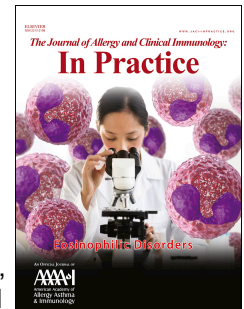


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Janssen COVID-19 vaccine tolerated in 10 patients with confirmed polyethylene glycol allergy

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Clinical implications: The safety of COVID-19 vaccination in patients with confirmed polyethylene glycol (PEG) allergy, with or without skin test sensitization to the PEG-derivative polysorbate 80, is unknown. We report tolerance of the polysorbate 80-containing Janssen adenoviral vector vaccine in ten PEG-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 monoclonal antibodies. While 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 only contains a few cases of convincing skin test confirmed immediate hypersensitivity to polysorbate 80 in monoclonal antibodies, 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 While 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 COVID-19 vaccine from Pfizer-BioNTech is now licenced in the United States (US) and Europe (Comirnaty®) and Moderna COVID-19 mRNA vaccine under emergency use authorization in the US, 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 US (Janssen (Johnson&Johnson)), and the two-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 ten patients with confirmed allergy to PEGs from 2 specialized allergy clinics (7 patients from Denmark and 3 patients from the US) who were assessed for vaccination to the polysorbate 80-containing Janssen COVID-19 vaccine (See Table 1 for demographic and clinical

data). Allergy to PEGs was confirmed by a combination of histories of 1 or more episodes of allergy and/or anaphylaxis (WAO grades 1-5)⁸ to PEG-containing products and positive skin testing to PEGs. Skin prick testing (SPT) to PEGs and derivatives was performed at the time of diagnosis.. Intradermal testing was only performed in the US, and only if SPT was negative. Prior to vaccination SPT with vaccines from Janssen, Pfizer/BioNTech and Moderna were done in 9/10 cases. See Table 1 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 ten patients. Demographic and clinical characteristics are summarized in Table 1. 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 prior to COVID-19 vaccination with 8/10 patients reporting anaphylaxis (WAO 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) in 2019 and 2020 which contains a PEG-like derivative octoxynol-9 (Triton-X-100).

At the time of diagnosis of PEG allergy all patients were SPT positive to PEGs ranging in molecular weight between 3000 and 20,000 g/mol. Two Danish patients (patient 9 and 10) were SPT positive to polysorbate 80 at the time of diagnosis and three patients from the US (all male) (patients 1-3) were positive on intradermal testing (IDT) with polysorbate 80-containing triamcinolone acetonide. Of the 9/10 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 prior to vaccination had a positive SPT to the Pfizer-BioNTech and Moderna vaccines, and 1 (patient 10) diagnosed 10 months prior to vaccination had itching, but no objective signs, at the site of all 3 vaccines and polysorbate 80.

In summary, we have reported tolerance, without any evidence of an allergic reaction, of the polysorbate 80-containing Janssen COVID-19 vaccine in ten patients with confirmed allergy to PEGs.

Our approach may be considered conservative given the fact that 8/9 of our cases tested negative on SPT with mRNA vaccines, and 7/7 of the Danish cases were SPT negative 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 a 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 second dose, had a reaction to the first dose occurred. In addition, as tolerance of the Janssen COVID-19 vaccine was observed in all patients in this report, including the 3 US patients who were IDT positive to triamcinolone which contains polysorbate 80, and 2 Danish patients who were SPT positive 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 tests 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.

Keywords skin testing, polysorbate 80, polyethylene glycol, COVID-19 vaccination, anaphylaxis

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TABLE 1. Demographic data, clinical characteristics, skin test and vaccine results in ten PEG allergic patients who tolerated Janssen COVID-19 vaccine.

