Hypersensitivity to the Moderna COVID-19 vaccine caused by tromethamine: PEG is not always the culprit excipient

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To the Editor,

Vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are considered the cornerstone of the solution to the current global pandemic crisis. The first vaccines to receive authorization for emergency use in humans were the BNT162b2 Pfizer-BioNTech® [1] and the mRNA-1273 Moderna®[2] mRNA vaccines. Both contain synthetic mRNA that encodes for the SARS-CoV-2 Spike (S) protein, encased in a lipid nanoparticle envelope. Anaphylaxis and immediate hypersensitivity reactions were noted in only 1 case, respectively, during phase III trials for the 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 the initiation of the vaccination campaign [5].

Even though there is a lack of robust evidence on the underlying mechanisms for 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 several drug formulations, cosmetics and food additives, while the mRNA-1273 vaccine further contains tromethamine, a buffer additive present in drug formulations, contrast media and cosmetics. The first CDC reports 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 (e.g. gadolinium and contrast media), an excipient recently shown to have been involved in an anaphylactic reaction to gadolinium-based contrast media [7], but evidence on the association between hypersensitivity to tromethamine-containing-vaccines is lacking.

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We report a case of a female patient that had urticarial with in 1 hour following receiving the mRNA-1273, that later tolerated the BNT162b2 vaccine.

A 45-year-old female, with asthma, allergic rhinitis, psoriasis and an anxiety disorder was referred to our Allergy and Clinical Immunology Department due to suspected hypersensitivity to the mRNA1273vaccine.Approximately 1 hour following inoculation she developed a generalized urticarial exanthem. Angioedema, vomiting, diarrhea, hypotension, or hypoxia were not noted. The exanthem lasted for around 48 hours as the patient looked for medical assistance only 2 days after its onset, and resolved around 2 hours after treatment with desloratadine 5 mgPO.Prior to vaccination, the patient had tolerated several PEG-containing drug formulations, had no previous history of anaphylaxis, nor cutaneous mastocytosis, and had never been submitted to the administration of radiocontrast media of any kind.

Skin prick and intradermal tests with non-irritant concentrations of excipients or excipient-containing drugs were performed 5 weeks after the first inoculation and included PEG 3350, PEG 1500 (ROXALL, Medizin GmbH, Hamburg, Germany), polysorbate 20, methylprednisolone succinate and acetate, dexamethasone, triamcinolone acetonideas suggested by Banerji et al [3], gadobutrol (Gadovist®, contains tromethamine) and gadoteric acid (Dotarem®, does not contain tromethamine) in accordance with the EAACI/ENDA guidelines [8]. Only gadobutrolwas positive on intradermal testing (60,5 mg/mL), confirming tromethamine as the culprit excipient. She received the Pfizer-BioNTech mRNA vaccine, BNT162b2, 6 weeks after the first dose. The patient reported no immediate or late hypersensitivity reactions in the 24 hours following vaccination.

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

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