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Safety and Tolerability of mRNA COVID-19 Vaccines in Kidney Transplant Recipients

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ABSTRACT

Background. COVID-19 mRNA vaccines have demonstrated excellent short-term safety in phase 3 trials. However, no kidney transplant recipients (KTR) were included. The aim of the study was to assess the safety and tolerability of COVID-19 mRNA vaccines in KTR.

Materials and Methods. A longitudinal controlled study was conducted in 300 KTR and 143 control patients (CRL) without chronic kidney disease who had received 2-dose vaccinations with the mRNA vaccine. Solicited local and systemic reactogenicity and unsolicited adverse events were assessed with a standardized questionnaire. The toxicity grading scales were derived from the FDA guidelines.

Results. KTR (62.7% men) with a median (interquartile range) age of 53 (41-63) and transplant vintage of 7.25 (3-13) years did not differ with respect to age and sex distribution from CRL. One hundred percent CRL and 83.3% KTR were vaccinated with BNT162b2 (BionTech/Pfizer); 16.7% KTR received mRNA-1273 (Moderna) vaccine. Any local reactions were present in 84.7% (first dose) and 65.3% (second dose) KTR vs 67.1% and 60.1% CRL within 7 days after the vaccination. Any systemic reactions were reported by 26.7% (first dose) and 20.9% (second dose) KTR vs 24.7 and 35.7% CRL. The most common systemic reactions in KTR were fatigue, headache and myalgia. No serious adverse events were observed. Many systemic reactions were observed less frequently in KTR than CRL. Younger KTR (<54 years) reported any local and any systemic reactions significantly more frequently than older patients.

Conclusion. mRNA COVID-19 vaccines are safe and well-tolerated by KTR. The results may resolve patients' doubts and reduce their vaccine hesitancy.

KIDNEY transplant recipients (KTR) are particularly vulnerable to infections including SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. It is a result of the impaired immunity of patients with chronic kidney disease and the need to take immunosuppressive drugs after kidney transplantation. KTR in the UK registry were infected less frequently than patients on the waiting lists, but their mortality rate was 2.5-times higher (10.2% vs 25.8%) [1]. It was found that the COVID-19-related mortality among KTR ranged from 17.9% to 28%. The mortality in hospitalized KTR was 37.8%, 23% of them required kidney replacement therapy and 6.3% lost their allografts [2,3]. Moreover, even 60% short-term mortality has been reported in the case of older KTR [1,4]. In the absence of an effective COVID-19 treatment the only chance to improve prognosis is an effective COVID-19 vaccination [5]. Many patients refuse vaccination because of the possibility of side effects. This vaccine hesitancy, according to a survey performed on 1000 adult Poles, reaches 49.2% [6]. Patients are concerned over solicited local, systemic reactogenicity, and most of all unsolicited adverse events such as rare

The paper was supported by educational grant ST 02-0004/07/122 of the Medical University of Gdańsk.

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2022.02.025

thrombotic events, anaphylaxis and ischemic stroke. mRNA vaccines against SARS-CoV-2 approved for use in the United States and Europe were shown to have a favorable safety profile, and its reactogenicity was generally mild or moderate [7,8]. However, pivotal studies were not performed in the population of KTR. The aim of the study was to assess the safety and tolerances of vaccinations with COVID-19 mRNA vaccines performed in KTR according to the manufacturer's protocol, and comparing the results in the general population that received the same vaccines. Awareness of the anticipated side effects and their frequency and severity may resolve patients' doubts and reduce their vaccine hesitancy.

MATERIALS AND METHODS

Retrospective and longitudinal analysis was conducted in the whole population of KTR from the Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk vaccinated with the first dose of intramuscular mRNA-Covid vaccine between March 8, 2021 and the March 24, 2021. According to the rules of the national immunization program, and the manufacturer's recommendations, patients received the second dose after no more than 42 days. The control group, matched for age and gender, consisted of patients without chronic kidney disease vaccinated in the University Center of Maritime and Tropical Medicine in Gdynia with the same vaccines and doses. Medical data of participants from both groups were taken from their medical history. In this report, safety data are reported for all patients who signed an informed consent form.

