Successful Covid-19 vaccination of a patient with hypersensitivity against polyethylene glycol and polysorbate

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Soon after the mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna) have been approved for vaccination against Covid-19 infection, several cases of anaphylaxis were described in association with their application, with the excipient polyethylene glycol (PEG) suspected as elicitor [1-4]. Subsequently, administration of Covid-19 vaccines containing PEG or the cross-reactive polysorbate has been cautioned against in people with known hypersensitivity against PEG. We report a 59-year-old female patient with anaphylactic reactions against PEG-containing drugs, showing positive skin tests against PEG, polysorbate and different Covid-19 vaccines as well as positive basophil activation tests (BAT) against PEG and various Covid-19 vaccines. Interestingly, vaccination with the Covid-19 vaccines Janssen® (Ad26.COV2.S; Janssen-Cilag) and Comirnaty® (BNT162b2; BioNTech), containing polysorbate or PEG, respectively, were well tolerated.

History showed that she developed generalized itching, swelling of the hands and feet, laryngeal edema and acute dyspnea after oral administration of Moviprep® (containing PEG, molecular weight (MW) of 3,350). Symptoms quickly resolved after intravenous treatment with prednisolone and an antihistamine by her general practitioner. Likewise symptoms occurred a few minutes after the administration of several drugs (ibuprofen, pantoprazole, novamine sulfone, and oxycodone), of which the original compositions were unknown. Furthermore, she experienced a similar reaction about 4 hours after taking Magnesium Verla® (containing, among others, PEGs with MW of 6,000 and 35,000 as excipients). Allergy diagnostics comprised both laboratory (total IgE 419 kU/l, specific IgE for latex, ethylene oxide,

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disinfectant, alpha-gal all CAP class 0, tryptase 4.19 μg/l) and skin tests. Skin prick tests with PEG 6,000 (1:100 dilution) and PEG 3,350 (1:10) as well as intradermal tests (IDT) with polysorbate 80 (1:100) revealed positive results (table 1; **supplementary fig. 1a**). Furthermore, IDT with Vaxzevria® (AstraZeneca) and Covid-19 vaccine Janssen® (both containing polysorbate 80) but not with Comirnaty® (all 1:100) showed positive results. To further examine these findings, BAT were conducted, which showed positive results to PEG 2,000 (lipid component), Comirnaty® and Vaxzevria® (**supplementary fig. 1b**). Thus, taking into account her history of anaphylactic reactions to PEG-containing drugs, the positive skin tests and BAT results (**table 1**), diagnosis of PEG hypersensitivity with immunologic cross-reactivity against polysorbate 80 was assumed.

PEG is found either as an active ingredient in laxatives (making use of its hygroscopic activity) or as a stabilizing or solubilizing additive in various drugs, including the Covid-19 vaccines Comirnaty® and Spikevax® [5-9]. Polysorbate 80, which is an excipient in a variety of drugs including the Covid-19 vaccines Janssen® and Vaxzevria®, is a potential cross-allergen. Thus, vaccination with one of the currently available four Covid-19 vaccines entailed an unpredictable risk of anaphylaxis for our patient. However, trying to attain protection against Covid-19 infection we decided in mutual agreement with the patient to perform fractionated vaccination with the polysorbate-containing Covid-19 vaccine Janssen® (Ad26.COV2.S). Thirty minutes after receiving 4 mg of dimetinden maleate i.v. as premedication, the patient was administered 0.05 ml (10%), 0.15 ml (30%) and 0.3 ml (60%) of the vaccine (cumulative volume 0.5 ml) with 10 minutes between the respective applications, which was well tolerated. Encouraged by this outcome, we decided to perform a recommended booster vaccination 6 months later with Comirnaty®, containing PEG as a lipid component. Following the same injection scheme, the fractionated i.m. vaccination was applied without any adverse reaction (**table 1**).

Our results are noteworthy in regard of several aspects. First, they confirm data from a study by Wolfson et al. showing that PEG- or polysorbate-containing Covid-19 vaccines can be safely applied in most patients suggestive of being allergic against these excipients due to their history and positive skin tests [10]. Moreover and extending beyond these investigational findings, we here show that this holds also true for positive skin and in-vitro test results with the vaccine itself. This outcome questions the

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significance of skin and in-vitro test results with PEG, polysorbate and the vaccines containing these additives. However, as the vast majority of both patients investigated by Wolfson et al. [10] and individuals tested in our department during the last 11 months showed negative skin tests for PEG of various molecular weight, polysorbate 80 and the different Covid-19 vaccines we do not believe the findings in our patient to resemble unspecific, irritative test results. Premedication, dosage, formulation, route and/or the way of application of the vaccine might affect the tolerability. In conclusion, we suggest to consider Covid-19 vaccination also in patients with potential hypersensitivity against the vaccine or their excipients, giving proper attention to certain safety measurements like preventive premedication with antihistamines, emergency monitoring and fractionated administration.

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Conflict of interest

All authors declare there are no conflicts of interest.

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Table. Results of different tests with drug excipients or Covid-19 vaccines.

substance [MW]	SPT reactivity [mm]			IDT reactivity [mm]	BAT	Challenge
	1:100	1:10	undiluted	1:100		
Excipients						
polysorbate [80]	N/P	neg.	neg.	**6**	neg.	N/P
PEG [400]	N/P	N/P	neg.	N/P	N/P	N/P
PEG linear [2,000]	neg.	neg.	neg.	neg.	neg.	N/P
PEG lipid component [2,000]	N/P	N/P	N/P	N/P	**pos.**	N/P
PEG [3,350][1]	N/P	**5**	N/P	N/P	N/P	N/P
PEG [6,000]	**5**	N/P	N/P	N/P	neg.	N/P
COVID-19 vaccines						
BNT162b2 Comirnaty®	neg.	neg.	neg.	neg.	**pos.**	**neg.**[2]
AZD1222 Vaxzevria®	neg.	neg.	neg.	**7**	**pos.**	N/P
Ad26.COV2.S Janssen®	neg.	neg.	neg.	**10**	neg.	**neg.**[3]

BAT: basophil activation test; IDT: intradermal test; N/P: not performed; SPT: skin prick test

[1] includes tests with Movicol® and Macrogol®

[2] tolerated titrated vaccination (35%/65%)

[3] tolerated titrated vaccination (10%/30%/60%)