EDITORIAL

Anaphylaxis is a rare reaction in COVID-19 vaccination

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Anaphylaxis is a severe multisystem reaction that occurs rapidly after the introduction of an antigen that would otherwise be a harmless substance. It is characterized by airway and respiratory problems, cardiovascular collapse, mucosal inflammation, and other complications, all severe symptoms that can cause death. IgE-dependent anaphylaxis involves mast cells (MCs) which are the main sources of biologically active mediators that contribute to the pathological and lethal phenomena that can occur in anaphylaxis. Antibody-mediated anaphylaxis can follow multiple pathways such as that mediated by MCs carrying the FceRI receptor, which can be activated by very small amounts of antigen including a vaccine antigen and trigger an anaphylactic reaction. In addition, anaphylaxis can also be provoked by high concentrations of IgG antibodies that bind to the FcγR receptor present on basophils, neutrophils, macrophages and MCs. For this reason, the IgG concentration should be kept under control in vaccinations. Activation of MCs is a major cause of anaphylaxis, which requires immediate treatment with epinephrine to arrest severe lethal symptoms. MCs are activated through the antigen binding and cross-linking of IgE with release of mediators such as histamine, proteases, prostaglandins, leukotrienes and inflammatory cytokines. The release of these compounds causes nausea, vomiting, hives, wheezing, flushing, tachycardia, hypotension, laryngeal edema, and cardiovascular collapse. mRNA and viral vector vaccines have been cleared by the United States, Food and Drug Administration (FDA), generating hope of prevention and cure for COVID-19 around the world. Scientists advise against giving the vaccine to individuals who have had a previous history of anaphylaxis. The US Centers for Disease Control and Prevention (CDC) advises people with a previous history of any immediate allergic reaction to remain under observation for approximately 30 minutes after COVID-19 vaccination. To date, vaccines that prevent SARS-CoV-2 infection have not raised major concerns of severe allergic reactions, although, in some cases, pain and redness at the injection site and fever have occurred after administration of the vaccine. These reactions occur in the first 24-48 hours after vaccination. It has been reported that probable forms of anaphylaxis could also occur, especially in women approximately 40 years of age. But after tens of millions of vaccinations, only a few patients had this severe reaction with a low incidence. Anaphylactic and severe allergic reactions can also occur to any component of the vaccine including polysorbates and polyethylene glycol. To date, there is no precise information on allergic reactions to COVID-19 vaccines. Individuals with MCs and complement with higher activation than others may be at greater allergic risk. Moreover, the reactions called anaphylactoids, are those not mediated by IgE because they do not involve this antibody and can

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also occur in COVID-19 vaccination. These not-IgE-mediated reactions occur through direct activation of MCs and complement with tryptase production, but to a lesser extent than IgE-mediated anaphylaxis. However, at the moment it is not known exactly which component of the vaccine causes the allergic reaction and which vaccine causes the most side effects, including anaphylaxis. Thus, individuals who have a known allergy to any component of the vaccine should not be vaccinated. However, should an anaphylactic reaction occur, this requires immediate treatment with epinephrine to arrest severe lethal symptoms. In conclusion, the purpose of this editorial is to encourage the population to be vaccinated in order to extinguish this global pandemic that is afflicting the world population, and to reassure individuals that anaphylactic reactions do not occur with a higher incidence than other vaccinations.

Key words: COVID-19; anaphylaxis; vaccine; SARS-CoV-2; immunity; inflammation; allergy

It has been clearly confirmed and reported that the new coronavirus SARS-CoV-2 causes COVID-19 disease. The virus has provoked a global pandemic, hospitalizing millions of individuals in intensive care (1). Fortunately, precautions and treatments have been taken that have avoided a greater number of infections, and therefore deaths. The serious pathological situations were caused by lung inflammation and thromboembolism with consequent asphyxiation. SARS-CoV-2 is biologically formed from RNA and N-proteins, while outside the membrane it made up of two proteins, E and M, lipids and the glycoprotein (S) spike (2). Coronavirus-19 infects humans, usually starting in the airways, nose and mouth, binding to the target cell ACE2 receptor and the immune cell TLR. Once SARS-CoV-2 has entered the cell and therefore the human body, it replicates quickly, carrying out its pathogenic action with the release of interferon that stimulates immune cells such as T and B lymphocytes, neutrophils, macrophages and mast cells. The production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF is essentially given by macrophages and mast cells causing edema, bleeding, intravascular coagulation, thrombosis, respiratory failure and patient death.

Vaccines induced by microbial antigens prevent the spread of infectious diseases and reduce disease and mortality. On December 11, 2020, Pfizer-BioNTech and Moderna mRNA vaccines packaged in lipid nanoparticles**,** were cleared for emergency use (EUA) by the United States Food and Drug Administration (FDA), generating hope of prevention and cure for COVID-19 worldwide. After tens of millions of vaccinations, only a small number of patients had a severe allergic reactions with an incidence of 1 in 100,000, about 10 times higher than that of other vaccinations (3).

