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.

Graded coronavirus disease 2019 vaccine administration

A safe alternative to vaccine avoidance

As the coronavirus disease 2019 (COVID-19) pandemic has unfolded and evolved over the past 2 years, so too have recommendations surrounding COVID-19 vaccination. Third and fourth vaccine doses are being approved for a wide variety of age groups, signaling the ongoing need for safe vaccine administration in hopes of controlling the pandemic. Concerns surrounding COVID-19 vaccine allergy have persisted throughout the vaccination period. A strategy for skin testing to evaluate these concerns was previously outlined, but subsequent studies reported limited utility in its use.[1-3] Emphasis has now shifted toward methods of safe vaccine administration in patients with concern for vaccine allergy in a model consistent with existing vaccine allergy practice parameters.[4,5] There is minimal reported experience using graded dosing protocols for COVID-19 vaccine administration. One case report described 2 patients with an immediate reaction on the first dose of the Moderna COVID-19 vaccine who successfully received their second dose using a 5-step protocol.[6] This protocol, along with a 4-step protocol for the Pfizer-BioNTech vaccine, was used in 16 patients in a separate report, with 2 patients experiencing anaphylaxis at the end of the graded dosing protocol.[7] A separate series utilized a 2-step protocol for administering the Pfizer-BioNTech COVID-19 vaccine in 12 patients.[8] One patient received levocetirizine for pruritus, but all 12 patients successfully completed the protocol without anaphylaxis.[8]

In this report, we describe multiple dosing protocols for all 3 currently available COVID-19 vaccines in the United States. In this multicenter retrospective review, more than 30 adult patients referred to the Mayo Clinics in Rochester, Minnesota, Scottsdale, Arizona, and Jacksonville, Florida, received a COVID-19 vaccine via a graded dosing protocol. The need for graded dosing and the protocol used were provider determined at the time of evaluation. Following the graded dosing, patient charts were reviewed to extract demographic characteristics, reason for graded dosing, prior COVID-19 vaccine reaction, and graded dosing outcome. The primary outcome was successful completion of graded dosing. Data were analyzed using BlueSky Statistics Software v7.2 (BlueSky Statistics LLC, Chicago, Illinois). Statistical comparisons were made between those who experienced symptoms with graded dosing and those who did not. Continuous variables between groups were compared using independent group *t* tests. Proportions of categorical variables between groups were compared using Fisher's exact test. Results were deemed significant when a 2-sided *P* value was less than .05.

Between May 13, 2021 and December 31, 2021, 42 COVID-19 vaccine graded dosing protocols were performed in 36 patients, with 6 patients undergoing 2 separate graded dosing protocols. Demographic characteristics and vaccination details are shown in Table 1. The most common indication for a graded dosing protocol was a previous COVID-19 vaccine reaction (n = 23) followed by patient concern for multiple drug allergies (n = 8), prior non–COVID-19 vaccine reaction (n = 6), and mast cell disease (n = 5). The Pfizer-BioNTech and Moderna vaccines were most commonly used (n = 20 and 17, respectively) followed by Johnson & Johnson (n = 5). A 2-step protocol was most frequently used (n = 21) followed by 3- and 4-step (n = 10 each) and 5-step (n = 1). There were 6 patients who reported symptoms during the graded dosing protocol, with 2 of these patients experiencing symptoms during separate graded dose administrations. One patient developed urticaria without other systemic symptoms within 30 minutes of finishing 2 separate graded dosing protocols that were both successfully treated with diphenhydramine. One patient experienced subjective chest tightness without wheezing during 2 separate graded dosing protocols that were both successfully treated with albuterol. Additionally, 4 other patients experienced either pruritus (n = 2), nasal congestion (n = 1), or cough (n = 1) without any objective findings. No patient experienced changes in vital signs during the graded dosing protocol. All 42 graded dosing protocols were successfully completed with no cases of anaphylaxis. There were no substantial differences in vaccine used, graded dosing indication, or dosing protocol in those who reported symptoms during the graded dosing protocol compared with those who did not. There was a significantly higher prevalence of allergic rhinitis ($P = .01$) and patient-reported food allergy history ($P = .04$) in those who had symptoms during the graded dosing protocol compared with those who did not.

