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ORIGINAL ARTICLE

Comparison of antibody response to two different mRNA Covid-19 vaccines in patients on hemodialysis

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Abstract

Introduction In hemodialysis patients, coronavirus disease 2019 is associated with high morbidity and mortality. Aim of the study was to evaluate the antibody level against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients treated with two different mRNA-based vaccines, in a multicenter survey.

Patients and methods Since April 2020, in the 5 participating Centers, periodic screening of all patients with PCR testing has been performed every 2 weeks. The study included two cohorts of patients on maintenance hemodialysis treated with the BNT162b2 or with the mRNA-1273 Covid-19 vaccine. The tests for antibodies against the receptor-binding domain was performed by the anti–SARS-CoV-2 S enzyme immunoassay (Roche Elecsys).

Results Of the 398 included patients, 303 received the BNT162b2 and 95 the mRNA-1273 vaccine. In patients without previous infection, the median levels of anti-S antibodies were 297 U/mL and 1,032 U/mL for those treated with BNT162b2 or mRNA-1273, respectively ($p < 0.001$). In patients with previous infection, the median levels of SARS-CoV-2 anti-S antibodies were 7,516 U/mL and 17,495 U/mL for those treated with BNT162b2 or mRNA-1273, respectively ($p = 0.005$). The Charlson comorbidity index (CCI) was significantly associated with protective levels of anti-spike IgG, with 3.6% of low- or non-responders having a CCI of 2–4 versus 18.9% in those with a CCI of 8 or more. The adjusted OR of developing a sufficient antibody level between the two vaccines was 3.91 ($p = 0.0766$) in favor of mRNA-1273.

Conclusions Both of the evaluated mRNA-based vaccines for SARS-CoV-2 showed good efficacy. Preliminary data may data suggest a higher antibody response to the mRNA-1273 vaccine.

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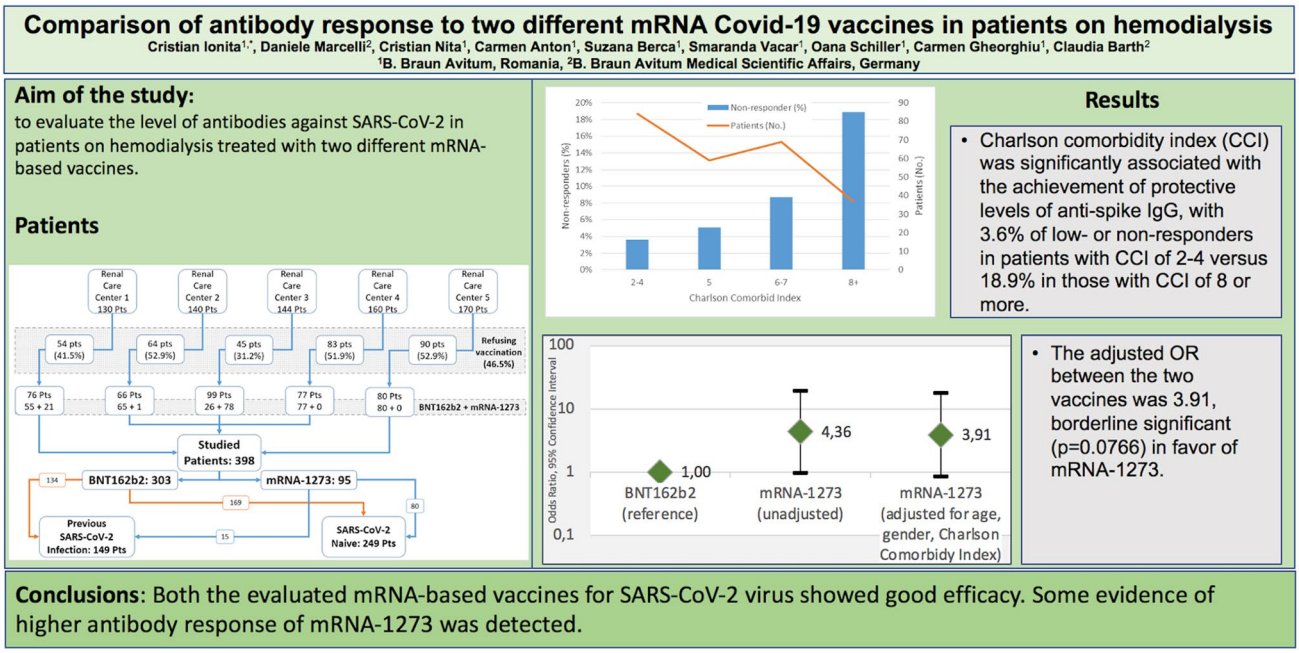
Graphical abstract



