



ORIGINAL ARTICLE

OPEN ACCESS

Evaluation of pediatric patients with suspected polyethylene glycol and polysorbate allergy before mRNA SARS-CoV2 vaccination

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Received 19 November 2022; Accepted 29 January 2023

Available online 1 May 2023

KEYWORDS

SARS-CoV2;
vaccination;
mRNA;
PEG-polysorbate;
allergy

Abstract

mRNA vaccines, particularly, have been associated with an increased risk of allergic reactions and rarely anaphylaxis. Although rare, vaccine reactions can cause significant anxiety and fear in the population, leading to indecision and vaccine refusal. This study aimed to retrospectively evaluate the role of polyethylene glycol (PEG) sensitivity in vaccination decision-making in pediatric patients at high risk of allergy or with suspected allergic reactions to the first dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) vaccine. Seventeen enrolled patients were found to have decreased readiness to receive the Coronavirus Disease 2019 (COVID-19) vaccine after developing hypersensitivity to multiple and/or injectable drugs. Skin testing was performed. A basophil activation test with PEG-2000 and 4000 was performed on three patients who were ineligible for skin prick tests. Nine patients with negative tests received the vaccine without complications. One patient had urticarial angioedema despite negative tests. Three patients with positive tests did not agree to desensitization with the mRNA vaccine, and one of them was vaccinated with the inactivated COVID-19 vaccine. Four patients recurred despite negative tests. The general recommendation for patients describing severe reactions to drugs, foods, and allergens, such as toxins that do not contain the adjuvants of the SARS-CoV-2 vaccines, is to be routinely vaccinated with safety precautions. Excipients such as PEG and polysorbate-80 used in COVID-19 vaccines could be potential allergens, but this hypothesis is unclear. The predictive values of these adjuvants for skin testing and in vitro testing are controversial. Further research is needed on the hypersensitivity reactions of adjuvants, the predictive values of skin tests, and etiopathogenesis.

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<https://doi.org/10.15586/aei.v51i3.800>

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Introduction

Since the last months of 2019, new Coronavirus Disease 2019 (COVID-19) has spread and caused a pandemic. There is no effective treatment for SARS-CoV-2, so infection prevention has become more important to tame the pandemic. mRNA, viral vectors, and inactivated SARS-CoV-2 vaccines have been approved with conditional licensure and are already in use. While the vaccines have demonstrated safety and efficacy, side effects, particularly local reactions, have been noted after marketing. In particular, mRNA vaccines have been associated with an increased risk of allergic reactions, including rare anaphylaxis.^{1,2}

After the initial cases of anaphylaxis were reported, authorities advised that all patients be observed for 15-30 minutes after SARS-CoV-2 vaccination, that all personnel be trained in the management of anaphylaxis, and that vaccine administration centers be equipped with appropriate equipment to manage anaphylaxis.³

Although rare, vaccine reactions can cause significant anxiety and fear in the population, leading to indecision and vaccine refusal. Failure to address uncertainty, particularly in the population with allergies, results in vaccination delays. Given the importance of preventive treatment in the pandemic, vaccination is critical. Therefore, proper assessment and treatment of allergic reactions can help prevent vaccine refusal and ensure effective vaccination.¹

Risk factors and underlying mechanisms of allergic reactions in vaccination against SARS-CoV2 infection are not yet clear. In general, vaccine-related hypersensitivity reactions (HR) may be due to the classic four mechanisms of Gell and Coombs classification. Apart from this, complement activation-related pseudoallergy (CARPA) is a new phenomenon that is not of the IgE type, is unpredictable, has an immediate onset, and is milder or absent with repeated exposure.¹

Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines do not contain nutrients, drugs, or latex but buffer components and lipid nanoparticles. Polyethylene glycol (PEG) is present to stabilize the lipid nanoparticles in mRNA vaccines in cells.⁴ In contrast, the COVID-19 vaccines from AstraZeneca and Johnson & Johnson do not contain PEG but the excipient polysorbate 80. In mRNA vaccine-related allergic reactions, the primary responsible molecule, PEG, is thought to be the most common allergen in the vaccine. All studies to date have primarily examined PEG and its cross-reactant partners (e.g., polysorbate 80 and 20). Standard dilutions for the skin prick test (SPT) and intradermal test (IDT) have been prepared, and *in vitro* evaluation with the basophil activation test (BAT) has been found to be reliable in patients whose evaluation with the SPT was suboptimal.⁵⁻⁷ However, it is known that not every patient with PEG sensitization develops a reaction to mRNA vaccines. In addition, false-positive and false-negative results have been reported in IDTs with PEG.⁸

Furthermore, although reactions to other substances in the contents of vaccines are known in patients without PEG sensitization, no testable molecule other than the vaccine itself and PEG could be determined. Several studies have proposed diagnostic algorithms based on clinical evaluation and skin testing for adjuvants with PEG and polysorbate 80.^{9,10} After the allergological evaluation of patients who

reacted to the first vaccine dose, rapid desensitization protocols have been developed for safe vaccination.¹¹

In this study, we retrospectively evaluated the role of PEG sensitivity in vaccination decision-making in pediatric patients at high risk of allergy or patients with suspected allergic reactions to the first dose of the SARS CoV2 vaccine since 2021 in our Pediatric Allergy and Immunology Unit.

Materials and Methods

Study participants

This cohort included patients referred to the pediatric allergy/immunology department for evaluation who were found to have decreased readiness to receive the COVID-19 vaccine in 2021 after developing hypersensitivity to multiple and/or injectable drugs.

In the assessment, patients were categorized before vaccination with respect to four questions: (1) history of severe allergic reaction to an injectable (intravenous, intramuscular, or subcutaneous) drug, (2) history of severe allergic reaction to a vaccine, (3) severe allergic reaction to another allergen (e.g., food, poison, or latex) in history, and (4) ever had a sudden or severe allergic reaction to an injectable drug or vaccine containing PEG, polysorbate, or polyoxyl-35 castor oil (e.g., paclitaxel). Patients who answered “yes” to question 4 were considered high-risk, and skin testing with PEG and polysorbate 80 was recommended, depending on the patient’s response. Patients who answered “no” to question 4 but “yes” to the first three questions were considered to be in the intermediate-risk group. These patients were recommended to be routinely vaccinated, with an observation period of 30 minutes. Patients who answered “no” to all questions were recommended to be routinely vaccinated. mRNA vaccines were considered contraindicated in patients with a positive skin test.⁹

Skin testing was performed on patients who reported a reaction to PEG or a polysorbate-containing drug/vaccine or a HR to multiple drugs of unknown or uncertain name that might contain PEG or a polysorbate, or who had drug hypersensitivity but refused COVID-19 vaccination without testing.⁹

Study procedures

PEG skin tests (SPT and IDT) were performed with Depo-Medrol (Pfizer, USA, Methylprednisolone acetate containing only PEG-3350), and polysorbate 20 tests were also performed with Havrix (GlaxoSmithKline Biologicals s.a. Wavre, Belgium, Hepatitis A vaccine), and polysorbate 80 tests with Prevenar 13 (Pfizer, USA). Methylprednisolone sodium succinate does not contain PEG or polysorbate 80 and was used as an additional control to rule out methylprednisolone hypersensitivity. For epicutaneous testing and ID, skin testing required appropriate positive (histamine) and negative (saline) control. We used skin testing with adjuvants (without skin testing with the mRNA COVID-19 vaccine) because we did not have access to the mRNA COVID-19 vaccine for skin testing at that time, except for

one patient. A BAT was performed with PEG 2000 and 4000 (Buhmann, Flow Cast, Switzerland) on one patient who was receiving concomitant immunosuppressive therapy and whose treatment could not be interrupted for a prolonged period, on one patient whose skin test could not be performed due to dermatographism, and on one patient who suffered anaphylaxis during the first administration of mRNA vaccine (Biontech). Patients with a negative skin test or BAT were advised to be vaccinated, except for those with anaphylaxis to the mRNA vaccine. Patients with a positive skin test for PEG and/or polysorbate 80 shared decision-making with patients and parents.

