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Polyethylene glycol/polysorbate skin testing can be useful in risk assessment and management of allergic/pseudoallergic reactions to nanolipid/adenoviral vaccines

To the Editor:

Since the time when adverse events to anti-COVID vaccines were reported, allergists have been overwhelmed by a tide of urgent requests for proper evaluations not only in the event of suspect allergic reactions to vaccines but also before the first anti-COVID doses, on the basis of any possible and impossible reason. Allergy societies/academies quickly released specific guidelines to avoid senseless chores, leaving the "real" work to be done. The other side of the coin is that most of us have been forced to face the almost-neglected/somewhat-underrated problem of excipient allergy and shade a light upon hidden/undiagnosed cases of polyethylene glycol (PEG) and/or polysorbate (PS) true allergic reactions—though definitely very few, in agreement with the very low prevalence of PEG/PS allergy.

Greenhawt et al[1] wrote the last chapter of a series of publications about the utility of excipient skin testing before anti-COVID vaccine administration.[2,3] Many of their statements are embraceable, but it must be remarked how the evidence-based approach applies on data too weak to be accountable for calculating either sensitivity or predictive values.[2] In fact, the series reported by Wolfson et al[2] consists of only 2 cases of possible/probable postvaccine anaphylaxis with positive skin tests; moreover, none of them was re-exposed to the very product involved in the reaction (patient 1 switched from Pfizer-BioNTech's Comirnaty to Janssen's Jcovden, which means polysorbate instead of PEG exposure; patient 2 did not receive a second dose). Looking back to past evidence, we have to mention the milestone review by Wenande and Garvey,[4] where 23 of 24 PEG-allergic patients showed positive skin tests, which makes a sensitivity of 95.8%.

Facing the PEG/PS diagnostic path, we have to deal with 2 peculiar core problems: (1) PEGs are able to induce immediate adverse reactions via non–IgE-mediated mechanisms (eg, Complement Activation Related PseudoAllergy), thus affecting the negative predictive value of the skin tests; (2) the quantity of PEG or PS contained in nanolipid and adenoviral vaccines, respectively, is very low—approximately 0.1 mg, or even less, per dose—thus affecting the positive predictive value of the skin tests.

As a matter of fact, it has been already reported that some PEG-allergic individuals overtook the administration of PS- and also PEG-containing vaccines uneventfully.[5,6] On the other hand, some of the immediate reactions to anti-COVID vaccines can be reasonably attributed to PEG allergy.[2,6]

We believe that excipient testing is useful for detecting those who—with a personal history compatible with PEG/PS allergy—have developed a specific IgE reactivity, to address the consequent decision-making and estimate the risks of other possible PEG/PS exposures. That is obviously time and resource consuming, but in the end it is not different from what we do in any case of a suspect adverse drug reaction.

Another debatable issue is whom to test. Because the number of adverse reactions to vaccines appears to be highly overestimated,[7] a strict selection is needed, and it must be made before the patients reach the allergists. From our experience, general practitioners are not able to filter efficaciously by themselves; they should be then backed up by clear-cut and easy-to-use new specific guidelines coming from allergy societies with the advocacy of national governments.

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Reply to "Polyethylene glycol/polysorbate skin testing can be useful in risk assessment and management of allergic/pseudoallergic reactions to nanolipid/adenoviral vaccines"

To the Editor:

Immediate allergic- and stress-related responses to COVID-19 vaccines, both mRNA and viral-vector types, continue to occur.[1] Thankfully, the incidence of these reactions has leveled off from the experience of the initial few weeks of vaccine availability, and our work has shown that the global incidence of anaphylaxis to mRNA COVID-19 vaccines is unlikely to exceed 7.9 cases per