Immediate Hypersensitivity Reactions Induced by COVID-19 Vaccines

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As the world deals with the COVID-19 pandemic, vaccination remains vital to successfully end this crisis. However, COVID-19-vaccine-induced immediate hypersensitivity reactions presenting with potentially life-threatening systemic anaphylactic reactions are one of the reasons for vaccine hesitancy. Studies have suggested that different mechanisms, including IgE-mediated and non-IgE-mediated mast cell activation, may be involved in immediate hypersensitivity. The main culprits triggering hypersensitivity reactions have been suggested to be the excipients of vaccines, including polyethylene glycol and polysorbate 80. Patients with a history of allergic reactions to drugs, foods, or other vaccines may have an increased risk of hypersensitivity reactions to COVID-19 vaccines. Various strategies have been suggested to prevent hypersensitivity reactions, including performing skin tests or in vitro tests before vaccination, administering different vaccines for the primary and following boosters, changing the fractionated doses, or pretreating the anti-IgE antibody.

Keywords: COVID-19 vaccines ; IgE-mediated pathway ; immediate hypersensitivity reactions ; skin test

1. Introduction

Since its discovery, coronavirus disease 2019 (COVID-19) has remained a global public health pandemic [1]. With the announcement of its genetic sequence, researchers and companies have raced to develop vaccines to end the pandemic. The administration of vaccines has successfully reduced the morbidity and mortality of COVID-19 [2][3][4][5]. According to the World Health Organization [6], the increasing availability and utilization of vaccines effectively protects people from the disease severity [7][8][9]. Currently, four classes of vaccines against COVID-19 are available. (1) mRNA vaccines use an innovative approach for inducing messenger RNA (mRNA) molecules to safely produce COVID-19 proteins, resulting in an immune response. (2) Viral vector vaccines use genetically engineered viral vectors to produce COVID-19 proteins to stimulate the host's immunity. (3) Inactivated virus vaccines use a weakened state of the COVID-19 virus that the host is capable of mounting an immune response against. (4) Protein subunit vaccines use COVID-19 protein fragments as a stimulus to trigger immune responses [10].

2. Clinical Phenotypes of Vaccine-Induced Immediate Hypersensitivity Reactions

Although vaccination has dramatically improved the control of COVID-19 transmission [11], vaccination hesitancy remains a significant issue owing to adverse reactions, particularly unpredictable hypersensitivity reactions [12][13]. Most hypersensitivity reactions to vaccines occur immediately and abruptly within minutes to hours after administration [14][15][16]. The clinical manifestations may range from mild cutaneous eruptions, such as urticaria or angioedema, to life-threatening systemic anaphylaxis [17]. Urticaria is characterized by transient wheal formation and may produce an itching or burning sensation. Angioedema is characterized by painful swelling in the deep dermis and subcutis layers of the skin. Both presentations are part of a spectrum of systemic symptoms, including anaphylaxis [18]. Anaphylaxis is rare but frequently leads to death [19][20].

Most immediate hypersensitivity reactions have occurred after administrating the first dose. However, reactions after the second dose of the COVID-19 vaccine have also been reported [21]. Approximately 86% of anaphylaxis cases induced by COVID-19 vaccines occur within 30 min of inoculation. On the contrary, the onset of other symptoms, such as urticaria, often happens within 3–8 days of the first dose and 2–5 days after the second dose [21][22][23].

Many vaccine-induced hypersensitivity reactions could not be confirmed and have been attributed post factum to alternative diagnoses, such as vasovagal syncope, vocal cord dysfunction, exacerbation of existing chronic spontaneous

urticaria, and anxiety. Using an updated global standard for case definitions and guidelines for hypersensitivity reactions following vaccinations may help with clinical differential diagnosis and management [24][25].

3. Epidemiology of Immediate Hypersensitivity Induced by Vaccines

Vaccine-induced anaphylaxis cases are estimated to occur in approximately 1 case per 15 million to 2 cases per million individuals [14]. Micheletti F. et al. reported that the risk of anaphylaxis after vaccination in children and adults was estimated to be 1.31 (95% confidence interval [CI], 0.90~1.84) per million doses before the COVID-19 pandemic [26]. The authors identified 33 confirmed vaccine-triggered anaphylaxis cases in the study after 25,173,965 vaccine doses [26]. Among the patients with vaccine-induced immediate hypersensitivity reactions, approximately 66% had urticaria, and 10% had angioedema [27].