Statement of ethics

This study protocol was reviewed and approved by Istanbul University-Cerrahpasa Ethic Committee, approval number 08.07.2022-431161. Written informed consents were obtained from patients before the study.

Results

Demographics and comorbidities

Seventeen patients underwent skin testing for excipients in our department with specific/suspected hypersensitivity to several drugs, including PEG/polysorbate 80-20 (Table 1).

Half of the patients (50%) were female, and the mean age was 15.25 ($\pm$ 2.75 SDS) years. Comorbid atopic diseases included asthma (50%), allergic rhinitis (18.75%), food allergy (6.25% n = 1), and idiopathic anaphylaxis (6.25% n = 1). Inflammatory diseases (Crohn's disease and ulcerative colitis) were documented in two (12.5%) patients. Only one patient had clinical features suggestive of familial Mediterranean fever (FMF) and was treated with colchicine. In addition, one patient had a malignancy (BCOR/CCN3 sarcoma) and one patient had primary immunodeficiency.

Allergological work-up

A total of 16 patients reported an immediate reaction; anaphylaxis occurred in 10 within the first 30 minutes. Of these, 5 (31.2%) reported a reaction with PEG or a polysorbate-containing drug/vaccine [one was the COVID-19 mRNA vaccine (Biontech) and one was the COVID-19 inactivated vaccine (Sinovac)]; the others are listed in Table 1. A total of six patients (37.5%) reported a HR with multiple and unknown or undetermined names of drugs that may contain PEG or a polysorbate. Moreover, five patients with drug hypersensitivity had refused the COVID-19 vaccination without testing, three of whom reported anaphylaxis.

SPTs/IDTs and BATs

All 16 patients underwent skin testing with the adjuvants PEG, polysorbate 80, and 20. One patient had dermatographism, so invalid test results were noted. In the other three

patients who had an immediate allergic reaction, the skin test was positive (18.75%) (Table 2), for both PEG and polysorbate 20 skin test positivity in 2 patients, and PEG, polysorbate 80 and 20 skin test positivity in one. Of the three patients with positive skin tests, one had anaphylaxis to intravenous ceftriaxone (PEG and polysorbate 20 positives), one had anaphylaxis to subcutaneous house dust immunotherapy (PEG and polysorbate 20 positives), and one had anaphylaxis to the first dose of COVID-19 mRNA vaccine (Biontech) (Table 2). No allergic or adverse events occurred with any of the skin test procedures.

A BAT with PEG 2000 and 4000 was performed on three patients. Of these, one with a negative skin test had a history of anaphylaxis with the COVID-19 mRNA vaccine (Biontech), but also had a history of idiopathic anaphylaxis. The other patient was receiving immunosuppressive therapy, and it was suspected that this may have suppressed the skin test. The last patient had dermatographism. In all three cases, the BATs were negative.

General vaccine tolerability

Of the 16 patients who underwent skin testing for adjuvants or BAT, 11 (68.7%) received the vaccine (n = 1 inactivated or n = 10 mRNA), and 10 tolerated vaccination without reaction (62.5%); one patient had an initial reaction to Sinovac, IVIG, and multiple parenteral medications (including tocilizumab) and reported facial angioedema after COVID-19 mRNA vaccine (Biontech) in 30 minutes.

Of the three patients (18.7%) who had a positive SPT, two declined desensitization for the mRNA vaccine (Biontech) or alternative vaccination, and one received the inactivated COVID-19 vaccine (Sinovac).

Tolerability of mRNA vaccine in test-negative patients

A total of 13 patients (81.2%) were negative in both the skin test and BAT, and 10 (76.9%) of these patients subsequently received the COVID-19 mRNA vaccine (Biontech). Nine patients (90%) had no reactions. One patient was skin test negative but reacted to the first dose of vaccine, with symptoms being generalized urticarial angioedema (Table 3).

