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Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study

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ABSTRACT

Background. Chronic kidney disease (CKD) patients are at high-risk for severe coronavirus disease 2019 (COVID-19). The multicentric, observational and prospective SENCOVAC study aims to describe the humoral response and safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in CKD patients. Safety and immediate humoral response results are reported here.

Methods. Four cohorts of patients were included: kidney transplant (KT) recipients, and haemodialysis (HD), peritoneal dialysis (PD) and non-dialysis CKD patients from 50 Spanish centres. Adverse events after vaccine doses were recorded. At baseline and on Day 28 after the last vaccine dose, anti-Spike antibodies were measured and compared between cohorts. Factors associated with development of anti-Spike antibodies were analysed.

Results. A total of 1746 participants were recruited: 1116 HD, 171 PD, 176 non-dialysis CKD patients and 283 KT recipients. Most patients (98%) received mRNA vaccines. At least one vaccine reaction developed after the first dose in 763 (53.5%) and after the second dose in 741 (54.5%) of patients. Anti-Spike antibodies were measured in the first 301 patients. At 28 days, 95% of patients had developed antibodies: 79% of KT, 98% of HD, 99% of PD and 100% of non-dialysis CKD patients

($P < 0.001$). In a multivariate adjusted analysis, absence of an antibody response was independently associated with KT (odds ratio 20.56, $P = 0.001$) and with BNT162b2 vaccine (odds ratio 6.03, $P = 0.023$).

Conclusion. The rate of anti-Spike antibody development after vaccination in KT patients was low but in other CKD patients it approached 100%, suggesting that KT patients require persistent isolation measures and booster doses of a COVID-19 vaccine. Potential differences between COVID-19 vaccines should be explored in prospective controlled studies.

Keywords: antibodies, COVID-19, humoral response, SARS-CoV-2, vaccine

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused millions of deaths worldwide, being especially lethal in vulnerable populations, such as patients with chronic kidney disease (CKD), those on dialysis and kidney transplant (KT) recipients [1]. Dialysis, organ transplantation and CKD patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² represent three of the four comorbidities associated with the highest mortality risk from COVID-19 [2]. Several circumstances exacerbate the impact of severe acute

KEY LEARNING POINTS

What is already known about the subject?

- Coronavirus disease 2019 (COVID-19) has caused millions of deaths worldwide, being especially lethal in vulnerable populations, such as chronic kidney disease (CKD), dialysis and kidney transplant (KT) patients.
- Dialysis, organ transplantation and CKD patients with estimated glomerular filtration rate < 30 mL/min/1.73 m² represent three of the four comorbidities associated with the highest mortality risk from COVID-19.
- Low seroconversion rate to mRNA vaccines has been preliminarily reported in KT patients.

What this study adds?

- SENCOVAC demonstrated the safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines in peritoneal dialysis, haemodialysis, KT and non-dialysis CKD patients.
- Vaccination with mRNA-1273 (Moderna) resulted in better serological response than vaccination with BNT162b2 (Pfizer-BioNTech) in KT recipients and other CKD populations.
- Absence of antibody response was independently associated with KT (odds ratio 20.56) and BNT162b2 vaccination (odds ratio 6.03).

What impact this may have on practice or policy?

- Isolation measures should be maintained in CKD patients, especially in KT recipients, at high-risk of COVID-19.
- KT patients may benefit from a booster dose of a COVID-19 vaccine, as some authorities are now recommending.
- CKD patients at high-risk for SARS-CoV-2 infection should be monitored, even if they are asymptomatic, as 50% of them could be reinfecting by SARS-CoV-2.

respiratory syndrome coronavirus 2 (SARS-CoV-2) on the morbidity and mortality of CKD patients. Beyond the inherent immunosuppression secondary to impaired renal function [3], haemodialysis (HD) and KT patients present specific characteristics, such as immunosuppressive therapy and comorbidities, that enhance their risk for developing severe COVID-19.

The fast development and approval of SARS-CoV-2 vaccines has decreased the severity of the COVID-19 pandemic in countries with high immunization rates. However, there is concern regarding the humoral response of CKD patients to vaccination against SARS-CoV-2. Data on KT patients are the most worrisome, with a seroconversion rate lower than 50% in the majority of published studies [4]. In addition, recent series have shown limited development of anti-Spike antibodies, even after three vaccine doses [5]. In contrast, preliminary studies suggest that HD patients reach higher anti-Spike antibody levels after the administration of mRNA vaccines than KT patients, but lower than the general population [6]. Two recent reports involving peritoneal dialysis (PD) patients suggest that this population acquires similar humoral and cellular responses to HD patients, at least in the short term [7, 8]. Regarding non-dialysis CKD patients, available data are limited as those patients are systematically excluded from clinical trials, and to our knowledge no specific studies have been published to date [9].

Despite the heterogeneous available data, a correct understanding of the efficiency and safety of SARS-CoV-2 vaccines in different populations of CKD patients with different immunological and comorbid backgrounds is a priority for delineating further actions according to their specific susceptibility and response to COVID-19 vaccination.

The aim of the multicentric SENCOVAC study was to evaluate the humoral response and safety of the SARS-CoV-2 vaccines in CKD patients, comparing the humoral response in four different cohorts: PD, HD, KT and non-dialysis CKD patients. We now present the SENCOVAC study results in

terms of adverse events (AE) and the preliminary report on the immediate humoral response as assessed by the antibody response 28 days after complete COVID-19 vaccination.

