

ABSTRACT

BACKGROUND: International guidelines suggested skin tests with Polyethylene-glycol (PEG) and polysorbate 80 (PS-80), to investigate a possible hypersensitivity to these excipients either to identify subjects at risk of developing allergic reactions to Covid-19 vaccines, or in patients with suspected IgE mediated hypersensitivity reactions (HR) to the Covid-19 vaccine.

OBJECTIVE: The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected Covid-19 vaccine immediate HR.

METHODS: This was a multicenter retrospective study conducted by allergists belonging to 20 Italian medical centers. Skin testing was performed in 531 patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS-80 (group 1:362 patient) or a suspected HR to Covid-19 vaccines (group 2: 169 patient), as suggested by the AAIITO/SIAAIC guidelines for the “management of patients at risk of allergic reactions to Covid-19 vaccines” [1].

RESULTS: 10/362 (0.02%) had positive skin test to one or both excipients in group 1, 12/169 (7.1%) in group 2 ($p<0.01$). In group 2 HRs to Covid-19 vaccines were immediate in 10/12 of cases and anaphylaxis occurred in 4/12 of patients.

CONCLUSION: the positivity of skin test with PEG and or PS before vaccination is extremely rare and mostly replaceable by an accurate clinical history. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a Covid-19 vaccine, in particular in patients with anaphylaxis.

INTRODUCTION

In December 2020, at the beginning of the Covid19 vaccination campaign, 2 anaphylaxes were reported after the administration of the first 500 BNT162b2 vaccines. For this reason, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) temporarily contraindicated this vaccine in patients with a severe allergic background. [2]

This contraindication was revoked in January 2021 and more recent data on the safety of Covid-19 vaccines show that severe hypersensitivity reactions are rare even in patients with an allergic background.[3,4,5]

In mRNA vaccines (Comirnaty by Pfizer BioNTech and Spikevax by Moderna), the components suspected of being the cause of IgE-mediated hypersensitivity reactions (HR) are the excipient Polyethylene glycol (PEG or macrogol, with a molecular weight of 2000 kDa) and Trometamol (contained at time only in Spikevax), while in the adenoviral vector vaccines (Vaxzeviria by AstraZeneca and Jcovden by Janssen) polysorbate 80 (PS-80), a substance chemically correlated with PEGs, has been incriminated. Non-IgE mediated mechanisms with activation of immunological mechanisms triggered by complement activation (CARPA, Complement Activation-Related PseudoAllergy) have also been hypothesized. [6]

According to current national and international guidelines, an allergological evaluation is still needed in individuals with suspected hypersensitivity to excipients of Covid-19 vaccines, PEG and PS-80.

An evaluation by allergy specialist is recommended also in patients with a suspected HR to Covid-19 vaccination, in order to evaluate the indication to a further vaccine dose and which vaccine could be administered [1,6,7].

According to the aforementioned guidelines, individuals with allergy to foods, inhalants, hymenoptera venom and drugs (with the exception of PEG/PS containing injective drugs) can be vaccinated in a standard setting and don't need a "preventive" allergological evaluation.

Among these patients, even those with a history of anaphylaxis can be vaccinated in a standard setting with a prolonged observation period (60 minutes according to Italian guidelines).

Instead, an allergy evaluation is needed in subjects with a previous reactions to drugs containing PEG or PS. In these patients, skin tests with PEG and/or PS are suggested as a useful test to evaluate a possible contraindication to vaccination. Trometamol was contained at that time as an excipient only in Spikevax. This substance may have an irritative effect, and for this reason, is not recommended for skin testing.

In individuals with a severe anaphylactic reaction to prior doses of Covid-19 vaccines, both in case of positive and negative tests, it is preferable not to administer the following dose of the same vaccine.

It should be emphasized that data on skin tests currently available in the literature indicate their low positive and negative predictive value and the need for the diagnostic procedure to be entrusted to the allergy specialist. These guidelines highlight the central role of allergist in the evaluation of subjects with suspected hypersensitivity to Covid-19 vaccines or to the excipients contained in these preparations.

