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Variability of eliciting thresholds in PEG allergy limits prediction of tolerance to PEG-containing mRNA COVID vaccines

To the Editor:

With great interest we have read the article "Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: a case series" by Picard et al.[1] In 3 of the 6 polyethylene glycol (PEG)-allergic patients, the diagnosis was confirmed by the positive oral provocation test (OPT) to PEG 3350 after ingestion of 2 to 7 g of PEG 3350, respectively, and 4 of them tolerated messenger RNA (mRNA) vaccines with PEG. There are also other reports in the literature, including ours, showing that patients may tolerate COVID-19 mRNA vaccination despite PEG allergy.[2,3] We would like to extend these observations with 5 patients with PEG allergy, presenting systemic symptoms either at skin prick tests (SPT), intradermal tests (IDT), and/or OPT, and discuss possible consequences of different eliciting thresholds for the tolerance of COVID-19 mRNA vaccines.

From February 2021 to September 2021, we encountered systemic reactions to PEG allergy testing in 5 patients confirming PEG allergy (2 male, 3 female; age: 27-73 years): SPT with PEG led to systemic reactions in 1, IDT in 3, and OPT in 1 patient. All had a history positive for immediate-type allergic reactions to PEG and positive skin test or positive OPT (Table I) and have had anaphylaxis after ingestion of PEG 2 months to 20 years before testing at our center. Patients developed either generalized urticaria (n = 2), erythema and dizziness (n = 2), or skin symptoms and gastrointestinal cramps (n = 1). Notably, elicitation thresholds varied strongly from reacting already to SPT with a 10% solution of PEG in *aqua destillata* to tolerating 13 g of PEG 4000 in OPT. Vaccination was tolerated in 3 of 5 patients with DNA vaccines; at that time, we did not offer mRNA vaccination.

Our data demonstrate that in some patients only minute amounts applied by skin testing may suffice to elicit systemic reactions, whereas in others, eliciting thresholds are multifold higher. Variables for tolerance are the dose, application mode, type of PEG, and time interval since the last positive reaction. The amount of PEG of 1 full dose of the Moderna vaccine is 0.05 mg,[4] whereas the quantity of PEG in our IDT was much lower (0.0005 mg) and the one of the SPT cannot be estimated. PEG applied parenterally is more likely to trigger anaphylaxis as compared with oral application.[5] SPT allergenicity of PEG increases with molecular weight and may be low for PEG 2000, and it may also be altered when presented within micelles.[6] Nevertheless, patients already reacting with systemic symptoms at SPT or IDT likely have a higher risk of systemic reactions at COVID-19 mRNA vaccination than others tolerating ≥1 g of PEG 3350.

Whether or not our patients tolerate PEG-containing mRNA vaccines remains speculative. It appears likely for patient 5 tolerating 13 g of PEG 4000 at OPT, but for the others tolerance is more difficult to predict. There is a need to generate more data on comparing PEG threshold levels in patients with PEG allergy and tolerance of PEG-containing mRNA vaccines before drawing final conclusions. We aim for vaccinating PEG-allergic patients with mRNA vaccines, beginning with those with low level of sensitization.

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TABLE I. Clinical details on 5 patients with PEG allergy and systemic reactions to allergy tests

Patient	Elicitor	Reaction	SPT results	IDT results	BAT results	OPT	SARS CoV2 vaccination
28, female	(1) Cold medication syrup (PEG 6000) (2) Local anesthetic injection (mepivacaine, contains PEG) (3) Colon cleansing solution (Movicol, is PEG 3350) (4) Iodide solution (contains PEG)	(1) Few minutes after intake throat swelling, dyspnea, generalized pruritus (2) Few minutes after injection urticaria, dyspnea, drop in blood pressure, runny nose (3) 5 min after intake urticaria, dyspnea, drop in blood pressure (4) One hour after application (on foot) urticaria	2013: SPT: positive to PEG 4000 2021: SPT: negative to PEG 2000, 4000, 6000, PS 80, Comirnaty 2013: After SPT generalized urticaria	2021: IDT: positive to Comirnaty Negative to PEG 2000, 4000, 6000, PS 80, Vaxzevria Generalized urticaria 1 h after IDT	BAT: negative to PEG 2000, 4000, 6000, PS 80, Vaxzevria Positive to Comirnaty, Spikevax	No OPT performed because of systemic reaction after skin test	Tolerated first shot of fractionated Vaxzevria (0.1 mL; 0.4 mL) under inpatient emergency preparedness, without premedication
73, male	Colon cleansing solution (=PEG 3350)	30 min after third or fourth cup of PEG preparation palmar erythema, generalized itch, dizziness	SPT: positive to PEG 3350, 4000 Negative to PEG 2000, PEG 6000, PS 80	IDT: positive to PEG 3350, 4000, 6000 Negative to PEG 2000 and PS 80 After IDT generalized itch and palmar erythema	BAT: positive to PEG 4000,6000, Comirnaty, Spikevax Negative to PEG 2000, 3350, PS 80, Vaxzevria	No OPT performed because of systemic reaction after skin test	Tolerated first shot of fractionated Vaxzevria (0.1 mL; 0.4 mL) under inpatient emergency preparedness, without premedication
59, female	(1) Colon cleansing solution (Movicol Orange) (=PEG 3350) (2) Corticosteroid + local anesthetic injection (lidocaine/triamcinolone + PEG)	(1) 1 h after intake of Moviprep Orange swelling of hands, generalized urticaria, nausea, vomiting, diarrhea (2) Few minutes after injection of lidocaine/triamcinolone preparation generalized urticaria, dyspnea, dizziness	SPT: positive to PEG 4000, 6000 Negative to PEG 2000, PS 80, Moviprep Orange. After SPT nausea and dizziness	No IDT performed after systemic symptoms at SPT	BAT: positive to Spikevax Negative to PEG 2000, 3350, 4000, 6000, PS 80, Comirnaty, Vaxzevria	No OPT performed because of systemic reaction after skin test Subcutaneous challenge to triamcinolone articaine (without PEG), negative	Tolerated Vaccine Janssen unfractionated under emergency preparedness
27, male	Erythromycin syrup (Infekto mycin, contains PEG 6000)	Generalized urticaria, angioedema of the eyelids, dizziness, pruritus in the throat, dyspnea after 30 min	2006: SPT: positive to PEG 4000 After SPT systemic reaction with itching at the palate and dizziness 2021: negative to PEG 2000, 4000, 6000, Vaxzevria, Comirnaty, Spikevax	2021: IDT: Systemic reaction with generalized urticaria 20 min after start of IDT	BAT: NTX	Labial and OPT tolerated until the maximal dose of 30 mg of PEG 4000, discontinued because of systemic reaction in SPT	No vaccination

