




Re-Administration Experience Following Allergic Reaction After Vaccination with BNT162b2 mRNA COVID-19

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ABSTRACT

Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human coronavirus, has caused the global COVID-19 pandemic. Allergic reactions and anaphylaxis have been reported rarely following the release of the COVID-19 vaccine. In general, administration of the second dose to patients experiencing an adverse reaction after the first dose was considered contraindicated, whereas full-dose vaccination is now recommended. Although uneventful administration of a second dose is also mentioned in the current literature, management is not standardized in this regard. Our aim was to establish a successful re-administration protocol in patients with a history of allergic reaction to the first dose of vaccine and to safely vaccinate the most people with the least amount of vaccine.

Materials and Methods: Nine patients presenting to our clinic between September 2021 and November 2021 were evaluated. Allergy skin tests with PEG 3350 and PS 80 were planned. With the results, existing literature protocols were modified according to the conditions and applied with gradual dose increase/desensitization.

Results: Despite the reactions that developed after the first dose of the BNT162b2 mRNA vaccine, 8 patients were successfully re-administered.

Conclusion: We believe that recommendations for successful vaccination with gradual dose increase/desensitization will be beneficial for patients and clinicians in the treatment of patients who develop an allergic reaction with the first dose, in the current period when re-administration is advocated.

Keywords: Allergy, covid-19, BNT162b2 mRNA, desensitization

Abbreviations: SARS-CoV- 2: Severe Acute Respiratory Syndrome Coronavirus 2
FDA: Food and Drug Administration
COVID-19: Coronavirus disease 2019
USA: United States of America
CDC: The Center for Disease Control and Prevention
VAERS: The Vaccine Adverse Event Reporting System
PEG: Polyethylene glycol
SPT: Skin prick test
IDT: Intradermal test

NPV: Negative predictive value
MPE: Maculopapular exanthema
FDE: Fixed drug eruption
SCARs: Severe cutaneous allergic reactions
EAACI: European Academy of Allergy and Clinical Immunology
ENDA: European Network on Drug Allergy
EAACI: European Academy of Allergy & Clinical Immunology

INTRODUCTION

The COVID-19 pandemic was a global disaster. Since December 2020, the BNT162b2 mRNA-based COVID-19 vaccine has been used to prevent the 2019 coronavirus disease (COVID-19) (1-4). The COVID-19 vaccine is a very important global measure in the fight against SARS-Cov-2.

Many of the substances known to cause vaccine allergic reactions, such as latex, egg protein, gelatin, surfactant, and polysorbate 80(PS80), are not present in the BNT162b2 mRNA vaccine. Cases of anaphylaxis were surprising as no anaphylaxis was seen in phase 2/3 clinical trials. The rate of anaphylaxis from COVID mRNA vaccines is estimated to be two to five times higher than other regularly administered vaccines, such as the inactivated flu vaccine (1,3-5).

When the first allergy cases were reported, it caused great concern in people with a history of atopic and allergic reactions, which we frequently encounter in our daily practice (6). The task of answering patients' questions was first entrusted to us allergists and immunologists. While it is true that the Centers for Disease Control and Prevention(CDC) continues to recommend an alternative vaccine for patients suffering from an allergic reaction (7), this is expected to change soon as evidence now convincingly shows that safe administration of the same vaccine is possible (8,9).

In our study, we aimed to develop the healthiest approach to our patients, taking into account the country and clinical conditions in the light of the available literature. In particular, it was aimed to prevent patients from avoiding unnecessary vaccination due to their allergy history and to ensure that they are vaccinated with the necessary counseling service and appropriate approach.

MATERIAL and METHODS

Patient Population

Patients who presented to our outpatient clinic with a history of allergic reaction after the first dose of BNT162b-2mRNA vaccine between September 2021 and November 2021 were targeted. Demographic features, comorbidities, atopy history, severity of allergic reaction, and chronology of the cases were evaluated (Table I). The Ring and Messmer anaphylaxis classification was used to classify the severity of allergic reaction (10). Patients who wanted

to receive a dose of the vaccine and gave consent to the tests and re-administration protocol were included in the study. A total of nine subjects were included. Only patient number 6, who presented to our clinic before the first vaccination because of a history of multiple drug allergy and asthma, was considered to have Polyethylene Glycol (PEG) allergy and skin tests were performed before the first dose, although there was no history of a reaction with the vaccine. Patients were referred from different vaccination centers. Post-reaction tryptase levels were not available in any of the nine cases.

