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Hypersensitivity to polyethylene glycol (PEG)

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Abstract: The need for mass population vaccination against Covid-19 poses a public health problem. Allergic symptoms occurring after the 1st dose of the vaccine may result in resignation from the administration of the 2nd dose. However, the majority of patients with mild and/or non-immediate symptoms may be safely vaccinated. The only absolute contraindication to administration of the vaccine is an anaphylactic reaction to any of its ingredients. Polyethylene glycol (PEG), widely used as an excipient in various vaccines, is considered the primary cause of allergic reactions associated with administration of Comirnaty (Pfizer/BioNTech) and Covid-19 Vaccine (Moderna) vaccines. However, hypersensitivity to PEG reported to date seems very rare, considering its widespread use in multiple everyday products, including medicines and cosmetics. In the paper, current literature data describing mechanisms of hypersensitivity reactions to PEG, their clinical symptoms and diagnostic capabilities are presented. Undoubtedly, the issue of hypersensitivity to PEG warrants further research, while patients with the diagnosis require individual diagnostic and therapeutic approach.

Keywords: Polyethylene glycol, PEG, hypersensitivity to PEG, Covid-19 vaccine.

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Introduction — hypersensitivity reactions after vaccination against Covid-19

The need for mass population vaccination against Covid-19 poses a public health problem. Allergic symptoms occurring after the first dose of the Covid-19 vaccine may result in resignation from the administration of the second dose. In a report

published by one of U.S. clinical centers in prestigious *JACI: In Practice* journal, authors specified than among 61,057 healthcare employees, 2.5% reported allergic reactions after the first dose of the vaccination. After an allergy consultation, 97% members of this group decided to receive the second dose and did not sustain any severe reactions. Self-reported severe allergic symptoms after administration of the first dose were rare and associated with a markedly increased risk of incomplete vaccination cycle among healthcare employees. However, the majority of patients with mild and/or non-immediate symptoms may be safely vaccinated. The only absolute contraindication to administration of a vaccine is an anaphylactic reaction to any of its ingredients [1]. Therefore, patients should be individually assessed to confirm or rule out the anaphylaxis diagnosis and provide the possibility for the challenge with the vaccine to ensure completion of the vaccination cycle [2].

According to U.S. data, between December 14 and December 23, 2020, 21 cases of anaphylaxis among those who were administered the Pfizer-BioNTech vaccine were reported to the Vaccine Adverse Event Reporting System (Fig. 1) [3]. And after an administration of the Moderna vaccine (between December 21, 2020, and January 10, 2021), 10 cases of anaphylaxis were reported (Fig. 2) [4].

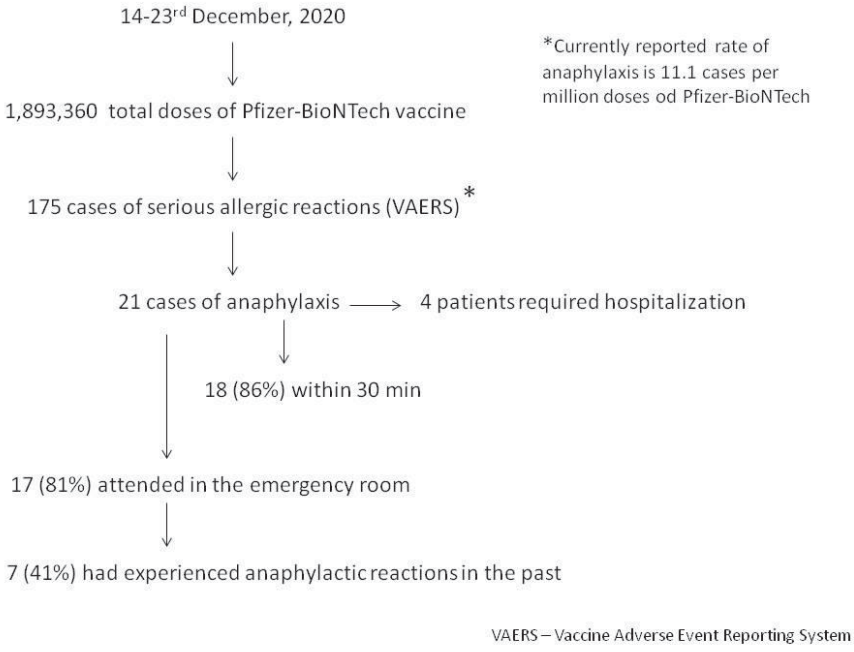

Fig. 1. Allergic reactions including anaphylaxis after the first dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020 [3].

