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REVIEWS

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Prophylactic vaccinations management in patients undergoing allergen immunotherapy – a review

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Summary Allergen immunotherapy (AIT) is the only casual method of allergy treatment. It is based on regular administration of a gradually increasing dose of an allergen to induce immunological tolerance to a particular sensitising factor. Due to proven efficacy, including preventive effect as well as favourable safety profile, it should be widely applicable, particularly among older children and adolescents. While the number of patients suffering from non-communicable diseases, including allergies, is rising, there is a false impression that the impact of infectious diseases can be disregarded. Thanks to prophylactic vaccines, many infectious diseases that used to be a threat to people's lives have been forgotten. In order to tackle familiar and emerging infectious diseases (such as COVID-19), there is a need to keep in mind vaccinations in all age groups. As allergen immunotherapy and prophylactic vaccines affect the immunologic system, performing both interventions in one patient may raise concerns about safety and effectiveness. However, a large-scale study on this topic has not been performed to date. This article summarises immunological responses occurring after contact with pathogens and allergens as well as describes reactions triggered by prophylactic vaccines and AIT. What is more, possible interference of receiving both a prophylactic vaccine and AIT is discussed.
Key words: hypersensitivity, immunologic desensitization, communicable diseases, vaccines.

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Background

The number of patients suffering from allergic diseases is increasing. According to the World Allergy Organisation, 10–40% of the global population is affected by these ailments, while in most developed countries the prevalence is higher than 20% [1]. However, these estimations were made almost 10 years ago, therefore current figures may be even higher, as some patients are probably not properly diagnosed. The European Academy of Allergy and Clinical Immunology (EAACI) predicts that by the year 2025, half of the entire population of European Union will be suffering from allergy diseases [2]. Like every chronic disorder, allergy diseases are connected with lower quality of life of patients [3–5] and significant costs for national healthcare systems [2]. The casual method of treatment of some of allergy diseases is allergen immunotherapy (AIT). It is based on regular administration of increasing doses of an allergen responsible for triggering symptoms to induce immunological tolerance [6]. This form of treatment is characterised by high efficacy and safety profile proven in randomised clinical trials and real-life studies. The unique feature of AIT is its long-term efficacy, which continues after cessation of treatment as well as its preventive effect – a suppression of allergy progression. That is why AIT represents a perfect form of treatment particularly for children and adolescents. Allergen immunotherapy has been known for more than 100 years, but recent decades have contributed to a dynamic development of knowledge regarding its mechanisms of action, the modes of application of allergen vaccines, and the efficacy of allergen immunotherapy in children depending on the particular allergen types.

Because non-communicable diseases are prevalent in high income countries, there is a false impression that the impact of infectious diseases can be disregarded. However, ongoing COVID-19 pandemics has proved that infectious diseases can be still associated with high prevalence and mortality [7] and generate considerable costs for national economies [8], even in developed countries. The most efficient way of preventing infectious diseases is administration of prophylactic vaccines. Their mechanism of action involves inducing immune response similar to natural immunity achieved during infection. As a result, protection against a specific pathogen is generated [9].

Given the fact that both AIT and prophylactic vaccines influence a host's immune system, a problem of vaccinating patients undergoing allergen immunotherapy emerges.

Objectives

The aim of this article is to summarise immunological responses occurring after contact with pathogens and allergens and to describe reactions triggered by prophylactic vaccines and AIT. We will consider if these two procedures, receiving both a prophylactic vaccine and AIT by the same patient, can influence each other.

Host's immunological response to allergens and pathogens

Pathogens

Pathogens are agents capable of causing a disease. Proper elimination of pathogens is the sum of actions of both innate

