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EDITORIAL

The form of PEG matters: PEG conjugated with lipids and not PEG alone could be the specific form involved in allergic reactions to COVID-19 vaccines

To the Editor

The excipient polyethylene glycol (PEG) contained in the mRNA vaccines for COVID-19 has been pointed out as one of the possible triggers of the hypersensitivity reactions that have been described since the beginning of the vaccine campaigns for COVID-19 protection.[1] However, PEG is not present in the mRNA vaccines in an isolated form but in conjugation with lipid nanoparticles (LNPs), which are spherical vesicles constituted by ionizable lipids, thanks to a process called PEGylation, which could potentially alter the immunogenic properties of PEG. PEG coats the surface of the LNPs reducing opsonization, aggregation, and improving mRNA delivery to the target cells. Both mRNA vaccines for COVID-19 contain PEG/lipid conjugates as part of the LNPs (Figure 1), more specifically, mRNA-1273 vaccine (produced by Moderna Therapeutics) contains DMG-PEG 2000 which is formed by the PEGylation of the lipid dimyristoyl glycerol. On the other hand, BNT162b2 vaccine (Comirnaty, produced by Pfizer-BioNTech) contains PEG-DTA also named as ALC-0159, which is also a PEG/lipid conjugate.[2]

Initial guidelines advised that sensitization to PEG should be taken into consideration in suspected subjects before a recommendation on the administration of vaccines for COVID-19 containing PEG or its cross-reactive analogues.[3] However, PEG shows an important variability in terms of molecular weights (MW) and conjugation forms. In that sense, although it is known that PEG-2000 (MW: 2000 g/mol) conjugated with lipids is the form contained in the vaccines for COVID-19, there has been great variability in the PEG molecules used in allergy tests to evaluate sensitization of suspected subjects in the context of the current COVID-19 vaccination campaigns.[4] In this context, recent findings have shed light on the specific form of PEG that could be responsible of the hypersensitivity reactions to the mRNA vaccines for COVID-19. Importantly, Troelnikov et al, found that BNT162b2 vaccine and PEGylated liposomes but not PEG alone (200–6000 g/mol) without lipid conjugation induced a robust basophil activation in a dose-dependent manner in three patients with a history of PEG allergy. The results were negative in the 3 healthy controls included in this study. The results suggested that during PEGylation process, possible changes in the conformation and/or chemical structure of PEG covalently linked to the surface of lipid nanoparticles may occur which could potentially change and increase its immunogenicity[5] (Figure 1). On support of these findings that seem to indicate that PEG in its native form could not be as immunoreactive as PEG/lipid conjugates, there is a number of studies that have failed to demonstrate positive skin testing results using PEG in its native form in patients with a history of allergic reaction to mRNA vaccines for COVID-19, having skin testing with PEG a poor sensitivity.[4] Interestingly, other studies outside the setting of mRNA vaccines have found that the reactivity of skin prick test (SPT) with native PEG decreased over time in PEG allergic patients, however, it was observed that such reactivity increased if PEGs of higher MW, that is, PEG 20,000, were tested.[6] Therefore, a loss in the reactivity of SPT with low-MW PEGs over time in sensitized individuals should be taken into consideration. An algorithm was proposed for patients with suspected allergy to PEG based solely on titrated SPT with PEGs of increasing MW, taking into account that PEGs of higher MW (such as PEG 20,000) seem to be more reactive than PEGs of lower MW. Intradermal tests were only recommended when negative SPT results were obtained and, in that case, diluted solutions should be used.[6,7] A single case study, however, did not fully align with the observation that the higher MW of PEGs the higher reactivity in SPT in sensitized individuals.[8]

A recent study used the PEG/lipid conjugate DMG-PEG 2000 (which is the exact compound contained in mRNA-1273 vaccine) and not PEG in its native form and found that 91% and 100% of patients with anaphylactic reactions to mRNA COVID-19 vaccine ($n = 11$) had positive basophil activation test (BAT) results with DMG-PEG 2000 and with the administered mRNA vaccine, respectively. The results were negative when DMG-PEG 2000 was assessed in SPT, and only 1 out of 11 patients had a positive SPT with the brand of mRNA vaccine which they reacted to, which suggested that BAT performed with PEG/lipid conjugate and with the mRNA vaccine itself could be a more robust experimental tool to assess PEG-2000/lipid sensitization. The study also found augmented tryptase levels in the patients that experienced anaphylaxis with the mRNA vaccine and had positive results to BAT, which suggests an involvement of mast cells.[9] The results of all tests were negative in the 3 control participants included in this study.[9] In addition to direct IgE-mediated degranulation reactions, it should be considered that IgG to various PEGs may be playing a role in rapid complement activation followed by mast cell and basophil degranulation[10,11] (Figure 1).

