Tolerance of SARS CoV-2 vaccines with polyethylene glycol in allergic patients to polysorbate 80

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0772

Key words: COVID-19. Vaccines. PEG. Polyethylene glycol. Polysorbate 80. Excipients.

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Data from this manuscript has been used for making a poster for the 33rd SEAIC congress.

The development of a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be our greatest weapon to overcome the current global pandemic. Only a few hours after the start of the mass vaccination in the U.K, two probable cases of anaphylaxis after the administration of Pfizer-BioNTech vaccine were reported and polyethylene glycol 2000 (PEG 2000), a macrogol used as excipient of new SARS CoV-2 mRNA vaccines, was suggested to be the culprit agent [1]. Recently published articles demonstrate the involvement of PEG in systemic reactions after vaccination with COVID-19 mRNA vaccines [2-5].

In Spain, at the moment of the present study, three vaccines had been approved for the prevention of Coronavirus-19 disease by regulatory agencies; the mRNA vaccines BNT162b2 (produced by Pfizer- BioNTech) and mRNA-1237 (developed by Moderna Therapeutics), containing polyethylene glycol 2000 and the DNA vaccine AZD1222 by AstraZeneca-Oxford University that contains polysorbate 80 and trometamol [3].

doi: 10.18176/jiaci.0772

Macrogols, including polyethylene glycol and the structurally related polysorbates, are compounds whose primary feature include polyether groups [6]. Their molecular weight (MW) ranges from 200 to 35000 g/mol according to the length of their chains and they are widely used as excipients in food, cosmetics and topical and systemic drugs because of their stabilizing properties [7,8]. In addition, cross-reactivity between polyethylene glycols and polysorbate 80 has been described due to shared structures [7,8].

The aim of the present study is to evaluate the sensitization to COVID-19 vaccines and to assess the tolerance to SARS-CoV-2 Pfizer- BioNTech and Moderna Therapeutics vaccines containing polyethylene glycol in patients with a diagnosis of polysorbate 80 allergy.

For that purpose, we recruited all patients previously diagnosed with polysorbate 80 allergy in our department. Out of 5 patients, 3 suffered from an anaphylaxis [9] and 2 reported acute urticaria after the administration of Inzitan® (cyanocobalamin, dexamethasone, lidocaine, thiamine and polysorbate 80). Patients were diagnosed between 3 and 7 years before the current research. At the time of diagnosis, skin tests yielded positive results with polysorbate 80 and with corticosteroids (triamcinolone, budesonide and prednisolone) containing that excipient (Supplementary Table).

A written informed consent was obtained from all patients. Skin testing (prick-tests and intradermal tests) with COVID-19 vaccines (Pfizer-BioNTech, Moderna Therapeutics and AstraZeneca-Oxford University), PEG 4000, PEG 3350, PEG 2000, PEG 1500, polysorbate 80 and trometamol were performed sequentially with intervals of 30 minutes between each concentration. Prick-tests were considered positive when a wheal greater than 3 mm in diameter was developed in 15 minutes and intradermal tests when an increase in wheal size greater than 3 mm in diameter was present. Peripheral venous lines were placed due to the described risk of systemic reactions with intradermal tests with PEG [4,5,8,10].

doi: 10.18176/jiaci.0772

Test results with vaccines and with different excipients, including polysorbate 80, were negative in four patients (Table I). All of them tolerated the administration of COVID-19 vaccines containing PEG 2000, 3 of them received Pfizer BioNTech vaccine and 1 of them Moderna Therapeutics vaccine. The remaining patient showed positive intradermal tests with polysorbate 80 and with Pfizer-BioNTech, Moderna Therapeutics and AstraZeneca-Oxford University vaccines (Supplementary Figure), so she was advised to avoid vaccination. Ten control subjects were tested with the three SARS-CoV-2 vaccines and excipients with negative results.

Although *in vitro* cross-reactivity between PEG and polysorbate 80 has been described in some published cases, this cross-reactivity is not always detected and its clinical implication is not clearly defined [1,4,7,8].

In this report, the four patients with a previous diagnosis of polysorbate 80 allergy and with current negative skin tests with polysorbate and PEG, show a good tolerance to COVID-19 vaccines containing PEG. The negativity of skin tests in four of our patients, suggests a tendency towards the remission of the sensitization to polysorbate 80, as happens with some other drugs as penicillin. Since an average of five years have elapsed since the diagnosis, we could think that allergy has remitted. Nonetheless, we recommended to these four patients to avoid vaccines with polysorbate 80 because skin tests could have lost sensitivity over the time [8] and patients may still be allergic, leading to an allergic reaction with the administration of the first vaccine dose. Less likely, this first dose could activate immunological memory and trigger an allergic reaction with the second dose.