This is one of the largest reported experiences utilizing COVID-19 vaccine graded dosing protocols. Prior reports describe utilizing a 2-step or 5-step protocol with the Moderna and Pfizer-BioNTech vaccines in 2 to 16 patients who had a prior COVID-19 vaccine reaction.[6-8] This report is unique in the number of graded dosing protocols performed, the variety of protocols used, and its inclusion of the Johnson & Johnson vaccine. We have shown success using multiple protocols with each of the vaccines currently in use in the United States with guidance from existing practice parameters, which should provide allergists with ample options for graded vaccine administration in the future. In addition, we demonstrated safety in 5 patients vaccinated with mast cell disease, adding to previous evidence demonstrating safety of COVID-19 vaccines in this population.[9] Lastly, we have shown the utility and safety of graded dosing protocols in patients expressing vaccine hesitancy for reasons other than a previous COVID-19 vaccine reaction. Given the high rate of vaccine tolerance in our cohort and prior reports of successful full-dose vaccine administration in patients with a prior COVID-19 vaccine reaction,[2] it should be emphasized that full-dose vaccine administration with observation is likely a safe, time-effective option for patients who have concerns regarding COVID-19 vaccine allergy. In patients who are hesitant to proceed with this, we have shown that graded vaccine dosing can be a safe alternative. Although direct full-dose vaccination should be encouraged as much as possible, if the offering of graded dosing leads to vaccination when it would otherwise be deferred, that should be considered a success.

In summary, we have shown the success of multiple graded dosing protocols for all 3 COVID-19 vaccines currently available in the United States in 36 patients undergoing 42 graded dosing protocols. There was no anaphylaxis in our cohort receiving a COVID-19 vaccine via a graded dosing protocol. If full-dose vaccination with observation is declined, graded vaccine dosing should be considered in lieu of strict avoidance to facilitate vaccination in patients with concerns about possible COVID-19 vaccine allergic reactions.

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Table 1
Demographic Characteristics and Outcomes of Patients Undergoing Graded COVID-19 Vaccine Dosing

Characteristic	Total (N = 42)	Symptoms with graded dosing (n = 8)	No symptoms with graded dosing (n = 34)	*P* value[a]
Age, mean (SD)	51.7 (13.7)	51.0 (8.1)	51.9 (14.7)	.87
Sex (%)				.99
Female	39 (92.9)	8 (100)	31 (91.2)	
Male	3 (7.1)	0 (0)	3 (8.8)	
Race (%)				.91
White	40 (95.2)	8 (100)	32 (94.1)	
African American	1 (2.4)	0 (0)	1 (2.9)	
Hispanic	1 (2.4)	0 (0)	1 (2.9)	
Non-atopic comorbidities (%)				
Obesity	19 (45.2)	6 (75.0)	13 (38.2)	.11
Hypertension	9 (21.4)	1 (12.5)	8 (23.5)	.66
Diabetes	1 (2.4)	0 (0)	1 (2.9)	.99
Chronic obstructive pulmonary disease	1 (2.4)	1 (12.5)	0 (0)	.19
Prior COVID-19 disease	4 (9.5)	1 (12.5)	3 (8.8)	.99
Allergic and atopic comorbidities (%)				
Allergic rhinitis	19 (45.2)	7 (87.5)	12 (35.3)	.01
Asthma	13 (31.0)	4 (50.0)	9 (26.5)	.23
Mast cell disease[b]	7 (16.7)	2 (25.0)	5 (14.7)	.60
Non–COVID-19 vaccine allergy	8 (19.0)	3 (37.5)	5 (14.7)	.16
Chronic spontaneous urticaria	4 (9.5)	1 (12.5)	3 (8.8)	.99
Food allergy[c]	16 (38.1)	6 (75.0)	10 (29.4)	.04
Anaphylaxis[c]	18 (19.0)	6 (75.0)	12 (35.3)	.06
Drug allergy[c]	42 (100)	8 (100)	34 (100)	.99
Venom allergy	3 (7.1)	0 (0)	3 (8.8)	.99
Reason for vaccine challenge (%)				.39
Prior COVID-19 vaccine reaction	23 (54.8)	6 (75.0)	17 (50.0)	
Patient concern for multiple drug allergies	8 (19.0)	0 (0)	8 (23.5)	
Prior non–COVID-19 vaccine reaction	6 (14.3)	2 (25.0)	4 (11.8)	
Mast cell disease[b]	5 (11.9)	(0)	5 (14.7)	
Vaccine given (%)				.34
Pfizer-BioNTech	20 (47.6)	4 (50.0)	16 (47.1)	
Moderna	17 (40.5)	2 (25.0)	15 (44.1)	
Johnson & Johnson	5 (11.9)	2 (25.0)	3 (8.8)	
Dosing regimen[d] (%)				.18
2-step[e]	21 (50.0)	3 (37.5)	18 (52.9)	
3-step[f]	10 (23.8)	1 (12.5)	9 (26.5)	
4-step[g]	10 (23.8)	3 (37.5)	7 (20.6)	
5-step[h]	1 (2.4)	1 (12.5)	0 (0)	
Change in vaccine[i] (%)	6 (14.3)	0 (0)	6 (17.6)	.58
Pfizer-BioNTech to Moderna	4 (9.5)	0 (0)	4 (11.8)	
Pfizer-BioNTech to Johnson & Johnson	1 (2.4)	0 (0)	1 (2.9)	
Moderna to Johnson & Johnson	1 (2.4)	0 (0)	1 (2.9)	
Previous vaccine or excipient skin testing (%)	28 (66.7)	7 (87.5)	21 (61.8)	.23
Previous positive vaccine or excipient skin testing (%)	5 (11.9)	0 (0)	5 (14.7)	.20
Symptoms experienced				NA
Pruritus	NA	2 (25.0)	NA	
Urticaria	NA	2 (25.0)	NA	
Cough	NA	1 (12.5)	NA	
Nasal congestion	NA	1 (12.5)	NA	
Chest tightness	NA	2 (25.0)	NA	
Treatment received (%)	NA	7 (87.5)	NA	NA
Antihistamines	NA	5 (62.5)	NA	
Albuterol	NA	2 (25.0)	NA	
Challenge successfully completed (%)	42 (100)	8 (100)	34 (100)	.99

