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BRIEF REPORT

Graded Administration of Second Dose of Moderna and Pfizer-BioNTech COVID-19 mRNA Vaccines in Patients With Hypersensitivity to First Dose

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Two mRNA coronavirus disease 2019 (COVID-19) vaccines, Moderna and Pfizer-BioNTech, require 2 doses for maximum efficacy. This case series reports the safety and immunogenicity of a graded administration of the second dose of the Moderna and Pfizer-BioNTech COVID-19 vaccines in patients with immediate hypersensitivity reactions to the first dose.

Keywords. COVID-19; graded administration; mRNA vaccine; SARS-CoV-2 spike protein.

Widespread administration of coronavirus disease 2019 (COVID-19) vaccines is crucial to controlling the COVID-19 pandemic. Two messenger RNA (mRNA) vaccines by Moderna and Pfizer-BioNTech received Emergency Use Authorization from the US Food and Drug Administration in December 2020. As of August 24, 2021, 144 million doses of Moderna and 205 million doses of Pfizer-BioNTech have been administered in the United States among the 5 billion doses administered worldwide [1]. Although up to 2% of individuals self-report allergic reactions to the first dose [2], anaphylactic reactions are rare and reported at a rate of 2.5 per million doses for Moderna and 4.7 per million doses for Pfizer-BioNTech [3]. Both vaccines require 2 doses for maximum efficacy, and there are limited data regarding best practice for subsequent dose administration in patients with an immediate hypersensitivity response to the first dose.

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OBJECTIVE

We report a case series of outpatients referred from the community to the Division of Allergy and Immunology at Rochester Regional Health (Rochester, NY, USA) from January to May 2021 for evaluation of symptoms consistent with immediate hypersensitivity reactions to the first dose of the Moderna or Pfizer-BioNTech COVID-19 vaccine, who subsequently received their second dose through a graded administration protocol.

METHODS

Patients were evaluated with a thorough clinical history. Those with symptoms supportive of an immediate hypersensitivity reaction underwent unblinded skin prick and intradermal testing to vaccine components (polyethylene glycol [PEG] using Miralax [prick] and methylprednisolone acetate 0.4 mg/mL, 4 mg/mL [intradermal]; polysorbate-80 using Refresh tears [undiluted [prick], 1:10 dilution [intradermal]) and the mRNA vaccine using vaccine overfill (undiluted [prick] and 1:10, 1:100 dilutions [intradermal]) [4]. Patients underwent graded administration of the vaccine (Table 1) regardless of skin testing results due to the uncertain predictive values of skin testing.

Immunoglobulin G (IgG) titers to the SARS-CoV-2 spike (S) protein were quantified by enzyme immunoassay using sera collected at least 2 weeks following the second dose and compared with 11 healthy adults (mean age, 61.9 ± 5.9 years) who received either mRNA vaccine under standard schedules 15–57 days previously. End point titers are expressed as the $\log_2$ dilution/mL.

RESULTS

We evaluated 102 patients with suspected immediate hypersensitivity reactions to the first dose of the mRNA vaccines. Fifteen (Pfizer-BioNTech, n = 7; Moderna, n = 8) patients had convincing objective and subjective histories of immediate hypersensitivity reactions and received dose 2 through a graded administration protocol (Table 2), whereas 87 patients (females, n = 85) did not have convincing symptoms and were advised to receive dose 2 without any special precautions, with none reporting subsequent reactions. All study patients were female and were between 21 and 64 years of age. Immediate symptoms included urticaria (n = 7, 47%), lightheadedness (n = 4, 27%), angioedema (n = 4, 27%), nonurticarial rash (n = 4, 27%), dyspnea (n = 3, 20%), and nausea/vomiting (n = 3, 20%), all occurring 10–45 minutes after the first dose. One patient was treated with epinephrine. Skin testing was performed in 11 patients: 3 (27%) positive to components (PEG, polysorbate-80),

Table 1. Protocol for Graded Administration of mRNA COVID-19 Vaccine Given Every 15 Minutes

Step	Pfizer-BioNTech Vaccine	Moderna Vaccine
1	0.05 mL of 1:10 dilution	0.05 mL of 1:10 dilution
2	0.05 mL of full strength	0.05 mL of full strength
3	0.1 mL of full strength	0.1 mL of full strength
4	0.15 mL of full strength	0.15 mL of full strength
5		0.2 mL of full strength

Abbreviation: COVID-19, coronavirus disease 2019.

3 (27%) positive to vaccine (Moderna, n = 2; Pfizer-BioNTech, n = 1), and 1 (7%) positive to both (Pfizer-BioNTech). Four of 15 patients did not do skin testing due to lack of vaccine overflow (n = 2) or dermatographia (n = 2).