The primary end points of the study were solicited local and systemic reactogenicity, unsolicited adverse events reported by the participants of the study. The questionnaire used in registry studies of the mRNA vaccines, mRNA Comirnaty (Pfizer/BioNTech) and mRNA Spikevax (Moderna), was used to assess the adverse events [7,8]. Solicited local (pain, redness, and swelling) and systemic reactogenicity (fever, fatigue, headache, chills, vomiting, diarrhea, and new/worsened muscle or joint pains) were graded in a 1 to 4 scale as we previously described [9]. Data were registered within the 7 days from the first and second dose of vaccination, and within 30 days of the second dose of vaccine, assessed with a standardized questionnaire during a telephone interview. The grading scales (the same as in the pivotal trial) used in this study were derived from the FDA Center for Biologics Evaluation and Research guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials [7,8]. In secondary analyses we evaluated the vaccine safety in subgroups. We used the following strata: age (18-55 years vs >55 years, the same as in the pivotal study), sex, diabetes, neoplastic disease, median body mass index (BMI) (<25.31 vs ≥25.31), median Charlson Comorbidity Index (CCI) (<4 vs ≥4), and the median time after kidney transplantation (<7.25 vs ≥7.25). The study is part of the "COVID-19 in Nephrology" project registered in ClinicalTrials.gov, identifier NCT04905862. The results were compared with the results published in the registry study and the results of the control group.

STATISTICAL ANALYSIS

We report descriptive results of the safety analyses, and the sample size was not determined on statistical hypothesis testing. Data were presented as a percentage for categorical variables, and as a median (interquartile range) for continuous variables. $\chi 2$ or Fisher's exact test was used for categorical variables. Mann-Whitney *U*-tests or *t* tests were used to compare continuous variables as appropriate. $P < .05$ was considered significant.

RESULTS

Between March 8, 2021, and the March 24, 2021, 326 patients were vaccinated with 1 dose of mRNA vaccine. One patient refused to participate in the study. Twelve patients got sick (ie, 9 got COVID-19 [1 patient died] and 3 had other infections). It proved impossible to contact 14 patients by phone. Finally, 300 patients got the second dose of the mRNA vaccine, and were included to the study. A total of 250 participants were vaccinated with mRNA Comirnaty (Pfizer/BioNTech) and 50 were vaccinated with mRNA Spikevax (Moderna). One hundred eighty-eight participants were men (62.7%) and 112 were women, with a median age (interquartile range) of 53.0 years (41-63). The median transplant vintage was 7.25 (3-13), 7% had living donors. Median Comorbidity Index was 4 (2-5), median BMI was 25.31 (22.6-28.4). Seventy-four patients (24.7%) had diabetes, 48 patients (16%) had neoplastic disease, and 279 patients (93%) had hypertension. The control group consisted of 143 patients without chronic kidney disease—90 men (62.9%) and 53 women (37.1). The median age, BMI, and sex distribution were similar in both groups. The median Charlson Comorbidity Index was significantly lower in the control group and less patients suffered from hypertension in the control group (Table 1).

Local Reactogenicity

Of the KTR, 84.7% and 65.3% ($P < .001$) of patients reported at least 1 local side effect within 7 days after first and second doses of the mRNA vaccination, respectively. Most of the adverse reactions were mild. Only 1 participant reported severe (grade 3) redness after the first dose of the vaccine. The most frequently reported local adverse reaction was pain at the injection site (84.3% after first dose and 64.3% after second dose).

