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

Alba Juárez Guerrero, MD^{1,2*}, Alicia Dominguez Estirado, MD^{1,2*}, Jimena Crespo Quirós^{1,2}, Patricia Rojas-Pérez Ezquerro, MD^{1,2}

¹ Allergy Department. University Hospital Gregorio Marañón. Madrid. Spain.

² Gregorio Marañón Health Research Institute, Madrid, Spain

*These authors contributed equally to this work.

Corresponding Author:

Dr. Patricia Rojas-Perez-Ezquerro

Allergy Department. Hospital General Universitario Gregorio Marañón. Dr. Esquerdo, 46. 28007 Madrid, Spain.

Telephone: + 0034915868089

E-mail: projasperezquezquerra@gmail.com/ patricia.rojas@salud.madrid.org

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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 one 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, USA) [1] and COVID-19 Vaccine Moderna® (ModernaTX, Inc; Cambridge, Massachusetts) [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 to 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 ≥ 10 cm in diameter accompanied by pain or pruritus at the site of the mRNA vaccination, and other cutaneous reactions.

Personal data include the gender, 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) (Nonwoven Patch 31 Test Strips Curatest®; Lohmann & Rauscher International, Rangsdorf, Germany) with readings at day 2 (D2) and day 4 (D4). The study protocols

for the clinical data collection were reviewed and approved by the Ethics Committee of our hospital.

The study population was comprised of 26 patients (Table 1): 19 (73%) received the Moderna and 7 (27%) the Pfizer-BioNTech vaccines. Twenty-five (96%) were female with a mean age was 45 ± 4.66 years. Fifteen (58%) had a previous history of one 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 methylchoroisothiazolinone/methylisothiazolinone allergic contact dermatitis.

Most patients (23/26, 88.5%) reacted to the first dose. Almost half (10/23, 43.5%) had detectable serum specific IgG anti SARS-CoV-2 nucleocapsid protein antibodies, collected in the last 2-3 months before vaccination.

DLLR occurred in 13/23 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 skin of the palms; 1, acute generalized exanthematous pustulosis (AGEP); 1, generalized micropapular exanthema accompanied by a 7-centimeter 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 non-follicular 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 1st dose of Moderna vaccine. She

developed 4 well-defined, oval, erythematous-violaceous patches on the forearms and abdomen, non-pruritic nor painful.

They did not improve with topical corticosteroid treatment. Seven days after the 2nd 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 four (15.3%) with oral antihistamines. The mean duration of the reactions was 5 ± 1.4 days when treated and 4.84 ± 0.60 days without treatment ($p=0.83$).

Patch tests, done on all subjects, were negative in 100% of cases. Only one patient refused to receive the booster dose, but the remaining patients (22/23, 96%) successfully received the second dose of the vaccine. DLLR reoccurred in 62% (8/13) 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 which developed after the first dose (mean: 4.4 days) ($p<0.05$). 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 26-series of delayed reactions after the administration of Pfizer–BioNTech or Moderna vaccines. Of these, 23 reactions occurred after the 1st dose. Only one patient did not receive two doses whereas 96% received both. Therefore, these reactions were mild, self-limiting, and did not preclude a second vaccine dose.

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