MATERIALS AND METHODS

Study design

SENCOVAC is a Spanish Society of Nephrology prospective and multicentric study including four cohorts of adult patients with CKD: KT recipients, HD, PD and non-dialysis CKD patients (stages 4 and 5, eGFR < 30 mL/min/1.73 m²). All the screened participants received the complete immunization schedule with any of the available vaccines: BNT162b2 (Pfizer-BioNTech®), mRNA-1273 (Moderna®), ChAdOx1-S (AstraZeneca®) or Ad26.COV.2 (Janssen®) as per local public health authorities' prescription at their respective Autonomous Communities during routine clinical care.

Patients

Fifty centres in Spain participated in the study. Out of the 1930 screened patients, 1746 were included (Figure 1). Inclusion criteria were age older than 18 years, capability of understanding the purpose and risks of the study, fully informed written consent and a diagnosis of CKD as KT recipients, HD, PD or non-dialysis CKD with eGFR < 30 mL/min/1.73m². Exclusion criteria were contraindication for vaccination, solid organ transplantation different from kidney, active oncological or haematological disease, primary immunodeficiency disease, human immunodeficiency virus and immunosuppressive treatment 6 months before vaccination for non-KT recipients.

Objectives

The primary objective was to determine the rates of anti-SARS-CoV-2 Spike antibody development in CKD patients. Anti-Spike antibodies correlate with neutralizing activity

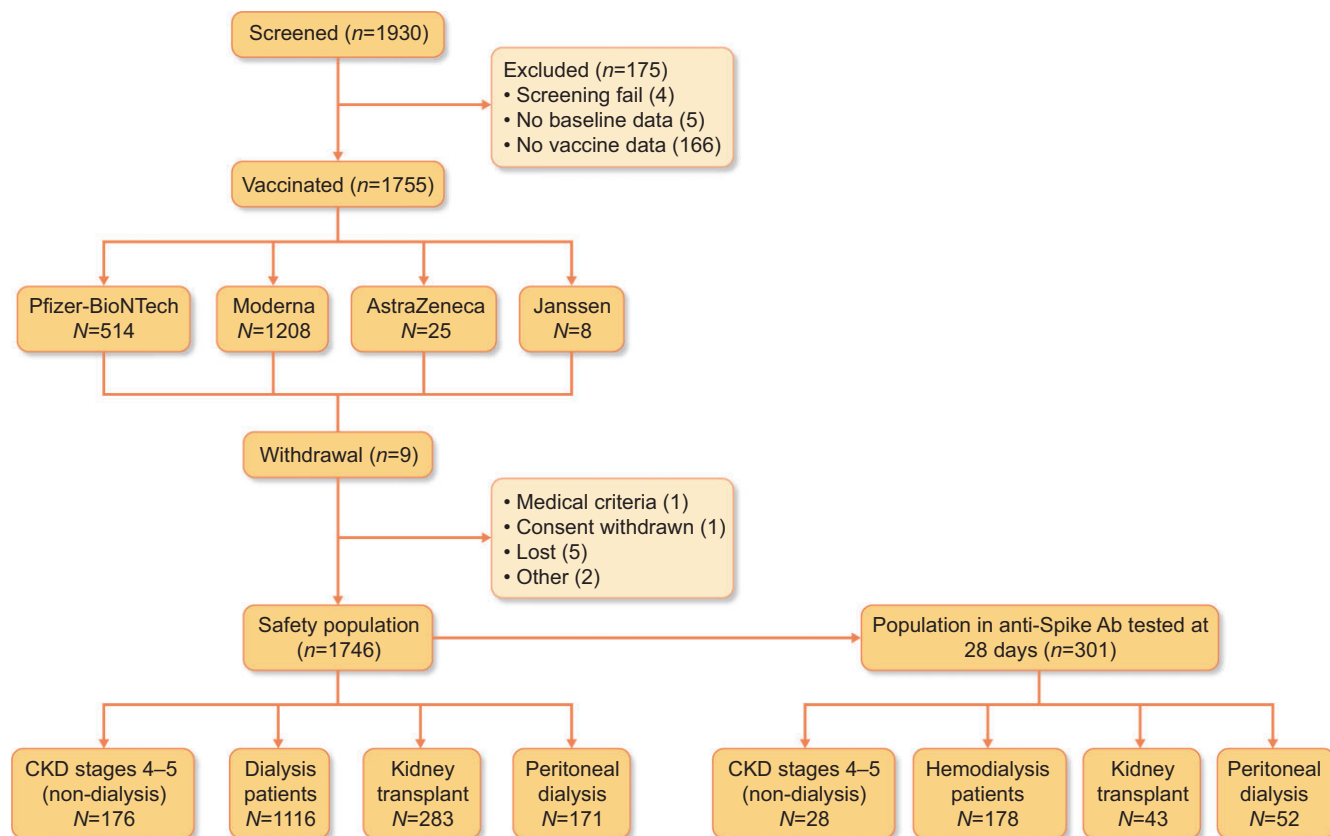


FIGURE 1: Participant flow chart. The humoral response evaluation population represents the first 301 patients with anti-Spike antibody results at 28 days after completing the vaccination schedule. Ab, antibodies.

[10]. Secondary objectives included safety (immediate local and systemic reactions and other AE) and effectiveness at preventing further SARS-CoV-2 infection.

Variables and outcomes

In this interim analysis, we assessed safety and the humoral response at 28 days after completion of the vaccination schedule. Patients were studied at baseline, after the administration of the vaccine doses and at 28 days. At baseline, investigators registered epidemiological data, comorbidities [including previous COVID-19 infection (defined by the investigator with a positive antigen or polymerase chain reaction against SARS-CoV-2)], long-term treatments, vital signs and laboratory values. In addition, each cohort had specific registries based on the kidney situation (Kt/ V_{urea} , dialysis vintage, technique and vascular access for HD and PD patients; immunosuppressive therapy for KT).

