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Evaluation of anaphylaxis risk by skin testing with coronavirus disease 2019 messenger RNA vaccines on patients with anaphylaxis

Vaccination has been found to be effective in reducing the risks of infection of severe acute respiratory syndrome coronavirus 2 and severe coronavirus disease 2019 (COVID-19) outcomes. In the United States, Pfizer-BioNTech and Moderna COVID-19 vaccines (aka the messenger RNA [mRNA] vaccines) have been used safely for these purposes.[1,2] First postmarket reports on the use of these vaccines describe 4.7 cases of anaphylaxis per million doses of Pfizer vaccine and 2.5 cases per million Moderna doses given.[3] These early reports also describe 43.8 cases of nonanaphylactic allergic reactions per million Pfizer doses given.[4] Among individuals who experienced anaphylaxis to the Pfizer vaccine, 81% had a documented history of allergies triggered by drugs, vaccines, medical products, foods or insect stings, and 33% of these individuals experienced anaphylaxis in the past. Similarly, 90% of individuals with a history of anaphylaxis to the Moderna vaccine had a documented history of allergic reactions, and 50% of these individuals experienced anaphylaxis in the past.

The presumed causes of allergic reactions are the different polyethylene glycols (PEGs) in the mRNA vaccines. Although PEG allergy is rare, PEG has been found to cause anaphylaxis.[5] Moreover, skin testing of PEGs of differing molecular weights has been found to be effective in confirming anaphylaxis to PEGs in patients with a documented history of anaphylaxis to PEG.[6] Nevertheless, in a cohort of 8 individuals with allergic reactions to the first dosage of an mRNA vaccine, PEG skin testing result was found to be negative.[7]

The 2012 vaccine practice parameters published by the American Academy of Allergy, Asthma, and Immunology (AAAAI), recommend that individuals with suspected anaphylaxis to a particular vaccine receive skin testing with that vaccine to evaluate their risk of anaphylaxis.[8] Because the mRNA vaccines contain components other than PEG that may cause allergic reactions, the AAAAI recommendations for evaluating risk of anaphylaxis to vaccines are appropriate for the mRNA vaccines as well. In fact, Greenhawt et al[9] recently suggested using the 2012 parameters for patients with a previously documented allergy to one of the mRNA vaccines.[9]

Many of our patients who have experienced anaphylaxis express hesitancy toward receiving vaccines, owing to fears of anaphylaxis, and continue to delay their COVID-19 vaccination. To meet this demand, we offered skin testing with mRNA vaccines for our patients who requested evaluation of their risk of anaphylaxis.

In this communication, we will describe our first 30 patients (female, n = 27; male, n = 3) who had skin testing with the mRNA vaccines. The patients were either self-referred or referred to us by other physicians. All patients had a self-reported history of anaphylaxis to a variety of substances, including foods, venoms, drugs, environmental, flu vaccine, unknown sources or the first dosage of a COVID-19 mRNA vaccine. The risks and benefits of skin testing were discussed with the patients, and consent forms were accordingly signed. The patients were probed for self-reported reactions to PEG-containing products (ie, toothpaste and colonoscopy preparation). Ages of the patients ranged from 27 to 80 years. Of the patients, 2 had a history of COVID-19 confirmed by polymerase chain reaction testing.

Skin testing occurred from January 22, 2021, to March 25, 2021. Remnants of the mRNA vaccines were collected on the morning of testing from the Johnson City Medical Center in coordination with the Tennessee Department of Health and used for skin testing within 6 hours from opening of the vials. The patients were advised to refrain from using antihistamines and oral glucocorticoids starting 3 days before the testing. Skin testing was performed on the ventral forearms of the patients using the protocol recommended by the AAAI with modifications to increase safety. Testing began with standard histamine and normal saline applied by prick technique and by intradermal injection of 0.05 mL of each as positive and negative controls, respectively. Next, a 1:10 dilution with normal saline of the Pfizer or Moderna vaccine was applied by prick technique. After 20 minutes, wheal sizes were measured and recorded. Whenever the result was negative, every 20 minutes a dosage of 0.05 mL of diluted vaccine was applied intradermally, starting with a 1:1000 dilution, then a 1:100 dilution, and finally a 1:10 dilution. After recording the final wheal size, pictures of the skin tests were taken, the patients were observed for an additional 30 minutes, and they were requested to submit pictures of their skin test at 4 to 6 hours after testing to evaluate late-phase reactions and at 24 hours after testing to evaluate delayed reactions. Afterward, the patients were evaluated by direct interviews for their reaction to subsequent vaccination.

