

Delayed Hypersensitivity Reactions Following First Dose of the SARS-CoV2 mRNA Vaccines



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BACKGROUND

Vaccination is crucial to curtail the spread of SARS-CoV2; however, reports of adverse reactions including allergic reactions have increased public fears of the vaccine.¹ The incidence of true hypersensitivity including both immediate and delayed reactions is estimated at ~13 cases per million.² Delayed allergic reactions are heterogeneous, and there are limited reports regarding delayed reactions to the SARS-CoV2 mRNA vaccines.

OBJECTIVE

In this study, we characterize delayed hypersensitivity reactions to Pfizer/Moderna SARS-CoV2 mRNA vaccines at a single institution, and outcomes with second-dose administration.

METHODS AND FINDINGS

This was a retrospective study of delayed adverse reactions to the COVID-19 vaccine in healthcare workers at a single institution obtained through occupational health records. Patients included in the study experienced delayed reactions > 6 h following their first dose of Pfizer-BioNTech or Moderna SARS-CoV2 mRNA vaccine at vaccine clinics between 12/17/2020 and 02/16/2021. Subjects were identified through a review of occupational health records that documented delayed reactions reported by employees via telephone. Patients with immediate reactions (≤ 6 h from vaccine administration) and known vaccine side effects were excluded.

Patients with delayed adverse reactions concerning true hypersensitivity were evaluated by an allergist and infectious disease specialist via in-person or e-consult visits. Based upon reaction severity, a recommendation was made for second-dose avoidance versus administration via full- or graded-dose challenge.

A total of 138 reactions were reported out of 20,657 first doses of Pfizer and Moderna vaccines administered (0.66%) during this period. One hundred nine patients were excluded due to immediate reactions and 5 patients were excluded due to known adverse reactions such as fever and fatigue. Of the 29 patients with delayed reactions, 14 patients were excluded due to symptoms that were incongruent with an underlying allergic mechanism. Ten of the 138 patients (7.25%) were classified as having probable delayed onset hypersensitivity reaction to the first dose of vaccination (Table 1), with female predominance (80%).

Delayed reactions included swelling around the eyes or face, systemic hives or rash, serum-sickness-like reaction, and large localized reaction. Two patients developed periorbital or perioral swelling within 24 h that rapidly resolved with antihistamines. Six patients described systemic hives or rash within 8 h to 4 days after vaccination that resolved spontaneously or following treatment with antihistamines and systemic steroids. One patient developed isolated large local reaction without systemic symptoms. The last subject experienced a serum-sickness-like reaction that developed approximately 7 days post-vaccination. Symptoms included urticaria, arthralgias, and myalgias, and labs demonstrated mild eosinophilia (350 cells/mcL), transaminitis (ALT 129/AST 212), elevated D-dimer (1302), and elevated CRP (21.8). COVID test was negative. Repeat labs 2 weeks later showed resolution of eosinophilia, transaminitis, and inflammatory markers.

Eight of the 10 patients elected to receive the second dose of vaccination and all 8 patients tolerated it without additional adverse events. Of the 8 patients, 6 patients received the second vaccine dose following standard protocol and 2 patients received the vaccine via graded-dose challenge, receiving 10% first followed by 90% the following week based on the time course of the index reaction. Two of the 10 patients elected not to receive the second dose of vaccine.

DISCUSSION

Although immediate type 1 anaphylactic reactions to vaccinations are most concerning, any vaccine reactions can dissuade patients from receiving their second dose to be fully vaccinated.³ In our cohort, common delayed reactions to vaccination included hives/rash, swelling/angioedema, and localized reactions. These reactions were largely self-limited and managed

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Table 1 Patient Demographics and Delayed Reactions to SARS-CoV2 mRNA Vaccine

Patient	Age (years)	Sex	Medical history	Allergy history	Vaccine type	Time of onset (after vaccination)	Clinical features	Treatment	Time to resolution (after onset)	Outcome of the second dose
1	35	Female	None	Unknown	Pfizer	1 day	Periorbital and nasal swelling. Hives on hands and feet	Antihistamine	Unknown, resolved	No reaction
2	34	Male	None	No known allergies	Pfizer	7 days	Serum-sickness-like reaction. Lip swelling and diffuse urticaria	IV steroids, antihistamine, H2 blocker	9 days	Graded-dose challenge, no reaction
3	28	Female	None	No known allergies	Pfizer	1 day	Eyelid and lip swelling	Antihistamine	Within 1 day	No reaction
4	43	Female	None	No known allergies	Moderna	4 days	Hives on neck and shoulders	Antihistamine H2 blocker	Within 1 day	No reaction
5	28	Male	None	Mustard	Pfizer	3 days	Pruritic rash over abdomen, thighs, and groin	Oral steroids	2 days	No reaction
6	46	Female	None	Pseudoephedrine	Moderna	3 days	Large local injection site reaction	Oral steroids, antihistamine	Unknown, resolved	Not received
7	61	Female	Crohn's disease, hypertension	Peanuts	Moderna	2 days	Upper body rash	None	Unknown	No reaction
8	33	Female	None	Tramadol	Unknown	8 h	Pruritic rash on legs	None	2 days	Graded-dose challenge, no reaction
9	40	Female	History of COVID pneumonia	Propranolol	Moderna	10 h	Rash over face, neck, chest, abdomen.	Antihistamine	2 days	No reaction
10	53	Female	Crohn's disease	Promethazine	Moderna	1 day	Tingling of lips Rash over arms and chest	None	3 days	Not received

with antihistamines, oral steroids, or self-resolved, similar to previously described delayed vaccine reactions.³ Large localized vaccine reactions have been attributed to a T-cell-mediated response and are not a contraindication to the second dose.⁴ Interestingly, one patient experienced a serum-sickness-like reaction that traditionally prohibits re-challenge. However, following recovery, the patient elected to receive his second vaccine dose without issues.

The limitations of this study were that it was retrospective and relied on subject self-reporting. Despite temporal correlation with the reaction, the vaccine may or may not have been causal.

Our study characterizes delayed hypersensitivity reactions and outcomes with second-dose administration. Patient-reported delayed reactions did not preclude tolerance of subsequent vaccine doses in any of the patients who elected to receive their second vaccine dose. Understanding the mechanism and implication of immune-mediated vaccine reactions is essential for maintaining this intervention.

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DECLARATIONS:

CONFLICT OF INTEREST: The authors declare that they do not have a conflict of interest.

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