Administration of the Comirnaty® Vaccine in a Fractional Regimen in Two Patients with Immediate Acute Urticaria after the First Dose

Article *in* Journal of investigational allergology & clinical immunology: official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunología · June 2021

DOI: 10.18176/jiaci.0717

5 authors, including:

Francisco Manuel Marco
Hospital General Universitario de Alicante Dr Balmis
62 PUBLICATIONS **633** CITATIONS

SEE PROFILE

Administration of the Comirnaty® Vaccine in a Fractional Regimen in Two Patients with Immediate Acute Urticaria after the First Dose

Antón Gironés M[1], Montoro Lacomba J[2], Navarro Cascales T[3], Lindo Gutarra M[3], Marco de la Calle FM[4]

[1]Servicio de Alergología. Hospital Universitario del Vinalopó. Elche (Alicante). Facultad de Medicina. Universidad Católica San Antonio de Murcia

[2]Unidad de Alergia. Hospital de Liria (Valencia). Facultad de Medicina. Universidad Católica de Valencia "San Vicente Martir"

[3]Servicio de Alergología. Hospital Universitario del Vinalopó. Elche (Alicante)

[4]Sección de Inmunología. Hospital General Universitario de Alicante

Corresponding author

Mónica Antón Gironés

Calle Alicante, 21-1B San Vicente del Raspeig 03690 (Alicante)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0717

doi: 10.18176/jiaci.0717

Key words: Comirnaty® vaccine. SARS-COV2. Immediate urticaria. Fractional administration. Polyethylene glycol.

Palabras clave: Vacuna Comirnaty®. SARS-COV2. Urticaria inmediata. Administración fraccionada. Polietilenglicol.

In Spain, since vaccination against SARS-CoV2 began on December 27, 2020, the Spanish Agency for Medicines and Health Products (AEMPS) has received 1,537 reports of adverse events with Comirnaty®[1]. Eight cases (0.52%) were reported with criteria for anaphylaxis. In 63% of cases symptoms began within the first 30 minutes after vaccination (63%) and 75% of cases required epinephrine. EAACI (European Academy of Allergy and Clinical Immunology) and SEAIC (Spanish Society of Allergy and Clinical Immunology), have contraindicated Comirnaty® administration only in patients who have had an allergic reaction to a previous dose or to any of its components [2,3,4].

Of the components of the Pfizer-BioNTech vaccine (Comirnaty®), polyethylene glycol (PEG) is considered a possible responsible for allergic reactions, although it has not yet been confirmed [5].

PEG 2000 is an excipient of theComirnaty® vaccine which is part of the lipid nanoparticle where the mRNA is carried to ensure its preservation. PEGs are hydrophilic polymers with sensitization capacity demonstrated with immediate-type hypersensitivity reported cases in a MW range from 300 to 20000 g/mol [6].It is widely used as an excipient in daily use products, including medicines, cosmetics or food, but it is the first time that PEG has been included as an excipient in a vaccine, and it is

doi: 10.18176/jiaci.0717

different from the one more commonly used in other medical devices in its MW and by its coformulation as a stabilizing portion of a liposome [7].

In 1978 the first case of allergic contact dermatitis due to PEG [8] was described, but it was in 2008 when the first cases of immediate allergy [9] (including anaphylaxis) were reported; in recent years, a great number of allergic reactions caused by PEG have been described [6,10].

The Vinalopó University Hospital in Elche (Alicante) vaccinated its staff from January 8, 2021 with the Comirnaty® vaccine. Of the total of 1136 doses administered, there were two cases of immediate urticaria within the first 20 minutes after administration, which represent an incidence of 0.18%. One of the patients had a systemic reaction (patient 1) and the other a located reaction in neckline (patient 2).

Case 1: 57-years-old female patient with a history of allergy to quinolones, mild intermittent pollen rhinitis and recurrent acute urticaria with negative allergy study, tryptase included.

