

Antibody Response to Graded Dosing of COVID-19 mRNA Vaccines
After Allergic Reaction to First Dose

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Title: Antibody Response to Graded Dosing of COVID-19 mRNA Vaccines After Allergic Reaction to First Dose

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Sara W Van Meerbeke, Merritt L Fajt, and Rachel V Marini report no conflict of interest.

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In December 2020, an Emergency Use Authorization was issued for Pfizer-BioNTech and Moderna 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 Continued safety monitoring through the Vaccine Adverse Event Reporting System since then has shown lower rates of anaphylaxis.³ While rare, systemic reactions have occurred, making administration of subsequent doses problematic in some patients, resulting in vaccine hesitancy. While single dose administration of second vaccination has been reported to be safe in patients with first dose immediate reaction, some patients decline this option.⁴ Therefore, shared decision making about additional options for subsequent vaccination in these patients are needed. Here, we report a pilot study showing that graded COVID-19 mRNA vaccination is safe in patients with prior immediate allergic reactions and results in antibody titers comparable to healthy controls who received full dose vaccination.

We present data on eight 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 ~15% of patients evaluated for COVID 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 5-60 minutes of receiving vaccination. Four out of eight patients met diagnostic criteria for anaphylaxis based on the Brighton Collaboration case definition (3 patients met Brighton level 3 and 1 patient met level 2).⁵ While the remaining 4 had non-anaphylactic hypersensitivity reactions, 3 of these 4 patients were evaluated in the emergency room. Furthermore, 3 of eight patients met criteria for anaphylaxis based on National Institute for Allergy and Infectious Disease (NIAID) definition.⁶

All eight patients had negative COVID-19 vaccine component skin testing to polyethylene glycol and polysorbate 20 and 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 eight patients consented to undergo a second dose graded vaccine administration, which occurred 30 to 52 days after initial vaccination. For the Moderna vaccine graded dosing, patients received 0.05 mL, 0.1mL, 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.

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 to a healthy control group matched by sex, age, and vaccine type (Table 1). The study and control patients were tested by ELISA measuring IgG to SARS-COV2 spike protein using two 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, NC). 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, $p=0.30$]. 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), $p=0.008$]. There was a significantly longer time between the 1st and 2nd vaccine doses for the graded dosing patients vs. the healthy controls [median (interquartile range) 45(32-51) vs. 24(22-27) days, $p=0.005$]. However, the time between the 2nd vaccination and the time when the spike protein antibody levels were obtained was not different in the graded dosing group vs. healthy controls [median (interquartile range) 201(186-222) vs. 227(193-261) days, $p=0.38$]. It is plausible that a longer time between 1st and 2nd vaccine doses in the graded dosing patients accounts for better antibody response as has been suggested by previous studies.

In some patients, vaccine hesitancy may be due to prior hypersensitivity reactions resulting from the 1st dose of COVID-19 vaccine. Here, in this small pilot study, we show that graded dosing administration with COVID-19 mRNA vaccines is safe and provides reactive SARS-COV2 spike protein antibody response at least 6 months after completion of the initial COVID-19 vaccination series. Furthermore, when compared to age, sex and vaccine matched healthy control population that received the full dose vaccination, the graded dosing provides comparable antibody responses. Previous published studies have assessed graded vaccine dosing.⁸ Patel et al. published their 2-step protocol for Pfizer vaccine only but did not evaluate antibody response to graded dosing. Tuong et al. presented data on their longer graded dosing protocol (4-step for Pfizer and 5-step for Moderna) in a female-only population. Unlike our matched healthy control population, Tuong et al. reported comparisons in unmatched healthy controls. The authors of the study presented data as a log₂ 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.⁸

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 FDA expanded authorization of semiquantitative tests.

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

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Table 1: Characteristics of Subjects who underwent COVID-19 mRNA Vaccine Graded Dosing and matched Healthy Controls

Sex	Age, yrs	COVID-19 Vaccine	Symptoms after 1 st Vaccination	Time in Between 1st and 2nd Vaccination, days	Time in Between 2nd Vaccination and COVID ab testing, days	COVID Ab Test	COVID Ab Category (Reactive, Non-reactive)	COVID ab Value
F	31	Moderna	Dizziness, palpitations, throat swelling and tightness, abdominal cramping (within 10 minutes) ++	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 minutes)	52	232	COVID SARS TOTAL AB, SPIKE, SEMI-QUANTITATIVE	Reactive	231.7

M	37	Pfizer	None (Healthy control)	22	265	SARS-COV2 IgG AB SPIKE PROTEIN	Reactive	2.04
M	55	Pfizer	Throat swelling, lightheadedness, vomiting (within 5 minutes) ++	49	212	COVID SARS TOTAL AB, SPIKE, SEMI-QUANTITATIVE	Reactive	11.8
M	48	Pfizer	None (Healthy control)	23	164	SARS-COV2 IgG AB SPIKE PROTEIN	Reactive	2.65
F	57	Moderna	Diffuse hives, throat swelling (within 60 minutes) +	50	218	SARS-COV2 AB (IGG), SPIKE, SEMI-QUANTITATIVE	Reactive	18.12
F	65	Moderna	None (Healthy control)	25	202	SARS-COV2 IgG AB SPIKE PROTEIN	Reactive	3.1
F	51	Moderna	Diffuse hives, lip tingling (within 40 minutes)	30	190	SARS-COV2 AB (IGG), SPIKE, SEMI-QUANTITATIVE	Reactive	4.85
F	34	Moderna	None (Healthy control)	27	210	SARS-COV2 IgG AB SPIKE PROTEIN	Reactive	2.56
F	51	Pfizer	Diffuse hives (within 5 minutes)	41	187	SARS-COV2 AB (IGG), SPIKE, SEMI-QUANTITATIVE	Reactive	>20
F	56	Pfizer	None (Healthy control)	21	244	SARS-COV2 IgG AB SPIKE PROTEIN	Non-Reactive	0.58
F	34	Pfizer	Throat itching and swelling, nausea (within 5 minutes) ++	52				
F	59	Moderna	Mental foggy, throat itching, diffuse erythematous rash (within 15 minutes)	30				

*AB= Antibody; yr= years

+ Met Brighton Collaboration Case Definition of Anaphylaxis

‡ Met NIAID Criteria for Anaphylaxis

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