High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients

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ABSTRACT

Background. Patients with chronic kidney disease, dialysis patients and kidney-transplant patients are at high risk of developing severe coronavirus disease-19 (COVID-19). Data regarding the immunogenicity of anti-Severe Acute Respiratory Syndrome coronavirus-2 messenger RNA (anti-SARS-CoV-2 mRNA) vaccines in dialysis patients were published recently. We assessed the immunogenicity of anti-SARS-CoV-2 mRNA vaccine in dialysis patients.

Patients and Methods. One hundred-nine patients on hemodialysis (n=85) or peritoneal dialysis (n= 24) have received two injections of 30-µg doses of BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech), that were administered intramuscularly 28 days apart. Those who were still seronegative after the second dose were given a third dose one month later. Anti-SARS-CoV-2 antibodies were tested before and after vaccination.

Results. Ninety-one out of the 102 patients who had at least a one-month follow-up after the second (n=97) or the third (n=5) vaccine doses had anti-SARS-CoV-2 antibodies. The seroconversion rate was 88.7% (86 out of 97 patients) among SARS-CoV-2 seronegative patients at the initiation of vaccination. Receiving immunosuppressive therapy was an independent predictive factor for non-response to vaccination.

Conclusion. Due to high immunogenicity and safety of mRNA vaccines, we strongly recommend prioritizing a two-doses vaccination of dialysis patients. A third dose can be required in non-responders to two doses. When possible, patients waiting for a kidney transplantation, should be offered the vaccine before transplantation.

Keywords: COVID-19, hemodialysis, immunosuppression, peritoneal dialysis, SARS-CoV-2, seroconversion

KEY LEARNING POINTS

What is already known about this subject?

- Dialysis patients are at high risk of developing severe coronavirus disease-19
- Few data regarding the immunogenicity of anti-Severe Acute Respiratory Syndrome coronavirus-2 messenger RNA (anti-SARS-CoV-2 mRNA) vaccines in dialysis patients were published so far.

What this study adds?

- The study shows a high immunogenicity and safety of mRNA vaccines in dialysis patients
- It shows that patients given immunosuppresssants have a weak immunological response
- It shows that a third dose vaccine may be useful in non-responders to 2-doses.

What impact this may have on practice or policy?

- Dialysis patients should be prioritized to be vaccinated
- All patients awaiting for a kidney transplantation should be offered the vaccine

Abbreviations:

COVID-19, coronavirus disease-19

SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2

mRNA, messenger RNA

INTRODUCTION

Patients with chronic kidney disease, dialysis patients and kidney-transplant patients are at high risk of developing severe coronavirus disease-19 (COVID-19) [1] [2] [3]. A high COVID-19-related mortality rate was reported in dialysis patients that accumulate several risk factors for severe COVID-19, i.e. elderly, diabetes mellitus, cardiovascular risk factors, and for some of them immunosuppression due of a previous kidney transplantation or to ongoing non-kidney organ transplantation [3]. Despite enhanced barrier measures, the risk of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection remains high. Therefore, similarly to the general population, anti-SARS-CoV-2 vaccination is strongly recommended [4]. Anti-SARS-CoV-2 messenger RNA (mRNA) vaccines have been shown to be very efficient in preventing severe COVID-19 infections [5] [6]. They also induced a high immunogenicity [7]. In solid-organ-transplantation, recent data showed a week immunogenicity after mRNA anti-SARS-CoV-2 vaccination [8] [9]. In dialysis patients, the rate of seroconversion after vaccination is often reduced [10]. However, recent publications report high immunogenicity of anti-SARS-CoV-2 mRNA vaccine in dialysis patients [11] [12] [13] [14] [15] [16]. Very recently, the French National Authority for Health recommended the use of a third dose in immunosuppressed patients and dialysis patients [17]. In the present study, we assessed the immunogenicity of anti-SARS-CoV-2 mRNA vaccine in a population of patients on hemodialysis or peritoneal dialysis given two or three doses vaccine.