For COVID-19 vaccines, cutaneous reactions were reported by 1.9% of individuals after receiving the first dose of an mRNA COVID-19 vaccine. Approximately 2.3% of those who had no adverse events following the first dose developed hypersensitivity reactions after receiving the second dose [28]. Based on a U.S. study, cutaneous reactions induced by the mRNA COVID-19 vaccines were more common in women than in men (85% vs. 15%, $p < 0.001$) [28]. Furthermore, the estimated incidence rates for anaphylaxis in the U.S. were 11.1 cases per million doses administered with the BNT162b2 (Pfizer-BioNTech) vaccine and 2.5 cases per million doses administered with the mRNA-1273 (Moderna) vaccine [16][29][30][31]. The vaccine adverse event reporting system (VAERS) [32] showed that there were 1592 urticaria cases among 15703 (10.13%) cases with adverse reactions, 32 (4.92%) out of 650 adverse event cases of angioedema, and 66 (3.54%) out of 1867 adverse event cases of anaphylaxis from 2020 to January 2022 attributed to COVID-19 vaccines.

A recent meta-analysis study suggested that the estimated incidence of COVID-19-vaccine-induced anaphylaxis ranged from 2.5 to 7067 per one million individuals receiving mRNA COVID-19 vaccines, with an overall pooled prevalence estimate of 5.58 (95% CI, 3.04–8.12; $I^2 = 76.32\%$, $p < 0.01$) [21]. In contrast, the incidences of nonanaphylactic reactions to mRNA COVID-19 vaccines ranged from 10.6 to 472,973 per one million, with an overall pooled prevalence estimate of 89.53 (95% CI, 11.87–190.94; $I^2 = 97.08\%$, $p < 0.01$) [21]. Chu, DK. et al. performed a meta-analysis of 22 studies, including 1366 patients, and found a low incidence (0.16%) of immediate severe allergic reactions associated with the second dose of the mRNA COVID-19 vaccine among individuals who had an allergic history of their first dose [33]. In a separate study, the incidence rates of anaphylaxis were lower for the viral COVID-19 vaccine (odds ratio [OR], 0.47; 95% CI, 0.33–0.68) and the inactivated COVID-19 (OR, 0.31; 95% CI, 0.18–0.53) vaccine [34]. Different setups of studies may observe different incidence rates. **Table 1** lists the incidence rates of anaphylactic and nonanaphylactic hypersensitivity reactions to COVID-19 vaccines.

Table 1. Incidence rates of anaphylactic and nonanaphylactic hypersensitivity reactions to COVID-19 vaccines.

Type of Reaction	Number of Participants	Number of Anaphylactic Reactions	Type of Vaccine	Incidence of Reactions (per One Million)	Reference
anaphylactic					
	890,604	**15**	**mRNA-1273; BNT162b2**	**17**	**[35]**
	4,041,396	**10**	**mRNA-1273**	**37.1**	**[29]**
	1,893,360	**21**	**BNT162b2**	**11**	**[36]**
	1116	**1**	**BNT162b2; mRNA-1273**	**890**	**[37]**
	283	**5**	**mRNA-1273 and AZD1222**	**17,668**	**[38]**
nonanaphylactic					
	277	**14**	**BNT162b2**	**50,540**	**[39]**
	5589	**1391**	**AZD1222 (Astra Zeneca)**	**248,880**	**[39]**
	5574	**6**	**BNT162b2**	**1070**	**[40]**
	3170	**11**	**BNT162b2**	**3470**	*** [41]**
	1,893,360	**83**	**BNT162b2**	**43.8**	*** [36]**

Type of Reaction	Number of Participants	Number of Anaphylactic Reactions	Type of Vaccine	Incidence of Reactions (per One Million)	Reference
	877	10	BNT162b2	11,400	[42]
	1116	7	BNT162b2; mRNA-1273	6270	[37]
	74	35	BNT162b2	472,973	[23]

* Nonanaphylactic reactions were classified under skin rashes, including hives, pruritus, and eczematous papules.

The available information suggests that the incident rate of adverse events after the administration of the protein-based vaccine (Nuvaxovid/NVX-CoV2373 produced by Novavax, Gaithersburg, MD, USA) is lower than the mRNA vaccines [43][44][45]. Almost all the reported incidences of vaccine-induced adverse reactions come from passive reporting systems (such as VAERS), which may underestimate the true burden [46]. In addition, limited prospective studies have been performed, which could result in a much higher rate of acute allergic reactions, possibly due to a nocebo effect [47].

