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Predictors and Dynamics of the Humoral and Cellular Immune Response to SARS-CoV-2 mRNA Vaccines in Hemodialysis Patients: A Multicenter Observational Study

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ABSTRACT

Background Preliminary evidence suggests patients on hemodialysis have a blunted early serological response to SARS-CoV-2 vaccination. Optimizing the vaccination strategy in this population requires a thorough understanding of predictors and dynamics of humoral and cellular immune responses to different SARS-CoV-2 vaccines.

Methods This prospective multicenter study of 543 patients on hemodialysis and 75 healthy volunteers evaluated the immune responses at 4 or 5 weeks and 8 or 9 weeks after administration of the BNT162b2 or mRNA-1273 vaccine, respectively. We assessed anti–SARS-CoV-2 spike antibodies and T cell responses by IFN-γ secretion of peripheral blood lymphocytes upon SARS-CoV-2 glycoprotein stimulation (QuantiFERON assay) and evaluated potential predictors of the responses.

Results Compared with healthy volunteers, patients on hemodialysis had an incomplete, delayed humoral immune response and a blunted cellular immune response. Geometric mean antibody titers at both time points were significantly greater in patients vaccinated with mRNA-1273 versus BNT162b2, and a larger proportion of them achieved the threshold of 4160 AU/ml, corresponding with high neutralizing antibody titers *in vitro* (53.6% versus 31.8% at 8 or 9 weeks, $P<0.0001$). Patients vaccinated with mRNA-1273 versus BNT162b2 exhibited significantly greater median QuantiFERON responses at both time points, and a larger proportion achieved the threshold of 0.15 IU/ml (64.4% versus 46.9% at 8 or 9 weeks, $P<0.0001$). Multivariate analysis identified COVID-19 experience, vaccine type, use of immunosuppressive drugs, serum albumin, lymphocyte count, hepatitis B vaccine nonresponder status, and dialysis vintage as independent predictors of the humoral and cellular responses.

Conclusions The mRNA-1273 vaccine's greater immunogenicity may be related to its higher mRNA dose. This suggests a high-dose vaccine might improve the impaired immune response to SARS-CoV-2 vaccination in patients on hemodialysis.

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The mortality of coronavirus disease 2019 (COVID-19) is particularly important in patients on hemodialysis, even after adjustment for age,[1] suggesting the uremic environment creates a background for a more severe disease course. As a result, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination of patients on hemodialysis has been prioritized in many

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countries. However, because patients on hemodialysis have been excluded from the large SARS-CoV-2 mRNA vaccine efficacy trials,[2,3] the ability of these vaccines to protect the hemodialysis population from the devastating consequences of COVID-19 is unknown.

Preliminary evidence suggests the early serological response to the BNT162b2 vaccine is blunted in patients on hemodialysis.[4–10] Whether this represents a lower intensity or slower maturation of the immune reaction is presently unclear. A balanced humoral and cellular immune response appears to be important for protection from COVID-19,[11] but data on the cellular immune response to SARS-CoV-2 vaccination in patients on hemodialysis are scarce and limited to small patient numbers.[12,13] Further, the different quantities of mRNA in the BNT162b2 (30 μg per dose) and mRNA-1273 (100 μg per dose) vaccines offers a unique opportunity to explore whether a higher-dose vaccine may result in a better immune response, but a systematic comparison of these vaccines in patients on hemodialysis has not been done. Finally, although advanced age appears to be associated with a reduced response to SARS-CoV-2 vaccination in some[4,5,8] but not all[14] studies, dialysis-specific factors responsible for the broad heterogeneity of the immune response have been incompletely defined. As such, we conducted a prospective multicenter observational study to assess the magnitude and time course of both humoral and cellular responses to two different SARS-CoV-2 mRNA vaccines and to identify clinical, biochemical, and immunologic predictors in a large, unselected, and well-characterized cohort of patients on hemodialysis.

COVID-19 experienced individuals, including health care workers,[15] nursing home residents,[16] and patients on dialysis[4–6,14] generally have an intense serological response to SARS-CoV-2 vaccination, indicating that a previous natural infection acts as an analog to immune priming. We therefore stratified our study population into patients who are COVID-19 naïve and COVID-19 experienced.

Significance Statement

Patients on hemodialysis characteristically have an impaired response to vaccination. This large multicenter cohort study found an incomplete and delayed humoral and a blunted cellular immune response to SARS-CoV-2 vaccination in patients on hemodialysis. Recipients of the mRNA-1273 vaccine had mean responses that were substantially larger than responses of BNT162b2 vaccine recipients, and were significantly more likely to achieve the higher antibody thresholds thought to be required for preventing infection. A multivariate analysis identified COVID-19 experience, vaccine type, use of immunosuppressive drugs, serum albumin, lymphocyte count, hepatitis B vaccine nonresponder status, and dialysis vintage as independent predictors of humoral and cellular responses. The strikingly better responses in mRNA-1273 recipients may be related to the vaccine's higher mRNA content, suggesting that a high-dose vaccine may help improve SARS-CoV-2 vaccine effectiveness in patients on hemodialysis.

METHODS

Trial Design and Participants

We conducted an investigator-driven, prospective clinical trial at four sites in Belgium (AZ Sint-Jan Brugge, Groeninge Ziekenhuis Kortrijk, Ziekenhuis Oost-Limburg Genk, OLV Ziekenhuis Aalst). The study was approved by the Institutional Review Boards in all participating sites and registered on EudraCT (number 2021–000930–32). Adults on chronic hemodialysis that agreed to SARS-CoV-2 vaccination and had not yet received a vaccine were eligible for inclusion. Adults aged 18–60 years, without known medical conditions, not taking any medication, and without serologic or virologic evidence of SARS-CoV-2 infection up to the day of vaccination were recruited as controls. This control group was chosen such as to quantify the "normal" immune response to SARS-CoV-2 vaccination in healthy adults. All participants provided written informed consent. Each participant received two intramuscular doses of either the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech, Mainz, Germany) 30 μg per dose with a 3-week interval, or the mRNA-1273 COVID-19 vaccine (Moderna, Cambridge, Massachusetts) 100 μg per dose with a 4-week interval. Allocation to the BNT162b2 or mRNA-1273 vaccine occurred at the discretion of the COVID-19 Task Force of the Department of Public Health and Surveillance of the federal Belgian State, independent of individual patient choice and characteristics.

Interventions and Measurements

Demographic, clinical, and biochemical data were systematically extracted from the electronic medical records at baseline (Supplemental Methods) and stored in the Electronic Data Capture system Castor. Blood samples were taken at baseline and at 4 and 8 weeks after the first vaccine dose in BNT162b2 recipients, and at 5 and 9 weeks after the first vaccine dose in mRNA-1273 recipients. In patients on dialysis, samples were drawn at the start of dialysis before the blood had contact with the dialyzer membrane.

Safety assessments included monitoring of solicited local and systemic adverse events for 7 days after each injection, unsolicited adverse reactions for 28 days after each injection, and adverse events leading to discontinuation after the first dose.

Humoral Immune Response

IgG antibodies, including neutralizing antibodies, to the receptor binding domain of the S1 subunit of the spike (S) protein of SARS-CoV-2 were determined in serum by a chemiluminescent microparticle immunoassay on the ARCHITECT i System according to the manufacturer's instructions (SARS-CoV-2 IgG II Quant assay, Abbott). The cutoff for positivity is 50 arbitrary units per ml (AU/ml).

