Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Graded-dosing immunization in adults at risk for immediate-type reactions to mRNA SARS-CoV-2 vaccines

Dear Editor,

Shortly after the COVID-19 vaccination campaign, the risk of anaphylaxis was identified as a concern. Even though the frequency of hypersensitivity reactions turned out to be low, those persons may not be eligible for a booster dose considering the risk of anaphylaxis.[1] The diagnostic approaches and underlying mechanisms defining vaccine hypersensitivity remain hotly debated. The group of Banerji examined the role of excipient skin testing with Polyethylene glycol (Peg) and polysorbates-80 and found that the negative predictive value of such test was limited. They concluded that the decision to take to booster should be primarily based on clinical phenotyping and risk assessment.[2] Our group found that intradermal testing and Basophil Activation Tests (BAT) with mRNA vaccines help identify vaccine-sensitized patients and select individuals who can tolerate mRNA vaccines.[3] Yet, administering a second or third dose in sensitized patients can be problematic.[4] Herein, we share our experience using a five-step graded dosing vaccination protocol in high-risk allergic patients.

The protocol for a graded challenge with the mRNA vaccines 1273 from Moderna and BNT162b2 from Pfizer/BioNTech was adapted from the 5-step protocol for allergic patients to vaccines as proposed by the American Pediatrics Society[5] (Supplementary Fig. 1). All participants underwent premedication with a second-generation antihistamine 12 and 2 h before the procedure. Patients were categorized into four groups (Table 1). Group A included vaccine-sensitized patients with prior history of anaphylaxis to a drug containing Polysorbate-80 or PEG e.g., PEG 3350 (Moviprep), Cremophor EL (Paclitaxel), or Flammazine, but who were never exposed to mRNA vaccines. Group B regrouped vaccine-sensitized patients who reported an immediate reaction to the vaccine but did not fulfill the criteria for anaphylaxis. Group C were vaccine-sensitized patients who reported an immediate reaction to the vaccine and fulfilled the criteria for anaphylaxis as defined by the European Academy of Allergy and Clinical Immunology. Finally, we included two patients (Group D) who developed a severe immediate reaction to a 10% challenge with one of mRNA vaccines despite a negative allergy workup. Details about the different group characteristics are listed in Table 1. Patients were considered vaccine-sensitized upon positive skin tests (by prick or intradermal skin test) and/or positive basophil activation tests (stimulation Index>2 compared to negative control at two different dilutions, Laboratory ADR AC – Bern–Switzerland). A summary of the BAT results is shown in Supplementary Figure 2. Written informed consent was obtained from all participants. The local ethics IRB committee approved the study (BASEC number 2021-00735).

All four patients of group A, i.e., with a history of anaphylaxis to a drug sharing similar excipients with the mRNA COVID-19 vaccines and positive skin tests and/or BAT to one of the mRNA vaccines, tolerated the 5-step immunization protocol (Fig. 1, Table 1). Similarly, all three patients of group B with a non-severe immediate-type hypersensitivity reaction to the mRNA vaccine and positive tests tolerated the 5-step immunization protocol (Fig. 1, Table 1). Group C regrouped seven patients with grade II or III anaphylaxis (Ring-Messmer) after the first dose of mRNA vaccine and who tested positive for the mRNA vaccine. Brighton criteria were fulfilled in 6/7 patients. In this group, the 5-step vaccination protocol was fully administered to 6/7 patients. One patient developed a grade II (Ring-Messmer) reaction (cough, pruritus, dyspnea) after the third step, resulting in the termination of the protocol. Two patients presented mild reactions, which were managed without epinephrine injection. Finally, we included two patients with negative skin tests and/or BAT to the vaccine (Group D), but who reacted upon vaccination with the 10% challenge. Both patients had a history of anaphylaxis to iodinated contrast media and were asthmatics. Upon graded challenge, one patient presented a flush and diffuse wheezing with respiratory distress, which subsided after intramuscular epinephrine but precluded further vaccine administration. The other patient presented a light wheezing with a 10% drop in peak flow compared to baseline and was successfully treated with salbutamol, with subsequent completion of the immunization protocol. Both patients returned home within 24 h after the graded challenge.

