Second-dose mRNA COVID-19 vaccine safety in patients with immediate reactions after the first dose: A case series

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Background: The rates of suspected allergic reactions to the first dose of the coronavirus disease 2019 (COVID-19) mRNA vaccines have been reported to be as high as 2%, with an anaphylaxis incidence up to 2.5 per 10,000 individuals. Anaphylaxis in response to the first dose may be considered a contraindication to administration of the second dose, even though the second dose is necessary for optimal protection against severe disease. Many individuals with anaphylactic reactions to the first dose still want to receive a second dose. However, there are few published data to support the safety of administration of a second dose in this population.

Objective: The primary objective of this study was to determine the percentage of patients tolerating a second COVID-19 mRNA vaccine dose after an immediate reaction to the first dose.

Methods: This was a retrospective chart review of 47 patients at a Canadian hospital who had immediate, suspected allergic reactions following their first COVID-19 mRNA vaccine dose and received a second dose within our allergy clinic.

Results: Of 47 patients, 46 tolerated the second dose; 43% of patients developed mild, transient symptoms. There were no patients who developed anaphylaxis or needed epinephrine after the second dose.

Conclusion: Our case series adds to current evidence that administration of a second COVID-19 mRNA vaccine dose has a good safety profile in patients with a history of immediate reactions after the first dose, including those with a history of anaphylaxis in response to the first dose. (J Allergy Clin Immunol Global 2022;1:172-4.)

Key words: Coronavirus disease 2019, COVID-19, mRNA, vaccine, anaphylaxis, allergy, Pfizer, Moderna

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has now affected every country in the world, resulting in considerable morbidity, mortality, and health care spending. In December 2020, Health Canada first authorized the use of 2 COVID-19 vaccines based on novel mRNA technology. The Pfizer-BioNTech and Moderna mRNA vaccines have since been given to more than 28 million Canadians and are currently approved in patients aged 12 years and older.

Soon after the approval of these vaccines, reports of allergic reactions and anaphylaxis after first doses emerged. A prospective study from the United States showed that the rate of acute allergic reactions was as high as 2%, with anaphylaxis occurring in up to 2.5 per 10,000 individuals. However, the US Centers for Disease Control and Prevention, using voluntary reporting data, showed much lower rates of anaphylaxis, at 4.5 cases per million mRNA vaccine doses given. Notably, 82% of these reactions occurred after the first dose and 94% were in women.

Although anaphylactic reactions to the first dose of an mRNA COVID-19 vaccine may be considered a contraindication to a second dose, the current highly transmissible COVID-19 variants require 2 or more vaccine doses for protection from severe disease. Many individuals with anaphylactic reactions to the first dose still want to receive subsequent doses, and currently, this is considered on a case-by-case basis with allergists. However, there are few published data to support the safety of administration of a second dose.

After a reaction to the first dose of a COVID-19 mRNA vaccine, the current approach by expert consensus has been to stratify patients into low-, medium-, or high-risk categories. Patients at low risk include those with large local reactions, nonallergic symptoms, or delayed reactions after the first dose, and they can be given the second dose under the normal protocol. Medium-risk patients are those who have had potential immediate allergic symptoms but not anaphylaxis in response to the first dose. These patients can receive a second dose after shared decision making with their allergist, which may include pretreatment with antihistamines. Patients who have had potential anaphylaxis in response to the first dose are considered high-risk. These patients may receive a second mRNA dose after shared decision making with their allergist. Polyethylene glycol (PEG) skin testing in this
group has been found to be of limited utility but could be considered for patients with a very convincing history of anaphylaxis. Pretreatment in this group can also be considered, although an optimal regimen has not been studied.²

A recent US multicenter retrospective study of 189 patients who had immediate reactions to the first dose of an mRNA COVID-19 vaccine showed that the second dose is well tolerated.³ A total of 159 patients received the second dose, including 19 who had anaphylaxis in response to the first dose. Notably, patients with severe anaphylaxis and PEG allergy were excluded from this study. Of the enrolled patients, 20% had mild, self-limited symptoms that resolved with no more than antihistamines for treatment. All of the patients tolerated the second dose with no instances of anaphylaxis. Although this study is encouraging, in Canada and elsewhere in the world, there remains considerable uncertainty as to the safety of the second dose of mRNA COVID-19 vaccines in patients who have had immediate reactions to the first dose.

METHODS

A retrospective chart review of patients at St Michael’s Hospital who received a second dose of a COVID-19 mRNA vaccine was performed. The study patients received the vaccine within the hospital’s allergy clinic between January 1 and September 23, 2021. The study had 2 inclusion criteria: patients had to be at least 18 years of age and have a history of immediate, suspected allergic symptoms after receiving the first dose of a COVID-19 mRNA vaccine. Immediate was defined as symptom onset less than 4 hours after vaccine administration. Although patients with a history of PEG allergy were not excluded from the study, none met the inclusion criteria. Skin testing to vaccine is not required. All of the patients but 1 were female (98%); their mean age was 48.7 years. The majority of patients received the Pfizer vaccine for their first and second doses (91% and 94%, respectively); 32% of the patients met the clinical criteria for anaphylaxis after their first dose, and 38% received treatment with epinephrine.

For their second dose, 89% of the patients were given the same vaccine brand as their first dose. Most patients (81%) were given pretreatment with 3 to 5 days of a second-generation antihistamine or a combination of montelukast and antihistamine. All but 2 patients received their second vaccine in a single dose. With this approach, no patients developed anaphylaxis with second dose administration or required epinephrine. All but 1 patient tolerated the second dose with either no symptoms (55%) or mild symptoms (43%) requiring no more than antihistamines for treatment. There were no patients who reported biphasic allergic symptoms within 24 hours of their second dose.