A SARS-CoV-2 IgG concentration of 1050 AU/ml, 3550 AU/ml, 4160 AU/ml, and 6950 AU/ml corresponds to a 95% probability of being at or above a plaque reduction neutralization test with 50% inhibition of infection of cultured cells (PRNT50) dilution of 1:80, 1:160, 1:250, and 1:640, respectively.[17] On the basis of the results of the World Health Organization International Standard study,[18] the mathematical relationship of the Abbott unit (AU/ml) to the World Health Organization binding antibody units follows the equation: binding antibody units/ml = 0.142× AU/ml.[17]

The detection of serum IgG antibodies to the nucleocapsid (N) protein of SARS-CoV-2 was performed using a chemiluminescent microparticle immunoassay on the same ARCHITECT i analyzer (SARS-CoV-2 IgG assay, Abbott). A signal/cutoff ratio of ≥1.4 was interpreted as reactive.

Cellular Immune Response

Cellular immunogenicity was assessed by measuring the secretion of IFN-γ by peripheral blood lymphocytes upon SARS-CoV-2 glycoprotein stimulation using the QuantiFERON SARS-CoV-2 test (Qiagen). The QuantiFERON SARS-CoV-2 Starter Set contains two antigen tubes, SARS-CoV-2 antigen 1 and SARS-CoV-2 antigen 2, which use a combination of SARS-CoV-2–specific antigens, predominantly S-derived, to stimulate lymphocytes (CD4 by antigen 1, both CD4 and CD8 by antigen 2) in heparinized whole blood. The tubes were gently mixed with the whole blood, to resolubilize the contents that had been dried onto the inner walls. IFN-γ was measured by ELISA in plasma from the stimulated and incubated (37°C for 16–24 hours) samples. QuantiFERON Nil and Mitogen blood collection tubes were used as negative and positive controls, respectively. The threshold for positivity is 0.15 IU/ml.

Statistical Analysis

Data analyses were undertaken using SAS statistical software (release 9.4). Descriptive statistics used were proportions and frequencies, medians, and interquartile ranges. Given their high degree of skewness, distributions of anti–S IgG titers (geometric mean titers) and IFN-γ concentrations by QuantiFERON (geometric mean concentrations) were summarized according to their geometric means, calculated as the antilog of the mean of log10-transformed levels. Offsets of 10 AU/ml for anti–S IgG titers and 0.01 IU/ml for QuantiFERON levels were used before transformation. Characteristics were compared between BNT162b2 and mRNA-1273 recipients by means of the Mann–Whitney *U* test for continuous variables and Fisher's exact for categorical variables. Groups of patients who are COVID-19 naïve with humoral and cellular responses classified qualitatively as adequate or impaired were compared using the Kruskal–Wallis test and Fisher's exact test. Linear models were fitted to compare distributions of log10-transformed anti–S IgG titers and QuantiFERON levels between BNT162b2 and mRNA-1273 recipients (equivalent to *t* tests). Proportions of patients exceeding the different thresholds were compared using logistic models. To evaluate whether the effect of both vaccines was consistent across patients on hemodialysis and healthy volunteers, crossproducts of vaccine type and subject type were entered as an interaction term in these statistical models. To identify sets of significant predictors for impaired humoral and cellular responses, multivariate models were fitted following a stepwise approach with significance thresholds of 0.15 and 0.05 for entering and removing variables from the model. Model statistics shown here are regression coefficients (β), their standard errors, *T* statistics, and *P* values. Model fits were evaluated by graphical analysis of the Pearson residuals. Data were missing in <1% of patients for most potential predictors. However, the hepatitis B vaccine response status was unknown in 75 patients (13.8%). As a result, we used multiple imputation to replace these missing values by a chained equations method (SAS procedure PROC MI). We created 25 imputed datasets and fitted the linear models in each of these datasets. Point estimates and variances were then combined across all 25 datasets by applying Rubin's rule to obtain final model estimates (SAS procedure PROC MIANALYZE). Spearman rank correlations were calculated to characterize the strength of the association between anti–S IgG titers and QuantiFERON levels. Taking a positive QuantiFERON test as reference matching thresholds for anti–S IgG titers were identified by analysis of receiver operating characteristic curves for the patients on hemodialysis and healthy volunteers separately. Thresholds were obtained through determination of the Youden index, finding an optimal balance between sensitivity and specificity. Overall, a type I error level of α=0·05 was used to indicate statistical significance.

RESULTS

Participants

Vaccination coverage expressed as the overall proportion of patients on hemodialysis vaccinated in the participating dialysis centers was 98% (873 out of 894). Reasons for not receiving a vaccine were either medical (n=2) or patient choice (n=19). A total of 678 patients on hemodialysis was evaluated for inclusion and 569 were enrolled. A total of 26 patients was excluded because of incomplete follow-up (n=13), development of symptomatic or asymptomatic SARS-CoV-2 infection during the course of the study (n=7) or irregularities in vaccine administration (n=6) (Supplemental Figure 1). The final study population (n=543) was almost exclusively of western European ancestry, had a male to female distribution of 62% to 38%, a median age of 75 years, and a median dialysis vintage of 2.15 years. Baseline demographic and clinical characteristics

(Table 1) were similar between the BNT162b2 and mRNA-1273 recipients, except for the male to female distribution, causes of renal failure, and proportion of patients treated with hemodiafiltration. Baseline biochemical characteristics (Supplemental Table 1) and baseline maintenance medication (Supplemental Table 2) were comparable between the BNT162b2 and mRNA-1273 recipients.

From the group of healthy volunteers ($n=82$), seven individuals were excluded because of withdrawal of informed consent or evidence of SARS-CoV-2 infection at baseline or during the course of the study (Supplemental Figure 1). The remaining individuals ($n=75$) were exclusively of western European ancestry, with a male to female distribution of 51% to 49%, and median age of 40 years (range 24–60) in

Table 1. Demographic and clinical characteristics at baseline

Characteristics	All Patients ($n=543$)	BNT162b2 Recipients ($n=322$)	mRNA-1273 Recipients ($n=221$)	P[a]
Age, yrs	75 (65–82)	76 (66–82)	75 (65–82)	0.568
Age category, % (*n*)				
18 to <65 yrs	23 (126)	23 (73)	24 (53)	
65 to <85 yrs	63 (342)	64 (207)	61 (135)	
≥85 yrs	14 (75)	13 (42)	15 (33)	
Male, % (*n*)	62 (339)	67 (217)	55 (122)	0.005
Ethnicity, % (*n*)				0.834
White	96 (519)	95 (307)	96 (212)	
Other	4.4 (24)	4.7 (15)	4.1 (9)	
Nursing home resident, % (*n*)	1.8 (10)	2.5 (8)	0.9 (2)	0.212
BMI, kg/m^2	25.6 (22.5–29.1)	25.6 (22.6–28.9)	25.6 (22.4–29.4)	0.857
BMI ≥30 kg/m^2, % (*n*)	21 (112)	20 (64)	22 (48)	0.666
Smoking, % (*n*)				0.054
History of	43 (235)	42 (136)	45 (99)	
Active	13 (69)	16 (50)	8.6 (19)	
Comorbid disease, % (*n*)				
Coronary artery disease	36 (195)	40 (130)	29 (65)	0.011
Heart failure	21 (115)	24 (77)	17 (38)	0.069
Cerebrovascular disease	21 (112)	21 (66)	21 (46)	1.000
Peripheral vascular disease	20 (108)	22 (72)	16 (36)	0.100
Abdominal vascular disease	9.2 (50)	11 (34)	7.2 (16)	0.227
COPD	9.9 (54)	9.3 (30)	11 (24)	0.562
Diabetes type 1, type 2	39 (212)	39 (125)	39 (87)	0.929
Liver disease	2.8 (15)	3.4 (11)	1.8 (4)	0.300
Immunodeficiency	8.1 (44)	9.0 (29)	6.8 (15)	0.424
Malignancy	16 (87)	19 (61)	12 (26)	0.032
Hepatitis B vaccine nonresponder	11 (53)	12 (32)	11 (21)	1.000
Influenza vaccination in 2020	91 (491)	92 (296)	88 (195)	0.231
ESRD causes, % (*n*)				0.001
Diabetes	24 (132)	24 (76)	25 (56)	
Vascular disease	34 (185)	30 (96)	40 (89)	
Glomerular disease	15 (82)	15 (49)	15 (33)	
Tubulointerstitial disease	6.3 (34)	8.7 (28)	2.7 (6)	
ADPKD or other genetic disease	5.7 (31)	4.7 (15)	7.2 (16)	
Other	15 (79)	18 (58)	9.5 (21)	
Dialysis vintage, yrs	2.15 (0.98–4.39)	2.05 (0.96–4.47)	2.30 (1.03–4.32)	0.559
Hemodiafiltration, % (*n*)	58 (316)	68 (219)	44 (97)	<0.001
Online Kt/V urea	1.35 (1.18–1.60)	1.35 (1.15–1.62)	1.35 (1.20–1.53)	0.684
Medication, % (*n*)				
ACEI/ARB	28 (154)	29 (94)	27 (60)	0.629
Immunosuppressive drugs	11 (57)	12 (37)	9.0 (20)	0.395
SARS-CoV-2 experienced, % (*n*)				
Overall	12 (65)	12 (37)	13 (28)	0.688
PCR confirmed	7.6 (41)	6.8 (22)	8.6 (19)	0.509
Anti–N/anti–S IgG at baseline	11 (59)	10 (33)	12 (26)	0.578
QuantiFERON at baseline	5.3 (29)	5.6 (18)	5.0 (11)	0.847

