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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Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing

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Since the coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines became available, Vaccine Adverse Event Reporting System data and early reports identified rare cases of anaphylaxis.[1] Banerji et al[2] proposed a suggested approach to skin test for COVID-19 vaccine excipients, specifically polyethylene glycol, polysorbate 80, and polysorbate 20. Using this algorithm, and skin testing with COVID-19 mRNA vaccine leftover from vial overfill, we report findings in a case series of 39 patients referred to an allergy and immunology practice for possible COVID-19 vaccine hypersensitivity from January to May 2021.

Expanded skin testing for COVID-19 vaccine excipients was performed as previously published.[2] In addition, percutaneous and intradermal skin tests (1:10 dilution and full strength both for pricks and intradermals) with Moderna and Pfizer COVID-19 vaccines were completed. We recorded whether premedication was used and analyzed available laboratory data (serum tryptase, soluble terminal complement complex, complete blood cell count with differential). Premedication could consist of H_1 blockers, H2 blockers, and leukotriene antagonists. An example regimen was cetirizine 20 mg, famotidine 40 mg, and montelukast 10 mg daily starting 3 days before the vaccine. Patient outcome or vaccine tolerance was assessed through follow-up and chart review.

Patient characteristics and atopic conditions are illustrated in Table 1. Notably, 77% (n = 30) of the patients were referred for reactions to COVID-19 mRNA vaccine. The remaining 23% (n = 9) were referred for other high-risk history for potential reaction to the vaccine. The most common clinical presentation (Table 1) was urticaria and angioedema, immediate (within 4 hours) in 36% of the patients (n = 14) and delayed (beyond 4 hours) in 28% of the patients (n = 11). Overall, 46% of the reactions were immediate (n = 18), and the mean time to occurrence was 32 minutes. Furthermore, 31% of the reactions were delayed (n = 12), and average time to manifestation was 3.8 days. Such designation was not applicable in 23% (n = 9) patients referred for other high-risk history.

None of the patients demonstrated positive percutaneous or intradermal skin test results for COVID-19 vaccine excipients. Furthermore, 11% of the patients (n = 4) had positive intradermal skin testing result to COVID-19 vaccines of unclear clinical significance (3 patients with immediate positive intradermal skin testing result to Moderna vaccine, 1 patient with delayed full-strength positive intradermal result to Pfizer vaccine). The patients with positive skin test results also tolerated the subsequent vaccine.

Of the patients, 95% (n = 37) tolerated their succeeding COVID-19 vaccine without serious allergic reaction. Furthermore, 92% (n = 36) have received 2 doses of COVID-19 vaccines. There was 1 patient who was prescreened owing to severe chronic idiopathic urticaria and angioedema who elected to receive the Janssen vaccine. Of the patients who tolerated their subsequent COVID-19 vaccine, 62% (n = 23) received premedication.

One patient with initial reaction to Moderna experienced nausea and pruritus during skin testing, similar but milder than initial reaction. Despite negative skin test results, this necessitated

Table 1
Patient Characteristics and COVID-19 Vaccine Hypersensitivity

Characteristic	Value
Age, mean (SD), y	56 (16)
Sex, n (%)	
Female	34 (87)
Male	5 (13)
Ethnicity, n (%)	
White	34 (87)
African American	3 (8)
Hispanic	2 (5)
Vaccine, n (%)	
Moderna	19 (47.5)
Pfizer	19 (47.5)
Janssen	2 (5)[a]
Patients on baseline antihistamine, n (%)	14 (36)
Patients on baseline montelukast, n (%)	8 (21)
Peripheral eosinophilia, n (%)	3 (8)
Elevated serum tryptase, n (%)	2 (5)
Atopic, n (%)	37 (95)
Concomitant allergic disorders, n (%)[b]	
Allergic rhinitis	21 (54)
Antibiotics allergy	21 (54)
Asthma or COPD	12 (31)
Food allergy	8 (21)
Chronic idiopathic urticaria and angioedema	16 (41)
Mastocytosis	1 (3)
Most common reactions, n (%)	
Immediate urticaria and angioedema (<4 h after vaccine)	14 (36)
Delayed urticaria and angioedema (>4 h after vaccine)	11 (28)
Asthma, COPD chest tightness, or shortness of breath	3 (8)
Syncopal or vasovagal	2 (5)
Concerning high-risk history for potential to have allergic reaction on receipt of vaccine	
Allergy to meds or other high-risk allergy history (includes latex and hymenoptera)	5 (13)
Reaction to other vaccines or injectables	6 (15)[c]
Clinical history of concern for polyethylene glycol allergy	2 (5)
Treatments of acute vaccine reactions requiring intramuscular epinephrine and systemic corticosteroids	
Received intramuscular epinephrine and systemic corticosteroids, n (%)	2 (5)
Received systemic corticosteroids only, n (%)	2 (5)