Study Design

Consent was obtained from all patients and the allergic skin tests shown in Table II were performed in all patients. Prick tests were performed to detect PEG 3350 and PS 80 allergy using drugs that use these products as excipients. PEG 3350 (Medroxyprogesterone acetate - Depomedrol®), PS80 (Triamcinolone acetonide - kenakort®), methyl-prednisolone (Precort® was chosen in order detect possible methyl-prednisolone allergy because it does not contain PEG and PS80 as an excipient) (11). The Skin Prick Test (SPT) was performed with the drug itself and at a diluted ratio of 1:10. Intradermal tests (IDT) were also at 1:100 and 1:10. These were applied separately for the 3 drugs as diluted. The routine application time of the prick and intradermal skin tests was 20 minutes. The total test time was determined as 80 minutes.

SPT results were discussed with the patients. Patients who wanted to be vaccinated were informed and their consent was obtained. Patient 7, who had a history of food-induced anaphylaxis and was treated with adrenaline after the first dose of the vaccine, did not give consent and the second dose of vaccine was not administered.

Other patients were administered the vaccine with a gradual increase in the dose. The vaccine was diluted as the total dose of the vaccine was not very suitable for disintegration (only 0.3 cc). 0.3 ml of vaccine was diluted with 2.7 ml of saline. A total of 3 ml of vaccine was administered gradually. Since there was no tryptase level in the patients and the allergic test result was not positive in the other patients except patient 6 who was tested with suspicion of PEG allergy, it would be appropriate to call this application as re-administration with gradual dose increase instead of desensitization (Table III).

Table 1: Case summary.

ID	Age	Sex	History of anaphylaxis	Atopy history	Onset of symptoms (min)	Symptoms and signs	Classification of anaphylaxis severity (Ring and Messmer)	Epinephrine received	Vaccine Dose	Allergometric test results	Result
Case 1	47	F	None	None	30	Generalized urticaria, labial AE	Grade 1	No	1.	Negative	2 nd dose applied without problem.
Case 2	44	F	None	Penicillin allergy	30	Uvula edema lip numbness, palate itching, hypertension	Grade 1	No	1.	Negative	2 nd dose applied without problem
Case 3	45	M	None	None Gout disease	20	Dizziness, lightheadedness, hypotension 70/50	Grade 2	No	1.	Negative	2 nd dose applied without problem
Case 4	21	M	None	AR, pollen scit CIU	360	Generalized urticaria	Grade 1	No	1.	Negative	2 nd dose applied without problem
Case 5	49	F	None	Paracetamol allergy	120	Isolated angioedema around the eyes	Grade 1	No	1.	Negative	2 nd dose applied without problem
Case 6	50	F	None	NSAID allergy, Asthma, HT					0.	Depomedrol 1/10 intradermal; 9 mm enduration	1 st dose applied without problem
Case 7	24	F	Milk allergy 3 times rx	AR, pollen	60	Tongue swelling, AE, itching, vomiting, diarrhea	Grade 2	Yes	1.	Negative	the patient did not want
Case 8	47	F	None	CIU, AR, pollen Asthma Antibiotics allergy Cefuroxime, Cefaclor	5	Flushing, urticaria, itching, numbness in the tongue, palpitation hypertension	Grade 2	No	1.	Negative	2 nd dose applied without problem
Case 9	36	F	None	CIU, Asthma, Naproxen	300	Generalized urticaria, shortness of breath, edema in the face	Grade 2	No	1.	Negative	2 nd dose applied without problem

AR: Allergic rhinitis, Scit: Subcutaneous immunotherapy, NSAID: Nonsteroidal anti-inflammatory drug, CIU: Chronic idiopathic urticaria, HT: Hypertension, AE: Angioedema

Table II: Skin test protocol.