Antibody testing

At baseline and at 28 days, a 2-mL serum sample was obtained and sent to a central laboratory for antibody determinations. All samples were tested by a CE-marked commercial method, a quantitative chemiluminescence immunoassay (CLIA, COVID-19 Spike Quantitative Virclia[®] IgG Monotest, Vircell S.L., Spain), with a sensitivity and specificity of 96% and

100%, respectively, which detects IgG antibodies against the SARS-CoV-2 Spike protein. This assay was calibrated against the First World Health Organization International Standard for anti-SARS-CoV-2 human immunoglobulin (NIBSC code: 20/136) and results were expressed as IU/mL. According to the performance studies of the manufacturer, based on the analysis of pre-pandemic serum samples, values ≤ 32 IU/mL were considered as negative, between 32 and 36 IU/mL as equivocal and values > 36 IU/mL as positive, reflecting the presence of anti-Spike IgG antibodies as a consequence of either previous infection or vaccination.

Adverse events and vaccine reactions

After each vaccine dose, patients were asked to complete the AE questionnaire.

During the study all patients were followed, and any AE was registered. Serious AE were considered if they led to death, were life-threatening, needed hospitalization or caused disability, as considered by the investigators.

Ethical concerns

The study was approved by the Ethical Committee of Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz in February 2021.

Table 1. Baseline characteristics of participants

	Total (n = 1746)	KT (n = 283)	PD (n = 171)	HD (n = 1116)	CKD (n = 176)	P
Sex (male), n (%)	1092 (62)	171 (60)	100 (58)	719 (64)	102 (58)	0.170
Age (years)	64 (13)	56 (13)	60 (14)	65 (12)	64 (14)	<0.001
Diabetic kidney disease, n (%)	369 (22)	10 (4)	37 (22)	280 (25)	42 (26)	<0.001
Haemodialysis technique, n (%)		—	—		—	—
HFHD	486 (44)			486 (44)		
HDx	39 (3)			39 (3)		
OL-HDF	589 (53)			589 (53)		
Vascular access, n (%)		—	—		—	—
AVF	696 (64)			696 (64)		
Catheter	394 (36)			394 (36)		
Immunosuppression, n (%)			—	—	—	—
Steroids	182 (64)	182 (64)				
Calcineurin inhibitors	216 (73)	216 (73)				
Mycophenolate mofetil	200 (71)	200 (71)				
mTORi	46 (16)	46 (16)				
Azathioprine	9 (3)	9 (3)				
Anticoagulants, n (%)	270 (15)	23 (8)	28 (16)	190 (17)	29 (16)	0.003
Antiplatelet agents, n (%)	627 (36)	76 (27)	56 (31)	435 (39)	63 (36)	0.001
RAASi, n (%)	584 (33)	128 (45)	89 (52)	300 (27)	67 (38)	<0.001
ESA, n (%)	1105 (63)	42 (15)	111 (65)	853 (77)	99 (56)	<0.001
Vaccine, n (%)						<0.001
BNT162b2	511 (29)	54 (19)	26 (15)	331 (30)	100 (57)	
mRNA-1273	1202 (69)	225 (79)	142 (83)	766 (69)	69 (39)	
ChAdOx1-S	25 (1)	4 (1)	3 (2)	15 (1)	3 (2)	
Ad26.COV.2	8 (1)	0 (0)	0 (0)	4 (0)	4 (2)	
Previous COVID-19, n (%)	162 (9)	17 (6)	20 (12)	117 (10)	8 (4)	0.051
Baseline anti-Spike Ab+, n (%)	69 (23)	13 (30)	11 (21)	37 (21)	8 (29)	0.124
Haemoglobin (g/dL)	11.6 (10.7–12.6)	13.3 (11.9–14.7)	11.4 (10.6–12.4)	11.3 (10.5–12.2)	11.6 (10.7–12.4)	0.002
Leukocyte (10 ³ /mm ³)	6.5 (5.3–8.0)	6.9 (5.6–8.9)	6.8 (5.5–8.0)	6.0 (4.9–7.7)	7.0 (6.1–10.7)	<0.001
Lymphocytes (10 ³ /mm ³)	1.3 (1.0–1.8)	1.8 (1.3–2.6)	1.4 (1.0–1.8)	1.3 (0.9–1.9)	1.6 (1.2–2.7)	<0.001
Albumin (g/dL)	3.9 (3.6–4.2)	4.2 (3.9–4.5)	3.6 (3.3–3.9)	3.9 (3.6–4.1)	4.0 (3.6–4.3)	<0.001
Prealbumin (mg/dL)	27 (22–32)	27 (21–33)	30 (26–36)	26 (22–30)	28 (22–34)	<0.001
C-reactive protein (mg/L)	0.5 (0.2–1.5)	1.1 (0.3–3.8)	1.1 (0.3–3.2)	3.9 (1.0–10.3)	1.0 (0.2–3.0)	0.006
eGFR (mL/min/1.73 m ²)	36 (14–62)	49 (35–66)	—	—	13 (9–21)	<0.001 ^a
Influenza vaccine, n (%)	1274 (73)	218 (77)	117 (68)	831 (75)	108 (61)	0.001
Anti-HBs, n (%)	710 (64)	40 (33)	83 (77)	524 (67)	63 (59)	<0.001

Data are presented as mean (standard deviation) or median (IQR). HFHD, high flux haemodialysis; HDx, expanded haemodialysis therapy; OL-HDF, online haemodiafiltration; AVF, arteriovenous fistulae; mTORi, mammalian target of rapamycin inhibitors; RAASi, renin-angiotensin-aldosterone inhibitors; Ab, antibodies.

