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Polythylene glycol severe allergy and SARS-CoV-2 vaccines: usefulness of testing with PEG 1500 extract

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Key words

Anaphylaxis; COVID-19 vaccine; drug allergy; PEG allergy; skin testing.

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Impact statement

First study describing allergy work-up testing with PEG 1500 extract in the scope of SARS-CoV-2 vaccination. The new algorithm designed revealed usefulness for diagnosis of severe PEG allergy, contraindicating PEG-containing vaccines.

Summary

Background. *Polyethylene glycol (PEG) is being used for first time as an excipient for mRNA anti-SARS-CoV-2 vaccines containing PEG 2000, highlighting it as a potential cause of anaphylaxis.* ***Methods.*** *We evaluated 126 patients with moderate-high risk of allergy to SARS-CoV-2 vaccines referred to our department from March-December 2021. Skin tests were performed with PEG 1500 extract (Roxall), using a stepwise approach, with readings at 30 minutes: prick tests with 0.1%, 1% and 10% concentrations; if negative, intradermal tests with 0.0001%, 0.001% and 0.01% concentrations. The same protocol was applied to 5 healthy controls.* ***Results.*** *Six patients had positive immediate intradermal tests with PEG 1500, all with severe PEG allergy: one with a near-fatal anaphylaxis after glucocorticoid injection containing PEG 3350 and five with systemic allergic reactions after mRNA vaccines containing PEG 2000 (Pfizer-BioNTech or Moderna). One patient developed anaphylaxis during intradermal test. These six patients were negative to polysorbate 80. The remaining 120 patients had negative tests to PEG 1500; seven had positive tests to polysorbate 80. All controls had negative tests.* ***Conclusions.*** *To our knowledge this is the first study describing the allergy work-up testing with PEG 1500 commercial extract in the scope of SARS-CoV-2 vaccination. The algorithm designed for skin tests revealed to be a useful tool. Severe PEG allergy was diagnosed in 5% of patients, contraindicating PEG-containing vaccines. PEG allergy was excluded in one hundred patients that afterwards took SARS-CoV-2 vaccines containing PEG 2000. Investigation should be conducted in specialized drug allergy centers.*

Introduction

Polyethylene glycol (PEG), also called macrogol (E1521), is a hydrophilic polymer with a variable molecular weight (MW) that ranges from 200 to 35,000 g/mol which is widely used in several pharmaceutical products, including drugs and cosmetics (1).
Allergy to PEG is rare, although its prevalence is unknown (1-3). For a long time, PEG was assumed to be a non-immunogenic polymer which led to underreported allergy (2, 4). The immunological mechanisms underlying PEG anaphylaxis are not clear, but an Immunoglobulin E (IgE)-mediated mechanism has been suggested (1, 2, 5-9).
The different MW of PEG alter the absorption process through the different routes of exposure (oral, intramuscular, intra-articular, intravenous and cutaneous) (1). This seems to have implications on the sensitization process and the severity

of the reactions (1, 9). Most cases of proven hypersensitivity to PEG described in the literature were caused by laxatives and bowel preparations for colonic procedures (*e.g.*, Miralax®, Moviprep®, Klean-Prep® or Movicol®, containing PEG 3350) or injectable depot-steroids formulations (*e.g.*, Depo-Medrol® or Solu-Medrol®, containing PEG 3350) (1, 3, 6, 7, 9-11). The clinical manifestations can vary from mild systemic reactions to life-threatening anaphylaxis and patients often present with repeated systemic allergic reactions (SAR) to structurally different drugs containing PEG (7, 9-11). Patients may also report immediate skin symptoms on exposure to skin care products (1, 7).

A few cases of anaphylaxis were later proven to be hypersensitivity to PEG by skin tests (ST) (4-6, 11-13). The diagnostic work-up for PEG allergy is not standardized and there are many different protocols and extracts being used for ST (1, 8, 9, 11, 14, 15). The most common protocol consists of a panel of skin prick tests (SPT) with different MW PEG, from low to high (1,16). Systemic reactions, including anaphylaxis, have been reported during SPT and intradermal tests (IDT) (1, 6, 8, 11, 13, 17-19).

Recently, with the advent of messenger ribonucleic acid (mRNA)-based vaccines for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), PEG began being used as a stabilizer for the nanomedicine formulations, which demonstrated to be crucial to maintain the colloidal stability of the nanoparticles in biological fluids and to reduce their uptake by filter organs (1, 2, 4, 20). PEG is being used for the first time as an excipient in the mRNA anti-SARS-CoV-2 vaccines containing PEG 2000 from Pfizer-BioNTech and Moderna (1, 2, 10, 21, 22).

