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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors equally contributed to the manuscript, read and approved the final version of the manuscript.

History.—Manuscript accepted: December 1, 2022. - Manuscript revised: September 5, 2022. - Manuscript received: June 26, 2022.

(Cite this article as: Quattri E, Zussino M, Marzano AV, Genovese G. Lung cancer-associated erythema gyratum repens rapidly evolving to erythroderma. *Ital J Dermatol Venereol* 2023;158:71–2. DOI: 10.23736/S2784-8671.22.07408-4)

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Italian Journal of Dermatology and Venereology 2023 February;158(1):72–3

DOI: 10.23736/S2784-8671.22.07410-2

Self-reported allergy to medications containing the same excipients as SARS-CoV2 vaccines: importance of skin testing with excipients

The anti-SARS-CoV2 vaccines used in Italy contain the following excipients: polyethylene glycol (PEG) 2000, polysorbate 80, and tromethamine. Phases 2 and 3 clinical trials on anti-SARS-CoV2

vaccines excluded not only patients with proven allergy to excipients contained in these vaccines but also subjects self-reporting muco-cutaneous adverse reactions to drugs or products containing the same excipients.¹ Herein, we report the results of skin testing with anti-SARS-CoV2 vaccine excipients in a cohort of patients with history of allergy to other medications containing the same excipients.

From March to December 2021, patients with self-reported muco-cutaneous adverse reactions to systemic and topical drugs containing PEG 2000, polysorbate 80, and tromethamine were collected. Patients underwent patch test (PT) with PEG 2000 and polysorbate 80 (5% pet.) and tromethamine (1% aq.), skin prick test (SPT) with PEG 2000 and polysorbate -80 (0.01-0.1-1% eth.) and tromethamine (0.1% eth.), and intradermal test (ID) with PEG 2000, polysorbate 80, and tromethamine (0.01% aq.). The allergens were obtained from Sigma-Aldrich (Milan, Italy) and prepared by our hospital Pharmacy. PT were applied on the back and were occluded for 2 days with Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Sofix tape (Artsana, Grandate, Italy), and readings were done on day (D)2, D4 and D7. SPT and IDT were performed on the volar aspect of forearms and readings were done at 30 minutes and D1.²

We collected 30 patients (6 males, 24 females; mean age 59.5 years) (Table I). Seventeen patients (56.7%) reported adverse reactions to vaccines other than anti-SARS-CoV2, 8 (26.7%) to systemic drugs, 3 (10.0%) to contrast media, and 2 (6.7%) to topical drugs. The incriminated excipients were polysorbate 80 in 17 (56.7%), PEGs in 10 (33.3%), and tromethamine in 5 (16.7%), with patients n.14 and n.26 reporting both 2 excipients.

Patient n. 14 showed positive PT reactions to PEG 2000 and polysorbate 80 on D2 and D4. She reported a generalized itching rash after taking zolpidem and ibuprofen containing PEG 400 and polysorbate 80, respectively. SPT and ID with tromethamine resulted negative. Given the presence of these excipients in all anti-SARS-CoV2 vaccines, the patient was recommended not to be vaccinated.

In the remaining 29 (96.7%) patients with negative skin tests, anti-SARS-CoV2 vaccination was recommended and they underwent it without any adverse reaction.

In patients with reported adverse reactions to drugs containing PEGs, polysorbate 80, or tromethamine skin tests with these excipients are recommended also to identify an alternative anti-SARS-CoV2 vaccine.³

Among our patients, only in patient n. 14 positive PT reactions to PEG 2000 and polysorbate 80 were observed. PEGs are hydrophilic polymers of ethylene oxide widely used in medical and cosmetic fields, both as osmotic laxatives and drug excipients. Polysorbate 80, extensively used as an excipient in drugs (e.g. vaccines) and cosmetics and as an emulsifier in the food industry, is a PEGylated sorbitan, and cases of cross-reactivity between PEGs and polysorbate 80 are reported.⁴ Tromethamine is an organic compound mainly used as a pH stabilizer in systemic and topical drugs, and responsible both for immediate and delayed reactions.⁵

In conclusion, we underline the good negative predictive value of skin tests with vaccine excipients in almost all of our patients, who subsequently received anti-SARS-CoV2 vaccine without adverse reactions. However, our data need to be verified in a larger study population. Skin tests with vaccine excipients should be especially performed in those subjects who otherwise would be unwilling to undergo vaccination.

