Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letters

Antibody response to graded dosing of coronavirus disease 2019 messenger RNA vaccines after allergic reaction to first dose

In December 2020, an Emergency Use Authorization was issued for Pfizer-BioNTech and Moderna coronavirus disease 2019 (COVID-19) vaccines. Shortly thereafter, allergic reactions including anaphylaxis to vaccination were described.[1] Initial rates of anaphylaxis were reported at 11.1 cases per million doses administered.[2] Since then, continued safety monitoring through the Vaccine Adverse Event Reporting System has shown lower rates of anaphylaxis.[3] Although rare, systemic reactions have occurred, making the administration of subsequent doses problematic in some patients, resulting in vaccine hesitancy. The single dose administration of a second vaccination has been reported to be safe in patients who had an immediate reaction to the first dose; however, some patients decline this option.[4] Therefore, shared decision making about additional options for subsequent vaccination in these patients is needed. In this study, we report a pilot study showing that graded COVID-19 messenger RNA (mRNA) vaccination is safe in patients with previous immediate allergic reactions, and results in antibody titers comparable with those of healthy controls who received full-dose vaccination.

We present data on 8 patients with immediate reactions to first dose Pfizer-BioNTech and Moderna COVID-19 vaccines (4 from each vaccine) who underwent a graded second dose vaccination. This subset of patients represented approximately 15% of patients evaluated for COVID-19 vaccine reaction at a University Allergy-Immunology clinic from December 2020 to February 2021. Patient-reported symptoms after initial COVID-19 mRNA vaccination included cutaneous, oropharyngeal, respiratory, gastrointestinal, and hemodynamic changes (Table 1). Symptom onset occurred within 5 to 60 minutes of receiving the vaccination. Four of 8 patients met the diagnostic criteria for anaphylaxis based on the Brighton Collaboration case definition (3 patients met Brighton level 3, and 1 patient met level 2).[5] Although the remaining 4 patients had nonanaphylactic hypersensitivity reactions, 3 of these 4 patients were evaluated in the emergency department. Furthermore, 3 of 8 patients met the criteria for anaphylaxis based on the National Institute for Allergy and Infectious Disease definition.[6]

All 8 patients had negative results in COVID-19 vaccine component skin testing to polyethylene glycol and polysorbate 20 and polysorbate 80.[7] Patients were counseled about the low risk of second dose vaccination, and the full second dose was recommended. However, despite negative testing and counseling, all patients declined to receive the second full vaccine dose. To facilitate complete vaccination dosing, patients were offered a graded and monitored vaccine dosing administration.

All 8 patients consented to undergo a second dose graded-vaccine administration, which occurred 30 to 52 days after the initial vaccination. For the Moderna vaccine graded dosing, patients received 0.05 mL, 0.1 mL, 0.15 mL, and 0.2 mL intramuscularly, every 15 minutes. For the Pfizer vaccine graded dosing, patients received 0.05 mL, 0.1 mL, and 0.15 mL intramuscularly, every 15 minutes. For both vaccine-graded–dosing regimens, patients were observed for 60 minutes after the last dose. All patients tolerated the graded dosing without evidence of allergic reaction.

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) spike protein antibody levels were obtained approximately 6 months after graded dosing in 6 of the 8 patients, and the antibody levels were compared with a healthy control group matched by sex, age, and vaccine type (Table 1). The study and control patients were tested through enzyme-linked immunosorbent assay measuring immunoglobulin G to SARS-COV2 spike protein, using 2 different laboratories. Study patient assays were performed through Quest Diagnostic, and control patient assays were performed through Beckman Coulter. Statistical analysis was performed using JMP software (Cary, North Carolina). Spike protein antibody levels were evaluated both qualitatively and quantitatively. There was no difference in qualitative assessment of response between the 2 groups (all 6 had reactive antibody levels in the graded-dosing group vs 5 in the control group; $P = .30$). There was a statistically significant difference in quantitative antibody levels, with the graded-dosing group having a higher level (median [interquartile range] 19.6 [10.1-73.7] vs 2.6 [1.7-4.1]; $P = .008$). There was a significantly longer time between the first and second vaccine doses for the graded-dosing patients than there was for the healthy controls (median [interquartile range] 45 [32-51] vs 24 [22-27] days; $P = .005$). However, in the graded-dosing group, the time between the second vaccination and the time when the spike protein antibody levels were obtained did not differ from the healthy controls (median [interquartile range] 201 [186-222] vs 227 [193-261] days; $P = .38$). It is plausible that a longer time between first and second vaccine doses in the graded-dosing patients accounts for a better antibody response, as has been suggested by previous studies.