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; meds, medications.
[a]A total of 40 vaccines, 39 patients (1 received Moderna and then Janssen).
[b]Total percentages exceeded 100% owing to overlap.
[c]4 patients had reaction to influenza vaccine. 2 patients had reaction to omalizumab.

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intramuscular epinephrine. An elevated serum tryptase level (11.6 μg/L) was obtained with 24-hour delay (basal and post unavailable). Subsequently, the patient tolerated Janssen vaccine without incident in lieu of the second Moderna dose. Another patient with chronic urticaria starting 4 days after Moderna had an elevated serum tryptase level obtained weeks after his vaccine (25.7 μg/L). Subsequent bone marrow and diagnostic criteria confirmed indolent systemic mastocytosis.

Of the patients who tolerated their succeeding dose of COVID-19 vaccine, 16% (n = 6) did experience mild allergic symptoms that were self-limited or treatable with antihistamines. Furthermore, 5% (n = 2) were either unreachable for follow-up or the patient declined the ensuing dose.

Our data in a private practice setting reveal similarities to the findings of Banerji et al[3] in 16 health care employees of a large university hospital system. They completed pre-mRNA vaccination excipient skin testing and had an 88% tolerance of first-dose COVID-19 vaccine in individuals with a high-risk allergy history. Our population differs in that a high percentage (77%, n = 30) of patients in our report had vaccine reactions as their referral reason. Furthermore, 3 case reports of 4 to 14 patients revealed negative vaccine or excipient skin test results and tolerance of consequent mRNA COVID-19 vaccine in patients with first-dose reactions or other high-risk history.[4-6] Recently, Robinson et al[7] published prospective data from 1261 employees from Mass General Brigham with self-reported COVID-19 mRNA vaccine allergic symptoms. Most of the patients with mild hypersensitivity or nonimmediate symptoms safely completed the 2-dose vaccine series. To our knowledge, we report the first large series of COVID-19 vaccine hypersensitivity referrals in a private allergy and immunology practice.

Because private practices did not have access to full vials of vaccine for administration during the period of study, there was not an option of graded challenge. Some patients with more severe symptoms of immediate hypersensitivity reactions with or without positive skin test results to the vaccine may have benefited from graded dose challenge or desensitization.[8] Our findings, though, suggest a simpler paradigm in that most individuals with previous reactions would be able to receive their subsequent COVID-19 vaccine dose with or without premedication or by treating through mild to moderate allergic symptoms.

A limitation of this study was that nonirritant skin test concentrations of COVID-19 vaccine have not yet been established. We did skin test control in individuals on our health care team, and skin test results were negative, suggesting positive immediate intradermal skin test results at 1:10 and full strength were likely nonirritant. A study of 131 patients with idiopathic anaphylaxis found negative prescreening percutaneous test results for COVID-19 mRNA vaccines and excipients, including trometamol (buffer in Moderna vaccine associated with anaphylaxis to gadolinium contrast).[9] Nevertheless, intradermal skin testing was not performed.

Our findings did not reveal an immunoglobulin E–mediated pathogenesis for immediate-type COVID-19 vaccine hypersensitivity, given the vastly negative skin test results. There may be nonspecific mast cell histamine release which can be countered with premedication or treating through the reactions. Other researchers espoused that theory on the basis of their clinical findings and experience with premedication for possible allergic reactions to COVID-19 mRNA vaccine.[6] We could not confirm whether complement activation-related pseudoallergy was a putative mechanism but found no evidence of abnormal complement levels in the few patients where soluble terminal complement complex was obtained.

A systematic review cites the overall use of skin testing for COVID-19 vaccine and excipients to be of uncertain diagnostic value.[10] Nevertheless, there are limited patients with COVID-19 vaccine hypersensitivity skin tested with the vaccine in the published literature to guide the decision making. Further research in this area is urgently warranted.

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