The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in Italian patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected Covid-19 vaccine immediate HR.

METHODS:

This was a multicenter retrospective study conducted, from March to December, 2021, by allergists belonging to 20 Italian medical centers located either in hospitals (n= 9) or outpatient clinics (n= 13).

Skin testing was performed in patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS 80 (group 1) or a suspected HR to Covid-19 vaccines (group 2), as suggested by the AAIITO/SIAAIC guidelines for the “management of patients at risk of allergic reactions to Covid-19 vaccines” [1].

Skin tests were performed in 6 steps: 3 steps for prick tests followed by 3 steps for intradermal tests using increasing concentrations of PEG and PS, as suggested by national and international guidelines [1,7]. Demographic and clinical data were collected: age, previous anaphylaxis or HR to drug or vaccine (either containing or not containing PEG and PS), allergic comorbidities. Data were collected by means of an anonymous survey, filled out online by an allergist. No data on gender and ethnicity were collected. The approval by the ethical committee was not requested being an anonymous survey.

STATISTICAL ANALYSIS

Microsoft Excel 2019[®] , OpenEpi online (www.openepi.com, accessed on 25 January 2022), and JASP 0.16.0.0 were used for statistical analysis. The distribution of categorical variables among groups were compared using the chi-square test. Categorical variables are reported as absolute numbers (percentage). *p*-Values below 0.05 were considered significant

RESULTS

531 patients were enrolled: 362 (68.2%) were referred to carry out the skin tests to exclude PEG/PS hypersensitivity before vaccination (group 1), and 169 (31.8%) for a suspected HR to the first or second dose of Covid-19 vaccine (group 2).

10/362 (0.02%) scored positive on skin test to one or both excipients in group 1, vs 12/169 (7.1%) in group 2 ($p < 0.01$). All patients of group 1 had a previous drug anaphylaxis and 50% had a previous HR to drugs containing PEG. In group 2, HRs to Covid-19 vaccines occurred after the first dose in all patients. HRs were immediate in 10/12 (83%) patients and anaphylaxis occurred in 4/12 (33%) patients. ~~Co-sensitization to PEG and PS is extremely rare.~~

PATIENTS WITH A HISTORY OF ADVERSE REACTIONS TO DRUGS CONTAINING PEG

Demographic and clinical features

362 patients were enrolled. Patients between 40 and 70 years old represented the most numerous age group. 160 patients had a clinical history of anaphylaxis (128 induced by drugs, 15 by vaccines, and 6 by Hymenoptera stings). 41 patients (11,7%) had a clinical history of multiple anaphylaxis (≥ 2)Antibiotics, NSAIDs, and vaccines were the most common causes of previous anaphylaxis. 50,6% (n= 179) had a clinical history of multiple drug reactions (most caused by antibiotics and NSAIDs). 165 patients reported adverse reactions to drugs or vaccines containing PEG (most commonly amoxicillin/clavulanate, paclitaxel, ciprofloxacin, methylprednisolone, and docetaxel).

253 (72,5%) showed allergic or pseudoallergic comorbidities (asthma, rhinitis, conjunctivitis, dermatitis, chronic spontaneous urticaria), and 60% of the population suffered from extra-allergological comorbidities (cardiovascular diseases, endocrinopathies, hyperuricemia, osteoporosis).

CHARACTERISTICS OF PATIENTS WITH POSITIVE SKIN TEST TO PEG/POLYSORBATE

10 patients scored positive on Skin Test with PEG and PS (Table 1):

2 patients (Pt n. 204,351) scored positive only to skin test with PS (antipneumococcus vaccine and Optive plus);

3 patients (Pt n. 346,359,360) scored positive on both PS (Kenacort® “Triamcinolone acetonide” and/or Optive plus) and PEG (Depomedrol® “Methylprednisolone acetate” and Macrogol) testing;

5 (Pt n. 32,9,89, 168, 265) patients showed a PEG positive skin test (one with macrogol 1:1 on SPT, and the others ID with Depomedrol® [doubtful SPT result]).

