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Is polyethylene glycol allergy a real contraindication to COVID-19 mRNA vaccines?

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Dear Editor,

The SARS-CoV2 pandemic is still ongoing and keeps representing a hard challenge for the Health Systems of several Countries. The actual considerable deficiency of specific therapies for the viral infection and the lack of valid treatments for all, or for at least the majority, of patients affected by COVID-19, makes mass vaccinations the only way to get out from the pandemic emergency.

One of the main problems that seem to hamper the success of the vaccination is represented by the fear of anaphylactic reactions to available vaccines. The first cases were reported in UK and USA in early December 2020 (1), prompting the need to establish the actual prevalence of allergic reactions to the vaccines.

Allergic reactions to vaccines, including anaphylaxis, are rare events and generally are due to sensitization to excipients, adjuvants or other components, rather than to active ingredients.

The most recent data in Italy have downsized the problem, reducing the frequency of anaphylactic reactions to 3 cases out of one million of doses administered by Pfizer-BioNTech Comirnaty and to 2 cases out of millions of doses by Moderna Spykevax (2).

Nevertheless, concern keeps being widespread.

A possible cause of these vaccine-induced anaphylaxis events could be the polyethylene glycol (PEG), excipient of both Pfizer and Moderna vaccines. Immediate hypersensitivity reactions to PEG, also known as macrogol, are probably little recognized and poorly understood and anaphylactic reactions to macrogol have been reported infrequently. However, an increasing trend of allergic reactions to certain medications and personal hygiene products that contain PEGs has been observed in previous years (3, 4) in terms of immediate hypersensitivity reactions to the structurally similar molecule Polysorbate 80 (PS80), which has shown a certain degree of cross-reactivity with PEG (5).

This way, several International Scientific Organizations, Universities and General Hospitals produced guidelines and accurate allergy risk-assessment protocols (6, 7, 8, 9, 10) to reduce the number of patients who would have avoided SARS-CoV2 Vaccination because of their allergy. International and local protocols agree not to administer PEG-containing vaccines to subjects allergic to this excipient (11, 12).

However, we report three cases in which a close fractional administration could allow to vaccinate against SARS-CoV-2 virus even subjects sensitive to PEG.

The fractional administration method indicated below is usually performed in some of the main Allergy Centers of the Veneto region (Italy) for subjects considered at risk of anaphylaxis.

T.A., a 46-year-old woman, with history of urticaria-angioedema after the consumption of NSAID, developed after almost five minutes from the administration of the first dose of Comirnaty Pfizer a generalized urticaria, treated in the vaccination center with chlorphenamine 10 mg intramuscular and methylprednisolone 40 mg intravenous. The skin prick test with a similar solution of a laxative preparation containing macrogol (PEG) gave a negative result, but the intradermal test subsequently performed with Depo-Medrol (containing PEG 3350), after the dilution of 1:10, resulted in an 8 mm diameter wheal with a hyperemic halo of 14 mm; the control intradermal tests with Urbason (methylprednisolone sodium succinate, without PEG), diluted and undiluted, resulted negative.

The patient, on 2nd August 2021, was undergoing the intramuscular injection of the second dose in a safe environment and through fractionated administration: 0.05cc + 0.25 (reaching this way the standard amount of 0.3cc) 20 minutes apart with a following observation of 90 minutes.
Not a single adverse event has been noticed.

A second case concerns R.I., a 27-year-old man with history of allergic oculorhinitis to house dust mites. He came to the allergological visit, sent from the vaccination center, since he complained of two episodes of spread and severe urticaria a few minutes after the consumption of a laxative containing macrogol (PEG). The skin prick test with a similar solution of a laxative preparation containing macrogol (PEG) gave a weakly positive result, but the intradermal tests performed with Depo-Medrol (containing PEG 3350), after the dilution of 1:100, resulted after almost 15 minutes in a wheal of at least 10 mm with an 18 mm diameter hyperemic halo and a slight systemic urticaria reaction, with scattered wheals in limbs, chest and abdomen, solved after almost 40 minutes from the assumption of cetirizine 10 mg.

The patient submitted to the intramuscular injection of both the first and the second dose in a safe environment and through the fractioned administration: 0.05 mL + 0.25 mL (reaching this way the standard amount of 0.3 mL) 20 minutes apart, with a following observation of 90 minutes.
Not a single adverse event has been noticed, not even a wheal during the inoculation.

The third case to write about is that of V.DA, a 29-year-old female nurse in a hospital in Milan, with allergic rhinoconjunctivitis, and history of polysensitization versus pollen (graminaeae, urticacee, cupressacee), Alternaria alternata, dog, and then allergic oral syndrome with drupacee. She experienced an adverse reaction after the first vaccination with Comirnaty Pfizer with immediate and diffuse erythema of the upper limb, ipsilateral to the injection site, and after 40 minutes oral pruritus and dysphagia with dyspnoea, successfully treated with antihistamines and intravenous steroids.

The patient was tested at a hospital in Milan (see attached photo) and the comment was as follows: “Skin prick tests negative with PEG 4000, PEG 3350 and polysorbate 80; positive intradermal

reactions with PEG 3350 and negative with polysorbate 80. The negativity of the skin reactions with soluble cortisone without PEG or polysorbate confirms the positivity to the PEG. According to clinical history and test results, the patient has a predictable increased risk of IgE allergic reactions mediated to the PEG component present in mRNA vaccines …". The inoculation of PEG-containing vaccines was strongly discouraged.

At our Allergy Center, this patient also underwent intramuscular injection of the second dose of Comirnaty in a safe environment and by means of the fractional administration: 0.05 mL + 0.25 mL (thus reaching the standard amount of 0.3 mL) after 20 minutes, with a subsequent 90-minute observation.

Not a single adverse event was noted, not even a wheal during inoculation.

In the first two patients, antibodies against SARS CoV-2 were measured (SARS-CoV-2 IgG anti-RBD CLIA method on the Maglumi automated platform, SNIBE, Shenzen, China) after the vaccine administration.

T.A. showed antibodies levels of 144.6 BAU/mL (results ≥ 4.33 AU/mL were considered as positive) after 85 days from the last dose.

R.I. showed antibodies levels of 3624 BAU/mL after 32 days from the last dose. The results were consistent with the concentrations found in other vaccinated subjects using the same method at the corresponding timing from vaccination (13).

These experiences, although anecdotal, seem to demonstrate that the administration of the vaccine through fractionated doses could be a valid and effective proposal for patients prone to sensitization to the excipients of both Pfizer and Moderna vaccines.

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Conflict of interest
The authors declare that they have no conflict of interest