Ann Allergy Asthma Immunol 129 (2022) 22–23

Contents lists available at ScienceDirect

Perspective

Allergy evaluation of messenger RNA vaccine reactions is crucial, with a specific role for polyethylene glycol testing

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ARTICLE INFO

Article history:
Received for publication December 7, 2021.
Received in revised form January 3, 2022.
Accepted for publication January 14, 2022.

The US Food and Drug Administration granted emergency authorization to both Pfizer-BioNTech's BNT162B2 messenger RNA (mRNA) and Moderna's mRNA-1273 coronavirus disease 2019 (COVID-19) vaccines in December 2020. Uncommon (2.5-4.7 events per million) anaphylactic reactions were observed that had not been reported in phase III studies which excluded individuals with a history of an allergy to a vaccine or components of the mRNA vaccines. From that moment on, allergists have played a crucial role in the vaccine rollout and have clarified a very specific role for polyethylene glycol (PEG) testing.

The construct of the COVID-19 mRNA vaccines is a lipid nanoparticle with a PEG2000 lipid ([PEG-2000]-N,N-ditetradecylacetamide) or PEG-2000 dimyristoyl glycerol, which helps in the stabilization of the lipid nanoparticles. PEG is a rare cause of immunoglobulin (Ig)E-mediated anaphylactic reactions to medications, bowel preparations, or laxatives containing this compound and was therefore, hypothesized to be a potential culprit allergen in mRNA-vaccine reactions.[1,2] Though clinically relevant reactivity seemed to be rare, a general population sample revealed that 5% to 9% of patients had anti-PEG IgG and 0.1% had anti-PEG IgE, and most true cases were likely unrecognized before the pandemic. Recommendations from the Centers for Disease Control and Prevention included avoidance of mRNA COVID-19 vaccines in individuals with a history of anaphylaxis to PEG or its derivatives. Therefore, it became critical for allergists to be involved in the risk stratification of patients with vaccine-related reactions and to grapple with the emerging knowledge of PEG allergy.

Subsequently, we believe that the value of an allergist's involvement is clear. Most cases characterized and managed as mRNA-vaccine anaphylaxis, were either not truly anaphylaxis episodes or not IgE-mediated, supported by tolerance of the second dose of COVID-19 mRNA vaccines.[3,4] The value of a careful assessment that includes detailed clinical history and allergist assessment before labeling an individual as "vaccine allergic," cannot be overstated.

This pro and con debate regarding the value of PEG skin testing primarily originates because PEG is an emerging allergen with the key unknowns of (1) the molecular weight threshold necessary for a reaction (eg, PEG2000 in mRNA COVID-19 vaccine lipid nanoparticle vs PEG3350 in laxatives/bowel preparations or methylprednisolone acetate injections),[1,2] and (2) a possible cross-reactivity with polysorbate 80 that was observed on skin testing series. Vaccine skin testing in reactors might have been more optimal but was heretofore difficult owing to the need to wisely use our limited supply. Nevertheless, vaccine skin testing also has a lack of known sensitivity or specificity for tolerance of subsequent doses currently, and the potential immunogenicity of mRNA vaccines in the intradermal space may complicate interpretation.

Within the context of these unknowns and constraints, we believe that our field responded beautifully to the society's call for rapid action by testing multiple hypotheses simultaneously. Doing so led to a crowd-sourced decision model that is continually being updated. On the basis of this emerging framework from colleagues all around the world, the value of PEG skin testing is not higher for a history of a previous vaccine reaction in isolation. As with other immediate skin test modalities, the utility is likely to be highest among individuals with a higher pretest probability, namely a history of anaphylaxis to PEG.[2-4] Although the positive and negative predictive values of skin testing to PEG in terms of mRNA COVID-19 vaccine allergy are unclear, it has become even more evident that IgE-mediated PEG allergy is overall quite rare and that an mRNA-vaccine reaction by itself may not imply a higher likelihood of IgE-mediated PEG allergy.[4]

Nevertheless, the possibility of a PEG allergy contraindication to mRNA COVID-19 vaccines has been so well publicized that it is likely that most of the patients with true allergy have been hesitant to be immunized. Validating their concern in part, at least 2 cases of anaphylaxis to an mRNA COVID-19 vaccine have been reported in patients

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Disclosures: The authors have no conflicts of interest to report.
Funding: Dr Stone is the recipient of an American Academy of Allergy, Asthma & Immunology Foundation Faculty Development Award.

https://doi.org/10.1016/j.anai.2022.01.046

with subsequent positive PEG allergy skin testing. In our patients with skin and blood test-confirmed IgE-mediated PEG allergy at Vanderbilt University Medical Center, only 4 of 7 (57%) chose to be immunized so far, despite our encouragement, all of whom elected to receive the Johnson & Johnson Janssen vaccine after we performed vaccine skin testing. They tolerated this vaccine under observation despite their clinical skin test reactivity to polysorbate 80 (which only has a short chain of PEG, molecular weight at approximately 880 g/mol). We know that PEG allergy reactivity may be, in part, patient specific and based on the molecular weight of PEG used.[1] The main knowledge gap that remains therefore is determining if and how often a patient with true PEG allergy can react to PEG2000 or PEG2000 in the context of the lipid nanoparticles of an mRNA vaccine. On the basis of the available information, we currently believe that most *but not all* patients with IgE-mediated PEG allergy will tolerate an mRNA-vaccine containing PEG2000, and we have observed so far that they will tolerate polysorbate 80-containing vaccines. Patients with true allergy will need very close monitoring and prolonged observation when doses are given, owing to the severity of this allergy and the parenteral delivery route of the vaccine.

Apart from considering IgE-mediated allergic reactions to the mRNA COVID-19 vaccines, hypothetical non-IgE pathways leading to activation of inflammatory cells are also being entertained. PEG IgM and IgG can cause complement activation-related pseudoallergy. Mast cell degranulation occurs through complement activation (C3a, C4a, and C5a) by IgG or IgM antibodies to PEG.[2] This does raise a question of IgG anti–PEG-induced complement activation-related pseudoallergy, which may correspond with positive basophil activation test result or alternative mast cell degranulation pathways as per recent publications.[5] Nevertheless, these findings need further validation.

In conclusion, our opinion is that the most crucial element for patients with possible immediate-type allergic reactions to mRNA COVID-19 vaccines is to undergo allergy evaluation to determine the nature of the reaction and concern for a “true anaphylaxis” episode. As most “anaphylactic” reactions attributed to the mRNA COVID-19 vaccine seem to be non–IgE-mediated, risk stratification before PEG skin testing is important. In light of what we have learned in the past year, exclusions before immunization against COVID-19 should be pared down to the minimum necessary. We agree that routine PEG skin testing for all reactors is low yield and may delay subsequent doses. Nevertheless, select higher-risk patients whose history suggests a preexisting PEG allergy, those with severe immediate mRNA-vaccine reactions, or those who refuse immunization without skin testing may still benefit from testing to PEG.

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