Numbers displayed are median (interquartile range) unless otherwise specified. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ADPKD, autosomal dominant polycystic kidney disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; N, nucleocapsid; S, spike.

[a]According to Fisher's exact test or Mann–Whitney *U* test.

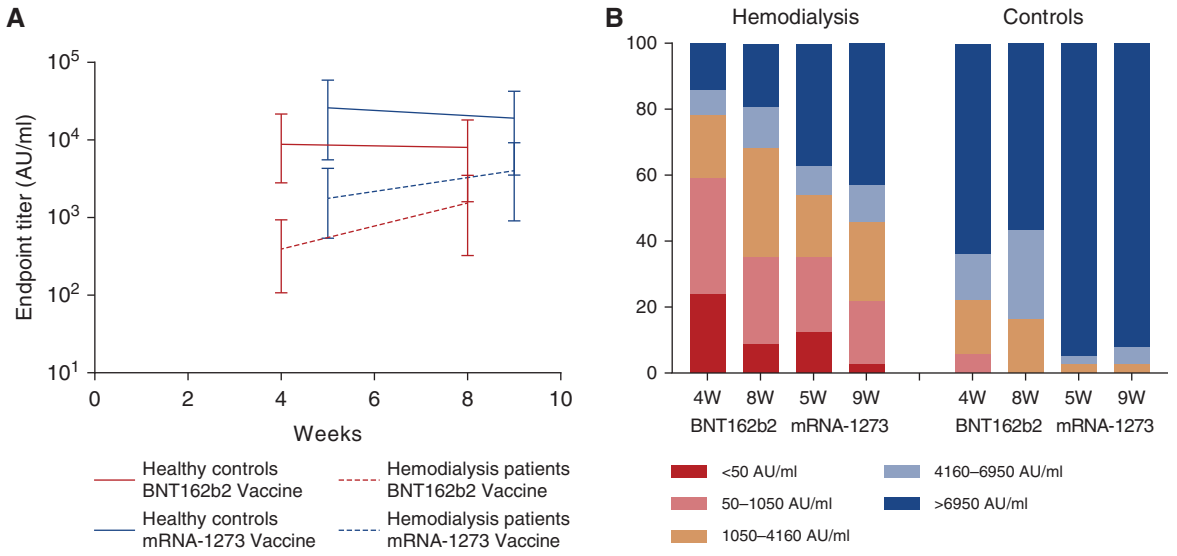

Figure 1. Humoral immune response. (A) Geometric mean titers (95% confidence intervals) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antibody at week 4 and week 8 after BNT162b2 vaccination in patients on hemodialysis (red dashed line) and healthy volunteers (red solid line), and at week 5 and week 9 after mRNA-1273 vaccination in patients on hemodialysis (blue dashed line) and healthy volunteers (blue solid line). (B) Proportion of patients on hemodialysis and controls with SARS-CoV-2 spike antibody levels within a given range 4 or 5 weeks and 8 or 9 weeks after BNT162b2 or mRNA-1273 vaccination.

the BNT162b2 recipients (n=37), and a male to female distribution of 58% to 42% and median age of 36 years (range 18–59) in the mRNA-1273 recipients (n=38).

COVID-19 experienced subjects (n=65) were identified by a history of a positive SARS-CoV-2 PCR (n=41), positive anti–S IgG at baseline (n=47), positive anti–N IgG at baseline (n=43), a positive QuantiFERON test (defined as ≥0.15 IU/ml for both antigen 1 and antigen 2) at baseline (n=29), or a combination of these. The proportion of COVID-19 experienced subjects was similar in BNT162b2 and mRNA-1273 recipients. The median time interval between PCR-proven infection to baseline sampling was 154 days (interquartile range, 124–338). Patients were stratified into three groups on the basis of severity of disease: those identified by positive baseline anti–S IgG, anti–N IgG, or QuantiFERON levels without history of PCR-documented infection (n=24), those with history of PCR-documented infection and asymptomatic or mildly symptomatic disease (n=24), and those with history of PCR-documented infection and severe disease requiring hospitalization (n=17).

Patients that acquired a SARS-CoV-2 infection after the first vaccine dose (n=7) were identified by a positive SARS-CoV-2 PCR or development of anti–N IgG (because this

Table 2. Humoral immune response: Geometric mean titers

	Hemodialysis (n=543)			Healthy Volunteers (n=75)			P[a]
	BNT162b2 Recipients (n=322)	mRNA-1273 Recipients (n=221)	P	BNT162b2 Recipients (n=37)	mRNA-1273 Recipients (n=38)	P	
Overall							
Baseline	4	4	0.244	3	3	0.622	0.556
4 or 5 weeks	393	1757	<0.0001	8779	26,007	<0.0001	0.537
8 or 9 weeks	1536	4037	<0.0001	8060	19,069	<0.0001	0.824
COVID-19 naïve							
Baseline	3	2	<0.0001	3	3	0.622	0.045
4 or 5 weeks	258	1230	<0.0001	8779	26,007	<0.0001	0.447
8 or 9 weeks	1143	3147	<0.0001	8060	19,069	<0.0001	0.731
COVID-19 experienced							
Baseline	174	210	0.787	–	–	–	–
4 or 5 weeks	9995	20,455	0.248	–	–	–	–
8 or 9 weeks	14,928	22,464	0.398	–	–	–	–

COVID-19, coronavirus disease 2019.
[a]Testing the interaction between vaccine type and subject type.