TABLE I.—Demographics, atopy, drug and related excipients, adverse reaction and latency time in 30 subjects with self-reported mucocutaneous reactions.

Patient N.	Gender, age (years)	Atopy	Drug	Excipient	Adverse reaction	Latency time
1	F, 45	None	Macrogol	PEG 3350	Urticaria	20 min
2	F, 52	AR	SARS-CoV1 vaccine	Polysorbate 80	Anaphylaxis	15 min
3	F, 53	AR	Smallpox vaccine	Tromethamine	Urticaria	20 min
4	M, 57	AA	DTaP vaccine	Polysorbate 80	Anaphylaxis	10 min
5	F, 42	AD	Influenza vaccine	Polysorbate 80	Anaphylaxis	Few s
6	M, 76	AR	Amiodarone injectable	Polysorbate 80	Dyspnea	Few s
7	F, 71	AR, AS	Influenza vaccine	Polysorbate 80	Injection site reaction	30 min
8	F, 57	AR	Smallpox vaccine	Tromethamine	Generalized rash	Not known
9	M, 27	AD	DPaT vaccine	Polysorbate 80	Injection site reaction	24 hs
10	F, 28	AD	Gentamicin cream	PEG 400	ACD	6 hs
11	F, 74	AR, AS	DPaT vaccine	Polysorbate 80	Generalized rash	Not known
12	F, 77	None	Influenza vaccine	Polysorbate 80	Injection site reaction	12 hs
13	F, 76	AA	Influenza vaccine	Polysorbate 80	Generalized rash	48 hs
14	F, 57	None	Zolpidem tablets, ibuprofen tablets	PEG 400, polysorbate 80	Generalized rash and itch	30 min
15	F, 64	AR	Nimesulide tablets	Cetomacrogol 1000	Anaphylaxis	5 min
16	M, 60	AR, AS	Influenza vaccine	Polysorbate 80	Flushing of the face	20 min
17	M, 80	None	Paracetamol/ propyphenazone tablets	PEG 6000	Anaphylaxis	10 min
18	F, 53	AR, AS	DPaT vaccine	Polysorbate 80	Anaphylaxis	Not known
19	F, 75	None	Meningococcal vaccine	Polysorbate 80	Injection site reaction	6 days
20	F, 66	None	Ursodeoxycholic acid tablets	PEG 6000	Urticaria	1 h
21	F, 83	None	Triamcinolone acetone injectable	Polysorbate 80	Anaphylaxis	10 min
22	F, 77	None	Influenza vaccine	Polysorbate 80	Injection site reaction	24 hs
23	F, 52	AR	DPaT vaccine and influenza vaccine	Polysorbate 80	Throat angioedema	3 hs
24	F, 24	AD	DPaT vaccine	Polysorbate 80	Anaphylaxis	1 h
25	F, 43	None	Gentamicin cream	PEG 400	ACD	Not known
26	F, 58	AR, AA	Amoxicillin tablets	PEG 4000, PEG 6000	Generalized rash	Not known
27	F, 62	None	Cyproterone acetate/ethinylestradiol tablets	PEG 6000	Generalized rash	2 months
28	F, 45	AR	Gadoteric acid (contrast media)	Tromethamine	Acute urticaria	10 min
29	F, 74	None	Iomeprole (contrast media)	Tromethamine	Maculo-papular exanthema	10 hs
30	M, 76	None	Iobitridole(contrast media)	Tromethamine	Generalized rash	30 min

AA: allergic asthma; AD: atopic dermatitis; AR: allergic rhinitis; DTaP: diphtheria, tetanus and pertussis; PEG: polyethylene glycol.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

History.—Article first published online: November 24, 2022. - Manuscript accepted: November 10, 2022. - Manuscript revised: November 3, 2022. - Manuscript received: June 27, 2022.

(Cite this article as: Biondi F, Bianchi L, Tramontana M, Marietti R, D'arpino A, Hansel K, *et al.* Self-reported allergy to medications containing the same excipients as SARS-CoV2 vaccines: importance of skin testing with excipients. *Ital J Dermatol Venereol* 2023;158:72-3. DOI: 10.23736/S2784-8671.22.07410-2)