4. Causality of Vaccine-Induced Immediate Hypersensitivity Reactions

Vaccine excipients and active components could cause allergens to elicit hypersensitivity reactions. These antigen components, such as toxoids or constituents of pneumococcal vaccines, cause symptoms ranging from urticaria to anaphylaxis. Hypersensitivity reactions may be induced when patients receive the first or the second dose of a vaccine [48][49].

Vaccine excipients are known to be ingredients other than the active components of vaccines. These are inactive ingredients that stabilize or preserve the viability of the vaccines and maintain their bioavailability. Egg and ovalbumin (a residual component of egg processing) are considered the most frequent food allergies in children and the most suspected culprits for allergies induced by the administration of traditional vaccines [49][50][51][52]. Gelatin is another culprit excipient for vaccine-induced immediate hypersensitivity reactions [51][52][53].

Vaccine adjuvants are also possible allergens [54]. Aluminum hydroxide and aluminum phosphate are adjuvants that are more commonly found in vaccines but are not in the COVID-19 vaccine. Although rare, they are commonly associated with delayed-type hypersensitivity reactions. Aluminum can also induce immediate-type hypersensitivity by stimulating mast cells and other immune cells [49][55]. Another vaccine adjuvant, AS03, is a squalene derivative that is incorporated into influenza vaccines. Epidemiological studies in Canada have shown an approximately 20-fold increase in the incidence of immediate hypersensitivity using AS03-adjuvanted vaccines compared with non-AS03 vaccines. The immune mechanism underlying vaccine-adjuvant-induced immediate hypersensitivity reactions remains unclear [49][54][56][57].

5. Proposed Immune Mechanisms for Vaccine-Induced Immediate Hypersensitivity Reactions

According to cellular and molecular features defined by Gell and Coomb, there are four types of hypersensitivity reactions: I, II, III, and IV [58]. Type I hypersensitivity reactions involve IgE-mediated immune responses and occur rapidly after exposure to allergens. Type II hypersensitivity is mediated by IgG or IgM antibodies, and type III hypersensitivity involves the immune complexes. Type IV hypersensitivity is mediated by T lymphocytes, also known as delayed-type reactions.

Mast cells are considered the most critical immune cells responsible for immediate hypersensitivity reactions, as they secrete various inflammatory cytokines and induce various systemic immune responses [52]. There are four proposed mechanisms for immediate hypersensitivity reactions, including (1) immunoglobulin E (IgE)-mediated, (2) complement-receptor-mediated, (3) MRGPRX2 (Mas-related G-protein coupled receptor member X2)-mediated mast cell direct activation, and (4) an unknown mechanism (**Figure 1**).