MATERIALS AND METHODS

Since anti-SARS-CoV-2 vaccines became available in France in January 2021, they were proposed to all patients undergoing hemodialysis or peritoneal dialysis in the dialysis unit of Toulouse University Hospital, a tertiary hospital.

Eighty-eight of the 132 hemodialysis patients gave their consent to be vaccinated (66.7%) (Figure 1). Of the remaining patients, 33 patients decline the vaccine, 9 patients had been infected by the SARS-CoV-2 within the last three months, and 2 patients had an ongoing medical complication requiring hospitalization. Eighty-five out the 88 patients had received at least two doses.

Twenty-four of the 33 patients on peritoneal dialysis gave their consent to be vaccinated (72.7%) (Figure 2). Of the remaining patients, 7 patients decline the vaccine, and 2 patients had been infected by the SARS-CoV-2 within the last three months. All 24 patients had received two doses. The characteristics of patients who received the vaccine are presented in Table 1.

According to French law (*loi Jardé*), anonymous retrospective studies do not require institutional review board approval.

Vaccine

Two injections of 30-µg doses of BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech), were administered intramuscularly 28 days apart. Vaccines were given at the dialysis center the day of dialysis session. A third dose vaccine was proposed to patients who were still seronegative at one month after the second dose, i.e. at one month after the second dose. After vaccination, patients were under medical surveillance for 30 minutes.

Virological parameters

Total antibodies against SARS-CoV-2 in serum samples were tested using an enzyme linked immunosorbent assay (ELISA) kit supplied by Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China, according to the manufacturer's instructions. Briefly, the ELISA for total antibodies detection was developed based on double-antigens sandwich immunoassay, using mammalian cell expressed recombinant antigen containing the receptor binding domain of the

spike protein of SARS-CoV-2 as the immobilized and HRP conjugated antigens. Samples were considered as positive if the S/Co was > 1.1 [18]. Antibodies concentrations were also determined.

Statistical analyses

Data are presented either as means (± SD) or medians (ranges). Proportions were compared by the χ^2 test or Fisher's exact test. Quantitative variables were compared by either Student's t-test or the Mann-Whitney test. Independent factors associated with non-response to vaccine were studied using a stepwise multivariate logistic regression model that used initial inclusion criteria that had a significance of p <0.05. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Immunogenicity in hemodialysis patients

Before vaccination, anti-SARS-CoV-2 antibodies were detected in 5 out of the 88 patients (5.7%) (Figure 1). All five patients had previously presented symptomatic COVID-19. After the first dose, one patient who was still seronegative developed one week after vaccination a symptomatic COVID-19 requiring hospitalization, another one who was also seronegative had undergone a heart transplantation and unfortunately deceased of multiorgan failure, and finally a third one who was seropositive (due to COVID-19 followed by a single vaccine dose) had undergone a successful kidney transplantation. The 85 remaining patients, were given the second dose. Before the injection of the second dose, anti-SARS-CoV-2 antibodies were detected in 22 patients (26%): 5 patients who were already positive before the first dose and 17 patients who seroconverted. Hence, the seroconversion rate after the first dose was 21.25% (17 out of 80 patients). Eighty-two patients had a follow-up of one month after the second dose. At

that time, anti-SARS-CoV-2 antibodies were detected in 69 patients (84.1%): 5 patients who were already positive before the first dose and 64 patients who seroconverted after vaccination. Among the 13 patients who didn't develop anti-SARS-CoV-2 antibodies after the two-doses vaccines, a third dose was offered to 12 patients. It was given one month after the second dose. The last patient died before the third dose from a cardiovascular event. All 12 patients had a one-month follow-up after the third dose. Of these 5 seroconverted. Hence, overall, anti-SARS-CoV-2 antibodies were detected in 74 out of 82 patients (90.2%). The seroconversion rate after two or three doses was 89.6% (69 out of 77 patients). All patients who were positive after the first dose were still positive one month after the second dose or third dose. Anti-SARS-CoV-2 antibodies concentrations are presented in Figure 2A.

