## Hypersensitivity to the Moderna COVID-19 Vaccine Caused by Tromethamine: PEG Is Not Always the Culprit Excipient

Azenha Rama T[1,2,3], Moço Coutinho R[1], Mota D[1], Moreira A[1,2,3], Cernadas J[1,4]

[1]*Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João, Porto, Portugal*

[2]*Serviço de Imunologia Básica e Clínica, Departamento de Patologia, Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

[3]*EPIUnit, Institute of Public Health, University of Porto, Portugal and Laboratory for Integrative and Translational Research in Population Health (ITR), Porto, Portugal*

[4]*Unidade de Imunoalergologia, Hospital Lusíadas, Porto, Portugal*

J Investig Allergol Clin Immunol 2022; Vol. 32(5): 414-415
doi: 10.18176/jiaci.0773

Key words: COVID-19. Vaccines. Urticaria. Excipients. Tromethamine.

Palabras clave: COVID-19. Vacunas. Urticaria. Excipientes. Trometamina.

*To the Editor:*

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are considered the cornerstone of the solution to the current global pandemic. The first vaccines to receive authorization for emergency use in humans were the BNT162b2 Pfizer-BioNTech [1] and the mRNA-1273 Moderna vaccines [2]. Both contain synthetic mRNA that codes for the SARS-CoV-2 spike (S) protein, which is encased in a lipid nanoparticle envelope. Anaphylaxis and immediate hypersensitivity reactions were noted in only 1 case during phase III trials for BNT162b2, while no immediate hypersensitivity reactions were noted for the mRNA-1273 vaccine [3]. However, a history of hypersensitivity to any component of the vaccines was an exclusion criterion [1,2,4]. Nonetheless, cases of anaphylaxis were reported shortly after initiation of the vaccination campaign [5].

Despite the lack of robust evidence on the underlying mechanisms of said reactions, IgE-mediated hypersensitivity to excipients may be the cause in a number of cases [6]. Both mRNA vaccines contain polyethylene glycol (PEG) 2000, a polymer of ethylene oxide, which is used to promote water solubility in drug formulations, cosmetics, and food additives, while the mRNA-1273 vaccine additionally contains tromethamine, a buffer additive present in drug formulations, contrast media, and cosmetics. The first reports from the United States Centers for Disease Control and Prevention showed that anaphylaxis caused by the mRNA-1273 vaccine was more frequent among patients with a prior history of drug hypersensitivity, namely, drugs containing tromethamine (eg, gadolinium and other contrast media), an excipient recently shown to have been involved in an anaphylactic reaction to gadolinium-based contrast media [7], although evidence on the association between hypersensitivity to tromethamine-containing vaccines is lacking.

We report the case of a patient who developed urticaria within 1 hour of receiving the mRNA-1273 vaccine and later tolerated the BNT162b2 vaccine.

A 45-year-old woman with asthma, allergic rhinitis, psoriasis, and anxiety disorder was referred to our Allergy and Clinical Immunology Department for suspected hypersensitivity to the mRNA1273 vaccine. Approximately 1 hour after inoculation, she developed generalized urticarial exanthem. She did not experience angioedema, vomiting, diarrhea, hypotension, or hypoxia. The exanthem lasted around 48 hours—the patient sought medical assistance only 2 days after onset—and resolved around 2 hours after treatment with oral desloratadine 5 mg. Prior to vaccination, the patient had tolerated several PEG-containing drug formulations, had no previous history of anaphylaxis or cutaneous mastocytosis, and had never received contrast media.

Five weeks after the inoculation, skin prick and intradermal tests were performed with nonirritant concentrations of the excipients or excipient-containing drugs, including PEG 3350, PEG 1500 (ROXALL, Medizin GmbH), polysorbate 20, methylprednisolone succinate and acetate, dexamethasone, triamcinolone acetonide (as suggested by Banerji et al [3]), gadobutrol (Gadovist, which contains tromethamine), and gadoteric acid (Dotarem, which does not contain tromethamine) in accordance with EAACI/ENDA guidelines [8]. The only positive results on intradermal testing were for gadobutrol (60.5 mg/mL), thus confirming tromethamine as the culprit excipient. The patient received the Pfizer-BioNTech mRNA vaccine, BNT162b2, 6 weeks after the first dose. No immediate or late hypersensitivity reactions were reported in the 24 hours following vaccination.

In conclusion, this case provides further evidence that the excipient, and specifically IgE-mediated hypersensitivity to tromethamine, may be an underlying mechanism for immediate hypersensitivity to mRNA COVID-19 vaccines.

### *Funding*

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

### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

## References


1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
2. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403-16.
3. Banerji A, Wickner PG, Saff R, Stone CA, Jr., Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract. 2021;9(4):1423-37.
4. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
5. Garvey LH, Nasser S. Allergic reactions to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? Br J Anaesth. 2021;126:e106-8.
6. Pitlick MM, Sitek AN, Kinate SA, Joshi AY, Park MA. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: Early report. Ann Allergy Asthma Immunol. 2021;126(6):735-8.
7. Lukawska J, Mandaliya D, Chan AWE, Foggitt A, Bidder T, Harvey J, et al. Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging. J Allergy Clin Immunol Pract. 2019;7(3):1086-7.
8. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12.


*Manuscript received October 7, 2021; accepted for publication December 15, 2021.*

**Tiago Azenha Rama**

Serviço de Imunoalergologia
Centro Hospitalar Universitário de São João
Alameda Prof. Hernâni Monteiro
4200-319 Porto, Portugal.
E-mail: tarama@med.up.pt