Delving Into COVID-19 Vaccination-Induced Anaphylaxis: Are mRNA Vaccines Safe in Mast Cell Disorders?

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To the Editor,

The COVID-19 outbreak is the worst pandemic in the last 100 years. The rapid development of vaccines [1, 2], and the report of anaphylactic reactions during the early phase of worldwide mass vaccination [3, 4], have caused safety concerns. These are particularly relevant in mastocytosis, mast cell (MC) activation syndromes (MCAS) and hereditary α-tryptasemia (HAT) since anaphylaxis is frequent in these disorders.

The first vaccines to receive authorization for emergency use in humans were the BNT162b2 Pfizer-BioNTech[1] and the mRNA-1273 Moderna [2] mRNA vaccines. No severe systemic reactions were reported during clinical trials, but it should be noted that patients with previous allergic reactions were not included in the trials [1, 2].

In novel mRNA vaccines, synthetic SARS-CoV-2 spike (S) glycoprotein enconding-mRNA is vehiculated through a polyethylene glycol (PEG)-containing envelope into cells where mRNA is translated into the viral S glycoprotein, against which neutralizing antibodies are further produced [1, 2]. Because these are the first mRNA vaccines approved for human use, little is known about the underlying mechanisms of anaphylactic reactions related with their administration.

The USA Centers for Disease Control and Prevention (CDC) have reported 157 reactions out of almost 6 million doses of mRNA vaccines [3, 4],which translates into an overall incidence below 0.003%, with only 1 out of 5 reactions corresponding to anaphylaxis (Table 1). Thus, the incidence of vaccine-related anaphylaxis is low (i.e. 5 out of 1,000,000 doses) but at least 5 times higher than that reported for other vaccines [5]. Such reactions usually developed within 45 minutes following administration, and predominantly affect women with a history of allergic reactions(Table 1). Data from CDC also show that the mRNA-1273 seems to be associated with less frequent adverse reactions but more severe anaphylaxis when compared with the BNT162b2 vaccine (Table 1), which results in a similar incidence of severe anaphylaxis with both vaccines (i.e. 1 out of 1,000,000 individuals) [3, 4].

It has been suggested that theunderlying mechanism for anaphylaxis caused by mRNA vaccines might be IgE-mediated hypersensitivity to PEG, a rare but increasingly recognized cause for anaphylaxis [5, 6]. PEG is a polymer of ethylene oxide present in a wide range of

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drugs, cosmetics, and food additives [5, 6].Moreover, PEG may cross-react with polysorbate, a non-ionic surfactant also present in other developing vaccines for SARS-CoV-2, which is also widely used in cosmetics, drugs, monoclonal antibodies and food products [5, 6]. Anaphylaxis to PEG may also be due to complement activation and anaphylatoxin release caused by antibodies against PEG [5]. IgE-mediated anaphylaxis caused by excipients has been reported in patients with a prior history of allergic reactions caused by drugs that may contain PEG (e.g. corticosteroids), polysorbate (e.g. influenza vaccines), or tromethamine (e.g. gadolinium) [3, 4]. Besides PEG, the mRNA-1273 vaccine contains tromethamine, which is present in contrast media and other healthcare and cosmetic products and has been recently involved in an allergic reaction to gadolinium-based contrast media [7, 8]. Thus, to assess whether a patient can safely receive one of these vaccines, a thorough clinical history including previous allergic reactions to drugs and self-care products is mandatory.

At present, little is known about the safety of these new COVID-19 vaccines among patients at potential risk of anaphylaxis such as those with mastocytosis. Moreover, anaphylaxis is frequently the presenting feature of systemic mastocytosis(SM) in a significant proportion of patients who lack skin involvement, for whom the REMA score constitutes a validated, highly efficient predictive tool[9]. Scores assigned in this model include: gender (male +1, female -1), symptoms (absence of pruritus, urticaria and angioedema +1; presence of pruritus, urticaria and/or angioedema -2; presyncope and/or syncope +3) and baseline serum tryptase (<15 μg/l -1; >25 μg/l +2). A REMA score ≥2 predicts the presence of SM with a sensitivity and specificity of 92% and 81%, respectively. The high frequency of women (94%) with mucocutaneous symptoms in the absence of cardiovascular manifestations (87%) among the cases of vaccine-related anaphylaxis reported by the CDC, translates into a score <2 (i.e. low probability of SM) in the majority of cases, without the need for a baseline serum tryptase determination (Table 1).