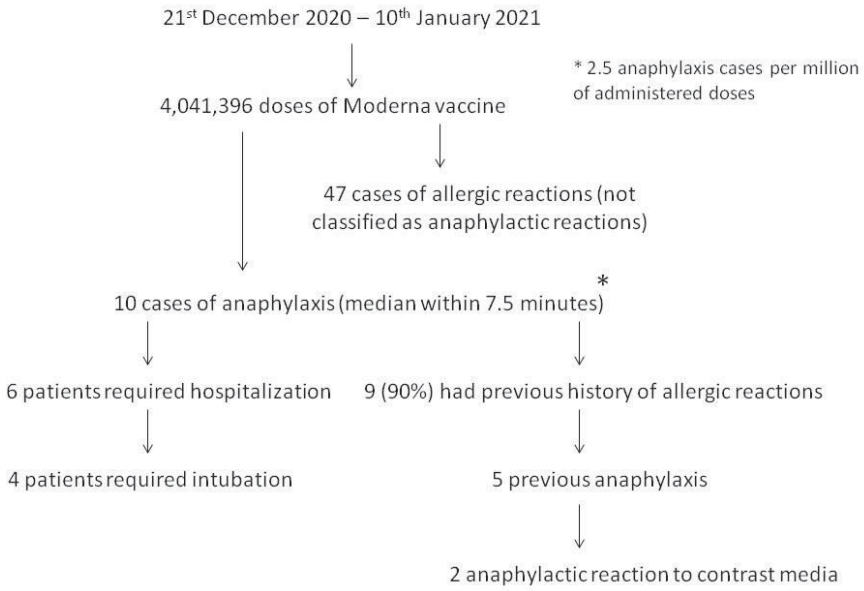

Fig. 2. Allergic reactions including anaphylaxis after the first dose of Moderna COVID-19 vaccine — United States, December 21, 2020–January 10, 2021 [4].

In Poland, for instance, from December 27, 2020 to July 31, 2021 the total number of 34,463,736 doses of Covid-19 vaccines were administered and 13,862 adverse post-vaccination reactions were registered, that is approximately 0.05%. Overall, 260 allergic reactions after mRNA vaccines were reported, including 241 ones after Comirnaty vaccine and 19 ones after Moderna. According to the report by the National Institutes of Public Health, 53 anaphylactic shocks, 51 ones after Comirnaty vaccine and 2 ones after Moderna, were recorded [5].

Extreme predominance of anaphylactic reactions was found in female subjects for both mRNA-1273 and BNT162b2 vaccines (100% for mRNA-1273 vaccine and 90% for BNT162b2 vaccine). Although the vaccines were administrated to a higher percentage of women than men at the time of the analyses (61% for mRNA-1273 vaccine, and 64% for BNT162b2 vaccine), this fact cannot explain the high predominance of anaphylactic reactions among women [6].

Although culprit or culprits of the allergic reactions have not been identified to date, vaccines' excipients have been recognized as potential compounds with the ability to elicit allergic reactions. And among others, polyethylene glycol (PEG) is

such an example [6]. In fact, PEG is considered the primary cause of post-vaccination allergic reactions associated with administration of Comirnaty (Pfizer/BioNTech) and Covid-19 Vaccine (Moderna) vaccines [7]. Some authors suggest that administration of the second dose following suspected anaphylactic reaction to the first dose may be safely achieved in controlled allergy clinic setting, in patients without known allergy to PEG [2].

Thus, the aim of our narrative review was to summarize the potential mechanisms of PEG-induced allergy.