In spite of the efficacy and safety demonstrated in phase-III clinical trials, 4.7 and 2.8 cases of anaphylactic reactions per million doses administered have been registered during the first two months of the Coronavirus disease 2019 (COVID-19) vaccination campaign with the Pfizer-BioNTech and the Moderna vaccines, respectively (23). PEG was proposed as the main suspect for these anaphylactic reactions to SARS-CoV-2 vaccines (1, 8, 10, 13, 20, 22, 24).

Although in vaccines PEG 2000 is used, this is not commercially available as an extract for allergy testing. Until the present time, the only commercial extract available in the market is PEG 1500.

To date, although other mRNA SARS-CoV-2 vaccines have been developed worldwide (1, 25, 26), Pfizer-BioNTech and Moderna vaccines are the only two mRNA vaccines approved for human use in Europe and in the United States, respectively by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Anaphylaxis following mRNA SARS-CoV-2 vaccines is still rare (7.91 to 11.1 cases per million doses administered have been reported), although it is about 10 times higher than for other vaccines (1, 8, 27). The continued global exposure to mRNA SARS-CoV-2 vaccines increased the number of patients suspected to be allergic to PEG over the past two years and raised awareness on this hidden allergen.

This study aimed to assess the usefulness of ST performed with the PEG 1500 commercial extract for the allergy work-up of patients with suspected PEG allergy in the scope of SARS-CoV-2 vaccination.

Materials and methods

During a 9-month period (March to December 2021), we evaluated 126 patients with moderate to high risk of allergy to SARS-CoV-2 vaccines referred to our Allergy Department. The sample selection was carried out by a detailed symptoms description plus using the criteria for defining moderate to high risk of allergy to SARS-CoV-2 vaccines, adapted from Banerji *et al*. (14), which are summarized in **figure 1**. Clinical data and circumstances of the reaction were collected from clinical files.

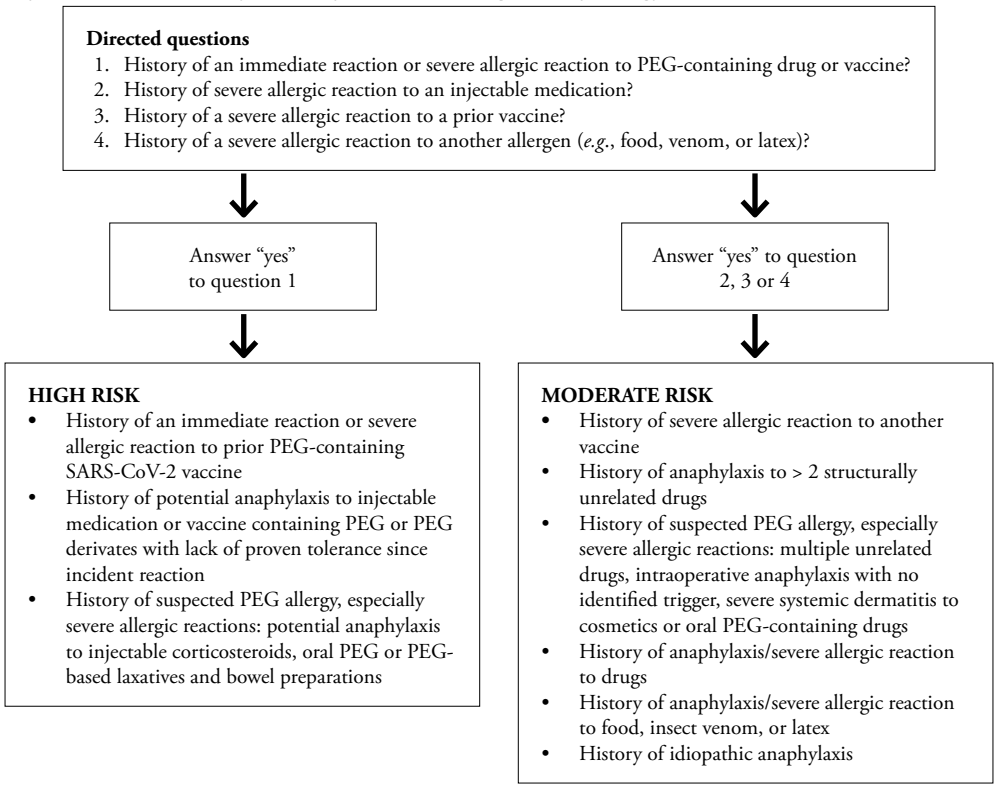
ST were performed with PEG 1500 extract (Roxall, Hamburg, Germany), always using the same methodology and by the same allergists, with experience in recognition and management of SAR. Adrenaline and other appropriate medication and resuscitation equipment were always available during the execution of the tests.

