LETTER TO THE EDITOR

Safe administration of subsequent mRNA COVID-19 vaccine doses following a possible allergic reaction to the first dose

The mRNA COVID-19 vaccines are highly effective in preventing severe COVID-19. After the first vaccination dose, allergic reactions are reported in up to 2.2%,[1] while severe anaphylaxis is very rare (estimated <1/100 000).[2] IgE-mediated allergy to polyethylene glycol (PEG), non-IgE-mediated PEG-reactions, and direct lipid nanoparticle (LNP)-mediated mast cell activation have been proposed as immune mechanisms causing anaphylactoid reactions.[3] Severe allergic reactions to the first dose of an mRNA vaccine are considered a relative contraindication for a second dose. Graded dosing protocols have been suggested for the next administration after suspected allergic reactions.[4]

We retrospectively analysed data from 17 patients, with possible allergic reactions to the first dose of an mRNA COVID-19 vaccine (Table 1). Patients were included in the study between April and October 2021. Follow-up of the patients lasted until February 2022 to also include the outcome of the booster dose. All patients gave informed consent, and the local ethics committee approved the study (EKZN #2021–02063). The mean age was 44.2 years (range 20–60 years), and 82.4% were female. Eleven patients had symptoms within the first 30 min following vaccine administration, and the remaining developed symptoms between 1 and 10 h post-vaccination. The majority (11/17; 65%) had skin reactions or facial angio-oedema (10/17, 59%). The remaining patients reported dyspnoea, dizziness and other symptoms.

We systematically assessed all patients by skin prick testing (SPT) and intradermal testing (IDT) using: macrogol 400 and macrogol 6000 (1:10 SPT / 1:100 IDT), polysorbate 80 (20%; SPT), trometamol (0.1/1% / 0.01/0.1%) and the mRNA-1273 vaccine (Moderna, 1:10/pure / 1:100/1:10). Histamine and saline solution were used as controls. Testing was considered positive at a weal diameter ≥3 mm in the presence of erythema. One patient each had a positive SPT reaction to macrogol 400 and an irritative skin reaction to the mRNA-1273 vaccine (Table 1). In the IDT, five patients had a positive reaction to mRNA-1273 within the first hour after testing (3 after 15 min, 1 after 30 min and 1 after 60 min), and nine showed a skin reaction occurring within the first 24 h. These later reactions presented either as weals (typically within 4 h) or erythema (presumably first-dose-induced T-cell response). Baseline serum tryptase was normal in all patients.

We administered the second dose of the mRNA-1273 vaccine using either a five-step[4] or a two-step graded protocol, that is, 1%–10%–20%–30%–40% or 10%–90% of the total mRNA-1273 vaccine dose (i.e. 0.5 mL; 100 µg mRNA) given 30 min apart and followed by a 1-h observation. Considering that the five-step protocol may also result in tolerance induction, the five-step graded protocol was used in patients with more severe reactions and a positive skin test. In contrast, patients with milder reactions and negative skin tests were vaccinated using the two-step graded protocol (Table 1). All subjects received prophylactic treatment with a standard dose of an H1-antihistamine once daily for 6 days, starting 3 days before the vaccination. We opted to initiate the prophylactic antihistamine already 3 days before the vaccination – instead of a single dose before the vaccination – given that urticaria is often insufficiently suppressed by a single dose.[5] None of the 17 patients experienced severe allergic symptoms during observation and follow-up. Three subjects developed very mild symptoms with spontaneous improvement (Table 1). Over the next months, 13 of 17 patients also received a booster vaccination (Table 2). The four subjects who had received the second dose with the five-step protocol were booster vaccinated with the two-step graded protocol. The remaining nine subjects received the booster as an unfractionated vaccination. All but one patient received antihistamines. Fractionated and unfractionated booster vaccinations were tolerated well in all these patients (Table 2). Within the four patients not booster vaccinated during our follow-up period, one patient had COVID-19 infection before he was able to get the booster and three patients decided against the booster.

