Tolerance to SARS-CoV-2 mRNA vaccination in a patient with challenge-confirmed PEG 2000 allergy

Faihs V, Bent R, Darsow U, Biedermann T, Brockow K

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

Corresponding author:
Prof. Dr. med. Knut Brockow
Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein
Technische Universität München
Biedersteiner Str. 29
80802 Munich
E-mail: knut.brockow@tum.de

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.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 (PEG) in different molecular weights are widely used in medicine and are known to be a rare cause of anaphylaxis. PEG 2000 (molecular weight 2000) is being used as 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 a rare event with an estimated incidence of 7.91 cases per million, patients' concerns regarding a self-reported increased allergy risk for SARS-CoV-2 vaccination are a major topic [1,2]. PEG 2000 is suspected to be a relevant allergen in cases of SARS-CoV-2 mRNA vaccine anaphylaxis [1-3]. Polysorbate 80, used as excipient in the vector-based DNA vaccines of Johnson & Johnson (Janssen®) and AstraZeneca (ChAdOx1-S,Vaxzevria®), is structurally related to PEG and a potential cross-reactivity between the two substances is hypothesized [2,3]. In general, allergies to vaccine components, i.e. PEG allergy for the mRNA vaccines, are 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 currently 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 published before, two patients diagnosed with PEG allergy at our department previously were ignorant of the potential risk and tolerated vaccination with Comirnaty® without any medical problems [1]. Recently, two patients with PEG 3350 allergy confirmed by challenge tolerated SARS-CoV-2 mRNA vaccines [8]. Possible reasons of this tolerance may be the lower molecular weight of PEG 2000, a

doi: 10.18176/jiaci.0829

potential alteration of the allergenic potential of PEG due to the conjugation with lipid-nanoparticles in mRNA vaccines [9] or the small amount of 0.05 mg per dose in Comirnaty® [2].

Here, we report the case of a 66-year-old female patient with intermittent mild allergic rhinitis who experienced multiple anaphylactic reactions to PEG-containing medication. The first reaction with generalized urticaria occurred after the consumption of a lozenge containing ambroxol and PEG 6000. Thereafter, the patient experienced two additional anaphylactic reactions with generalized urticaria as well as 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. Finally, a clearly positive skin prick test (SPT) to PEG 4000 and the past medical history led to the diagnosis of a PEG allergy.

14 years after the initial documented diagnosis, the patient presented at our department for allergologic assessment regarding SARS-CoV-2 vaccination. No SARS-CoV-2 infection was found in the patient's history and SARS-CoV-2 vaccination had not been performed. SPTs to pure and diluted (10%) PEG 2000, PEG 3350, PEG 4000, PEG 6000 and polysorbate 80 were performed and tested 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 to PEG has been shown to have a poor sensitivity, although specifity is high [2]. SPTs and intradermal tests to SARS-CoV-2 mRNA vaccines (Comirnaty®, Spikevax®, Janssen® and Vaxzevria®) remained negative after 20 minutes. Oral provocation test is the gold standard in drug allergy, so we performed an oral challenge starting with 30 mg PEG 2000, followed by 300 mg PEG 2000 after 45 minutes. 35 minutes after the second dose (300 mg), the patient developed itching and approximately 20 wheals on her extremities and trunk. The symptoms subsided

doi: 10.18176/jiaci.0829

after approximately one hour without the need of any medication. After this mild reaction, no significant rise in tryptase levels was measured (baseline tryptase: 4.87 µg/l).

The provocation test results, the current evidence regarding PEG allergy as relative contraindication to SARS-CoV-2 mRNA vaccines as well as the spreading SARS-CoV-2 Omicron variant and its discussed impact on vaccine-induced immunity were extensively discussed with the patient. In a shared decision-making process, we decided for a fractionated immunization with Spikevax® in an inpatient setting under close observation and emergency preparedness. Five titrated intramuscular injections with Spikevax® were administered in the left deltoid following the protocol shown in table 1 with at first 30 minutes and later at least 60 minutes intervals. For better monitoring of symptoms, the injections were performed without any premedication. The patient tolerated all injections without any subjective or objective symptoms, so that she was discharged from our department the day after. Five weeks afterwards, the patient presented for the administration of the second dose of Spikevax® under inpatient conditions. As the patient had tolerated all doses of the initial protocol, we decided for a fractionated vaccination with two injections, again without any premedication. As shown in table 1, at first 30% of the total dose were administered, followed by 70% of the total dose after 90 minutes. Again, all injections were fully tolerated. 7 weeks after the second dose, the patient showed positive SARS-CoV-2 spike IgG antibodies (>384 BAU/ml in quantitative immunoassay).

To our knowledge, this is the first case report of a patient with a challenge-confirmed allergy to PEG 2000 who tolerated a fractionated immunization with a SARS-CoV-2 mRNA vaccine. The patient had an unequivocal history of reactions to PEG in different molecular weights (PEG 3350, 4000, and 6000). PEGs with higher molecular weight are thought to have a higher responsiveness in SPT and challenge tests [10]. Interestingly, our patient showed a positive oral challenge test not to 30 mg, but to 300 mg of PEG 2000 and subsequently tolerated the fractioned vaccination with PEG 2000-containing Spikevax®. While only 0.05 mg of PEG 2000 are contained in Comirnaty®, the exact dose of PEG 2000 in Spikevax®

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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 small enough to be tolerated even by many PEG allergic patients. A challenge test may be helpful to estimate 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 this pandemic [2]. With this case report we show that even a patient with challenge-confirmed PEG 2000 allergy tolerated a SARS-CoV-2 mRNA vaccination.

Funding

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

Conflicts of Interest

KB received honoraria for an advisory board meeting of Novavax company. T.B. gave advice to or got honorarium for talks or research grant from the following companies: Celgene-BMS, Lilly, Novartis, Sanofi-Genzyme, Regeneron, Viatris, Abbvie, ALK-Abello, Boehringer-Ingelheim, Leo Pharma. The other authors declare that they have no conflicts of interest.

Acknowledgement

The authors thank Prof. Dr. Johann Wilhelm Weidringer for the cooperation.

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Table. Protocol for fractionated intramuscular administration of Spikevax® vaccine.

Dose	Sequence	Portion of total dose	Total volume in ml	Dilution*
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

* Dilution was performed in water for injection. For the first dose, time intervals between the injections were 30 minutes after the first step and at least 60 minutes afterwards. For the second dose, the time interval between injections was 90 minutes.