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Original Article

Humoral immune response to an mRNA-1273 booster after chAdOx1-nCoV-19-priming among patients undergoing hemodialysis

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Abstract

Objectives: Patients who are undergoing dialysis due to end-stage kidney disease are susceptible to greater coronavirus disease 2019 (COVID-19) complications. While vaccination is seen as the most effective tactic against COVID-19, the dialysis population usually has impaired immune responses to vaccination. Owing to the global vaccine supply shortage in the early phase of the COVID-19 pandemic, hemodialysis patients in Taiwan were administered homologous ChAdOx1 nCoV-19/ChAdOx1 nCoV-19 at 12-week intervals, with a third booster shot of mRNA-1273 given 12 weeks after the second dose. We assessed the antibody responses of these patients to this extended-interval dosing protocol. **Materials and Methods:** A total of 168 hemodialysis patients (mean age: 67 ± 13 years) without prior COVID-19 infection were vaccinated between June 16, 2021, and January 5, 2022, and followed until February 10, 2022. The primary outcome was seroconversion with an antispike immunoglobulin G (IgG) antibody level ≥50 arbitrary units (AU)/mL at 4 weeks after the administration of an mRNA-1273 booster shot. The secondary outcome was the level of antispike IgG antibodies. Multivariable linear regression models were used to evaluate the associations between the baseline characteristics and the antispike IgG level. **Results:** A total of 163 (97.0%) patients reached the primary endpoint, with antibody levels after the third booster dose of mRNA-1273 being significantly higher than those after the second dose of ChAdOx1 nCoV-19 (median IgG titer 12,007 [4394–23,860] vs. 846 [interquartile range 295–2114] AU/mL; $P < 0.001$). Patients who were male, older, had a higher body mass index, had a lower total lymphocyte count, and used immunosuppressants had lower antibody levels. **Conclusion:** A third booster dose of mRNA-1273 after two consecutive priming doses of ChAdOx1 nCoV-19 with extended intervals resulted in adequate humoral immune responses among hemodialysis patients.

Keywords: *Antibody, Booster, Coronavirus disease 2019, Hemodialysis, Immunogenicity*

Introduction

Patients who are undergoing dialysis are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection due to numerous factors, including older age and multiple comorbidities [1]. As vaccinations are one of the most effective defensive tools in the fight against coronavirus disease 2019 (COVID-19) [2], it is of utmost importance that this vulnerable population be prioritized to receive protection to mitigate the effect of SARS-CoV-2 infection. However, many patients are reluctant to receive vaccinations because they are worried about the potential side effects [3]. Furthermore, they may have concerns that vaccination will not be able to provide adequate protection from COVID-19.

Due to global vaccine shortages, the Taiwan Centers for Disease Control implemented a mixed vaccination protocol in June 2021, prioritizing patients undergoing hemodialysis with homologous ChAdOx1 nCoV-19/ChAdOx1 nCoV-19 at 12-week intervals, followed by a third booster dose with mRNA-1273 12 weeks after the second dose of ChAdOx1 nCoV-19. We hypothesized that hemodialysis patients who have received all three vaccine doses would be able to generate adequate humoral immune responses. Therefore, we aimed to determine the antibody seroconversion rate following this

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vaccination protocol. We further analyzed the association of antibody levels with different patient characteristics pertaining to immunity.

Materials and Methods

Study design and patients

This was a prospective cohort study, including patients undergoing hemodialysis in the hemodialysis unit of Taipei Tzu Chi Hospital, Taiwan. Eligibility criteria included clinically stable on dialysis for ≥3 months, an age of 20 years or older, and no SARS-CoV-2 infection before receipt of the first vaccine dose. Patients who had inadequate dialysis (defined as a Kt/V urea value <1.2 or treatment time <12 h per week), were previously vaccinated, refused vaccination, or declined to participate were excluded. Patients were inoculated with three vaccine injections (two separate doses with ChAdOx1 nCoV-19 of 0.5 mL each [AstraZeneca; covid19.astrazeneca.com], followed by a third booster dose with mRNA-1273 of 0.25 mL [Moderna; eua. modernatx. com]) from June 2021 to January 2022.

Diabetes mellitus was defined based on the usage of antidiabetic agents, including insulin. Hypertension was defined as a blood pressure >140/90 mmHg or the use of antihypertensive medications. Coronary artery disease (CAD) was diagnosed if there was either a history of myocardial infarction or >50% stenosis in at least one major coronary artery as documented by coronary angiography.

Participants were observed for 30 min after vaccination and were asked to document any adverse events and respond appropriately. Blood samples were taken on the day of vaccination before dialysis and then at 28 days postvaccination for serological testing. This study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Tzu Chi Hospital (10-XD-117). Written informed consent was obtained from all the study participants.