Patient n. 168 scored positive on SPT with both to Depomedrol® “Methylprednisolone acetate” and Urbason® “Methylprednisolone”, suggesting methylprednisolone rather than PEG hypersensitivity.

5 patients experienced a previous reaction to PEG- containing drugs (Cetirizine, Paclitaxel, Augmentin® “Amoxicillin/Clavunate”, Pantoprazole, Movicol® “Macrogol”). 3 patients showed allergic comorbidities (rhinitis, asthma, conjunctivitis).

9/10 patients had a clinical history of drug anaphylaxis: 1 patient to Depomedrol® and Lidocaine “Methylprednisolone acetate” , 1 to Bentelan® “Betamethasone”. The drug is not known for the other 7.

mRNA vaccines have been discouraged to patient with PEG skin test positivity.

PATIENTS WITH SUSPECTED HYPERSENSITIVITY REACTIONS TO COVID-19 VACCINES

Demographic and clinical features (details in Table 2a)

A total of 169 patients with suspected hypersensitivity reactions to Covid-19 vaccine were registered in the participating centers and subsequently submitted to skin testing with vaccine excipients [1]. 14% of subjects had a clinical history of allergic reactions at least to 2 different drugs and 17% had a clinical history of anaphylaxis. Other allergic comorbidities were reported in 57% of subjects. Among patients with previous anaphylaxis there was a significantly higher percentage of subjects with positive skin tests than in patients without anaphylaxis (17% vs 5%, $p < 0.01$) while there was not a significative difference in patient with multiple drug hypersensitivity.

DETAILS OF THE SUSPECTED HR: (details in Table 2b)

147/169 (95%) of suspected HRs to Covid-19 vaccines occurred after the 1st dose, 8/169 (4,7%) after the 2nd dose and 14/169 (8,2%) after both doses. This means that globally 22 patients had HRs after the 2nd dose. 104/161 (64%) of HRs after first dose and 13/22(68%) of HRs after 2nd dose were immediate (>time of onset within 4 hours from vaccination). Skin reactions were the most common HRs, occurring in 69.6% of patients. 12/169 of HR were classified as anaphylaxis according to modified WAO grading system [7]. Antihistamines were used in 57% of cases, corticosteroids in 41%, and Epinephrine in 11% of cases.

POSITIVE SKIN TESTS IN PATIENTS WITH SUSPECTED HYPERSENSITIVITY REACTIONS (details in Table 3)

Among the 169 patients with suspected HRs, 12 (7.1%).had positive skin test results. 7 patients showed positive tests for PEG (Pt n. 1,3,4,5,8,11,12) and 3 for PS (Pt n. 2,6,10), while only 2 (Pt n. 7,10) patient had positive tests for both excipients.

In this subgroup HRs to Covid-19 vaccines occurred after the first dose in all patients.

HRs were immediate in 10/12 (83%) of cases and anaphylaxis occurred in 4/12 (33%) of patients.

5/12 (41%) had both a history of anaphylaxis and allergic comorbidities.

Only 2 patients out of 12 received the 2nd dose of vaccine:

-Patient n. 8 received the 2nd dose of the same vaccine (BNT162b2) despite HR to the first dose and reported the same reaction (dyspnea and bronchospasm);

-Patient n. 12, who developed a generalized urticaria after the first dose of mRNA vaccine and was positive to PEG received the 2nd dose with adenoviral vaccine, administered in fractioned doses, with no adverse events.

Considering the medical history of those patients, 4/12 (33%) reported past reactions to PEG-containing drugs, while 5/12 (41,7%) reported, before Covid-19 vaccination, the tolerance of at least one PEG- containing drug. HRs to PEG- containing vaccines in subjects who tolerated PEG- containing drug could be explained by the role of lipidic nanoparticles. Those nanoparticles, when conjugated to PEG, may determine an HR mediated by complement activation.

