Asia Pac Allergy. 2021 Apr;11(2):e18
https://doi.org/10.5415/apallergy.2021.11.e18
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Hypothesis & Experience

Letter to the Editor

Skin testing with Pfizer SARS-CoV-2 vaccine and PEG 2000

João Vieira *, **João Marcelino**, **Fátima Ferreira**, **Sofia Farinha**, **Rita Silva**, **Miguel Proença**, **and Elza Tomaz**

Immunoallergology Department, Centro Hospitalar de Setúbal EPE, Setúbal, Portugal

***Correspondence to**
João Vieira
Immunoallergology Department, Centro Hospitalar de Setúbal EPE, Rua Camilo Castelo Branco 175, Setúbal, Portugal.
Tel: +351-912874432
Email: joaomhpvieira@gmail.com

ORCID iDs
João Vieira
https://orcid.org/0000-0003-3539-249X
João Marcelino
https://orcid.org/0000-0001-8462-8847
Fátima Ferreira
https://orcid.org/0000-0003-4141-0594
Sofia Farinha
https://orcid.org/0000-0002-5215-9473
Rita Silva
https://orcid.org/0000-0002-8279-4726
Miguel Proença
https://orcid.org/0000-0002-5526-7533
Elza Tomaz
https://orcid.org/0000-0001-8880-9629

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Elza Tomaz, João Marcelino, Fátima Ferreira. Formal analysis:

To the editor

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has rapidly become one of the biggest health threats the world has faced. The importance of controlling the disease and its worldwide spread cannot be understated. Vaccination arises as the cornerstone of this fight against coronavirus disease 2019 (COVID-19), though new challenges have emerged with it.

Anaphylactic reactions to vaccines are very rare, occurring at a rate of 1.31 per million doses administered [1]. Reports on the new mRNA Pfizer-BioNTech SARS-CoV-2 vaccine show a higher rate of anaphylactic reactions: 4.7 cases/million doses administered [2]. There is great uncertainty about which patients might be at risk of developing an anaphylactic reaction to the vaccine. Current recommendations state that the vaccine should not be administrated if subjects have hypersensitivity to COVID-19 vaccines or any of its components [3].

The Pfizer-BioNTech SARS-CoV-2 vaccine is an mRNA vaccine that uses a lipid-based nanoparticle carrier system, stabilized by polyethylene glycol (PEG) 2000. Although evidence on the pathogenesis of severe immediate reactions to the SARS-CoV-2 vaccine is lacking, the PEG molecule has been proposed as a possible culprit for these reactions due to existing evidence of its ability to cause immunoglobulin E (IgE)-mediated anaphylaxis [4-6].

Assuming the reactions to the Pfizer-BioNTech vaccine resulted from IgE-mediated mechanisms, skin testing might prove a valuable method to identify patients with allergy to the vaccine or its components. Published data by Marcelino et al. [7] showed that skin prick (SP) and intradermal (ID) testing with the Pfizer-BioNTech SARS-CoV-2 vaccine in its undiluted form can be performed and are not irritant. However, multicentric data on the usefulness and validity of skin testing with the SARS-CoV-2 vaccine is still lacking.

Our aim is to evaluate skin test positivity to the Pfizer-BioNTech SARS-CoV-2 vaccine and its association with PEG 2000 skin tests and with allergic reactions to the vaccine.

As part of our national COVID-19 vaccination program, 2,755 healthcare workers were vaccinated at our Hospital. A total of 115 performed skin tests with the Pfizer-BioNTech SARS-CoV-2 vaccine (83% women, mean age of 44±12 years). Fifty-five of them were control subjects, who had tolerated the vaccine, and confirmed the nonirritant test concentrations (Marcelino et

João Vieira, Rita Silva, Miguel Proença. Investigation: João Vieira, João Marcelino, Fátima Ferreira, Sofia Farinha, Rita Silva, Miguel Proença, Elza Tomaz. Methodology: Elza Tomaz, João Marcelino, Sofia Farinha. Project administration: Elza Tomaz, João Marcelino. Writing - original draft: João Vieira, João Marcelino, Fátima Ferreira. Writing - review & editing: João Vieira, João Marcelino, Elza Tomaz.

al. [7]). Sixty reported a previous history of drug anaphylaxis and underwent skin testing prior to the vaccination. SP and ID tests were performed for each person with the undiluted vaccine and a 1/10 dilution with saline solution. Readings were performed after 15 and 30 minutes.

Four subjects had positive results to the ID tests, detailed on **Table 1**. The positive reactions were as follows: (1) 1 of the 4 developed a systemic urticaria within 10 minutes of performing the ID test with the undiluted vaccine, (2) 2 others had a positive ID test with the vaccine at a 1/10 dilution, (3) the last one had a positive ID test with the undiluted vaccine.

All 4 were then tested with PEG 2000 (BioUltra, SIGMA-ALDRICH Co., St. Louis, MO, USA) diluted in saline solution with SP tests (0.1 mg/mL and 1 mg/mL) and ID test (0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL). Readings were performed after 30 minutes. There were no positive reactions to the prick tests. Only one tested positive to the ID tests at the 0.001-mg/mL dilution. This patient reported a history of anaphylaxis with nimesulide tablets, which contained macrogol 6000 (PEG 6000).