Keywords SARS-Cov-2 vaccination · mRNA-based SARS-Cov-2 vaccine · Hemodialysis patients · Humoral response

Introduction

The first cases of coronavirus disease 2019 (Covid-19) were detected in Wuhan, China, in December 2019. Since the first onset of the illness it has spread to millions of people worldwide. Finally, the WHO declared the pandemic status. This disease is characterized by high mortality among the elderly and patients with pre-existing morbid conditions.

Innate immunity is a defense mechanism for immediate response to a variety of stimuli, including viruses. It consists of the activation and participation of pre-existing mechanisms, involving (the monocyte subsets) natural killer cells and natural killer T cells. In end-stage renal disease the -cell counts of both are diminished, indicating innate immune-system dysregulation [1]. In addition, patients on hemodialysis have a higher risk of infection for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to comorbidities, as well as to limited capacity to respect rigid social distancing. In fact, they often travel to and from the dialysis unit by common transportation, they undergo a 3-session per week schedule in rooms with many other patients, and they may have to spend time in the waiting room of the dialysis unit. In hemodialysis patients, who are usually affected by several comorbidities, Covid-19 is associated with higher morbidity and mortality [2], as occurred in 2009 with the influenza A(H1N1)v pandemic in Latin America [3]. For these reasons, patients on dialysis were prioritized for vaccination in many countries, including Romania [4]. Finally, patients with advanced chronic renal insufficiency, and especially those on dialysis, are known to have a reduced immune response to vaccinations [5]. Nevertheless, the possible hyporesponsiveness to vaccines due to reduced innate and adaptive immune systems should not prevent patients on dialysis from receiving vaccination [6]. Higher vaccine dosage or scheduling changes were required in patients with Hepatitis B [7].

In an attempt to gain control of the pandemic, several vaccines were developed and approved within a very few months. Nonetheless, live attenuated vaccines should be avoided in patients on hemodialysis because of their dysregulated immune system. In Romania, both the mRNA Covid-19 vaccines BNT162b2 [8] and mRNA-1273 [9] were available for patients on hemodialysis. However, the pivotal trials that demonstrated 94–95% protection against Covid-19 infection following a 2-dose regimen of the BNT162b2 or mRNA-1273 vaccine did not report data concerning patients on maintenance hemodialysis [8, 9]. Actually, the Pfizer BiONTech trial of the BNT162b2 vaccine included 256 patients with renal disease but no further details on the stages of chronic kidney disease were reported [8]. A novel vaccine candidate (NVX-CoV2373) in a newly initiated phase III trial is prioritizing the enrollment of patients