^aeGFR difference between KT and non-dialysis CKD.

Statistical methods

Data are displayed as mean (standard deviation) or median [interquartile range (IQR)] depending on the variable distribution (tested with the Shapiro–Wilk test). Categorical variables were compared using Fisher's test and continuous variables with *t*-test or Mann–Whitney, according to the variable distribution. For comparison of continuous variables from more than two groups, analysis of variance or Kruskal–Wallis tests were used. Correlations were calculated using the Spearman test. The statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Plots were drawn using GraphPad Prism version 9.02 (Graphpad Holdings, LLC).

RESULTS

Baseline characteristics

Among the 1746 participants in SENCovac, 1092 (62.5%) were male and the mean age was 63.67 ± 13.28 years (Table 1). Vaccine distribution was as follows: 1202 patients

(69%) received mRNA-1273, 511 (29%) BNT162b2, 25 (1%) AstraZeneca and 8 (0.5%) Janssen vaccines. As shown in Figure 1, 1116 (64%) patients were on HD, 283 (16%) were KT patients, 176 (10%) were non-dialysis CKD patients and 171 (19%) were on PD. The distribution of the different types of vaccines differed between groups (Table 1). KT recipients, and HD and PD patients were more likely to receive mRNA-1273, and non-dialysis CKD patients BNT162b2 (*P* < 0.001). Table 2 shows baseline characteristics for participants that received mRNA vaccines (BNT162b2 or mRNA-1273) in the safety and humoral response population. The analysis restricted to patients without anti-Spike antibodies at baseline is shown in Supplementary data, Table S1.

Local and systemic reactions after vaccination

The adverse reactions form after the first dose was completed by 1426 participants. Among them, 763 (53.5%) patients developed at least one reaction. Reactions were more frequent in KT recipients, followed by PD and HD patients

Table 2. Baseline characteristics regarding the type of mRNA vaccine in safety and humoral response evaluation population

	Safety population			Humoral response evaluation population		
	BNT162b2 (n = 511)	mRNA-1273 (n = 1202)	P	BNT162b2 (n = 65)	mRNA-1273 (n = 236)	P
Sex (male), n (%)	315 (62)	755 (63)	0.041	45 (69)	165 (70)	0.915
Age (years), mean (standard deviation)	68 (13)	60 (13)	<0.001	65 (15)	61 (12)	0.018
Diabetic kidney disease, n (%)	113 (23)	246 (22)	0.495	12 (18)	61 (27)	0.349
Haemodialysis technique, n (%)			<0.001			0.931
HFHD	103 (31)	375 (49)		7 (21)	34 (24)	
HDx	15 (5)	24 (3)		1 (3)	4 (3)	
OL-HDF	212 (64)	366 (48)		26 (76)	106 (74)	
Vascular access, n (%)			0.310			0.681
AVF	197 (60)	487 (66)		20 (59)	78 (55)	
Catheter	132 (40)	255 (34)		14 (41)	64 (45)	
Immunosuppression, n (%)						
Steroids	41 (8)	217 (18)	<0.001	13 (20)	37 (16)	0.407
Calcineurin inhibitors	42 (8)	188 (16)	<0.001	13 (20)	27 (11)	0.097
Mycophenolate mofetil	38 (7)	173 (14)	0.001	11 (17)	29 (12)	0.311
mTORi	9 (2)	38 (3)	0.306	1 (1)	5 (2)	1.000
Azathioprine	2 (0)	9 (1)	0.815	1 (1)	2 (1)	0.519
Anticoagulants, n (%)	91 (18)	178 (15)	0.089	17 (26)	34 (14)	0.038
Antiplatelet agents, n (%)	188 (37)	425 (35)	0.789	26 (40)	83 (35)	0.471
RAASi, n (%)	156 (30)	416 (35)	0.109	23 (35)	109 (46)	0.158
ESA, n (%)	354 (69)	729 (61)	0.003	41 (63)	160 (68)	0.552
CKD cohort, n (%)			<0.001			0.002
KT	54 (11)	225 (19)		12 (18)	31 (13)	
PD	26 (5)	142 (12)		6 (9)	46 (19)	
HD	331 (65)	766 (64)		34 (52)	144 (61)	
CKD	100 (20)	69 (6)		13 (20)	15 (6)	
Previous COVID-19, n (%)	33 (6)	127 (11)	0.037	2 (3)	51 (22)	0.001
Baseline anti-Spike Ab+, n (%)	—	—	—	12 (18)	57 (24)	0.585
Influenza vaccine, n (%)	349 (68)	901 (75)	0.011	54 (83)	165 (70)	0.041
Anti-HBs, n (%)	229 (63)	465 (64)	0.612	36 (64)	120 (60)	0.856

Safety population included patients included in the study. Humoral response evaluation population included patients with tested anti-Spike antibodies.

HFHD, high flux haemodialysis; HDx, expanded haemodialysis therapy; OL-HDF, online haemodiafiltration; AVF, arteriovenous fistulae; mTORi, mammalian target of rapamycin inhibitors; RAASi, renin-angiotensin-aldosterone inhibitors; Ab, antibodies.