Immunogenicity in patients on peritoneal dialysis

Before vaccination, none of the 24 patients had detectable anti-SARS-CoV-2 antibodies (Figure 3). Before the injection of the second dose, anti-SARS-CoV-2 antibodies were detected in 10 patients (41.7%). Twenty patients had a follow-up of one month after the second dose. At that time point, anti-SARS-CoV-2 antibodies were detected in 17 patients (85%). Anti-SARS-CoV-2 antibodies concentrations are presented in Figure 2B.

Factors associated with seroconversion

Among the 97 patients (both hemodialysis patients and those on peritoneal dialysis) who were seronegative before vaccination and received ~~the~~ at least 2 doses and who had at least one month follow-up after the last dose, 86 patients had anti-SARS-CoV-2 antibodies (88.7%). We looked for predictive factors for non-response to vaccination among the 97 seronegative patients at baseline. In univariate analysis, the proportion of patients having a non-kidney transplant, and consequently receiving immunosuppressive drugs, especially steroids was significantly higher

among dialysis patients who didn't develop anti-SARS-CoV-2 antibodies (Table 1). By means of multivariate analysis, receiving immunosuppressive therapy was an independent predictive factor for non-response to vaccination: OR 0.075 ($IC_{95\%:}$ 0.019-0.303), p=0.0003.

Safety

No serious adverse events were reported by patients who received the vaccine. With respect to adverse events, 20 patients experienced fatigue (n=15), myalgia (n=15) and low fever (n=7) for 24 hours.

DISCUSSION

Dialysis patients are at high risk of severe COVID-19 [1] [2] [3]. Therefore, it is recommended to offer them anti-SARS-CoV-2 vaccine. In dialysis patients, the seroconversion rate after vaccination is often reduced [19] [20]. For instance, the seroconversion rate after influenza vaccine ranges from 30 to 80% in dialysis patients [10]. The seroconversion rate after influenza A/H1N1 vaccination in hemodialysis patients is only 30% [21]. The poor response for anti-hepatitis B virus vaccination is also well known [22]. Several studies have recently reported a high immunogenicity of mRNA-based anti-SARS-CoV-2 vaccines in dialysis patients ranging from 81 to 96% [11] [12] [13] [14] [15] [16].

In this monocentric study, we have assessed the seroconversion rate after mRNA anti-SARS-CoV-2 vaccination. At one month after the first vaccine dose, anti-SARS-CoV-2 antibodies were detected in 26% on hemodialysis patients and 41.7% of patients on peritoneal dialysis. However, one month after the second dose, the proportion of seropositive patients raised to 84.1% and 85% in hemodialysis and peritoneal dialysis, respectively. Recently the French National Authority for Health recommended the use of a third dose in immunosuppressed patients and dialysis patients. Hence, we offered a third dose to 12 hemodialysis patients who

had failed to seroconvert after two vaccine doses. Five of these patients seroconverted. This report of use of a third vaccine dose is encouraging for non-responders. Overall, anti-SARS-CoV-2 antibodies were detected in 89.2%. This high response suggests that mRNA-based vaccines targeting non-SARS-CoV2 viruses could be tested in dialysis patients. After exclusion of patients who were positive at baseline, the seroconversion rate was 88.7%. Our results are in line with those published recently in this setting [11] [12] [13] [14] [15] [16]. In the general population, the seroconversion rate was at 100% at day 21 following vaccination [7]. A lower humoral response was reported in dialysis patients compared to a control group [11] [12].

In the present study, receiving immunosuppressive therapy was an independent predictive factor for non-response to vaccination. This finding is in line with recent data showing a weak immunogenicity of mRNA vaccines after the first dose in solid-organ-transplant patients [8] [9]. Grupper et al. have shown that a low lymphocyte count was associated with a low-humoral response [13].

This study has several limitations. It is a single center in which we measured the humoral response but not the cellular one. Neutralizing antibodies were not assessed. Only the BNT162b vaccine was used. Finally, we didn't compare data in dialysis patients to a control group with normal kidney function.