Step	Tested drug	Dilution	Time (min)
Positive control	Histamine	1:1	
Negative control	SF	1:1	
Prick test 1 st step	Methyl-prednisolone acetate (depo-medrol)	1:10	20
	Triamcinolone acetonide (kenacort, sinakort)	1:10	
	Methyl-prednisolone acetate (precort-liyo, prednol)	1:10	
SPT 2 nd step	Methyl-prednisolone acetate (depo-medrol)	undiluted 1:1	20
	Triamcinolone acetonide (kenacort, sinakort)	undiluted 1:1	
	Methyl-prednisolone acetate (precort-liyo, prednol)	undiluted 1:1	
Intradermal 1 st step	Methyl-prednisolone acetate (depo-medrol)	1:100	20
	Triamcinolone acetonide (kenacort, sinakort)	1:100	
	Methyl-prednisolone acetate (precort-liyo, prednol)	1:100	
Intradermal 2 nd step	Methyl-prednisolone acetate (depo-medrol)	1:10	20
	Triamcinolone acetonide (kenacort, sinakort)	1:10	
	Methyl-prednisolone acetate (precort-liyo, prednol)	1:10	
		Total time	80 (min)

Allergometric tests modified from Banerji et al. (11) used for patients with suspected polyethylene glycol (PEG) and/or Polysorbate 80 (PS80) hypersensitivity. To test PEG 3350 and PS80 intradermally, Methyl-prednisolone Acetate (Depo-Medrol) 40 mg/ml and Triamcinolone acetate

Table III: Desensitization/gradual dose escalation protocol.

Step	Dose (ml) (1:10 diluted)	Dose (ml)	Cumulative Dose (ml)	Time (min)
1	0.3	0.03	0.3	30
2	0.7	0.07	1	30
3	1	0.1	2	30
4	1	0.1	3	30
			3	120

The desensitization/gradual dose escalation protocol used for BNT162b2 mRNA vaccine administration in patients with PEG positive or hypersensitivity reactions after the first vaccine dose. The protocol applied by Paoletti et al. (26) has been modified. 0.3 ml of vaccine was diluted with 2.7 ml of physiological saline. A total of 3 ml of the vaccine was administered gradually.

During the applications, the dissolution and storage conditions of the vaccine were taken into account. Again, unlike the literature, no premedication was administered.

The study was approved by the Medical Specialization Education Board and the Local Ethics Committee (Approval no: 111-08/2022) Informed consent forms were obtained from all patients before treatment.

RESULTS

A total of 9 patients were evaluated in our study. The majority of the patients were female (F/M; 7/2). Demographic information of the patients with the mean ages

is detailed in Table I. Only two of them had no known allergy history. While one of the patients had gout and one had hypertension, the diagnoses of asthma, allergic rhinitis, and chronic idiopathic urticaria were more common. There were no diseases such as chronic renal failure or liver failure that would pose a risk in terms of drug allergy (Table I). Reaction periods were described in the first 2 hours, except for 3 patients. Two patients complained of urticaria in the late period. All patients described findings consistent with early-stage drug reaction. According to the anaphylaxis severity classification (Ring and Messmer), four patients were grade 2. Epinephrine was administered to one patient. Those whose baseline tryptase values were

measured among our patients were within the normal reference range. Mastocytosis was not considered in the cases. SPT and IDT were performed on nine patients as shown in Table II. Test results of the depomedrol 1/10 intradermal test resulted in 9 mm + induration and hyperemia in only one patient. Skin tests of other patients were negative. During the skin tests, no allergic reaction or side effects were observed. The test results were re-evaluated with the patients. Consent was obtained from 8 patients who wanted to be vaccinated.

The vaccine application process was successfully performed for 8 patients with the protocol specified in Table III. The re-administration process was completed in 120 minutes with the protocol we prepared. No allergic reaction or side effects were observed in the patients during or after the vaccination.

