COVID-19 mRNA vaccine allergy

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Severe immediate allergic reactions, including anaphylaxis, have been reported since the second day of the mass vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the US Centers for Disease Control and Prevention, the initially estimated rate of anaphylaxis was up to 11.1 cases per million administered doses of the Pfizer-BioNTech vaccine and 2.5 cases per million administered doses of the Moderna vaccine.[1-3] Because anaphylaxis in response to vaccines is generally rare (1 case per million administered doses), the higher incidence led to scrutiny of the mRNA vaccines and their excipients.[3] Polyethylene glycol (PEG) was initially identified as a possible culprit with allergenic potential.[2-4] PEG had not been utilized as a vaccine excipient before the mRNA vaccine era, and given that serious allergic reactions due to PEG or its derivatives had been described previously, it was not just an object of research but even gained public attention. The aim of this brief review is to summarize the recent evidence regarding immediate allergic reactions due to coronavirus disease 2019 (COVID-19) mRNA vaccines and discuss the different underlying mechanisms.

We searched systematic reviews, meta-analyses, and guidelines published on PubMed and Embase addressing immediate hypersensitivity reactions to mRNA vaccines using key words such as COVID vaccine, mRNA vaccine, allergy, and hypersensitivity. A total of 229 records were identified. Publications dealing with immediate allergic reactions were assessed for eligibility (Fig 1). Noneligible reports (eg, articles addressing select patient groups, duplicates, conference abstracts) were removed. We additionally searched PubMed and Embase by cross-checking the references in the selected articles. The 10 most relevant publications detailing underlying mechanisms for immediate allergic reactions to the mRNA vaccines, risk factors of immediate reactions, outcomes of skin testing, and revaccination were selected to inform this brief review. Other manifestations, such as delayed hypersensitivity reactions, nonallergic postvaccination complications such as myocarditis, autoimmune reactions, vaccine-induced thrombocytopenia, and so forth are not discussed in this review.

Tolerance of the second mRNA vaccine dose after a suspected allergic reaction was proved in most of the patients. Chu et al demonstrated that only 6 people (0.4%) of 1366 with an immediate reaction to the first COVID-19 vaccine dose developed severe reactions after administration of the second dose; additionally, among 78 persons with severe immediate allergic reactions to their first mRNA vaccine, 4 (4.9%) had a second severe immediate reaction.[5] Although there are scarce case reports of patients with anaphylaxis in response to the mRNA vaccines and positive skin test results for PEG or its derivatives, case series have shown that patients with confirmed allergy to PEG tolerated the mRNA vaccines.[1-4] According to a meta-analysis evaluating data on 317 individuals with first-dose vaccine reactions who underwent 578 skin tests to vaccine excipients and/or COVID-19 vaccines, the skin tests could not accurately predict vaccine tolerance to a second dose.[6] It was concluded that skin testing with mRNA vaccines or their excipients is not recommended as a routine approach for risk assessment before vaccination or after an immediate reaction to mRNA vaccines.[1-3,6] Also, PEG allergy may not predict mRNA vaccine reactions, and mRNA vaccine tolerance may not exclude PEG allergy.[6]

The most likely underlying mechanisms behind immediate reactions to the mRNA vaccines are thus not mediated by IgE.[1-4,6] A well-known nonimmunologic phenomenon, immunization stress–related response (ISRR), comprising anxiety, hyperventilation, and vasovagal reactions, has been concluded to mimic immediate allergic reactions in several cases, leading to administration of epinephrine, hospitalization, and unnecessary avoidance of the culprit vaccine.[2-4]

Complement activation–related pseudoallergy (CARPA) and other complement system activation–related non-IgE–mediated immunologic reactions have also been proposed as underlying mechanisms in addition to ISRR.[2-4] Previous data have shown that the binding of anti-PEG IgM antibodies to PEGylated liposomes leads to complement activation and hypersensitivity reactions in animals; however, this pathway has not been confirmed in human models.[7] Shah et al[8] have recently demonstrated that sera from patients with immediate-type reactions to the mRNA vaccines induced stronger complement activation than do sera from nonreacting subjects following *ex vivo* vaccine exposure. Vaccine-mediated activation of the complement system correlated with anti-PEG IgG levels, whereas no correlation was seen for anti-PEG IgM.[8]

Studies indicate that the Brighton Collaboration scoring system overestimates the rate of anaphylaxis, given that stress-related subjective symptoms meet several minor criteria.[1,2,9] Reassessment of cases reported as anaphylaxis according to the Brighton Collaboration Criteria showed that up to 71% of these reactions did not meet the criteria for anaphylaxis according to criteria defined by National Institute

