The century of mRNA vaccines: COVID-19 vaccines and allergy

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On 2 December 2020, the COVID-19, mRNA BNT162b2 vaccine was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and six days later, UK began mass vaccination. Only 24 hours after, Dr June Raine, Chief Executive of MHRA, issued updated guidance to COVID-19 vaccination centers about the management of anaphylaxis, following two reports of anaphylaxis and one report of a possible allergic reaction following immunization. The guidelines say verbatim "Any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer/BioNTech vaccine. A second dose should not be given to anyone who has experienced anaphylaxis following administration of the first dose of this vaccine." [1]. This letter has been generated as a response to the great amazement induced by the first part of this sentence in the Spanish allergists community.

The mRNA vaccines are experiencing a burst in basic and clinical research. Whereas the majority of early work in mRNA vaccines was focused on cancer applications. In the same way a number of recent reports have demonstrated the potency and versatility of mRNA to protect against a wide variety of infectious pathogens, including parasites and finally the one that concerns us coronavirus 2 (SARS-CoV-2) [2-4].

These mRNA vaccines are safety because mRNA is a non-infectious, non-integrating platform and therefore, there is no potential risk of infection or insertional mutagenesis. The various modifications make mRNA more stable and highly translatable [5,6]. The mRNA vaccines have the poten-

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tial for rapid, inexpensive, and scalable manufacturing, mainly owing to the high yields of in vitro transcription reactions [2].

The COVID-19 mRNA Vaccine BNT162b2 manufacture by Pfizer/BioNTech, is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2. As excipients this vaccine contains polyethylene glycol/macrogol (PEG) as part of ALC-0159. This vaccine use fat bubbles called lipid nanoparticles to deliver messenger RNA (mRNA) to cells. Once there, the mRNA directs cells to produce the virus spike protein provoking an immune response to that foreign protein [3]. This same technology is used in mRNA-1273 vaccine, manufactured by Moderna, as the mRNA-1273 is being encapsulated into LNP (lipid nanoparticle) with "PEG-lipid" [4].

PEG is a polyether compound that is widely used as an additive in pharmaceuticals, cosmetics, and food because of its stabilizing properties [7]. Anaphylactic reactions to PEG are rarely reported. It is more frequently the incidence of contact sensitivity to PEG [8].

Both COVID-19 mRNA Vaccines, BNT162b2 vaccine manufactured by Pfizer/BioNTech and mRNA-1273 vaccine manufactured by Moderna, have been reported to be safe in clinical trials. The most common reported adverse reactions (AR) were injection site reactions, fatigue, headache, muscle pain, chills, joint pain and fever. Severe adverse reactions were more frequent after Dose 2 than after Dose 1, in similar proportions in both vaccines. There is a third vaccine that uses mRNA, CureVac, it has taken a slightly different approach, choosing to use the potency of untranslated regions to optimize the RNA rather than make chemical modifications. CureVac is on track to initiate phase 3 testing of its COVID-19 vaccine by the end of this year [9].

A list of potential allergens in currently available vaccines is maintained on the Institute for Vaccine Safety Web site, and listed in recently published reviews, too, [4, 8, 10, 11]. The advice of MHRA

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avoiding the administration of the SARS-CoV2, BNT162b2 vaccine should not be generalized to all patients who had suffered severe reactions to drugs and/or foods. The adverse effects that occurred these English patients after the administration of the vaccine must be studied in greater depth.

The immunization is highly effective in preventing infectious diseases. Allergic patients deserve access to the same publicly recommended immunizations as non-allergic patients unless risks associated with vaccination outweigh the gains. Whereas the number of reported possible AR to vaccines is high, confirmed vaccine-triggered allergic reactions are rare [12].

The BNT162b2 vaccine, Pfizer/BioNTech, has the same contraindications as any other vaccine, with regards allergic patients. That is, its use is not recommended in patients who had suffered previous allergic reactions to its components. Only patients with documented history of allergy to PEG, Tween 80 or previous reaction to vaccines that may contain them, should avoid these Pfizer/BioNTech -Moderna vaccines against COVID-19 if we take into account the contraindications from the strictly allergic point of view.

The adverse events related to the BNT162b2 vaccine are explained in the drug data sheet. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]), but the overall risk is relatively low [11]. It is mandatory carrying out an allergy study in subjects who refer allergic reactions to SARS-CoV2 vaccines, in order to identify the culprit substance. It is not necessary carrying out a systematic preventive study of allergy, previous to the administration of the vaccine to all individuals who had suffered severe allergic reactions to drugs and/or foods.

Data related to risk in individuals with a history of allergic reactions to previous vaccinations is very limited and evolving. A decision to receive the Pfizer-BioNTech COVID-19 vaccine should be undertaken by the patient with his physician using their professional judgment balancing the benefits and risks associated with taking the vaccine.

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The Pfizer-BioNTech COVID-19, and Moderna vaccine are not live virus vaccines and therefore, it can be administered to immunocompromised patients. It does not know at this time if people with a weakened immune system will respond to the vaccine and be protected from COVID-19 [13]. Table 1 summarizes the management of COVID-19 vaccination for allergic patients, as suggested by SEAIC recommendations here presented. These recommendations are based on the best knowledge to date and follow CDC guidelines for allergic patients vaccination [14]. On the same day that the cases of anaphylactic reactions to the Pfizer/BioNTech COVID-19 vaccine were reported, SEAIC released an official statement. The purpose of this letter is to make available to the entire scientific community these recommendations in order of carrying out the vaccination in the safest way possible in allergic patients.

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Table 1. Recommendations for allergic patients vaccination with COVID-19 mRNA vaccines.

Modified of CDC guidelines for allergic patients vaccination

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The SARS-CoV2 vaccines should be administered in a health care setting where anaphylaxis can be treated.
*Severe allergic reaction: e.g., anaphylaxis

	Proceed with Vaccination	Precaution to Vaccination	Contraindication to Vaccination
	- History of food, latex, insect venom, inhalant, etc., allergies - History of drug allergy - Mild allergic reactions to vaccines or other injectable medications (e.g., no anaphylaxis) - Family history of anaphylaxis	- History of severe allergic reaction* to food, latex, insect venom or inhalant. - History of severe drug allergy* - History of severe allergic reaction* to another vaccine (not including currently authorized mRNA vaccines) - History of mastocytosis, mast cell activation syndrome, idiopathic anaphylaxis. - Moderate/severe acute illness - Pregnancy and lactation	- History of severe allergic reaction* to any component of the currently authorized COVID-19 mRNA vaccines
ACTIONS	- 30 minute observation period	- Risk assessment - Additional counseling - Potential deferral of vaccination - 45 minute observation period if vaccinated	- Do not vaccinate

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