Table 3. Humoral immune response: Proportion of patients with titer above threshold

	Hemodialysis (*n*=543)			Healthy Volunteers (*n*=75)			*P*[a]
	BNT162b2 Recipients (*n*=322)	mRNA-1273 Recipients (*n*=221)	*P*	BNT162b2 Recipients (*n*=37)	mRNA-1273 Recipients (*n*=38)	*P*	
% >50 AU/ml							
4 or 5 weeks	76.5% (248)	87.8% (195)	0.0014	100.0% (37)	100.0% (38)	–	0.996
8 or 9 weeks	92.3% (299)	97.7% (217)	0.0095	100.0% (37)	100.0% (38)	–	0.994
% >1050 AU/ml							
4 or 5 weeks	41.0% (133)	64.9% (144)	<0.0001	94.6% (35)	100.0% (38)	0.942	0.958
8 or 9 weeks	65.7% (213)	78.8% (175)	0.0010	100.0% (37)	100.0% (38)	–	0.997
% >3550 AU/ml							
4 or 5 weeks	24.7% (80)	46.4% (103)	<0.0001	83.8% (31)	97.4% (37)	0.075	0.374
8 or 9 weeks	35.5% (115)	59.0% (131)	<0.0001	91.9% (34)	100.0% (38)	0.953	0.956
% >4160 AU/ml							
4 or 5 weeks	21.6% (70)	46.4% (103)	<0.0001	78.4% (29)	97.4% (37)	0.033	0.287
8 or 9 weeks	31.8% (103)	53.6% (119)	<0.0001	83.8% (31)	97.4% (37)	0.075	0.358
% >6950 AU/ml							
4 or 5 weeks	14.2% (46)	37.4% (83)	<0.0001	64.9% (24)	94.7% (36)	0.0046	0.235
8 or 9 weeks	9.1% (62)	42.3% (94)	<0.0001	56.8% (21)	92.1% (35)	0.0015	0.157

[a]Testing the interaction between vaccine type and subject type.

antibody is specific to infection and not induced by vaccination) and excluded from further analysis. Six patients acquired PCR-positive COVID-19 with a median time between the first vaccine dose and diagnosis of 24.5 days (range 0–32). Three patients were symptomatic, of whom two were hospitalized, with one death. One patient had an asymptomatic anti–N IgG seroconversion 8 weeks after the first vaccine dose without documented positive PCR.

Immune Responses

Geometric mean antibody titers were substantially lower in patients on hemodialysis than in healthy volunteers at both time points (Figure 1A, Table 2). In healthy volunteers, the peak response was achieved at 4–5 weeks with stable values thereafter, whereas antibody titers continued to rise in patients on hemodialysis. The large differences between patients on hemodialysis and healthy volunteers were evident for each age category (Supplemental Figure 2A), indicating the different age distribution of both populations is insufficient to explain the disparity. Responses in patients who were COVID-19 experienced and on hemodialysis were similar to those in the COVID-19 naïve healthy volunteers. Although the large majority of patients on hemodialysis seroconverted (anti–S IgG >50 AU/ml), incremental antibody thresholds were achieved in declining proportions of patients (Figure 1B, Table 3, Supplemental Table 3). The serologic responses elicited by the mRNA-1273 vaccine were significantly greater than those induced by the BNT162b2 vaccine in both patients on hemodialysis and healthy volunteers. There was no evidence for an interaction between vaccine type and subject type.

Multivariate analyses were undertaken to determine the pattern of predictors of the immune response in patients on hemodialysis (Tables 4 and 5). COVID-19 experience, vaccine type, use of immunosuppressive drugs, serum

Table 4. Multivariate analysis of factors associated with humoral response in all patients on hemodialysis

Variable[a]	Humoral Response at 4 or 5 wks[b]			Humoral Response at 8 or 9 wks[b]		
	β (SE)	*T* statistic	*P*	β (SE)	*T* statistic	*P*
SARS-CoV-2 experienced	+1.391 (0.141)	+9.87	<0.0001	+0.967 (0.101)	+9.59	<0.0001
Immunosuppressive drugs	−0.741 (0.152)	−4.89	<0.0001	−0.671 (0.108)	−6.20	<0.0001
Vaccine type (mRNA-1273)	+0.548 (0.093)	+5.90	<0.0001	+0.335 (0.066)	+5.04	<0.0001
Serum albumin	+0.053 (0.015)	+3.67	0.0002	+0.048 (0.010)	+4.59	<0.0001
Ln (lymphocyte count)	+0.472 (0.104)	+4.53	<0.0001	+0.271 (0.075)	+3.63	0.0003
Dialysis vintage	−0.030 (0.013)	−2.37	0.018	−0.025 (0.009)	−2.79	0.0052
IgG	+0.038 (0.015)	+2.58	0.010	+0.029 (0.010)	+2.73	0.0063
Hepatitis B vaccine nonresponder	−0.421 (0.153)	−2.74	0.0061	−0.289 (0.111)	−2.60	0.0094
Age	−0.018 (0.004)	−5.07	<0.0001	−0.004 (0.003)	−1.55	0.122

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Ranked according to T-statistic at 8–9 weeks.
[b]Log_{10}-transformed.

Table 5. Multivariate analysis of factors associated with humoral response in patients who are COVID-19 naive and on hemodialysis

Variable[a]	Humoral Response at 4 or 5 wks[b]			Humoral response at 8 or 9 wks[b]		
	β (SE)	T Statistic	P	β (SE)	T Statistic	P
Immunosuppressive drugs	−0.769 (0.154)	−4.99	<0.0001	−0.707 (0.110)	−6.43	<0.0001
Vaccine type (mRNA-1273)	+0.603 (0.097)	+6.22	<0.0001	+0.377 (0.069)	+5.46	<0.0001
Serum albumin	+0.053 (0.015)	+3.42	0.0006	+0.045 (0.011)	+4.09	<0.0001
Ln (lymphocyte count)	+0.503 (0.108)	+4.64	<0.0001	+0.271 (0.077)	+3.51	0.0005
IgG	+0.043 (0.016)	+2.74	0.0062	+0.038 (0.011)	+3.43	0.0006
Hepatitis B vaccine nonresponder	−0.468 (0.171)	−2.74	0.0065	−0.321 (0.117)	−2.74	0.0062
Dialysis vintage	−0.028 (0.013)	−2.18	0.029	−0.025 (0.009)	−2.66	0.0079
Age	−0.023 (0.004)	−6.23	<0.0001	−0.007 (0.003)	−2.59	0.0097

[a]Ranked according to T-statistic at 8 or 9 weeks.
[b]Log_{10}-transformed.

albumin, lymphocyte count, immunoglobulin G levels, hepatitis B vaccine nonresponder status, and dialysis vintage were identified as independent predictors of the serological response at 4 or 5 weeks and at 8 or 9 weeks, whereas age was an independent predictor of the immune response at 4 or 5 weeks only.

Mean QuantiFERON responses to antigen 2 were markedly lower in patients on hemodialysis than in healthy volunteers at both time points (Figure 2, Table 6). The QuantiFERON response to antigen 1 followed a similar trajectory than the response to antigen 2 (Supplemental Figure 3, Supplemental Table 4). In both healthy volunteers and patients on hemodialysis, the response peaked at 4 or 5 weeks, followed by a decline at 8 or 9 weeks. The large differences between patients on hemodialysis and healthy volunteers were evident for each age category (Supplemental Figure 2B). The mean QuantiFERON responses elicited by the mRNA-1273 vaccine were significantly greater than those induced by the BNT162b2 vaccine in both patients on hemodialysis and healthy volunteers. There was no evidence for an interaction between vaccine type and subject type. Among the patients on hemodialysis, a significantly greater proportion of mRNA-1273 recipients than BNT162b2 recipients exceeded the threshold of positivity (0.15 IU/ml) at 8 or 9 weeks.