An allergy diagnostic work-up protocol for ST using the commercial extract PEG 1500 in a stepwise approach was designed (**figure 2**), as following: 1) SPT were the first step of investigation, and were performed using increasing concentrations of 0.1%, 1% and 10%, with readings at 30 minutes (according to manufacturer's instructions); 2) if SPT were negative, IDT were performed with 1/10 dilution (0.01%), except in cases of SAR where dilutions 1/1,000 and 1/100 were used beforehand (adapted from previous publication by Sellaturay *et al.* using PEG 20000) (11). The IDT were prepared every day, and were carried out with increasing dilutions, until the appearance of a positive skin response, or until reaching the maximum non-irritant concentration recommended (0.01%). Immediate IDT readings were made at 30 minutes and delayed readings at 24 hours.

ST were performed at least 4 weeks after the clinical reaction and were carried out on the volar surface of the forearm, according to the published European Network of Drug Allergy guidelines (28). Histamine (10 mg/mL) and 0.9% saline solutions were used as positive and negative control for SPT, respectively. SPT were considered positive if the wheal had a mean diameter of at least 3 mm (with negative response to the negative control). IDT involved the injection of 0.02-0.05 mL of the solution and were considered positive if the size of the initial marked wheal increased more than 3 mm in diameter (28).

All patients were fully informed about the procedures (risks and possible adverse reactions) and all of them signed a written in-

Figure 1 *- Criteria for risk assessment definition of moderate to high risk of allergy to SARS-CoV-2 vaccines.*



Adapted from Banerji *et al.* (14) and from Ortega-Rodríguez *et al.* (20).

formed consent form before ST according to the Helsinki Declaration.

In order to complete the study of the patients in the scope of SARS-CoV-2 vaccination, whenever needed, ST were also performed with polysorbate 80. The criterion was used whenever patients had not previously tolerated vaccines containing polysorbate 80 (*e.g.*, influenza vaccine or pneumococcal 13-valent vaccine). ST with polysorbate 80 were performed using Prevenar 13 vaccine (Pfizer Europe, Bruxelles, Belgium) with 1/10 dilution in the SPT and 1/100 dilution in the IDT according to previously published guidelines (14), with readings at 15 minutes for SPT and 20 minutes for IDT, and delayed reading at 24 hours.

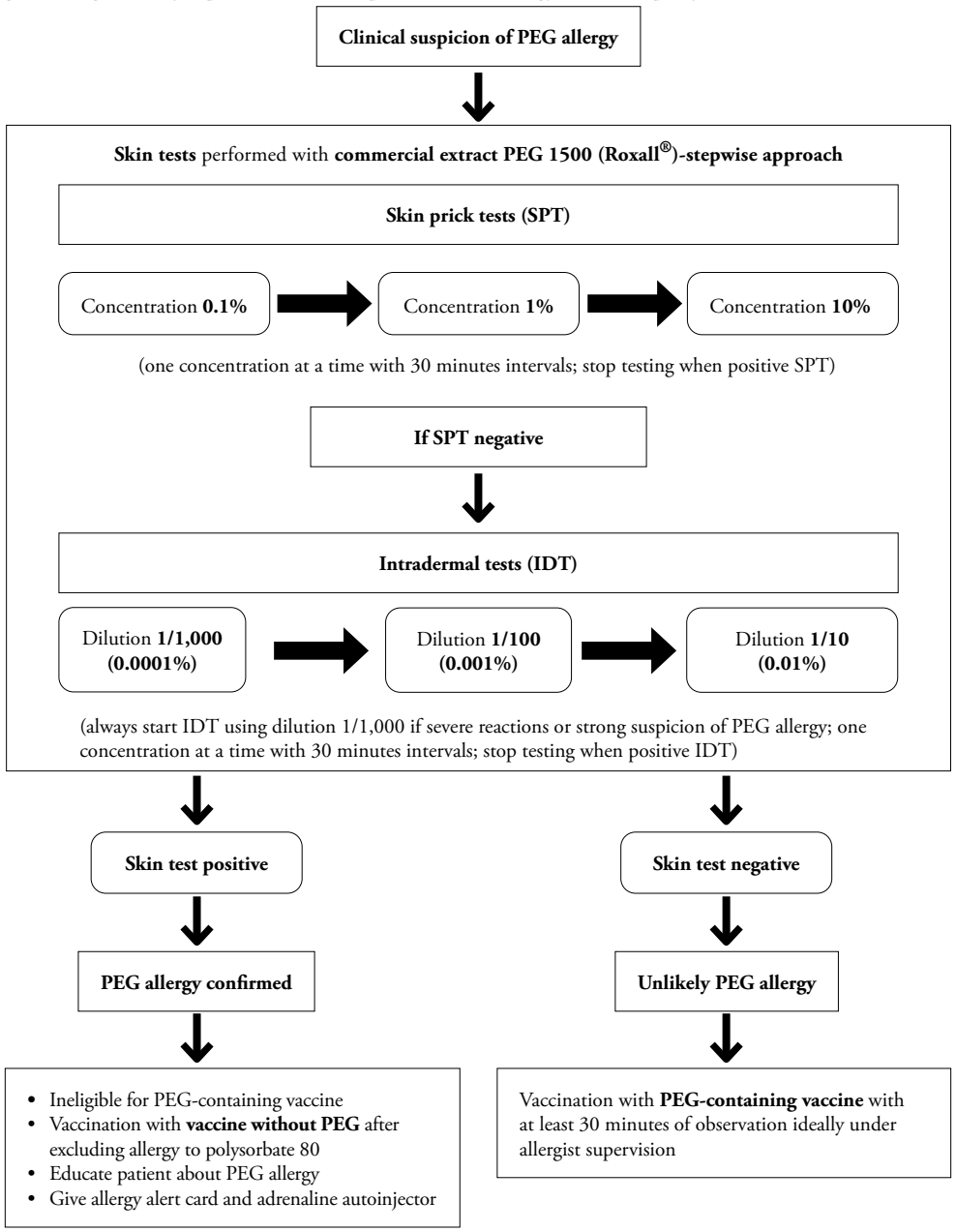
ST with PEG 1500 extract were performed using the same protocol to 5 healthy controls, who had previously received two doses of SARS-CoV-2 vaccines containing PEG 2000 (two from Pfizer-BioNTech and three from Moderna) without adverse reaction.

