Factors associated with this reduced response included the use of tacrolimus as well as mycophenolic acid; the latter inhibits B-cell function and has been documented to influence antibody response to influenza vaccine in a dose-dependent manner [7,8]. Chronic kidney disease is associated with impaired innate and adaptive immunity, and inadequate antibody production after vaccination has been reported in this population [9].

A trend for lower rate of antibody response was observed in our cohort among recipients vaccinated during the first 3 months following transplantation, and among recipients treated with high-dose corticosteroids or rituximab. However, the numbers were too small to draw conclusions.

Although the correlation between antibody levels after vaccination and clinical protection has not yet been proven, evidence is accumulating to support antibody response as a potential correlate of disease protection [10]. In addition, using the SARS-CoV-2 IgG II Quant assay in non-immunocompromised haemodialysis patients, we found ~90% seropositivity [11].

Limitations of our study include lack of cellular immunity testing and/or neutralizing antibody testing. As maintenance immunosuppressive therapy for prevention of organ rejection is aimed at T-cell suppression, a reduced T-cell response to vaccination among kidney transplant recipients could be expected, although this will have to be evaluated in future studies. Regarding neutralizing antibody testing, strong correlation has been reported between anti-S antibody titres and neutralization antibody levels following BNT162b2 vaccine [12].

Several strategies have been suggested to improve immunogenicity in response to BNT162b2. These include a third booster dose of BNT162b2 [13], serology-based vaccine dosing [14], or a heterologous prime–boost combination (i.e. mixing different vaccine types) [15]. Transplant centres may consider either of these strategies, with a possible immunosuppression reduction prior to vaccination, taking into consideration the individual risk of rejection. In a previous cohort of kidney transplant recipients, temporary reduction of immunosuppression during sepsis was not associated with an increased risk of rejection or long-term graft failure [16]. Nevertheless, no data are currently available to support any of these strategies, and adequately designed clinical trials are needed to evaluate their role in augmenting immunogenicity. Studies should also assess immunogenicity in transplant candidates, considering according to the results a recommendation to complete vaccination series prior to transplantation.

Author contributions

BRZ, RR, DY, TA, and BZ conceptualized and participated in the design of the study. Conductance of the study and data collection were performed by RR, TM, TA, BZ, EN, AA, and NT. HBZ conducted the microbiological analyses. Data analysis was performed by RR, BRZ and DY. RR, BRZ, NT, AA, and DY drafted the initial manuscript and all authors revised subsequent drafts. All authors read and approved the final manuscript for submission.

Transparency declaration

The authors declare that they have no conflicts of interest. No external funding was received for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.04.028.

References

[1] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412–23.
[2] Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013;8:e56974.
[3] American Society of Transplantation. American society of transplantation COVID-19 vaccination guidance. 2020. Available from: https://www.myast.org/sites/default/files/ASTCOVID-info.pdf [cited 19th February 2021].
[4] Abbott laboratories. SARS-CoV-2 IgG II Quant. 2020. Available from: https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2 [cited 24th February 2021].
[5] Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA 2021:e214385. https://doi.org/10.1001/jama.2021.4385.
[6] Birdwell KA, Ikizler MR, Sannella EC, Wang L, Byrne DW, Ikizler TA, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. Am J Kidney Dis 2009;54:112–21.

[7] Boey L, Curinckx A, Roelants M, Derdelinckx I, van Wijngaerden E, De Munter P, et al. Immunogenicity and safety of the nine-valent human papillomavirus vaccine in solid organ transplant recipients and adults infected with human immunodeficiency virus (HIV). Clin Infect Dis 2020:ciaa1897. https://doi.org/10.1093/cid/ciaa1897.
[8] Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. Clin Infect Dis 2018;66:1698–704.
[9] Haddiya I. Current knowledge of vaccinations in chronic kidney disease patients. Int J Nephrol Renovasc Dis 2020;13:179–85.
[10] Harvey RA, Rassen JA, Kabelac CA. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 2021. https://doi.org/10.1001/jamainternmed.2021.0366. Published online 24th February.
[11] Agur T, Ben-Dor N, Goldman S, Lichtenberg S, Herman-Edelstein M, Yahav D, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—a prospective cohort study. Nephrol Dial Transplant 2021:gfab155. https://doi.org/10.1093/ndt/gfab155.
[12] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
[13] Pfizer. Pfizer and biontech initiate a study as part of broad development plan to evaluate Covid-19 booster and new vaccine variants. 2021 [Internet]. [cited 2021 Feb 26]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development.
[14] Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet 2021. 25th Feb [cited 2021 Feb 26]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00501-8/abstract.
[15] Ledford H. Could mixing COVID vaccines boost immune response? Nature 2021;590:375–6.
[16] Yahav D, Sulimani O, Green H, Margalit I, Ben-Zvi H, Mor E, et al. Immunosuppression reduction in kidney transplant recipients during bacterial infection—a retrospective study. Clin Transplant 2019;33:e13707.