In some patients, vaccine hesitancy may be because of hypersensitivity reactions resulting from the first dose of the COVID-19 vaccine. Here, in this small pilot study, we show that graded-dosing administration with COVID-19 mRNA vaccines is safe and provides a reactive SARS-COV2 spike protein antibody response at least 6 months after completion of the initial COVID-19 vaccination series. Furthermore, when compared with age, sex, and the vaccine-matched healthy control population who received the full-dose vaccination, the graded dosing provides comparable antibody responses. Previous published studies have assessed graded vaccine dosing.[8] Patel et al[9] published

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Table 1
Characteristics of Subjects Who Underwent COVID-19 mRNA Vaccine Graded Dosing and Matched Healthy Controls

Sex	Age, y	COVID-19 vaccine	Symptoms after first vaccination	Time in between first and second vaccination, d	Time in between second vaccination and COVID-19 ab testing, d	COVID-19 AB test	COVID-19 AB category (reactive, nonreactive)	COVID-19 AB value
F	31	Moderna	Dizziness, palpitations, throat swelling and tightness, abdominal cramping (within 10 min)[a,b]	33	183	SARS-COV2 AB (IgG), spike, semi-quantitative	Reactive	>20
F	33	Moderna	None (Healthy control)	28	259	SARS-COV2 IgG AB spike protein	Reactive	7.19
M	37	Pfizer	Tachycardia, hypertension, chest tightness, cough, dizziness (within 10 min)	52	232	COVID-19 SARS-CoV-2 total AB, spike, semi-quantitative	Reactive	231.7
M	37	Pfizer	None (Healthy control)	22	265	SARS-CoV-2 IgG AB spike protein	Reactive	2.04
M	55	Pfizer	Throat swelling, lightheadedness, vomiting (within 5 min)[a,b]	49	212	COVID-19 SARS-CoV-2 total AB, spike, semi-quantitative	Reactive	11.8
M	48	Pfizer	None (Healthy control)	23	164	SARS-COV-2 IgG AB spike protein	Reactive	2.65
F	57	Moderna	Diffuse hives, throat swelling (within 60 min)[a]	50	218	SARS-COV-2 AB (IgG), spike, semi-quantitative	Reactive	18.12
F	65	Moderna	None (Healthy control)	25	202	SARS-COV-2 IgG AB spike protein	Reactive	3.1
F	51	Moderna	Diffuse hives, lip tingling (within 40 min)	30	190	SARS-COV-2 AB (IgG), spike, semi-quantitative	Reactive	4.85
F	34	Moderna	None (Healthy control)	27	210	SARS-COV-2 IgG AB spike protein	Reactive	2.56
F	51	Pfizer	Diffuse hives (within 5 min)	41	187	SARS-COV-2 AB (IgG), spike, semi-quantitative	Reactive	>20
F	56	Pfizer	None (Healthy control)	21	244	SARS-COV-2 IgG AB spike protein	Nonreactive	0.58
F	34	Pfizer	Throat itching and swelling, nausea (within 5 min)[a,b]	52				
F	59	Moderna	Mental fogginess, throat itching, diffuse erythematous rash (within 15 min)	30				

Abbreviations: AB, antibody; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.
[a]Met Brighton Collaboration Case Definition of Anaphylaxis.
[b]Met National Institute for Allergy and Infectious Disease Criteria for Anaphylaxis.

their 2-step protocol for the Pfizer vaccine only but did not evaluate antibody response to graded dosing. Tuong et al[10] presented data on their longer graded-dosing protocol (4-step for Pfizer and 5-step for Moderna) in a women-only population. Unlike our matched healthy control population, Tuong et al[10] reported comparisons in unmatched healthy controls. The authors of the study presented data as a $\log_2$ antibody response, and antibody levels were checked at a minimum of 2 weeks after vaccination, unlike our study, where antibody response was checked at a minimum of 6 months after vaccination.[10]

The limitations of our study include that the laboratory assays used were different between the 2 cohorts, and antibody values may not be used interchangeably as per the expanded authorization of semiquantitative tests of the US Food and Drug Administration.

All patients with an immediate hypersensitivity reaction to COVID-19 vaccine should be referred to an allergy-immunology specialist. In patients hesitant to receive a subsequent COVID-19 vaccine owing to a history of immediate allergic reaction, a graded-dosing vaccine administration should be considered and may provide protection like a standard full-dose vaccination.

Sara W. Van Meerbeke, MD*
Merritt L. Fajt, MD*
Rachel V. Marini, PharmD†
Robyn T. Domsic, MD‡
Andrej A. Petrov, MD*
* *Division of Pulmonary Allergy, and Critical Care Medicine*
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
† *Department of Pharmacy*
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
‡ *Division of Rheumatology and Clinical Immunology*
University of Pittsburgh Medical Center
PittsburghPennsylvania
petrovaa@upmc.edu

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