

Hypothesis & Experience
Letter to the Editor



Utility of skin testing in assessment of post-AZD1222 vaccine (AstraZeneca) allergic reactions: case series in Vietnam

Mai Thi Vu ¹, Anh Quynh Nguyen ¹, Bo Duy Nguyen¹, Huong Thu Duong ², Quyet Van Nguyen³, Ha Hai Nguyen⁴, Lam Nam Phung^{5,6}, and Dinh Van Nguyen ^{1,6,*}

¹Respiratory, Allergy and Immunology Unit, Internal Medicine Department, Vinmec Healthcare System, Hanoi, Vietnam

²Pharmacy Department, Vinmec Healthcare System, Hanoi, Vietnam

³Health Check Department, Vinmec Healthcare System, Hanoi, Vietnam

⁴Vaccine Center, Vinmec Healthcare System, Hanoi, Vietnam

⁵Intensive Care Unit, Vinmec Healthcare System, Hanoi, Vietnam

⁶College of Health Sciences, VinUniversity, Hanoi, Vietnam



Received: Sep 29, 2021

Accepted: Oct 19, 2021

*Correspondence to

Dinh Van Nguyen

Respiratory, Allergy and Immunology Unit, Internal Medicine Department, Vinmec Healthcare System, College of Health Sciences, VinUniversity, 458 Minh Khai, Hai Ba Trung, Hanoi, Vietnam.

Tel: +842439743556

Email: v.dinhnv6@vinmec.com

Copyright © 2021. Asia Pacific Association of Allergy, Asthma and Clinical Immunology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Mai Thi Vu

<https://orcid.org/0000-0002-5383-5429>

Anh Quynh Nguyen

<https://orcid.org/0000-0002-2640-6354>

Huong Thu Duong

<https://orcid.org/0000-0002-5296-8123>

Dinh Van Nguyen

<https://orcid.org/0000-0002-5675-0850>

To the editor,

The coronavirus disease 2019 (COVID-19) pandemic is a global health emergency with more than 200 million cases and 4.5 million deaths. Vaccination is one of the main preventive measures to bring the current COVID-19 pandemic under control. Vaccines may cause adverse events; however, the majority of those adverse events are not allergic. Anaphylaxis induced by vaccines occurs approximately at a rate of 1.3:1,000,000 doses of vaccine [1]. Recent data indicate that the incidence of COVID-19 vaccine-induced anaphylaxis is higher than that of all previous vaccines. The rates of anaphylaxis caused by the novel mRNA vaccine BNT162b2 (Pfizer-BioNTech, Mainz, Germany) and mRNA-1273 (Moderna, Cambridge, MA) are 4.7:1,000,000 doses and 2.8:1,000,000 doses, respectively [2]. Early data estimates the anaphylaxis rate after AZD1222 vaccination is 7.4:1,000,000 doses [3].

Vaccine allergy is mainly caused by excipients rather than an active ingredient of the vaccine. For mRNA COVID-19 vaccines, PEG 2000 (a component of BNT162b2 and mRNA-1273) and tromethamine (in mRNA-1273) are thought to be the allergenic components, while polysorbate 80, a derivative of polyethylene glycol (PEG), is proposed as the culprit antigen of the AZD1222 vaccine [4]. However, it remains unclear whether PEG, tromethamine, or polysorbate 80 cause all of the allergic reactions to these vaccines.

It is currently recommended for those at high-risk of allergic reactions, such as people with suspected or confirmed allergy to the first dose of COVID-19 vaccine to have a vaccine from a different vaccine group or to have a graded dose of the same vaccine administered [5]. Use of skin testing for COVID-19 vaccines and their components such as PEG and polysorbate in high-risk groups has been reported to confirm the diagnosis of vaccine-induced allergic reactions. However, the sensitivity, specificity, and predictive value of skin testing have not been evaluated [4-8].