No patients were premedicated for the second vaccine dose. Nine patients (60%) fully tolerated the protocol, while 1 (7%) had limited pruritus and 4 (27%) symptoms (cough, throat tightness, nausea, pruritus, or dyspnea) requiring treatment (albuterol and/or cetirizine). Following the final step of graded administration, 2 patients (13%) experienced anaphylaxis manifesting as throat tightness, 1 patient experienced cough and wheezing on chest auscultation, and 1 patient experienced nausea with generalized urticaria. Both received 1 dose of epinephrine with prompt resolution of symptoms and were discharged home after an additional hour of monitoring. One of these patients had positive skin testing to the Moderna vaccine, but not to PEG or polysorbate-80. Mean serum IgG levels to the SARS-CoV-2 spike protein following the second dose in 13 patients were not statistically different from healthy controls (log2 17.4 ± 1.1 vs 16.7 ± 1.2). IgG was not checked in 2 patients due to lack of follow-up. In the study group and the healthy control group, there was 1 patient in each group with previous COVID-19 infection.

DISCUSSION

There are limited data on how best to proceed with the second mRNA COVID-19 vaccine dose in patients with allergic reactions to the first dose. Symptoms suggestive of allergic reactions include urticaria, angioedema, gastrointestinal manifestations, and respiratory or cardiac compromise within an hour of vaccination. These patients should all have consultation with an allergist, as recommended by the Centers for Disease Control and Prevention (CDC) [5] and the World Allergy Organization (WAO) [6]. The CDC and WAO currently recommend against administration of the second dose in these cases. While this may be the safest option to avert future reactions, patients remain at increased risk for COVID-19 infection, and deferral of the second dose may promote viral resistance [7]. In contrast, the Canadian Society of Allergy and Clinical Immunology and the European Academy of Allergy and Clinical Immunology endorse graded administration as an option [8, 9]. Others have suggested administration of the Janssen (Johnson and Johnson) adenovirus type 26 vaccine in lieu of a second dose of an mRNA vaccine [10]. There have been no studies on the safety or efficacy of this approach to date. We are the first to report graded administration of the second dose of the COVID-19 vaccine in patients with a reaction to the first dose and to demonstrate the immunogenicity of this approach.

Graded administration of other vaccines is well described and routinely performed in outpatients [11]. Due to the theoretical risk of rapid mRNA degradation, there is concern regarding the immunogenicity of split-dosing or graded administration of mRNA vaccines [4]. Our group previously described the successful graded administration of the second dose of Moderna vaccine for 2 patients who had immediate hypersensitivity reactions to the first dose, demonstrating both safety and postvaccination IgG against COVID-19 [12]. This case series provides further preliminary data supporting both the feasibility of this approach and quantification of serum S IgG titers, which are noninferior to a standard vaccination protocol.

Additionally, graded administration could obviate the need for skin testing to vaccine components or the vaccine itself, which has been previously suggested [4, 13]. Skin testing for mRNA vaccines and their vaccine components has undetermined predictive value. In our study, skin testing was not predictive, nor was it deemed necessary for evaluation. In a recent cohort of patients with allergic reactions to the COVID-19 vaccine, none had positive testing to the vaccine components [14]. Furthermore, using vaccine for skin testing may lead to wastage, which is suboptimal in areas with vaccine scarcity. Alternatively, negative skin tests to the vaccine can rule out IgE-mediated reactions, which promotes giving the second dose in the usual manner [15]. Even if predictive values for skin testing are eventually established, patients with positive testing still require a safe approach to receive subsequent vaccines doses. In this study, skin test results were used as part of the shared decision-making process with patients but otherwise played no significant role in clinical decision-making.

The mechanism of hypersensitivity reaction to mRNA COVID-19 vaccines remains poorly understood. All patients in our study were female; this gender predominance is similar to previous reports [2, 3, 16], the significance of which should be further evaluated. Reactions may be due to direct complement activation, leading to mast cell degranulation, but may also involve an IgE-mediated mechanism [4]. If the sentinel immediate reaction is IgE-mediated, regardless of severity, then administering the second full dose puts the patient at risk for subsequent anaphylaxis. Although a recent study of patients with allergic reactions to the first dose tolerated an observed 1-step second dose of the Pfizer-BioNTech vaccine with minimal or no symptoms [16], 6 of our 15 patients experienced reactions during their graded administration, with 2 requiring epinephrine. Given the unknown mechanism and lack of tools to predict the severity of future immediate hypersensitivity

Table 2. Patient Characteristics, Skin Test Results, and Outcomes of Second Dose Given by Graded Administration for Patients With Reaction to First mRNA COVID-19 Vaccine Dose (n = 15)