and adaptive immune systems, which rely on properly distinguishing pathogens and microbially infected host cells from healthy host cells. The innate immune system, which represents the first line of defence against microbes consisting of natural barriers (skin, mucous membranes), innate immune cells (phagocytic cells, mast cells, natural killer cells, basophils, eosinophils) and bioactive molecules (cytokines, chemokines and other mediators of inflammation). Its main functions are to prevent the entry of pathogens, recognise pathogens and damaged host cells, remove pathogens through phagocytosis and cytotoxic mechanisms, and to activate the adaptive immune system. The adaptive immune system is highly specific to a particular pathogen thanks to antigen-specific receptors expressed on the surfaces of T- and B-lymphocytes [10]. A leading function of T lymphocytes is to select and destroy infected cells. To identify appropriate cells, the family of MHC (major histocompatibility complex) molecules are used. These surface glycoproteins bind and display peptides produced inside the cell (class I MHC) or peptides absorbed through endo- or phagocytosis and processed in the cell (class II MHC). Antigens presented by MHC molecules are recognised by T-cell receptor (TCR), found on the surface of T lymphocytes. Peptides presented by MHC class I are recognised by $CD8^+$ T cells, which have a cytolytic function and whose main role is to kill cells infected with intracellular microbes. MHC class II are mainly expressed on professional antigen-presenting cells – B cells, dendritic cells and macrophages, which present antigens to $CD4^+$ T cells. $CD4^+$ T cells, known as 'helper cells', regulate the cellular and humoral immune responses. After stimulation, T helper cells (Th cells) differentiate into Th1, Th2, and Th17 depending on the type of cytokines present at the activation site. Th1 cells, producing IFN-γ and IL-2, are engaged in providing cell-mediated response (primarily by macrophages and cytotoxic T cells). Th2 cells produce IL-4, IL-5, IL-9, IL-13 and lead to humoral and allergic response. Th17 cells produce cytokine IL-17, which by targeting many immune cells induces production of G-CSF and IL-8, resulting in neutrophil proliferation and recruitment. There is also a subpopulation of T cells, known as T regulatory cells, which down-regulate or suppress immune responses. B cells, capable of producing antibodies, cooperate with T cells in immune reactions. As mentioned before, B lymphocytes can act as antigen-presenting cells. The internalisation, preparation and presentation of an antigen by B cells leads to T cell activation. In return, thanks to the assistance of co-stimulatory proteins, T cells interact by inducing antibodies isotype switching and activating antibodies' somatic mutations. These processes are crucial for B cell memory – prompt production of large amounts of specific antibodies after other contact with an antigen provides adequate host protection. B cells can also respond independently from T cells. This type of reaction is possible during exposure to polymeric antigens (bacterial lipopolysaccharide and certain other polymeric polysaccharides and proteins). In most cases, the absence of T-cell co-stimulatory proteins results in lack of antibodies' somatic mutation, thus immune memory to these reactions is rather weak [11–13]. A proper functioning of the host's immunity relies on the mutual effort of adaptive and innate immune systems.

One of the important parts of the innate immune system are toll-like receptors (TLR), which are found mainly on first-line defence cells such as macrophages and dendritic cells. Their role is to recognise molecules shared by many pathogens, called pathogen-associated molecular patterns (PAMP). When activated, TLR propagate expression of inflammatory mediators and trigger processes of autophagy, cell death and phagocytosis. The major role in phagocytosis can be attributed to neutrophils, macrophages, and monocytes. With the use of different receptors (including Fc and complement receptors) they ingest pathogens and destroy them thanks to different proteases and reactive oxygen species [11, 14–16]. Another very important group of cells involved in innate immunity are NK cells, which can be referred as analogues of cytotoxic T cells in adaptive immune system. Their activity depends on the balance of inhibitory and activating receptor stimulation. Natural killer cells act via cytotoxicity and destroy virus-infected cells and other intracellular pathogens. What is more, they have the ability to recognise and kill infected cells without the presence of antibodies or MHC molecules. It is a significant function, as some viruses have the ability to down-regulate class I MHC expression in infected cells as a strategy to avoid being detected and destroyed by $CD8^+$ cells [11, 17, 18]. Another part of the innate immune system that cooperates with the adaptive immune system is the complement. It consists of small proteins which are present in the host's organism as inactive precursors. If stimulated by different triggers, the activation cascade, as the classical pathway, the alternative pathway, or the lectin pathway begins. The main goal of complement activation is destroying pathogens and infected cells by phagocytosis and rupturing the pathogen's cell walls as well as promoting inflammation by attracting macrophages and neutrophils [11]. Although the innate and adaptive immune system differ in mechanisms of action, they act synergistically and are both relevant to proper effective immune response [10].