In conclusion, due to high immunogenicity and safety of mRNA vaccines, we strongly recommend prioritizing a two-doses vaccination of dialysis patients. A third dose can be given in non-responders. When possible, patients waiting for a kidney transplantation, should be offered the vaccine before transplantation.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the current paper to declare.

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Figure legend:

Figure 1: Vaccination chart flow and seroconversion rate in hemodialysis patients

Figure 2: Anti-SARS-Cov-2 antibodies concentrations in hemodialysis patients (2A) and patients on peritoneal dialysis (2B)

Figure 3: Vaccination chart flow and seroconversion rate in patients on peritoneal dialysis.

Table 1. Patients' characteristics at vaccination and comparison between patients who converted and those who did not one month after the second dose

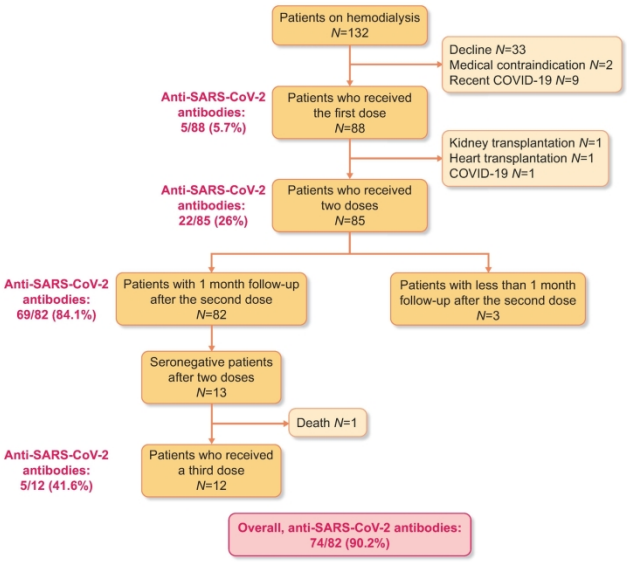
Variables	All population *N*=112	Patients who seroconverted *N=88*	Patients who didn't seroconvert *N=11*	*P*-value
Age (years)	64±14	64±14	70±12	0.12
Gender M/F	77/35	56/30	9/2	0.33
Hemodialysis/Peritoneal dialysis	88/24	69/17	8/3	0.69
Time on dialysis (months)	39±40	37±36	31±49	0.61
History of kidney transplantation (Y/N)*	19/93	13/73	4/7	0.1
Non-Kidney-transplantation (Y/N)**	5/107	1/85	4/7	0.0004
Diabetes mellitus	33%	37%	36%	0.99
Immunosuppressive therapy (Y/N)	20/92	10/76	7/4	0.0003
Calcineurin inhibitors (Y/N)	5/107	1/85	4/7	0.004
mTOR inhibitors (Y/N)	3/109	1/85	2/9	0.03
Mycophenolic acid (Y/N)	4/108	1/85	2/9	0.03
Steroid (Y/N)***	19/93	10/76	6/5	0.002
Hemoglobin level at baseline (g/dL)	11.6±1.8	11.6±1.8	11.6±1.8	0.96
Leucocyte count at baseline (/mm^3)	6735±2121	6707±2060	6947±2630	0.72
Neutrophils at baseline (/mm^3)	4761±1826	4462±1792	4755±2173	0.99
Lymphocyte count at baseline (/mm^3)	1021±660	993±490	1249±664	0.30
CD4-positive cell count (/mm^3)	386±228	394±227	308±237	0.34
CD8-positive cell count (/mm^3)	243±164	237±153	308±263	0.31
CD19-positive count (/mm^3)	104±85	103±160	80±84	0.45

Abbreviations: M, male; F, female; Y, yes; N, no; mTOR, mammalian target of rapamycin.

* Ten out of the 19 patients with history of kidney transplantation had received T-cell depleting agents. For the 19 patients, the time between kidney-allograft loss and vaccination was 36 (4-187) months.