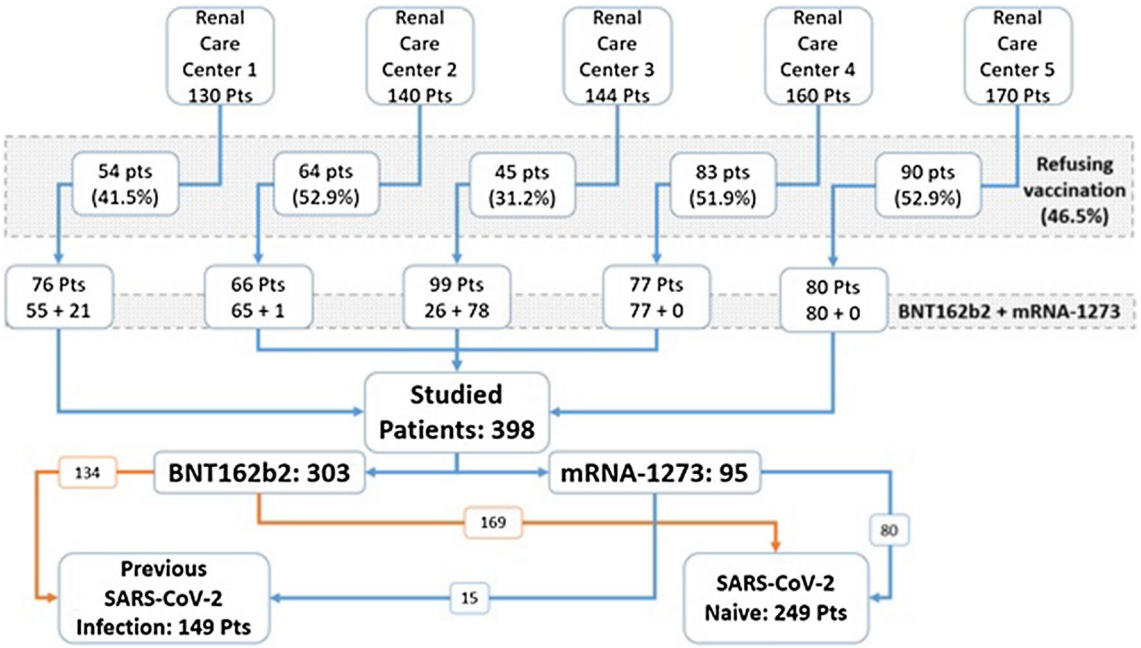


Fig. 1 Flow-chart from the patients treated in the 5 Renal Care Centers to those selected for the study

with underlying medical conditions including CKD [10]. Of course, results will come in due time. A recent review [11] reported 9 studies comparing the effectiveness of Covid-19 vaccinations. Altogether, 853 patients on maintenance dialysis (range 22–154) were compared to 465 controls (range 7–132). Ninety-eight point two% of patients were treated with BNT162b2, only 12 of whom, as reported by Lesny et al. [12], received a viral vector-based vaccine (AZD1222).

Due to the paucity of evidence on the response to the standard protocol for mRNA Covid-19 vaccines, the aim of our study was to evaluate the level of antibodies against SARS-CoV-2 in patients on hemodialysis treated with two different mRNA-based vaccines.

Patients and methods

Study design

In the five Renal Care Centers participating in the study, periodic screening of all patients has been performed every 2 weeks, irrespective of symptoms, since April 2020. This was the policy set by health authorities. More in detail, the diagnosis of SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) testing of nasopharyngeal swabs, processed according to the diagnostic protocol, which was standardized following the WHO guidelines.

The study included two cohorts of patients on maintenance hemodialysis treated with either the BNT162b2 or with the mRNA-1273 Covid-19 vaccine. The vaccine was chosen according to its availability at the time, and was maintained for the second dose as well. The recommended dosing interval of 21 days between the first and the second doses of the BNT162b2 and of 28 days for the mRNA-1273 vaccine was respected. Vaccination was delivered between January 8 and March 20, 2021. Altogether, 398 of 744 patients on maintenance hemodialysis in 5 Renal Care Centers of the B. Braun Avitum network in Romania had received two doses of the vaccines and were eligible to participate in this study. The flow chart describing the patient selection process is reported in Fig. 1.

Blood samples for the immunogenicity assessment (antibody testing) were taken between March 21 and May 4, 2021. The samples were tested using the anti–SARS-CoV-2 S enzyme immunoassay (Roche Elecsys) that tests for antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein. The test is semiquantitative, corresponds to mRNA vaccine antigens, and is consistently correlated with neutralizing immunity. The sensitivity and specificity of the enzyme immunoassay is excellent for detecting the anti-spike humoral response to SARS-CoV-2 infection (sensitivity of 84.0% and specificity of 100%) and is analogous to the anti-spike antibody assays used for immunogenicity assessments in mRNA vaccine clinical trials.

