Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Janssen COVID-19 vaccine tolerated in 10 patients with confirmed polyethylene glycol allergy

Maria A. Bruusgaard-Mouritsen, MD[a,*], Grace Koo, MD[b,*], Anne Sophie Heinrichsen, MD[a], Birgitte Bech Melchiors, MD[a], Matthew S. Krantz, MD[b], Jessica H. Plager, MD[b], Mitchell Boxer, MD[c], Elizabeth J. Phillips, MD[d,e,†], Cosby A. Stone, Jr., MD, MPH[b,d,†], and Lene H. Garvey, MD, PhD[a,f,†]

Clinical Implications

The safety of coronavirus disease 2019 vaccination in patients with confirmed polyethylene glycol allergy, with or without skin test sensitization to the polyethylene glycol derivative polysorbate 80, is unknown. We report tolerance of the polysorbate 80–containing Janssen adenoviral vector vaccine in 10 polyethylene glycol–allergic patients.

Polyethylene glycols (PEGs) and the structurally related polysorbates (PEG sorbitans—PEG molecular weight, 880-1056 g/mol) are excipients commonly used in small-molecule pharmaceutical drugs, as well as in some vaccines and most mAbs. Although polysorbates are common excipients in many vaccines, there is only a single case of vaccine anaphylaxis attributed to polysorbate 80 in a recent literature review.[1,2] Similarly, the literature contains only a few cases of convincing skin test–confirmed immediate hypersensitivity to polysorbate 80 in mAbs, disinfectant solutions, intraarticular depot-steroids such as methylprednisolone acetate and triamcinolone acetonide, dexamethasone-lidocaine preparations for intramuscular and intraarticular injection (in Europe and some other countries), and subcutaneously injected erythropoietin.[3-5] Although patients with immediate hypersensitivity to PEGs may show cross-sensitization to polysorbates, the clinical relevance of this sensitization is not clear.[6,7]

The mRNA coronavirus disease 2019 (COVID-19) vaccine from Pfizer-BioNTech is now licensed in the United States and Europe (Comirnaty), and Moderna COVID-19 mRNA vaccine under emergency use authorization in the United States is now licensed in Europe (Spikevax). The rollout of the mRNA vaccines in December 2020 was associated with cases of anaphylaxis that sparked new interest in the cross-sensitizing potential between PEGs and polysorbates.[6,7] The liponanoparticles of the mRNA COVID-19 vaccines are stabilized by a PEG 2000-lipid. The single-dose adenoviral vector COVID-19 vaccine available in the United States (Janssen; Johnson&Johnson) and the 2-dose adenoviral vector vaccine used in the United Kingdom, Europe, Australia, and Canada (ChAdOx1 [AZD1222, Vaxrevia]) contain polysorbate 80 as a stabilizer. In most countries, contraindications to the COVID-19 vaccines have therefore included a history of allergic reactions to a vaccine component, such as PEG or polysorbate 80. For this reason, the rare patients with confirmed or suspected allergy to PEGs have not been offered vaccination.

Here, we report 10 patients with confirmed allergy to PEGs from 2 specialized allergy clinics (7 patients from Denmark and 3 patients from the United States) who were assessed for vaccination to the polysorbate 80–containing Janssen COVID-19 vaccine (see Table I for demographic and clinical data). Written informed consent to vaccination and publication of clinical data was obtained from all patients. For VUMC, the collection of patient data was covered under IRB#161455 and IRB#150754.

Allergy to PEGs was confirmed by a combination of histories of 1 or more episodes of allergy and/or anaphylaxis (World Allergy Organization grades 1-5)[8] to PEG-containing products and positive skin testing results to PEGs. Skin prick testing (SPT) to PEGs and derivatives was performed at the time of diagnosis. Intradermal testing was performed only in the United States, and only if the SPT result was negative. Before vaccination, SPT with vaccines from Janssen, Pfizer/BioNTech, and Moderna was done in 9 of 10 cases. See Table I for details of tested products, concentrations, and diagnostic criteria.

Vaccination without premedication was performed with the standard single-dose 0.5-mL Janssen COVID-19 vaccine (containing 0.160 mg polysorbate 80) in the deltoid muscle in an Allergy Clinic setting with intravenous access, continuous monitoring, and emergency equipment and expertise in treating anaphylaxis at all sites. Vaccination was tolerated without allergic reaction in all 10 patients.