** Four out the 5 patients who had received a non-kidney transplant had received T-cell depleting agents

*** Steroids were given in non-kidney-transplant patients, patients with recent kidney allograft loss and patients with recent history auto-immune diseases. In patients with failed kidney allograft, calcineurin inhibitors and anti-metabolites were stopped at the initiation of dialysis and steroids are pursued for 6 months.



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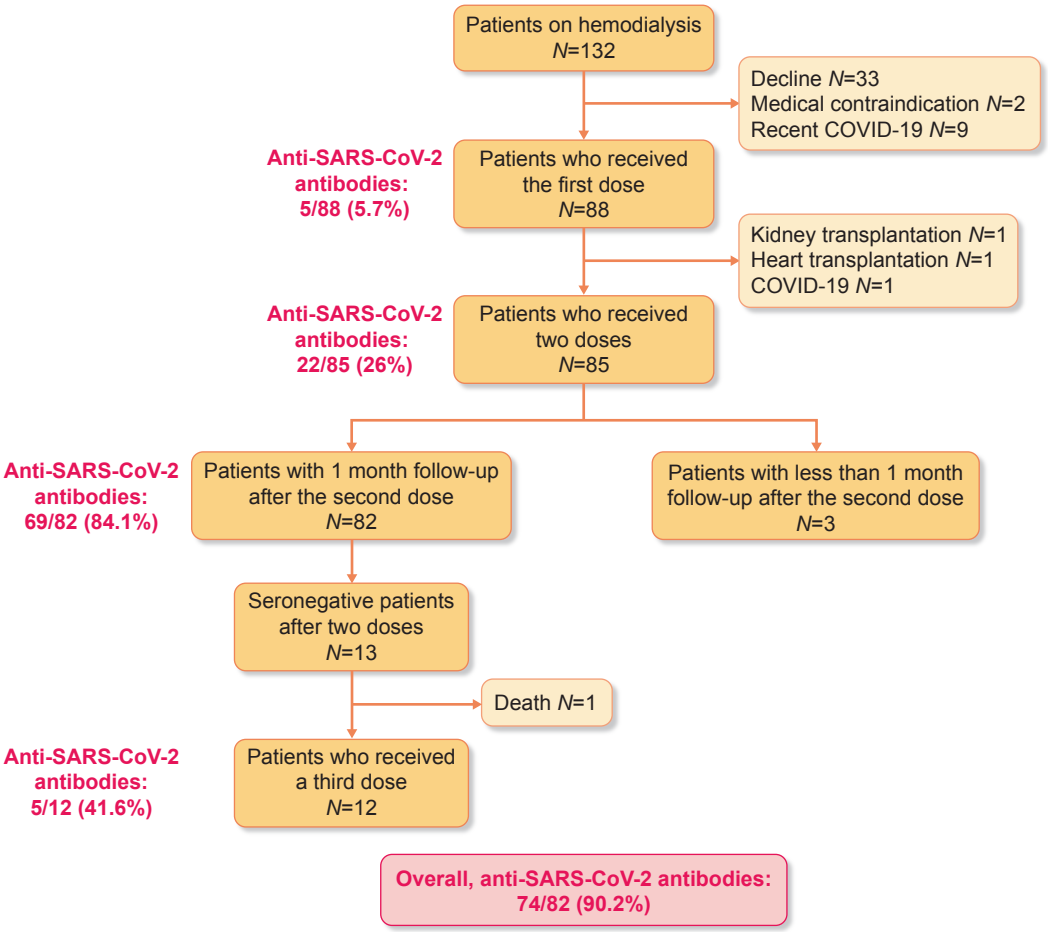

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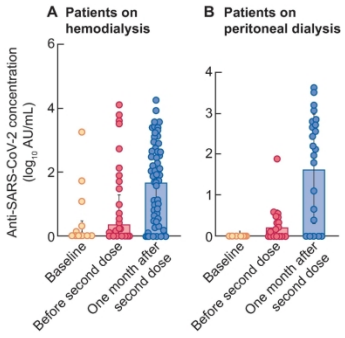

