LETTER TO THE EDITOR

Non-allergic nature of vast majority of cutaneous adverse reactions to mRNA COVID-19 vaccines: implications on treatment and re-vaccination

To the Editor,

A spectrum of adverse cutaneous reactions has been reported after COVID-19 vaccinations, with 15%–35% of patients reporting erythema, swelling, induration and/or itch. The commonest are delayed large local reactions, with other reported reactive dermatoses including morbilliform eruptions, urticaria, pityriasiform and purpuric eruptions.[1] However, these reports have dampened enthusiasm and further perpetuated vaccine hesitancy. Recognition and understanding of the types of vaccine-associated reactions is vital to avoid unnecessarily limiting patient options.

Drug allergies are adaptive immune responses with the development of drug-specific antibodies or T cells recognizing a specific drug antigen.[2] The literature to date indicates that most vaccine reactions are non-allergic in nature. First, adverse reactions to the vaccine have not worsened with each subsequent administration, as would be expected in allergic reactions. A study on 80 patients with prior 'allergic' reaction to the first dose of mRNA vaccines found 89% of patients who had a second dose were able to safely tolerate it with mild to no reactions, regardless of results from excipient skin testing.[3] A report by the CDC on COVID-19 vaccine safety also displayed similar rates of local and systemic reactions between the second and third doses.[4] Other studies have found that with the second dose of COVID-19 vaccination, cutaneous reactions from the vaccine recur in less than half the patients with first-dose reactions, and the majority of patients had recurrent reactions of equal or less severe than their initial reaction. While isolated urticaria within 6 h of vaccination may raise concerns of allergy, the fact that most patients with an initial acute-onset hypersensitivity event can tolerate a subsequent dose suggests otherwise.[5] Secondly, several studies have found adverse events to the vaccine are unlikely to be IgE-mediated, which occurs in immediate-type (Type 1) allergic reactions.[2] Warren *et al.*[6] found no IgE antibodies to polyethylene glycol (PEG) in those with suspected allergic reactions to mRNA COVID-19 vaccines. Thirdly, there are also several reports of severe systemic inflammatory symptoms occurring after COVID-19 vaccination, such as arthralgias, fever and rashes, that were successfully treated with IL-1 antagonists.[7] While these reactions may be similar in severity to drug-induced hypersensitivity syndrome, the shorter latency of a few days from vaccination to symptom onset is a helpful differentiating feature. The successful treatment with IL-1 antagonists indicates over-reactivity of the innate immunity as the underlying pathology, rather than allergic reactions which are mediated by the adaptive immunity.

What could the mechanism of these non-allergic reactions be? We posit that autoimmune/inflammatory syndrome induced by adjuvants (ASIA), represents a significant proportion of these reactions. ASIA is characterized by innate and subsequent adaptive immune system over-reactivity consequent to adjuvants, which are added to vaccines to boost immune reactivity towards antigens and are known to trigger autoimmune/autoinflammatory events. Proposed diagnostic criteria has been broadly divided into major and minor features – where major criteria include the exposure to an external stimulus prior to clinical manifestations, the appearance of typical clinical manifestations, improvement with removal of the inciting agent and typical histological findings on biopsy. A study on 500 patients in an ASIA international registry found that autoinflammatory and polygenic autoimmune diseases were found more frequently after exposure to the Hepatitis B virus and influenza vaccines.[8] COVID-19 vaccines have also been implicated with ASIA, with Graves' disease reported in previously healthy subjects several days after exposure to the mRNA vaccine containing PEG as its adjuvant.[9] Additionally, delayed inflammatory reactions to hyaluronic acid filler, a common adjuvant in ASIA syndrome, have also occurred post-vaccination.[1,8] In patients presenting with vaccine-associated reactions, clinicians should check for clinical features of systemic organ involvement, as autoinflammatory and autoimmune reactions are systemic in nature. When clinically indicated, laboratory screening comprising thyroid hormone levels and anti-nuclear antibodies may be helpful, as these are raised in cases of ASIA.[8] Besides ASIA, complement activation-related pseudo-allergy (CARPA) and other complement-related non-allergies have been suggested as mechanisms behind anaphylactoid reactions to the COVID-19 vaccine, where pre-existing anti-PEG IgM bind to liposomes, resulting in subsequent complement activation.[10]

Most patients recover from adverse events without any intervention.[1,5] However, some reactions can be prolonged and severe. Immunosuppressants used in ASIA include prednisone, hydroxychloroquine and other disease-modifying antirheumatic

drugs.[8] Further research is needed in vaccine-associated reactions to elucidate the optimal therapies to use at different stages of the disease. For patients who need additional vaccine doses, we recommend providing them with other efficacious vaccines with differing adjuvants to reduce the risk of a recurrent flare-up, although attenuation of innate immunity response can occur with repeated exposure to the same stimulus. If allergy testing is indicated, such as in patients with anaphylaxis, it should be conducted no earlier than 2 weeks after the allergic event and under safe conditions. With better recognition and understanding of non-allergic COVID-19 vaccine-induced reactions, we can provide better treatment and prognostication for patients and improve people's confidence in the safety of COVID-19 vaccines.

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None declared.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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References

1 Sun Q, Fathy R, McMahon DE, Freeman EE. COVID-19 vaccines and the skin: the landscape of cutaneous vaccine reactions worldwide. *Dermatol Clin* 2021; **39**: 653–673.
2 Demoly P, Adkinson NF, Brockow K *et al*. International consensus on drug allergy. *Allergy* 2014; **69**: 420–437.
3 Wolfson AR, Robinson LB, Li L *et al*. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. *J Allergy Clin Immunol Pract* 2021; **9**: 3308–3320.e3303.
4 Hause AM, Baggs J, Gee J *et al*. Safety monitoring of an additional dose of COVID-19 vaccine – United States, august 12-September 19, 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 1379–1384.
5 Macy E, Pandya S, Sheikh J *et al*. Population-based incidence, severity, and risk factors associated with treated acute-onset COVID-19 mRNA vaccination-associated hypersensitivity reactions. *J Allergy Clin Immunol Pract* 2021; **10**: 827–836.
6 Warren CM, Snow TT, Lee AS *et al*. Assessment of allergic and anaphylactic reactions to mRNA COVID-19 vaccines with confirmatory testing in a US regional health system. *JAMA Netw Open* 2021; **4**: e2125524.
7 Bindoli S, Giollo A, Galozzi P, Doria A, Sfriso P. Hyperinflammation after anti-SARS-CoV-2 mRNA/DNA vaccines successfully treated with anakinra: case series and literature review. *Exp Biol Med (Maywood)* 2022; **247**: 338–344.
8 Watad A, Bragazzi NL, McGonagle D *et al*. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: insights from an analysis of 500 cases. *Clin Immunol* 2019; **203**: 1–8.
9 Vera-Lastra O, Ordinola Navarro A, Cruz Domiguez MP, Medina G, Sánchez Valadez TI, Jara LJ. Two cases of Graves' disease following SARS-CoV-2 vaccination: an autoimmune/inflammatory syndrome induced by adjuvants. *Thyroid* 2021; **31**: 1436–1439.
10 Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: possible involvement of polyethylene glycol and IgG-mediated complement activation. *Allergy* 2021; **76**: 3307–3313.

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