Tolerance to SARS-CoV-2 mRNA Vaccination in a Patient With Challenge-Confirmed PEG 2000 Allergy

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J Investig Allergol Clin Immunol 2023; Vol. 33(2): 149-150
doi: 10.18176/jiaci.0829

Key words: SARS-CoV-2. COVID-19. Polyethylene glycol. mRNA vaccine. Anaphylaxis.

Palabras clave: SARS-CoV-2. COVID-19. Polietilenglicol. Vacuna mRNA. Anafilaxia.

Polyethylene glycols (PEGs) of different molecular weights are widely used in medicine and are known to be a rare cause of anaphylaxis. PEG with a molecular weight of 2000 (PEG 2000) is used as an excipient in the SARS-CoV-2 mRNA vaccines of Pfizer-BioNTech (BNT162B24, Comirnaty, as 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide) and of Moderna (mRNA-1273, Spikevax, as PEG 2000 dimyristoyl glycerol). Although anaphylaxis to SARS-CoV-2 vaccines is rare, with an estimated incidence of 7.91 cases per million, patients' concerns regarding a self-reported increased allergy risk for SARS-CoV-2 vaccination have received considerable attention [1,2]. PEG 2000 is suspected to be a relevant allergen in cases of anaphylaxis induced by SARS-CoV-2 mRNA vaccine [1-3]. Polysorbate 80, which is used as an excipient in the vector-based DNA vaccines of Johnson & Johnson (Janssen) and AstraZeneca (ChAdOx1-S, Vaxzevria), is structurally related to PEG, and potential cross-reactivity between the 2 substances has been hypothesized [2,3]. In general, allergy to vaccine components (ie, to PEG in the case of mRNA vaccines) is a contraindication for vaccination [4]. However, there is no convincing evidence that PEG or polysorbate 80 are the allergens responsible for anaphylaxis to SARS-CoV-2 vaccines, and alternative mechanisms leading to anaphylactic reactions are being discussed [2,5]. In one case, anaphylaxis to the Comirnaty vaccine was attributed to PEG allergy [6]. In another, recent case, PEG allergy was diagnosed in a diagnostic work-up following an immediate-type reaction to Comirnaty [7]. As previously published, 2 patients diagnosed with PEG allergy in our department were ignorant of the potential risk and tolerated Comirnaty without complications [1]. Recently, 2 patients with challenge-confirmed PEG 3350 allergy tolerated the SARS-CoV-2 mRNA vaccine [8]. Possible reasons for this tolerance include the lower molecular weight of PEG 2000, a potential alteration of the allergenic potential of PEG due to conjugation with lipid-nanoparticles in mRNA vaccines [9], and the small amount per dose (0.05 mg) in Comirnaty [2].

We report the case of a 66-year-old woman with intermittent mild allergic rhinitis who experienced multiple anaphylactic reactions to PEG-containing medication. The first reaction, which involved generalized urticaria, occurred after the consumption of a lozenge containing ambroxol and PEG 6000. Subsequently, the patient experienced 2 additional anaphylactic reactions, which involved generalized urticaria and gastrointestinal and cardiovascular symptoms a few minutes after orthopedic injections containing triamcinolone acetonide, polysorbate 80, and PEG 4000. In both cases, the patient was treated with intravenous corticosteroids and antihistamines. In another episode, the patient developed generalized urticaria, dyspnea, nausea, and dizziness after ingestion of a PEG 3350–containing colonoscopy preparation and was again treated with intravenous corticosteroids and antihistamines. PEG allergy was diagnosed based on a clearly positive skin prick test (SPT) result with PEG 4000 and the medical history.

Fourteen years after the initial documented diagnosis, the patient presented at our department for an allergology evaluation before receiving the SARS-CoV-2 vaccine. No SARS-CoV-2 infection was found in the patient's history, and she had not been vaccinated against SARS-CoV-2. SPTs to pure and diluted (10%) PEG 2000, PEG 3350, PEG 4000, PEG 6000, and polysorbate 80 were performed and proved marginally positive to pure PEG 2000 (wheal/flare sizes of 4/5, 8/20, and 1/2 mm for pure PEG 2000, histamine, and saline, respectively). Skin testing with PEG is poorly sensitive, although highly specific [2]. SPTs and intradermal tests with SARS-CoV-2 mRNA vaccines (Comirnaty, Spikevax, Janssen, and Vaxzevria) remained negative after 20 minutes. Given that the oral provocation test is the gold standard in drug allergy, we performed an oral challenge starting with 30 mg PEG 2000, followed by 300 mg PEG 2000 after 45 minutes. Thirty-five minutes after the second dose (300 mg), the patient developed itching and approximately 20 wheals on her extremities and trunk. The symptoms subsided after approximately 1 hour without the need for medication. No significant rise in tryptase levels was recorded after this mild reaction (baseline tryptase, 4.87 µg/L).