Immunogenicity assessments

On the 28th day after receiving each vaccine dose, immunoglobulin G (IgG) antibodies directed against the receptor-binding domain of the spike protein's S1 subunit of SARS-CoV-2 were measured using the AdviseDx SARS-CoV-2 IgG II assay (Abbott Laboratories, Abbott Park, IL), with titers ≥50 arbitrary units (AUs) per milliliter considered to be seroconversion.

Outcome

The primary endpoint was seroconversion with an antispike IgG antibody level ≥50 AU/mL 4 weeks after the administration of an mRNA-1273 booster shot. The secondary endpoint was the level of antispike IgG antibodies.

Statistical analysis

Categorical data were expressed as frequencies and compared through the Chi-square test. Continuous data with or without a normal distribution were presented as the mean ± standard deviation or median (interquartile range) and compared by the Student's *t*-test or the Mann–Whitney *U*-test, respectively. Linear regression models were used to evaluate the relationship between the baseline characteristics and the outcomes of interest. Models were adjusted for patient characteristics, which were selected on the basis of clinical relevance and the results from prior studies and included age, sex, body mass index (BMI), diabetes, CAD, the use of immunosuppressants, serum albumin levels, and the lymphocyte count [4-6]. Two-tailed $P < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 242 patients undergoing hemodialysis who were screened for eligibility, 168 underwent the full vaccination protocol and were included in the final analysis. Antispike antibody titers were substantially increased following the sequential doses of vaccination. The median antibody levels 4 weeks after the first dose (ChAdOx1 nCoV-19), the second dose (ChAdOx1 nCoV-19), and the third dose (mRNA-1273) were 177 (24–494) AU/mL, 846 (295–2114) AU/mL, and 12,007 (4394–23,860) AU/mL, respectively [$P < 0.001$, Figure 1]. After the first dose of the ChAdOx1 nCoV-19 vaccine, nonresponders (antispike IgG antibody levels < 50 AU/mL, $n = 53$) accounted for 31.5% of all individuals. After the second dose of the ChAdOx1 nCoV-19 vaccine, nonresponders ($n = 9$) accounted for 5.4% of all individuals. After the third booster shot of mRNA-1273, nonresponders ($n = 5$) accounted for only 3.0% of all participants. The baseline characteristics of all participants were divided into tertiles according to their antispike antibody levels after the booster shot of mRNA-1273, as shown in Table 1. Overall, the mean age was 67 ± 13 years, 51.8% of the participants were male, and 56.0% of the participants had diabetes, with a mean dialysis vintage of 8.2 ± 5.9 years. Compared with patients in the higher tertiles, patients in the lowest antibody tertile were older, had lower serum albumin levels and total lymphocyte counts, and had higher fasting

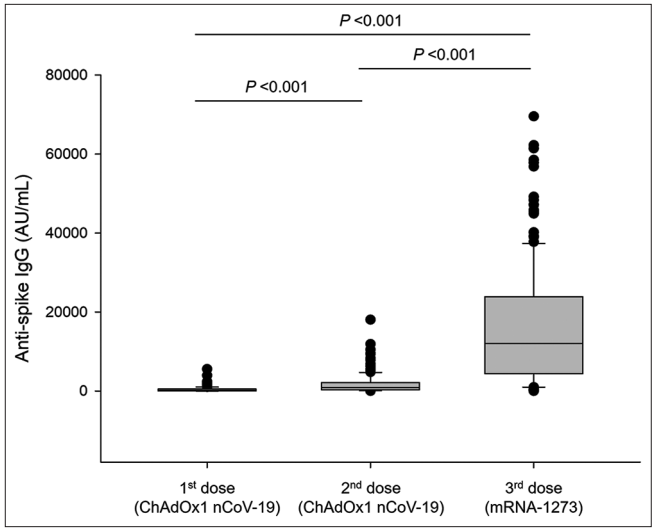

Figure 1: Severe acute respiratory syndrome coronavirus 2 antispike antibody response 4 weeks after the first dose (ChAdOx1 nCoV-19), the second dose (ChAdOx1 nCoV-19), and the third dose (mRNA-1273) of coronavirus disease 2019 vaccine among patients undergoing hemodialysis. IgG: Immunoglobulin G

plasma glucose concentrations. There were no intergroup differences concerning sex, smoking habits, dialysis vintage, the presence of diabetes or CAD, a positive history of malignancy, or the use of immunosuppressants.