Demographic and clinical characteristics are summarized in Table I. Clinical details, not related to COVID-19 vaccination of 4 patients, have been published previously.[6,9] All patients had been diagnosed with PEG allergy 1.5 months to 9 years before COVID-19 vaccination, with 8 of 10 patients reporting anaphylaxis (World Allergy Organization grade 3-5)[8] following documented PEG exposure. No patient had a history of previous adverse reactions to any vaccine, and none had experienced a clinical reaction to polysorbate 80–containing products. However, none of the patients had a history of exposure to polysorbate 80 since the diagnosis of PEG allergy was made. Patient 2 had tolerated influenza vaccine (Fluzone), which contains a PEG-like derivative octoxynol-9 (Triton-X-100), in 2019 and 2020.

At the time of diagnosis of PEG allergy, all patients had positive SPT results to PEGs ranging in molecular weight between 3000 and 20,000 g/mol. Two Danish patients (patient 9 and patient 10) had positive SPT result to polysorbate 80 at the time of diagnosis, and 3 patients from the United States (all male) (patients 1-3) were positive on intradermal testing with polysorbate 80–containing triamcinolone acetonide.

Of the 9 of 10 patients who were skin prick tested to the Pfizer-BioNTech, Moderna, and Janssen vaccines, all tested negative to the Janssen COVID-19 vaccine. One patient (patient 7) diagnosed with PEG allergy 3 months before vaccination had a positive SPT result to the Pfizer-BioNTech and Moderna vaccines, and 1 (patient 10) diagnosed 10 months before vaccination had itching, but no objective signs, at the site of all 3 vaccines and polysorbate 80.

TABLE I. Demographic data, clinical characteristics, skin test, and vaccine results in 10 PEG-allergic patients who tolerated Janssen COVID-19 vaccine

Country, patient no.	Age (y), sex	Drugs causing reactions before diagnosis	Severity WAO grade[8]	Positive skin test results at diagnosis*†‡	Time interval from diagnosis to vaccination/ Time interval from last anaphylaxis to vaccination	Skin prick test results before vaccination‡§	Tolerance of Janssen vaccine
US, 1	62, M	Colonoscopy preparation (PEG 3350) × 1 Intraarticular steroid (PEG 3350) × 2	Anaphylaxis × 1 WAO grade 5 Anaphylaxis × 2 WAO grade 5	PEG 3350 PEG 8000 Methylprednisolone acetate (PEG 3350) Poloxamer 407 IDT positive to triamcinolone acetonide (PS 80)	8 y/5 y	Pfizer negative Moderna negative Janssen negative	Tolerated Flare at injection site at 45 min
US, 2[9]	60, M	Liposomal perflutren echocardiogram contrast (PEG 5000) Colonoscopy preparation (PEG 3350) Intraarticular steroid (PEG 3350)	Anaphylaxis × 1 WAO grade 5 Anaphylaxis × 1 WAO grade 5 Anaphylaxis × 1 WAO grade 5	PEG 3350 PEG 8000 Methylprednisolone acetate (PEG 3350) Poloxamer 407 IDT positive to triamcinolone acetonide (PS 80)	2 y/2 y	Pfizer negative Moderna negative Janssen negative	Tolerated No allergic symptoms
US, 3	33, M	Allegra (PEG 6000) Colonoscopy preparation (PEG 3350) Amlodipine (PEG 3350) Toothpaste (PEG unknown)	WAO grade 2 WAO grade 2 WAO grade 2 WAO grade 2	PEG 3350 Methylprednisolone acetate (PEG 3350) IDT positive to triamcinolone acetonide (PS 80)	2 y/2 y	ND	Tolerated No allergic symptoms
DK, 4[6]	68, F	Intraarticular steroid (PEG 3350) × 1	Anaphylaxis × 1 WAO grade 5	PEG 3000 PEG 6000	9 y/9 y	Pfizer negative Moderna negative Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms
DK, 5[6]	59, M	Unidentified perioperative exposure during coronary stent insertion	Anaphylaxis × 1 WAO grade 4	PEG 3000 PEG 6000 PEG 20,000 Poloxamer 407	7 y/7 y	Pfizer negative Moderna negative Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms
DK, 6	60, F	Intraarticular steroid (PEG 3350) Balancid Novum reflux tablet (PEG 6000) Ibuprofen (PEG unknown)	Anaphylaxis × 1 WAO grade 3 WAO grade 1 WAO grade 1	PEG 20,000 Poloxamer 407	3 y/4 y	Pfizer negative Moderna negative Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms

