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Immune parameters during anaphylaxis to messenger RNA coronavirus disease 2019 vaccines

Not the usual suspects?

Soon after the release of the new anti–coronavirus disease 2019 messenger RNA vaccines, reports of anaphylactic reactions came in from the United States.[1-3] Cases were reported for both Pfizer *BNT*162b2 and Moderna mRNA-1273 vaccines with an estimated frequency of 4.7 and 2.5 cases per million doses, respectively.[3] Allergic reactions to vaccines are rare and mostly due to vaccine excipients.[4] Therefore, the polyethylene glycol present in both mRNA formulations was soon suspected to be the culprit.[5] Several hypersensitivity mechanisms to polyethylene glycol have been described, such as classical immunoglobulin E (IgE)–dependent anaphylaxis and complement activation-related pseudoallergy.[6]

In their interesting work, Kohli-Pamnani et al[7] conclude to the absence of an IgE-mediated mechanism in 39 individuals, based on negative skin testing and negative serum mast cell tryptase results. In addition, they did not confirm a complement activation-related pseudoallergy syndrome owing to normal sC5b9 levels in an undisclosed number of individuals. To expand on these findings, we explored in more detail putative immunologic mechanisms in patients presenting with COVID-19 anaphylaxis.

As a reference clinical laboratory for anaphylaxis in Paris, France, we collected samples from 5 patients suspected of having anaphylaxis from more than 208,000 people who were vaccinated in Paris hospitals during this period. All received the *BNT*162b2 vaccine.

We received a sample within 2 hours of the reaction for all patients, an early (<30 minutes) sample for 4 of 5 patients and a late (basal) sample for 2 of 5 patients.

All patients had normal tryptase levels for all time points. In addition, histamine levels were normal in all patients but one at the first time point. Interestingly, histamine levels normalized in the second sample in this patient, suggesting that histaminoliberation could be involved. We also measured levels of C5a and soluble C5b9 complexes in the blood. These levels did not change over time nor substantially differed from basal levels of unvaccinated healthy controls (n=18). Finally, we previously described in neuromuscular blocking agent anaphylaxis an IgG-dependent mechanism with neutrophil activation.[8] Accordingly, we measured neutrophil elastase plasma levels and found them comparable with those of healthy controls. Finally, using mass spectrometry, we measured leukotrienes (B4, B5) and prostaglandins (D2, E2, F2) but did not find marked difference with normal plasma levels.

All in all, we did not find any sign of immune system activation in these patients at the time of the reaction except for one case of histamine release. More importantly, 3 of 5 patients could be revaccinated with the same mRNA vaccine (patient 1 had already received both doses and patient 4 died of unrelated cause before his second dose). Consistently with the data of Kohli-Pamnani et al,[7] all re-exposures went without any incident.

In summary, we found that COVID-19 mRNA vaccine anaphylaxis does not seem to rely on an IgE-, IgG-, or complement-mediated mechanism. Even nonspecific histamine liberation does not seem to be frequent because it was present in only 1 patient. Although more work is needed to understand the exact nature of the mechanism behind the symptoms, it seems safe, based on the available evidence for Kohli-Pamnani et al[7] and ours, to recommend vaccine reintroduction under antihistamine premedication.

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Coronavirus disease 2019 messenger RNA vaccine skin tests and serum histamine levels in allergic reactions

Check for updates

We thank de Chaisemartin et al[1] for their correspondence in regard to our manuscript, "Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing."[2] De Chaisemartin et al[1] elucidate their findings of transient elevation of serum histamine levels in 1 of 5 patients with anaphylaxis after messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine. Conversely, 4 of 5 patients had normal serum histamine and tryptase levels within 2 hours of anaphylaxis.

De Chaisemartin et al[1] reflect that their findings of transient or lack of elevated serum histamine levels after COVID-19 mRNA anaphylaxis parallel with our findings of negative excipient skin test results (polyethylene glycol [PEG], polysorbate 20 and 80) and limited positive intradermal skin test results with the vaccine. Our 4 of 39 patients with positive intradermal skin testing results to the vaccine tolerated their ensuing dose of COVID-19 mRNA vaccine. The common thread in our findings and those of de Chaisemartin et al[1] is the suggestion that antihistamine premedication may prevent some allergic reactions.[3] Most patients will tolerate subsequent vaccination with the mRNA COVID-19 vaccine with or without premedication.[1-7] In the report of de Chaisemartin et al,[1] 3 of 5 patients tolerated their consequent COVID-19 mRNA vaccine. Furthermore, 1 patient already received their second dose to which anaphylaxis had occurred. In addition, 1 patient passed away from unrelated cause before the receipt of vaccine dose 2. In our case series, 95% (n = 37) tolerated their succeeding COVID-19 vaccine without serious allergic reaction. Moreover, 92% (n = 36) received 2 doses of their COVID-19 vaccines. Of the patients who tolerated their subsequent mRNA vaccines, 62% received premedication, which could include H_1 and H_2 antihistamines and leukotriene inhibitors.

A potential explanation of transiently elevated serum histamine levels in the patient described by de Chaisemartin et al[1] could be basophil activation. Warren et al[8] revealed that 11 patients with anaphylactic reactions to the COVID-19 mRNA vaccine had negative skin test results to the vaccine and excipients. Nevertheless, most had positive basophil activation test results to PEG. All had positive basophil activation test results to the mRNA vaccine. Notably, PEG immunoglobulin G was found despite undetectable PEG immunoglobulin E in the tested patients with allergic reactions.

In summary, de Chaisemartin et al[1] raise an interesting point on possible transient elevation of serum histamine levels. Further research is necessary to characterize skin tests with the specific vaccines and biomarkers such as serum histamine levels to evaluate which endotypes of post–COVID-19 mRNA vaccine allergic reactions may benefit from premedication or desensitization to COVID-19 mRNA vaccines.

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