Results

The overall population studied is detailed in **table I**, regarding age, sex, reason for allergy work-up in the scope of SARS-CoV-2 vaccination, and personal history of allergic comorbidities. The 126 patients included had a mean age of 52.6 years (14 to 89 years), with a predominance of females (85%), and the majority (68%) had concomitant allergic diseases. The most frequent reason (30%) for allergy work-up pre-vaccination was a history of allergic reaction to vaccines: 21 patients to SARS-CoV-2 vaccines (Pfizer-BioNTech (n = 11), Moderna (n = 8), AstraZeneca (n = 1), and Johnson & Johnson (n = 1)), and 17 to other vaccines (Influenza (n = 6), Pneumococcal (n = 3), Tetanus (n = 5), Yellow fever (n = 1), Poliovirus (n = 1), and subcutaneous aeroallergen specific immunotherapy (n = 1)). The second reason (27%) for allergy work-up pre-vaccination was a history of allergic reaction to PEG-containing products: injectable corticosteroids (n = 7), intraoperative anaphylaxis (n = 6), severe systemic dermatitis to cosmetics and oral PEG-containing drugs (n = 10), other injectable or oral PEG-containing drugs (n = 10), and after bowel preparation containing PEG (n = 1).

Regarding the results of ST with commercial PEG 1500 extract, the 126 patients were divided in two groups: one group with positive ST, all with severe clinical allergy (severe PEG allergy patients), and one group with negative ST (patients non allergic to PEG).

Figure 2 - *Investigation algorithm for patients with suspected PEG allergy in the scope of SARS-CoV-2 vaccination.*



Adapted from Banerji *et al.* (14) and from Bruusgaard-Mouritsen *et al.* (16).

ST using PEG 1500 extract were negative in immediate and delayed reading of IDT in all healthy controls.

Severe PEG allergy patients

Six patients who performed the allergy work-up in the scope of SARS-CoV-2 vaccination had positive immediate IDT with commercial PEG 1500 extract, all with severe PEG allergy. These patients are detailed in **table II** regarding the clinical data and in **table III** regarding the allergy work-up.

The clinical manifestations include one near-fatal anaphylaxis immediately after intramuscular Depo-Medrol® (methylprednisolone acetate containing PEG 3350), and five SAR after mRNA vaccines containing PEG 2000 (Pfizer-BioNTech or Moderna). Three patients had an immediate SAR after the vac-

Table I – *Description of the 126 patients included in the study, regarding age, sex, reason for allergy work-up pre-vaccination SARS-CoV-2, and personal history of allergic comorbidities.*