Discussion

The mechanisms of Gell and Coombs classification explain HR to conventional vaccines. CARPA is also related to the etiopathogenesis of non-IgE reactions. Serum tryptase and complement levels help clarify the mechanism of post-vaccination reactions. In addition, nonimmunologic reactions may present as allergic reactions, vasovagal reactions, inducible laryngeal obstruction, panic attacks, or anxiety-related symptoms that require differential diagnosis with anaphylaxis. A Centers for Disease Control and Prevention (CDC) report indicates that 35% of cases reported as severe allergic reactions were not allergic reactions.^{12,13} Within this context, we aimed to share

Table 1 Patients with certain/suspicious multiple drug hypersensitivity including PEG/polysorbate 80-20.

Patient number	Age(y), sex	Drug names/groups	Administration route	Reaction type	Other allergies/comorbidities
P1	17, F	Etoposide (containing P80)	iv	Anaphylaxis	BCOR/CCN3 sarcoma
P2	21, F	COVID-19 inactive vaccine (Sinovac)	im	Angioedema	Primary immunodeficiency
		Intravenous immunoglobulin	iv	Urticaria-angioedema	
		Multiple parenteral drugs, Tocilizumab	iv, im	Urticaria-angioedema	
P3	8, M	Infliximab (containing P80)	iv	Anaphylaxis	Crohn's Disease
P4	16, F	COVID-19 mRNA vaccine (BioNTech)	im	Anaphylaxis	Asthma, Food allergy
		DTaP - IPV - Hib Vaccine	im	Urticaria	Chronic urticaria
					Idiopathic anaphylaxis
					Allergic rhinitis
P5	15, M	Infliximab (containing P80)	iv	Anaphylaxis	Dermographism
					Ulcerative colitis
P6	17, M	House dust mite immunotherapy	sc	Anaphylaxis	Asthma
					Allergic rhinitis
P7	16, M	House dust mite immunotherapy	sc	Anaphylaxis	Asthma
					allergic rhinitis
P8	13, F	Cefixime	po	Anaphylaxis	Asthma
		Cefuroxime	iv		
		General anesthetics	iv		
P9	14, M	Ceftriaxone	iv	Anaphylaxis	Asthma
P10	16, M	Benzathine penicillin G	im	Urticaria-angioedema	Asthma
		Influenza vaccine?	im	Dyspnea	
P11	17, M	Multiple ampicillin/sulbactam or unknown drugs?	im/iv	Urticaria-angioedema	FMF
					Asthma
P12	13, F	Multiple penicillin? group antibiotics (unknown)	iv	Anaphylaxis	None
P13	16, M	Ibuprofen, Acetaminophen	po	Urticaria-angioedema	Asthma
		Unknown herbal medicine	po	Anaphylaxis	
		Marjoram (an aromatic herb)			
P14	14, F	Local anesthetic (Unknown name).	sc		None
		Cetirizine, Clarithromycin, Ibuprofen	po	Urticaria	
P15	17, F	Multiple penicillin? group antibiotics (unknown)	im/iv	Urticaria	None
			iv	Type 2 HR	
		Ceftriaxone			
P16	15, F	Cefazoline	iv	Angioedema	None

JIA, juvenile idiopathic arthritis; FMF, familial mediterranean fever; HR, hypersensitivity reactions; iv, intravenous; im, intramuscular; sc, subcutaneous.

the patients referred to our clinic with suspected PEG/polysorbate or mRNA vaccine allergies.