In patient number 5 with persistent sensitization to polysorbate 80, skin tests with different polyethylene glycols yielded a negative result but they were positive with Pfizer-BioNTech and Moderna Therapeutics vaccines. We can´t explain with certainty this finding. Both mRNA vaccines contain PEG 2000 as part

doi: 10.18176/jiaci.0772

of the PEGylation process of the lipid nanoparticles that surround the mRNA molecules [2,3]. We suggest that this structural arrangement may lead to a higher affinity of PEG for the IgE bound to its receptor in mast cells and could explain the positive skin test with the vaccines but not with PEG. Recently, Troelnikov et al. studied three patients with a previous history of PEG allergy and they found that the basophil activation test was exclusively positive in the presence of PEGylated drugs (Pfizer BioNTech vaccine and PEGylated liposomal doxorubicin) and not in the presence of different PEGs [3]. Those findings support our hypothesis that PEGylated compounds have a higher avidity for the IgE than PEG itself. Therefore, as a preventive measure, we thought it would be advisable not to administer any vaccine in patient number 5, even though the COVID serology was negative, and wait for PEG- and polysorbate 80-free vaccines to be marketed.

To date, there is not a consensus on how to perform skin testing with COVID-19 vaccines and excipients and the sensitivity and specificity of skin tests in predicting severe allergic reactions is unknown. For this reason, in a recently published meta-analysis, the authors suggest against routinely performing skin or in vitro testing, outside of the research setting [1].

In conclusion, we confirm that patients with a previous diagnosis of polysorbate 80 allergy with current negative skin tests with COVID-19 vaccines, PEG and polysorbate 80 tolerate COVID-19 vaccines containing PEG.

Further studies are needed to assess the diagnostic accuracy of skin testing with COVID-19 vaccines and the role of excipients in the reported reactions in order to develop guidelines for the management of patients with allergy to macrogols.

doi: 10.18176/jiaci.0772

Funding

The authors declare that no funding was received for the present study.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Table. Results of skin tests.

			Patients				
			1	**2**	**3**	**4**	**5**
Years since diagnosis			7	6	3	4	5
Clinical manifestation at diagnosis			Anaphylaxis	Acute urticaria	Anaphylaxis	Acute urticaria	Anaphylaxis
Pfizer BioNTech	PT	undiluted	-	-	-	-	-
	ID	1:100	-	-	-	-	+
Moderna Therapeutics	PT	undiluted	-	-	-	-	-
	ID	1:100	-	-	-	-	+
AstraZeneca-Oxford Univ.	PT	undiluted	-	-	-	-	-
	ID	1:100	-	-	-	-	+
PEG 4000 (Casenlax ®)	PT	2.5 mg/ml	-	-	-	-	-
		25 mg/ml	-	-	-	-	-
	ID	0.00025 mg/ml	-	-	-	-	-
		0.0025 mg/ml	-	-	-	-	-
PEG 3350 (Movicol ®)	PT	2.5 mg/ml	-	-	-	-	-
		25 mg/ml	-	-	-	-	-
	ID	0.00025 mg/ml	-	-	-	-	-
		0.0025 mg/ml	-	-	-	-	-
PEG 2000	PT	1 mg/ml	-	-	-	-	-
		10 mg/ml	-	-	-	-	-
		100 mg/ml	-	-	-	-	-
	ID	0.0001 mg/ml	-	-	-	-	-
		0.001 mg/ml	-	-	-	-	-
PEG 1500 (Roxall)	PT	1 mg/ml	-	-	-	-	-
		10 mg/ml	-	-	-	-	-
		100 mg/ml	-	-	-	-	-
	ID	0.01 mg/ml	-	-	-	-	-
Trometamol	PT	1 mg/ml	-	-	-	-	-
	ID	0.001mg/ml	-	-	-	-	-
		0.01 mg/ml	-	-	-	-	-
		0.1 mg/ml	-	-	-	-	-
Polysorbate 80	PT	0.4 mg/ml	-	-	-	-	-
	ID	0.004 mg/ml	-	-	-	-	-
		0.04 mg/ml	-	-	-	-	+
Tolerance to vaccine			Yes (Moderna)	Yes (Pfizer)	Yes (Pfizer)	Yes (Pfizer)	Not vaccinated

PT: Prick test. ID: Intradermal test.