

**Safe administration of SARS-CoV-2 vaccine after desensitization to a biologic containing polysorbate 80 in a patient with polyethylene glycol-induced severe anaphylaxis and sensitization to polysorbate 80**

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## CASE REPORT

Polyethylene glycols (PEGs) and structurally related polysorbates (PEG sorbitans) are polyether compounds derived from ethylene oxide, which are widely used as excipients and conjugated pharmaceuticals. PEG has recently been studied as an unsuspected, high-risk "hidden" allergen that can cause systemic allergic reactions. [1]

In November 2020, a 61-year-old man developed a severe allergic reaction to a PEG-based colonoscopy preparation containing PEG-3350 (Moviprep®). Immediately after taking this drug, he experienced generalized urticaria with labial angioedema, vomiting, dysphagia, presyncope, hypotension and tachycardia. He was treated with intravenous fluids, metoclopramide 10 mg, methylprednisolone 40 mg and dexchlorpheniramine 5 mg with little improvement, requiring treatment in the emergency room with a second dose of all these drugs together with intravenous hydrocortisone 200 mg, with total resolution of his symptoms. It should be noted that despite the severity of the reaction, epinephrine was not administered. The patient reported that he had previously presented pruritic erythematous macules when using some shower gels.

In January 2021, an allergy workup was carried out in the allergy department, skin prick tests (SPTs) were performed with undiluted Moviprep® and PEG-2000 (0.16 mg/ml) with positive results (wheals of 7x7 and 4x5 mm, respectively). He was diagnosed with anaphylaxis due to Moviprep® and sensitization to PEG-2000. It was advised to avoid all drugs and vaccine preparations containing PEG of any molecular weight (MW).

Two months later, the patient was diagnosed with Crohn's disease with stenosing debulking and the gastroenterologist indicated treatment with adalimumab. Given the need for vaccination for COVID 19 before starting the biological, he was referred back to our department since all available vaccines against SARS-CoV2 contain PEG or polysorbate. It is also noted that adalimumab contains polysorbate 80 (PS80) as an excipient.

SPTs were performed with Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca) vaccines, trometamol, PS80 and PS20 with negative results. Intradermal test with trometamol (0.1 mg/mL) was negative, whereas it was positive with PS80 (0.04mg/mL) and PS20 (0.04mg/mL) (both wheals of 7x7 mm).

Basophil activation test (BAT) was performed with positive results to Comirnaty vaccine® (10% basophil activation), Vaxzevria vaccine® (9.6%), PEG-2000 (18.8%), PS20 (21.8%), PS80 (9.4%), PEG-3350 (13%) and adalimumab (8.4%).

Since no anti-TNF alpha treatment was available for Crohn's disease that did not contain polysorbate excipients, it was decided to perform a desensitization procedure with infliximab, an intravenous biological drug containing PS80, after consultation with the gastroenterologist and informed consent of the patient. Table I shows the adjusted

protocol that was carried out according to the dose prescribed by the gastroenterologist. The protocol was based on that designed by Lee et al. [2] and adjusted to the dose prescribed by the gastroenterologist with administration scheme according to the manufacturer's protocol (infliximab dose of 470 mg containing 2.35 mg of PS80, maintenance schedule every 8 weeks). The patient tolerated all six infliximab desensitization procedures to date without incident; in the latter, the dose of infliximab was doubled, and it was also well tolerated. On the second day of infliximab desensitization, Janssen SARS-CoV-2 vaccine containing 0.16 mg of PS80 was also administered at the end of the infliximab administration, and was well tolerated by the patient. The Janssen vaccine was chosen because it contained PS80 as an excipient and only one dose of this vaccine was needed to immunize the patient.

After some time, a new dose of Jansen or AstraZeneca SARS-CoV2 vaccine was requested but it was not available. A study of the immune response against SARS-COV-2 was carried out by the immunology department, verifying good levels of humoral and cellular response to SARS-COV-2. The cellular immunity pattern showed that the patient had been in contact with the SARS-CoV2 virus after vaccination.

From 1989 through 2017, there were 53 reports to the US Food and Drug Administration (FDA) describing anaphylactic reactions in which PEG-containing bowel preparations or laxatives were the primary or only suspected causative agent. Regarding biologics, in the last 20 years there has been an increase in reports to the FDA of anaphylaxis to these drugs. The mechanisms of these reactions are not clear, however, in a large number of them PEG or polysorbates were involved. [3]

It is interesting that in our patient, whose anaphylactic reaction was due to PEG-3350 contained in a laxative, sensitization to PEG-3350 and PEG-2000 was found together with PS80 and PS20, demonstrated by skin tests and BAT. Although there is limited evidence that PEGs may cross-react with certain polysorbates, cross-reactivity between PEG-3350 and PS80 has been seen in patients who reacted to both [4] and has also been shown in patients with positive skin testing to both excipients and a history of immediate hypersensitivity reactions to PEG. [5]

In our patient, given the risk of this cross-reactivity and the history of severe anaphylaxis but also the need to use a biological drug for his underlying disease, desensitization with a biological drug containing PS80 was the best option. In addition, infliximab was chosen for desensitization due to its maintenance intravenous administration rather than other biologics that require subcutaneous administration.

The Pfizer-BioNTech and Moderna SARS-CoV-2 vaccines were approved in December 2020 and some cases of anaphylaxis have been reported following their administration [6]. PEG and polysorbate have been postulated to cause these potential IgE-mediated reactions; however, in very few cases they were demonstrated [7, 8]. Our patient had risk factors for a severe reaction to these vaccines, so the administration of one of them during the desensitization regimen with infliximab/PS80 was adequate.

In conclusion, we report the safe administration of a SARS-CoV-2 vaccine and a biologic drug containing PS80 to a PS80-sensitized patient, after following a desensitization regimen. To our knowledge, this is the first report of such a procedure.

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The authors declare that they have no conflicts of interest.

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**Table. Outpatient desensitization protocol for a total Infliximab dose of 470 mg**

<b>Solution</b>	<b>Dose in each solution</b>	<b>Volume</b>	<b>Solution concentration</b>				
A (1/100)	0.94 mg	50	0.0188 mg/ml				
B (1/10)	9.4 mg	50	0.188 mg/ml				
C	470 mg	250	1.88 mg/ml				
<b>Step</b>	<b>Solution</b>	<b>Rate (ml/h)</b>	<b>Time (min)</b>	<b>Infliximab administered dose</b>	<b>Infliximab cumulative dose</b>	<b>PS80 administered dose</b>	<b>PS 80 cumulative dose</b>
1	A	3	15	0.0141	0.0141	0,0000705	0,0000705
2	A	6	15	0.0282	0.0423	0,000141	0,0002115
3	A	12	15	0.0564	0.0987	0,000282	0,0004935
4	A	25	15	0.1175	0.2162	0,0005875	0,001081
5	B	5	15	0.235	0.4512	0,001175	0,002256
6	B	10	15	0.47	0.9212	0,00235	0,004606
7	B	20	15	0.94	1.8612	0,0047	0,009306
8	B	40	15	1.88	3.7412	0,0094	0,018706
9	C	9	15	4.23	7.9712	0,02115	0,039856
10	C	19	15	8.93	16.9012	0,04465	0,084506
11	C	39	15	18.33	35.2312	0,09165	0,176156
12	C	77	180	434.28	469.5112	2,1714	2,347556

Premedication with intravenous acetanomiphen 1g, methylprednisolone 20 mg and dexchlorpheniramine 5 mg was performed 30 minutes, according to manufacturer's regimen.