Age, y Sex	Atopic History	Vaccine Manufacturer	Symptoms After First Dose	Time to Symptom Onset, min	Treatment After First Dose	ED Evaluation	Skin Test Performed	Positive Skin Test Component	Reaction to Second Dose Via Graded Administration (Step Number)	Treatment With Graded Administration (Step Number)	Serum S IgG Titer, Log2 Dilution
40 F	Asthma	Pfizer-BioNTech	Dyspnea, lightheadedness	10	Albuterol	No	No	N/A	Cough (1, 4), throat tightness (4)	Cetirizine (1), albuterol (1, 4), epinephrine (4)	15.85
32 F	FA, AR, asthma, venom allergy	Moderna	Urticaria, nausea	15	Diphenhydramine	No	Yes	Vaccine (ID)	Nausea (3, 5), urticaria (5)	Cetirizine (3, 5), epinephrine (5)	16.85
28 F	None	Moderna	Angioedema, nonurticarial rash	15	Diphenhydramine	Yes	Yes	None	Throat tightness (3)	Cetirizine (3)	19.35
39 F	AR	Moderna	Urticaria,	15	Famotidine, methylprednisolone	Yes	Yes	Vaccine (ID)	None	None	17.85
64 F	FA	Moderna	Urticaria	10	Diphenhydramine	No	Yes	Vaccine (ID)	Pruritus (1, 5)	None	16.35
60 F	AR	Pfizer-BioNTech	Urticaria	10	Diphenhydramine	No	No	N/A	Pruritus (4), rhinorrhea (4)	Cetirizine (4)	15.85
37 F	Asthma AR	Moderna	Nonurticarial rash, dyspnea	10	Diphenhydramine, dexamethasone	Yes	Yes	PEG (ID), polysorbate (ID)	None	None	–[b]
47 F	AR	Pfizer-BioNTech	Angioedema	30	None	No	Yes	None[a]	None	None	16.85
44 F	None	Pfizer-BioNTech	Nonurticarial rash,	30	Diphenhydramine	Yes	No	N/A	None	None	17.85
49 F	AR, FA	Pfizer-BioNTech	Nonurticarial rash, angioedema	10	Diphenhydramine	No	Yes	PEG (ID), polysorbate (ID), vaccine (ID)	None	None	16.85
63 F	None	Pfizer-BioNTech	Urticaria	40	None	No	Yes	None	None	None	17.35
41 F	AR	Moderna	Lightheadedness, urticaria	10	None	No	No	N/A	None	None	18.85
39 F	Asthma, FA	Moderna	Urticaria	45	Cetirizine	No	Yes	PEG (ID), polysorbate (ID)	None	None	–[b]
39 F	AR	Moderna	Nausea/vomiting lightheadedness	30	None	No	Yes	None	None	None	17.85
21 F	Asthma, AR	Pfizer-BioNTech	Angioedema, dyspnea, nausea, lightheadedness	20	Epinephrine	Yes	Yes	None	Dyspnea, pruritus (1)	Albuterol (1), cetirizine (1)	17.85

Abbreviations: AR, allergic rhinitis; COVID-19, coronavirus disease 2019; ED, emergency department; FA, food allergy; ID, intradermal; mRNA, messenger RNA; PEG, polyethylene glycol.

[a]Skin test positive to vaccine 24 hours later.

[b]Results not available.

reactions, a graded administration may be the most prudent method to facilitate introduction of the second dose of the vaccine in this setting through shared decision-making [17] and may be more appealing to hesitant patients vs a single second dose. Regardless, administering a second dose as a single dose or 2-step regimen might be appropriate for certain patients and may provide similar efficacy and safety to our graded dosing protocol.

An important limitation to this study is that the diagnosis of immediate hypersensitivity to dose 1 of the mRNA vaccine was made based on subjective symptoms, in the absence of objective measurements such as serum tryptase. The authors used strict criteria to diagnose immediate hypersensitivity reactions, deeming the majority of patients appropriate to proceed with dose 2 with no special precautions. There was also an age difference between healthy controls vs study patients. Also, further studies would help us fully understand the immunogenicity of graded dosing.

This case series is the first to report the safety and efficacy of a graded administration of the second dose of the Moderna or Pfizer-BioNTech vaccine in 15 patients with immediate hypersensitivity reactions to the first dose. Patients reporting allergic reactions to dose 1 of mRNA vaccines therefore should not automatically defer dose 2, but rather be referred to an allergist for shared decision-making and consider receiving dose 2 through a graded dosing protocol.

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Patient consent. The patient's written consent was obtained. The design of the work has been approved by local ethical committee, Rochester Regional Health Institutional Review Board, Rochester, New York, USA.

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