Table 1. Characteristics of Kidney Transplant Recipients and the Control Group

	Kidney Transplant Recipients n = 300	Control Group n = 143
Age in years median (IQR)	53 (41-63)	56 (43-64)*
Male gender n (%)	188 (62.7)	90 (62.9)*
BMI kg/m^2 median (IQR)	25.31 (22.6-28.4)	26.08 (23.04-28.58)*
Transplant vintage (y) median (IQR)	7.25 (3-13)	NA
Diabetes mellitus n (%)	74 (24.7)	NA
Neoplastic disease n (%)	48 (16)	NA
Arterial hypertension n (%)	279 (93)	53 (37.1)†
Charlson Comorbidity Index median (IQR)	4 (2-5)	2 (0-3)†

BMI, body mass index; NA, not applicable.
* Significance (study group vs control group): Nonsignificant.
† $P < .001$.

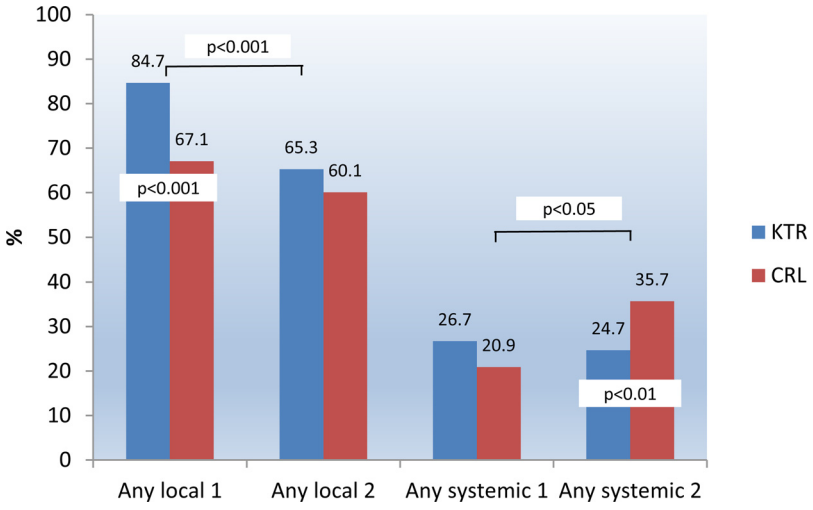

Fig 1. Any local solicited and any systemic adverse events after the first and second vaccine doses in kidney transplant recipients (KTR) and in the control group (CRL).

After the first dose of the vaccine control patients reported any local reaction less frequently than participants from the study group (lower pain reporting), but they reported swelling and redness significantly more often. After the second dose the groups did not differ in respect to any local adverse reaction. The grade of all local symptoms was also higher in the KTR group (moderate and severe reactions were reported more often). However, any local adverse events in KTR were reposted significantly less frequently after the second dose ($P <$ .001) Details are presented in Fig. 1 and 2.

Systemic Reactogenicity

Of the KTR, 26.7% and 24.7% patients reported any solicited systemic adverse event after first and second dose of the vaccine, respectively. Fatigue, headache, and muscle pains were the most often reported symptoms. The vast majority of reported symptoms were mild. Grade 3 symptoms were reported by a few participants, and no grade 4 symptoms were reported. The participants from the control group reported any systemic reactions in 20.9% and 35.7% ($P < .05$) after the first and second doses, respectively. After the second dose they reported any systemic events more often than KTR from the study group. Most adverse events in this group were mild, however participants reported grade 2 and 3 symptoms more often than patients after kidney transplantation. Details are presented in Fig. 1 and 3.

ANALYSES OF SUBGROUPS

In univariable analyses any local adverse events were more frequent after the first and second doses of vaccine in younger rather than in older patients (90.6 vs 76.7%; $P < .001$ and 70.8 vs 58.1%; $P = .02$ respectively). The younger patients reported any systemic reactions more frequently than older patients after the second dose (30.4 vs 17.1%; $P < .01$).