Abbreviations: COVID-19, coronavirus disease 2019; NA, not applicable.
[a] *P* values represent comparison between the "symptoms with graded dosing" group and "no symptoms with graded dosing" group.
[b] Includes systemic mastocytosis, monoclonal mast cell activation syndrome, and hereditary alpha tryptasemia.
[c] Patient reported.
[d] All steps administered intramuscularly with 30-minute observation period after each step. Dilution steps made with sterile 0.9% saline solution. All other steps are utilizing non-diluted vaccine.
[e] Pfizer-BioNTech: 0.1 mL, 0.2 mL or 0.06 mL, 0.24 mL; Moderna and Johnson & Johnson: 0.05 mL, 0.45 mL or 0.1 mL, 0.4 mL.
[f] Pfizer-BioNTech: 0.05 mL, 0.1 mL, 0.15 mL.
[g] Pfizer-BioNTech: 0.05 mL 1:10 dilution, 0.05 mL, 0.1 mL, 0.15 mL; Moderna and Johnson & Johnson: 0.05 mL, 0.1 mL, 0.15 mL, 0.2 mL.
[h] Johnson & Johnson: 0.05 mL 1:10 dilution, 0.05 mL, 0.1 mL, 0.15 mL, 0.2 mL.
[i] Refers to using an alternative vaccine when the reason for graded dosing was a reaction to a previous COVID-19 vaccine.

Mitchell M. Pitlick, MD*
Alexei Gonzalez-Estrada, MD†
Miguel A. Park, MD*
* *Division of Allergic Diseases*
Mayo Clinic
Rochester, Minnesota

† *Division of Pulmonary, Allergy, and Sleep Medicine*
Mayo Clinic
Jacksonville, Florida
Pitlick.mitchell@mayo.edu

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SARS-CoV-2 vaccines are well tolerated in patients with mastocytosis

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) initially emerged in December 2019 in Wuhan, People's Republic of China, and its rapid spread led to a global pandemic. Vaccines are the single, most effective method of stopping the pandemic and concerns about vaccine safety have necessitated updates to the knowledge, especially in terms of allergic diseases. Patients with mastocytosis, who frequently experience recurrent anaphylaxis, constitute an important group that needs to be investigated as to whether the COVID-19 vaccines can be administered safely.[1]