($P < 0.001$) (Supplementary data, Figure S1). Vaccine reactions were more frequent in younger patients ($P < 0.001$ for all groups combined, not shown). Specifically, vaccine reactions were more frequent in younger KT recipients ($P = 0.016$) and in younger persons with non-dialysis CKD ($P = 0.012$) than in older participants from these groups (not shown). Previous COVID-19 infection was also associated with higher rates of reactions after the first dose (64% versus 53%) ($P = 0.038$). The most frequent reaction was local pain (556, 73%), followed by general discomfort (163, 22%) and asthenia (160, 21%) (Supplementary data, Table S2). mRNA-1273 vaccine was associated with higher rates of local pain, erythema, swelling, skin hypersensitivity, low-grade fever and fever, headache, asthenia, chills and general discomfort. Among patients who were working, those who had received mRNA-1273 requested a work leave more frequently ($P = 0.015$).

The adverse reactions form after the second dose was completed by 1359 patients. Among them, 741 (54.5%) developed at least one reaction. Reactions were more frequent in KT patients ($P = 0.006$) (Supplementary data, Figure S1). Vaccine reactions to the second dose were also more frequent in younger patients ($P < 0.001$ for all groups combined, not shown). Specifically, vaccine reactions were more frequent in younger KT patients ($P = 0.035$) and in younger non-dialysis CKD patients ($P = 0.003$) than in older participants from these

groups (not shown). Previous COVID-19 infection was also associated with higher rates of reactions after the second dose (65% versus 53%) ($P < 0.001$). The most frequent reaction was local pain (493, 68%) followed by general discomfort (261, 36%) and asthenia (258, 36%) (Supplementary data, Table S3). The second dose of mRNA-1273 produced more frequent local pain, erythema, swelling, itching, skin hypersensitivity, low-grade fever and fever, headache, asthenia, myalgia, chills, general discomfort and arthralgias than the other vaccines. Among patients who were working, those who had received mRNA-1273 asked for a work leave more frequently ($P = 0.002$).

Anti-Spike antibodies

Development of anti-Spike antibodies 28 days after completing vaccination has been tested in 301 patients (28 non-dialysis CKD patients, 43 KT recipients, 52 PD and 178 HD patients). Baseline characteristics for these patients are presented in Supplementary data, Table S4. At baseline, 69 patients (23%) presented anti-Spike antibodies, 6 (2%) had an equivocal result and 226 (75%) had no anti-Spike antibodies. Among patients with baseline anti-Spike antibodies, 35 (51%) had a known history of COVID-19.

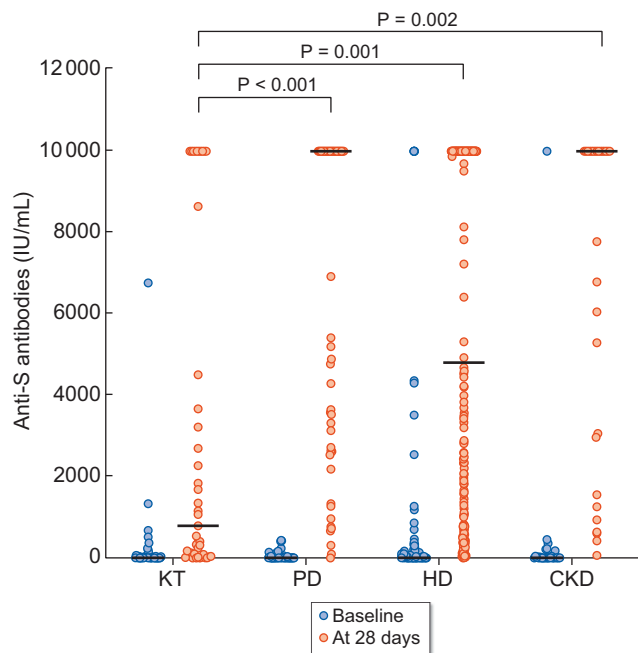


FIGURE 2: Titre of anti-Spike antibody titres at baseline and 28 days after completing vaccination in KT recipients, persons on PD or HD and persons with CKD not on non-dialysis CKD. Data are for all participants, independently of a history of COVID-19 or baseline presence of anti-Spike antibodies.

Twenty-eight days after completing vaccination, 289 patients (95%) presented anti-Spike antibodies, 2 (1%) were equivocal and 14 (5%) had a negative result. Patients that did not develop anti-Spike antibodies post-vaccination included nine (21%) KT recipients, four (2%) HD patients and one (1%) PD patient ($P < 0.001$) (Supplementary data, Figure S2).

Among the 226 patients that did not have anti-Spike antibodies at baseline, the rate of *de novo* antibody development was 94% for all groups combined. Among these patients, 170 (98%) of patients receiving mRNA-1273 developed anti-Spike antibodies as compared with 42 (81%) patients receiving BNT162b2 ($P < 0.001$). Specifically, among patients without anti-Spike antibodies at baseline, 12 (5.3%) did not develop a humoral response. Patients who did not develop *de novo* antibodies included seven (26%) of the KT recipients, one (2%) PD patients and four (3%) HD patients ($P < 0.001$) (Supplementary data, Figure S3).

Interestingly, in two patients who had positive or equivocal anti-Spike antibodies at baseline, these were not observed 28 days following vaccination. These two patients belonged to the KT group, displayed very low baseline anti-Spike antibody titres (34 and 42 IU/mL) and received mRNA-1273 and BNT162b2 vaccines, respectively. Among KT patients with a history of COVID-19, 100% had antibodies after vaccination.