Herein, we report 16 patients at risk of immediate-type reactions upon immunization with mRNA-based vaccines. While this protocol is generally well-tolerated in sensitized patients to mRNA COVID-19 vaccines (13/14), two individuals with a negative allergy workup reacted during the 5-step procedure. Both patients had previously reacted to a fractionated vaccine challenge. The reason for absent skin and BAT reactivity in these patients could result from non-IgE-mediated hypersensitivity (e.g., through complement activation) or failure to detect IgE. Interestingly, both patients that reacted twice to the fractioned vaccine challenge did not display a rise in serum tryptase levels during the reaction, although this does not exclude mast cell activation.[6] Additionally, the potential relation to iodinated contrast media anaphylaxis in those patients warrants further investigation.

Growing evidence suggests that patients can be safely revaccinated after an immediate allergic reaction.[7] A recent metanalysis concluded that the risk of severe anaphylaxis following a booster

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Table 1
Characteristics and outcomes of 16 patients at risk for anaphylaxis that underwent 5-step graded challenge with mRNA vaccines.

Group	Age	Sex	Basal Tryptase (ug/l)	Known Asthma	Responsible Drug	Anaphylaxis (EAACI)	Ring and Messmer Severity Scale	Brighton Scale	Vaccines used for 5-Step	Cumulative Dose (μg)	Comments
A1	48	F	2.9	No	Moviprep	Yes	III	1	BNT-162b2	30.3	–
A2	48	F	14.4	No	Paclitaxel	Yes	III	1	BNT-162b2	30.3	–
A3	58	F	18.6	No	Flammazine	Yes	III	1	BNT-162b2	30.3	–
A4	56	M	3.2	No	Moviprep	Yes	III	1	BNT-162b2	30.3	–
B1	52	F	3.6	No	mRNA-1273	No	I	0	mRNA-1273	101	–
B2	37	F	1.9	Yes	mRNA-1273	No	I	0	mRNA-1273	101	–
B3	53	F	1.5	No	mRNA-1273	No	I	0	mRNA-1273	101	–
C1	21	F	3.2	Yes	mRNA-1273	Yes	III	2	mRNA-1273	101	12.5% Reduction of the Peak flow treated with salbutamol
C2	52	F	4.1	–	mRNA-1273	Yes	III	2	mRNA-1273	101	–
C3	27	F	3.6	–	mRNA-1273	Yes	II	2	mRNA-1273	101	Local Urticaria
C4	25	F	3.2	Yes	mRNA-1273	Yes	II	2	mRNA-1273	101	–
C5	38	F	3.3	No	mRNA-1273	Yes	II	2	mRNA-1273	31	Grade II (R&M)
C6	60	F	4.4	No	mRNA-1273	Yes	II	0	mRNA-1273	101	–
C7	49	F	4.3	Yes	mRNA-1273	Yes	III	2	mRNA-1273	101	–
D1	46	F	3.3	Yes	mRNA-1273	No	III	0	BNT-162b2	30.3	10% Reduction of the Peak flow treated with salbutamol
D2	48	F	2.8	Yes	BNT-162b2	Yes	III	2	BNT-162b2	3.3	Grade III (R&M)

