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Delayed cutaneous reactions after the administration of mRNA vaccines against COVID-19

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Clinical Implications

Twenty-six subjects experienced a variety of delayed cutaneous reactions to SARS-CoV-2 mRNA vaccines. Such reactions did not contraindicate a second immunization except in 1 case.

Vaccination is an effective intervention to prevent coronavirus disease 2019 (COVID-19). Two mRNA vaccines, Comirnaty (BioNTech, Mainz, Germany; Pfizer, New York City, NY)[1] and COVID-19 Vaccine Moderna (ModernaTX, Inc, Cambridge, Mass),[2] are approved for mass administration.

There were no major differences in hypersensitivity-related side effects versus placebo with either vaccine during clinical trials; they were observed in 0.63% of Pfizer-BioNTech and 1.5% of Moderna vaccine clinical trial participants who received the vaccine compared with 0.51% and 1.1%, respectively, in the placebo groups.[1,2] Both vaccines contain polyethylene glycol or polyoxyethylene (PEG) lipid conjugate as an excipient.[3] PEG and its derivatives (polysorbates or PEG sorbitan monooleates, laureth-9 or PEG-9 lauryl ether, poloxamer or PEG-polyoxypropylene) cross-react and are common excipients in pharmaceutical products.[4] Moderna vaccine also contains trometamol or tromethamine, an organic amine used extensively.[3]

Twenty-six patients were referred to our allergy department during January and February 2021 for delayed large local reactions (DLLR), defined as erythematous and edematous plaques $\geq$10 cm in diameter accompanied by pain or pruritus at the site of the mRNA vaccination, and other cutaneous reactions.

Personal data include the sex, age, history of atopic diseases, and previous SARS-CoV-2 infection. The cutaneous manifestations, times of onset, duration of the lesions, and treatment are described. Evaluation included a patch test (PT) on the upper back with PEG 400 1% in petrolatum (pet), PEG 3350 10% in pet, PEG 3350 in aqueous solution (aq), PEG 4000 10% in pet, polysorbate 80 1% in pet, polysorbate 80 10% in pet, laureth-9/sodium lauryl sulfate 1% pet, and trometamol 0.50% aq (only in Moderna vaccinated patients) (Nonweven Patch 31 Test Strips Curatest; Lohmann & Rauscher International, Rangsdorf, Germany) with readings at day 2 and day 4. The study protocols for the clinical data collection were reviewed and approved by the ethics committee of our hospital.

The study population comprised 26 patients (Table I): 19 (73%) received the Moderna and 7 (27%) the Pfizer-BioNTech vaccines. Twenty-five (96%) were female with a mean age of 45 $\pm$ 4.66 years. Fifteen (58%) had a previous history of 1 or more of the following: 9 (60%) rhinoconjunctivitis, 10 (66.7%) asthma, 5 (33.3%) anaphylaxis (latex, kiwi and Hymenoptera, arylpropionics, contrast media), 2 (13.3%) chronic urticaria, and 1 (6.7%) nickel and methylchloroisothiazolinone/methylisothiazolinone allergic contact dermatitis.

Most patients (23 of 26, 88.5%) reacted to the first dose. Almost half (10 of 23, 43.5%) had detectable serum specific IgG anti−SARS-CoV-2 nucleocapsid protein antibodies, collected in the last 2 to 3 months before vaccination. DLLR occurred in 13 of 23 patients (57%). Ten of these 23 subjects (43.4%) experienced delayed skin reactions different from DLLR: 5 developed a generalized maculopapular exanthema, 2 exfoliation of the skin of the palms, 1 acute generalized exanthematous pustulosis (AGEP), 1 generalized micropapular exanthema accompanied by a 7-cm blister on the shoulder, and 1 multiple fixed drug eruptions (MFDE). AGEP was diagnosed in a 22-year-old woman who developed fever and an acute pruritic nonfollicular pustular eruption on an erythematous base involving most of her body surface but which accentuated in the skin folds 5 days after the first dose of Pfizer-BioNTech vaccine. EuroSCAR score for AGEP points was compatible with the diagnosis. It resolved in 5 days with oral and topical corticosteroids. High protective titers of IgG antibodies against SARS-CoV-2 spike protein were detected, so the patient refused the second dose of the vaccine. MFDE was diagnosed in a 60-year-old woman 10 days after the first dose of Moderna vaccine. She developed 4 well-defined, oval, erythematous-violaceous patches on the forearms and abdomen, nonpruritic nor painful.

They did not improve with topical corticosteroid treatment. Seven days after the second dose of Moderna vaccine, the original patches enlarged and darkened, and more patches appeared. The lesions progressively improved over weeks but left residual hyperpigmentation.

Three of the 26 subjects who had tolerated the first dose developed a reaction after the second dose: 1 DLLR, 1 maculopapular exanthema, and 1 delayed bilateral eyelid edema.

Eleven of the 26 patients (42.3%) were treated with topical corticosteroids and 4 (15.3%) with oral antihistamines. The mean duration of the reactions was 5 $\pm$ 1.4 days when treated and 4.84 $\pm$ 0.60 days without treatment ($P = .83$).

Patch tests, performed on all subjects, were negative in 100% of cases. Only 1 patient refused to receive the booster dose, but the remaining patients (22 of 23, 96%) successfully received the second dose of the vaccine. DLLR reoccurred in 62% (8 of 13) who had developed them after the first dose, of a similar (38%) or smaller size (63%). They resolved earlier (mean: 1.7 days) than those that developed after the first dose (mean: 4.4 days) ($P < .05$). Five of 13 patients (38%) had no recurrence of DLLR.