Chemical structure, properties and application of PEG

Polyethylene glycol, belonging to group of synthetic polymers of ethylene oxide, has general formula $H–(O–CH2–CH2)_n–OH$. Polyethylene glycol is colorless, has hygroscopic properties and has no specific odor. In room temperature it may have the form of liquid or solid body, depending on its molecular weight. The length of polymer chain, and therefore the size of molecules, varies significantly from several (e.g. PEG-6) to many thousand (e.g. PEG-25M) units of ethylene glycol in the molecule. The substance is available in the market under various names, such as: PEG (poly(ethylene glycol)), PEO (poly(ethylene oxide)) or POE (polyoxyethylene). Pegylation, an attachment of active ingredients to PEG by means of various chemical bonds (covalent, non-covalent, amalgamation), is widely used in the pharmaceutical industry to stabilize active ingredients, to mask its antigenic properties, and to reduce immunogenicity of medicinal products [8, 9].

PEGs are used, among other things, as solvents, emulsifiers, and agents increasing the viscosity of liquid cosmetics and medications. PEG with a molecular weight of 3350 Da (PEG 3350) is approved from 1980 as a laxative for preparation of intestines before colonoscopy procedure. PEG with a molecular weight of 3350–6000 Da is commonly used as an excipient in liquid or solid medications, mostly in film coated tablets, gels for external use and injectables, including glucocorticosteroids [10]. Table 1 contains a list of examples of PEG-containing medications, except vaccines. PEG with a molecular weight of 2000 Da (PEG 2000) is added to vaccines to prevent premature degradation of nanoparticles by the mononuclear phagocyte system. Due to its hygroscopic properties, it facilitates penetration of particles to the cytosol. It is also used as an adjuvant with immunogenic potential [11].

Table 1. A list of examples of PEG-containing medications, except vaccines.

Macrogol	Example of drug	Drug category	Route of administration
400	Tramundin (tramadoli hydrochloridum)	Analgesic	Oral
	Amoxicillin + clavulanic acid Aurovitas	Antibiotic	
	Axyven (venlafaxinum)	Antidepressive	
	Cezarius (levetiracetam)	Antiepileptic	
	Atarax (hydroxyzini hydrochoridum) (25 mg)	Antihistamine	
	Avasart Plus (amlodypinum + valsartanum)	Antihypertensive	
	Lakea (losartanum kalicum)		
	Teveten (eprosartanum)		
	Ridlip (rosuvastatinum)	Antilipemic	
	ApoTiapina (quetiapinum) (25 mg & 100 mg)	Antipsychotic	
	Egolanza (olanzapinum)		
	Combivir (lamivudine + zidovudine)	Antiretroviral	
	Tussal Antitussicum (dextromethorphan)	Antitussive	
	Proursan (acidum ursodeoxycholicum)	Choleretic	
	Ulgix Laxi (docusatum natricum)	Laxative	
400 & 3350	Bactroban (mupirocinum)	Antibiotic	Topical
	Kaletra (lopinavir + ritonavir)	Antiretroviral	Oral
400 & 6000	Avamina (metformin)	Anti-diabetic	
400 & 8000	Falcimar (atovaquonum + proguanili hydrochloridum)	Antimalarials	
	Malarone (atovaquonum + proguanili hydrochloridum)		
1450	Wellbutrin XR (bupropion)	Antidepressant	Oral
	Afrin ND (oxymetazolinum)	Nasal decongestants	Nasal

Table 1. cont.

Macrogol	Example of drug	Drug category	Route of administration
1500 & 3000	Lidoposterin (lidocainum)	Anesthetic	Topical
3000	Simvachol (simvastatinum) (10 mg & 20 mg)	Antilipemic	Oral
3350	Xarelto (rivaroxabanum)	Anticoagulant	
	Xigduo (dapagliflozin + metformin)	Anti-diabetic	
	Invokana (canagliflozin)		
	Janumet (sitagliptin + metformin)		
	Steglatro (ertugliflozin)		
	Briviact (brivaracetam)	Antiepileptic	
	Voriconazol Polpharma (voriconazolum)	Antifungal	
	Elestar HCT (amlodipinum + hydrochlorothiazidum + olmesartanum medoxomil)	Antihypertensive	
	Simvachol (simvastatinum) (40 mg)	Antilipemic	
	Bosulif (bosutinib)	Antineoplastic	
	Cotellic (cobimetinib)		
	Tagrisso (osimertinib)		
	Zelboraf (vemurafenib)		
	Clarzole (letrozole)	Antineoplastic/ Aromatase Inhibitor	
	Abrea (acidum acetylsalicylicum)	Antiplatelet	
	Agregex (clopidogrelum)		
	Atripla (efavirenz + emtricitabine + tenofovir disoproxil)	Antiretroviral	
	Descovy (emtricitabine + tenofovir alafenamide)		
	Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate)		
	Maviret (glecaprevir + pibrentasvir)		