Variables	
Age, mean ± SD	52.6 ± *15.1* years
< 18 years-old, n (%)	2 (2%)
18 to 64 years-old, n (%)	95 (75%)
≥ 65 years-old, n (%)	29 (23%)
Sex, ratio female/male	5.6/1
Female, n (%)	107 (85%)
Male, n (%)	19 (15%)
Reason for allergy work-up pre-vaccination, n (%)	126 (100%)
Prior allergic reaction to SARS-CoV-2 vaccine, n (%)	21 (17%)
Prior allergic reaction to other vaccine, n (%)	17 (13%)
Prior allergic reaction to products containing PEG, n (%)	34 (27%)
Severe multiple drug allergy, n (%)	17 (13%)
Idiopathic anaphylaxis, n (%)	1 (1%)
Anaphylaxis to drugs, food, venom or latex, n (%)	27 (22%)
Others (severe drugs or food allergy), n (%)	9 (7%)
Allergic comorbidities, n (%)	86 (68%)
Allergic rhinitis, or conjunctivitis, n (%)	75 (60%)
Asthma, n (%)	34 (27%)
Allergy to drugs, food, venom or latex, n (%)	22 (17%)
Chronic urticaria, atopic or contact dermatitis, n (%)	14 (11%)
Other*, n (%)	3 (2%)

SD: standard deviation; %: percent; *other immunoallergic diseases include two patients with eosinophilic esophagitis, and one women with systemic mastocytosis.

cine, including 2 patients with anaphylaxis: one 15 minutes after the first dose of Pfizer-BioNTech SARS-CoV-2 vaccine, requiring intramuscular adrenaline; and the other one, 2 minutes after the second dose of Moderna SARS-CoV-2 vaccine, with a biphasic reaction 24 hours later with diarrhea, oropharyngeal pruritus, palpebral and ear edema and cough. Two patients had delayed SAR: one with generalized pruritus and erythema which evolved to generalized urticaria within 48 hours after the first dose of Moderna SARS-CoV-2 vaccine; and the other had generalized pruritus and erythema that evolved to bullous exanthema in the first 24 hours after the second dose of Pfizer-BioNTech SARS-CoV-2 vaccine.

Regarding the allergy work-up, in these patients the diagnosis of severe PEG allergy was confirmed by ST, allowing the selection of a vaccine without PEG. For the patient with anaphylactic shock after Depo-Medrol®, the allergy work-up also included SPT and IDT with Depo-Medrol® and methylprednisolone, which were negative. Subsequently, an oral challenge with methylprednisolone was also performed, which was negative, excluding corticosteroid allergy. All patients with severe PEG allergy had negative ST to polysorbate 80.

Regarding the occurrence of systemic reaction during IDT with PEG 1500, one patient developed anaphylaxis during IDT with PEG 1500 at 0.01% (palmar and generalized itching, hands edema, nausea, generalized erythema, cough and bronchospasm) requiring intramuscular adrenaline, inhaled salbutamol, and oral bilastine and deflazacort. Other 3 patients developed mild systemic reactions during immediate IDT with PEG 1500 at 0.01%.

All patients (n = 6) with severe PEG were ineligible for PEG-containing vaccines, and therefore had indication for a vaccine without PEG. Among these, 3 patients successfully completed doses of AstraZeneca SARS-CoV-2 vaccine without reaction; 1 had COVID-19 shortly after (hence the vaccine was not administered) and 2 refused a third dose of SARS-CoV-2 vaccine. Afterwards, one patient had a SAR (crampy abdominal pain, generalized pruritus, face and trunk urticaria, nausea and dizziness) after taking Ferro-Gradumet® (ferrous sulfate containing macrogol 8000), which resolved after oral bilastine and deflazacort.

Patients non allergic to PEG

One hundred and twenty patients studied for allergy work-up in the scope of SARS-CoV-2 vaccination were negative to commercial PEG 1500 extract in SPT, and in immediate and delayed readings of IDT. If the patients had not previously tolerated vaccines containing polysorbate 80, ST were also performed with polysorbate 80. Seven patients were positive to polysorbate 80 (3 in immediate IDT and 4 in delayed reading of IDT).

In these patients, suspected PEG allergy was excluded by ST, allowing SARS-CoV-2 vaccination using vaccines containing PEG 2000.

Discussion

In a real-life study focused on allergy work-up testing of patients with suspected PEG allergy in the scope of SARS-CoV-2 vaccination, ST using PEG 1500 extract proved to be a useful tool in the diagnosis of PEG allergy. Severe PEG allergy was diagnosed in 5% (6 out 126) of the patients evaluated during the period of the study.