DK, 7	57, F	Intraarticular steroid (PEG 3350) × 1 Provocation intraarticular steroid (PEG 3350) Vepicombin (PEG 6000) tablet × 2 (phenoxymethylpenicillin)	Anaphylaxis × 1 WAO grade 3 WAO grade 1 WAO grade 1	PEG 20,000 Poloxamer 407	3 mo/7 mo	Pfizer positive Moderna positive Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms
DK, 8	67, F	Colonoscopy preparation (PEG 3350)	WAO grade 1	PEG 20,0000	2 mo/3 mo	Pfizer negative Moderna negative Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms
DK, 9[6]	43, M	Vepicombin (PEG 6000) tablet × 2 (phenoxymethylpenicillin) Mucoangin throat lozenge (PEG 6000) Burana (ibuprofen) tablet (PEG 6000) Xerodent (sodium fluoride) tablet (PEG 6000) Balancid Novum reflux tablet (PEG 6000)	Anaphylaxis × 2 WAO grade 5 Anaphylaxis × 1 WAO grade 3 WAO grade 1 WAO grade 1 WAO grade 1	PEG 6000 PEG 20,000 Poloxamer 407 PS 80	7 y/7 y	Pfizer negative Moderna negative Janssen negative PEG 2000 negative PS 20 negative PS 80 negative	Tolerated No allergic symptoms
DK, 10	28, F	Colonoscopy preparation (PEG 3350)	Anaphylaxis × 1 WAO grade 4	PEG 3000 PEG 6000 Poloxamer 407 PS 80	10 mo/10 mo	Pfizer negative (itch) Moderna negative (itch) Janssen negative (itch) PEG 2000 negative PS 20 negative PS 80 negative (itch)	Tolerated No allergic symptoms

DK, Denmark; *F*, female; *IDT*, intradermal testing; *M*, male; *ND*, not done; *PEG*, polyethylene glycol; *PS*, polysorbate; *US*, United States; *WAO*, World Allergy Organization.

*Skin testing at time of PEG allergy diagnosis, Gentofte Hospital, Denmark: All patients were skin prick tested with PEG 300 (1 g/mL), PEG 2000 (500 mg/mL), PEG 3000 (500 mg/mL), PEG 6000 (500 mg/mL), PEG 20,000 (0.1 mg/mL, 1 mg/mL, 10 mg/mL, 100 mg/mL, 200 mg/mL), Poloxamer 407 (100 mg/mL), and polysorbate 80 (200 mg/mL). All products were purchased as pure solutions from SIGMA-Aldrich. Details of preparation of solutions have been previously published (see Bruusgaard-Mouritsen et al[6]).

†Skin testing at time of PEG allergy diagnosis, Vanderbilt Allergy Clinic, United States: All patients were skin prick tested with PEG 300 (0.1 mg/mL) (Professional Compunding Centers of America [PCCA]), PEG 3350 (using 17 g Miralax in 100 cc sterile water) (1.7 mg/mL, 17 mg/mL, 170 mg/mL), PEG 8000 (0.1 mg/mL, 1 mg/mL, 10 mg/mL) (Professional Compunding Centers of America [PCCA]), Poloxamer 407 (0.1 mg/mL, 1 mg/mL, 10 mg/mL) (Professional Compunding Centers of America [PCCA]), triamcinolone acetonide containing polysorbate 80 (0.1 mg/mL and 1 mg/mL), and methylprednisolone acetate containing PEG 3350 (0.04 mg/L 0.4 mg/mL, and 4 mg/mL). Intradermal testing with methylprednisolone acetate was used only if SPT testing result was negative across all reagents (see Stone et al[7]).

‡SPT: A positive reaction was defined as a wheal diameter of >3 mm. IDT: A positive reaction was defined as a wheal ≥ saline wheal + 3 mm and flare.

§SPT before vaccination was performed with the 3 COVID-19 vaccines from Pfizer, Moderna, and Janssen "as is." DK cases were additionally skin prick tested with PEG 2000 (500 mg/mL), polysorbate 20 (200 mg/mL), and polysorbate 80 (200 mg/mL).