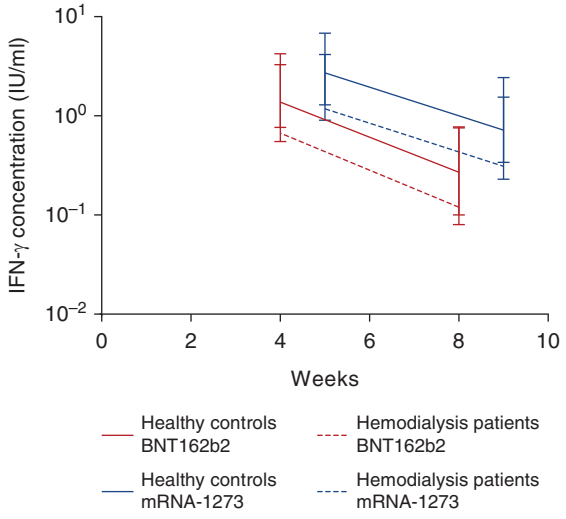

Figure 2. Cellular response. Median (interquartile range) QuantiFERON response to antigen 2 at week 4 and week 8 after BNT162b2 vaccination in patients on hemodialysis (red dashed line) and healthy volunteers (red solid line) and at week 5 and week 9 after mRNA-1273 vaccination in patients on hemodialysis (blue dashed line) and healthy volunteers (blue solid line).

Multivariate analyses identified COVID-19 experience, vaccine type, use of immunosuppressive drugs, serum albumin, lymphocyte count, dialysis vintage, and hepatitis B vaccine nonresponder status as independent predictors of the cellular response at 4 or 5 weeks and at 8 or 9 weeks (Tables 7 and 8). Age was not an independent predictor of the cellular response at 4 or 5 weeks and at 8 or 9 weeks.

Anti–S IgG titers and QuantiFERON levels were strongly related, with Spearman correlations of +0.57 and +0.44 in patients on hemodialysis and healthy volunteers respectively (Figure 3). Receiver operating characteristic analysis revealed anti–S IgG titers levels of 2000 AU/ml in patients on hemodialysis and 10.000 AU/ml in healthy volunteers as optimal thresholds matching QuantiFERON levels of ≥0.15 IU/ml.

Only 26% of patients who were COVID-19 naïve and on hemodialysis had an adequate immune response to vaccination, defined as anti–S IgG titers >4160 AU/ml and QuantiFERON levels ≥0.15 IU/ml. This population was younger and comprised fewer males and fewer hepatitis B vaccine nonresponders. Peripheral vascular disease, chronic obstructive pulmonary disease, and immunosuppressive drug use were less common. They had a higher serum albumin and lymphocyte count and more had received the mRNA-1273 vaccine (Supplemental Table 5).

A multivariate logistic model analyses of factors associated with a combined impaired humoral and cellular response, defined as anti–S IgG titers ≤4160 AU/ml and QuantiFERON levels <0.15 IU/ml at 8 or 9 weeks, identified diabetes as an independent predictor in addition to the already recognized risk factors (Supplemental Table 6).

Table 6. Cellular response (antigen 2)

	Hemodialysis (*n*=543)			Healthy Volunteers (*n*=75)			
	BNT162b2 Recipients (*n*=322)	mRNA-1273 Recipients (*n*=221)	*P*	BNT162b2 Recipients (*n*=37)	mRNA-1273 Recipients (*n*=38)	*P*	*P*[a]
GMC							
Overall							
Baseline	0.016	0.018	0.216	0.016	0.013	0.162	0.236
4 or 5 weeks	0.497	0.809	0.0035	1.106	2.091	0.018	0.742
8 or 9 weeks	0.151	0.300	<0.0001	0.293	0.727	0.0005	0.607
COVID-19 naïve							
Baseline	0.012	0.013	0.040	0.016	0.013	0.162	0.026
4 or 5 weeks	0.430	0.739	0.0019	1.106	2.091	0.018	0.829
8 or 9 weeks	0.130	0.256	<0.0001	0.293	0.727	0.0005	0.580
COVID-19 experienced							
Baseline	0.129	0.135	0.929	–	–	–	–
4 or 5 weeks	1.487	1.614	0.869	–	–	–	–
8 or 9 weeks	0.519	1.095	0.160	–	–	–	–
% ≥0.15 IU/ml							
Overall							
4 or 5 weeks	72.1% (230/319)	81.0% (175/216)	0.019	91.7% (33/36)	94.6% (35/37)	0.674	0.969
8 or 9 weeks	46.9% (145/309)	64.4% (134/208)	<0.0001	78.4% (29/37)	86.8% (33/38)	0.375	0.856
COVID-19 naïve							
4 or 5 weeks	70.6% (199/282)	80.6% (154/191)	0.0136	91.7% (33/36)	94.6% (35/37)	0.674	0.928
8 or 9 weeks	42.9% (118/275)	62.7% (116/185)	<0.0001	78.4% (29/37)	86.8% (33/38)	0.375	0.752
COVID-19 experienced							
4 or 5 weeks	83.8% (31/37)	84.0% (21/25)	0.999	–	–	–	–
8 or 9 weeks	79.4% (27/34)	78.3% (18/23)	0.999	–	–	–	–

COVID-19, coronavirus disease 2019.
[a]Testing the interaction between vaccine type and subject type.

In COVID-19 experienced subjects, the humoral and cellular response to vaccination significantly increased with growing severity of historic natural SARS-CoV-2 infection (Supplemental Table 7).

Safety Outcomes

Solicited systemic adverse events and reactions at the injection site occurred more frequently in patients on hemodialysis that received a mRNA-1273 vaccine than in those that received a BNT162b2 vaccine (P=0.001 for at least one side effect) and in healthy volunteers versus patients on hemodialysis (P<0.001 for at least one side effect) (Figure 4). One patient on hemodialysis developed a severe and generalized rash 3 days after receiving the first dose of the BNT162b2 vaccine. After 3 weeks, a single dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca, Oxford, United Kingdom) was administered without further events.

DISCUSSION

This comprehensive analysis of the humoral and cellular immune response in a large cohort of well-characterized patients on hemodialysis reveals an incomplete and delayed

Table 7. Multivariate analysis of factors associated with cellular response (antigen 2) in all patients on hemodialysis

Variable[a]	QuantiFERON at 4 to 5 wks[b]			QuantiFERON at 8 to 9 wks[b]		
	β (SE)	*T* statistic	*P*	β (SE)	*T* statistic	*P*
SARS-CoV-2 experienced	+0.506 (0.102)	+4.94	<0.0001	+0.647 (0.103)	+6.28	<0.0001
Serum albumin	+0.039 (0.010)	+3.75	0.0002	+0.042 (0.011)	+3.94	<0.0001
Immunosuppressive drugs	−0.570 (0.110)	−5.19	<0.0001	−0.401 (0.107)	−3.73	0.0002
Vaccine type (mRNA-1273)	+0.136 (0.067)	+2.01	0.044	+0.219 (0.067)	+3.28	0.0010
Ln (lymphocyte count)	+0.338 (0.074)	+4.54	<0.0001	+0.239 (0.074)	+3.24	0.0012
Dialysis vintage	−0.031 (0.009)	−3.30	0.001	−0.022 (0.009)	−2.37	0.018
Hepatitis B vaccine nonresponder	−0.261 (0.112)	−2.32	0.021	−0.244 (0.106)	−2.29	0.022
Age	+0.001 (0.003)	+0.57	0.572	+0.001 (0.002)	+0.38	0.704

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Ranked according to *T* statistic at 8 or 9 weeks.
[b]Log_{10}-transformed.