Any systemic side effects occurred more frequently in women than in men after the first dose of the vaccine (35.7 vs 21.3%; $P < .01$). Patients with diabetes reported any local reactions less frequently after the first dose of vaccine in comparison

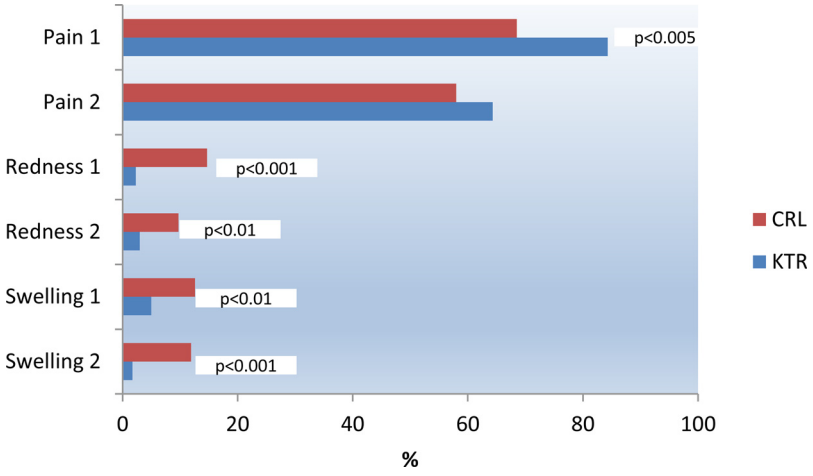

Fig 2. Detailed local solicited adverse events after the first and second vaccine doses in kidney transplant recipients (KTR) and in the control group (CRL).

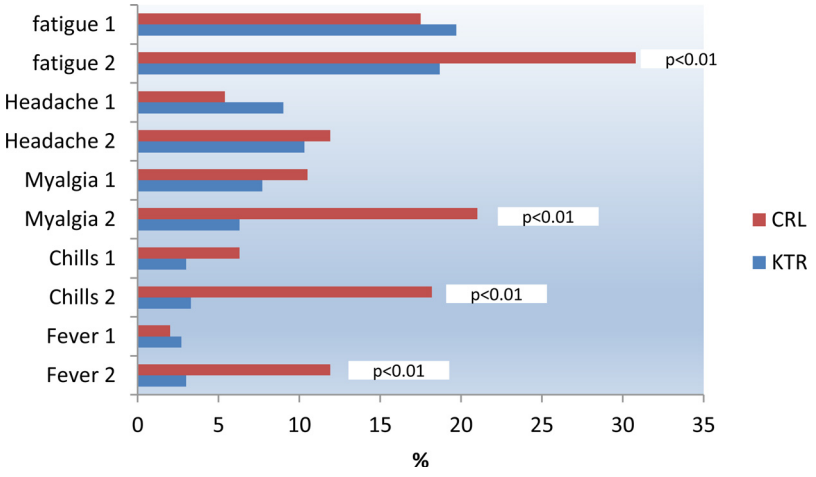

Fig 3. Any systemic solicited adverse events after the first and second vaccine doses in kidney transplant recipients (KTR) and the control group (CRL).

with subjects without diabetes (51.4 vs 70%; $P < .01$). Patients with BMI ≥25.31 reported any systemic reactions (after first dose) less frequently as compared with patients with BMI <25.31 (19.7 vs 33.8%; $P < .01$) (Table 2).

We also checked the local and general reactogenicity of patients vaccinated with 2 types of mRNA vaccines (BNT162b2 mRNA and mRNA-1273). We showed no significant differences in local and overall reactogenicity in these 2 groups (see details in Table 3).

UNSOLICITED SERIOUS ADVERSE EVENTS

No serious adverse events within 30 minutes of the vaccinations occurred in KTR and in the control group. No serious adverse events and clinical rejection or kidney graft failure episodes had occurred by the end of the follow-up in the 30 days after vaccination.