The results are presented in Table 1. There were 5 patients who had positive immediate skin reactions at doses ranging from 1:100 to 1:10 dilution of an mRNA vaccine. Of these patients, 1 had an anaphylactic reaction during skin testing of 1:100 dilution of the Moderna vaccine. These 5 patients also had positive late-phase reactions. There were 6 patients who had late-phase reactions without immediate reactions. Unfortunately, most patients did not comply with our request to submit pictures from delayed reaction. Patients with positive immediate reactions were recommended to receive the Janssen COVID-19 vaccine. Patients with negative immediate reactions (n = 25) were recommended to receive their choice of COVID-19 vaccine. None of the patients with negative skin test result to an mRNA

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Table 1
Data From mRNA Vaccine Skin Testing

Demographics				Previous medical history					Pfizer-BioNTech COVID-19 vaccine			Moderna COVID-19 vaccine			COVID-19 vaccination history	
									Skin test reaction[a]			Skin test reaction[a]				
Date tested	Pt	Age	Sex	Anaphylaxis		Self-reported reactions to products containing PEG		COVID-19 infection	Immediate	LPR	Delayed	Immediate	LPR	Delayed	COVID-19 vaccination[b]	Anaphylaxis to vaccination
				Self-reported history	Self-reported cause	Toothpaste	Colonoscopy prep									
January 22, 2021	1	54	F	Yes	Food, lidocaine	No	**Yes**	**Yes**[c]	Neg	**Pos**	No data	Not tested	Not tested	Not tested	Janssen (4/30)	None
January 22, 2021	2	80	F	Yes	Environmentals, animal	**Yes**	No	No	Neg	**Pos**	No data	Not tested	Not tested	Not tested	Janssen recommended	N/A
January 22, 2021	3	65	F	Yes	Foods	No	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Moderna (3/5)	None
January 22, 2021	4	77	F	Yes	Meds, foods	**Yes**	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Pfizer (2/1, 2/22)	None
January 22, 2021	5	59	F	Yes	Food	No	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Did not receive	N/A
January 22, 2021	6	74	F	Yes	Foods, cosmetics	**Yes**	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Pfizer (2/12, 3/5)	None
January 22, 2021	7	62	F	Yes	Foods	**Yes**	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Moderna (3/18, 4/25)	None
January 22, 2021	8	74	F	Yes	Mold	**Yes**	No	No	Neg	Neg	No data	Not tested	Not tested	Not tested	Pfizer (3/2, 3/23)	None
January 22, 2021	9	77	F	Yes	Food, contrast media	No	No	No	Neg	Neg	**Pos**	Not tested	Not tested	Not tested	Pfizer (2/8, 3/1)	None
January 22, 2021	10	27	F	Yes	Foods, meds	No	No	**Yes**[c]	**Pos (1:10)**	**Pos**	No data	Not tested	Not tested	Not tested	Janssen recommended	N/A
February 2, 2021	11	69	F	Yes	Bee, foods	**Yes**	No	No	**Pos (1:100)**	**Pos**	No data	**Pos (1:100)**	**Pos**	No data	Janssen recommended	N/A
February 2, 2021	12	63	F	Yes	Environmentals, food	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Did not receive	N/A
February 2, 2021	13	71	F	Yes	Food	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (3/18, 4/15)	None
February 2, 2021	14	65	F	Yes	Food	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (2/12)	None
February 2, 2021	15	76	F	Yes	Food	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (4/30, 5/29)	None
February 26, 2021	16	61	F	Yes	Unknown	No	**Yes**	No	**Pos (1:10)**	Neg	No data	**Pos (1:10)**	**Pos**	No data	Janssen recommended	N/A
February 26, 2021	17	68	F	Yes	Unknown	No	No	No	Neg	**Pos**	**Pos**	Neg	**Pos**	**Pos**	Moderna (1/6, 3/1)	None
February 26, 2021	18	80	F	Yes	Iodine and sulfa	No	No	No	Neg	**Pos**	**Pos**	Neg	Neg	**Pos**	Did not receive	N/A
February 26, 2021	19	74	M	Yes	Venom, shellfish	No	No	No	Neg	No data	No data	Neg	No data	No data	Moderna (3/3, 3/31)	None
February 26, 2021	20	59	F	Yes	Red dye, ampicillin	**Yes**	No	No	Neg	**Pos**	**Pos**	**Pos (1:10)**	**Pos**	**Pos**	Janssen recommended	N/A
February 26, 2021	21	59	F	Yes	Venom, food, Moderna first dosage (immediate generalized pruritus, followed by asthma exacerbation, tongue swelling, myalgia)	No	No	No	Testing D/C[d]	Testing D/C[d]	Testing D/C[d]	**Pos (1:100)**	**Pos**	**Pos**	Moderna (2/8, 4/12)	After desensitization, none[e]
February 26, 2021	22	66	F	Yes	Antibiotics	**Yes**	**Yes**	No	Neg	**Pos**	No data	Neg	Neg	No data	Pfizer (3/4, 3/25)	None
February 26, 2021	23	67	F	Yes	Unknown	No	No	No	Neg	**Pos**	No data	Neg	Neg	No data	Did not receive	N/A
February 26, 2021	24	37	F	Yes	Venom	No	No	No	Neg	No data	Neg	Neg	No data	**Pos**	Did not receive	N/A
March 19, 2021	25	59	F	Yes	Venom	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Pfizer (4/6, 4/27)	None
March 19, 2021	26	65	M	Yes	Flu vaccine	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (3/23, 4/20)	None
March 25, 2021	27	78	M	Yes	Tdap	No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (3/25, 4/22)	None
March 25, 2021	28	35	F	Yes		No	No	No	Not tested	Not tested	Not tested	Neg	Neg	No data		None