According to Simon et al. [13], patients were classified as low- or non-responders to the BNT162b2 or to the mRNA-1273 vaccine if they did not achieve protective antibody titers greater than 29 U/mL after their second vaccine dose. In addition, patients were considered to have

achieved a robust response in case of an antibody result of ≥ 200 U/mL. This limit was found to correlate with the maximal neutralizing capacity in the neutralization assays [14].

For the correlation between Hepatitis B vaccination responders and SARS-CoV-2 vaccination responders, Hepatitis B vaccine responders were defined as having a Hepatitis B antibody titer > 20 IU/mL after the completed Hepatitis B vaccination cycle.

The dialysis dose was measured by eKt/V based on pre and post dialysis blood urea samples, calculated using the Daugirdas formula [15]. Hemodialysis prescription details, dialysis vintage, age, gender, presence of comorbidities, Hb_SAg and HCV status, previous Hepatitis B vaccination, HBsAb levels, presence of previous Covid-19 infection and prescription of immunosuppressive therapy were obtained from the patients' medical charts.

All patients were being treated with B. Braun Dialog + ® machines, equipped with B. Braun Sol-Cart® B and connected to 10-L B. Braun SW acidic bicarbonate concentrate 1 + 34 canisters. The bloodlines were B. Braun A/V Set for Dialog with recirculation system for ECOPRIME concept, and the dialyzers were mainly B. Braun Xevonta®.

Statistical analysis

All data were summarized and displayed as mean (SD) or as median and interquartile range for the continuous variables, and as number of patients and the percentage in each group for categorical variables. For all categorical variables, the chi-square statistic was used to assess the statistical significance between groups. Continuous variables were first tested for normal distribution using the Kolmogorov–Smirnov test and quantile–quantile plots, then parameters were compared by using a t-test if normally distributed or by Mann–Whitney U test if not normally distributed.

A logistic regression model was applied to evaluate the relationship between the achievement of a level of protective antibody titer greater than 29 U/mL after a second vaccine dose and a list of predictors, including age and gender, as already reported by Simon et al. [13], Charlson Comorbidity Index (CCI), dialysis vintage, eKt/V, the time in days between the test for antibodies and the second vaccine dose, and the type of SARS-CoV-2 vaccine.

$P < 0.05$ was considered statistically significant for all analyses. IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY) was used for all statistical analyses.

Results

Seven hundred forty-four patients were on treatment in the 5 participating Renal Care Centers at the time of the study. Forty-six point five% of the patients refused the vaccination or even just the second dose of the vaccine after rumors of adverse events reported by the media (Fig. 1). Of the 398 patients included in the study, 303 (76.1%) received 2 doses of the BNT162b2 and 95 of the mRNA-1273 vaccine (23.9%). Among the patients treated with the BNT162b2 vaccine, 44.2% had had a previous SARS-CoV-2 infection, whereas only 15.8% of subjects receiving the mRNA-1273 vaccine had had a previous infection. The median number of days between the detection of SARS-CoV-2 infection and the delivery of the first dose of the vaccine was 98 (25–75% percentiles: 66–165 days) and 95 days (25–75% percentiles: 30–123 days) for patients treated with