DISCUSSION

More than 13.3 billion doses of COVID-19 vaccine have been administered worldwide for the SARS-CoV-2 epidemic, which infected more than 673 million people and resulted in more than 6.7 million deaths (4). It should be our aim not to deprive people with a history of allergic disease, who have an allergic reaction to vaccines or additives, and to encourage them to be vaccinated. Contrary to our initial knowledge, many studies support the reuse of vaccines (7-9). This is where the persuasive power of clinicians and clients comes into play. Scientific evidence is needed for this.

Possible allergic reaction mechanisms (12) of mRNA vaccines are being investigated. Various mechanisms are blamed, from contact system activation to mast cell degranulation due to mast cell hypersensitivity caused by genetic and environmental factors, from IgE-mediated reaction to PEG to complement system activation. Potential mechanisms include mast cell hypersensitivity due to host factors (12). There is an increased frequency in female patients. The majority of the patients in our study were women. A history of atopy and previous anaphylaxis seem to be important risk factors (12). As seen in our patients, the current literature reveals that most patients have a history of asthma, allergic rhinitis, chronic urticaria, and food, drug or venom allergy (13). Pre-vaccination testing was neither possible nor necessary for all of these patients. However, high risk is a reality that needs to be taken into account. Therefore, these patients should be vaccinated under observation for at least 30-60 minutes

in health institutions where immediate intervention can be performed for anaphylaxis. It would be appropriate for allergy and immunology specialists to pre-evaluate patients with multiple allergies, a history of allergic reaction to the vaccine itself, or an allergic reaction to the excipients (14,15). In Case 6, we evaluated the patient before vaccination and suspected PEG allergy. The patient had allergies to different preparations of the same active substance. She also had multiple drug allergies and asthma. When PEG intradermal test was positive at 1:10 dilution, an alternative vaccine was recommended to the patient. After the patient stated that she wanted to be vaccinated with BNT162b2 mRNA, the first dose was administered without any problems.

It is not possible to detect all of these mechanisms with tests that are part of daily practice. Among these mechanisms, testing recommendations are only made to detect allergic reactions associated with PEG or PS 80 (9-16). Banerji et al. (11) recommended skin testing with PEG to evaluate anaphylactic reactions to BNT162b2 mRNA vaccines. Skin prick and intradermal test early assessment can detect only IgE-mediated reactions to PEG-PS80 allergies. However, IgE-mediated hypersensitivity reactions are not the only mechanisms by which allergic reactions to PEG develop (17). Incidentally, it is also known that PEG or PS 80 is not the only component in vaccines that has the potential to cause allergy. Therefore, we think that the usefulness of skin tests is limited. While the necessity of skin testing is being discussed, what to do the tests with is also a subject of research in the literature (18,19). In a study conducted among Italian healthcare workers, SPT and IDT were performed with 1/100-1/1000 dilution of pure BNT162b2 mRNA vaccine (19). SPT was negative in all patients, but IDT at 1/1000 dilution was positive in all patients. However, all patients completed their second dose of vaccine without any allergic reaction. Large-scale studies are needed to investigate the benefit of SPT and IDT in combination with the vaccine itself (19). We did not perform testing with the vaccine.

Many studies have discussed how these skin tests are performed and their effectiveness (8,20,21). Among the studies investigating the efficacy of skin tests, Wolfson et al. (8) have evaluated 80 patients with allergic reactions to the first dose of mRNA vaccines with skin tests. Regardless of the test result, 74% of the 80 patients tolerated the second dose of the vaccine without problems. The negative predictive values of the tests were found to be around

75%. These and similar results have raised questions about patient referral based on skin tests. Similarly, the skin test results of the patients in our study were positive in only one patient, and none of our patients, including our positive patient, experienced any problems with the administration of two doses.

Delayed type reactions were included in another part of the same study (8). When delayed type reactions are examined, it is emphasized that they are mostly cutaneous (93%). However, they do not include severe cutaneous allergic reactions (SCAR). The recommended dose is to administer the full dose with 15 minutes of observation (8). We think that such a definition may lead to misunderstandings. The delayed type drug reactions in the study are symptoms such as urticaria, diarrhea, and vomiting that occur after 4-6 hours. The immunological mechanism of delayed urticaria is not fully understood (22). Since only a small proportion of patients (about 40%) experienced recurrent urticaria after the second dose of the vaccine, we believe that patients may tolerate the vaccine. Some of our patients were late cases of urticaria and tolerated 2 doses.