Case 2: 40-years-old male patient, with a history of adverse reaction with cephalosporin and acetylsalicylic acid, mild intermittent asthma due to mites and recurrent acute urticaria with negative allergological study, tryptase included.

Both were treated with oral antihistamines and patient 1 also received systemic intramuscular corticosteroids (methylprednisolone 60 mg), which resolved in less than 1 hour in both patients.

Considering the recommendations of the EAACI [11], as well as the experience with adverse reactions with other vaccines [12], we carried out a complete allergological

doi: 10.18176/jiaci.0717

study in both patients following the diagnostic-therapeutic algorithm summarized in the Figure. The same skin tests with the vaccine and PEGs were performed on 5 healthy controls, with negative results.

Basophil activation test (BAT; Basotest, Glycotope Biotechnology, Germany) [13]was carried out with COVID vaccine (Comirnaty®, as is and 3 additional serial1/10 dilutions), and PEG 400, 1500, 4000 and 20000 (Merck, Germany, at 10 mg/ml and five serial 1/10 dilutions). Cut off was set at 5% CD63 induction over negative control. BAT with Comirnaty® was negative in both patients at all tested dilutions. Patient 2 showed weak positive results with PEG 400 (0.01 mg/ml 10% and 0.001 mg/ml 7%); PEG 4000 (1 mg/ml 7%) and PEG 20000 (0.001 mg/ml 9%). Healthy controls were negative.

The study of the hypersensitivity reactions with a possible involvement of PEG is complicated by the difficulties in setting up of specific IgE assays, so that diagnostic work up is generally limited to “in vivo” tests. PEG may induce the production of IgG and IgM antibodies both in patients showing PEG-related adverse effects and in healthy individuals [13,14]. These antibodies may also mediate immune reactions to PEG involving activation of the complement system. PEG compounds are usually linear or branched polymers. The epitope of PEGs is not known, and there is heterogeneity in their allergenic capacity [6].

Taking into account the positive results obtained in the study by prick and ID testing for both patients, the compatible symptoms with an immediate allergic reaction, the need to safely receive the second dose, and the lack of previous experience with Comirnaty®, we decided to perform the vaccine administration by means of a fractional regimen with

doi: 10.18176/jiaci.0717

premedication as follow. First, 60 mg of methylprednisolone iv, 5mg of dexchlorpheniramine iv, 150 mg of ranitidine iv and 10mg of oral montelukast; 30 minutes later, administration of the second dose of Comirnaty® divided into 3 doses of 0.1 ml, with an interdose period of 1 hour and an additional 1 hour of observation after the last dose administered. Both patients presented itching 20 minutes after the first and second doses, without hives and with spontaneous disappearance before administration next dose. All doses were completed without immediate or late incidents.

As conclusion, a fractional regimen for the administration of the second dose of Comirnaty vaccine has proven useful in two patients with immediate allergic reaction during administration of their first dose.

Funding

The authors declare that no funding was received for the present study.

Conflicts of interest

The authors have no conflict of interests to declare.

doi: 10.18176/jiaci.0717

References

1. 2º Informe de Farmacovigilancia sobre Vacunas COVID-19. Agencia Española de Medicamentos y Productos Sanitarios. Published February 9, 2021.Disponible en: https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/2o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/

2. Klimek L, Jutel M, Akdis CA, Bousquet J, Akdis M, Torres-Jaen M,et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - an EAACI-ARIA position paper. Allergy. 2020 Dec 30. doi: 10.1111/all.14726. Epub ahead of print. PMID: 33378789.