60, female	(1) Docetaxel (PS 80) (2) Paclitaxel (macrogolglycerol ricinoleate) (3) TriamHEXAL (PEG 4000, PS 80) and MepiHEXAL (4) Colon cleansing solution (PLENVU (=PEG 3350) (5) Contrast media	(1) Generalized itching (2) Nausea, clouding of consciousness, rash (3) 10 min after injection generalized itch, rise in blood pressure, sensation of heat (4) Generalized urticaria (5) After 20 min generalized urticaria, sensation of heat	SPT: negative to PEG 2000, 4000, 6000, 3350, PS 80, Comirnaty, Spikevax, Vaxzevria, Vaccine Janssen, TriamHEXAL, Gadotersäure (Dotagraf), Gadoxetsäure (Primovist), Gadobutrol (Gadovist)	IDT: positive to Comirnaty Negative to PEG 2000, 4000, 6000, 3350, PS 80, Spikevax Vaxzevria, Vaccine Janssen, TriamHEXAL, Gadotersäure (Dotagraf), Gadoxetsäure (Primovist), Gadobutrol (Gadovist)	BAT: positive to DMG-PEG (BühlMann), Comirnaty, Spikevax Borderline positive to PEG 2000 (BühlMann), PEG 2000, 4000, 6000, 3350, PS 80 Vaxzevria, Vaccine Janssen Negative to PEG 200	Tolerated OPT with PEG 4000 up to 900 mg. Systemic reaction at OPT with PEG 3350 at 38 g (tolerated up to 13 g of PEG 3350): urticaria, tingling of fingertips, shivering, nausea, stomach/ abdominal cramps	No vaccination

BAT, Basophil activation test; *IDT*, intradermal test (wheal ≥5 mm); *OPT*, oral provocation test; *NTX*, not tested, *PEG*, polyethylene glycol; *PS*, polysorbate; *SPT*, skin prick test (wheal ≥3 mm).

Reply to "Variability of eliciting thresholds in PEG allergy limits prediction of tolerance to PEG-containing mRNA COVID vaccines"

To the Editor:

We thank Mathes et al[1] for their correspondence regarding our article "Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: a case series."[2] The authors raise the interesting issue that some polyethylene glycol (PEG)-allergic patients with low reaction thresholds and systemic reactions to PEG skin testing could be at risk of reacting to messenger RNA (mRNA) COVID-19 vaccines, which contain very small amounts of PEG 2000 linked to a lipid. Although this hypothesis is plausible, we would like to point out that the only mean of ascertaining this risk is to vaccinate these patients with an mRNA vaccine.

In our case series,[2] we identified 3 patients with a positive skin test to an mRNA vaccine who then tolerated the vaccine (one of them—patient 1—in a single dose on 2 occasions). This patient also had a low reaction threshold as he was positive on skin prick testing (SPT) to PEG 3350 at a concentration of 0.7 mg/mL.

Since the publication of the case series, we evaluated 2 other patients with a positive SPT to PEG 3350 (Table I). One accepted vaccination and tolerated an mRNA vaccine in a single dose. In addition, 1 patient (patient 6) from the original case series with a positive SPT to PEG 3350 tolerated an mRNA vaccine in a single dose, which she received as a booster after receiving the AstraZeneca vaccine for her initial immunization (Table I). Hennighausen et al[3] recently published a case report showing tolerance to an mRNA vaccine (in divided doses and with antihistamine premedication) in a patient with a positive basophil activation test to the vaccine and to the PEG 2000 lipid component. Taken together, these findings argue that skin testing and/or a basophil activation test to PEG of any molecular weight or to the vaccine itself does not reliably predict reactivity on vaccine inoculation.

As pointed out by Kelso in a recent review article,[4] important lessons can be learned from the egg allergy and influenza vaccine story: before an allergy to a vaccine constituent is considered a contraindication to this vaccine, allergists need to thoroughly evaluate this risk, which entails provocation testing.

In conclusion, given the high benefits of COVID-19 vaccination, especially with mRNA vaccines, and the reassuring data on their safety,[5,6] even in patients with a documented PEG allergy,[2,3,7] we would encourage allergists to offer supervised administration of mRNA vaccines to PEG-allergic patients either in a single or divided doses.

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