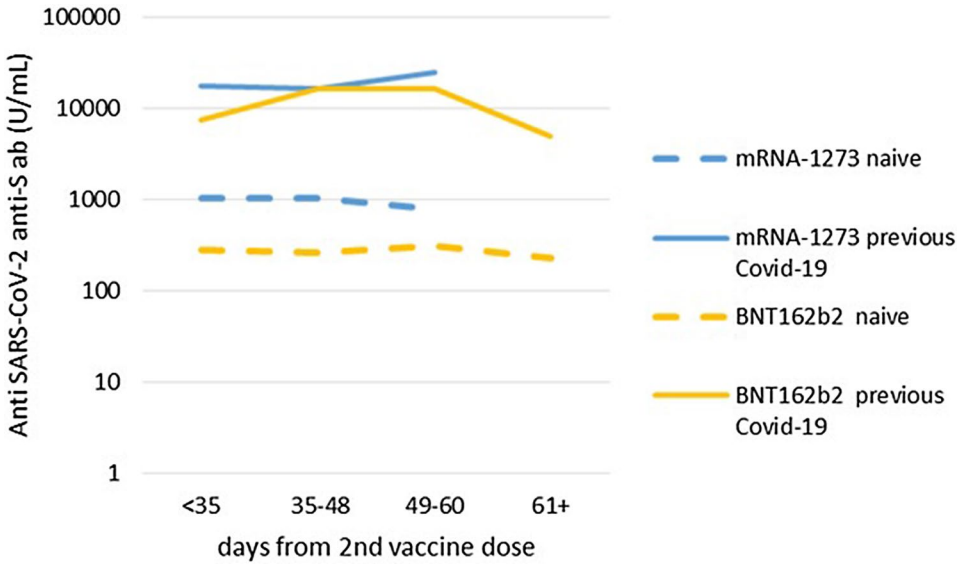


Fig. 2 Median levels of SARS-CoV-2 anti-S antibodies by vaccine type, presence of previous Covid-19 and by days from the second dose of the vaccine

Table 1 Patient description by vaccine type in non-previously infected patients

	All	BNT162b2	mRNA-1273 vaccine	p-value
Patients (No.)	249	169	80	
Age (years)	63.1 ± 11.5	62.2 ± 12.0	65.0 ± 10.0	0.074
Gender, females (%)	35.3	36.1	33.8	0.777
Dialysis vintage (years)	5.3 ± 4.4	5.4 ± 4.5	5.1 ± 4.2	0.621
Presence of comorbidities (%)				
Myocardial infarction	10.0	12.4	5.0	0.075
Congestive heart failure	20.1	23.7	12.5	0.043
Peripheral vascular disease	21.3	26.6	10.0	0.003
Cerebrovascular disease	14.1	17.2	7.5	0.050
Dementia	2.4	1.2	5.0	0.086
Chronic pulmonary disease	11.2	9.5	15.0	0.204
Rheumatologic disease	3.6	4.7	1.3	0.279
Peptic ulcer disease	10.4	11.8	7.5	0.377
Liver disease	9.6	10.1	8.8	0.822
Diabetes	24.5	20.7	32.5	0.058
Hemiplegia or paraplegia	0.8	1.2	0.0	1.000
Malignancy	10.0	10.7	8.8	0.822
Leukemia	0.0	0.0	0.0	-
Lymphoma	0.4	0.0	1.3	0.321
AIDS	0.0	0.0	0.0	-
Charlson Comorbidity Index (%)				
2–4	33.7	35.5	30.0	0.114
5	23.7	20.7	30.0	
6–7	27.7	26.0	31.3	
8 +	14.9	17.8	8.8	
Hepatitis Markers (%)				
HBsAg +	5.2	5.3	5.0	1.000
HCV	6.0	5.3	7.5	0.571
Time from 2nd dose vaccine to SARS-CoV-2 Ab test (days)	48 ± 14	53 ± 14	37 ± 7	> 0.001

Table 2 Main dialysis dose components of the evaluated patients by vaccine type

	All	BNT162b2	mRNA-1273	p-value
Patients (No.)	249	169	80	
Treatment frequency sessions/week)				
1	1	1	0	0.682
2	2	1	1	
3	246	167	79	
Treatment time (hours/week)	11.9 ± 0.9	11.8 ± 1.0	12.0 ± 0.5	0.221
eKt/V	1.35 ± 0.21	1.38 ± 0.22	1.28 ± 0.16	0.001

BNT162b2 or mRNA-1273, respectively (p = 0.799). As compared to patients treated with the mRNA-1273 vaccine, the group treated with BNT162b2 was significantly younger (61.0 ± 12.6 vs. 64.7 ± 11.1 years, p = 0.01) and had a significantly lower proportion of patients with diabetes (22.8 vs. 33.7%, p = 0.033) and dementia (1.0 vs. 4.2%, p = 0.037), but a significantly higher proportion of patients with congestive heart failure (21.8 vs. 12.6%, p = 0.050), peripheral vascular disease (27.4 vs. 10.5%, p = 0.001) and cerebrovascular disease (17.2 vs. 7.4%, p = 0.019).

