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

million (95% confidence interval [CI], 4.02-15.59), which is a very rare occurrence.[2] We would like to address a few misconceptions in the correspondence from Marchi and Carabelli[3] regarding skin test precision for polyethylene glycol (PEG) and polysorbate (PS) as a way to predict the risk of an initial COVID-19 vaccine's immediate allergic reaction. Data continue to show that skin testing to predict either a first-dose reaction or any subsequent dose reaction is of little to no utility.[4]

An international consensus of expert guidance from 2021 cautioned against the use of skin testing, in large part, because evidence demonstrates that the great majority of reactions to COVID vaccination are not IgE-mediated.[2] In addition, the quantity of PEG (or PS) in the vaccines is very low and is likely subthreshold to provoke a reaction.[2] A recent systemic review and meta-analysis of second-dose severe reactions demonstrated that such events occur at a very low rate (0.16%; 95% CI, 0.01%-2.94%).[1]

Skin testing to predict these rare reactions is hampered by poor testing precision.[4] In another systematic review and meta-analysis, pooled sensitivity for skin testing to the mRNA vaccines, PEG, and PS in persons with initial reactions (being assessed for repeat vaccination) was remarkably low (combined for any agent, 0.03; 95% CI, 0.00-0.08) in predicting second dose reactions.[4] In fact, PEG skin testing has fairly poor sensitivity (0.59) even when evaluating persons with suspected PEG allergy for the non-mRNA vaccine reactions.[2] Although specificity of excipient and vaccine skin testing in persons with first dose reactions is high, this finding must be interpreted cautiously, as the overall testing accuracy suggests that the reagents are not suitable for use in skin testing or the reactions are not IgE-mediated.[4]

It is likely that the "last chapter" in the approach to COVID vaccine reactions is yet to be written, though we feel we are close to stable guidance.[2] Still, like many other things in medicine, engaging patients and families in a shared decision-making approach to vaccination is central to providing optimal care to patients with adverse reactions to COVID vaccination.[2] An important part of these conversations involves the assessment of prior reactions and reassurance that the great majority of persons experiencing immediate reactions to COVID vaccines can safely receive them again—often in a setting facilitated by the supervision of a clinician highly trained in the management of severe allergic reactions (in the unlikely event this occurs).[2] Perhaps the greatest benefit such precautions provide is reassurance to allow revaccination in those with prior reactions.[2,5] Although skin testing to vaccine and vaccine excipients is highly unlikely to inform decision-making (because the testing lacks precision and the mechanism is less likely to be IgE-mediated), we do share agreement that the ability of an allergist-immunologist to help patients navigate past a frightening reaction to a COVID vaccine is instrumental.[2,4]

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Conflicts of interest: M. Greenhawt is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Nutricia, Novartis, Acquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, and Prota, with all activity unrelated to vaccines/vaccine development or COVID-19 treatment; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, MedLearningGroup, RMEI Medical Education, and multiple state/local allergy societies. M. Shaker serves on the editorial board of the *Journal of Allergy and Clinical Immunology: In Practice*; is an associate editor of the *Annals of Allergy, Asthma, and Immunology*; is a member of the Joint Task Force on Practice Parameters; and has participated in research that has received funding from DBV.
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Hyperthyroidism in patients with asthma

To the Editor:

We read with great interest the study by Gau et al[1] on the risk of hyperthyroidism in patients with asthma. In this retrospective cohort study using an insurance claims database, the authors hypothesized that patients with asthma had a higher risk for hyperthyroidism. To augment the findings, several recommendations on covariates that could be included in the study may be adopted.

Firstly, although the authors had considered potential confounders, including esophageal reflux, hypertension, and coronary artery disease in propensity score matching, residual confounders such as allergic rhinitis and obesity should also be adjusted, as those diseases are also comorbidities associated with asthma.[2,3] As such, it would be recommended that the authors include allergic rhinitis and body mass index as covariates.

Secondly, to strengthen the validity of the inclusion criteria for asthma, the authors set additional criteria based on the prescription of fluticasone propionate with salmeterol and budesonide with formoterol; however, other treatment options such as beclomethasone/formoterol that have been widely used, were not included.[4] It is advised that the authors refer to the Global Initiative for Asthma guideline[5] to define the population of asthma and the severity of asthma based on prescriptions in their insurance claims dataset.