As shown in Figure 2, in the overall analysis, KT recipients presented lower titres of anti-Spike antibodies than HD ($P = 0.001$), PD ($P < 0.001$) and non-dialysis CKD ($P = 0.002$) patients. When the analysis was restricted to patients without anti-Spike antibodies at baseline, similar results were obtained: KT was the group with lower *de novo* antibody generation ($P = 0.011$ versus HD; $P < 0.001$ versus

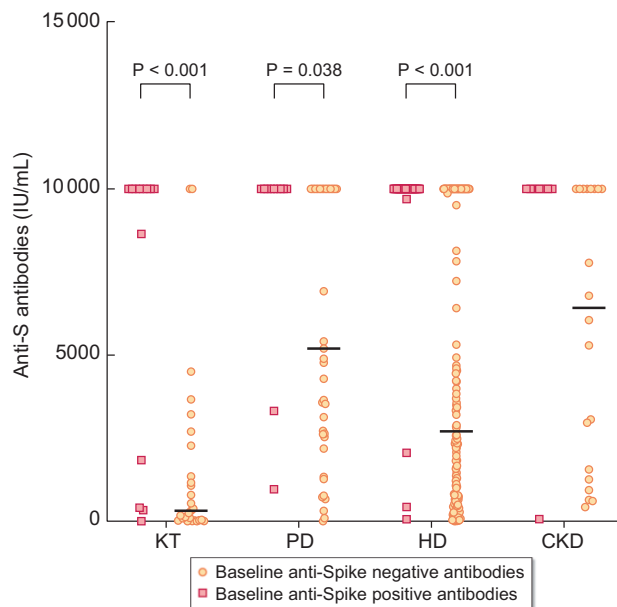


FIGURE 3: Anti-Spike antibodies 28 days after completing vaccination in KT recipients, persons on PD or HD and persons with CKD not on dialysis according to prior COVID-19 history. Data are for all participants, independently of baseline presence of anti-Spike antibodies.

PD; and $P = 0.013$ versus CKD) (Supplementary data, Figure S4).

Focusing specifically on KT recipients without baseline anti-Spike antibodies, anti-Spike antibodies developed in 14 (82%) of those receiving mRNA-1273 and in 6 (60%) of those receiving BNT162b2 vaccines ($P = 0.365$).

Factors associated to the development of anti-Spike antibodies

Among patients in whom antibodies were assessed, 53 had a history of COVID-19. Of these, 35 (66%) patients had anti-Spike antibodies at baseline [4 (80%) of KT recipients with prior COVID-19, 5 (50%) of PD, 25 (68%) of HD and 1 (100%) of non-dialysis CKD patients ($P = 0.249$)].

Previous COVID-19 infection was associated with higher anti-Spike titres at 28 days [median 10 000 (IQR 5722–10 000) IU/mL versus 3529 (IQR 661–10 000); $P < 0.001$]. Within specific groups, these differences were significant in KT recipients and in HD patients (Figure 3). Patients with baseline positive anti-Spike antibodies also presented higher anti-Spike antibody titres at 28 days [median 10 000 (IQR 2686–10 000) IU/mL versus 2928 (IQR 655–10 000); $P < 0.001$] (Supplementary data, Figure S5).

Patients receiving mRNA-1273 developed higher anti-Spike titres [median 10 000 (IQR 1716–10 000) IU/mL] than those receiving BNT162b2 [median 964 (IQR 109–4213) IU/mL] ($P < 0.0001$). These differences were significant in KT, PD and HD patients (Figure 4). Restricting the analysis to those with negative baseline anti-Spike antibodies, mRNA-1273 was superior in developing antibodies in KT, HD and CKD patients (Supplementary data, Figure S6). A mild but significant indirect correlation was observed between age and anti-Spike

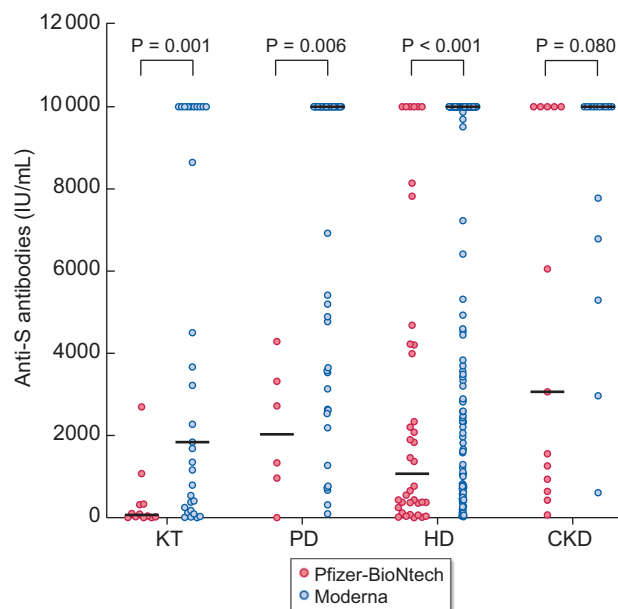


FIGURE 4: Anti-Spike antibodies 28 days after completing vaccination in KT recipients, persons on PD or HD and persons with CKD not on dialysis according to the received vaccine [Pfizer (BNT162b2) or Moderna (mRNA-127)]. Data are for all participants, independently of baseline presence of anti-Spike antibodies.