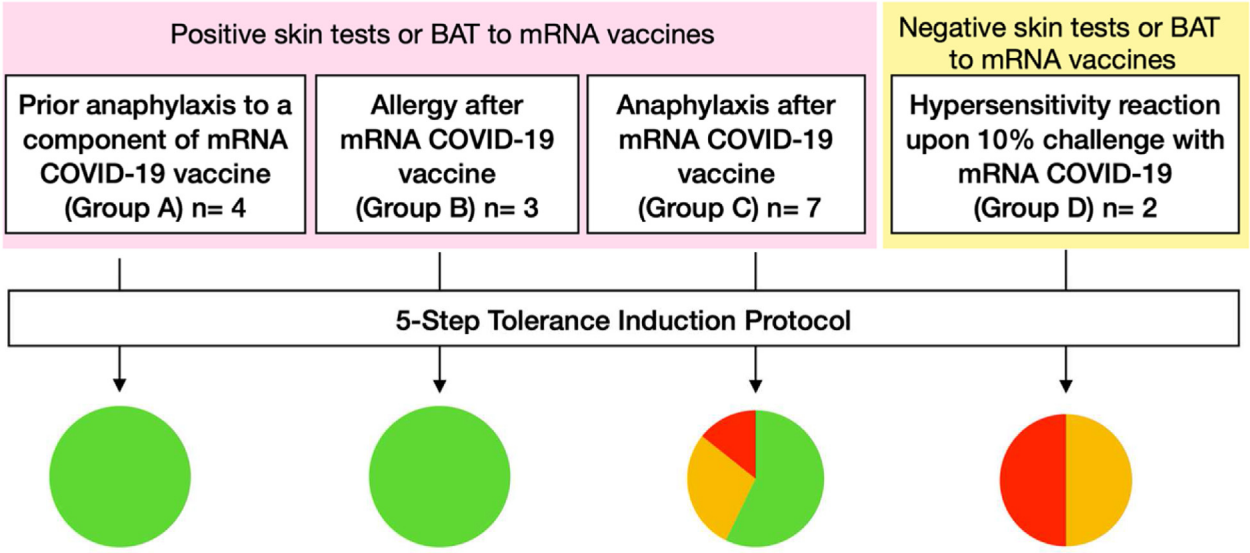

Fig. 1. Five-step graded challenge in 16 individuals at risk for vaccine-induced anaphylaxis. Outcomes after vaccination in each group are shown as pie charts: Green = tolerance of the full graded challenge without adverse events; Orange = mild symptoms not impeding the completion of the full graded challenge; Red = severe immediate hypersensitivity leading to discontinuation of the graded challenge.

dose is low among persons who experienced an immediate allergic reaction to their first dose. On the one hand, these results suggest that non-IgE mediated mechanisms are primarily involved in those allergic-like reactions. On the other hand, in approximately 13.5% of the cases, non-severe immediate symptoms were still observed. Additionally, in most studies, substantial numbers of patients were not rechallenged, representing a potential selection bias. Finally, anti-PEG IgE-mediated anaphylaxis has been reported by many groups.[8–10]

In conclusion, a five-step vaccination protocol can be safely administrated in most vaccine-sensitized individuals at risk for vaccine-induced anaphylaxis. However, individuals with negative skin testing and/or BAT and a reaction to previous graded vaccine challenges should be handled more cautiously, especially if asthmatic. Whether these patients may benefit from a protocol with slower up-dosing remains to be established.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2022.10.001.

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Conflict of interest

DY is an employee of ADR-AC GmbH (Switzerland). The rest of the authors have no conflict of interest.

Florian Stehlin [a], Francesco Tommasini [a], Véronique Monzambani-Banderet [a], Cedric Girard [b], Daniel Yerly [c], Camillo Ribi [a], Yannick D. Muller [a,*]

[a] *Division of Immunology and Allergy, University Hospital of Lausanne, Lausanne, Switzerland*
[b] *Pharmacy, University Hospital of Lausanne, Hospital and University of Lausanne, Lausanne, Switzerland*
[c] *Adverse Drug Reactions - Analysis & Consulting (ADR-AC) GmbH, Bern, Switzerland*

* Corresponding author. Service d'immunologie et d'allergie, Département de médecine, BH010-511. Rue du Bugnon 46, CH-1011 Lausanne, Switzerland.
E-mail address: Yannick.muller@chuv.ch (Y.D. Muller).

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