Four patients, i.e., 3 with multiple myeloma and 1 with granulomatosis with polyangiitis, were on immunosuppressive treatment (2 with Lenalidomide, 2 with glucocorticoid medications), one of whom had previously been infected by SARS-CoV-2 virus. Two received the BNT162b2 and two

Table 3 Results of Univariate logistic regression in patients not previously infected by SARS-CoV-2 aimed at testing the association with the presence of SARS-CoV-2 antibodies on a protective level. Univariate Odds Ratios between patients' characteristics, Charlson Comorbidity Index, key dialysis features, length of interval between the date of 2nd vaccine dose and of SARS-CoV-2 antibody evaluation, type of mRNA vaccine and presence of SARS-CoV-2 antibodies on a protective level

Variable	Reference	Odds ratio	95% CI	p-value
Age ≥ 60 years	Age < 60 years	0.54	0.17–1.68	0.2885
Male gender	Female	0.63	0.22–1.82	0.3953
Charlson Comorbidity Index	per point	0.77	0.57–0.89	0.0033
Dialysis vintage	per year	1.06	0.93–1.20	0.3783
eKt/V	per eKt/V unit	1.15	0.12–10.90	0.9028
interval test—2nd vaccine dose	per day	0.99	0.96–1.02	0.5764
mRNA-1273	BNT162b2	4.36	0.98–19.36	0.0527

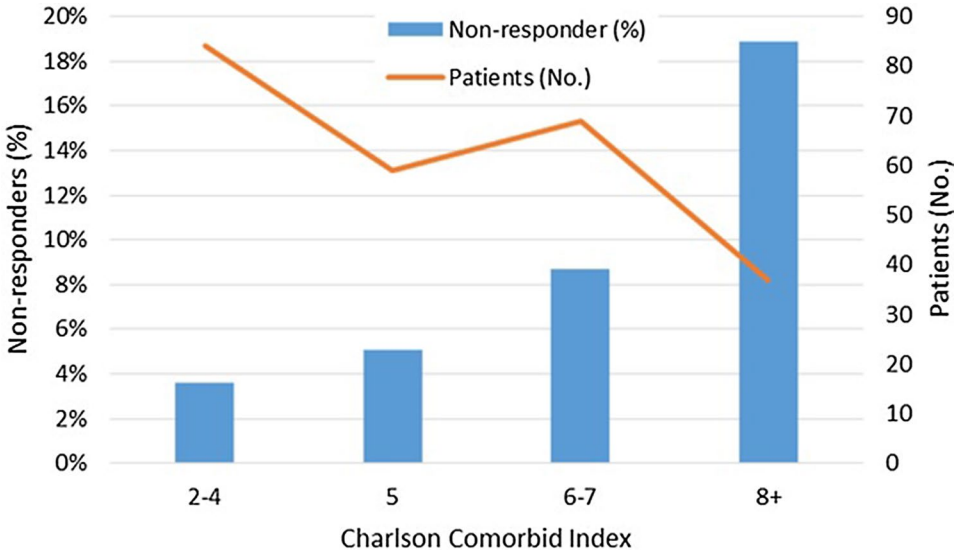


Fig. 3 Proportion of patients not developing SARS-CoV-2 antibodies on the protective level by Charlson Comorbid Index

received the mRNA-1273 vaccine. All four patients showed a positive response to the vaccination.

Figure 2 reports the median levels of SARS-CoV-2 anti-S antibodies by vaccine type, by the presence of previous Covid-19, and by the number of days from the second dose of the vaccine. In the time interval explored by the study, the median levels of antibodies did not show significant changes. Patients with previous infection showed significantly higher levels of SARS-CoV-2 anti-S antibodies (median, 25–75% percentiles: 8,085, 3,061–23,932 vs. 486, 123–1,940 U/mL, $p < 0.001$). In patients without previous infection, the median levels of SARS-CoV-2 anti-S antibodies were 297 U/mL (25–75% percentile: 78–939 U/mL) and 1,032 U/mL (25–75% percentile: 440–2,687 U/mL) for those treated with BNT162b2 or mRNA-1273, respectively ($p < 0.001$). In patients with previous infection, the median levels of SARS-CoV-2 anti-S antibodies were 7,516 U/mL (25–75% percentile: 2,846–22,590 U/mL) and 17,495 U/mL (25–75% percentile: 7,605–35,127 U/mL) for those treated with BNT162b2 or mRNA-1273, respectively ($p = 0.005$). Patients without previous Covid-19.