One of the subjects with a positive ID test to the vaccine but no positive tests to PEG 2000 proceeded to vaccination with the Pfizer-BioNTech vaccine, premedicated with 20 mg of cetirizine. Inoculation was fractioned into 2 doses. Immediately after one-third of the vaccine's total dose was administered, the healthcare worker developed a sudden onset generalized urticaria. The other 3 subjects did not receive the Pfizer-BioNTech vaccine, one due to a systemic reaction with the ID test, the other 2 due to safety concerns.

The AstraZeneca COVID-19 vaccine has not been associated with a higher incidence of anaphylaxis, does not contain PEG 2000, and there is no evidence suggesting that hypersensitivity to the Pfizer-BioNTech vaccine would increase the risk of reaction to the AstraZeneca COVID-19 vaccine [5]. For the prementioned reasons, 2 of the 4 subjects were later inoculated with the AstraZeneca COVID-19 vaccine, with no immediate reactions (**Table 1**). A third subject awaits vaccination with a non-mRNA vaccine (AstraZeneca or Johnson & Johnson's Janssen COVID-19 vaccine). A fourth subject refused vaccination with a COVID-19 vaccine.

The 111 healthcare workers with negative tests were vaccinated with the Pfizer-BioNTech vaccine without any immediate reaction. None of the remaining 2,640 healthcare professionals reacted to the Pfizer-BioNTech vaccine.

Table 1. Patients with a positive skin test to Pfizer-BioNTech SARS-CoV-2 vaccine and their reported allergic history

Age	Gender	Non–drug-related reported atopic comorbidities	Reported history of drug anaphylaxis	Vaccine skin testing	PEG 2000 skin testing	SARS-CoV-2 vaccine administration
31	F	Allergic rhinitis	Erythromycin (suspension)	Positive to 1/10 ID test	Negative	Systemic reaction to 0.1 mL of the Pfizer vaccine. Non-mRNA vaccine administrated*
42	F	Allergic rhinitis	Penicillin (IM), aspirin (tablet), metamizole (tablet)	Positive to 1/1 ID test - Systemic reaction	Negative	Subject refused vaccine administration
28	F	Allergic rhinitis, asthma	Nimesulide (tablet)	Positive to 1/10 ID test	Positive to 0.001 mg/mL ID test	Non-mRNA vaccine administrated*
38	F	Allergic rhinitis	Amoxicillin clavulanate (tablet and IV), metamizole (IV), ketorolac (IV), etoricoxib (tablet)	Positive to 1/1 ID test	Negative	Subject awaiting non-mRNA vaccine administration†

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PEG, polyethylene glycol; F, female; IM, intramuscular; ID, intradermal; IV, intravenous; COVID-19, coronavirus disease 2019.
*AstraZeneca COVID-19 vaccine. †AstraZeneca or Johnson & Johnson's Janssen COVID-19 vaccine.

https://doi.org/10.5415/apallergy.2021.11.e18

In conclusion, SP and ID testing using the Pfizer-BioNTech SARS-CoV-2 vaccine (undiluted and 1/10 dilution) was proved nonirritant.

Skin test positivity to the vaccine was associated to a systemic reaction in 2 of 4 subjects. Although the dimension of our data is limited and does not allow definitive conclusions, it suggests that skin tests with the vaccine may prove useful to predict immediate reactions to the Pfizer-BioNTech vaccine.

Only 1 of the 4 skin tests to PEG 2000 had a positive result. This suggests a role of PEG in some immediate reactions to the Pfizer-BioNTech SARS-CoV-2 vaccine, but it also points out that there may be non-PEG related immediate reactions to the vaccine.

This study was approved by the Institutional Review Board of Centro Hospitalar de Setúbal E.P.E. (approval number: PI-008/2021).

REFERENCES

1. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, Hambidge SJ, Lee GM, Jackson LA, Irving SA, King JP, Kharbanda EO, Bednarczyk RA, DeStefano F. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol 2016;137:868-78.
PUBMED | CROSSREF
2. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US-December 14, 2020-January 18, 2021. JAMA 2021;325:1101-2.
PUBMED | CROSSREF
3. Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Del Giacco S, Jutel M, Nadeau KC, Palomares O, Rabin RL, Riggioni C, Vieths S, Agache I, Shamji MH. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy 2021 Jan 16;10.1111/all.14739. Epub ahead of print.
PUBMED | CROSSREF
4. Castells M, Phillips E. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med 2021;384:643-9.
PUBMED | CROSSREF
5. Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Ebisawa M, El-Gamal Y, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Leung ASY, Levin ME, Muraro A, Sánchez Borges M, Senna G, Tanno LK, Yu-Hor Thong B, Worm MWAO Anaphylaxis Committee. COVID-19 vaccine-associated anaphylaxis: a statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J 2021;14:100517.
PUBMED | CROSSREF
6. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, Wolfson AR, Williams P, Khan DA, Phillips E, Blumenthal KG. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. J Allergy Clin Immunol Pract 2021;9:1423-37.
PUBMED | CROSSREF
7. Marcelino J, Farinha S, Silva R, Didenko I, Proença M, Tomás E. Non-irritant concentrations for skin testing with SARS-CoV-2 mRNA Vaccine. J Allergy Clin Immunol Pract 2021. Published online March 22, 2021.
PUBMED