The provocation test results, the current evidence regarding PEG allergy as a relative contraindication to SARS-CoV-2 mRNA vaccines, and the spreading SARS-CoV-2 Omicron variant and its impact on vaccine-induced immunity were extensively discussed with the patient. In a shared decision-

Table. Protocol for Fractionated Intramuscular Administration of the Spikevax Vaccine

Dose	Sequence	Percentage of total dose	Percentage of total dose	Dilution[a]
1	1	1.0%	0.50	1/100
	2	3.3%	0.17	1/10
	3	10.0%	0.50	1/10
	4	33.3%	0.17	Full-strength
	5	52.3% (rest)	0.26	Full-strength
2	1	30%	0.15	Full-strength
	2	70%	0.35	Full-strength

[a]The dilution was performed in water for injection. For the first dose, the intervals between the injections were 30 minutes after the first step and at least 60 minutes subsequently. For the second dose, the time interval between injections was 90 minutes.

making process, we opted for fractionated immunization with Spikevax in an in-patient setting with close observation and emergency preparedness. Five titrated intramuscular injections (left deltoid) with Spikevax were administered following the protocol shown in the Table, initially with 30-minute intervals and later with at least 60-minute intervals. The injections were administered without premedication to better monitor symptoms. The patient tolerated all the injections without subjective or objective symptoms and was therefore discharged from our department the following day. Five weeks later, she presented for administration of the second dose of Spikevax under in-patient conditions. As she had tolerated all doses of the initial protocol, we opted for a fractionated vaccination with 2 injections, again without premedication. As shown in the Table, 30% of the total dose was administered initially, followed by 70% of the total dose after 90 minutes. Again, all injections were fully tolerated. Seven weeks after the second dose, the patient had positive SARS-CoV-2 spike IgG antibodies (>384 BAU/mL in quantitative immunoassay).

To our knowledge, this is the first report of a patient with challenge-confirmed allergy to PEG 2000 who tolerated fractionated immunization with a SARS-CoV-2 mRNA vaccine. The patient had an unequivocal history of reactions to PEG of different molecular weights (PEG 3350, 4000, and 6000). PEGs with higher molecular weights are thought to induce a more marked response in SPT and challenge tests [10]. Interestingly, we recorded a positive oral challenge test result not to 30 mg, but to 300 mg of PEG 2000, and subsequent tolerance of the fractioned vaccination with PEG 2000–containing Spikevax. While Cominarty contains only 0.05 mg of PEG 2000, the exact dose of PEG 2000 in Spikevax is not stated but can be expected to be similar [2]. We hypothesize that the amount of PEG in SARS-CoV-2 mRNA vaccines is so small that many PEG-allergic patients can tolerate the injection. A challenge test may be helpful when estimating the threshold dose, although oral and intramuscular applications may not be directly comparable. Anaphylaxis to SARS-CoV-2 vaccines is rare, and vaccination is considered the most effective strategy to end the pandemic [2]. Our findings show that even a patient with challenge-confirmed PEG 2000 allergy can tolerate SARS-CoV-2 mRNA vaccination.

Acknowledgments

The authors thank Professor Dr Johann Wilhelm Weidringer for his contribution to the study.

Funding

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

Conflicts of Interest

K.B. has received honoraria for an advisory board meeting from Novavax. T.B. has provided consultancy to and received honoraria for talks and research grants from the following companies: Celgene-BMS, Lilly, Novartis, Sanofi-Genzyme, Regeneron, Viatris, AbbVie, ALK-Abello, Boehringer-Ingelheim, and Leo Pharma. The remaining authors declare that they have no conflicts of interest.

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Manuscript received March 4, 2022; accepted for publication May 24, 2022.

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