Letters

RESEARCH LETTER

Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose

Allergic reactions after messenger RNA (mRNA) COVID-19 vaccines have been reported to be as high as 2%, with anaphylaxis occurring in up to 2.5 per 10 000 individuals.[1] There is uncertainty as to whether to administer a second dose of mRNA COVID-19 vaccine after a first-dose reaction.[2,3] In this study, we examine the safety of the second dose of Pfizer-BioNTech or Moderna vaccine in those with a history of immediate and potentially allergic reactions to the first dose.

Supplemental content

Methods | This multicenter, retrospective study conducted by Massachusetts General Hospital (Boston), Brigham and Women's Hospital (Boston, Massachusetts), Vanderbilt University Medical Center (Nashville, Tennessee), Yale School of Medicine (New Haven, Connecticut), and University of Texas Southwestern Medical Center (Dallas) from January 1, 2021, to March 31, 2021, included patients with an immediate allergic reaction to the Pfizer-BioNTech or Moderna vaccine, which was defined as: (1) symptom onset within 4 hours of dose 1, (2) at least 1 allergic symptom, and (3) referral for an allergy/immunology consultation with in-clinic or telehealth assessment (eMethods in the Supplement). Anaphylaxis was scored using the Brighton and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria.[4,5] Confirmed anaphylaxis required meeting at least 1 of these 2 criteria.

The primary outcome was second dose tolerance, which was defined as either: (1) no immediate symptoms after second dose administration or (2) symptoms that were mild, self-limited, and/or resolved with antihistamines alone. For any individuals who did not have their second dose observed by allergy/immunology departments, phone calls elicited clinical details. This study was approved by the Mass General Brigham human research committee with waiver of informed consent.

Results | There were 189 patients who participated in this study (mean [SD] age, 43 (14) years; 163 women [86%]) (**Table**). Of the mRNA COVID-19 vaccine first-dose reactions evaluated, 130 (69%) were to Moderna and 59 (31%) to Pfizer-BioNTech. The most frequently reported first-dose reactions were flushing or erythema (53 [28%]), dizziness or lightheadedness (49 [26%]), tingling (46 [24%]), throat tightness (41 [22%]), hives (39 [21%]), and wheezing or shortness of breath (39 [21%]). Thirty-two (17%) met anaphylaxis criteria.

A total of 159 patients (84%) received a second dose. Antihistamine premedication before the second dose was given in 47 patients (30%). All 159 patients, including 19 individuals with first-dose anaphylaxis, tolerated the second dose. Thirty-two (20%) reported immediate and potentially allergic symptoms that were associated with the second dose that were self-limited, mild, and/or resolved with antihistamines alone.

Discussion | This multisite US study supports the safety of Pfizer-BioNTech or Moderna vaccine second dose administration in patients who report immediate and potentially allergic reactions after the first dose. Although mild symptoms were reported in 20% of patients with second dose administration, all patients who received a second dose safely completed their vaccination series and could use mRNA COVID-19 vaccines in the future when indicated. Second dose tolerance following reactions to the first dose argues that either many of these initial reactions are not all truly allergic reactions, or supports an allergic, but non-immunoglobulin E-mediated mechanism in which symptoms can typically be abated with premedications.[6]

Because the Janssen vaccine received emergency use authorization, the US Centers for Disease Control and Prevention recommended that individuals with an immediate and potentially allergic reaction to the first dose of the Pfizer-BioNTech or Moderna mRNA COVID-19 vaccine could receive a Janssen single dose subsequently.[2] However, our data suggest that most patients with immediate and potentially allergic reactions to mRNA COVID-19 vaccines tolerate a second dose. Therefore, it may not be necessary to consider this, to our knowledge, largely unstudied alternative mixed series approach. Although earlier work provided a shared framework for the clinical approach,[3] our pooled study was limited by its retrospective study design, referral bias, and lack of a shared evaluation protocol among participating institutions.

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Table. Characteristics of Patients Who Experienced Potential Immediate Allergic Reactions to the First Dose of an mRNA COVID-19 Vaccine and Second Dose Outcomes

				No. (%)								
Institution	Cases, No.	Female, No. (%)	Age, mean (SD), y	Moderna	Pfizer-BioNTech	First-dose anaphylaxis[a]	Allergist skin testing performed[b]	Dose 2 administered	Dose 2 premedication given[c]	Dose 2 administered within guideline-recommended window[d]	Immediate allergic symptoms with dose 2[e]	Dose 2 tolerance[f]
MGH	76	66 (87)	39.5 (12.7)	60 (79)	16 (21)	6 (8)	34 (45)	65 (86)	7 (11)	62 (95)	8 (12)	65 (100)
BWH	54	45 (83)	43.0 (12.6)	41 (76)	13 (24)	5 (9)	30 (56)	50 (93)	11 (22)	44 (88)	7 (14)	50 (100)
VUMC	27	22 (81)	49.8 (18.2)	6 (22)	21 (78)	8 (30)	5 (19)	19 (70)	15 (79)	18 (95)	7 (37)	19 (100)
YSM	25	23 (92)	46.3 (13.3)	20 (80)	5 (20)	7 (28)	11 (44)	18 (72)	16 (64)	18 (100)	7 (29)	18 (100)
UTSW	7	7 (100)	47.0 (13.2)	3 (43)	4 (57)	6 (86)	0	7 (100)	1 (17)	6 (86)	3 (43)	7 (100)
Pooled values	189	163 (86)	43.2 (14.1)	130 (69)	59 (31)	32 (17)[g]	80 (42)	159 (84)	50 (31)	148 (93)	32 (20)	159 (100)

Abbreviations: BWH, Brigham and Women's Hospital; MGH, Massachusetts General Hospital; mRNA, messenger RNA; UTSW, University of Texas Southwestern Medical Center; VUMC, Vanderbilt University Medical Center; YSM, Yale School of Medicine.

[a] Anaphylaxis defined as meeting at least 1 of the following criteria: Brighton and/or the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria.

[b] Skin testing was variably performed in some higher-risk patients, of whom none were positive for polyethylene glycol 3350 with percutaneous skin testing.

[c] The most common pretreatment was nonsedating oral antihistamines (47 of 50 patients).

[d] Forty-two days, US Centers for Disease Control and Prevention (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html).

[e] All reactions experienced with dose 2 were lower in severity compared with first-dose reactions and none required treatment with epinephrine or urgent care/emergency department visits. Reaction symptoms included: tachycardia (n = 6), dizziness/lightheadedness (n = 6), throat tightness (n = 6), flushing/erythema (n = 5), swelling (n = 4), hives (n = 3), wheezing/shortness of breath (n = 3), hypertension (n = 2), tingling (n = 2), and nausea/vomiting/abdominal pain (n = 1). Numbers do not sum to 32 because some patients had more than 1 symptom. No patients experienced hypoxia, hypotension, bradycardia, metallic taste, or tingling.

[f] Tolerance was defined as no immediate symptoms present, or if immediate symptoms were present, they were self-limited, mild, and managed with antihistamines only.

[g] Of these 32 patients, 19 (59%) received and tolerated dose 2 (2 for MGH, 4 for BWH, 6 for VUMC, 1 for YSM, and 6 for UTSW).

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