In this case series, we examined the utility of skin testing in patients who had allergic reactions after the first dose of the AZD1222 vaccine. Ten patients with suspected allergic

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Mai Thi Vu, Anh Quynh Nguyen, Bo Duy Nguyen, Lam Nam Phung, Dinh Van Nguyen. Formal analysis: Mai Thi Vu, Anh Quynh Nguyen, Bo Duy Nguyen, Dinh Van Nguyen. Investigation: Mai Thi Vu, Anh Quynh Nguyen, Bo Duy Nguyen, Huong Thu Duong, Quyet Van Nguyen, Ha Hai Nguyen, Dinh Van Nguyen. Methodology: Mai Thi Vu, Anh Quynh Nguyen, Bo Duy Nguyen, Dinh Van Nguyen. Project administration: Lam Nam Phung, Dinh Van Nguyen. Writing - original draft: Mai Thi Vu, Huong Thu Duong, Dinh Van Nguyen. Writing - review & editing: Mai Thi Vu, Anh Quynh Nguyen, Bo Duy Nguyen, Huong Thu Duong, Quyet Van Nguyen, Ha Hai Nguyen, Lam Nam Phung, Dinh Van Nguyen.

reactions post vaccination visited our clinics of allergy and clinical immunology at Vinmec International Hospital, Times City. Their history of allergy and clinical manifestations were examined carefully. Of those, 6 had symptoms within 4 hours, defined as immediate reactions [6] and the remaining 4 showed nonimmediate allergic reactions with onset of symptoms 5 to 12 hours after vaccination. Testing with PEG, polysorbate, and COVID-19 vaccines including AZD1222, BNT162b2, and mRNA-1273 was performed prior to the administration of a second dose of a vaccine.

PROTOCOLS

Selected pharmaceutical products containing PEG 3350, PEG 4000, polysorbate 20, and polysorbate 80 were used for skin testing (**Table 1**). Skin testing with PEG 3350 and PEG 4000 aimed to assess the risk of allergy to PEG 2000, a component of mRNA vaccines. PEG 3350 and PEG 4000 were used for a skin test based on the report of Banerji et al. [7], due to an unavailability of PEG 2000 in Vietnam. Skin testing with polysorbate 20 and polysorbate 80 aimed to evaluate the risk of polysorbate allergy in the AZD1222 vaccine. Dilutions used and the order of testing is illustrated in **Table 1**. Time intervals between steps were 20 minutes.

Skin prick tests with undiluted AZD1222, BNT162b2, and mRNA-1273 vaccines were performed undiluted and intradermal (ID) tests were conducted using 1/10 dilutions of each vaccine. The result was read and recorded after 20 minutes (**Fig. 1**).

The results are presented in **Table 2**. Of 6 patients (#01, #04, #05, #06, #07, and #08) who developed allergic symptoms rapidly following the AZD1222 vaccine, 4 of them (patient #01, #04, #05, and #06) had positive prick and ID tests to the AZD1222 vaccine. These 6 patients had negative skin tests to polysorbate 20 and polysorbate 80. Patient #01 then received the BNT162b2 vaccine for the second dose without prior BNT162b2 skin testing. Patient #05 had a negative skin test with PEG but a positive test with the BNT162b2 vaccine at a 1/10 dilution (ID test). This patient was then vaccinated with the BNT162b2 vaccine in graded doses without any subsequent allergic reaction (outcomes for patients #4 and #6).

Of the remaining 2 patients who had suffered rapid allergic symptoms, patient #08 had a negative skin test with the AZD1222 vaccine and patient #07 refused to have a skin test with the AZD1222 vaccine because of a clear clinical history of anaphylaxis after AZD1222 vaccination. Patient #08 then received the second dose of AZD1222 in graded doses due to the immediate reaction the patient suffered after the first dose. Patient #07 had a negative skin test with BNT162b2. This patient refused skin testing with PEG, however, she tolerated the BNT162b2 vaccine as her second COVID 19 vaccine dose.

Table 1. Diluted concentrations and steps of a skin test to polyethylene glycol (PEG) and polysorbate

Step	Skin test	Positive control	Negative control	PEG-4000		PEG 3350		Polysorbate 20	Polysorbate 80	
		Histamine	NaCl 0.9%	Forlax (80 mg/mL)	Depo-Medrol (40 mg/mL)	Negative control: Solumedrol (40 mg/mL)	Twinrix vaccine	Triamcinolone (40 mg/mL)	Vitamin K (10 mg/mL)	
1	Prick test	-	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
2	Intradermal test	-	1/1	-	1/100	1/100	1/100	1/100	1/100	1/10
3	Intradermal test	-	-	-	1/10	1/10	1/10	1/10	1/10	-