DISCUSSION

Since December 2020, many regulatory agencies (including the European and the American Societies for Transplantation) approved a 2-dose regimen of the SARS-CoV-2 mRNA vaccines in solid organ transplant recipients [10]. The efficacy of SARS-CoV-2 vaccination in solid organ transplant recipients however is low, fewer than 50% of KTR responded after the second dose and also the immunity is rapidly waning [11−15]. There are reports that showed improved antibody-mediated response to the administration of a third dose of mRNA vaccines, which was recently recommended [15−18]. A study of populations prioritized for early immunization found that around 50% of respondents were either not likely, or only somewhat likely, to receive a vaccine [19]. Concern for safety has been the main reason for fear and hesitancy to vaccinate against SARS-CoV-2. As there is a risk that SARS-CoV-2 may remain a persistent threat to the health and life of KTR,

Table 2. Univariable Strata Analyses of Local and Systemic Solicited Adverse Events in Kidney Transplant Recipients

	N1- First dose N2- Second dose	Any local 1 N (%)	Any local 2 N (%)	Any Systemic 1 n (%)	Any Systemic 2 n (%)
Age ≤55	N1=171 N2=171	155 (90.6)*	121 (70.8)†	53 (31)	52 (30.4)‡
Age >55	N1=129 N2=129	99 (76.7)	75 (58.1)	27 (20.9)	22 (17.1)
Women	N1=112 N2=112	99 (88)	78 (69.6)	40 (35.7)‡	34 (30.4)
Men	N1=188 N2=188	155 (82.4)	118 (62.8)	40 (21.3)	40 (21.3)
Diabetes (+)	N1=74 N2=74	58 (78.4)	38 (51.4)	17 (23)	14 (18.9)
Diabetes (-)	N1=226 N2=226	196 (86.7)	158 (70)	63 (27.9)	60 (26.6)
Neoplastic disease (+)	N1=48 N2=48	41 (85.4)	34 (70.8)	9 (18.8)	13 (27)
Neoplastic disease (-)	N1=252 N2=252	186 (73.8)	162 (64.3)	71 (28.2)	61 (24.2)
CCI <4	N1=179 N2=179	155 (86.6)	121 (67.6)	55 (30.7)	47 (26.3)
CCI ≥ 4	N1=121 N2=121	99 (81.8)	75 (62)	25 (20.7)	27 (22.3)
BMI <25.31	N1=148 N2=148	124(83.8)	102 (68.9)	50 (33.8)‡	35 (23.7)
BMI ≥25.31	N1=152 N2=152	130 (85.5)	94 (61.8)	30 (19.7)	39 (25.7)
TX < 7.25	N1=150 N2=150	125 (83.3)	96 (64)	42 (28)	36 (24)
TX ≥ 7.25	N1=150 N2=150	129 (86)	100 (66.7)	38 (25.3)	38 (25.3)

Gray fields indicate statistically significant differences.
BMI, body mass index; CCI, Charlson Comorbidity Index; TX, kidney transplantation vintage.
* Significance: $P < .001$.
† $P < .05$.
‡ $P < .01$.

Table 3. Characteristics of Kidney Transplant Recipients Vaccinated With Different mRNA Vaccines, and Their Reactogenicity

	BNT162b2 mRNA N = 250	mRNA-1273 N = 50	*P* Value
Age in years median (IQR)	53 (40-63)	50 (44-64)	.24
Male gender n (%)	153 (61.2)	90 (72)	
BMI kg/m^2 median (IQR)	25.3 (25.6-28.6)	25.8 (23.8-28)	.95
Diabetes mellitus n (%)	64 (25.6)	10 (20)	
Neoplastic disease n (%)	40 (16)	8 (16)	
Arterial hypertension n (%)	231 (92.4)	48 (96)	
Transplant vintage (y) median (IQR)	6.75 (3-13)	9.75 (6-16)	.06
Charlson Comorbidity Index median (IQR)	4.1 (2-5)	3.9 (2-6)	.73
Local reactogenicity 1 (%)	209 (83.6)	45 (90)	.25
Local reactogenicity 2 (%)	157 (62.8)	39 (78)	.06
Systemic reactogenicity 1 (%)	64 (25.6)	16 (32)	.35
Systemic reactogenicity 2 (%)	64 (25.6)	10 (20)	0.14