Macrogol	Example of drug	Drug category	Route of administration
	Viekirax (ombitasvir + paritaprevir + ritonavir)	Antiviral (treatment of Chronic hepatitis C)	
	Moderiba (ribavirinum)		
	Kalydeco (ivacaftor)	CFTR modulator (treatment of Cystic Fibrosis)	
	Orkambi (ivacaftor + lumacaftor)		
	Ocaliva (acidum obeticholicum)	Farnesoid X Receptor Agonists (treatment of Primary Biliary Cholangitis)	
	Xeljanz (tofacitinib)	Janus kinase inhibitors (treatment of Rheumatoid Arthritis)	
	Moviprep (acidum ascorbicum + macrogolum + kalium chloratum + natrium chloratum + natrium sulphuricum)	Laxative	
	Remidia (sildenafilum)	Phosphodiesterase inhibitors (treatment of Pulmonary Hypertension)	
	Sildenafil SymPhar (sildenafilum)	Phosphodiesterase inhibitor	
	Esogno (eszopiclonum)	Sedative-hypnotics	
	Recombinate (octocog alfa)	Antihemophilic factor	Parenteral
	Depo-Medrol (methylprednisoloni acetas)	Corticosteroid	
	Arcalyst (rilonacept)	Interleukin-1 (IL-1) blocker	
	Depo-Provera (medroxyprogesteroni acetal)	Progestogen	
4000	Axudan HCT (valsartanum + hydrochlorothiazidum)	Antihypertensive	Oral
	Dipperam HCT (amlodipinum + valsartanum + hydrochlorothiazidum)		

Table 1. cont.

Macrogol	Example of drug	Drug category	Route of administration
	Lorista H (losartanum + hydrochlorothiazidum)		
	Amlator (amlodipinum + atorwastatinum)	Antihypertensive, antilipemic	
	Fortrans (macrogolum + natrium sulphuricum)	Laxative	
4000 & 6000	Augmentin (amoxicillinum + acidum clavulanicum)	Antibiotic	
6000	Vendal retard (morphini hydrochloridum)	Analgesics (opiate)	
	Agastin (omeprazolum)	Antacid	
	Amylan (amoxicillinum + acidum clavulanicum)	Antibiotic	
	Ospen (benzathini phenoxymethylpenicillinum)		
	Azimycin (azithromycinum)		
	Amitriptylinum VP (amitriptylinum)	Antidepressive	
	Allertec WZF (cetirizini dihydrochloridum)	Antihistamine	
	Atarax (hydroxyzinum) (10 mg)		
	Avasar (valsartanum)	Antihypertensive	
	Betaloc ZOK (metoprololi succinas)		
	Valsacor (valsartanum)		
	Grofibrat S (fenofibratum)	Antilipemic	
	Sumamigren (sumatriptanum)	Antimigraine	
	Usual (acidum ursodeoxycholicum)	Choleretic	
6000 & 3350	Keppra (levetiracetamum)	Antiepileptic	
8000	Aleve (naproxenum)	Analgesics (NSAID)	
	Epigapent (gabapentinum)	Antiepileptic	
	Avedol (carvedilolum)	Antihypertensive	