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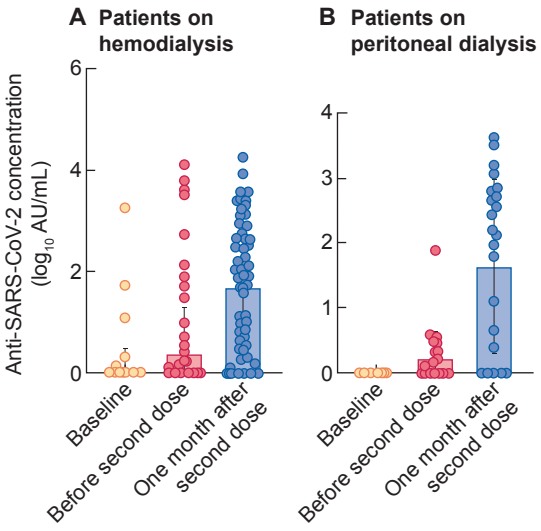

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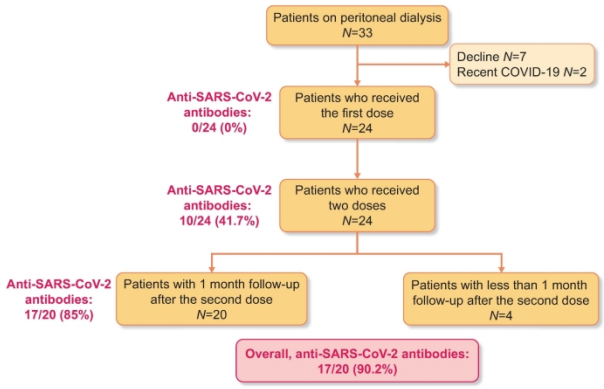

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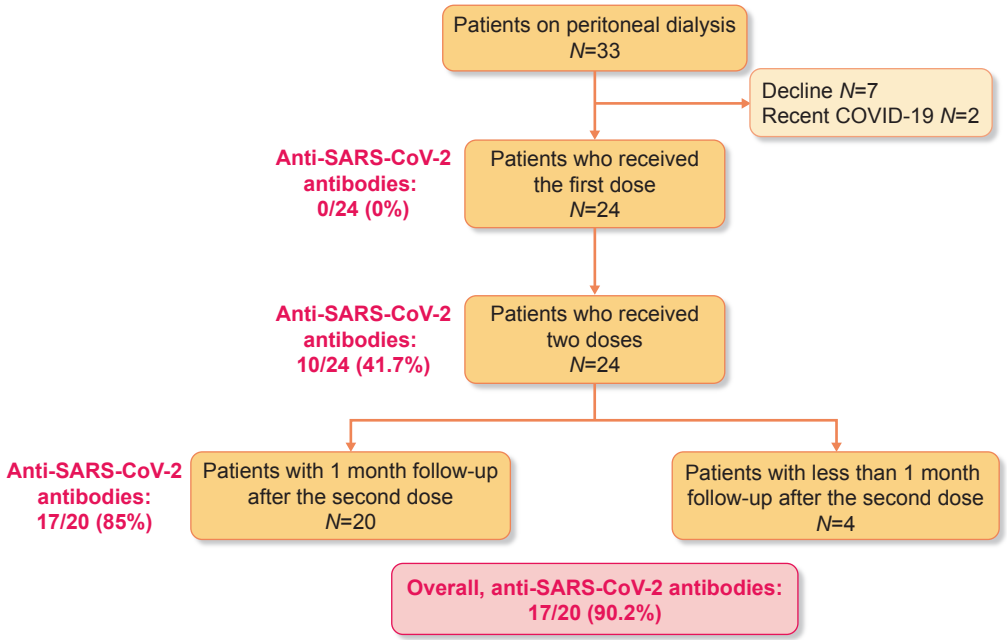

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