SHORT COMMUNICATION

Interstitial glucose monitoring, type 1 diabetes and COVID-19 vaccine: the patient-reported outcomes and vaccine-associated changes in glucose and side effects (PRO-VACS)

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Introduction

In the available phase 3 trial, mRNA-1273 (Moderna) COVID-19 vaccine showed a high efficacy together with a good tolerability [1]. Although the trial included a fraction of people with diabetes, no specific subgroup analyses on adverse events were performed in individuals with T1D. In addition, most adverse reactions are related to the activation of local and/or systemic inflammation, which could potentially impair glucose control in T1D, thus likely contributing to vaccine hesitancy in patients with diabetes [2]. On the other hand, since diabetes is associated with a worse outcome of COVID-19 [3], vaccination is particularly recommended in patients with T1D. Aim of the present study is the assessment of the safety profile of mRNA-1273 vaccine in patients with T1D, including its effects on glucose variability in patients with interstitial glucose monitoring devices.

Methods

This observational retrospective study was performed on a consecutive series of adult patients with T1D, attending the Diabetes Center in Careggi Hospital, Florence, Italy, who

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received the first and second dose of mRNA-1273 COVID-19 vaccine between March 16th and April 16th, 2021, who provided their informed consent. Subjects who received corticosteroid treatment, or affected by any concomitant condition capable of affecting glucose control in three previous months, were excluded. Information on diagnoses of COVID-19 and adverse events following vaccination were collected using a structured interview, whereas data on duration of diabetes, HbA1c and complications were retrieved from clinical records. Adverse events were considered serious when they threatened survival or physical integrity of the patients, or required hospital admission. Patients using flash glucose monitoring (Freestyle Libre, Abbott) were asked to share their glucose data with the investigators for the assessment of the effects of vaccination on glucose variability. Patients were included in the analysis when available readings covered over 70% of study period.

Data were expressed as mean ± standard deviation (SD), unless otherwise specified. Student's paired t tests were used for comparison of means, after checking that the variable considered had a normal distribution. All analyses were performed on SPSS 27.

The study was approved by the Florence Ethical Board (approval number CEAVC 19833_oss/2021).

Results

This study enrolled 454 individuals (205 [45.2%] women) with a median age of 52.5 years, a median duration of diabetes of 22.0 years and a mean HbA1c of 7.4% (57.2 mmol/mol). Of those, 98 (21.2%) were on continuous subcutaneous insulin infusion (CSII). The prevalence of diagnosed retinopathy, previous major cardiovascular events, nephropathy

(albuminuria and/or reduced glomerular filtration) and neuropathy was 28.6, 11.5, 4.8 and 11.4%, respectively.

Reported adverse events are summarized in Table 1. Among all vaccine recipients, 69.7% (n = 316) and 66.5% (n = 302) reported at least one local or systemic reaction during the 7 days after 1st and 2nd vaccine dose, respectively. Overall the median onset of adverse events was 14 h after each vaccine dose and lasted a median duration of 36 h.

The most frequent are local reactions (pain, redness and swelling at the injection site) and fatigue, fever and myalgia/joint pain. The frequency of local reactions was higher after 1st dose, whereas fever, headache and myalgia/joint pain were more common and severe following the 2nd vaccine dose. There was only one serious (nonfatal) adverse event, i.e., recurrence of ischemic stroke in a 58-year-old woman, with hospital admission 23 days after first dose, which was considered by physicians unrelated to vaccination. No anaphylactic reaction or urticaria was reported. Among enrolled patients, 5 (1.0%) and 13 (2.6%) reported a perceived deterioration of glucose control after first and second dose, respectively.

The majority of patients (n = 345; 76%) were using interstitial glucose monitoring instead of traditional self-monitoring blood glucose system; of those, 302 (87%) were using a flash glucose monitoring (FGM) system. Among patients on FGM, 81 did not share their interstitial glucose data; therefore, the analysis on glucose variability was performed on 221 patients (73 [33%] on CSII), with a median age of 49.5 years and a mean HbA1c of 7.0% (52.7 mmol/mol). When comparing the week after each dose with the previous week, no significant difference was observed in mean glucose, glucose coefficient of variation, time in range, time in hyperglycemia or time in hypoglycemia (Table 2).

Conclusions

In this observational retrospective study, the safety and tolerability profile of mRNA-1273 (Moderna) vaccine in people with T1D was reassuring. No unexpected patterns of concern were identified. The only one recorded serious adverse event was considered by physicians in charge unrelated to vaccination and the patient received the 2nd dose of the vaccine with a 10-day delay. Fewer episodes of local and general reactions as headache, fatigue, and myalgia/joint pain, diarrhea, vomiting were reported in this study in comparison with those collected in the randomized trial [1]. On the other hand, fever resulted twofold more common in T1D subjects. It is important to note that all the local and systemic solicited reactions to vaccination, including fever, were predominantly mild without any reports of symptoms preventing daily activity or requiring hospital or emergency room admission.