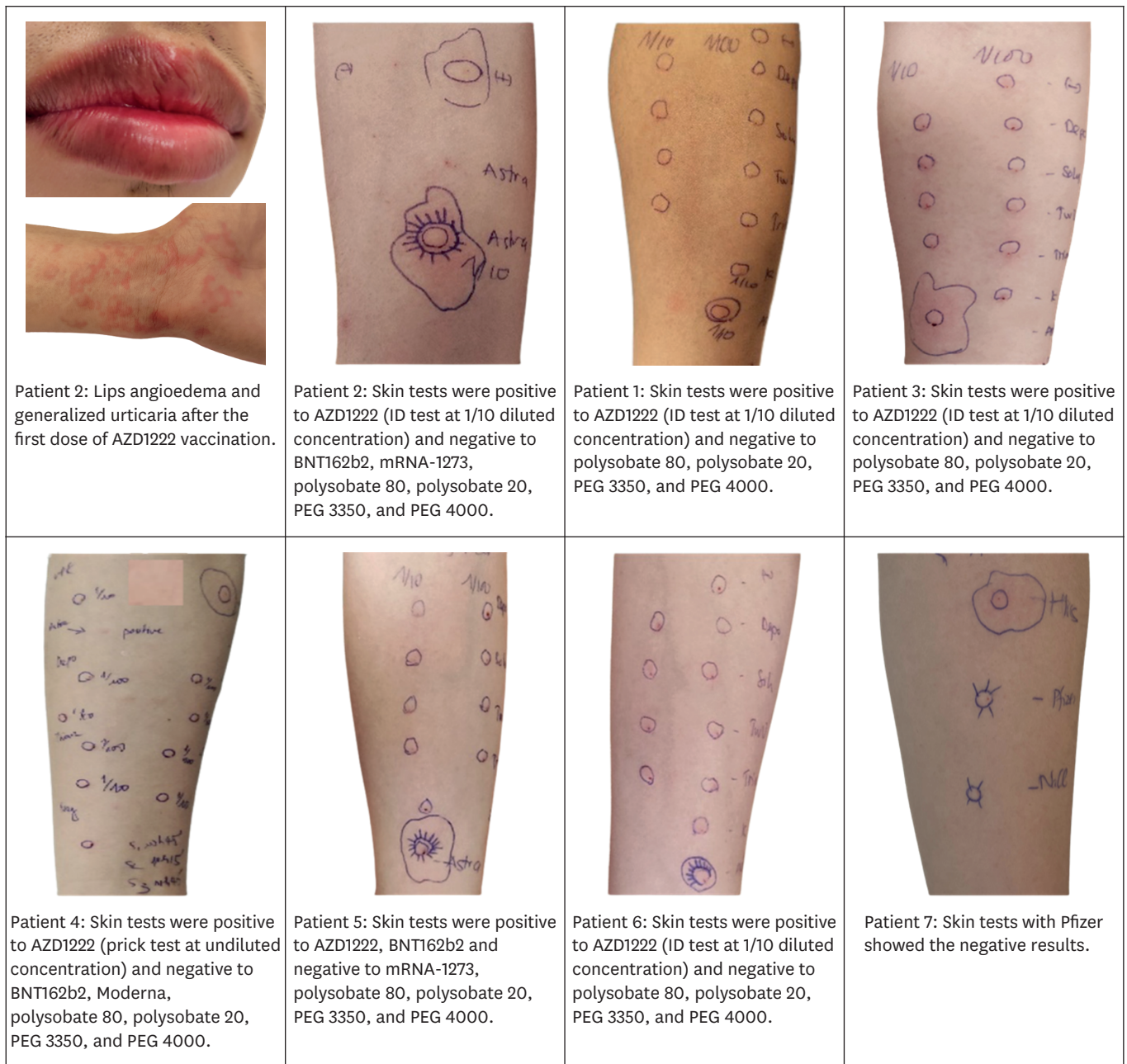


Fig. 1. Skin testing results to polyethylene glycol (PEG), polysorbate and coronavirus disease 2019 vaccines.