Patients who had anaphylaxis after their first dose were somewhat more likely to develop immediate symptoms with the second dose than were patients without anaphylaxis (53% vs 41%). Patients who were given epinephrine after their first dose were also more likely to develop immediate symptoms with the second dose than were patients who had not been given epinephrine (50% vs 41%). There was a higher rate of immediate reactions seen in the premedication group than in those patients who did not receive premedication (50% vs 22%). No other risk factors were identified for having immediate symptoms after the second dose. Asthma and underlying autoimmunity were identified as risk factors for meeting the clinical criteria for anaphylaxis after the first dose. Of the patients who had asthma and autoimmunity, 42% and 33%, respectively, met the clinical criteria for anaphylaxis after their first dose. This was compared with 18% of patients who had neither asthma nor autoimmunity.

One patient, a 50-year-old female with underlying asthma and atrial fibrillation, developed fast-onset cough, globus sensation, and chest pressure after her second dose of the Pfizer vaccine and was given inhaled salbutamol and a dose of aspirin. Her symptoms were transient and resolved within an hour of monitoring. Her vitals remained normal throughout. She had met the clinical criteria for anaphylaxis with diffuse urticaria and cough and chest tightness after her first dose of the Pfizer vaccine and had been given epinephrine. Her second dose was administered in 1 step, 29 weeks following her first dose with 5 days of montelukast and bilastine pretreatment.

Our case series of 47 patients adds to the body of evidence showing that administration of a second dose mRNA COVID-19 vaccine has a good safety profile in patients with a history of immediate reactions after the first dose. Although mild symptoms were common after the second dose, none of the patients in our case series developed anaphylaxis or needed epinephrine. It is notable that 15 of our patients met the clinical criteria for anaphylaxis after their first dose and all but 1 tolerated the second dose. Our study findings support the recent case series of 159 US patients (19 with first-dose anaphylaxis), all of whom tolerated their second dose.⁵ When taken together, these data argue that anaphylaxis in response to the first dose of an mRNA COVID-19 vaccine should not be considered a contraindication to receiving the second dose. Rather, we believe that patients in

| TABLE I. First-dose characteristics of 47 patients who had suspected allergic reactions after an mRNA COVID-19 vaccine |
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| Cases, no. | Female, no. (%) | Age (y) mean (SD) | History of asthma, no. (%) | History of autoimmunity, no. (%) | Pfizer vaccine, no. (%) | Moderna vaccine, no. (%) | Anaphylaxis, no. (%)† | Epinephrine given, no. (%) |
| 47 | 46 (98) | 48.7 (15.5) | 14 (30) | 9 (19) | 43 (91) | 4 (9) | 15 (32) | 18 (38) |

*Patient autoimmune conditions included psoriasis (n = 3), lupus (n = 2), chronic spontaneous urticaria (n = 2), type 1 diabetes (n = 1), multiple sclerosis (n = 1), autoimmune gastritis (n = 1), dermatomyositis (n = 1), and Crohn disease (n = 1). Note that the numbers do not sum to 9, as some patients had multiple autoimmune conditions.

†Anaphylaxis after the first vaccine dose was defined by using the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria.
this category can be offered a second dose after shared decision making between the patient and his or her physician. Although their risk of repeat anaphylaxis with the second dose is very low, patients who experienced anaphylaxis after their first dose do appear to be at slightly higher risk of developing mild symptoms. Although the mechanism of reactions to mRNA COVID-19 vaccines remains an area of exploration, our findings suggest that many may not be mediated by IgE, as they are mitigated or in some cases eliminated after the use of pretreatment with antihistamines and montelukast. The absolute effect that pretreatment had on patient outcomes in this study is not clear and remains an area for future study. The increase in immediate reactions seen in the pretreatment group was likely due to patient selection, as patients with a more severe index reaction were more likely to be given pretreatment. Our study raises the question of whether many of the participants’ reactions to the first dose were truly anaphylaxis, given their tolerance of the second dose. This highlights the importance of thorough documentation in real time after reactions to COVID-19 mRNA vaccines so as to outline vital sign changes and objective physical examination findings. This documentation may be critical to help identify patients who truly experienced anaphylaxis in response to the first dose and thus may be at elevated risk with the second dose. Until our study, there were no Canadian data addressing the issue of the safety of a second dose of an mRNA COVID-19 vaccine in patients with reactions to the first dose. We hope that our findings will better inform our population and their treating physicians of the safety of second-dose mRNA vaccines. It is hoped that this evidence will lead to less vaccine hesitancy, increased numbers of second doses administered, and ultimately lower rates of COVID-19 in Canada and across the world.

### Key messages

- What is already known about this topic? Suspected allergic reactions to COVID-19 mRNA vaccines occur in up to 2% of individuals. There is emerging evidence that these patients may safely receive their second dose.
- What does this article add to our knowledge? Our case series provides evidence that second COVID-19 mRNA vaccine doses can be given with a good safety profile in patients with suspected allergic reactions to the first dose.
- How does this study affect current management guidelines? It is hoped that our safety data on second COVID-19 vaccine doses will lead to less vaccine hesitancy, increased numbers of second doses administered, and ultimately lower rates of COVID-19 in Canada and across the world.

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