CONCLUSIONS AND DISCUSSION:

The study, consistently with the latest national and international guidelines [2,3] demonstrates that after adequate diagnostic work-up, the positivity of skin test with PEG and or PS before vaccination is extremely rare and mostly replaceable by an accurate clinical history. In particular, we found a significantly lower prevalence of positive skin tests in group 1 than in group 2. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a Covid-19 vaccine, in particular in patients with anaphylaxis. Nonetheless, it is important to underline that the vast majority of patients who experience a suspected HR at the first dose of Covid-19 vaccine should not be automatically precluded from being re-vaccinated, in particular in patients with non-severe reactions and negative test, after an accurate allergological evaluation. This is also underlined by the latest Italian guidelines and recent review and meta-analysis of the available literature regarding immediate reactions to the first dose of Covid-19 vaccine, where the incidence of severe immediate reactions to re-vaccination with the second dose of Covid-19 vaccine was very low (0.16%) in the absence of related deaths. [1,4,8]. From our data, patients with previous anaphylaxis have also a major probability of scoring positive on skin tests. This further supports the importance of a complete anamnesis in the screening and management of these reactions

Only patients who received a new diagnosis of allergy to PEG/PS, ascertained by skin test, would not be suitable for the administration of the second dose. On this point, the Italian guidelines highlight the fact that skin tests seem to have a low positive and negative predictive value [9].

In addition to considering excipients as the cause of IgE-mediated allergic reactions to the currently approved Covid-19 vaccines, alternative non-IgE pathways for activating mast cells and other inflammatory cells must be considered, because they can lead to a similar clinical presentation. For example, activation of the complement system leads to the generation of C3a, C4a, and C5a, which are potent activators of inflammation and are called anaphylatoxins due to their ability to cause non-IgE-mediated mast cell degranulation. [2]

Depletion of complement levels and production of C3a and C5a have been seen in both mouse models of anaphylaxis and in clinical studies. C5a is the most potent anaphylatoxins and can contribute to vascular permeability as well as activation and chemotaxis of neutrophils, basophils, and mast cells. Infection and tissue injury can lead to activation of the complement system resulting in the generation of C3a and C5a, and these mediators can lead to anaphylaxis. PEG IgM and IgG can cause complement-activation-related pseudoallergy, a nonspecific immune response to PEGylated, nanoparticle-based medicines [2]

Clearly, it is important to consider both IgE and alternative mechanisms for the current reactions. Measurement of serum tryptase and complement may help elucidate the mechanism of the drug-induced reactions in patients following Covid-19 vaccination.[2]

For this reason, the panel of experts suggests not to limit the allergy evaluation to the result of skin tests, but to carry out an integrated evaluation for each patient based on 1) the precise allergological history, 2) the severity of the reported reactions and 3) the evaluation of the risk / benefit ratio deriving from vaccination (SIAAIC/AIIITO).

The survey demonstrates that the onset of symptoms suggestive for a HR to the first dose of Covid-19 vaccine should not automatically prevent the citizen from receiving the second dose, but requires an adequate allergy assessment that include a detailed clinical history associated with skin tests, when indicated by the allergist.

The authors wish to thank Dott. Riccardo Asero for his valuable contribution to this manuscript.

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Table 1 Demographic and clinical features of patients with a clinical history of HRs to drugs containing polyethylene-glycol (PEG) or/and polysorbate (PS)