The description of patients without previous SARS-CoV-2 infection by vaccine type is reported in Table 1. Of the 249 virus-naive patients, 169 (67.9%) received the BNT162b2 and 80 received the mRNA-1273 vaccine (32.1%). Compared to patients treated with the mRNA-1273 vaccine, the group treated with BNT162b2 was borderline significantly younger ($p = 0.074$) and with a lower proportion of patients with diabetes ($p = 0.058$), but with a borderline significantly higher proportion of patients with myocardial infarction ($p = 0.075$), and a significantly higher proportion of patients with congestive heart failure ($p = 0.043$), peripheral vascular disease ($p = 0.003$) and cerebrovascular disease ($p = 0.050$). The main components of the dialysis dose delivered to the evaluated patients are reported in Table 2. Treatment time and frequency were not significantly different between patients treated with the two vaccines. However, eKt/V was significantly greater in the patients who received the BNT162b2 vaccine ($p = 0.001$).

Table 4 Results of the multivariable logistic regression between type of mRNA vaccine and presence of SARS-CoV-2 antibodies on a protective level adjusted for age, gender and Charlson Comorbid condition in patients not previously infected by SARS-CoV-2

Variable	Reference	Odds Ratio	95% CI	p-value
Age ≥ 60 years	Age < 60 years	1.32	0.31–5.55	0.705
Male gender	Female	0.80	0.27–2.41	0.6917
Charlson Comorbidity Index	Per point	0.72	0.54–0.94	0.018
mRNA-1273	BNT162b2	3.91	0.86–17.70	0.0766

Among the 249 SARS-CoV-2 naive patients, 19 patients did not develop SARS-CoV-2 antibodies at a protective level, including 2 who were vaccinated with the mRNA-1273 (2.5%) and 17 with the BNT162b2 (10.1%) vaccine. The unadjusted odds ratio between mRNA-1273 and BNT162b2 was 4.36, borderline significantly (p = 0.0527) in favor of mRNA-1273. At univariate logistic regression (Table 3), the Charlson comorbidity index was significantly associated with the protective levels of anti-spike IgG after SARS-CoV-2 vaccination, with the proportion of low or non-responders ranging from 3.6% in patients with a CCI of 2–4 to 18.9% of those with a CCI of 8 or more (Fig. 3). After adjusting for age, gender, which were considered significantly associated by Simon et al. [13], and CCI, the odds-ratio between mRNA-1273 and BNT162b2 was 3.91 (p = 0.0766) in favor of mRNA-1273 (Table 4).

Discussion

The pivotal trials that demonstrated 95% protection against Covid-19 infection following a 2-dose regimen of the BNT162b2 and the mRNA-1273 vaccine did not include patients on maintenance hemodialysis [6, 7]. A recent review [11] showed that patients on hemodialysis present lower SARS-CoV-2 antibody titers compared with healthy controls. Therefore, they could be much less protected by SARS-CoV-2 mRNA vaccinations than expected. In our study, patients treated with BNT162b2 had a median of 297 U/mL (interquartile range 851 U/mL), which was comparable to what was detected by Simon et al. [13] (171 U/mL, interquartile range 478 U/mL), and by Yanay et al. [16], using a different assay. In the past, because of the immunocompromised status of uremic patients [17], different approaches were suggested in an attempt to improve the immune response, including increasing the dose of vaccine to protect from Hepatitis B [7]. Therefore, the first experiences with the vaccine against SARS-CoV-2 infection were very important to establish vaccination plans in this high risk population. The current study not only confirms what was reported by Grupper et al. [18], showing that patients on hemodialysis develop a humoral response after the 2-dose vaccination with BNT162b2, resulting in a protective antibody level of (90%), but also with the mRNA-1273 vaccine (97% protective antibody level). The nephrology community can thus be reassured and patients can be encouraged to receive the vaccine, thereby improving the current low acceptance rate recorded in may settings, that was of 53.5% in the evaluated Romanian renal care centers. However, the significant association with the Charlson Comorbidity Index suggests integrating the CCI score when deciding regular testing for neutralizing antibodies after vaccination. In addition, in our dialysis patients with no or weak seroconversion after vaccination further studies on alternative vaccination strategies (dosing and schedule, frequency) [13], or respiratory mucosal vaccination [10] are urgently needed.