During the protective vaccination foe SARS-CoV-2 allergic phenomena can occur and, in very rare cases, anaphylaxis, with serious consequences. The anaphylactic reaction is a severe pathological advent that can arise in a few minutes, but also after up to eight hours, leading to cardio-vascular collapse and insufficient pulmonary activity. These cases involve the activation of MCs through the FcεRI receptor, a reaction activated by IgE. Mast cells are immune but also inflammatory cells which perform a biological action partially overlapping that of basophilic granulocytes. When IgE binds to its FcεRI receptor it aggregates and activates the cell to immediately release biological mediators stored in its cytoplasmic granules (4). The mediators released by MCs in the tissue provoke an allergic reaction with local and systemic inflammatory problems. SARS-CoV-2 vaccines can cause an allergic response mediated by MCs which are activated by the binding of IgE with part of the vaccine, but also the allergic reaction can be non-IgE mediated. MC mediators such as histamine, heparin (and other proteoglycans), proteases (such as carboxypeptidase A3, tryptase and chymase), as well as the cytokine TNF, are released in seconds; while the products of arachidonic acid metabolism such as prostaglandins, cysteinyl leukotrienes, and cytokines/chemokines and growth factors are transcriptionally up-regulated, generated and released (5). MCs can also be activated by complement products such

as C3a and C5a, cytokines (IL-33), some peptides (substance P) and by products of microorganisms, all independent of IgE. These allergy-intervening immune cells contribute to host defense in the type 2 response of antigen-activated T helper lymphocytes, resulting the production of IgE antibodies against the antigen in B-cell.

After delayed allergic reactions 48-92 hours after vaccination, delayed allergic cell-mediated reactions may occur, not dependent on IgE antibodies, but due to the abnormal reaction of T cells, macrophages and MCs (without degranulation) with release of pro-inflammatory cytokines. These reactions result in endothelial and tissue damage, inflammation and, in severe cases, death of the patient.

Allergies are inflammatory immune responses against any antigen and can cause severe host harm, including death. They are known to affect about 25 of the world population and trigger an acquired type 2 response involving $CD4^+$ helper T cells. Antigens such as viral antigens can also sensitize individuals by causing an IgE-mediated anaphylactic allergic reaction. Anaphylaxis is an immediate systemic hypersensitivity reaction that can be triggered by any antigen (very rarely by SARS-CoV-2 vaccine) (6). It is characterized by diffuse edema and drop in blood pressure due to a strong vasodilatation spread throughout the body. The antigen introduced into the body by injection, insect bite or absorption by the intestinal mucosa, activates MCs simultaneously in many tissues which first release inflammatory chemical mediators and then pro-inflammatory cytokines, with serious damage to the organism that can even lead to death. The release of the mediators of inflammation causes plasma loss, a drop in blood pressure and anaphylactic shock which can be fatal. To these effects are often added constriction of the airways, hypersecretion of mucus (both in the intestine and in the lungs), hypersensitivity and cutaneous urticaria.

In severe allergic reactions mediated by tryptases and pro-inflammatory cytokines, renal failure and brain damage can also occur which can lead to death (7).

Mast cells (MCs)

MCs can mediate inflammatory phenomena with consequent implications of acute and sub-acute pathological processes. Therefore, MCs can participate in immediate or delayed immunological reactions as primary or secondary effector cells. The IgE antibody binds on the MC surface on which the antigen binds, leading to degranulation, which is the basis of the allergy. Activation of MCs can cause leaky gut and promote anaphylaxis. These reactions induce the release of IL-33 and IL-25 which synergize by activating the ILC2 innate lymphoid cells with consequent production of IL-4 and expansion of MCs, all phenomena that can favor the onset of anaphylaxis. Therefore, the release of IL-33 from sensitized tissue can activate ILC2 cells which release IL-4 and IL-13 and activate the multiplication of inflammatory MCs. The proliferation in the marrow of MCs is also due to other cytokines, such as IL-5 and IL-9, which can play a redundant role with IL-4 and IL-13 (8).

Mast cells can enhance the innate response to antigen, contributing to acquired resistance. Therefore, it is pertinent to think that these cells and IgE help protect individuals from foreign antigens, including viruses.

It has long been known that vaccines very rarely cause anaphylaxis. In fact, the administration of

Table I. *Some excipients contained in mRNA and viral vector vaccines*

Moderna: Acetic acid, lipids, SM-102, polyethylene glycol, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine, sodium acetate, sucrose(sugar), tromethamine, tromethamine hydrochloride.
Pfizer: Electrolytes potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dehydrate, lipids, polyethylene glycol, sucrose(sugar), saline (sodium chloride).
AstraZeneca vaccine: histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose (sugar), sodium chloride, disodium edetate dihydrate, water.

anti-COVID-19 vaccines has caused a small number of allergic reactions, causing apprehension in the world population (9). Vaccines can provoke, albeit in very few instances, severe acute systemic IgE or IgG-mediated and anaphylactic reactions with complement participation. These can also cause severe delayed systemic reactions mediated by $CD4^+$ T helper cells. The allergic reaction can occur either due to the active components of the vaccine or, more frequently, against excipients, substances which pharmacologically should be inactive and used to improve the absorption, stability and solubility of the active compounds present in vaccines (10). Several types of excipients could be added to the vaccine to better stimulate the immune response with a more copious production of antigen-neutralizing antibodies. Thus, in the vaccination process, excipients are the main culprits of IgE-mediated allergic reactions (Table I).

It has been reported that in viral vector vaccines the compound most suspected of allergic reactions is polysorbate; while in mRNA vaccines it appears to be polyethylene glycol (11).

In conclusion, the reactions described above must in no way hinder the anti-SARS-CoV-2 vaccination process as, as already mentioned, they occur very rarely and the benefit of vaccination is much greater than the risks of serious allergic reactions, including anaphylactic shock.

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