The World Allergy Organization (WAO) considers patients with a previous allergic reaction to a vaccine component (PEG and polysorbate 80) or a first dose of the vaccine to be at particular risk. Patients with immediate HR to multiple drugs or anaphylaxis with PEGylated parenteral monoclonal antibodies, mast cell disease, or idiopathic anaphylaxis were also included in the intermediate-risk group.¹⁴

PEG and polysorbate are hydrophilic polymers in many products, such as food and beverages, drugs, and cosmetics. Medical products, especially therapeutics and radio-contrast agents, contain PEG, but PEG-related HRs are rare. Different molecular weight structural forms of PEG affect tolerability. While the risk of HRs increases with higher molecular weight forms or parenteral administration, low molecular weight forms and oral administration are tolerable. There is limited evidence of cross-reactivity between PEG and polysorbate derivatives.^{3,10,15}

Table 2 Patients with positive skin testing results.

Patient number	Skin test results*	Basophil Activation test	Preferred vaccine	Vaccination outcome
P4	PEG 40 mg/mL SPT (Depomedrol: 3 mm Polysorbate 20 SPT (Havrix 1/1): 3 mm Polysorbate 80 SPT (Prevenar 1/1): 4 mm	PEG 2000 and 4000 were negative	None	Refused desensitization or alternative vaccination
P6	PEG 40 mg/mL SPT (Depomedrol: 3 mm Polysorbate 20 SPT (Havrix 1/1): 3 mm	None	COVID-19 inactivated vaccine (Sinovac)	No reaction
P9	PEG 40 mg/mL SPT (Depomedrol: 4 mm Polysorbate 20 SPT (Havrix 1/1): 3 mm	None	None	Refused desensitization or alternative vaccination

*IDT was not performed because SPT was positive
PEG, polyethylene glycol; SPT, skin prick test.

Table 3 Patients with negative skin testing results.

Patient number	Skin test results (DPT-IDT)	Basophil activation test	Preferred vaccine	Vaccination outcome
P1	Negative	None	None	Refused vaccination
P2	Negative	None	COVID-19 mRNA vaccine (Biontech)	Urticaria-angioedema
P3	Negative	PEG 2000 and 4000 were negative	None	Refused vaccination
P5	Dermographism	PEG 2000 and 4000 were negative	COVID-19 mRNA vaccine (Biontech)	No reaction
P7	Negative	None	None	Refused vaccination
P8	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P10	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P11	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P12	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P13	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P14	Negative	None	None	Refused vaccination
P15	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction
P16	Negative	None	COVID-19 mRNA vaccine (Biontech)	No reaction

IDT, intradermal test.

Presumably, PEG is more immunogenic than predicted. PEG sensitization develops with the production of anti-drug antibodies (ADA) and complement activation. Several products contain PEG as a “hidden allergen” and trigger HRs with IgE/non-IgE mechanisms, with clinical findings including anaphylaxis.¹⁶⁻¹⁸

The positive and negative predictive value of skin testing to PEG in evaluating potential allergy to mRNA vaccines is unclear. However, it has helped evaluate individuals with anaphylaxis in the past to PEG. PEG is the only component that can be tested with mRNA vaccines against SARS-CoV-2 using skin prick and intradermal testing. Banerji et al. identified three distinct risk groups for vaccine handling.⁹

In the risk assessment, five of our patients definitely had reactions with PEG-containing agents. Although the positive predictive value of the PEG skin test was not clear when our patients were evaluated, it was recommended to

be used to reduce the risks of vaccination. Six patients had a history of severe allergic reactions to several injectable drugs. However, it could not be excluded that PEG or polysorbate derivatives were present in the drug because the history was older, and the families needed help remembering the exact names of the drugs. Skin testing was performed on five patients because of the possibility that families would reject the vaccine without testing.

