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Invited Commentary | Allergy

Allergic Reactions After COVID-19 Vaccination—Putting Risk Into Perspective

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In December 2020, Israel initiated a successful national vaccination program with the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine. Shavit et al[1] conducted an 8-week prospective cohort study in which they risk stratified potentially allergic patients into low-risk and high-risk groups prior to vaccination. Patients considered to be at higher risk (or highly allergic) were monitored at a single specialty center for 2 hours after vaccination, while those considered to be at low risk of allergic reactions would undergo the regular protocol of 30-minute monitoring after vaccination in the routine setting. Interestingly, the low-risk allergy groups included many of those overrepresented in anaphylaxis reports in the Centers for Disease Control and Prevention's Vaccine Adverse Event Reporting System (VAERS)[2]: those who had chronic urticaria; sensitivity to foods, venoms, or aeroallergens; or nonanaphylactic reactions to drugs or contrast media. Patients at high risk for allergic reactions were those with a history of mast cell disorders, multiple drug allergies, multiple allergies, or a history of anaphylaxis to a drug or vaccine as well as those for whom their primary physician, allergist, or immunization team did not feel comfortable vaccinating in the routine setting. Patients with an allergy to polyethylene glycol (PEG) and/or 2 or more injectable drugs were rejected from vaccination.

As our approaches to the prevention and management of SARS-CoV-2 mRNA vaccine allergy become refined over time, this study—without necessarily defining what the correct risk-based approach is—provides an example of what can be accomplished with risk stratification in a country with centralized and universal health care. It highlights some important lessons and reassurance about allergic reactions associated with the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine. We assume that these lessons will be generalizable to the Moderna and other mRNA vaccines with similar excipients and constructs. Of 8102 patients screened, ultimately 94.7% were referred to be immunized in the routine setting based on a low-risk allergy history, of whom none were reported to the Israel Ministry of Health to have had vaccine-associated allergic reactions. Of 429 patients deemed highly allergic and triaged for 2 hours of observation after vaccination in a specialty setting, 9 patients (2.1%), all women, had immediate allergic reactions. In 6 patients (1.4%), reactions were mild; only 3 patients (0.7%) experienced anaphylaxis, all cases of which resolved with epinephrine in 2 to 6 hours without hospitalization.[1]

Notable limitations of this study include the lack of verification of allergic reactions, including those with multiple drug allergy warnings who typically do not have allergies to the drugs in question, are at low risk of allergic reaction, and can have drug allergy warnings removed for all medications. The exclusion of those with reactions to 2 or more non–PEG-containing injectable drugs from vaccination with the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine is a practice that would not be currently recommended.[3] In addition, this study also did not measure levels of serum tryptase, a marker of anaphylaxis, and therefore gives us no direct insight into mechanisms. Nonetheless, this work by Shavit et al[1] provides a pragmatic strategy and underscores the enormous success of the vaccine rollout in Israel. As of July 2, 2021, 80% of those older than 60 years and 60% of the Israeli population at large was fully vaccinated.

We have learned a lot since December 2020. Less than 1 year after the declaration of the COVID-19 pandemic, a new era in vaccinology emerged with the launch of a mass vaccination program for the SARS-CoV-2 mRNA vaccines.[4] The phase 2 and 3 clinical trials of the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines did not have any serious allergic events; however, the trials had excluded those with a history of an allergic reaction to any component of the vaccine. For the

Pfizer-BioNTech vaccine, a history of an allergic reaction to any vaccine was also an exclusion. By mid-January 2021, a total of 66 cases of anaphylaxis, among 17.5 million doses of the Pfizer-BioNTech and Moderna mRNA vaccines reported to be administered, had been reported to the VAERS.[5] This translated into an approximate rate of 4.7 cases of anaphylaxis per 1 million of the Pfizer-BioNTech vaccine and 2.5 cases per 1 million for the Moderna vaccine. It is striking that these reported cases of anaphylaxis for both mRNA vaccines occurred primarily on the first dose (82%), in women (>90%), and in those with a history of allergic reactions (79%). Indeed, 35% of individuals who reported anaphylaxis to the Pfizer-BioNTech or Moderna vaccine had a history of anaphylaxis.

There are still several questions to be answered. For instance, what are the risk factors and mechanisms of SARS-CoV-2 mRNA vaccine anaphylaxis? Is a severe allergic reaction to the first dose truly a contraindication to the second dose of the same vaccine? Amid the concern and uncertainty of allergic reactions and without knowledge of consequences or mechanism, early guidance suggested that those with a history of an allergic reaction to PEG, a component of the lipid nanoparticle carrier particle for the SARS-CoV-2 spike protein mRNA, be excluded from the mRNA vaccines. However, patients with true PEG allergy are rare, and reports to implicate PEG as a potential antigen in SARS-CoV-2 mRNA vaccine reactions have been lacking. Currently, it is unknown whether the primary mechanism of anaphylaxis associated with SARS-CoV-2 mRNA vaccines is related to an IgE-mediated or non–IgE-mediated mechanism, including activation of the complement or contact pathways. Increasing reports of tolerance of the second dose after an anaphylactic or other immediate reaction to the first dose argue strongly against an IgE-mediated mechanism, suggesting that, if it exists, it may be quite rare.[6]

It is currently recommended that those with any history of any type of non-PEG anaphylaxis be monitored for a minimum of 30 minutes after vaccination at the regular vaccine centers; however, we need further insights with regard to highly allergic people and SARS-CoV-2 mRNA vaccines.[7] Highly allergic individuals, and particularly women, appear to be at heightened risk for immediate reactions associated with SARS-CoV-2 mRNA vaccines, but these reactions have been mainly mild and treatable. The lack of intensification of the allergic reaction with the second dose and the fact that anaphylaxis is not occurring more commonly with the second dose argues strongly against an IgE-mediated mechanism.[6] Finally, delayed reactions such as mild urticaria or exanthem are common and, when apparent with the first dose, recur in less than 50% of those with the second dose. Can we identify more specifically who is at risk? Is there a role for premedication? What proportion of individuals are hesitant to be vaccinated because of an underlying allergic tendency? The study by Shavit et al[1] provides additional reassurance that most highly allergic persons will not have allergic reactions to the SARS-CoV-2 mRNA vaccines. Of note, however, a recent Gallup poll suggests that 2% of the US population may be hesitant to be vaccinated primarily because of fear of an allergic reaction.[8] Although the rollout of mRNA and other SARS-CoV-2 vaccines has identified some rare vaccine-associated serious adverse events, it has been an overall overwhelming success story, with more than 3 billion doses administered globally by July 2, 2021. However, we still need a multipronged approach to engage, educate, and optimize mass vaccination while minimizing adverse events and vaccine hesitancy.

Controlled studies of SARS-CoV-2 mRNA vaccines in observed populations with carefully timed samples will help define risk factors and mechanisms of allergic reactions. This understanding will be critical to the optimization of mRNA vaccine technology and is paramount because mRNA vaccines are a facile and adaptable platform that can be used to target new SARS-CoV-2 variants and a wide variety of pathogens and disease processes.[4]

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