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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose!

To the Editor,

Since the first two cases of anaphylaxis described in the United Kingdom in association with the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine on rollout December 8, 2020, there have been numerous cases of suspected anaphylaxis described across the United Kingdom, Europe, the United States, and Japan in association with both the Pfizer-BioNTech and Moderna mRNA vaccines. The safety of administering second doses of mRNA SARS-CoV-2 vaccines to patients with anaphylaxis to the first dose is unknown; however, currently, rechallenge is discouraged.[1] Prospective monitoring of anaphylaxis incidence in healthcare workers, as defined by the Brighton and/or National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria has been reported as occurring in 1 in 4000, which is over 100 fold higher than the 2.5–4.7 per million reported by the Centers for Disease Control.[2,3] The discordance between the CDC data,

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where the Brighton score was also used to define cases of anaphylaxis, and reports among healthcare workers with complete ascertainment of events and spontaneous reporting raises the question of whether anaphylaxis scoring systems overestimate the number of adults who have experienced vaccine anaphylaxis and are at risk for more severe second dose anaphylactic reactions.[4] Therefore, patients should be individually assessed to validate or disprove the anaphylaxis diagnosis and provide the possibility for the challenge with the vaccine to ensure completion of the vaccination program.

Two specialized allergy clinics (Nashville, USA, and Gentofte, Denmark) evaluated healthcare workforce members referred for potential immediate, allergic reactions to the first dose of the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine, with 13/23,035 (0.06%) and 34/54,567 (0.06%) of vaccinated healthcare workers being referred, respectively. Of these 47 total patients referred for potential immediate, allergic reactions, 39 had histories of mild reactions and 8 had histories consistent with anaphylaxis to the first dose of the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine on at least one of the Brighton, NIAID/FAAN, or Ring and Messmer validated scales (Table 1). All 8 went on to have an in-clinic observed second dose administration. Patient demographics, first-dose reaction history, polyethylene glycol (PEG) skin testing, and second dose administration outcome were evaluated.

A serum tryptase was obtained in 5/8 patients within the appropriate 30–90 min time frame of their first-dose reaction and none were elevated. Of all current SARS-CoV-2 mRNA vaccines, PEG 2000 is a component of the lipid nanoparticle carrier system. In all 8 cases, allergy to PEG was ruled out (by skin testing and/or challenge and tolerance history). All 8 went on to tolerate an observed one-step second 0.3 ml dose of the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine, without symptoms or significantly milder symptoms than experienced with the first dose (Table 1).

The lack of tryptase elevation during suspected first dose anaphylaxis, negative PEG testing, and observed tolerance of the second dose do not support an IgE-mediated mechanism. This further highlights that administration of the second dose following suspected first dose anaphylaxis can be safely achieved in an observed allergy clinic setting in patients without known PEG allergy. Skin testing with PEG 2000 was not performed in the US patients, because it is not readily available for clinical use; however, use of higher molecular weight PEG testing is associated with higher sensitivity in patients with PEG allergy, and therefore, we would not expect false negatives when testing with PEG 3350.[5] Although the mechanism(s) of anaphylaxis associated with SARS-CoV-2 mRNA vaccines are currently unknown, our collection of eight patients who have tolerated the second dose of the Pfizer-BioNTech COVID-19 mRNA vaccine despite anaphylaxis to the first dose highlights a likely non-IgE-mediated mechanism. Patients with potential anaphylaxis should undergo careful risk stratification, weighing the benefits and risks of second dose vaccination. Although pre-medication with non-sedating antihistamines may not be necessary and will clearly not prevent true IgE-mediated anaphylaxis, it can be helpful in blocking non-IgE-mediated histamine release and may have alleviated symptoms and improved tolerability of the second dose for our patients. Patients who demonstrate an IgE-mediated allergy to PEG would not fall into this category. Although we are still learning about the protective correlates of SARS-CoV-2 immunity, the second dose of the mRNA vaccines is associated with enhanced neutralizing antibody and T-cell responses, suggesting that it could be necessary for a more effective and durable immune response. The continued pressure of SARS-CoV-2 variants raises concern for continued viral replication in the community and a single vaccine dose may have lower sustained effectiveness. In someone who has had anaphylaxis on the first dose of an mRNA vaccine, although it may be considered safe to administer a different vaccine construct such as the AstraZeneca or Janssen adenoviral vector vaccines, there is no evidence to support that this is as effective as giving the same mRNA vaccine construct. Finally, an unnecessary allergy label to an mRNA vaccine is potentially harmful to future care, as these are facile constructs that are adaptable to the emergence of new variants of SARS-CoV-2 as well as other emergent viruses and cancers.