Table 8. Multivariate analysis of factors associated with cellular response (antigen 2) in patients who are COVID-19 naive and on hemodialysis

Variable[a]	QuantiFERON at 4 or 5 wks[b]			QuantiFERON at 8 or 9 wks[b]		
	β (SE)	*T* statistic	*P*	β (SE)	*T* statistic	*P*
Serum albumin	+0.041 (0.011)	+3.64	0.0003	+0.044 (0.011)	+4.02	<0.0001
Immunosuppressive drugs	−0.579 (0.113)	−5.11	<0.0001	−0.403 (0.110)	−3.65	0.0003
Vaccine type (mRNA-1273)	+0.161 (0.071)	+2.28	0.022	+0.224 (0.069)	+3.22	0.0013
Ln (lymphocyte count)	+0.377 (0.078)	+4.86	<0.0001	+0.241 (0.076)	+3.15	0.0016
Dialysis vintage	−0.033 (0.010)	−3.41	0.0007	−0.023 (0.009)	−2.47	0.014
Hepatitis B vaccine non-responder	−0.267 (0.114)	−2.35	0.019	−0.211 (0.120)	−1.76	0.079
Age	+0.000 (0.003)	−0.14	0.891	−0.002 (0.003)	−0.60	0.550

COVID-19, coronavirus disease 2019.
[a]Ranked according to *T* statistic at 8 or 9 weeks.
[b]Log_{10}-transformed.

humoral immune response, and a blunted cellular immune response. The salient observation is that the immunogenicity of the mRNA-1273 vaccine was significantly greater than that of the BNT162b2 vaccine, creating an opportunity to optimize the vaccination strategy in the hemodialysis population. The tolerance of the mRNA vaccines was excellent and no serious adverse events were reported.

Humoral immune responses to SARS-CoV-2 are mediated by antibodies that are directed to viral surface glycoproteins, mainly the S glycoprotein and the N protein. Although the relationship between antibody titers and effector function is poorly understood,[19] current insight is that neutralizing antibody levels may serve as an immune correlate of protection from infection.[20] Modeling of data obtained from vaccine trials and a convalescent cohort demonstrated a strong correlation between mean neutralizing antibody levels and protective efficacy,[20] suggesting the higher the antibody levels, the better the protection from infection. Conversely, results from a community-based surveillance study revealed a switch-like relationship between antibody levels and function,[19] implying that a distinct threshold of protective immunity may exist. We therefore assessed the geometric mean titers and the proportion of patients that developed a response above incremental prespecified cutoff values shown to correlate with virus neutralization *in vitro*. Although most patients on dialysis seroconverted (*i.e.*, developed an antibody titer >50 AU/ml, the cutoff for positivity of the test), only a minority achieved a threshold value of >4160 AU/ml, which corresponds with a 95% probability of high neutralizing antibody titers.[15] Peak antibody titers in healthy volunteers occurred at 4 or 5 weeks, whereas those in patients on hemodialysis continued to rise, indicating the serological responses in patients on hemodialysis are not only blunted, but also delayed. The relevance of these findings is supported

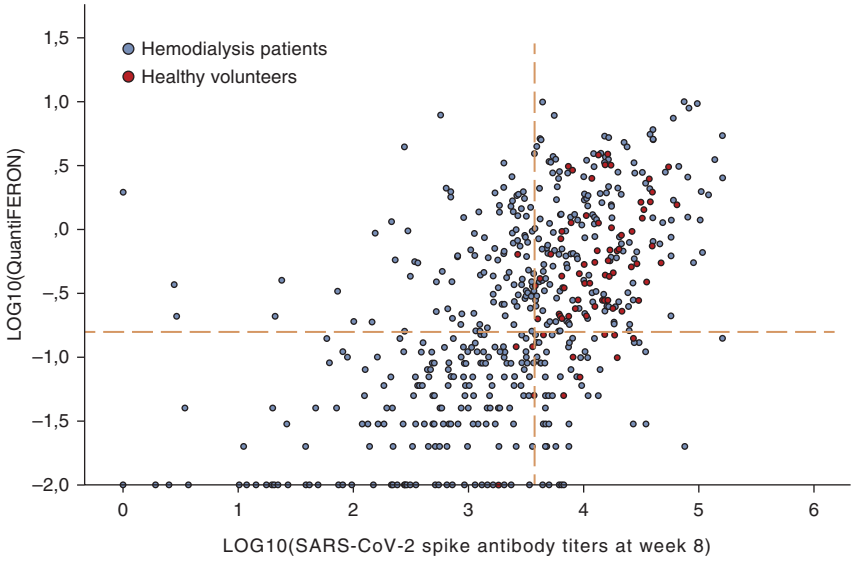

Figure 3. Correlation between the humoral and cellular immune response. Correlation between SARS-CoV-2 spike antibody titers and QuantiFERON at week 8 or 9 in patients on hemodialysis (blue) and healthy volunteers (red). The dashed lines represent the cutoffs of 4160 AU/ml and 0.15 IU/ml, respectively. The threshold of 4160 AU/ml corresponds with a 95% probability of high neutralizing antibody titer (PRNT50 at a 1:250 dilution).

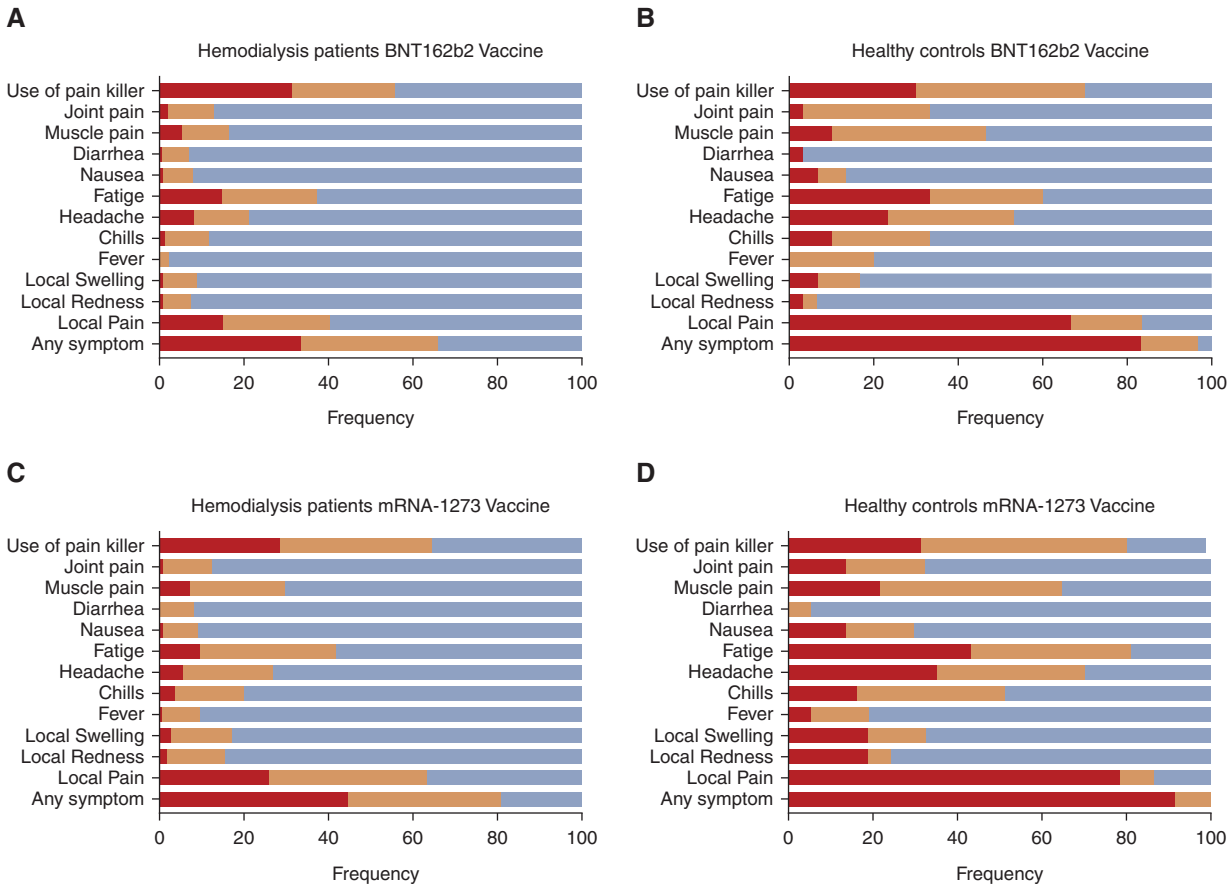

Figure 4. Frequency of local and systemic solicited side effects. Relative frequency of solicited local and systemic reactions for 7 days after each vaccine dose in the hemodialysis group for the BNT162b2 (A) and mRNA-1273 vaccine (C), and the control group for the BNT162b2 (B) and mRNA-1273 vaccine (D). The panels show the combined postvaccination 1 and postvaccination 2 periods, with the proportion of participants that reported the side effect in one of both periods displayed in brown and the proportion of participants that reported the same side effect in both periods displayed in red.