Table 1 Local and general reaction following 1st and 2nd dose of mRNA-1273 SARS-CoV-2 Vaccine

	After 1st vaccine dose	After 2nd vaccine dose
n	454	454
Headache, n (%) any	12 (2.6)	33 (7.2)
Mild	10 (2.2)	27 (5.9)
Moderate	1 (0.2)	5 (1.1)
Severe	1 (0.2)	1 (0.2)
Grade 4	0	0
Diarrhea, n (%)	5 (1.1)	2 (0.4)
Mild	3 (0.7)	1 (0.2)
Moderate	2 (0.4)	1 (0.2)
Severe	0	0
Grade 4	0	0
Vomiting, n (%)	5 (1.1)	2 (0.4)
Mild	3 (0.7)	1 (0.2)
Moderate	2 (0.4)	1 (0.2)
Severe	0	0
Grade 4	0	0
Local reactions, n (%)	265 (58.4)	157 (34.6)
Mild	256 (56.4)	148 (32.6)
Moderate	9 (2.0)	9 (2.0)
Severe	0	0
Grade 4	0	0
Fever 37–37.9 °C, n (%)	5 (1.1)	76 (16.7)
Mild	4 (0.9)	76 (16.7)
Moderate	1 (0.2)	0
Severe	0	0
Grade 4	0	0
Fever > 38 °C, n (%)	0	56 (12.3)
Mild	0	55 (12.1)
Moderate	0	1 (0.2)
Severe	0	0
Grade 4	0	0
Lymphadenopathy, n (%)	5 (1.1)	1 (0.2)
Mild	4 (0.9)	1 (0.2)
Moderate	1 (0.2)	0
Severe	0	0
Grade 4	0	0
New or worsening Myalgia or Joint pain, n (%)	22 (4.8)	72 (15.8)
Mild	19 (4.2)	65 (14.3)
Moderate	3 (0.6)	7 (1.5)
Severe	0	0
Grade 4	0	0
Perioral paresthesia, n (%)	1 (0.2)	0
Mild	1 (0.2)	0
Moderate	0	0
Severe	0	0
Grade 4	0	0
Fatigue, n (%)	51 (11.2)	69 (15.2)

Table 1 (continued)

	After 1st vaccine dose	After 2nd vaccine dose
Mild	49 (10.8)	62 (13.7)
Moderate	2 (0.4)	7 (1.5)
Severe	0	0
Grade 4	0	0
Fainting, n (%)	1 (0.2)	1 (0.2)
Mild	1 (0.2)	1 (0.2)
Moderate	0	0
Severe	0	0
Grade 4	0	0
Tachycardia, n (%)	2 (0.4)	1 (0.2)
Mild	2 (0.4)	1 (0.2)
Moderate	0	0
Severe	0	0
Grade 4	0	0
Anaphylactic reaction, n (%)	0	0
Urticaria, n (%)	0	0
Other (%)	18 (4.2)	69 (15.2)

Interestingly, in our study a fraction of enrolled patients complained unsolicited detrimental effects of the vaccine on glucose control, whereas no difference in glucose was observed after mRNA-1273 (Moderna) vaccine in the subgroup of patients sharing interstitial glucose monitoring data. A previous smaller study on T1D patients showed a modest, although statistically significant, reduction in TIR [4]; however, such results were obtained with different vaccines, in a sample of patients all on multiple insulin injections, with a lower mean TIR than our population.

It may be argued that casual and unexplained variations of glucose levels could be attributed by patients to an intercurrent event, such as vaccination, producing a cognitive distortion, potentially contributing to vaccine hesitancy in people with diabetes [2]. Although the activation of systemic inflammatory pathways by vaccine could theoretically impair glucose control [5], the extent of such activation could be insufficient to produce detectable effects on glucose mean levels or glucose variability.

In conclusion, available data showed that T1D adults infected with COVID-19 infection are at increased disease-related risk [3]. Since vaccination does not imply any relevant negative consequence on glycemic control, concerns about the effects of vaccine on glycemia should not contribute to vaccine hesitancy in people with T1D diabetes, and this is especially important for advocating clearly about the need for vaccinate all these subjects against COVID-19.

Table 2 Interstitial glucose monitoring data during the study

	Week before 1st vaccine dose	Week after 1st vaccine dose	p	Week before 2nd vaccine dose	Week after 2nd vaccine dose	P
n	221	221		221	221	
Glucose average (mg/dL)	158.4±25.5	159.6±30.2	0.479	160.3±26.7	159.1±28.4	0.426
Coefficient of variation (%)	36.7±7.6	36.6±7.7	0.689	36.2±7.0	36.7±7.9	0.219
Time in Range (%)	62.2±15.6	61.0±16.3	0.126	61.0±15.4	61.4±15.8	0.706
Time in hypoglycemia (%) <70 mg/dl	5.0±6.1	4.8±5.7	0.578	4.9±5.3	5.3±5.6	0.089
Time in hyperglycemia (%) >180 mg/dl	32.7±16.0	34.2±17.2	0.076	34.0±16.2	33.4±16.6	0.455

Values are presented as mean values ± standard deviation (SD)

Declarations

Conflict of interest EM has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis, and research grants from Merck, Novartis, and Takeda. MM has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Bristol Myers Squibb. ID has received speaking fees from Merck, Novo Nordisk, Eli Lilly, Abbott, Sanofi, and Boehringer Ingelheim.

Ethical approval The study was approved by the Florence Ethical Board (19833_oss).

Informed consent Participants provided their written informed consent.

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