Macrogol	Example of drug	Drug category	Route of administration
	Apo-Doperil (donepezili hydrochloridum)	Cholinesterase inhibitor (treatment of dementia)	
8000 & 2 000 000	Betmiga (mirabegron)	Beta-3 adrenergic agonists (treatment of overactive bladder)	
20 000	Spironol (spironolactonum)	Antihypertensive	
	Fenardin (fenofibratum)	Antilipemic	
Not specified	Ranexa (ranolazinum) (375 mg & 500 mg)	Antianginal	
	Fluoxetine Vitabalans (fluoxetinum)	Antidepressive	
	Epclusa (sofosbuvir + velpatasvir)	Antiviral agents (treatment of Chronic hepatitis C)	
	Harvoni (ledipasvir + sofosbuvir)		
	Oxycodone Vitabalans (oxycodonum)	Opioid analgesic	

Hypersensitivity reactions to PEG

Hypersensitivity to PEG reported to date seems very rare, considering its widespread use in multiple everyday products, including cosmetics and medicines. However, the issue becomes more and more significant due to the need for the universal use of Covid-19 vaccines that contain PEG 2000. It applies to mRNA vaccines, namely Comirnaty (BNT162b2) manufactured by Pfizer and BioNTech, and Spikevax (mRNA 1273) manufactured by Moderna.

The possibility of cross-hypersensitivity reaction between polyethylene glycol and other substances of structural similarity should be also taken into consideration. The structure of polysorbates is very similar to that of PEG. Therefore, there is a risk of cross-reaction between polyethylene glycol and Polysorbate 80 contained in viral vector Covid-19 vaccines: Vaxzevria (ChAdOx1 nCoV-19) manufactured by AstraZeneca and (Ad26.COV.2-S)] by Janssen [10, 11].

Mechanisms of hypersensitivity reactions to PEG

To minimize the risk of severe allergic reactions in vaccinated individuals, it is urgently required to understand the specific nature of severe allergic reactions reported, including underlying medical history of the individuals affected and mechanisms

involved [12]. Hypersensitivity reactions to PEG, both immediate-type and delayed-type reactions, occur irrespective to its molecular weight. Among immediate reactions, also a pseudo-allergy to PEG is described, which is associated with the complement system activation [13].

Immediate hypersensitivity to PEG

Mechanisms of immediate reactions are not completely understood. Some authors suggest that allergenicity of PEG correlates with its molecular weight. Most likely, PEG induces both specific (IgE-dependent), and non-specific (IgE-independent) response [14]. In the former case, specific IgE antibodies (sIgE) bond to receptors with high IgE affinity (FcεRI) on mastocytes and basophils. After bridging, that is bonding of two IgE molecules to one molecule of allergen (PEG in this case), various inflammatory mediators are released, such as histamine, serotonin, prostaglandins, leukotrienes, tryptases, proteases, etc. [15]. Literature data suggest that the majority of reactions may be IgE-dependent, though serum IgEs are not always detected. Wenande *et al.* confirmed IgE-dependent pathway activation in 37 patients with allergic reaction to PEG by means of skin tests, histamine release test and basophil activation test (BAT) [9, 16]. In other study, Wenande *et al.* performed inhibition of histamine release test by means of previous incubation of patient's serum with omalizumab, which provided indirect evidence for the contribution of sIgE in immediate reaction to PEG [17] Stone *et al.*, for the first time, detected anti-PEG sIgE in sera from two patients with the immediate reaction to PEG contained in medications [10].

Recently, the role of the IgE-independent pathway associated with the complement activation (complement activation-related pseudoallergy, CARPA) in the development of PEG allergy was also demonstrated. CARPA involves activation of C3a, C4a, C5a complement fragments, called anaphylatoxins. Most likely, other mechanisms also play role in direct, IgE-independent, activation of mastocytes [9, 13].