by a detailed analysis of seroconversion kinetics and COVID-19 disease outcomes, revealing that a delayed antibody response is associated with fatal disease.[21]

The particular cellular signature required for protection against SARS-CoV-2 is unknown. We assessed the cellular immune response by quantifying the IFN-γ released by peripheral blood CD4 and CD8 T cells after SARS-CoV-2 glycoprotein stimulation, an adequate measure of cell-mediated immunity against other viruses.[22] The mean IFN-γ production and the proportion of individuals exceeding the threshold for positivity was substantially lower among patients on hemodialysis than among healthy volunteers. Our results are at variance with those obtained in a small cohort of 26 patients on hemodialysis, which did not reveal a profound impairment in spike-specific CD4 and CD8 T cell responses and effector cytokine production versus controls,[12] possibly because of differences in technique used (an ELISA-based IFN-γ release assay versus a homemade T cell stimulation assay on the basis of fluorescence-activated cell sorting) and timing of sampling.

Patients on hemodialysis characteristically have less robust responses to vaccines, including pneumococcal, hepatitis B, and influenza vaccines, with lower seroconversion rates and more rapid decline of antibody titers as compared with healthy volunteers.[23] A high prevalence of false-negative tuberculin skin tests has also been reported.[24] Due to the paucity of adequately performed clinical trials, it remains uncertain to what extent these findings translate into higher rates of disease and mortality. We found the response to SARS-CoV-2 vaccination was strongly impaired in hepatitis B vaccine nonresponders independent of other predictors, indicating these patients represent a subpopulation with altered immunity. Strategies to improve vaccine immunogenicity in patients on hemodialysis, including increased vaccine doses, booster doses, adjuvants, and intradermal delivery, have been variably successful. The immune response in mRNA-1273 recipients was remarkably better than in BNT162b2 recipients. The allocation to the BNT162b2 or mRNA-1273 vaccine was determined by the Belgian government and occurred independently of

individual patient choice and characteristics. Although a systematic bias cannot be ruled out in the absence of randomization, it can assumed to be minimal. Both vaccines consist of mRNA encoding for the SARS-CoV-2 spike glycoprotein encapsulated in lipid nanoparticles, that protect the RNA from degradation by RNAses and enable transfection of host cells, with no other content relevant to immunogenicity.[25,26] We therefore submit that the presence of a higher mRNA dose in the mRNA-1273 vaccine (100 μg) than in the BNT162b2 vaccine (30 μg) is the most plausible explanation for our observations. The better immunogenicity of the mRNA-1273 than of the BNT162b2 vaccine was also observed in our control group and in a recent study of solid organ transplant recipients.[27] It could be argued that these differences may not be clinically relevant, because the large randomized trials in healthy participants did not reveal a disparity in the efficacy of the BNT162b2 and mRNA-1273 vaccines, demonstrating near-maximal protection against symptomatic SARS-CoV-2 infection with reduction rates of 95%[2] and 94%,[3] respectively. However, the high reported efficacies are on the basis of short-term data and waning over time may uncover differences between the respective vaccines. Further, adequate protection against the SARS-CoV-2 variants of concern may require higher levels of immunity. Recent data revealed that the neutralizing activity of serum from patients who were vaccinated was only mildly reduced against B.1.1.7 (α), but 5–12-fold lower against B.1.351 (β), five-fold lower against P.1 (γ), and six-fold lower against B.1.617.2 (δ), compared with the activity against wild-type viruses.[28,29(preprint),30] Finally, and of most relevance to the hemodialysis and other vulnerable populations, these differences may translate into clinically meaningful levels of protective immunity in patients with blunted immune responses. Modeling of the duration of immune protection after vaccination revealed nonlinear effects on the level of protection from SARS-CoV-2 infection, even if different vaccines are associated with a similar decay of neutralization titer.[20] As an example, an initial efficacy of 95% would be maintained at 77% 250 days after vaccination, whereas an initial efficacy of 70% would drop to 33% at the same point in time.[20]

We observed a striking heterogeneity in antibody titers and QuantiFERON levels across our hemodialysis population. In agreement with other studies,[4–6,14] COVID-19 experience was associated with a strong vaccine-induced response in patients on hemodialysis. In healthy volunteers with pre-existing immunity, the antibody response to the first vaccine dose is equal to titers observed in COVID-19 naïve individuals after the second dose,[15] hence the suggestion to give these individuals only one dose of vaccine. This policy may not apply to the dialysis population, because the response in patients who are COVID-19 experienced and on dialysis was similar in intensity but did not exceed that of COVID-19 naïve healthy volunteers. Other independent predictors besides COVID-19 experience and vaccine type, were use of immunosuppressive drugs, serum albumin, lymphocyte count, hepatitis B nonresponder status, and dialysis vintage, with remarkable concordance of the effect on humoral and cellular immunity. Not unsurprisingly, IgG levels only predicted the serological and not the cellular response. Somewhat counterintuitively, age had no independent effect on the cellular immunogenicity of SARS-CoV-2 vaccination and on the humoral response at 8 or 9 weeks. It is tempting to speculate that premature immunosenescence in patients on hemodialysis, caused by uremia, gut dysbiosis, and oxidative stress,[31] overrules the effects of chronological age.

Our study has several strengths. It is the largest to describe the humoral and cellular immune response to SARS-CoV-2 vaccination in patients on hemodialysis. Detailed data on key patient characteristics, comorbid conditions, and use of immunosuppressant medications were available, allowing the identification of independent predictors of the immune response. A limitation is that our study population was not ethnically diverse, which may reduce the generalizability of our findings. Our study was not designed or powered to assess the effect of vaccination on the incidence of COVID-19. SARS-CoV-2 infections were limited in number and occurred early after vaccination. The estimated neutralization level for protection from severe infection is thought to be approximately six-fold lower than the level required to protect from any symptomatic infection.[20] Longer follow-up in larger populations with statistical modeling to account for the dynamics of the epidemic and the effect of the virus variants will be required to evaluate the effect of vaccination on COVID-19–related hospitalization rates and mortality in patients on hemodialysis. Pending data from such studies, continued emphasis on droplet-infection control measures, and vaccination of caregivers and close contacts is recommended. Such an approach has already been shown to afford protection of unvaccinated residents in the nursing home setting.[32]

In conclusion, the immune response to SARS-CoV-2 vaccination is significantly impaired in patients on hemodialysis. The strikingly different responses in BNT162b2 and mRNA-1273 recipients suggest that an initial high-dose vaccine may be a valid strategy to improve vaccine effectiveness in vulnerable populations. Future analysis of the longevity of the immune response to vaccination will allow the determination of the potential additional role of booster doses.[33]

DISCLOSURES

A. De Bel reports consultancy agreements with Belac. A. De Vriese reports consultancy agreements with Amgen; reports receiving research funding from Amgen, Kaydence Pharma, and Nattopharma; reports receiving honoraria from Amgen, and Baxter; reports being a scientific

advisor or member of with Ablynck, Alexion, Amgen, Catenion, Navigant, and Novartis; and reports receiving speakers bureau from Amgen and Baxter. B. Van Vlem reports consultancy agreements with Amgen, Astellas, and Baxter. D. Steensels reports receiving research funding from Roche Diagnostics International Ltd. All remaining authors have nothing to disclose. The funding source had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021070908/-/DCSupplemental.