Country, Patient No	Age, sex	Drugs causing reactions prior to diagnosis	Severity WAO grade ⁸	Positive skin test results at diagnosis ^{a,b,c}	Time interval from diagnosis to vaccination / Time interval from last anaphylaxis to vaccination	Skin prick test results before vaccination ^{c,d}	Tolerance of Janssen vaccine
US, 1	62, M	Colonoscopy preparation (PEG 3350) x 1 Intraarticular steroid (PEG 3350) x 2	Anaphylaxis x 1 WAO grade 5 Anaphylaxis x 2 WAO grade 5	PEG 3350 PEG 8000 Methylprednisolone acetate (PEG 3350) Poloxamer 407 IDT positive to triamcinolone acetonide (PS 80)	8 yrs/5 yrs	Pfizer negative Moderna negative Janssen negative	Tolerated Flare at injection site at 45 minutes
US, 2 ⁹	60, M	Liposomal perflutren echocardiogram contrast (PEG 5000) Colonoscopy preparation (PEG 3350) Intraarticular steroid (PEG 3350)	Anaphylaxis x 1 WAO grade 5 Anaphylaxis x 1 WAO grade 5 Anaphylaxis x 1 WAO grade 5	PEG 3350 PEG 8000 Methylprednisolone acetate (PEG 3350) Poloxamer 407 IDT positive to triamcinolone acetonide (PS 80)	2 yrs/2 yrs	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 yrs/2 yrs	ND	Tolerated No allergic symptoms
DK, 4 ⁶	68, F	Intraarticular steroid (PEG 3350) x 1	Anaphylaxis x 1 WAO grade 5	PEG 3000 PEG 6000	9 yrs/9 yrs	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 x 1 WAO grade 4	PEG 3000 PEG 6000 PEG 20,000 Poloxamer 407	7 yrs/7 yrs	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 x 1 WAO grade 3 WAO grade 1 WAO grade 1	PEG 20,000 Poloxamer 407	3 yrs/4 yrs	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) x 1 Provocation intraarticular steroid (PEG 3350) Vepicombin® (PEG 6000) tablet x 2 (phenoxymethylpenicillin)	Anaphylaxis x 1 WAO grade 3 WAO grade 1 WAO grade 1	PEG 20,000 Poloxamer 407	3 mths/7 mths	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 20,000	2 mths/3 mths	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 x 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 x 2 WAO grade 5 Anaphylaxis x 1 WAO grade 3 WAO grade 1 WAO grade 1 WAO grade 1	PEG 6000 PEG 20,000 Poloxamer 407 PS 80	7 yrs/7 yrs	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 x 1 WAO grade 4	PEG 3000 PEG 6000 Poloxamer 407 PS 80	10 mths/10 mths	Pfizer negative (itch) Moderna negative (itch) Janssen negative (itch) PEG 2000 negative PS 20 negative PS 80 negative (itch)	Tolerated No allergic symptoms

Abbreviations: DK, Denmark; ND, Not done; PEG, polyethylene glycol; PS, polysorbate; US, United States.

^aSkin testing at time of PEG allergy diagnosis, Gentofte Hospital, Denmark: All patients were skin prick tested with PEG 300 (1g/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 ref 6)

^bSkin 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) (SIGMA-Aldrich), PEG 3350 (using 17g 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) (SIGMA-Aldrich), Poloxamer 407 (0.1 mg/ml, 1

mg/ml, 10 mg/ml) (SIGMA-Aldrich), triamcinolone acetonide containing polysorbate 80 (0.1 mg/ml and 1 mg/ml) and methylprednisolone acetate containing polyethylene glycol 3350 (0.04 mg/ml, 0.4 mg/ml and 4 mg/ml). Intradermal testing with methylprednisolone acetate was only used if SPT testing was negative across all reagents (see ref 7).

^cSPT: A positive reaction was defined as a wheal diameter of > 3 mm. IDT: A positive reaction was defined as a wheal $\geq$ saline wheal+3 mm and flare.

^dSPT prior to vaccination was performed with the three 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).