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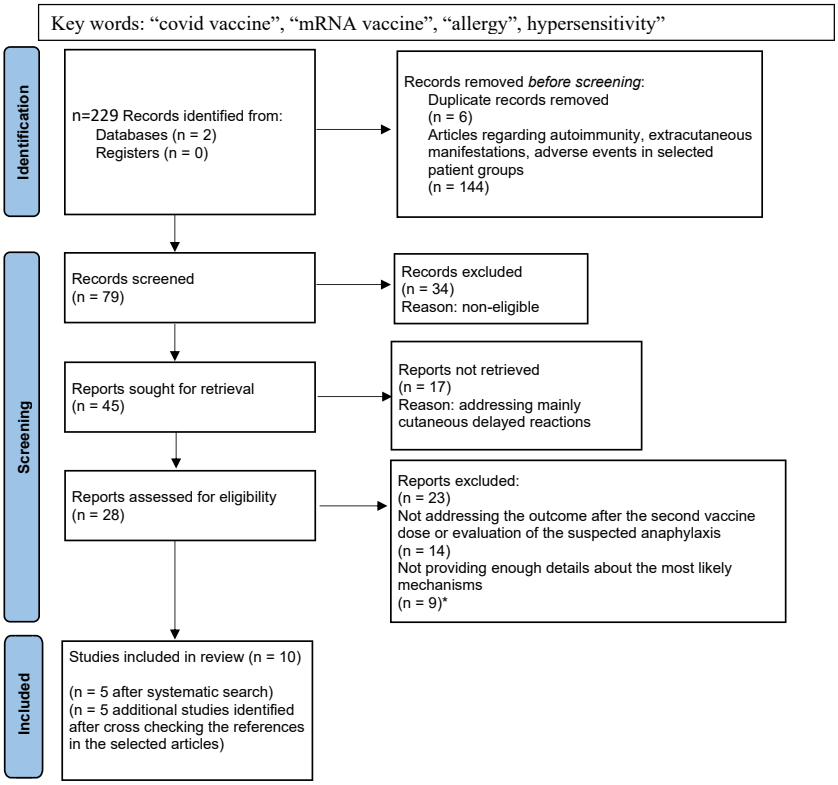

FIG 1. Identification of studies via databases and registers. The key terms *COVID vaccine*, mRNA *vaccine, allergy*, and *hypersensitivity* were searched in systematic reviews, meta-analyses, and guidelines. *The excluded publications (n = 9) describing the characteristics of the different populations with suspected anaphylaxis yielded the same significant conclusions, but compared with the included references, they were lacking some details about the likely mechanisms. They were excluded owing to the limited number of references allowed in this brief review.

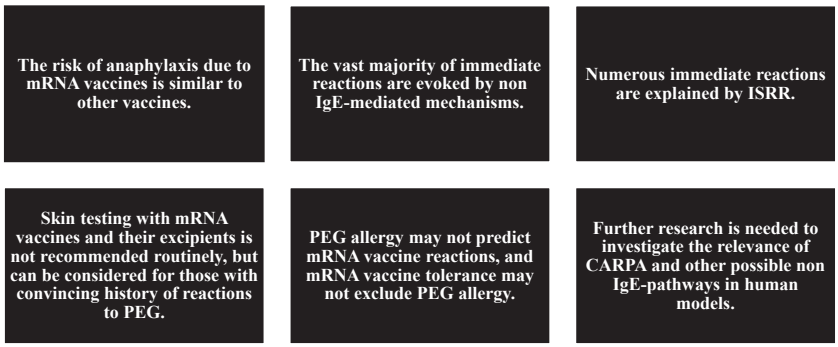

FIG 2. Current understanding of COVID-19 mRNA vaccine allergy. *CARPA*, Complement activation–related pseudoallergy.

of Allergy and Infectious Diseases in 2005 and the World Allergy Organization in 2020.[1] Macy et al analyzed data on 391 123 mRNA vaccine recipients and demonstrated that only 2 individuals (0.00033%) had reactions consistent with anaphylaxis. Anaphylaxis was defined according to the refinement of the World Allergy Organization/National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria when objective findings such as hives, hypotension, hypoxia, and so forth, were observed.[10]

The differences in anaphylaxis prevalence across various cohorts and populations are likely due to the use of diverse anaphylaxis scoring systems, differing attitudes toward vaccination and reporting of side effects within populations, and variations in health care infrastructure and surveillance systems.[1]

To summarize, systematic reviews have underlined that the early data overestimated the risk of anaphylaxis due to mRNA vaccines, whereas recent data have indicated that the rate of

anaphylaxis is comparable to that with other vaccines (Fig 2).[1] Although there are rare case reports of patients with PEG allergy and anaphylaxis in response to an mRNA vaccine, an IgE-mediated pathway against PEG or other culprits has not been proved convincingly.[2-4] Some studies have indicated that patients with confirmed allergy to PEG tolerated mRNA vaccines, and several case series have shown that revaccination with the same mRNA vaccine was uneventful in patients referred for immediate allergic reactions to the first dose.[1-5] These data support that idea that the majority of the suspected allergic reactions are triggered through non–immune-mediated pathways.[1-4] Evaluation with skin tests for the mRNA vaccines or their excipients is not recommended as a routine approach for the purpose of risk assessment before vaccination or after suspected allergic reactions to mRNA vaccines, and PEG skin testing should be considered only for those with additional convincing history of reactions to PEG in other contexts.[2,3,6] Numerous mRNA vaccine–related reactions are explained by a nonimmunologic phenomenon, namely, ISRR.[2-4] Recognizing ISRR and distinguishing it from allergy is essential for caregivers to combat vaccine hesitancy.

Although involvement of anti-PEG IgG and IgM antibodies and activation of the complement system (complement activation–related pseudoallergy) can be other possible pathways that underlie immediate hypersensitivity reactions, further research is necessary to investigate these possible mechanisms in humans.[2-4]

In conclusion, given that different underlying pathways can lead to immediate reactions to mRNA vaccines and revaccination is uneventful in the vast majority of the patients, allergists have a key role in evaluating patients, determining the likely mechanism, and administering the subsequent vaccine dose to ensure a high vaccination rate.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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