Skin tests with SARS-CoV2 vaccine excipients in patients with first-dose mucous-cutaneous adverse reactions: a purpose of allergologic workup

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To the Editor,

Vaccination is crucial to contrast the spreading of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and the second dose is necessary to prevent the Coronavirus disease-19 (COVID-19) induced by the emerging B.1.617.2 (delta) variant.[1]

During clinical approval studies and post-marketing phases, mucous-cutaneous adverse reactions have been rarely observed, both local (injection site) and systemic reactions. Among the hypersensitivity reactions, immediate (anaphylaxis, urticaria-angioedema syndrome) were more frequently observed than delayed (maculopapular eruptions) reactions; moreover, anaphylaxis is a rare event, estimated at 7.9 per million doses globally.[2] The causes of these allergic reactions remain unknown, but excipients with known sensitizing potential may play a role. Particularly, Pfizer-BioNTech vaccine contains polyethylene glycol (PEG)-2000, Moderna vaccine PEG-2000 and tromethamine, AstraZeneca and Janssen vaccines polysorbate 80. PEGs and polysorbate 80 are cross-reactive and may cause mostly IgE-mediated allergic reactions, while tromethamine is responsible for both immediate and delayed reactions.[3]

The European Academy of Allergy and Clinical Immunology (EAACI)[3] and the Italian Society of Dermatology (SIDeMaST)[4] recommended, in patients with suspected allergic reaction after the first dose of SARS-CoV2 vaccine, an accurate allergologic workup, performing skin tests with vaccines and their components, in order to investigate the allergy and eventually to find potential alternative SARS-CoV2 vaccines. According to these recommendations, and considering the limits of skin test with Pfizer-BioNTech vaccine,[5] we developed a skin test protocol with SARS-CoV2 vaccine excipients (Table 1). Readings were performed at 48 h and 96 h for patch test (PT), 20 min for skin prick test (SPT), and 20 min and 24 h for intradermal test (ID).

21 patients who referred adverse reactions to SARS-CoV2 vaccine first dose, summarized in Table 2, underwent to skin tests as previously described. None developed hypersensitivity or irritant reactions. The same tests were also performed, with negative results, in ten volunteers who had received the first dose of SARS-CoV2 vaccine and in ten volunteers who did not receive vaccine. All patients and controls referred transient local burning sensation after tromethamine ID, without skin lesions. All 21 patients then received the second dose of vaccine without relapses.

Skin tests with SARS-CoV2 vaccine excipients are not still standardized. Wolfson *et al* [6] tested 80 patients with immediate and delayed reactions to COVID-19 vaccines using MiraLAX and methylprednisolone acetate (both containing PEG-3350) for SPT and ID, and triamcinolone acetonide or Refresh Tears (both containing polysorbate 80) for SPT and ID. They observed 14 (17.5%) positive reactions, 12 of them with Refresh Tears, which was found to be an irritant in 52% of nonallergic controls. 75% of patients with negative skin test had the second vaccine dose without recurrent symptoms, while among the 14 patients with positive skin tests, 10 received the second dose, 3 of whom with recurrence of allergic reactions and 7 without relapses.

The Authors concluded that excipient skin testing "not impact tolerance of a second dose in patients with immediate or delayed reactions". Differently, we tested the pure excipients since the use of drugs can increase the risk of irritant and false positive reactions due to the presence of other components, including the active pharmaceutical ingredient. Moreover, the use of corticosteroids may lead to false negative reactions, due to their immunosuppressant effect. Finally, we tested PEG-2000 and not PEG-3350, since the molecular weight could influence the immunoreactivity of the compound.

A recent consensus[2] suggests against performing skin testing using SARS-CoV2 vaccines or excipients in patients with a history of anaphylaxis to SARS-CoV2 vaccine, because of their unknown sensitivity/specificity in predicting severe allergic reactions. As a matter of fact, our skin test protocol, conducted with pure excipients, demonstrated good tolerability and seems to be useful in patients who reported mucous-cutaneous adverse reactions after the first dose of SARS-CoV2 vaccine, despite the negative predictive value must be confirmed in larger cohort of patients.