In conclusion, we found that antihistamine premedication and graded immunization protocols allowed a safe administration of the mRNA COVID-19 vaccine in patients with a possible allergic reaction to the first dose. None of our patients showed apparent signs of an immediate-type allergy after the second or the booster vaccination. In contrast, others reported mild anaphylactic symptoms in 26–38% of subjects receiving the second dose of Pfizer/BioNTech with antihistamine premedication or graded dosing.[6,7] In another study, using a two-step graded dosing in a small cohort, reactions occurred in 5 of 12 subjects.[8] Furthermore, in a recent meta-analysis, the risk of severe hypersensitivity reactions after reactions to the first dose was 0.16%, and for mild reactions 13.7%.[9] Combined, our data suggest that the five-step graded protocol may not be necessary for further vaccinations in patients with mild reactions to the first dose of mRNA vaccine.

Table 1 Clinical characteristics of patients with possible allergic reaction to first dose of an mRNA COVID-19 vaccine and outcome after administration of second dose

No.	Age (y), sex	Allergy history	1st mRNA vaccination					Diagnostics															2nd mRNA vaccination	
			Vaccine 1st dose	Time to reaction	Symptoms	ANA grade (Ring and Messmer)	Therapy of ANA	Skin prick test					Intradermal test										Vaccination protocol	Outcome
													After 15 min					Within 24 h						
								Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273	Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273	Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273		
1	47, f	CSU, DA	mRNA-1273	5 min // 30 h	Dizziness, tachycardia, urticaria // dyspnoea and again urticaria	II°	AH, GC	–	–	–	–	–	–	–	–	–	+ (a)	–	–	–	–	+	5-step administration of mRNA-1273	No allergic symptoms
2	42, f	–	mRNA-1273	1 h	Urticaria	I°	AH	–	–	–	–	–	–	–	–	–	+	–	–	–	–	ND		No allergic symptoms
3	30, m	–	mRNA-1273	10 min	Nausea, dizziness, oral swelling	II°	AH, GC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	IR/+ (b)		No allergic symptoms
4	43, f	U, A, FA, DA, BA	mRNA-1273	2 min	Angio—oedema	I°	AH	–	–	–	–	–	–	–	–	–	+ (c)	–	–	–	–	ND		No allergic symptoms
5	26, f	DA, FA	mRNA-1273	5 min	Flush, pruritus	I°	AH	+	–	–	–	–	ND	–	–	–	+	ND	–	–	–	+		No allergic symptoms
6	56, f	–	mRNA-1273	15 min // 6 h	Fatigue // rash, pruritus, dyspnoea	II°	–	–	–	–	–	IR	–	–	–	–		–	–	–	–	+ (d)		No allergic symptoms
7	43, f	CSU, PEG-allergy	BNT 162B2	1 h	Rhinitis, tongue burning (persisting for 2 days)	I°	AH	NP (e)															2-step administration of mRNA-1273	Lip numbness, (h)
8	56, f	ARC, DA	mRNA-1273	20 min	Headache, pruritus, angio-oedema	I°	–	–	–	–	–	–	–	–	–	–	IR	–	–	–	–	–		No allergic symptoms
9	50, f	DA, BA	mRNA-1273	1 min // 1 h	Nausea, sore throat // urticaria, angio-oedema	II°	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		Tongue burning after 1st dose, (h)
10	60, f	–	mRNA-1273	5 min	Angio-oedema, pruritus	I°		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		Tongue and ear burning after 1st dose, (h)
11	32, f	ARC	mRNA-1273	5 min // 24 h	Fatigue, dizziness // urticaria, dyspnoea	I-II°	AH, BD/iCS	–	–	–	–	–	–	–	–	–	–	–	–	–	–	IR/+ (f)		No allergic symptoms
12	20, m	ARC, BA	mRNA-1273	4 h	Dyspnoea (lasting for 6 days)	II° / #	BD	–	IR	–	–	–	–	IR	–	–	–	IR	IR	–	–	–		No allergic symptoms
13	56, f	–	mRNA-1273	2 h	Headache, flush	I°	AH	–	–	–	–	IR	–	–	–	–	IR	–	–	–	–	ND		No allergic symptoms
14	53, f	–	mRNA-1273	4 h	Angio-oedema	I°	–	–	–	–	–	–	–	–	–	–	+ (g)	–	–	–	–	+		No allergic symptoms
15	37, f	ARC	mRNA-1273	30 min	Angio-oedema	I°	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	IR		Globus sensation after 2nd dose, (h)