Of the 4 patients (#02, #03, #09, and #10) with nonimmediate allergic reactions following the first dose of the AZD1222 vaccine, 2 patients (#02 and #03) had a positive ID test to the AZD1222 vaccine but had negative tests to polysorbate. They were skin tested with PEG and mRNA vaccine (either BNT162b2 or mRNA-1273) prior to the second dose. Patient #02 then tolerated BNT162b2 without any allergic reaction after having negative skin testing results to the mRNA vaccine. However, due to the shortage of mRNA vaccines and based on a shared decision after consultation, patient #03 received a second dose of the AZD1222 vaccine after 8 weeks using a graded dose protocol. She experienced generalized urticaria after the 4th dose of 0.15 mL of undiluted vaccine. She was advised to have an mRNA vaccine for any booster doses.

Table 2. Clinical manifestations, skin testing results and the outcome of the second COVID-19 vaccine in patients with allergic reactions to AZD1222 vaccine

Patient	Age	Sex	Allergy history	Vaccine dose 1	Allergic symptoms	Time onset	Treatment	Skin test			The second dose administration
								Components (PEG, polysorbate)	AZD1222 vaccine	mRNA vaccine	
01	42	M	None	AZD1222	Grade III anaphylaxis Hypotension, face and tongue numbness	45 Minutes	Corticoid and antihistamine	Negative	Positive to ID test	Shortage of BNT162b2	BNT162b2 vaccine without allergic reactions
02	29	M	Food (shrimp, crab)	AZD1222	Grade II anaphylaxis Generalized urticaria, facial edema, abdominal pain	5 Hours	Corticosteroid and antihistamine	Negative	Positive to 1/10 ID test	Negative to BNT162b2 and mRNA-1273	BNT162b2 vaccine without allergic reactions
03	25	F	Food (shrimp, crab) Ibuprofen	AZD1222	Generalized urticaria	9 Hours	None	Negative	Positive to 1/10 ID test	Shortage of BNT162b2	Graded-dose AZD1222 vaccine, generalized urticaria after administering 0.15 mL of an undiluted vaccine
04	29	F	MMR vaccine, food (shrimp)	AZD1222	Grade I anaphylaxis Generalized urticarial	4 Hours	None	Negative	Positive to prick test	Negative to mRNA-1273	BNT162b2 vaccine without allergic reactions
05	38	F	None	AZD1222	Grade II anaphylaxis Generalized urticaria, vomiting abdominal pain	4 Hours	Corticosteroid and antihistamine	Negative	Positive to 1/10 ID test	Positive to BNT162b2	Graded-dose BNT162b2 vaccine without allergic reactions
06	28	M	Food (shrimp, crab, soft turtle)	AZD1222	Grade II anaphylaxis Dizziness, hypertension, generalized urticaria	15 Minutes	Antihistamine and corticosteroid	Negative	Positive to 1/10 ID test	Shortage of BNT162b2	BNT162b2 vaccine without allergic reactions
07	43	F	Etoricoxib Media contrast anaphylaxis	AZD1222	Grade III anaphylaxis Urticaria, difficulty in breathing Hypotension	30 Minutes	Adrenalin, antihistamine, corticosteroid	Patient refused	Patient refused	Negative to BNT162b2	BNT162b2 vaccine without allergic reactions
08	30	M	None	AZD1222	Grade I anaphylaxis Limited spontaneous urticaria	40 Minutes	None	N/A	Negative	Not required	Graded-dose AZD1222 vaccine without hypersensitive reaction due to immediate reaction
09	38	M	None	AZD1222	Limited spontaneous urticaria	12 Hours	None	N/A	Negative	Not required	AZD1222 vaccine without allergic reactions
10	41	F	None	AZD1222	Limited spontaneous urticaria	8 Hours	None	N/A	Negative	Not required	AZD1222 vaccine without allergic reactions

Anaphylaxis grading: grade I, cutaneous symptoms; grade II, measurable but not life-threatening symptoms; grade III, life-threatening symptoms; grade IV, cardiac and/or respiratory arrest [10].

Patients #09 and #10 had negative results to all of the skin tests. They tolerated well their second doses of the AZD1222 vaccine.

Skin testing to polysorbate may not be sufficient to assess the allergy risk to the AZD1222 vaccine as all 6 patients with symptoms of hypersensitivity allergic reactions had negative prick tests and ID tests to polysorbate 20 and polysorbate 80. It is possible that another component of the AZD1222 vaccine is responsible for postvaccination allergic reactions. Although data examining the utility of skin testing to polysorbate in the evaluation of the risk of allergic reactions to AZD1222 is limited, there is some research which indicates there may be a role for excipient skin testing of mRNA COVID-19 vaccines [8, 9].