Table 3. Independent predictors for the development of humoral response

	OR (95% CI)	P
Age (years)	1.04 (0.96–1.13)	0.318
Gender (male)	1.78 (0.38–8.32)	1.781
Baseline anti-Spike Ab+	0.47 (0.16–1.38)	0.170
Influenza vaccine	1.00 (1.00–1.00)	0.729
Type of patient (KT versus others)	20.56 (3.24–130.45)	0.001
BNT162b2 vaccine	6.03 (1.28–28.23)	0.023

OR, odds ratio; CI, confidence interval; Ab, antibodies.

titres in both the whole sample and in those patients without baseline anti-Spike antibodies (Supplementary data, Figures S7 and S8). PD patients who had not received previously the seasonal influenza vaccine developed significantly higher anti-Spike titres at 28 days [median 4528 (IQR 1319–10 000) IU/mL versus 10 000 (IQR 5359–10 000); $P = 0.029$]. However, an adjusted linear regression by age and previous COVID-19 did not show any independent association between influenza vaccine and anti-Spike titres. No differences were found in anti-Spike antibodies titres between patients with or without anti-hepatitis B surface (anti-HBs) antibodies.

A multivariate analysis adjusted for age, baseline anti-Spike antibodies, gender and seasonal influenza vaccine, showed that KT [odds ratio 20.56 (95% confidence interval 3.24–130.45); $P = 0.001$] and BNT162b2 vaccine [odds ratio 6.03 (95% confidence interval 1.28–28.23); $P = 0.023$] were independent predictors for the lack of development of anti-Spike antibodies (Table 3).

Adverse events and SARS-CoV-2 infections

AE and occurrence of a SARS-CoV-2 positive antigen or PCR tests were recorded up to 52 days following completion

of vaccination. During follow-up, 40 AE were registered in 31 patients (1.8%). One HD patient suffered a stroke 1 month after the second dose of mRNA-1273. One KT recipient suffered a myocardial infarction 4 days after the first dose of BNT162b2. After recovering, the patient received the second dose without any AE. Eight patients died but death was not considered a vaccine-related event. The causes of death were two cardiovascular events, four infectious diseases, one neoplasm and one dialysis withdrawal. Among patients who died, four (50%) had received BNT162b2 and four (50%) mRNA-1273.

Between the first and the second dose, 17 (1.0%) SARS-CoV-2 positive tests were recorded (4 in PD and 13 in HD patients). Two patients had received BNT162b2 and 15 mRNA-1273, representing 0.5% and 1.5% of patients having received BNT162b2 and mRNA-1273, respectively ($P = 0.414$).

Twelve patients (1.0%) presented a SARS-CoV-2 positive test after the second dose. One was a KT recipient, one a PD patient, nine were HD patients and one patient had non-dialysis CKD. Of them, three had received BNT162b2 and nine received mRNA-1273, representing 1.0% and 1.1% of patients having received BNT162b2 and mRNA-1273, respectively ($P = 0.982$).

None of the post-vaccination SARS-CoV-2 infections was lethal.

DISCUSSION

The main findings of the interim analysis of the multicentric SENCovac study are the safety of current vaccination schedules for patients with advanced CKD and the poor serological response of KT in comparison with HD, PD and non-dialysis CKD patients. Due to the lack of a complete immunological response against SARS-CoV-2, KT recipients are candidates for an early third dose of the vaccine in some countries [5]. Our results demonstrated a suboptimal humoral response in KT recipients even in a very short-term assessment, only 28 days from the completion of the full vaccination schedule. In contrast to the other groups, more than 20% of KT patients did not develop anti-Spike antibodies. Moreover, loss of anti-Spike antibodies following vaccination was documented in at least one of KT recipients who had anti-Spike antibodies at baseline. Our study results agree with preliminary publications strongly suggesting that KT patients are at high risk of COVID-19 infection despite the complete two-dose vaccination schedule [11–13]. Our results also provide hypothesis-generating information on how to optimize seroconversion and anti-Spike antibody titres in advanced CKD patients, as the mRNA-1273 vaccine performed better from the antibody generation point of view than BNT162b2 in this population. These findings may be the basis for prospective randomized controlled studies in CKD patients, but especially, due to their enhanced risk for a suboptimal humoral response, in KT recipients. In this regard, although the study was observational, the administration of mRNA-1273 or BNT162b2 was a random choice by health authorities dependent on vaccine-type availability in different Spanish regional health systems at the time that each regional system decided to vaccinate persons with CKD based on different sequential criteria (advanced age, healthcare personnel and

consideration as a high-risk group). Consequently, analysis of patient subpopulations vaccinated with one or the other vaccine did not disclose any consistent bias, and multivariate analysis identified the type of vaccine as a driver of anti-Spike antibody responses and titres, including the population most in need of an optimized antibody response, i.e. KT recipients.

An important issue not addressed is the link between immune response and efficacy. This last term refers to the possibility of preventing SARS-CoV-2 infection, and even severe disease, hospitalization and deaths after vaccination [14]. Although the relationship between neutralizing antibodies and breakthrough infections has been confirmed in healthy persons, this should be confirmed in vulnerable populations [15].

Immunosuppression, age and previous COVID-19 infection influence the development of anti-SARS-CoV-2 antibodies [4, 16]. Surprisingly, in our study age did not predict the strength of the humoral response. This may in part be explained by the lower age in KT recipients and in patients receiving mRNA-1273 [17]. Interestingly, our data show that the type of vaccine was an independent predictor for humoral response. Indeed, mRNA-1273 was associated with higher rates of early anti-Spike antibodies. mRNA-1273 was also associated with more frequent vaccine reactions in this population, which may be interpreted as consistent with a more vigorous immune response. In this regard, a recent network study including maintenance HD patients demonstrated higher protection from SARS-CoV-2 infections with mRNA-1273 in comparison with BNT162b2. In that study, the authors hypothesized about the difficulties of handling BNT162b2 vaccine and its impact on the thermostability, which could decrease effectivity [12]. However, one of the most feasible reasons for these differences (in terms of adverse reactions and development of humoral response) might be the higher mRNA dose of mRNA-1273 (100 μg versus 30 μg in BNT162b2) [18]. Indeed, a higher dose of hepatitis B virus vaccine is recommended for patients with advanced CKD in order to optimize the immunological response. As the number of breakthrough SARS-CoV-2 infections was low, we cannot yet provide information of the impact of different vaccines on the occurrence of COVID-19 in advanced CKD patients. In this regard, in some vulnerable cohorts BNT162b2 has been suggested to limit the risk of vigorous vaccine reactions.