Univariable linear regression analyses showed that increased antispike antibody levels were significantly correlated with age, a history of malignancy, and the total lymphocyte count [Table 2]. In multivariable linear regression analysis, the total lymphocyte count was significantly and positively associated with the antispike antibody level (β coefficient: 0.932, $P = 0.004$), whereas age (β coefficient: −0.022, $P < 0.001$), male sex (β coefficient: −0.317, $P = 0.007$), BMI (β coefficient: −0.032, $P = 0.038$), and the use of immunosuppressants (β coefficient: −0.981, $P = 0.008$) were significantly and negatively associated with the antispike antibody level.

Discussion

The present study assessed the humoral immune response to an extended-interval mixed ChAdOx nCoV19/ChAdOx nCoV19/mRNA-1273 vaccination protocol administered to patients undergoing hemodialysis. We found that after the first vaccine dose, seroconversion was achieved in 68.5% ($n = 115$) of all test individuals with low antibody levels of 177 (24–494) AU/mL. After the second dose, we observed a successful seroconversion in 94.6% of individuals with moderate antibody levels of 846 (295–2114) AU/mL compared to 79.2% of normal healthy persons with higher

Table 1: Baseline characteristics of the study participants stratified by tertiles of antispike antibody levels

Variables	Tertile 1 (n=56)	Tertile 2 (n=56)	Tertile 3 (n=56)	P
Demographic data				
Age (years)	73.9±9.0	65.3±13.7	61.4±11.3	<0.001
Male sex, n (%)	32 (57.1)	29 (51.8)	26 (46.4)	0.525
Smoking history, n (%)	13 (23.2)	10 (17.9)	7 (12.5)	0.334
Dialysis vintage (years)	7.6 (3.2–12.7)	6.9 (3.0–12.2)	8.0 (3.2–12.1)	0.945
Kt/V	1.7±0.3	1.7±0.2	1.7±0.2	0.745
URR (%)	76.4±6.5	75.7±4.6	76.4±4.6	0.748
nPCR (g/kg/day)	1.04 (0.91–1.18)	1.06 (0.89–1.26)	1.09 (1.03–1.28)	0.196
BMI (kg/m^2)	23.1±3.7	22.8±3.2	24.5±4.0	0.047
Diabetes mellitus, n (%)	33 (58.9)	28 (50.0)	33 (58.9)	0.547
Hypertension, n (%)	52 (92.9)	51 (91.1)	48 (85.7)	0.427
CAD, n (%)	14 (25.0)	10 (17.9)	12 (21.4)	0.654
Cancer, n (%)	9 (16.1)	8 (14.3)	2 (3.6)	0.078
Use of ISs, n (%)	2 (3.6)	1 (1.8)	1 (1.8)	0.774
Laboratory data				
Albumin (g/dL)	3.7±0.2	3.9±0.3	3.9±0.3	0.008
Fasting glucose (mg/dL)	161 (131–197)	134 (116–180)	135 (107–194)	0.027
Lymphocyte (×10^9/L)	0.9 (0.6–1.4)	1.2 (0.9–1.4)	1.2 (1.0–1.6)	0.002
Hemoglobin (g/dL)	10.3 (9.2–10.8)	10.5 (9.7–11.0)	10.3 (9.4–11.2)	0.224
Ferritin (ng/mL)	455 (279–650)	438 (248–653)	485 (141–673)	0.956
Calcium (mg/dL)	9.3 (8.8–9.8)	9.3 (8.9–10.0)	9.3 (8.8–10.1)	0.911
Phosphate (mg/dL)	4.2 (3.5–5.0)	4.3 (3.5–5.2)	4.7 (3.8–5.3)	0.240
iPTH (pg/mL)	275 (120–532)	363 (146–566)	365 (143–646)	0.553
Antispike IgG (AU/mL)	2552 (605–4422)	12,007 (8077–16,733)	29,619 (23,735–39,163)	<0.001

BMI: Body mass index, CAD: Coronary artery disease, iPTH: Intact parathyroid hormone, ISs: Immunosuppressants, nPCR: Normalized protein catabolic rate, URR: Urea reduction ratio, IgG: Immunoglobulin G, AU: Arbitrary unit

Table 2: Univariate and multivariate analyses of factors associated with antispike immunoglobulin G antibody levels[a]