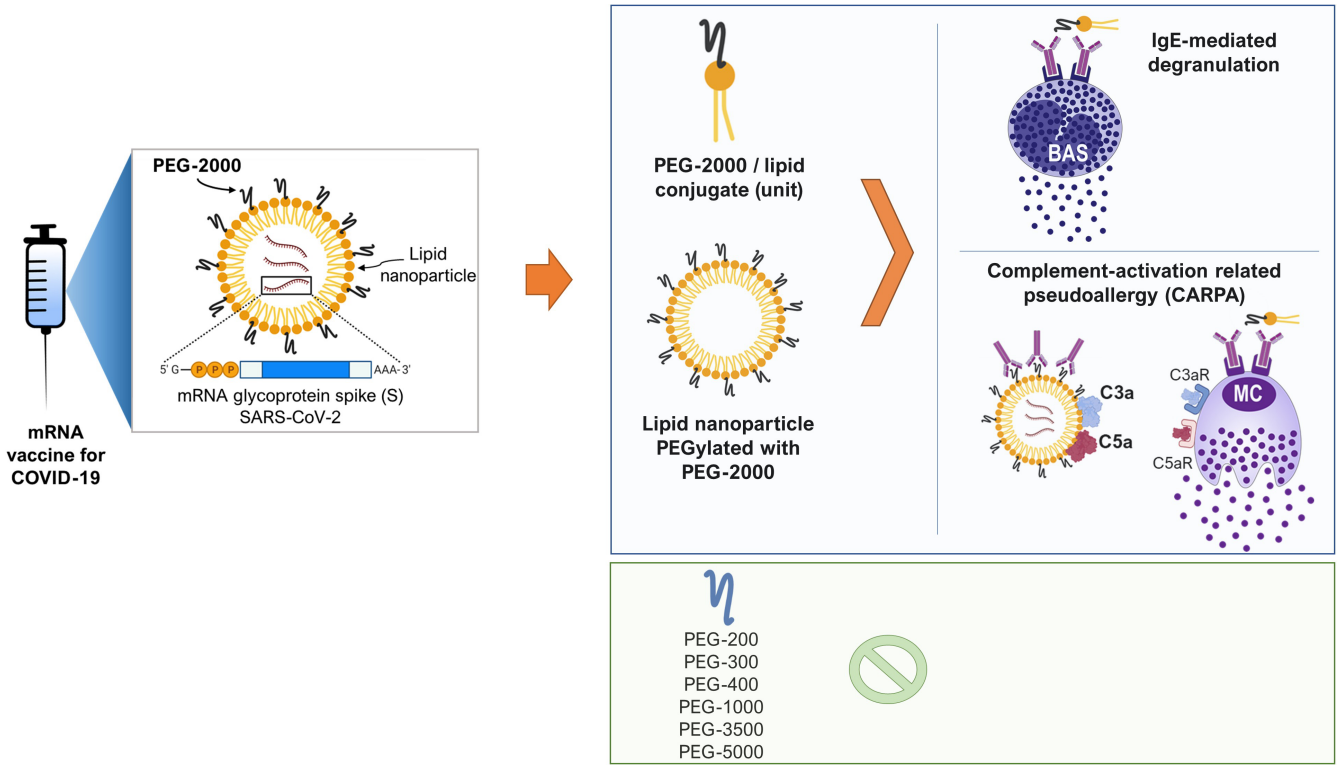

FIGURE 1 Schematic representation of the lipid nanoparticle PEGylated with PEG-2000 contained in mRNA vaccines for COVID-19 (left part). PEG-2000/lipid conjugate (individual unit) or PEGylated nanoparticle could be involved in the allergic reactions to the mRNA vaccines for COVID-19. The potential mechanisms involved (direct IgE-mediated degranulation or CARPA) are depicted in the right-upper part. PEG in its native form could not be as immunoreactive as PEG-2000/lipid conjugates (right-lower part)

In that sense, non-IgE-mediated mechanisms such as the mentioned complement activation through immune complexes in blood with vaccine components like PEG-2000/lipid conjugate could be implicated in the reactions and can explain the differences observed between SPT and BAT results in the study by Warren et al. [9] Yet, the underlying mechanism involved in anaphylaxis to mRNA vaccines for COVID-19 warrants a deeper study.

In light of the rapidly emerging novel findings and taking into consideration the new results discussed in this editorial, the choice of the PEG molecule to be tested could be based on the closest characteristics to the specific molecule contained in the vaccines for COVID-19, that is, PEG-2000/lipid conjugate or PEGylated liposomes. However, this hypothesis needs to be confirmed in larger cohorts of patients and controls.

The validation of the in vivo and ex vivo assays used for the diagnosis of allergy to mRNA vaccines for COVID-19 is essential. For that, the study of the particular component responsible for the reactions, its specific form, and the mechanism underlying the reactions should be thoroughly analyzed in additional studies. Current data strongly indicate that mRNA vaccines for COVID-19 are safe and well-tolerated by the vast majority of the population. In that respect, the small percentage of individuals who experience anaphylactic reactions to these mRNA vaccines should be carefully characterized in order to identify the risk factors involved in the allergic reactions to mRNA vaccines for COVID-19.

CONFLICT OF INTEREST

N. Novak reports honoraria from Alk Abello, Stallergens Geer, Hal Allergy, Leti Pharma, Sanofi Genzyme, Abbvie, Leo Pharma, Novartis, streamed up, and Blueprint outside the submitted work.

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