BMI, body mass index; IQR, interquartile range.

vaccination may stop the spread of new virus variants and limit the severe course of the disease, especially in immunocompromised individuals. Conducting studies demonstrating the safety and efficiacy of vaccines in the general population and also in vulnerable populations is an essential tool for the widespread acceptance and adherence to repeated vaccination.

Overall, the reactogenicity profile in our study was in line with the results observed in clinical trials in the general population and KTR [20−22]. The most frequently reported local solicited adverse reaction was mild-to-moderate pain at the injection site, and the most often reported systemic reactions were fatigue, headache, and muscle pains.

Any local solicited reactions were more frequent in KTR as compared with the controls owing to more often-noticed pain, although they reported swelling and redness significantly less often. The low incidence of swelling and redness in KTR was probably related to local anti-inflammatory effect of immunosuppressants. Any local reactions were more frequent in younger than in older patients. KTR with diabetes reported any local reactions less frequently after the first dose of vaccine in comparison with subjects without diabetes. The younger patients and females reported any systemic reactions more frequently than older patients and men, and patients with BMI ≥25.31 reported any systemic reactions less frequently as compared with patients with BMI <25.31. The vast majority of reported systemic symptoms were mild.

Many systemic reactions were observed less frequently in KTR than in the control group. As was mentioned above, local solicited reactions (except local pain) occurred less frequently in KTR with respect to the age- and sex-matched control group and much less frequently than that reported in the pivotal studies [7,8]. Comparing these results with our previous findings in chronic dialysis (CD) patients there were more local side reactions in KTR than CD patients after the first and second vaccination (84.7 vs 59.8% after first and 65.3 vs 61.4% after second dose). Regarding systemic symptoms, they were more frequent in KTR as compared with CD after the first dose (26.7 vs 15.9%) and less frequent after the second dose (20.9 vs, 29.4%) [9]. A higher percentage of adverse events in the KTR group may be associated with the lower age of our cohort as compared with CD patients (53 vs 67 years old). It is in line with the observation that the younger patients reported any systemic and some local solicited adverse reactions more frequently than older patients. Additionally, the poorer reactivity of CD patients may be related to uremia-associated immunodeficiency, aging of the immune system, and accelerated "inflammaging;" however, it is less probable because KTR also are immunocompromised [23,24].

Reactogenicity in our KTR was generally mild or moderate; reactions were transient and resolved in most participants by day 3 after vaccination, without sequelae. Similar to the control group and general population studies, younger patients and women were more likely to report adverse events than older subjects and men, respectively [22,24]. We did not find significant differences in reactivity after vaccination with 2 types of mRNA vaccines despite the higher dose of mRNA in the mRNA-1273 vaccine and reports of its slightly better immune effectiveness [13,14].

Our observational study has some limitations. The control group was not exactly matched, as there were too few people with comorbidities such as diabetes, hypertension, and neoplastic diseases. The influence of media interest on the excessive number of reports cannot be ruled out. In addition, patients receiving routine drugs in observational studies have a different level of awareness of side effects than those in an experimental study and typically report fewer adverse events. The tested sample was not large enough to reliably detect uncommon side effects and distinguish the immunogenicity of the vaccine in specific patient subgroups. After all, in our study, we only assessed short-term side effects.

In summary we would like to underline that there were no serious adverse events that warranted a safety concern regarding the use of mRNA COVID-19 vaccines in KTR. These vaccines were well tolerated by KTR, therefore the results of our studies can help patients make the decision to vaccinate and accept repeated doses.

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