## Tolerance to SARS CoV-2 Vaccines Containing Polyethylene Glycol in Patients Allergic to Polysorbate 80

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Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be our greatest weapon against the current global pandemic. Only a few hours after the start of the mass vaccination campaign in the UK, 2 probable cases of anaphylaxis induced by Pfizer-BioNTech vaccine were reported, and polyethylene glycol 2000 (PEG 2000), a macrogol used as an excipient in the new SARS CoV-2 mRNA vaccines, was thought 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].

At the time of writing, the Spanish regulatory agency had approved 3 vaccines for the prevention of COVID-19, namely, the mRNA vaccines BNT162b2 (produced by Pfizer-BioNTech) and mRNA-1237 (developed by Moderna Therapeutics), which contain PEG 2000, and the DNA vaccine AZD1222, which is produced by AstraZeneca-Oxford University and contains polysorbate 80 and trometamol [3].

Macrogols, including polyethylene glycol and the structurally related polysorbates, are compounds characterized primarily by polyether groups [6]. Their molecular weight ranges from 200 to 35 000 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 PEGs and polysorbate 80 has been reported to be due to shared structures [7,8].

We aimed to evaluate sensitization to COVID-19 vaccines and to assess tolerance to the Pfizer-BioNTech and Moderna Therapeutics vaccines (each of which contains PEG) in patients diagnosed with polysorbate 80 allergy.

We recruited all patients previously diagnosed with polysorbate 80 allergy in our department. Out of 5 patients, 3 experienced anaphylaxis [9] and 2 reported acute urticaria after 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

Table. Results of Skin Tests

| | | | Patient | | | | |
|---|---|---|---|---|---|---|---|
| | | | 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 | - | - | - | - | - |
| | IDT | 1:100 | - | - | - | - | + |
| Moderna Therapeutics | PT | Undiluted | - | - | - | - | - |
| | IDT | 1:100 | - | - | - | - | + |
| AstraZeneca-Oxford Univ. | PT | Undiluted | - | - | - | - | - |
| | IDT | 1:100 | - | - | - | - | + |
| PEG 4000 (Casenlax) | PT | 2.5 mg/mL | - | - | - | - | - |
| | | 25 mg/mL | - | - | - | - | - |
| | IDT | 0.00025 mg/mL | - | - | - | - | - |
| | | 0.0025 mg/mL | - | - | - | - | - |
| PEG 3350 (Movicol) | PT | 2.5 mg/mL | - | - | - | - | - |
| | | 25 mg/mL | - | - | - | - | - |
| | IDT | 0.00025 mg/mL | - | - | - | - | - |
| | | 0.0025 mg/mL | - | - | - | - | - |
| PEG 2000 | PT | 1 mg/mL | - | - | - | - | - |
| | | 10 mg/mL | - | - | - | - | - |
| | | 100 mg/mL | - | - | - | - | - |
| | IDT | 0.0001 mg/mL | - | - | - | - | - |
| | | 0.001 mg/mL | - | - | - | - | - |
| PEG 1500 (Roxall) | PT | 1 mg/mL | - | - | - | - | - |
| | | 10 mg/mL | - | - | - | - | - |
| | | 100 mg/mL | - | - | - | - | - |
| | IDT | 0.01 mg/mL | - | - | - | - | - |
| Trometamol | PT | 1 mg/mL | - | - | - | - | - |
| | IDT | 0.001 mg/mL | - | - | - | - | - |
| | | 0.01 mg/mL | - | - | - | - | - |
| | | 0.1 mg/mL | - | - | - | - | - |
| Polysorbate 80 | PT | 0.4 mg/mL | - | - | - | - | - |
| | IDT | 0.004 mg/mL | - | - | - | - | - |
| | | 0.04 mg/mL | - | - | - | - | + |
| Tolerance to vaccine | | | Yes (Moderna) | Yes (Pfizer) | Yes (Pfizer) | Yes (Pfizer) | Not vaccinated |

Abbreviations: IDT, intradermal test; PT, prick test.

(triamcinolone, budesonide, and prednisolone) containing that excipient (Supplementary Table).

All patients gave their written informed consent to undergo testing. 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. The results of the prick tests were considered positive when a wheal greater than 3 mm in diameter developed in 15 minutes; intradermal test results were considered positive when the wheal size was greater than 3 mm. Peripheral venous lines were placed due to the reported risk of systemic reactions in intradermal tests with PEG [4,5,8,10].

Test results with vaccines and with different excipients, including polysorbate 80, were negative in 4 patients (Table). All of them tolerated administration of COVID-19 vaccines containing PEG 2000, 3 of them received the Pfizer BioNTech vaccine, and 1 the Moderna Therapeutics vaccine. Since the results of intradermal tests with polysorbate 80 and with the Pfizer-BioNTech, Moderna Therapeutics, and AstraZeneca-Oxford University vaccines (Supplementary Figure) were positive in the remaining patient, she was advised to avoid vaccination. Testing was negative in the 10 controls who were tested with the 3 SARS-CoV-2 vaccines and excipients.

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

 

In this report, the COVID-19 vaccines containing PEG were tolerated by the 4 patients diagnosed with polysorbate 80 allergy who had negative skin test results for polysorbate and PEG. The negative skin test results suggest a tendency towards remission of sensitization to polysorbate 80, as happens with other drugs, such as penicillin. Since an average of 5 years has elapsed since the diagnosis, we might think that the allergy has remitted. Nonetheless, we recommended these 4 patients to avoid vaccines with polysorbate 80, because skin tests could have lost sensitivity over time [8] and patients may still be allergic, leading to an allergic reaction with the administration of the first dose of the vaccine. Less likely, this first dose could activate immunological memory and trigger an allergic reaction with the second dose.

In patient number 5, who remained sensitized to polysorbate 80, skin tests with different PEGs yielded a negative result, although they were positive with the Pfizer-BioNTech and Moderna Therapeutics vaccines. We cannot explain this finding. Both mRNA vaccines contain PEG 2000 as part 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 result with the vaccines but not with PEG. Recently, Troelnikov et al [3] studied 3 patients with a previous history of PEG allergy and found that the basophil activation test result was positive only in the presence of PEGylated drugs (Pfizer BioNTech vaccine and PEGylated liposomal doxorubicin) and not in the presence of different PEGs. These findings support our hypothesis that PEGylated compounds have a higher affinity for IgE than for 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-19 serology result was negative—and to wait for PEG- and polysorbate 80–free vaccines to be marketed.

To date, there is no 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, the authors of a recently published meta-analysis suggest not routinely performing skin or in vitro testing outside the research setting [1].

In conclusion, we confirm that patients with a previous diagnosis of polysorbate 80 allergy and 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 reactions reported in order to develop guidelines for the management of patients with allergy to macrogols.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

*Previous Presentations*

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