Patients with suspected PEG allergy or with previous SAR to mRNA SARS-CoV-2 vaccines containing PEG 2000 must be

Table II – *Clinical data of the 6 patients diagnosed with severe PEG allergy.*

Patient	Sex, Age	Occupation, risk group	Personal history, allergic disease	Reason for allergy work-up	Clinical manifestations
1	F, 48	HCW (Nurse)	Asthma, allergic rhinitis	Anaphylactic shock after depot-steroid	Dyspnea, hypotension, loss of consciousness, cardiac arrest
2	M, 39	Military	Shellfish allergy, asthma, allergic rhinitis	Anaphylaxis after SARS-CoV-2 vaccine	Palmar and plantar itching, dyspnea, oropharyngeal tightness, urticaria, tachycardia
3	F, 47	HCW (Medical doctor)	No	Anaphylaxis after SARS-CoV-2 vaccine	Generalized pruritus, face and neck erythema, ear edema, trunk urticaria, cough
4	F, 42	HCW (Dentist)	Rocuronium allergy, allergic rhinitis, atopic dermatitis	SAR after SARS-CoV-2 vaccine	Palmar itching, oropharyngeal tightness, face and neck erythema
5	F, 40	HCW (Pharmacist)	Allergic rhinitis	SAR after SARS-CoV-2 vaccine	Generalized pruritus and erythema, generalized urticaria
6	F, 59	No	Asthma, allergic rhinitis	SAR after SARS-CoV-2 vaccine	Generalized pruritus and erythema, bullous exanthema

F: Female; HCW: Health care worker; M: Male; SAR: Systemic allergic reaction.

Table III – *Allergy work-up of the 6 patients diagnosed with severe PEG allergy.*

Patient	Index reaction, timing	Culprit, PEG MW	Tryptase, baseline serum	Positive ST with PEG 1500, wheal diameter	Vaccine administered
1	Anaphylactic shock, 15 minutes	Depo-Medrol®, PEG 3350	Normal (7.7µg/L)	IDT 0.01% (10 mm, anaphylaxis[1])	AstraZeneca (3 shots)
2	Anaphylaxis, 15 minutes	Pfizer-BioNTech vaccine (1st shot), PEG 2000	Normal (4.2µg/L)	IDT 0.001% (11 mm)	AstraZeneca (2 shots)
3	Biphasic anaphylaxis, 2 minutes	Moderna vaccine (1st booster), PEG 2000	Normal (3.6µg/L)	IDT 0.01% (14 mm, mild systemic reaction[2])	Refused
4	SAR, 15 minutes	Pfizer-BioNTech vaccine (1st shot), PEG 2000	Normal (3.8µg/L)	IDT 0.01% (10 mm, mild systemic reaction[3])	Not done (2 infections of COVID-19)
5	Generalized urticaria, 48 hours	Moderna vaccine (1st shot), PEG 2000	Not done	IDT 0.01% (18 mm, mild systemic reaction[4])	AstraZeneca (1 shot, 1 infection of COVID-19)
6	Bullous exanthema, 24 hours	Pfizer-BioNTech vaccine (1st booster), PEG 2000	Not done	IDT 0.01% (20 mm)	Refused

COVID-19: Coronavirus disease 2019; IDT: Intradermal tests; MW: Molecular weight; PEG: Polyethylene glycol; SAR: Systemic allergic reaction; ST: Skin tests; [1]anaphylaxis 30 minutes after the IDT with PEG 1500 at 0.01%, which reverted after administration of adrenaline (0.5 mg intramuscular); [2]Immediate IDT accompanied by palmar itching, trunk erythema and cough, which resolved spontaneously; [3]immediate IDT accompanied by oropharyngeal tightness and trunk urticaria, requiring oral desloratadine; [4]immediate IDT accompanied by palmar pruritus and erythema, generalized pruritus and conjunctivitis, requiring oral bilastine.

investigated before vaccination (1, 2, 14, 20-22). Four patients allergic to PEG had immediate SAR to vaccine or drugs containing PEG, one with a near-fatal anaphylaxis resulting in cardiac arrest after a glucocorticoid injection containing PEG 3350. After diagnostic evaluation, we were able to offer a safe alternative SARS-CoV-2 vaccine to all the patients with confirmed PEG allergy, and those who accepted were fully vaccinated without any allergic symptoms.

PEG is a high risk hidden allergen and can cause SAR after an inadvertent re-exposure. Therefore, it is recommended to prescribe an adrenaline autoinjector whenever a PEG allergy is confirmed (2, 3, 11, 16). Education on when and how to use the autoinjector device must be provided (29, 30), since there is an ongoing risk of accidental exposure, especially in patients with immediate SAR. In these patients, systemic mastocytosis or mast cell activation syndromes must be ruled out. None of the severe PEG allergy patients included in the study had mast cell activation syndrome, but one patient in whom PEG allergy was excluded had systemic mastocytosis.

Patient education is paramount. Patients must have an allergy warning card and a written emergency treatment plan, and should always carry with them an adrenaline autoinjector (**figure 2**) (2, 16, 29, 30). They also need to be taught to check product labels, and should have access to advice from the allergy department.