PT	AGE	past anaphylaxis	drug anaphylaxis	multiple anaphylaxis	multiple drug reactions	past reactions to PEG and or PS containing drugs	Tolerance to PEG containing drugs	allergic comorbidities	antiFlu vaccine	positive skin test (PEG)	positive skin test (PS)
9	71-80	yes	yes	yes	yes	Yes (pantoprazole, amoxicillin/clavulanate)		no	no	ID MPDa 0,04 mg/ml	
32	41-50	yes	yes	no	yes	yes (cetirizine)			no	SPT macrogol 1:1	
89	41-50	yes	yes (lidocaine + MPDa)	no	yes	no		yes (rhinitis, conjunctivitis)	no	SPT MPDa 40 mg/ml, ID MPDa 0,04/0,4/4 mg/ml	
168	41-50	yes	yes (betamethasone)	no	no	no	yes	yes (asthma, rhinitis)	no	SPT MPDa 40 mg/ml, SPT MPD 40 mg/ml, ID MPD (control) 0,04/0,4/4 mg/ml , ID MPDa 0,04/0,4/4 mg/ml	
204	41-50	yes	yes	no	no	no			no		SPT e ID antipneumococcus vaccine
265	51-60	yes	yes	no	no	no		yes (rhinitis, conjunctivitis)		ID MPDa 0,4 mg/ml	
346	41-50	Yes	yes	no	no	yes (MPDa)	yes	no	no	ID MPDa 4 mg/ml	SPT e ID Optive plus
351	51-60	no	no	no	yes			no	no		ID Optive plus™
359	51-60	yes	yes	no	no	yes (paclitaxel)			no	ID MPDa 0,4 mg/ml	ID Triam 4mg/ml
360	61-70	yes	yes	no	yes	yes (macrogol)	no		no	SPT macrogol 1:1, SPT MPDa 40 mg/ml ID MPDa 4 mg/ml	SPT Triam 40 mg/ml; SPT Optive plus™

Abbreviations PT=patients PEG=polyethylene-glycol PS=polysorbate Triam= Triamcinolone MPDa=Methylprednisolone acetate (Depomedrol®) MPD=Methylprednisolone (Urbason)

Table 2a Demographic and clinical features of patients with HRs to Covid19 vaccines

Clinical and demographic features			HRs to antiSars-Cov2 vaccines		
	N	(%)	HR D1		
Age group	169	100	immediate	161	(95)
20-30	15	(9)	local reactions	104	(62)
31-40	39	(23)	diffuse itching	8	(8)
41-50	36	(21)	diffuse itching	41	(39)
51-60	31	(18)	urticaria	14	(13)
61-70	26	(15)	rash (other)	45	(43)
71-80	12	(7)	angioedema	41	(39)
>80	3	(2)	skin (total)	107	(103)
previous anaphylaxis	29	(17)	pharyngeal disclosure	17	(16)
drug	9	(5)	asthma/bronchospasm	21	(20)
vaccine	13	(8)	anaphylaxis/glottic edema	11	(7)
>1 anaphylaxis	5	(3)	paresthesia	28	(27)
> 1 drug HR	25	(15)	Drugs to treat HR	106	(66)
HR to PEG/polysorbate containig drug	26	(15)	antiH1	89	(86)
allergic comorbidities	96	(57)	GC	65	(63)
antiFlu vaccine (2020/2021)	21	(12)	epinephrine	9	(9)
			HR D2	19	(18)
			Immediate	13	(68)
			local reactions	5	(26)
			diffuse itching	5	(26)
			urticaria	2	(11)
			rash (other)	7	(37)
			angioedema	4	(21)
			skin (total)	12	(63)
			pharyngeal disclosure	2	(11)
			asthma/bronchospasm	4	(21)
			anaphylaxis/glottic edema	2	(11)
			paresthesia	1	(5)
			Drugs to treat HR 2D		
			antiH1	10	(53)
			GC	8	(42)
			epinephrine	2	(11)
			HR 1&2D	12	(63)
			Positive skin test	12	(63)

Table 2b Demographic and clinical features of patients with HRs to Covid-19 vaccines and positive skin tests

