

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

Natalija Novak², Cezmi A. Akdis^{3,4} Beatriz Cabanillas^{1*}, Natalija Novak², and Cezmi Akdis A³

¹Instituto de Investigacion Hospital 12 de Octubre

²Universitätsklinikum Bonn

³Universität Zurich Schweizerisches Institut für Allergie- und Asthmaforschung

October 4, 2021

Abstract

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 and conjugation forms. In that sense, although it is known that PEG-2000 (MW: 2000g/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.

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

Beatriz Cabanillas^{1*}, Natalija Novak², Cezmi A. Akdis^{3,4}

1. Department of Allergy, Research Institute Hospital 12 de Octubre, Avenida de Córdoba s/n, 28041 Madrid, Spain

2. Department of Dermatology and Allergy, University Hospital, Bonn, Venusberg Campus 1, 53127, Bonn, Germany

3. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.

4. Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

*Corresponding author: Dr. Beatriz Cabanillas. Department of Allergy, Research Institute Hospital 12 de Octubre de Madrid, Avenida de Córdoba s/n, 28041 Madrid, Spain. Phone: (+34) 913908763. E-mail: bcabanillas.imas12@h12o.es

Keywords: COVID-19; PEG; Polyethylene glycol; RNA Vaccine; SARS-CoV-2

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 thanks to a process called PEGylation, which could potentially alter its immunogenic properties. More specifically, mRNA-1273 vaccine (produced by Moderna Therapeutics) contains 1,2-dimyristoyl-rac-glycerol-3-methoxy-polyethylene glycol-2000 (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 2-[(polyethylene glycol) 2000]-N,N-ditetradecylacetamide (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 and conjugation forms. In that sense, although it is known that PEG-2000 (MW: 2000g/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 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 immunogenicity⁵ (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

Furthermore, 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 BAT results with DMG-PEG 2000 and with the administered mRNA vaccine, respectively. The results were negative when DMG-PEG 2000 was assessed in skin prick test (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.⁶ 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^{7,8} (Figure 1).

In light of these rapidly emerging new findings and due to the pressing nature of the investigations on the adverse reactions to vaccines for COVID-19, there is a need to reassess the initial recommendations on the evaluation of sensitization to excipients contained in COVID-19 vaccines. In the case of PEG, and taking into consideration the new findings, the choice of the PEG molecule to be tested should 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.

References

1. Cabanillas B, Akdis CA, Novak N. Allergic reactions to the first COVID-19 vaccine: A potential role of polyethylene glycol? *Allergy* . 2021;76:1617-1618. doi: 10.1111/all.14711.
2. Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: Possible involvement of polyethylene glycol and IgG-mediated complement activation. *Allergy* . 2021 Mar 3;10.1111/all.14794. doi: 10.1111/all.14794.
3. Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. *Allergy* . 2021;76:1629-1639. doi: 10.1111/all.14739.

4. Greenhawt M, Abrams EM, Shaker M, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. *J Allergy Clin Immunol Pract* . 2021 Jun 18:S2213-2198(21)00671-1. doi: 10.1016/j.jaip.2021.06.006.
5. Troelnikov A, Perkins G, Yuson C, Ahamdie A, Balouch S, Hurtado PR, Hissaria P. Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in patients with PEG allergy. *J Allergy Clin Immunol* . 2021;148:91-95. doi: 10.1016/j.jaci.2021.04.032. Epub 2021 May 12. PMID: 33991580.
6. Warren CM, Snow TT, Lee AS, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. *JAMA Netw Open* . 2021;4:e2125524. doi: 10.1001/jamanetworkopen.2021.25524.
7. Elieh Ali Komi D, Shafaghat F, Kovanen PT, Meri S. Mast cells and complement system: Ancient interactions between components of innate immunity. *Allergy* . 2020;75:2818-2828. doi: 10.1111/all.14413
8. Risma KA, Edwards KM, Hummell DS, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. *J Allergy Clin Immunol* . 2021;147:2075-2082.e2. doi: 10.1016/j.jaci.2021.04.002.

Conflict of interest

The authors declare no conflict of interest

Figure legend.

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).