TABLE 1. Skin test

Excipient	**Patch test**	**Skin prick test**	**Intradermal test**
Polyethylene glycol 2000	5% pet	0.01%, 0.1%, 1% et	0.01% aq
Polysorbate 80	5% pet	0.01%, 0.1%, 1% et	0.01% aq
Tromethamine	1% aq	0.1% et	0.01% aq

aq: in saline; et: in ethanol; pet: in petrolatum

Patient n°	**Gender, age**	**Personal atopic history**	**Allergy history**	**Anti SARS-CoV-2 vaccine**	**Type of reaction**	**Time of onset**	**Treatment**
1	F, 24	Allergic rhinitis	None	Pfizer-BioNTech	Acute urticaria	5 minutes	Systemic antihistamines
2	F, 31	Allergic rhinitis	None	Pfizer-BioNTech	Angioedema (tongue, gums)	24 hours	None
3	M, 28	Allergic rhinitis	None	Pfizer-BioNTech	Acute urticaria	5 minutes	None
4	F, 58	Allergic rhinitis Asthma	None	Pfizer-BioNTech	Face erythema	30 minutes	None
5	F, 50	Allergic rhinitis	None	Pfizer-BioNTech	Face erythema	20 minutes	None
6	F, 44	Allergic rhinitis Atopic dermatitis	Contact allergy (nichel sulphate, fragrances)	Pfizer-BioNTech	Angioedema (tongue, lips)	10 minutes	None
7	F, 49	Allergic rhinitis	Contact allergy (nichel sulphate)	Pfizer-BioNTech	Anaphylactoid reaction	20 minutes	Systemic antihistamines and corticosteroids

Patient n°	Gender, age	Personal atopic history	Allergy history	Anti SARS-CoV-2 vaccine	Type of reaction	Time of onset	Treatment
8	F, 32	Allergic rhinitis Asthma	Food allergy (milk and fish proteins)	Pfizer-BioNTech	Asthma exacerbation	13 hours	Inalatory formoterol and beclomethason
9	F, 39	Allergic rhinitis	Contact allergy (nichel sulphate)	Pfizer-BioNTech	Reflex syncope	20 minutes	Intravenous saline solution, oxygen
10	F, 50	Allergic rhinitis	Urticaria-angioedema (penicillin)	Pfizer-BioNTech	Reflex syncope	2-3 minutes	Systemic antihistamines and corticosteroids
11	F, 72	Allergic rhinitis Asthma	Contact allergy (nichel sulphate, potassium bichromate)	Pfizer-BioNTech	Angioedema (eyelids)	1 hour	Systemic antihistamines and corticosteroids
12	F, 75	None	Contact allergy (nichel sulphate) Food allergy (tomato proteins)	Pfizer-BioNTech	Angioedema (face)	72 hours	Systemic antihistamines
13	F, 49	Allergic rhinitis	Contact allergy (nichel sulphate)	Pfizer-BioNTech	Face erythema	2-3 minutes	Systemic antihistamines and corticosteroids
14	F, 59	Allergic rhinitis	None	Pfizer-BioNTech	Anaphylactoid reaction	30 minutes	Systemic antihistamines and corticosteroids
15	F, 53	Allergic rhinitis	None	Pfizer-BioNTech	Angioedema (tongue)	2-3 minutes	Systemic antihistamines
16	F, 54	Allergic rhinitis	None	Pfizer-BioNTech	Urticaria-angioedema, bullous injection site reaction	12 hours	Systemic antihistamines and corticosteroids
17	F, 31	None	None	AstraZeneca	Maculopapular rash	72 hours	None
18	F, 74	None	None	AstraZeneca	Maculopapular rash	24 hours	Systemic corticosteroids

Patient n°	Gender, age	Personal atopic history	Allergy history	Anti SARS-CoV-2 vaccine	Type of reaction	Time of onset	Treatment
19	F, 45	Allergic rhinitis	Contact allergy (nichel sulphate)	AstraZeneca	Urticaria-angioedema	10 hours	Systemic antihistamines and corticosteroids
20	M, 24	Allergic rhinitis Asthma	None	Moderna	Asthma exacerbation, acute urticaria	20 minutes	Systemic corticosteroids
21	F, 35	None	Contact allergy (paraphenylenediamine)	Moderna	Reflex syncope	2-3 minutes	None

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