

## Safety of New mRNA Vaccines Against COVID-19 in Severely Allergic Patients

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The impact of the global coronavirus disease 2019 (COVID-19) pandemic has been devastating. Safe and effective vaccines are needed to prevent the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Two mRNA vaccines were approved at the end of 2020: BNT162b2 (Pfizer-BioNTech) [1] and mRNA-1273 (Moderna) [2].

During the first days of the vaccination campaign, cases of anaphylaxis were reported after administration of both vaccines in patients who had a known history of severe allergies. An alert was triggered by regulatory bodies to contraindicate their administration to allergic patients, with no clear specific indications as to the type of allergy [3,4].

Confirmed allergic reactions to vaccines are not generally attributed to the active ingredients, but rather to the excipients [5,6]. Polyethylene glycol (PEG), which is widely used due to its stabilizing properties, is an excipient of both BNT162b2 and mRNA-1273 and a known potential allergen [7]. In addition, mRNA-1273 also contains trometamol [5].

The aim of this study was to evaluate the ability of a new protocol to identify patients with previous severe allergic reactions so that they could receive the vaccines safely and to detect patients in whom vaccines should be avoided.

Between January and February 2021, during the COVID-19 vaccination campaign, a specific questionnaire was administered to health care workers from a tertiary hospital in Madrid, Spain to select persons with previous severe allergic diseases. The questionnaires were sent from the Occupational Risk Prevention Department so that the vaccination could be administered in our Allergy Department.

We recorded sex, age, personal history of cardiovascular or respiratory diseases, autoimmunity, immunosuppression, chronic cutaneous diseases, treatment at the time of the study, and other nonsevere allergies.

Before administration of the vaccine, all patients underwent skin prick testing (SPT) with the vaccine to be administered (dilution 1:1) using the waste of each vial thawed in the previous 6 hours. We also performed SPT with PEG-3350 (530 mg/mL) in patients who were going to receive BNT162b2 and PEG-3350 and trometamol (10 mg/mL) in those who were to receive mRNA-1273. Tests were read at 20 minutes. We administered the first dose of the corresponding vaccine and observed the patient for 30 minutes.

The study protocols for clinical data collection were reviewed and approved by the local ethics committee.

A total of 186 persons were referred to our Allergy Department from the Occupational Risk Prevention Department. After evaluation by an allergist, 55 patients were ruled out because they did not meet the criteria for severe allergic reaction, had poorly controlled asthma, or declined to participate in the allergy study. The final study population comprised 131 patients, whose characteristics are summarized in Tables 1 and 2 (Online Repository). Of these, 112 (85.5%) were female, and the mean age was 47 (26-66) years. Twenty-eight (21.4%) patients had cardiovascular disease, 34 (26%) patients had respiratory disease, 6 (4.6%) had immunodepression, 21 (16%) had autoimmunity, and 3 (2.2%) had chronic skin conditions.

The main allergic condition was anaphylaxis (121/131, 92.4%), which was triggered by drugs in most cases (66/121, 54.5%), followed by food (40/121, 33.1%), hymenoptera venom (4/121, 3.3%), latex (4/121, 3.3%), and other allergens (10/121, 8.3%). In 3 cases (2.5%), the offending agent was unknown, and 13 patients (10.7%) had experienced anaphylactic reactions triggered by multiple agents. No delayed allergic reactions to the excipients were reported. Of the total of 45 asthmatic patients (34.4%), 9 (20%) had severe asthma. Seven patients (5.3%) were diagnosed with chronic urticaria, and 1 patient (0.8%) had mast cell activation syndrome. Thirteen (9.9%) reported contact dermatitis with cosmetics, although only 3 of them (18.8%) had previously undergone allergy studies.

SPTs with the mRNA vaccine and trometamol was negative in all cases. SPT with PEG-3350 was positive in 2 patients (1.6%), and the mRNA vaccine was contraindicated. Patient 1 was a 27-year-old woman with a history of drug-induced anaphylaxis and a previous episode of idiopathic anaphylaxis that occurred after the intake of a drug containing the excipient poloxamer 407, a PEG derivative with demonstrated cross-reactivity to PEG [8]. Patient 2 was a 39-year-old woman with a history of anaphylactic shock during vaginal delivery with epidural anesthesia. The anaphylactic episode remained unresolved after the allergy work-up, although the implication of PEG could not be ruled out.

During the current study, patients received the first dose of an mRNA COVID-19 vaccine. The only reaction recorded was a mild immediate reaction in a 43-year-old woman with a personal history of severe asthma 10 minutes after administration of BNT162b2. She developed nasal obstruction, rhinolalia, and pruriginous erythematous macules on the neck and upper thorax. Intramuscular dexchlorpheniramine was administered, and symptoms

resolved within 60 minutes. Tryptase levels remained unchanged compared with baseline.

Allergy to excipients is often overlooked owing to a lack of knowledge about their allergenic potential [5]. However, immediate hypersensitivity to PEG, including life-threatening allergic reactions, has been reported [9]. We identified 2 patients with positive SPT results to PEG-3350, both of whom had a history of idiopathic anaphylaxis that could be related to PEG derivatives. Although the positive predictive value of the SPT with PEG, a hidden high-risk and widespread allergen [8,9], is unknown, we recommend avoiding these vaccines in patients with a positive test result.

We used a questionnaire and an allergology study to select patients with severe allergic reactions who could safely receive BNT162b2 or mRNA-1273. In the present study, 99.22% of patients with previous severe allergic diseases tolerated mRNA vaccination with no reaction in 128 out of 129 vaccines administered.

Allergists must provide reliable alternatives for allergic patients within the COVID-19 vaccine rollout programs [10]. We recommend that all allergic patients be screened using a questionnaire to determine the possible risk for an allergic reaction to the COVID-19 mRNA vaccines. We must continue to search for solutions that guarantee safe vaccination procedures during this unprecedented immunization strategy.

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#### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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