One of the 5 patients who experienced a mild maculopapular exanthema after the first immunization developed the same reaction after the second dose, and MFDE also reoccurred after the second dose.

In summary, we reported a series of 26 delayed reactions after the administration of Pfizer-BioNTech or Moderna vaccines. Of these, 23 reactions occurred after the first dose. Only 1 patient did not receive 2 doses, whereas 96% received both.

Therefore, these reactions were mild, self-limiting, and did not preclude a second vaccine dose.

TABLE I. Clinical characteristics of the study population

Patient	Age	Sex	Type of vaccine	Allergy history	Prior SARS-CoV-2 infection	Dose	Cutaneous manifestation	Latency (d)	Treatment	Duration (d)
1	45	F	Moderna	RC, asthma	Yes (IgG)	1st	MPE	1	TCS	2
						2nd	None			
2	45	F	Moderna	RC	Yes (IgG)	1st	DLLR	2	None	4
						2nd	DLLR	1	None	2
3	53	F	Moderna	Asthma	Yes (IgG)	1st	DLLR	3	None	5
						2nd	DLLR	2	None	3
4	59	F	Pfizer-BioNTech	None	No	1st	DLLR	1	None	4
						2nd	None			
5	53	M	Moderna	None	No	1st	MPE	1	None	5
						2nd	None			
6	48	F	Moderna	None	No	1st	Flaking palms	3	None	7
						2nd	None			
7	47	F	Moderna	RC, asthma	Yes (IgG)	1st	DLLR	7	None	5
						2nd	None			
8	34	F	Moderna	None	No	1st	DLLR	7	TCS	5
						2nd	DLLR	2	None	2
9	43	F	Moderna	RC, asthma, CU	No	1st	DLLR	7	TCS	7
						2nd	None			
10	61	F	Moderna	Asthma	No	1st	DLLR	7	None	6
						2nd	None			
11	53	F	Moderna	Asthma	Yes (IgG)	1st	DLLR	1	TCS and AH1	4
						2nd	DLLR	1	None	3
12	53	F	Moderna	RC, asthma, ACD, latex anaphylaxis	Yes (IgG)	1st	DLLR	1	TCS	3
						2nd	DLLR	1	None	1
13	46	F	Pfizer-BioNTech	None	No	1st	MPE and blister	1	AH1	10
						2nd	None			
14	45	F	Moderna	None	No	1st	DLLR	7	None	4
						2nd	DLLR	2	None	2
15	44	F	Pfizer-BioNTech	Asthma	Yes (IgG)	1st	MPE	5	None	5
						2nd	None			
16	30	F	Pfizer-BioNTech	RC	No	1st	MPE	1	TCS and AH1	7
						2nd	MPE	1	None	6
17	59	F	Moderna	Kiwi and wasp anaphylaxis, CU	No	1st	Flaking palms	3	TCS	7
						2nd	None			
18	35	F	Moderna	RC, asthma, contrast media anaphylaxis	Yes (IgG)	1st	DLLR	1	None	5
						2nd	DLLR	1	None	3
19	52	F	Pfizer-BioNTech	RC	Yes (IgG)	1st	None			
						2nd	MPE	1	TCS	5
20	23	F	Pfizer-BioNTech	None	Yes (IgG)	1st	AGEP	5	OCS and TCS	5
						2nd	Not administered			
21	28	F	Moderna	None	No	1st	DLLR	10	None	3
						2nd	None			
22	27	F	Moderna	Arylpropionic anaphylaxis	No	1st	DLLR	6	None	5
						2nd	DLLR	4	None	3
23	23	F	Pfizer-BioNTech	None	Yes (IgG)	1st	MPE	1	TCS	1
						2nd	None			
24	50	F	Moderna	None	No	1st	None			
						2nd	DLLR	1	None	4
25	54	F	Moderna	None	No	1st	None			
						2nd	Eyelid edema	3	AH1	4
26	60	F	Moderna	RC, asthma, N-ERD	No	1st	MFDE	10	TCS	5
						2nd	MFDE	7	None	10

ACD, Allergic contact dermatitis; *AGEP*, acute generalized exanthematous pustulosis; *AH1*, antihistaminics H1; *CU*, chronic urticaria; *DLLR*, delayed large local reaction; *MFDE*, multiple fixed drug eruptions; *MPE*, maculopapular exanthema; *N-ERD*, NSAID-exacerbated respiratory disease; *OCS*, oral corticosteroids; *RC*, rhinoconjunctivitis; *TCS*, topical corticosteroids.

Blumenthal et al[5] described similar DLLR after Moderna vaccine, and they suggested that they are caused by a type IV hypersensitivity mechanism, based on the results of a single biopsy. As type IV hypersensitivity reactions required previous sensitization, the wide use of PEG and its derivatives with demonstrated cross-reactivity[4] could support type IV hypersensitivity underlying mechanism. There are no validated testing strategies for ascertaining cases of delayed hypersensitivity to vaccines, but PT with the vaccine and its excipients may be helpful when type IV hypersensitivity reactions are suspected.[6,7] However, results of the PT in this study were negative.

Delayed cutaneous reactions did not reoccur after the booster dose in more than half of the patients with previous delayed cutaneous reactions. Recurrence was independent of the prior presence of serum detectable IgG anti−SARS-CoV-2-nucleocapsid protein antibodies.

In this series, most reactions occurred after the first dose; however, these data could be prejudiced by the fact that patients would probably consult physicians more frequently after a first dose reaction rather than a second dose reaction.

These data indicate that DLLR and mild exanthemas are not a contraindication for a second mRNA vaccination.

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