Several studies have recommended different diagnostic algorithms based on clinical evaluation with PEG, polysorbate 80, and skin testing with excipients.^{9,10} In contrast, the evaluation of PEG-related HRs is complex. The positive predictive value of PEG skin testing has been investigated in many studies, and the “International Consensus” does not recommend its routine use to determine the risk of COVID-19 vaccine-related allergic reactions. Greenhawt et al. used skin testing to detect PEG allergy; sensitivity was 58.8%, and specificity was 99.5%.³

In another similar study,⁸ the diagnostic algorithm recommended by Banerji et al.⁹ was applied to 80 patients who reported an HR after the first dose of COVID-19 vaccine and were evaluated by a PEG and/or polysorbate 80 skin test. Sixty-five of the patients had a rapid response. All 65 patients had an immediate reaction. Of these, two patients had positive test results with PEG, four had positive skin tests with polysorbate 80, and two had both. The second dose of the SARS-CoV-2 mRNA vaccine was tolerated by 67% of patients. On the other hand, 25% of patients with a history of immediate allergic reactions and a negative PEG skin test result developed an allergic reaction after the second dose of the vaccine. Although most patients experienced mild skin reactions, two patients were reported to suffer anaphylaxis requiring epinephrine. Consequently, skin testing for adjuvants was not of value for clinical risk assessment in mRNA-SARS CoV-2 vaccine-related allergic reactions after the first dose. However, it helped evaluate patients with PEG-related anaphylaxis. Also, Brockow et al., in their study evaluating 421 patients, noted that skin tests have little diagnostic value.⁶ In our cohort, only one of the three patients with PEG and/or polysorbate sensitivity had a history of anaphylaxis from the PEG-containing vaccine. In contrast, two patients had anaphylaxis with PEG/polysorbate-free agents. Ten of the 13 patients with negative skin tests had allergic reactions to agents containing/suspected to contain PEG/polysorbate. Although skin tests were negative, one patient developed urticarial angioedema after vaccination. PEG/Polysorbate may not act through an IgE-mediated mechanism, and PEG/polysorbate may not be the only responsible factor. It has also been correctly observed that PEGs used in vaccines are formulated differently, which could affect tolerability. In addition, the molecular weight and co-formulation of PEG, used in mRNA vaccines, differ from PEG in other drugs and products, which may affect tolerability.¹

There is no standardization in skin testing with the SARS CoV2 mRNA vaccine, and the small number of patients tested with the vaccine results in limited certainty of results. Positive skin testing with the vaccine has been reported in a few patients who did not respond to vaccination.¹⁹⁻²¹

The use of PEG and polysorbate testing in the evaluation of SARS-CoV-2 mRNA-related HRs is questioned because there is no evidence that PEG is a causative agent in the reported SARS-CoV-2 mRNA vaccine-related reactions, and the diagnostic value of PEG and polysorbate testing is low. The cumulative data suggest that risk management of SARS-CoV-2 mRNA-related HRs should be independent of PEG skin testing. International consensus does not recommend skin testing or in vitro testing with mRNA vaccines or adjuvants because the sensitivity/specificity in predicting severe allergic reactions is unknown. However, this recommendation was noted as a conditional recommendation with a low level of evidence and recommended that PEG skin testing be considered in high-risk patients who would refuse vaccination if testing was not performed.³

The general recommendation for patients describing severe reactions to drugs, foods, and allergens, such as toxins that do not contain the adjuvants in the SARS-CoV-2 vaccines, is to be routinely vaccinated with safety precautions. The mechanisms of allergic reactions associated

with the mRNA COVID-19 vaccine are poorly understood. Excipients such as PEG and polysorbate 80 used in COVID-19 vaccines could be potential allergens, but this hypothesis is unclear. The predictive values of these excipients for skin testing and in vitro testing are controversial. The low number of participants and the need for more standardization of the skin tests are the limitations of our study.

Conclusion

Mislabeled drug allergies can be problematic for patients, especially for future prescriptions or vaccinations. Polysorbate and PEG are widely used as active ingredients in many drugs and vaccines. Sensitization to these substances may not necessarily be a true allergy and should be verified by provocation tests. Prompt diagnosis would avoid anxiety and allow patients to receive vaccinations without further complications.

In conclusion, further research on the HR of excipients, predictive values of skin tests, and etiopathogenesis is needed. High-risk patients should be evaluated according to the individual benefit/risk ratio assessed by the allergist/immunologist.

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