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CONSENT

Consent to the publication of clinical data was obtained from all patients.

KEYWORDS

anaphylaxis, SARS-CoV, vaccines

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CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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TABLE 1 Patient demographics, Pfizer-BioNTech mRNA COVID-19 dose 1 reaction history, and Pfizer-BioNTech mRNA COVID-19 dose 2 challenge history

			Past history			Dose 1 history	
Country, Patient No.	Age (yreas)	Sex	Atopic history	Any prior anaphylaxis? (cause)	Onset after receipt (min)	Signs and symptoms	Reaction tryptase[a], baseline tryptase (mcg/L)
US, 1	31	F	Chronic idiopathic urticaria, dermatographia	No	45	Lightheadedness, nausea, generalized urticaria	2.2, ND
US, 2	36	F	None	Yes (penicillin)	15	Lip tingling without swelling, tachycardia, generalized erythema with pruritus, decreased level of consciousness	ND, ND
US, 3	47	F	Chronic idiopathic urticaria, allergic rhinitis, food allergy, asthma	Yes (shellfish)	30	Generalized erythema with pruritus, shortness of breath	ND, ND
US, 4	29	F	None	No	5	Shortness of breath, tachycardia, generalized erythema without pruritus, muscle spasms	3.8, ND
DK, 5	40	F	Allergic rhinitis, asthma	Yes (penicillin, anti-Rh antibody)	5	Throat swelling sensation, shortness of breath, cough, tachycardia, generalized erythema, desaturation (83%), warm feeling	2.84, 1
DK, 6	54	F	Food allergy	No	5	Throat closure, cough, nausea, dizziness, hypotension	7.02, 8.16[d]
DK, 7	34	F	Allergic rhinitis, food allergy	Yes (ibuprofen)	8	Warm sensation, objective throat swelling, generalized exanthema, tachycardia, hypotension	13.7, 12.9[d]
DK, 8	43	F	Allergic rhinitis	No	20	Generalized flushing, dizziness, nausea, vomiting, lip tingling, shortness of breath	ND, 3.57

Abbreviations: DK, Denmark; Epi, epinephrine; ND, Not done; NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network; PEG, polyethylene glycol; PS, polysorbate; US, United States.

[a]Reaction tryptases obtained within 30–90 min of the onset of symptoms.

[b]For US cases PEG 300, 3350, and 8000 were used. For DK cases, PEG 300, 2000, 3000, and 6000 were used.

[c]Home medications that patient was receiving for treatment of chronic idiopathic urticaria both prior to dose 1 and continued prior to dose 2.

[d]KIT mutation analysis in peripheral blood negative.

[e]PEG and PS skin testing not performed because patient had known tolerance of PEG-containing medications.