The majority of studies concerning hypersensitivity to PEG described various substances conjugated with PEG, while there is lack of sufficient scientific data dealing with PEG as an independent antigen [10]. In recent years, cases of allergic reactions were reported, where PEG was confirmed as the causative factor. In 2016 review "Immediate-type hypersensitivity to polyethylene glycols: a review" 37 reported cases of PEG hypersensitivity from 1977 were identified [9]. Borderé *et al.* published a case of anaphylaxis after parenteral administration of a corticosteroid [18]. Wylon *et al.* reported a case of Caucasian patient experiencing recurrent severe allergic reactions to several medications. Extensive diagnostic workup including skin prick tests (SPTs), intradermal tests (IDTs) and a double-blind oral challenge was performed to identify the trigger of anaphylaxis. In the case presented, hypersensitivity to PEG as an additive was confirmed by IDT suggesting an immunoglobulin E-dependent mechanism as the

cause of the reaction [19]. Cox *et al.* described 6 cases of acute hypersensitivity to PEG. Accurate diagnoses in these cases posed a challenge, and although the triggering agents differed, PEG was demonstrated to be the common culprit. The diagnosis was based on th high index of suspicion leading to the focused clinical history, supported by skin tests with PEG solutions to demonstrate sensitization [20].

We do not have a reliable diagnostic tool to assess IgE-dependent hypersensitivity to PEG. The only common factor in all reported case reports was that skin testing did not always produce wheal and flare in subjects with true PEG allergy [21]. Pickert *et al.* described a case of 24-year-old woman who developed anaphylaxis following administration of PEG-containing medications. SPTs involving these medications were positive only for PEG with a high molecular weight (PEG 6000) and negative for PEG 400 and PEG 2000. This case confirmed the hypothesis that an immediate-type reactivity increases together with an increased molecular weight of PEG and a systemic exposure for PEG may still result in anaphylaxis despite a negative result of the skin test for PEG of a lower molecular weight. Bruusgaard-Mouritsen *et al.* evaluated the results of SPT on PEGs of different molecular weights. They first performed tests with lower molecular weight PEGs (PEG 300, 3000, 6000) and then with PEG 20 000, in progressively higher concentrations. In ten patients with previously diagnosed PEG allergy, SPTs with PEG were performed twice with an interval of 26 months. Patients with a longer interval from the first diagnostic tests had negative SPT results on lower molecular weight PEGs and positive results on a higher weight PEG (PEG 20 000). The authors of this publication concluded that SPT reactivity to PEG may decrease over time [22]. Moreover, the patient underwent skin tests with BNT162b2 vaccine (BioNTech/Pfizer) that contains PEG 2000, and SPT was negative, while IDT was positive. During performance of the IDT the patient developed anaphylaxis. That indicated higher sensitivity of IDT, and also higher reactivity of PEG conjugated with nanoparticles contained in the vaccine [23]. Currently, there is no commercially available PEG 2000 reagent for skin tests. However, the use of higher molecular weight PEG tests is associated with higher sensitivity in patients with PEG allergy, and therefore, we would not expect false negative results when testing with PEG 3350 [2].

In study conducted by Wolfson *et al.*, eighty patients with a reported allergic reaction to the first-dose of mRNA Covid-19 vaccine underwent excipient skin tests. Of those, 14 (18%) had positive skin tests for PEG. Skin test results were not associated in any way with the tolerability of the second dose in patients with immediate or delayed reactions. Of the 70 patients who received the second mRNA Covid-19 vaccine dose (88%), 62 had either no reaction or mild reaction managed with antihistamines (89%), but 2 patients required epinephrine treatment. Three patients with positive PEG 3350 (methylprednisolone) intradermal tests tolerated the second-dose mRNA Covid-19 vaccination well. More data are needed to assess usefulness of skin prick tests with PEG (MiraLAX) in evaluating patients with mRNA Covid-19 vaccine anaphylaxis [24].

Stone *et al.* investigated IgE-dependent mechanism of PEG allergy performing skin test with medications, after which patients experienced allergic reactions, that is methylprednisolone and laxatives used for preparation before the colonoscopy procedure. The first patient developed allergy to PEG 3350 when using products for preparation for colonoscopy and anaphylaxis after injection of methylprednisolone acetate into cervical spine as a treatment of radicular pain due to intervertebral disc bulge. He experienced another anaphylactic reaction after drinking PEG 3350-containing Gavilyte G before colonoscopy. In this patient, skin prick and intradermal tests with methylprednisolone acetate were positive. On the other hand, he tolerated well oral challenge with low-molecular weight PEG 3000. Another patient, with long-term workplace exposure to glycol-containing hydraulic fluids, developed anaphylactic reaction after epidural injection of methylprednisolone acetate product containing PEG 3350. Skin prick and intradermal tests with methylprednisolone acetate were negative, while oral challenge with PEG 3350 caused the development of anaphylactic reaction [13].

