

Skin tests in adverse reactions to Pfizer-BioNTech SARS-CoV-2 vaccine: limits of intradermal testing

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Skin tests in adverse reactions to Pfizer-BioNTech SARS-CoV-2 vaccine: limits of intradermal testing

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To the Editor,

Vaccination seems the most effective public health tools to contrast the spreading of Coronavirus disease-19 (COVID-19) pandemic. To date, the European Medicines Agency (EMA) authorized three anti SARS-CoV-2 vaccines. The Pfizer-BioNTech and the Moderna vaccines contain messenger RNA (mRNA) encapsulated in lipid nanoparticles, which encodes the SARS-CoV-2 viral spike (S) protein, inducing both antibody and cell-mediated responses. The AstraZeneca vaccine is based on a viral vector that uses a modified version of the chimpanzee adenovirus to provide instructions for synthesizing SARS-CoV-2 protein S. The vaccine series consists of two doses administered intramuscularly (Pfizer-BioNTech: 21 days apart; Moderna: 28 days apart; AstraZeneca: 28-84 days apart).

During clinical approval studies and early post-marketing phases, mucous-cutaneous adverse reactions have been rarely observed. Among hypersensitivity reactions, immediate reactions (anaphylaxis, urticaria-angioedema syndrome) were more frequently observed than delayed reactions (maculo-papular eruptions).^{1,2}

The anti SARS-CoV-2 vaccines contain excipients with known sensitizing potential: Pfizer-BioNTech vaccine contains polyethylene glycol-2000, Moderna vaccine polyethylene glycol-2000 and tromethamine, and AstraZeneca vaccine polysorbate 80.³

Considering this, before receiving anti-SARS-CoV-2 vaccination, an adequate medical history is mandatory to detect possible risk factors and, consequently, to minimize the incidence of adverse reactions. Furthermore, it is recommended to administer the vaccine by trained healthcare personnel in adequate medical settings in presence of emergency drugs and an observation period.^{3,4}

In General Hospital of Perugia and in Local Health Unit 1, Umbria Region, Italy, 5574 healthcare professional received the first dose of Pfizer-BioNTech vaccine. Six subjects (0.11%) developed mucous-cutaneous adverse reactions, summarized in Table 1.

These patients underwent an allergologic workup with Pfizer-BioNTech vaccine as suggested by EAACI⁴ and German allergy centers.⁵ In absence of standardized methodology for this vaccine testing, we referred to Italian⁶ and EAACI recommendations.⁷ Unusable vaccine residues, regain from the vaccine campaign, were used under sterile conditions. Skin prick test (SPT) with neat vaccine (reading: 20 mins), and intradermal test (IDT) vaccine dilution 1/100 (readings: 20 mins, 24 hrs) were performed. SPT resulted always negative, but IDT induced, 12 hours after, an erythematous, oedematous, and infiltrated asymptomatic reaction in all patients. A 1/1000 dilution test induced the same reaction in all patients (Figure 1A). The IDT reactions persisted for 2 days.

In order to verify these reactions, IDT with 1/1000 and 1/100 Pfizer-BioNTech vaccine dilution were performed in 6 healthcare volunteers who had received the 2 doses of Pfizer-BioNTech vaccine, in 6 healthcare volunteers who had received at least 2 weeks before only the first dose of Pfizer-BioNTech vaccine, and in 6 volunteers who did not receive Pfizer-BioNTech vaccine. All the 18 volunteers did not refer previous allergy to vaccines or drugs containing polyethylene glycols. IDT induced the same reaction 12 hours after in the 12 vaccinated volunteers (Figure 1B), while resulted negative in the 6 not-vaccinated volunteers (Figure 1C). All patients and controls have provided an informed consent to perform these skin tests.

Even if the morphology of the IDT reactions could suggest a type IVa immune reaction, we hypothesized that IDT reactions observed in patients and vaccinated volunteers could be a non-allergic reaction to SARS-CoV-2 viral S protein or to vaccine components.

It is impossible to draw conclusions about the utility of SPT to investigate Pfizer-BioNTech vaccine adverse reactions because of low number of subjects tested, but IDT results allow us to advice against IDT with this vaccine for the high risk of false positive reactions due to non-allergic immune stimulation.

Further studies are needed to investigate the utility of PT and SPT to investigate Pfizer-BioNTech vaccine allergy, and to better clarify the pathomechanism of the reactions observed to IDT.

References

Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. *JAMA* . 2021 Jan 21. doi: 10.1001/jama.2021.0600. Epub ahead of print. PMID: 33475702.

Center for Disease Control and Prevention. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm> Accessed 17.02.2021.

1. Caballero ML, Quirce S. Excipients as potential agents of anaphylaxis in vaccines: analyzing the formulations of the current authorized COVID-19 vaccines. *J Invest Allergol Clin Immunol*. 2021 Jan 12:0. doi: 10.18176/jiaci.0667. Epub ahead of print. PMID: 33433387.
2. Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. *Allergy* . 2021 Jan 16. doi: 10.1111/all.14739. Epub ahead of print. PMID: 33452689.
3. Worm M, Bauer A, Wedi B, et al. Practical recommendations for the allergological risk assessment of the COVID-19 vaccination - a harmonized statement of allergy centers in Germany. *Allergol Select*. 2021 Jan 26;5:72-76. doi: 10.5414/ALX02225E. PMID: 33521511; PMCID: PMC7841415.
4. Stingeni L, Bianchi L, Tramontana M, et al. Skin tests in the diagnosis of adverse drug reactions. *G Ital Dermatol Venereol*.2020;155(5):602-621.
5. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68(6):702-712.

TABLE 1 Patients characteristic and adverse mucous-cutaneous reactions in 6 patients after the first dose of Pfizer-BioNTech vaccine.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
<i>Gender</i>	Female	Female	Male	Female	Female	Female
<i>Age</i>	24	31	28	58	44	54
<i>Personal atopy</i>	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis and asthma	Allergic rhinitis	Allergic rhinitis, atopic dermatitis
<i>Allergy history</i>	-	-	-	-	-	Contact allergy (nichel sulphate, fragrances)
<i>Type of reaction</i>	Acute urticaria	Angioedema (tongue, gums)	Acute urticaria	Flushing of the face	Flushing of the face	Angioedema (tongue, lips)
<i>Time of onset</i>	5 mins	24 hrs	5 mins	30 mins	20 mins	10 mins
<i>Treatment</i>	betametason sodium phosphate (IV)	-	-	-	-	-

FIGURE 1 Intradermal test (IDT) with Pfizer-BioNTech vaccine. Erythematous, oedematous, and infiltrated reaction in 2 healthcare volunteers who had received the two doses (A) and only the first dose (B) of Pfizer-BioNTech vaccine. Negative IDT in a not-vaccinated volunteer (C).