In summary, we have reported tolerance, without any evidence of an allergic reaction, of the polysorbate 80—containing Janssen COVID-19 vaccine in 10 patients with confirmed allergy to PEGs. Our approach may be considered conservative given the fact that 8 of 9 of our cases tested negative on SPT with mRNA vaccines, and 7 of 7 of the Danish cases had negative SPT result to PEG 2000, suggesting that the PEG-containing mRNA vaccines may have been tolerated by these patients despite their history of PEG allergy.

However, by choosing the single-dose Janssen COVID-19 vaccine, we avoided the potential problem of the first dose of an mRNA vaccine causing an increase in sensitization to PEGs, thus escalating the risk of a reaction to the second dose, or having to make a decision about the second dose, had a reaction to the first dose occurred. In addition, because tolerance of the Janssen COVID-19 vaccine was observed in all patients in this report, including the 3 US patients who had positive intradermal testing result to triamcinolone, which contains polysorbate 80, and 2 Danish patients who had positive SPT result to polysorbate 80, the clinical relevance of skin test sensitization to polysorbate 80 is uncertain and may not directly translate to reactions to polysorbate 80—containing drugs in PEG-allergic patients.

In conclusion, patients with confirmed allergy, including anaphylaxis, and positive skin test results to PEGs appear to safely tolerate the Janssen COVID-19 vaccine despite its content of polysorbate 80 (0.160 mg per dose). This supports the safety of currently available adenoviral vector vaccines and other polysorbate 80—containing COVID-19 vaccines in development for future use, in those rare patients with confirmed PEG allergy, and strongly suggests that they need not be medically exempt from vaccination. As a final caveat, however, given the severity of presentation of PEG anaphylaxis, the potential heterogeneity of disease with respect to sensitivity at varying PEG molecular weights, and the lack of specific understanding of mechanisms, all PEG-allergic patients should still be carefully assessed by allergists, and COVID-19 vaccination performed with the shared decision of the patient under monitored observation.

[a]Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital-Herlev and Gentofte, Copenhagen, Denmark
[b]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[c]Department of Allergy & Immunology, Zucker School of Medicine at Hofstra/Northwell, New York, NY
[d]Center for Drug Safety and Immunology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[e]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia
[f]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[*]Co-first authors.
[†]Co-senior authors.

C.A.S. receives funding from the Agency for Healthcare Research and Quality/Patient-Centered Outcomes Research Institute (grant no. 1K12HS026395-01) and the American Academy of Allergy, Asthma & Immunology Foundation. E.G.P. reports direct support as a principal investigator from the National Institutes of Health (NIH; grant nos. R01HG010863, R01AI152183, U01AI154659, UAI109565, and R13AR078623) as well as other coinvestigator support from the NIH and the National Health and Medical Research Foundation of Australia.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication September 27, 2021; revised December 13, 2021; accepted for publication December 16, 2021.
Available online January 1, 2022.
Corresponding author: Lene Heise Garvey, MD, PhD, Allergy Clinic, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Gentofte Hospitalsvej 8, 1st Floor, 2900 Hellerup, Denmark. E-mail: lene.heise.garvey@regionh.dk.
2213-2198

https://doi.org/10.1016/j.jaip.2021.12.025

REFERENCES

1. Stone CA Jr, Rukasin CRF, Beachkofsky TM, Phillips EJ. Immune-mediated adverse reactions to vaccines. Br J Clin Pharmacol 2019;85:2694-706.
2. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. Case Rep 2012;2012:bcr0220125797.
3. Wenande E, Kroigaard M, Mosbech H, Garvey LH. Polyethylene glycols (PEG) and related structures: overlooked allergens in the perioperative setting. A&A Case Rep 2015;4:61-4.
4. Bergmann KC, Maurer M, Church MK, Zuberbier T. Anaphylaxis to mepolizumab and omalizumab in a single patient: is polysorbate the culprit? J Investig Allergol Clin Immunol 2020;30:285-7.
5. Steele RH, Limaye S, Cleland B, Chow J, Suranyi MG. Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. Nephrology 2005;10:317-20.
6. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Johansen JD, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. J Allergy Clin Immunol 2022;149:168-75.e4.
7. Stone CA, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 2019;7. 1533-40.e8.
8. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World Allergy Organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472.
9. Krantz MS, Liu Y, Phillips EJ, Stone CA Jr. COVID-19 vaccine anaphylaxis: PEG or not? Allergy 2021;76:1934-7.