Demographic and clinical features	n	%
	12	100
Age range		
31-40	2	16,7
41-50	2	16,7
51-60	5	41,7
61-70	2	16,7
71-80	1	8,3
past anaphylaxis	5	41,7
drug anaphylaxis	4	33,3
multiple anaphylaxis	3	25
multiple drug reactions	3	25
past reactions to PEG-containing drugs	4	33,3
Tolerance to PEG-containing drugs*	5	41,7
allergic comorbidities	5	41,7
antiFlu vaccine	2	16,7
HRs to Covid-19 vaccine		
HR 1D	12	100
HR immediate	10	83,3
HR not immediate	2	16,7
HR: symptoms		
Local reactions	1	8,3

* Tolerance to PEG containing drugs before Covid-19 vaccines

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Table 3 Patients with positive skin tests and hypersensitivity reaction to Covid-19 vaccine

Patient	Age	previous anaphylaxis	allergic comorbidities	HR 1D	Type of vaccine		Time of onset	therapy of HR	Received 2 nd dose	HyPR 2D	Time of onset	Therapy HypR 2D	positive skin test (PEG)	positive skin test (polysorbate)
Pt 1	51-60	no	no	local wheal and rash, angioedema	ND		< 1h	antiH1, GCs	ND	No	NA	NA	macrogol 3350 ID 0.4 mg/ml	No
Pt 2	61-70	vaccine	ACD	angioedema, dyspnea, bronchospasm (A)	ND		< 1h	epi	ND	No	NA	NA	No	p80 Triam ID 0,4 mg/ml
Pt 3	51-60	Food	drugs allergies	pharyngeal discomfort, mouth paraesthesia	ND		< 1h	GCs	ND	No	NA	NA	MPD ID 40mg/ml	No
Pt 4	31-40	other drugs	rhinoconjunctivitis	dyspnea, bronchospasm, anaphylaxis (without hypotension) (A)	ND		< 1h	epi	ND	No	NA	NA	SPT macrogol 3350 1:10; SPT aMPD 0.4 mg/ml; ID aMPD 40mg/ml	No
Pt 5	51-60	No	no	diffuse itching, mouth paraesthesia	ND		< 1h	antiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10; ID aMPD 0.4 mg/ml; ID aMPD 4 mg/ml;	no
Pt 6	41-50	No	no	Angioedema	Adenovirus (ChAdOx1 nCoV-19)		1-4 h	antiH1, GCs	ND	No	NA	NA	No	SPT p80 Triam 40mg/ml ID p80 Triam 40 mg/ml
Pt 7	71-80	No	no	angioedema, glottic edema (A)	ND		< 1h	antiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10	ID p80 Triam 0,4 mg/ml
Pt 8	51-60	vaccine, other drug	asthma	dyspnea, bronchospasm	mRNA (BNT162b 2)		< 1h	epi	Yes, mRNA (BNT162 b2)	dyspnea, bronchospasm	<1h	antiH1, GCs	SPT Macrogol 3350 1:100	No
Pt 9	61-70	No	no	angioedema	Adenovirus (ChAdOx1 nCoV-19)		>4 h	antiH1, GCs	ND	No	NA	NA	No	ID p80 eye drops 1:10
Pt 10	31-40	No	no	urticaria, itching	ND		>4 h	antiH1, GCs	No	NA	NA	NA	ID MPD 0,4 mg/ml	ID p80 eye drops 1:10
Pt 11	51-60	other drug	rhinoconjunctivitis	diffuse itching, angioedema, maculo-papular rash, hypotension, dyspnea, bronchospasm, rhinitis (A)	mRNA (BNT162b 2)		< 1h	antiH1, GCs, epi	ND	No	NA	NA	ID MPDa 4 mg/ml	No
Pt 12	41-50	No	no	Urticaria	mRNA (BNT162b 2)		<1h	ND	Yes *	No	NA	NA	SPT Macrogol 3350 1:100	no

Abbreviations Pt=patients HR= hypersensitivity reaction antiH1= antihistamines GCs= glucocorticoids Epi=epinephrine ID=intradermal SPT= skin prick test Triam= triamcinolone acetate MPDa=Methylprednisolone acetate (A)= anaphylaxis ND= no data NA= not applicable **Notes: * Adenovirus vaccine, fractioned doses**