A positive AZD1222 vaccine skin test was associated with allergic symptoms in 6 of our cases, which may suggest that the positive predictive value of AZD1222 vaccine skin testing is significant and useful in evaluating the risk of allergy to the vaccine prior to subsequent doses of vaccines.

In individuals with allergic reactions after the first dose of the AZD1222 vaccine, it is possible to change to an mRNA vaccine according to the current recommendations. Indeed, 5 out of 10 patients in our study tolerated BNT162b2 vaccination. Another of our cases had a positive

ID test to BNT162b2 vaccine before the second dose and then tolerated BNT162b2 vaccine with administration of divided doses. To date, there are no data which have determined the incidence of cross-reactive allergic reaction between mRNA vaccines and the AZD1222 vaccine; however, there are several reports of cross-reactivity between polysorbate and PEG [4]. Our results suggest a role for skin testing with mRNA vaccines in patients with previous allergic reaction to AZD1222 vaccine.

We conclude that skin testing to COVID-19 vaccines might be helpful in confirming the mechanism of immediate reactions to COVID 19 vaccines and in selecting an alternative vaccine for the subsequent doses. A limited role for excipients such as polysorbate and PEG in allergic reactions to COVID 19 vaccines has been observed in this case series. Further studies should be carried out to determine the precise utility of skin testing in patients with COVID-19 vaccine allergy.

ETHICS STATEMENT

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. This study was reviewed and approved by Vinmec Healthcare System-VinUniversity institutional ethical review board for biomedical research: No. 163.QD/VMEC.

ACKNOWLEDGEMENTS

Authors would like to thank all patients and their families for making this possible. We gratefully thank to Clinical Professor Sheryl van Nunen for reviewing this paper.

REFERENCES

1. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, Hambidge SJ, Lee GM, Jackson LA, Irving SA, King JP, Kharbanda EO, Bednarczyk RA, DeStefano F. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol* 2016;137:868-78.
[PUBMED](#) | [CROSSREF](#)
2. Shimabukuro T. COVID-19 vaccine safety update [Internet]. Atlanta (GA): Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices (ACIP); 2021 [2021 Sep 28]. Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf>
3. Kim MA, Lee YW, Kim SR, Kim JH, Min TK, Park HS, Shin M, Ye YM, Lee J, Choi JH, Jang GC, Chang YS. COVID-19 vaccine-associated anaphylaxis and allergic reactions: consensus statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group. *Allergy Asthma Immunol Res* 2021;13:526-44.
[PUBMED](#) | [CROSSREF](#)
4. Cabanillas B, Novak N. Allergy to COVID-19 vaccines: a current update. *Allergol Int* 2021;70:313-8.
[PUBMED](#) | [CROSSREF](#)
5. Vander Leek TK, Chan ES, Connors L, Derfalvi B, Ellis AK, Upton JEM, Abrams EM. COVID-19 vaccine testing & administration guidance for allergists/immunologists from the Canadian Society of Allergy and Clinical Immunology (CSACI). *Allergy Asthma Clin Immunol* 2021;17:29.
[PUBMED](#) | [CROSSREF](#)
6. Burks AW, Holgate ST, O'Hehir RE, Bacherier LB, Broide BH, Hershey GKK, Peebles RS. *Middleton's allergy: principles and practice*. 9th ed. Amsterdam: Elsevier; 2019.
7. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, Wolfson AR, Williams P, Khan DA, Phillips E, Blumenthal KG. mRNA Vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract* 2021;9:1423-37.
[PUBMED](#) | [CROSSREF](#)

8. Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, Wickner P, Samarakoon U, Saff RR, Blumenthal KG, Banerji A. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. *J Allergy Clin Immunol Pract* 2021;9:3308-20.e3.
[PUBMED](#) | [CROSSREF](#)
9. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipients allergy skin testing. *Ann Allergy Asthma Immunol* 2021 Sep 03. [Epub].
[PUBMED](#) | [CROSSREF](#)
10. Blumenthal KG, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, Landman AB, Wickner P. Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA* 2021;325:1562-5.
[PUBMED](#) | [CROSSREF](#)