In our study we found significantly higher antibody levels against SARS-CoV-2 in patients who had previously been infected by the virus. Prior to vaccination, patients were tested systematically every 2 weeks for the presence of the viral infection by using the real time PCR test on nasopharyngeal swabs. Our results confirm what was already reported for healthcare workers [19], i.e. a faster response to the vaccine in subjects on dialysis who had already recovered from a previous infection sharing the conclusion of Gobbi et al. [19] regarding uremic patients: 'in previously infected people, a single dose of the vaccine might be sufficient to induce an effective response'.

When comparing different vaccines, the advantages and disadvantages in the general population and in specific subgroups (i.e., patients on hemodialysis) with respect to immunogenicity, efficacy, safety and cost must be considered. In the case of the two vaccines evaluated in this study, the vaccine type is the same (mRNA). Both vaccines require a second boost for optimal response. According to the meta-analysis by McDonald et al. [20], in terms of antibody response, the mRNA vaccine achieving the highest antibody titer in healthy adults was mRNA-1273 [21, 22], showing dose and boosting dependent increases. In the network meta-analysis published by Rogliani et al. [23] the BNT162b2 was estimated as largely overlapping with mRNA-1273 (0.90; 95% C.I. 0.40–1.40).

Our study showed a non significant benefit (p = 0.0766) in terms of antibody protection in not previously infected dialysis patients treated with mRNA-1273,

thereby indirectly supporting the conclusions of the meta-analysis published by McDonald et al. [20]. In addition, in this study an antibody level corresponding to maximum neutralization was found in 58.6% of patients treated with BNT162b2. Simon et al. [13], evaluated the same vaccine with the same antibody assay and reported a 47% maximum neutralization antibody level. In our study, a significantly higher percentage (87.5%) of patients treated with 2 doses of mRNA-1273 vaccine achieved this threshold. However, given the limited number of patients treated with this vaccine, these results have to be evaluated with caution.

The general stress on the healthcare system and the complexity of isolating SARS-CoV-2 patients during in-center hemodialysis treatment forced some dialysis centers to decrease the number of weekly sessions [4]. This may compromise not only patient care but also the immune response to vaccine. In the 5 centers participating in the study, the treatment schedule of three sessions per week was maintained for 99% of patients. Kt/V was significantly lower in patients treated with the mRNA-1273 vaccine, but an association with lower response was not detected.

Finally, limited information is available regarding patients on immunosuppressive therapy. In this study the four patients on different immunosuppressive regimes developed an antibody response to the mRNA-based vaccines.

In conclusion, both of the evaluated mRNA-based vaccines for SARS-CoV-2 showed good efficacy in terms of development of antibodies. A high Charlson comorbidity index was associated with a lower response, and could serve as a risk stratifier in the frequency of monitoring the antibody titer.

Previously infected patients might need only one boosting dose, however, it has to be stressed that only humoral-mediated immunity was tested. The antigen-specific T-cell response induced by the investigated vaccines may also contribute to their long-term efficacy. In addition, T-cell response may diverge from the levels and quality of SARS-CoV-2 antibodies and this important aspect needs further investigation.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical statement Written informed consent was obtained from all participants; all participants were informed about the confidentiality of the information and the project's purpose. The authors confirm that all the methods used in this study comply with the ethical standards of the Helsinki Declaration. Ethical approval was not sought for the present study because not required.

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