Patients diagnosed with PEG allergy find challenging to avoid PEG-containing products (2, 7, 11, 16). One patient (patient 1) had a SAR after an iron supplement that was prescribed by the general practitioner, despite awareness regarding PEG allergy. Whenever PEG diagnosis is confirmed, patients should be very careful with new medications or brands. It is important to educate the patient to check excipients before taking a drug and to not use different brands from those prescribed. Reactions are usually more severe with higher doses and with higher MW PEG (2, 10, 11, 13, 16, 18, 31), and also with injectable drugs containing PEG, with emphasis on depot-steroids (*e.g.*, Depo-Medrol® with PEG 3350, as occurred in patient 1), laxatives and bowel preparations containing PEG (1, 3, 6, 9-11). These patients should also avoid PEG-containing vaccines (1, 8, 14, 15, 20, 21), which, at the present date in Europe and in the United States, are the mRNA SARS-CoV-2 Pfizer-BioNTech and Moderna vaccines.

This study demonstrated the usefulness of ST with commercial PEG 1500 extract in the scope of SARS-CoV-2 vaccination for patients with suspected PEG allergy. The strategy used permitted the confirmation of severe PEG allergy, and most of all its exclusion, allowing the successful vaccination to SARS-CoV-2 using vaccines containing PEG 2000. Moreover, all healthy controls had negative IDT, demonstrating the reliability of the proposed procedure, with no false positive results obtained in 120 patients and in five controls.

If a reliable *in vitro* test for PEG allergy were to be available, the risk of inducing SAR during ST would be eliminated. However, until the present date, *in vitro* tests using PEG at different MW or PEG-containing vaccines have showed a limited value (1, 2, 9, 16, 32). In a large cohort of PEG-allergic patients, Bruusgaard-Mouritsen *et al.* (16) performed basophil histamine release tests in ten patients with previously diagnosed PEG allergy, and showed that *in vitro* tests had limited usefulness.

An algorithm with practical recommendations for allergy work-up is proposed to safely investigate patients with suspected PEG allergy (**figure 2**), using the available commercial PEG 1500 extract with increasing ST dilutions in order to minimize the risk of SAR. Investigation carries considerable risk and, therefore, should only be conducted in specialized drug allergy centres, with equipment and expertise in treating immediate-type allergic reactions (1, 11, 13, 16). It must also be ensured that antihistamine tablets without PEG are available for treating early symptoms. From our experience, patients who are allergic to PEG are at risk of SAR to IDT with PEG 1500. Therefore, ST should always begin with diluted concentrations using a stepwise approach, both in SPT and IDT, waiting at least 30 minutes before progressing to the next concentration, as previously proposed by Sellaturay *et al.*, because wheals develop slowly and can take up to 30 minutes to unfold (11).

Sellaturay *et al.* (11) studied 5 patients with severe PEG allergy, four of them with anaphylaxis, using ST with PEG 200, 400, 3350, 4000 and 20000, with higher sensitivity for PEG 20000. The authors showed that PEG allergy work-up investigation carries a high risk of anaphylaxis, presenting two women who developed anaphylaxis during IDT with PEG 20000, 30 minutes and 1 hour after IDT, respectively. They therefore recommend that IDT should be performed using the maximum concentration at 0.01% dilution. In our study, the maximum non-irritant concentration of the commercial PEG 1500 extract for IDT was 0.01%. One patient had anaphylaxis 30 minutes after 0.01% dilution IDT, requiring intramuscular adrenaline.

Other authors did not perform IDT to avoid the risk of SAR, choosing to carry out SPT with PEG at increasing MW and concentrations (1, 13, 16, 32), or a prick-to-prick ST with the suspected vaccine (1, 12, 31). Most drug allergy centres do not have available purified excipients of PEG at different MW, nor the vaccine, and therefore we propose this new algorithm using the commercial extract PEG 1500. The sensitivity of SPT using PEG 1500 seems to be low (SPT were negative in all patients), thus we propose a stepwise-approach protocol using IDT with increasing concentrations. This protocol proved to be safe and had no false positives. Moreover, PEG allergy was excluded in 120 patients, and five healthy controls underwent IDT without adverse reaction. Nevertheless, we reinforce that IDT should only be performed in SPT-negative patients and using diluted solutions.

As in other drug allergies, the rate of SAR with IDT is obviously higher that with SPT, but it is important to note that studies using SPT with MW higher than PEG 1500 also documented the occurrence of SAR (11, 13, 16, 32). Sellaturay *et al.* (13) presented a patient with anaphylaxis during SPT with PEG 4000. Bruusgaard-Mouritsen *et al.* (16) had three patients developing systemic urticaria during SPT with PEG 3000.