Mastocytosis describes a group of disorders in which pathologic mast cells accumulate in tissues. Pruritus, flushing, recurrent anaphylaxis, nausea, vomiting, shortness of breath, drop in blood pressure, urticaria, angioedema, diarrhea, weakness, headache, and muscle pain are the symptoms of mast cell activation in these patients. The overall risk for anaphylaxis is considerably higher than that of the general population and has been reported in up to 49% of some cohorts.[1] Valent et al[2] recommended that anti–mediator-type drugs, venom immunotherapy, or vitamin D should be continued and chemotherapy or immunosuppressive drugs should be carefully evaluated on a case-by-case basis during COVID-19 in patients with mastocytosis. Rama et al[3] presented 2 patients with mastocytosis, who were vaccinated with the messenger RNA vaccine, the BNT162b2 (BioNTech) vaccine. Both were vaccinated with premedication with H_1 and H_2 antihistamines, 1 hour before, and montelukast 10 mg, at 1 and 24 hours, without adverse effects or a reaction, but 1 of the patients had myalgia on the following day. Kaakati et al[4] reported a series of 18 patients with history of mastocytosis who underwent SARS-CoV-2 vaccination, and none had an allergic reaction or anaphylaxis after the vaccination. Of the 18 patients, 13 received the Pfizer, 4 the Moderna, and 1 the Janssen vaccine. In addition, 4 patients took an antihistamine 30 to 60 minutes before vaccination.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (2021/29-11). The hospital records of 7 patients (4 females and 3 males) have been reviewed retrospectively. These patients had been diagnosed with having either cutaneous or systemic mastocytosis and were treated and followed up in our tertiary care center. The characteristics of the 6 vaccinated patients are summarized in Table 1. Anaphylaxis to drugs had been reported by 3 patients, and 1 patient had had a history of anaphylaxis owing to food allergy. The mean baseline tryptase level was 15.9 ng/mL (range, 3-200 ng/mL). The patients were contacted by telephone call and asked whether they have received any premedication before vaccination or experienced any reaction or adverse effect after vaccination. Only 1 patient (14%) had swelling of the throat, cough, and shortness of breath 2 minutes after Sinovac vaccination. This patient had received 45.5 mg pheniramine and 40 mg methylprednisolone intravenously 1 hour before the vaccine. Although the patient had received the same premedication intravenously 1 hour before the second dose of the same vaccine, the reaction has recurred, and the patient has been treated with 45.5 mg pheniramine and 40 mg methylprednisolone intravenously. The complaints have resolved in 1 hour. One patient, who had received 16 mg methylprednisolone and 22.7 mg pheniramine orally as premedication in each dose of the vaccines, has not experienced any reaction after the first 2 doses of Sinovac and the first dose of BioNTech. In addition, 1 patient has not been vaccinated on his will because of post-vaccine reaction concerns. A total of 15 vaccinations were administered to 6 patients, and 1 patient with cutaneous mastocytosis has experienced 2 non–life-threatening reactions after the vaccination. None of the patients had history of any vaccine, polyethylene glycol, or polysorbate allergy. We did not recommend our patients allergy testing with polyethylene glycol before BioNTech vaccine.

The European Competence Network on Mastocytosis and the American Initiative in Mast Cell Diseases recommended the use of COVID-19 vaccines in patients with mastocytosis, and by determining the individual risks of the patients, safety precautions, premedication, and post-vaccination observation should be considered in every patient with mastocytosis.[5] Although history of an anaphylactic reaction has been reported in up to 22% against other triggers in patients with mastocytosis, COVID-19 vaccines seemed to be well tolerated in the current study population.[4] There is a consensus among experts that antihistamine premedication should be administered 30 or 60 minutes before vaccination in patients with mastocytosis at high risk of anaphylaxis, and the use of systemic corticosteroids before the vaccines has been debated owing to concerns about vaccine efficacy.[5] In a previous report, 2 patients with mastocytosis and a history of anaphylaxis were able to tolerate BioNTech vaccine with premedication.[3] The current cohort includes 2 patients who had been premedicated with antihistamine and corticosteroid. Although one has had mild reactions after both doses of Sinovac, the other had no reaction

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