For all these reasons, we believe that reaction development will be prevented if the temperature of the vaccine administered is close to body temperature, the injection speed is slow, and it is administered by diluting and dividing the dose. In our study, we did not administer premedication to the patients. Only one patient continued routine montelukast/antihistamine combination therapy for allergic rhinitis, approximately 12 hours before the procedure. Recently, premedication was also used in the vaccine desensitization procedure published by Cahill and Kan (23). In other studies, re-administration protocols were created with premedication recommendations. Similar to contrast agent allergies, premedication (24) may be beneficial in preventing mast cell degranulation. It can be used, but desensitization/gradual dose increase can be successfully completed without the need for premedication with the protocol we have specified.

For patients who develop an allergic reaction after the first dose of mRNA vaccines prepared with the algorithm suggested by Wolfson et al. (8), it is recommended to administer the full dose of the vaccine and to keep the patient under observation for 30 minutes in cases of sudden allergic reactions other than anaphylaxis. At this point, we think it is difficult to adapt algorithms to real life. It is very difficult for the patient to decide on a second

dose of the vaccine, especially in the patient group with a history of allergic disease who are widely opposed to the vaccine, and who have intense reservations about the vaccine. It is difficult to persuade a patient given a first dose of epinephrine for anaphylaxis to accept a second dose. This situation is risky for us clinicians. In such cases, we think that an application recommendation such as gradual dose increase/desensitization will relieve the patient and the clinician.

Iemoli E et al. (25) have applied their protocol to severe asthma patients consisting of two cases, with or without dilution, but this which was terminated unsuccessfully (13). Again, there is a different protocol that Cahill and Kan (23) have successfully applied in two cases of anaphylaxis (15). With our protocol, the vaccination of eight patients was successfully completed. Unlike other protocols, a single dose of the vaccine was used for administration and a second dose of vaccine was not required. There was no loss of vaccine.

The limitation of this protocol may be the application duration. A protocol lasting 120 minutes instead of 15 minutes to 30 minutes of injection and observation seems to be a complicating factor for vaccination. The length of the waiting period did not cause any problems among our cases. We can say that they felt safe. Not testing the vaccine itself may be a limitation. The difficulty of accessing the vaccine is a factor.

In conclusion, there is no global consensus on optimal allergic research and management of patients who have previously responded to the BNT162b2 mRNA vaccines (9). A new recommendation report has been published following our clinical practice. The main area of disagreement in the content of the EAACI/ENDA status report, which emerged as a result of a survey of 64 participants from 19 countries, is whether doses should be segmented when vaccinating patients considered to be at high risk of allergic reactions (9). One-third of the participants were against administering the vaccine in divided doses. We also have reservations about this issue, but we think that it is difficult to develop full standardization of the matter as the situation is different in every country. The vaccination rate, vaccination perspective, alternative vaccines, and efficacy of alternative vaccines underlie the differences in decision making. Of course, there are question marks about the split-dose vaccine administration (9,26). There is no clear information about the destabilization of

the vaccine, the risk of damaging the lipid nanoparticles, and the risk of causing a change in the immunogenicity of the vaccine. We continue to be concerned about this issue. New evidence is needed regarding the antibody responses of patients receiving the split-dose vaccine. In addition, the case statement does not ethically recommend using an extra vaccine for allergy testing or fractional re-administration as there is a huge shortage of vaccine doses worldwide (9).

CONCLUSIONS

Patients with atopy and allergic diseases are at higher risk of allergic reactions to the vaccine. This does not prevent vaccination in a controlled manner. We do not think that it is correct to guide patients according to skin tests, but studies can be done on this subject. Algorithms may not be applicable in daily practice. According to the conditions of the countries, the patients should be evaluated and a decision made individually.

It may be possible to vaccinate patients who develop an allergic reaction to the first dose. We think that recommendations for gradual dose escalation/desensitization and successful vaccination will help clinicians and patients make better decisions.

Conflict of Interest

The authors report no conflicts of interest in this work.

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Authorship Contributions

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