In clinical practice, it is difficult to obtain several PEG purified extracts with increasing MW. Therefore, it is important to note that in our study we proved the safety of IDT with commercial PEG 1500 extract starting with a 1/1,000 dilution in patients with history of previous SAR to vaccines or drugs containing PEG. We also emphasize the fact that in previous studies IDT were made with pharmaceutical products available in the market (6, 14, 17, 33, 34), particularly Depo-Medrol® and Miralax® (containing PEG 3350), which have a limited value due to false negative results (6, 34). Banerji *et al.* (14) proposed an algorithm starting with SPT with Miralax® or the injectable corticoid Solu-Medrol® and proceeding (if negative SPT) to IDT with Solu-Medrol® at a maximum concentration of 1/10 dilution (methylprednisolone 4 mg/mL with PEG 3350). We highlight the fact that one patient (patient 1), with severe PEG allergy, had a negative IDT with Depo-Medrol® (methylprednisolone 4 mg/mL with PEG 3350), and the diagnosis was only possible after IDT with the commercial extract of PEG 1500 (available in our country since March 2021).

The etiopathogenic mechanism of SAR to mRNA SARS-CoV-2 vaccines is not clear. Besides the IgE-mediated mechanism, non-IgE mediated mechanisms such as complement activation-related pseudoallergy (CARPA) have been postulated with PEG and these vaccines (19, 35). PEG have demonstrated to cause delayed-type and immediate-type allergic reactions, with wide heterogeneity of clinical presentations (1, 2, 5); most delayed reactions are mild and do not contraindicate revaccination (1,9).

Two patients had positive immediate IDT despite presenting with severe delayed SAR. In these 2 patients, a mixed hypersensitivity mechanism is suspected. Confirming this hypothesis required a provocation test with PEG. The occurrence of a systemic reaction during IDT in the patient with delayed generalized urticaria is favourable to this hypothesis. The provocation test with PEG in the patient with bullous exanthema was not done due to ethical reasons.

The clinical suspicion of delayed-type or T-cell–mediated hypersensitivity motivated further investigation in these patients, to whom a mixed hypersensitivity mechanism was suspected. ST with the implicated vaccine (Moderna) were performed in one patient (patient 5), with the remaining of a vial used in the vaccination centre. The IDT was positive in the immediate reading at the dilution 1/10 and further evolved to a bullous reaction on the forearm and hand in the following 24 hours, in favour of a mixed mechanism.

Regarding other limitations of our study, we point out that the MW of the extract used (PEG 1500) is not the one used in the mRNA SARS-CoV-2 vaccines (PEG 2000). Until the present time, PEG 2000 is not available in the market as an extract for allergy testing. Other limitation of this study is the lack of confirmatory provocation tests with PEG after the positive ST results, which were not done due to ethical reasons. We stress out that 4 patients had systemic reaction during IDT. In those 2 patients that did not have systemic reaction during IDT, one had anaphylaxis and the other had bullous exanthema after Pfizer-BioNTech SARS-CoV-2 vaccine.

Cross-sensitization to polysorbate 80 was also assessed. None of the 6 PEG-allergic patients had cross-sensitization to polysorbate, and 3 of them where successfully vaccinated with SARS-CoV-2 polysorbate 80-containing vaccines without adverse reaction. In the patients non allergic to PEG, 6% (7 patients) showed sensitization to polysorbate 80. Other authors found different results (6, 15, 16, 31, 34). Bruusgaard-Mouritsen *et al.* (16) found that 3 out of 10 PEG allergic patients studied showed cross-sensitization to polysorbate 80.

The occurrence of multiple reports of anaphylaxis during the SARS-CoV-2 large scale worldwide vaccination highlighted the importance of PEG as a potential cause of life-threatening anaphylaxis. Because mRNA SARS-CoV-2 vaccines contain PEG 2000, it is important that patients with suspected allergy to PEG (especially anaphylaxis) are investigated before vaccination (1, 2, 13, 14, 20-22). Our study has important implications in clinical practice, since we demonstrated the usefulness of ST using commercial PEG 1500 extract in the diagnostic allergy work-up of these patients. In conclusion, to our knowledge this is the first study describing the allergy work-up testing with commercial PEG 1500 extract in the scope of SARS-CoV-2 vaccination. ST using PEG 1500 extract were a useful tool for the diagnosis of PEG allergy, since it allowed the confirmation of severe PEG allergy in six patients, contraindicating further administration of PEG-containing vaccines. It also allowed the exclusion of allergy in more than one hundred patients that afterwards took SARS-CoV-2 vaccines containing PEG 2000. Moreover, healthy controls had negative IDT, demonstrating the reliability of the proposed procedure. PEG allergy investigation carries the risk of anaphylaxis and should only be conducted in a specialized drug allergy center.

Fundings

None.

Contributions

ÂG: conceptualization, writing - original draft, project administration, formal analysis, methodology, resources, writing - review & editing. A-LM: formal analysis, writing - original draft,

resources, writing - review & editing. CC, L-MB: resources, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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