Variables	Univariate		Multivariate	
	β coefficient (95% CI)	P	β coefficient (95% CI)	P
Age (years)	−0.020 (−0.029–−0.011)	<0.001	−0.022 (−0.031–−0.012)	<0.001
Male sex	−0.223 (−0.456–0.101)	0.061	−0.317 (−0.545–−0.090)	0.007
Dialysis vintage (years)[a]	−0.264 (−0.554–0.026)	0.074	−0.236 (−0.514–0.042)	0.096
BMI (kg/m^2)	0.001 (−0.031–0.033)	0.951	−0.032 (−0.063–−0.002)	0.038
Diabetes mellitus	−0.093 (−0.330–0.144)	0.438	−0.096 (−0.319–0.128)	0.400
CAD	−0.015 (−0.302–0.272)	0.918	0.114 (−0.164–0.392)	0.418
Cancer	−0.395 (−0.762–−0.028)	0.035	−0.220 (−0.560–0.120)	0.204
Use of ISs	−0.640 (−1.407–0.127)	0.101	−0.981 (−1.703–−0.259)	0.008
Albumin (g/dL)	−0.326 (−0.111–0.762)	0.142	−0.043 (−0.486–0.400)	0.849
Lymphocyte (x10^9/L)[a]	1.186 (0.548–1.824)	<0.001	0.932 (0.304–1.561)	0.004

[a]Log10-transformed. CAD: Coronary artery disease, ISs: Immunosuppressants, BMI: Body mass index, CI: Confidence interval

antibody levels of 1501 (380–4939) AU/mL after two doses of the ChAdOx nCoV19 vaccine [7]. Following the booster dose of the mRNA-1273 vaccine, significantly higher antibody levels of 12,007 (4394–23,860) AU/mL were observed. We also found that patients who were male, older, had a lower total lymphocyte count and a higher BMI, and used immunosuppressants were more likely to have lower antibody titers after completing the vaccination protocol. From this result, we can infer that patients undergoing hemodialysis may require a minimum of at least three doses of COVID-19 vaccines to attain an acceptable seroconversion rate and antibody levels.

Our results are in agreement with prior studies showing a comparable humoral response with dual vaccination with viral vector-based vaccines compared with mRNA-based vaccines and a significantly higher antispike antibody titer following a third mRNA booster vaccination dose among hemodialysis patients. Martin *et al.* compared the humoral response and clinical effectiveness of the first two doses of mRNA-based (BNT162b2) vaccines versus viral vector (ChAdOx1 nCoV-19) SARS-CoV-2 vaccines in a large prospective study of 1021 hemodialysis patients in the UK [8]. They showed a comparably high seroconversion rate for both vaccine types in infection-naive patients (88.3% and 83.4% following BNT162b and ChAdOx1 respectively, $P = 0.09$). In addition, the third dose with BNT162b2 elicited a higher antispike antibody titer compared with the second dose in a subgroup of 267 infection-naive patients. Similarly, Meijers *et al.* examined the differences in the immunogenicity to vector-based (ChAdOx1 nCoV-19) versus two mRNA-based vaccines (BNT162b2 and mRNA-1273) using samples collected as part of a prospective longitudinal study [9]. After two vaccine doses, 88.3%, 96.6%, and 100% of patients developed seroconversion with ChAdOx1 nCoV-19, BNT162b2, and mRNA-1273, respectively. Moreover, the third dose with either BNT162b2 or mRNA-1273 elicited a stronger humoral response than dual-dosing regimens. These findings support the current vaccine strategies to protect the Taiwanese dialysis population from COVID-19 [10].

In this study, we identified that patients taking immunosuppressive agents had an impaired humoral response after the third booster vaccination. Prior studies have also demonstrated that the concurrent use of immunosuppressants is a predictor of nonresponse [8,9]. Clearly, optimal strategies to improve immunogenicity in dialysis patients who use immunosuppressive agents, such as double-dose vaccination, booster doses, adjustments in adjuvants, or scheduling changes, are needed. Interestingly, we found that age remained an independent predictor for antispike antibody titers following the booster dose, which was inconsistent with previous studies showing a lack of such an association [8,9]. This discrepancy may result from differences in the characteristics of study populations among different studies. Our patients had a longer dialysis vintage than those in the other studies; hence, it may be reasonable to presume that our patients were physiologically frailer. We, therefore, hypothesized that immunosenescence may have been more closely related to physiological age than chronological age in this study [11].

Limitations

While the data have shown that administering three heterologous vaccines to hemodialysis patients over an extended period of time increased the chance of successful antibody seroconversion, this only applies to this specific population in this specific environment. Additional testing needs to be completed before we can say for certain that this vaccine protocol is also applicable to other patient populations.

Conclusion

Our results showed that a triple-dosing regimen, including homologous ChAdOx1 nCoV-19/ChAdOx1 nCoV-19 and a booster dose of mRNA-1273 with an extended interval, produced a significant humoral response among hemodialysis patients, with a significant increase in the antispike antibody titer. Future studies on the longevity of the immune response to COVID-19 vaccinations among hemodialysis patients are needed.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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