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Safe administration of the Pfizer-BioNtTech COVID-19 vaccine following an immediate reaction to the first dose

To the Editor,

On December 2020, the U.S. Food and Drug Administration issued the first emergency use authorization for the Pfizer-BioNtTech vaccine (PBV) for the prevention of coronavirus disease 2019 (COVID-19) in individuals 16 years of age and older (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine). Subsequently, reports of immediate allergic reactions (4.7 cases per 1 million injections) were captured in the Vaccine Adverse Event Reporting System and sorted according to the Brighton Collaboration case definition anaphylaxis criteria.[1] While polyethylene glycol (PEG) is the suspected culprit excipient, the mechanism of these immediate reactions, especially when occurring after the first vaccine, is unclear.[2,3] Although cases where a 2nd vaccine dose was administered safely following immediate reactions to the first dose were reported,[4] currently, the Center of Disease Control recommends that patients who experienced an immediate allergic reaction of any severity after the first dose of the vaccine should avoid the second dose (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/allergic-reaction.html). Routine administration of the PBV in Israel began in January 2021. Here, we report the results of evaluation of patients experiencing immediate reactions to the 1st dose and the results of administration of a 2nd dose.

An allergist interviewed patients with suspected immediate reactions (within 4 h of PBV administration). Anaphylaxis was classified in accordance with the Brighton collaboration case definition for anaphylaxis.[5] Skin prick tests (SPT) with the PBV and with Methylprednisolone solution for injection containing PEG

TABLE 1 Demographics and reactions following the 1st dose of the Pfizer-BioNtTech COVID-19 vaccine

Pt.	Age	Gender	Atopic disease	Drugs/RCM/Food allergy	Signs and symptoms	Reaction onset (m)	Treatment setting	Drug treatment
1	75	F			Dyspnea	15	Primary physician	AH
2	59	M			Generalized rash, weakness	60	ER	AH, steroids
3	57	F			Diffuse pruritic rash	60	ER	AH, steroids
4	23	F			Diffuse pruritic rash	30	Emergency center	AH, steroids
5	70	F			Diffuse rash	30	Primary physician	AH
6	27	F			Diffuse pruritic rash	15	ER	AH
7	68	F			Generalized urticaria	30	ER	steroids
8	52	F	AR		Congestion, swelling of rt side of face[a]	20	ER	AH, steroids
9	53	M		Penicillin	Hoarseness, urticaria[a]	30	ER	AH, steroids
10	47	F			facial swelling	10	Vaccination center	AH
11	39	F			sensation of throat closure, tongue swelling[a]	5	ER	AH, steroids
12	73	F		Penicillin, ciprofloxacin	Tongue and lips swelling, generalized rash[a]	30	Vaccination center	AH, steroids
13	71	F		NSAID, Lipitor, Morphine	Swollen face and redness	60	Vaccination center	AH
14	51	M	Asthma, AR	RCM	Diffuse rash	15	Vaccination center	AH,steroids
15	61	M	AR		Pruritus, sensation of throat closure[a]	10	Vaccination center	AH
16	60	F	AR	Sterocort	Swollen face and redness	40	Vaccination center	AH, steroids
17	33	F		Latex	Diffuse pruritic rash, vomiting[a]	30	ER	AH, steroids
18	58	F	Asthma		Cough, Diffuse rash[a]	30	ER	AH, steroids

Abbreviations: AH, anti histamines; AR, allergic rhinitis; ER, emergency room; RCM, radiocontrast media.

[a]Patients meeting a definition of anaphylaxis (Patient 12, Brighton level 1; Patients 8, 9, 11, 18, Brighton level 2, patients 15, 17 Brighton level 3).

TABLE 2 Results of allergic evaluation and of administration of the second BioNtTech COVID-19 vaccine dose

Pt.	Vaccine SPT	PEG SPT/ID	Premedication before second dose	Reaction to second dose
1	Negative	Negative	No	No
2	Negative	Negative	No	No
3	Negative	Negative	No	No
4	Negative	Negative	No	No
5	Negative	Negative	No	No
6	ND	ND	No	No
7	Negative	Negative	AH	No
8	Negative	Negative	AH	Tongue swelling
9	Negative	Negative	AH	No
10	Negative	Negative	AH	No
11	ND	Negative	AH	Itching in the throat
12	Negative	Negative	AH	No
13	ND	ND	AH	No
14	Negative	Negative	AH	No
15	Negative	Negative	AH	No
16	Negative	Negative	AH	Swelling on the right side of the face
17	Negative	Negative	AH	No
18	Negative	Negative	AH	Persistent cough, facial redness

3350 (1:100, 1:10, and undiluted), and intradermal (ID) tests with Methylprednisolone (1:100) were performed, as recommended.[6] A second vaccine dose was administered under observation. Publication was approved by each institutional review board committee.