The lack of proven reliability of PEG skin tests suggests that clinicians should exercise caution when making decisions based on "positive" or "negative" results, because there is no positive predictive value for a non-standardized allergen testing agent. In such circumstances, the only factor that could be established would be a positive or negative likelihood ratio, but even that is lacking for PEG skin tests [21]. In the case of such diagnostic challenges, we are able to perform basophil activation test (BAT) that assesses the activation ability of basophils collected from the patient after exposure to sensitizing allergen. Basophils, affected by chemoattractants released by other cells, may migrate to tissues involved with inflammatory processes. BAT enables the diagnosis of causes of anaphylactic reactions, including reactions to medications. The test enables avoiding challenge tests with the above-mentioned factors that may be risky for a patient [25]. To date, BAT has been used mostly in testing immediate hypersensitivity reactions to neuromuscular blocking agents (NMBA), antibiotics (β-lactam ones and fluoroquinolones) and iodine contrast media (ICM). Sensitivity of BAT in diagnosing allergies to medications usually varies from 50% to 60%, while specificity is 80% [26]. Due to the need for diagnosis of anaphylactic reactions after Covid-19 vaccines, BAT is also proposed for that purpose. Positive results of BAT for PEG have been described, but the method warrants further research and validation [13].

Delayed hypersensitivity to PEG

In a type IV hypersensitivity reaction, an antigen is presented to Th1 cells by dendritic cells, which leads to activation of macrophages and cytotoxic T lymphocytes. Cytokines, such as IL-1β, TNF, GM-CFS, are important mediators in type IV reaction. Chemokines are responsible for the inflammatory infiltration. Maximum intensity of the reaction is achieved 24–48 after exposure to the antigen [15]. Exposure to low-

molecular weight PEG more frequently leads to the development of delayed-type allergy. Likely, the cause of this phenomenon is an enhanced percutaneous absorption of a low-molecular weight PEG. Thus, the reaction should most likely occur after topical application [14, 27].

Braun *et al.* reported a group of 40 patients with contact allergy to nitrofurazone-containing topical products. Twelve of them had allergy to PEG, but only three developed allergic contact dermatitis (ACD). All the patients used previously nitrofurazone-containing topical products [28]. Bajaj *et al.* described 8 patients with symptoms of contact allergy following the use of topical medications and only 5.3% of them had confirmed contact allergy to PEG [29]. In a more recent study to investigate the prevalence of PEG-induced ACD in 836 patients, 4.2% had positive patch tests for PEG [30].

Currently, it is possible to diagnose contact allergy by means of patch tests with polyethylene glycol 400 (PEG 400) only [27]. Caballero and Quirce pointed out that it would be very useful to provide patients with the PEG allergy with a list of commercial PEG-containing products as well as alternative list of products without the allergenic hapten [31].

Conclusions

Recently, medical doctors in out-patient allergy clinics happen to see patients disqualified from Covid-19 vaccination in mass vaccination centers, against published guidelines. Patients diagnosed with allergic reactions after the first vaccination dose are more and more frequently referred, as they pose a diagnostic and therapeutic challenge in the case of two-dose vaccines. Contrary to mild or delayed reactions, anaphylaxis after the first dose of mRNA vaccine provides contraindication to the second dose administration of the same type of vaccine. PEG is considered the most common cause of post-vaccination anaphylactic reactions in the case of Comirnaty (Pfizer/BioNTech) and Covid-19 vaccine (Moderna).

Clinical manifestations of PEG allergy are often dramatic. Improved awareness of their clinical presentation, clear product labelling and a standardized nomenclature are needed to ensure a timely diagnosis of PEG allergy, and thus to prevent repeated anaphylactic reactions with severe impact on patients' lives [32]. Undoubtedly, any hypersensitivity reaction should be assessed individually, also in terms of allergy to PEG, which may influence further therapeutic decisions regarding not only Covid-19 vaccination in a given patient.

Conflict of interest

None declared.

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