		Testing visit	Dose 2 history			
Epi received	Brighton level, NIAID/FAAN, Ring and Messmer	PEG[b] and PS skin testing result, PEG 3350 oral challenge	Time since dose 1 (days)	Premedication regimen 3 days prior to vaccination	1 h observation outcome	24-h follow-up phone call
No	2, No, II	Negative, Passed	29	Cetirizine 10 mg twice daily	No symptoms	No allergic symptoms
No	2, No, II	Negative, Passed	38	Cetirizine 10 mg twice daily	No symptoms	No allergic symptoms
No	2, Yes, II	Negative, Passed	37	Cetirizine 20 mg twice daily, famotidine 20 mg twice daily, montelukast 10 mg daily[c]	At 1 h, experienced warmth and facial flushing; fexofenadine 180 mg given and ice packs which resolved symptoms in 45 min	No allergic symptoms
No	2, Yes, II	Negative, Passed	31	Cetirizine 10 mg twice daily	No symptoms	No allergic symptoms
Yes	1, Yes, II	Negative, ND	40	Fexofenadine 360 mg 1 h prior	Throat swelling sensation, cough, milder than initial reaction, no treatment, stable vital signs	No allergic symptoms
Yes	2, Yes, III	Negative, ND	65	Fexofenadine 120 mg twice daily	Itchy throat, the feeling of throat closure, cough, milder than initial reaction, IV antihistamine, epinephrine inhalation in atmospheric air, stable vital signs	No allergic symptoms
Yes	1, Yes, III	Negative, ND	41	Fexofenadine 180 mg twice daily	Shivering, itchy throat, no treatment, stable vital signs	No allergic symptoms
No	2, Yes, II	ND, ND[e]	37	Cetirizine 10 mg once daily	Lip tingling, fexofenadine 360 mg given, symptoms resolved	No allergic symptoms

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Eosinophilic pleural effusion and stroke with cutaneous vasculitis: Two cases of dupilumab-induced hypereosinophilia

To the Editor,

Treatment with the anti-IL-4 receptor alpha antibody dupilumab can cause increases in blood eosinophils, typically without adverse effects.[1,2] This blood eosinophil increase is probably caused by an inhibition of the endothelial expression of VCAM-1 and ICAM-1 which is essential for eosinophil extravasation and dependent on IL-4 receptor alpha.[3] We report cases of dupilumab-induced hypereosinophilia with severe adverse effects occurring within the first 6 weeks after treatment initiation.

Case 1: A 49-year-old man (15 pack years until 2017) with severe intrinsic, adult-onset asthma and CRSwNP (not previously treated with biologics) suffered from recurrent asthma exacerbations requiring prednisolone bursts despite high-dose ICS/LABA/LAMA treatment. There were no other chronic diseases. In January 2020, poor asthma control (ACT: 8 points), a reduced FEV_1 (67% predicted), elevated blood eosinophils (800/µl, 12%) and high FeNO (66 ppb) were documented. Due to the high FeNO value and the well-established beneficial effects of dupilumab on CRSwNP,[4] treatment with dupilumab (200 mg every 2 weeks) was started on February 6th. Subsequently, asthma control, sense of smell and nasal airflow improved. However, the patient presented on March 18th with severe left-sided chest pain, chest X-ray revealed pleural effusion (Figure 1). Dupilumab was stopped and the patient was admitted to hospital where massive blood eosinophilia (10.530 eosinophils/µl; 50.2%) was recorded. Serum p-ANCA and c-ANCA titres were negative (<1:10). Thoracocentesis drained 2500 ml of an eosinophilic exudate (56 g protein/dl; 14.4 million leucocytes/ml: 58% eosinophils). Prednisolone treatment (0.5 mg prednisolone per kg body weight per day, for 2 weeks) led to clinical improvement. On April 2nd, benralizumab treatment was started and prednisolone treatment was stopped. In November 2020, asthma control was good (ACT: 25 points), FEV_1 improved (105% predicted), eosinophils were undetectable (0/µl). The pleural effusion was completely resolved (Figure 1).

Case 2: A 66-year-old woman (never-smoker) with severe intrinsic, adult-onset asthma (not previously treated with biologics) suffered from recurrent asthma exacerbations (one led to resuscitation/mechanical ventilation) requiring prednisolone bursts, despite high-dose ICS/LABA and montelukast treatment. In addition to asthma, she suffered from chronic lower back pain (due to herniated discs) and diffuse arthritis (with no established specific diagnosis): both conditions were treated with paracetamol on an as-needed