To our knowledge, our study is the first to also analyse non-dialysis CKD patients in comparison with patients on kidney replacement therapy. Interestingly, and despite the low eGFR of this subgroup, they displayed a very high rate of humoral response after completing the full vaccination schedule. Although uraemia alters humoral immunity, our data suggest that, at least in the short-term, non-dialysis CKD patients have higher seroconversion rates than CKD patients on kidney replacement therapy [19]. As previously demonstrated, PD and HD patients also reached high rates of seroconversion [4]. Interestingly, the stratified analysis according to previous SARS-CoV-2 exposure shows differences in antibody production in the different subgroups. Specifically, HD patients and KT recipients without prior SARS-CoV-2 infection developed significantly lower anti-Spike antibody

responses, suggesting higher risk for post-vaccine COVID-19 infection [20]. Indeed, asymptomatic SARS-CoV-2 infections seem to be an important trigger for higher humoral response to vaccines. Thus, around 50% of participants with baseline anti-Spike antibodies lacked a history of diagnosed COVID-19. This important rate of asymptomatic COVID-19 should alert about the need for maintaining monitoring and mitigation strategies among high-risk populations with impaired immunological response to vaccines. Our results showed that PD, KT and HD patients with anti-Spike antibodies at baseline developed higher antibody titres after vaccination. In concordance, in healthcare professionals, stronger vaccine responses were observed in individuals with prior COVID-19 [21]. However, our study also documented that around 33% of participants with a prior diagnosis of COVID-19 had no anti-Spike antibodies at the time of vaccination. We interpret this as a warning sign of waning of the immune response against SARS-CoV-2 in advanced CKD patients over a relatively short period of time (<15 months).

Serious AE that investigators considered related to the COVID-19 vaccine were registered in two patients. Both were cardiovascular events, one stroke and one myocardial infarction. Although cardiovascular events have been described after SARS-CoV-2 vaccination, the potential causality is unclear, given the high risk of cardiovascular events in CKD patients [22].

Some limitations should be acknowledged. First, the small sample size of patients with measured anti-Spike antibodies, as at the planned interim analyses antibody results were available for 301 patients. This has prevented a subanalysis on the impact of factors such as dialysis efficacy. However, the information obtained is clinically relevant regarding short-term serological responses. These results are of special interest for developing a 'nephrological' common strategy in the recommendation of booster doses of vaccines, mainly to KT recipients. In this regard, the similarity of immunosuppressive regimens for KT recipients precluded the analysis of the impact of different treatment schedules on humoral responses. Second, cellular immunity was not assessed. However, assessment of cellular immunity is unlikely to be available in routine clinical care in the near future. Thus, assessing antibody responses may provide more clinically relevant information. Third, in this first report of the SENCOVAC study, follow-up was short. This may condition the evaluation of the immediate humoral response in patients with delayed seroconversion (such as HD patients) [23]. Additionally, the dose and interval between doses of both mRNA vaccines is different, and this may impact on the dynamics of antibody development. Finally, this was an observational study. However, the choice of vaccine type was randomly dependent on availability of specific vaccine types for different regions, and decided by public health officials unrelated to study participants.

In conclusion, SENCOVAC demonstrates that HD, PD and non-dialysis CKD patients develop a robust early humoral response after SARS-CoV-2 vaccine, especially if they had previous COVID-19. In contrast, KT patients present lower rates of seroconversion and anti-Spike antibody titres at 28 days, suggesting that they may benefit from higher isolation

measures and booster doses of vaccines. Other CKD patients may benefit from individual monitoring (including assessment of antibody titres) to assess the need for a booster dose if these are not provided to all high-risk individuals by the local health system. Safety and tolerability are acceptable in all the studied CKD cohorts. Hypothesis-generating data suggest a stronger immune response to mRNA-1273 vaccines in advanced CKD patients that should be confirmed in prospective studies and longer-term follow-up of the present cohort. This information would be especially relevant for vaccination and booster vaccines for KT recipients.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](#) online.

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CONFLICT OF INTEREST STATEMENT

M.J.S. reports honorarium for conferences, consulting fees and advisory boards from Astra Zeneca, NovoNordisk, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, ICU Medical, and Boehringer. B.Q. has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme, Otsuka. A.O. has received consultancy or speaker fees or travel support from Astellas, Astrazeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Otsuka and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. C.J.J.M. has received honoraria for one conference from Vifor-Pharma. P.S. reports honorarium for conferences, consulting fees and advisory boards from Amgen, Astellas, Astra Zeneca, Baxter, Braun, Fresenius, Nipro and Vifor-Pharma. S.M.V, G.U., M.G.S.M., M.C., M.T.J.R., P.M.R., J.C.R.S., N.T., C.G., M.C.A.C., N.B.L., A.L., J.R. and R.T.G. do not present conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors, M.J.S and A.O., upon reasonable request.

APPENDIX

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