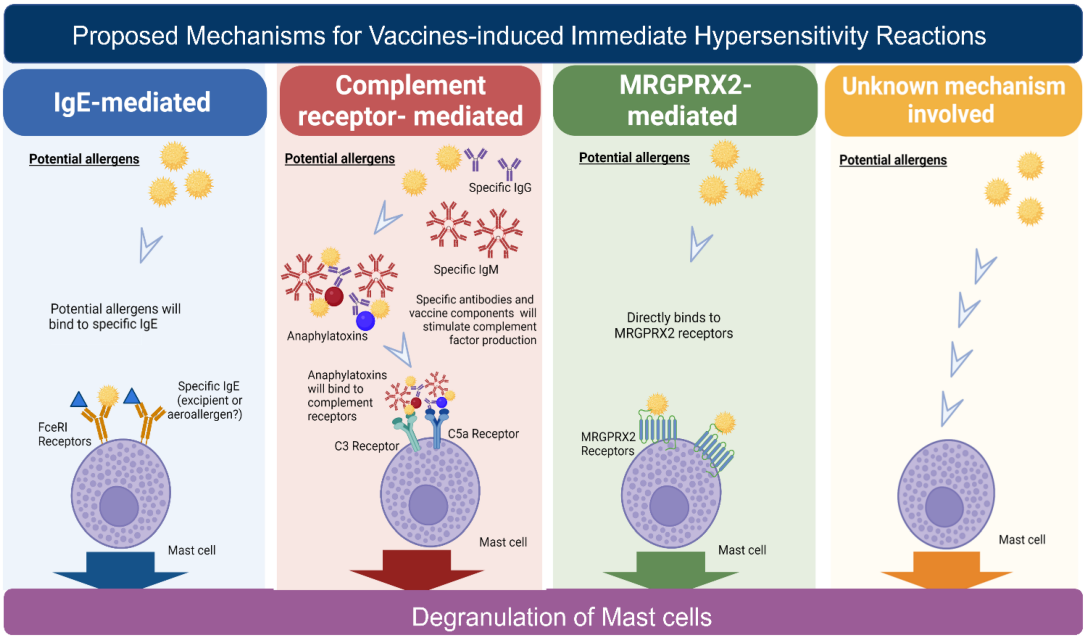

Figure 1. Proposed mechanismsfor immediate hypersensitivity reactions. There are four proposed mechanisms for immediate hypersensitivity: IgE-mediated, complement-receptor-mediated, Mas-related G protein-coupled receptor X2 (MRGPRX2)-mediated mast cell activation, and an unknown mechanism. Binding of allergens from the components of vaccines to antibodies or receptors may initiate the hypersensitivity reactions. The specific IgE antibodies recognize the active components or excipients of the vaccines. IgE antibodies are then coupled with receptor-FcεRI on the mast cells, resulting in mast cell degranulation. These specific IgE antibodies may be brought by previous exposure to allergens in cosmetics, drugs, aeroallergens, or food. Vaccine components may activate the complement-receptor-mediated pathway and induce anaphylatoxins that could be recognized by complement receptors on the mast cells. In addition, binding of the vaccine components and excipients to MRGPRX2 receptor may directly activate mast cells. Furthermore, immediate hypersensitivity reactions may be induced by an unknown mechanism. These proposed mechanisms could lead to mast cell degranulation and the release of effector mediators. Abbreviation: MRGPRX2, Mas-related G protein-coupled receptor X2; IgE, immunoglobulin E; PEG, polyethylene glycol.

The IgE-dependent pathway is the most common and well-known mechanism [52]. In IgE-mediated hypersensitivity reactions, a foreign allergen(s) is proposed to be recognized by IgE, which binds to its receptor Fc epsilon RI (FcεRI) on mast cells, thereby activating the mast cells and releasing highly active immune mediators [59] (**Figure 1**). The reactions often occur within minutes of the crosslinking of IgE to FcεRI receptors. Subsequently, the mediators secreted by mast cells can induce a late-phase reaction, usually 2–6 h after initiation, with a peak in activity after 6–9 h [60].

The second proposed mechanism, “the complement-receptor-mediated hypersensitivity,” can be initiated by the binding of allergens in vaccines and IgG or IgM and then activate the complement system to produce anaphylatoxins (e.g., C3a, C4a, and C5a) (**Figure 1**). These complement peptides can bind to complement receptors on mast cells, and then mast cell degranulation results in the release of immune mediators. In contrast to the IgE-dependent pathway, this proposed mechanism of hypersensitivity reaction does not involve IgE antibodies against allergens [61][62].

Third, several studies have suggested that the binding of allergens to MRGPRX2 (the mastocyte-related G-protein coupled receptor X2) protein, a class of G-protein-coupled receptors expressed on mast cells, may directly trigger mast cell activation and participate in non-IgE-mediated reactions [63] (**Figure 1**). It has been found that many molecules, such as antimicrobial host defense peptides, neuropeptides, and cationic amphiphilic drugs, could be the allergens for the induction [64].

However, no convincing evidence has demonstrated that MRGPRX2 or complements are involved in COVID-19-vaccine-induced immediate hypersensitivity reactions. An unknown mechanism may be involved in immediate hypersensitivity reactions induced by COVID-19 vaccines, which could trigger mast cell degranulation or other immune cell activations (**Figure 1**).

Many of the immediate hypersensitivity reactions are considered IgE-mediated, supported by skin prick tests and specific IgE levels [65]. Several excipients have been suggested to trigger the production of specific IgE antibodies and cause mast cell activation [65]. Patients with specific IgE antibodies against vaccine antigens may have higher risks of hypersensitivity reactions [66]. Several studies have attributed the development of hypersensitivity to increased specific IgE levels towards

vaccine antigens. However, increased IgE levels may be a false-positive result in atopic individuals [48][67][68]. It is proposed that both IgE-mediated and non-IgE mediated pathways are involved in vaccine-induced immediate hypersensitivity reactions. Further studies are needed to investigate the mechanisms of COVID-19-vaccine-induced immediate hypersensitivity reactions.

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