Recently, the BNT162b2 vaccine was reported to be safe with premedication in mastocytosis patients with severe MC mediator-related symptoms [10].Consistent data on the need and type of preventive measures in patients with MC-related disorders receiving COVID-19 vaccines are still lacking. We consider that all adult patients with mastocytosis, MCAS and HAT are candidates to receive these vaccines, except in cases with a prior history of allergic reactions caused by any of the aforementioned components of the vaccine or by the first dose of the vaccine. Until further information is available, we do recommend premedication with at least a H1 histamine blocker 1 hour before the vaccine, which should be administered by trained staff in appropriate health care facilities (i.e. hospital with available intensive care unit), and under medical surveillance that should be kept for 45 minutes. In high-risk patients (e.g. patients with a prior history of immediate reactions to contrast media, monoclonal antibodies or drugs containing PEG, polysorbate or tromethamine) the decision on whether the patient should be vaccinated must be made on an individual basis. If the assessment supports vaccination, a more

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intensive premedication including H1 plus H2 antihistamines 1 hour before vaccination, and montelukast 24 and 1 hour before vaccination, followed by an observation period of 90 minutes can be a reasonable approach. Specifically, in patients with non-IgE mediated reactions potentially related with tromethamine (e.g. contrast media, endovenous dexketoprofen, ketorolac and fosfomycin), tromethamine-free vaccines should be selected.

The next few months will be crucial for the success of COVID-19 vaccination, which will be the first step to defeat the current pandemic crisis. Although severe allergic reactions are increasingly being reported, the risk of anaphylaxis in patients with mastocitosis seems to be low, provided that appropriate premedication is given. As the mass vaccination campaign moves forward, more information should be gathered in order to establish whether more specific preventive protocols are needed for these patients. Meanwhile, the word of order is *to vaccinate*.

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None to disclose.

Conflict of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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Table 1. Main characteristics of allergy reactions and anaphylaxis reported by the CDC after administration of mRNA vaccines against SARS-CoV-2.

	BNT162b2 (Pfizer-BioNTech)		**mRNA-1273 (Moderna)**	
	Anaphylaxis (n=21)	Allergicreaction (n=83)	Anaphylaxis (n=10)	Allergicreaction (n=43)
Female	90%	90%	100%	91%
Time fromadministration*	13 (2-150)	12 (<1-1200)	7.5 (1-45)	15 (<1-1440)
< 15 min	71%	74%	90%	51%
< 45 min	90%	88%	100%	78%
Mucocutaneous without CV‡	21 (100%)	NA	7 (70%)	NA
Treatmentwithepinephrine	90%	NA	100%	NA
Hospitalization	19%	NA	60%	NA
Admittance to ICU	14%	NA	50%	NA
History of allergy	81%	67%	90%	60%
Insectstings	10%	NA	0%	NA
Vaccines	10%	NA	0%	NA
Drugs	38%	NA	60%	NA
Contrast media	5%	NA	20%	NA
Food	24%	NA	10%	NA
History of prior anaphylaxis	33%	NA	50%	NA
Incidence (by 100,000 doses)	1.1	4.4	0.2	1.1
Number of doses administered	1,893,360		4,041,396	
Excipients potentially involved	PEG-2000		PEG-2000, tromethamine	

Adapted from [4,5]

CDC, Centers for Disease Control and Prevention; CV, cardiovascular; ICU, Intensive Care Unit; NA, not available; PEG, polyethylene glycol.

*Median time in minutes (range).

‡Symptoms during anaphylaxis