(*continued*)

Table 1 (*Continued*)

Demographics				Previous medical history					Pfizer-BioNTech COVID-19 vaccine			Moderna COVID-19 vaccine			COVID-19 vaccination history	
				Anaphylaxis					Skin test reaction[a]			Skin test reaction[a]				
Date tested	Pt	Age	Sex	Self-reported history	Self-reported cause		Self-reported reactions to products containing PEG		COVID-19 infection	Immediate	LPR	Delayed	Immediate	LPR	Delayed	COVID-19 vaccination[b]	Anaphylaxis to vaccination
							Toothpaste	Colonoscopy prep									
March 25, 2021	29	71	F	Yes	Augmentin, doxycycline, hydrocodone		No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (3/25, 4/22) Moderna (4/1, 4/29)	None
					Egg												
March 25, 2021	30	79	F	Yes	Venom, lortab		No	No	No	Not tested	Not tested	Not tested	Neg	No data	No data	Moderna (4/1, 4/29)	None

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; COVID-19, coronavirus disease 2019; D/C, discontinued; F, female; LPR, late phase reaction; M, male; meds, medications; mRNA, messenger RNA; N/A, not applicable; neg, negative; PCR, polymerase chain reaction; PEG, polyethylene glycol; pos, positive; prep, preparation; Pt, patient.
NOTE. Positive results were bolded in the table.
[a]Skin testing performed using AAAAI-recommended protocol.
[b]Confirmed through Tennessee Immunization Information System.
[c]Confirmed by PCR.
[d]Owing to systemic and local reactions to 1:100 dilution of Moderna in this patient, testing of the Pfizer vaccine was discontinued after the intradermal application of the 1:100 dilution of Pfizer, which revealed no reaction.
[e]Patient given second dosage of Moderna after Moderna vaccine desensitization; subject of future publication.

vaccine who were subsequently vaccinated to COVID-19 (n = 19, confirmed through records in the Tennessee Immunization Information System) have had any allergic reaction to vaccination. After our risk assessment, 66% of the patients went on to receive full COVID-19 immunization.

On the basis of these observations, skin testing with the mRNA vaccines seems safe, and patients with negative immediate reactions to skin testing tolerated the corresponding mRNA vaccine (n = 19). Furthermore, 3 patients with only positive late-phase reactions to skin testing did not experience reactions to vaccination. Consequently, skin testing should be considered as an adjunct procedure to evaluate risk for patients with a history of anaphylaxis, especially when the patients are delaying vaccination. These data are limited owing to our reliance on self-reporting and small sample size. Furthermore, patients with positive immediate reactions to skin testing were advised to receive the Janssen vaccine; therefore, the positive predictive value of skin testing cannot be determined. Importantly, testing with the vaccine carries risk of causing anaphylaxis (as documented by 1 patient in our cohort), which is similar to the reporting of skin testing with PEG.[6] Consequently, skin testing with the mRNA vaccines needs to be performed according to the AAAAI guidelines.

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