3. Comunicado vacuna COVID-19 de Pfizer en alérgicos. Portal SEAIC. PublishedDecember 9, 2020. Disponible en: https://www.seaic.org/inicio/noticias-general/comunicado-vacuna-covid-19-de-pfizer-en-alergicos.html

4. Ortega NR, Audícana MT, de la Hoz B, Valero A. Thecentury of mRNAvaccines: COVID-19 vaccines and allergy. J Investig Allergol Clin Immunol. 2021;Vol 31 (1):89-91

5. Cabanillas B, Akdis C, Novak N. Allergic reactions to the first COVID-19 vaccine: a potential role of Polyethylene glycol? Allergy. Published online December 15, 2020:1423-37.

6. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy. 2016;46:907–22.

7. Caballero ML, Quirce S. Excipients as Potential Agents of Anaphylaxis in Vaccines: Analyzing the Formulations of Currently Authorized COVID-19 Vaccines. J Investig Allergol Clin Immunol. 2021;31:92-3

8. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. Contact Dermatitis. 1978;4:135–8.

9. AntónGironés M, Roan Roan J, de la Hoz B, Sánchez Cano M. Immediate allergic reactions by polyethylene glycol 4000: two cases. Allergol Immunopathol.2008;36(2):110-2.

10. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. J Allergy Clin Immunol Pract. 2019;7:1533-1540.e8.

11. Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Del Giacco S et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy. 2021 Jan 16:10.1111/all.14739.

12. Nilsson L, Brockow K, Alm J, et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol.2017;28(7):628-640.

13. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Adv Drug Deliv Rev. 2020;154-155: 163-175.

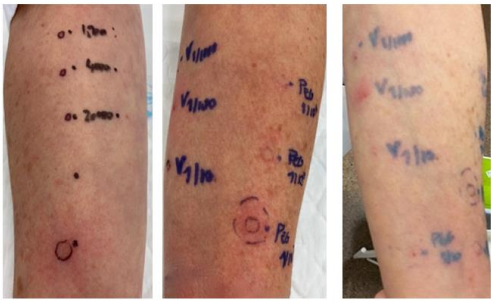
14. Zhou ZH, Stone CA, Jakubovic B, Phillips EJ, Sussman G, Park J, Hoang U, Kirshner SL et al. Anti-PEG IgE In Anaphylaxis Associated with Polyethylene Glycol, J Allergy Clin Immunol Pract. 2021; 9 (4): 1731-1733.e3.

doi: 10.18176/jiaci.0717

Figure legend

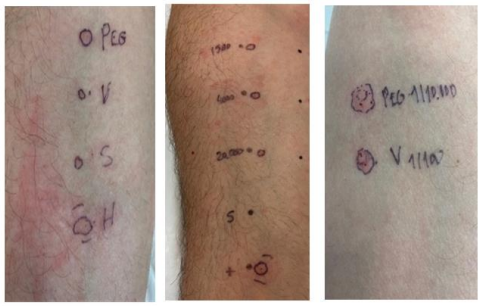
FIGURE: RESULTS OF THE STUDY

Patient 1



NEGATIVE RESULTS	POSITIVE RESULTS
• Prick test with vaccine • ID with vaccine 1/1000 and 1/10 • Prick test with PEG 400 • ID with PEG 400 1/10000 and 1/1000 • BAT with vaccine and PEG 400, 1500, 4000 and 20000	• **ID with vaccine 1/100** (late reading) (papule 6x3 mm) • **ID with PEG 400 1/100** (papule 7x6 mm, erythema 16x18 mm) • **Prick test with PEG 1500, 4000 and 20000** (papules 4x3 mm)

Patient 2



NEGATIVE RESULTS	POSITIVE RESULTS
• Prick test with vaccine • BAT with vaccine • BAT with PEG 1500	• **ID with vaccine 1/1000** (papule 4x5 mm, erythema 6x7 mm) • **Prick test with PEG 400** (papule 3x2 mm), **1500** (papule 4x5 mm), **4000** (papule 4x4 mm) **and 20000** (papule 3x3 mm) • **ID with PEG 400 1/10000** (papule 5x5mm, erythema 11x9 mm) • **BAT with PEG 400, 4000 and 20000**