Table 1 *Continued*

No.	Age (y), sex	Allergy history	1st mRNA vaccination					Diagnostics															2nd mRNA vaccination	
			Vaccine 1st dose	Time to reaction	Symptoms	ANA grade (Ring and Messmer)	Therapy of ANA	Skin prick test					Intradermal test										Vaccination protocol	Outcome
													After 15 min					Within 24 h						
								Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273	Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273	Macrogol 400	Macrogol 6000	Polysorbate 80	TRIS	mRNA-1273		
16	58, m	ARC, BA	BNT 162B2	10 h	Sore throat, hoarseness, angio-oedema, pruritus, rash	II°	AH, GC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		No allergic symptoms
17	42, f	ARC, BA, U, DA	mRNA-1273	5 min	Dizziness	§	–	–	–	–	–	–	–	–	–	–	ND	–	–	–	–	ND		No allergic symptoms

Grading of possible allergic reaction: §, patient 17 presented with dizziness only. Differential diagnosis includes a vasovagal reaction. #, patient 12 suffered from dyspnoea. Differential diagnosis includes uncontrolled asthma. Specifications to test results and reactions: (a) positive after 30–45 min; (b) positive after 6–24 h; (c) positive skin reaction and urticaria; (d) positive after 10 h; (e) not performed due to CSU and daily antihistamine therapy; (f) positive after 4 h; (g) positive after 60 min; (h) spontaneous improvement without therapy. A, angio-oedema; ANA, anaphylaxis; AH, antihistamine, ARC, allergic rhinoconjunctivitis; BA, bronchial asthma; BD, bronchodilator; CSU, chronic spontaneous urticaria; d, day(s); DA, drug allergy; FA, food allergy; f, female; GC, glucocorticoid, h, hour(s); iCS, inhaled corticosteroids; IR, irritative skin reaction; m, male; min, minutes; ND, not determined; NP, not performed; TRIS, trometamol/tromethamine; U, urticaria; +, skin prick testing defined as positive: weal >3 mm. // indicates a two-phase reaction.

Table 2 Follow-up and outcome of booster administration with mRNA COVID-19 vaccine

No.	Age (y), sex	Booster vaccination				
		Vaccine type	Vaccination protocol	Antihistamines	Outcome	Late onset symptoms (>24 h)
1	47, f	mRNA-1273	2-step administration	Yes	Ear redness after 1st dose	Urticaria 24 h after vaccination
2	42, f	mRNA-1273	2-step administration	Yes	No allergic symptoms	-
3	30, m	No booster vaccination				
4	43, f	mRNA-1273	2-step administration	Yes	Pruritus after 1st dose*	-
5	26, f	No booster vaccination				
6	56, f	mRNA-1273	2-step Administration	Yes	No allergic symptoms	-
7	43, f	mRNA-1273	Unfractionated	Yes	No allergic symptoms	-
8	56, f	mRNA-1273	Unfractionated	Yes	No allergic symptoms	-
9	50, f	mRNA-1273	Unfractionated	Yes	Tongue burning*	-
10	60, f	mRNA-1273	Unfractionated	Yes	Burning sensation of the skin, swallowing problems*	-
11	32, f	No booster vaccination				
12	20, m	mRNA-1273	Unfractionated	No	No allergic symptoms	-
13	56, f	mRNA-1273	Unfractionated	Yes	No allergic symptoms	-
14	53, f	BNT 162B2	Unfractionated	YES	No allergic symptoms	-
15	37, f	mRNA-1273	Unfractionated	Yes	No allergic symptoms	-
16	58, m	No booster vaccination				
17	42, f	mRNA-1273	Unfractionated	Yes	No allergic symptoms	Urticaria 5 d after vaccination

Abbreviations and specification: f, female; d, day(s); h, hour(s); m, male; *spontaneous improvement without therapy.

The limitations of our study include the small number of patients, absence of a control group and mainly mild reactions to the first dose. Also, the skin tests were not formally validated in healthy subjects without reactions. Unspecific positive skin tests can thus not be excluded. Nevertheless, we believe that our approach decreased hesitancy to get further vaccinations in subjects with possible allergic reactions and enabled us to complete immunization schedules, including the booster dose.

Further studies are needed to define the benefit of graded protocols as well as the effect of premedication with antihistamines in patients with a history of possible allergic reactions to mRNA COVID-19 vaccines.

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The patients in this study have given written informed consent to publication of their case details.

Conflicts of interests

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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