Eighteen patients with a mean age of 54.3 years (range, 23–75) were included (Table 1). Mean time interval from PBV receipt to symptoms onset was 28.9 min (range, 5–60 min). Eleven (63.2%) patients had non-anaphylactic immediate reactions, and seven patients (36.8%) experienced anaphylaxis. None had hypotension or syncope. Fifteen patients underwent SPT to PBV and sixteen underwent SPT and ID tests to Methylprednisolone, which were all negative (Table 2). All patients received a second PBV dose, 12 following pretreatment with antihistamines. Four individuals had an immediate reaction after the second PBV dose, which was milder than the index reaction, and none required emergency room treatment or adrenaline.

COVID-19 has caused more than 3 million deaths and a worldwide economic crisis since its emergence in December 2019.[7] The newly developed vaccines provide hope for ending the pandemic. However, allergic reactions to the vaccine might impair this effort not only by preventing the administration of a 2nd dose but also by reducing compliance with the 1st dose. Israel was among the first countries to implement a vaccination program on a population level, enabling investigation of allergic reactions. The current report presents a cohort of individuals who had immediate reactions to the first PBV dose and received a second dose with only minor side effects. The presented data raise a question regarding the mechanisms provoking these immediate reactions, especially given that most patients received the second dose with mild or no symptoms. Concerns were raised regarding the role of PEG allergy in immediate reactions. Although current diagnostic methods for PEG allergy are not optimal,[8] our workup expands reports by others[4] and questions the role of IgE-sensitization to the vaccine or to PEG as their cause. Finally, and most importantly, we demonstrated the safety of a second dose of PBV in patients with mild-moderate immediate reactions to the first dose. While a few patients experienced adverse reactions to the 2nd dose, those were mild and do not justify its avoidance. This study is limited because most patients had mild to moderate reactions to the first PBV dose reported. Still, those with a severe reaction received the second dose as well.

In conclusion, we suggest that routine SPT to the vaccine or to PEG, in patients with mild-moderate immediate reactions to the first dose of the PBV, need not be performed. A second dose of the vaccine should be considered in these patients, under appropriate medical supervision.

CONFLICT OF INTEREST

All authors report no conflict of interests.

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Inhaled corticosteroids in early COVID-19—A tale of many facets

To the Editor,

Following our early report in Allergy,[1] there was several studies published in the same direction showing the benefit of continuation of inhaled steroids in COVID-19. Inhaled budesonide represents a standard of care for patients with asthma, allergic rhinitis, and chronic rhinosinusitis.[1-3] It is recommended that in COVID-19, patients with chronic inflammatory airway diseases should continue guideline-based pharmacological treatment, including ICS and/or biological therapies.[1,2] New data indicate that patients with various asthma endotypes may show a different risk profile for SARS-CoV-2 infection and a different course of COVID-19. Patients suffering from allergic asthma (type 2 inflammation) seem to have a lower risk of developing COVID-19 than patients with non-type 2 asthma.[4]

Ramakrishnan et al. performed an open-label, parallel-group, randomized controlled trial to compare standard of care with the additive use of inhaled budesonide (Figure 1).[5] The authors claim that this is an easily accessible and effective intervention in early COVID-19. Their data also suggest a potential benefit in the prevention of long COVID-19.

However, these statements may not be sufficiently proven. This was an open study, in which patients and staff were aware of the therapy used. *Placebo* effects, for example, for inhalant asthma drugs, can be observed in 21 to 46% of cases, especially for subjective outcomes.[6] Effects assessed during this study, including the primary endpoint (COVID-19-related urgent care visit, including emergency department visits or hospitalization), may all be influenced by the subjective perception of the patients and their treating physicians. Secondary endpoints, including objective measures like blood oxygen saturation and SARS-CoV-2 load, were not different between the groups. The study population was small, including 146 participants of which 73 were randomized to usual care and 73 to the budesonide group. A cautious interpretation of these data is warranted, since an updated interim analysis from a larger phase-III study, including 2,617 people with risk factors for adverse outcomes with COVID-19, did not show such favorable results.[7] Inhaled budesonide reduced the time to self-reported recovery by a median of 3 days. However, it did not meet the primary outcome parameter (COVID-19 hospitalizations/deaths) even though these rates were