Supplemental Methods.

Supplemental Table 1. Laboratory parameters at baseline.

Supplemental Table 2. Baseline immunosuppressant medication.

Supplemental Table 3. Humoral response in patients who are COVID-19 naïve: proportion of patients with titer above threshold.

Supplemental Table 4. Cellular response (antigen 1).

Supplemental Table 5. Characteristics of patients with adequate and impaired response.

Supplemental Table 6. Multivariate analysis of factors associated with combined impaired humoral and cellular response at 8 or 9 weeks.

Supplemental Table 7. Immune response at 8 or 9 weeks in patients who are COVID-19 experienced and on dialysis according to disease severity.

Supplemental Figure 1. Study flow chart.

Supplemental Figure 2. Immune response by age category.

Supplemental Figure 3. Cellular response (antigen 1).

REFERENCES

1. De Meester J, De Bacquer D, Naesens M, Meijers B, Couttenye MM, De Vriese AS; NBVN Kidney Registry Group: Incidence, characteristics, and outcome of COVID-19 in adults on kidney replacement therapy: A regionwide registry study. *J Am Soc Nephrol* 32: 385–396, 2021
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group: Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 383: 2603–2615, 2020
3. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al.; COVE Study Group: Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 384: 403–416, 2021
4. Attias P, Sakhi H, Rieu P, Soorkia A, Assayag D, Bouhroum S, et al.: Antibody response to the BNT162b2 vaccine in maintenance hemodialysis patients. *Kidney Int* 99: 1490–1492, 2021
5. Billany RE, Selvaskandan H, Adenwalla SF, Hull KL, March DS, Burton JO, et al.: Seroprevalence of antibody to S1 spike protein following vaccination against COVID-19 in patients receiving hemodialysis: A call to arms. *Kidney Int* 99: 1492–1494, 2021
6. Goupil R, Benlarbi M, Beaubien-Souligny W, Nadeau-Fredette AC, Chatterjee D, Goyette G, et al.; Réseau Rénal Québécois (Quebec Renal Network) COVID-19 Study Investigators: Short-term antibody response after 1 dose of BNT162b2 vaccine in patients receiving hemodialysis. *CMAJ* 193: E793–E800, 2021
7. Simon B, Rubey H, Treipl A, Gromann M, Hemedi B, Zehetmayer S, et al.: Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls. *Nephrol Dial Transplant* 27: 1709–1716, 2021
8. Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al.; Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. *Clin J Am Soc Nephrol* 16: 1037–1042, 2021
9. Torreggiani M, Blanchi S, Fois A, Fessi H, Piccoli GB: Neutralizing SARS-CoV-2 antibody response in dialysis patients after the first dose of the BNT162b2 mRNA COVID-19 vaccine: The war is far from being won. *Kidney Int* 99: 1494–1496, 2021
10. Yanay NB, Freiman S, Shapira M, Wishahi S, Hamze M, Elhaj M, et al.: Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. *Kidney Int* 99: 1496–1498, 2021
11. Poland GA, Ovsyannikova IG, Kennedy RB: SARS-CoV-2 immunity: Review and applications to phase 3 vaccine candidates. *Lancet* 396: 1595–1606, 2020
12. Sattler A, Schrezenmeier E, Weber UA, Potekhin A, Bachmann F, Straub-Hohenbleicher H, et al.: Impaired humoral and cellular immunity after SARS-CoV-2 BNT162b2 (tozinameran) prime-boost vaccination in kidney transplant recipients. *J Clin Invest* 131: e150175, 2021
13. Bertrand D, Hamzaoui M, Lemée V, Lamulle J, Hanoy M, Laurent C et al.: Antibody and T cell response to SARS-CoV-2 messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients. *J Am Soc Nephrol* 32: 2147–2152, 2021
14. Anand S, Montez-Rath M, Han J, Garcia P, Cadden L, Hunsader P, et al.: Antibody response to COVID-19 vaccination in patients receiving dialysis. *J Am Soc Nephrol* 32: 2435–2438, 2021
15. Ebinger JE, Fert-Bober J, Printsev I, Wu M, Sun N, Prostko JC, et al.: Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. *Nat Med* 27: 981–984, 2021
16. Van Praet JT, Vandecasteele S, De Roo A, De Vriese AS, Reynders M: Humoral and cellular immunogenicity of the BNT162b2 mRNA Covid-19 vaccine in nursing home residents [published online ahead of print Apr 7, 2021]. *Clin Infect Dis* 10.1093/cid/ciab300 2021
17. *SARS-CoV-2 IgG II Quant Assay User Manual*, Abbott Laboratories, Diagnostics Division, 2020
18. World Health Organization: WHO/BS.2020.2403 Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody. 2020. Available at: https://www.who.int/publications/m/item/WHO-BS-2020.2403. Accessed July 5, 2021
19. Bartsch YC, Fischinger S, Siddiqui SM, Chen Z, Yu J, Gebre M, et al.: Discrete SARS-CoV-2 antibody titers track with functional humoral stability. *Nat Commun* 12: 1018, 2021
20. 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. *Nat Med* 27: 1205–1211, 2021
21. Lucas C, Klein J, Sundaram ME, Liu F, Wong P, Silva J, et al.; Yale IMPACT Research Team: Delayed production of neutralizing antibodies correlates with fatal COVID-19. *Nat Med* 27: 1178–1186, 2021
22. Valle-Arroyo J, Aguado R, Páez-Vega A, Pérez AB, González R, Fornés G, et al.: Lack of cytomegalovirus (CMV)-specific cell-mediated immune response using QuantiFERON-CMV assay in CMV-seropositive healthy volunteers: Fact not artifact. *Sci Rep* 10: 7194, 2020
23. Krueger KM, Ison MG, Ghossein C: Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation. *Am J Kidney Dis* 75: 417–425, 2020
24. Fang HC, Chou KJ, Chen CL, Lee PT, Chiou YH, Hung SY, et al.: Tuberculin skin test and anergy in dialysis patients of a tuberculosis-endemic area. *Nephron* 91: 682–687, 2002
25. European Medicines Agency: Assessment Report Comirnaty. 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf. Accessed July 5, 2021
26. European Medicines Agency: Assessment Report COVID-19 Vaccine Moderna. 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf. Accessed July 5, 2021
27. 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* 325: 1784–1786, 2021
28. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al.: Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 593: 130–135, 2021
29. Chen X, Chen Z, Azman AS, Sun R, Lu W, Zheng N, et al.: Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination. medRxiv. 10.1101/2021.05.03.21256506 (Preprint posted May 5, 2021)
30. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al.: Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 397: 2331–2333, 2021
31. Losappio V, Franzin R, Infante B, Godeas G, Gesualdo L, Fersini A, et al.: Molecular mechanisms of premature aging in hemodialysis: The complex interplay between innate and adaptive immune dysfunction. *Int J Mol Sci* 21: 3422, 2020
32. White EM, Yang X, Blackman C, Feifer RA, Gravenstein S, Mor V. Incident SARS-CoV-2 Infection among mRNA-vaccinated and unvaccinated nursing home residents. *N Engl J Med* 385: 474–476, 2021
33. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after three doses of BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int* 16: 1037–1042, 2021

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