Allergens

An allergen is an antigen that triggers hypersensitivity reactions in predisposed individuals. The most common allergens include food, pollen, mould, insect venom and pets. A dysregulated immune response to these antigens is characterised by excessive inflammatory reactions based on Th2 cells and allergen-specific IgE. Patients with genetic predisposition to allergies react to the first exposure to a specific allergen by inducing differentiation of naive T cells and Th2 cells. Th2 cells produce interleukins 4, 5 and 13 (IL-4, IL-5, IL-13). IL-4 and IL-13 affect B cells by stimulating them to produce allergen-specific IgE. IL-5 activates eosinophils. Repeated contact with the allergen leads to increased production of specific IgE which bind to FcεRI receptors present on effector cells: basophils and mast cells [19, 20]. These activated cells respond by releasing inflammatory mediators responsible for hypersensitivity reactions. Allergy symptoms can relate to one organ (as in rhinitis or asthma) or have a multi-organ character, as in food allergy or the most severe form of hypersensitivity, anaphylaxis [6].

Mechanisms of action of prophylactic vaccines and allergen immunotherapy

Prophylactic vaccines

Many anti-infectious vaccines were invented before the fundamental discoveries in the field of immunology were made. Nowadays, owing to the developments in both molecular biology and immunology, we are able to describe in more detail the mechanisms how immune reactions are induced post-vaccination. Such knowledge allows the creation of vaccines that are more efficient in preventing infectious diseases, particularly in those who are the most vulnerable – infants and elderly [21].

The main goal of administrating vaccines is to activate both humoral and cellular immune response, which results in the production of antigen-specific memory cells. These memory cells induce a quick response of B and T cells in case an individual is exposed again to the specific pathogen [21]. Although successful vaccine-induced protection against many diseases relies on antibodies, different T cells also play an important role. They regulate affinity-matured antibody responses, enable favourable CD8+ response and control viral infection if protective antibodies are insufficient [22].

Different vaccines, depending on their type, composition and routes of administration, trigger specific immune reactions. Traditionally, licensed vaccines are divided into live and inac-

tivated. Live vaccines contain attenuated viruses or bacteria. There is still little known about the exact immunological mechanisms these vaccines induce, however, it is believed that by activating different PPRs, including TLRs, they stimulate Th1 and Th2 response with the production of neutralising antibodies.

Inactivated vaccines consist of killed viruses/bacteria or their parts (proteins, polysaccharides). Due to lower immunogenicity of these types of vaccines, they require adjuvants to enhance immune response induced by inactivated antigens included in the vaccine. The use of adjuvants enables to decrease the quantity of applied antigen in a single vaccine and to avoid multiple vaccine injections. The most widely used type of adjuvant is alum. It triggers Th2 response as well as antibody production independently of TLR signalling [21].

Recently, during the ongoing COVID-19 pandemic, new vaccines have come into use. They are based on novel technologies – including mRNA or viral vectors. They do not contain viruses or their antigens, but genetic information (mRNA vaccines) or unable to replicate the adenoviral vector with integrated genetic material of SARS-CoV-2 (vector vaccines), thanks to which viral antigens would be produced in host cells to induce immune response [22, 23]. Adenoviral vectors are not only a platform delivering genetic material of the virus, but they also act as an adjuvant by stimulating signalling pathways, inducing secretion of proinflammatory cytokines and chemokines [23, 24].

In general, the aim of prophylactic vaccines is to stimulate the immune system. The proper response leads to generating immune memory, which is supposed to defend the organism during the invasion of pathogens [9, 25, 26].

Allergen immunotherapy

Generating immune tolerance due to allergen immunotherapy is a complex process that requires involvement of both innate and adaptive immunity.

The influence of AIT on innate immunity manifests mainly in inhibiting activation and degranulation of basophils and mast cells, as well as in modulating the action of dendritic cells and decreasing the level of innate lymphoid cells type 2 [6, 27]. The latter, owing to the production of IL-5 and IL-13, are elements of the allergic inflammation [27].

Changes in adaptive immunity during AIT primarily involve the induction of regulatory T and B cells, reversing the Th2 dominance and decreasing the level of Th2 lymphocytes [28].

Regulatory T cells, producing immunosuppressive cytokines IL-10 and TGF-β, are considered crucial for suppressing allergic inflammation. They can be divided into two major subsets – 'natural' Treg cells (nTreg) and 'induced' Treg cells (iTreg) [28]. Treg cells act in a multi-directional way. Their main functions are connected with the ability to release IL-10, which stimulates immunoglobulin class switching to IgG4 as well as reduces production and functioning of Th2 lymphocytes and inflammatory dendritic cells. What is more, Treg cells can block the activity of mast cells, basophils and eosinophils [19, 20, 29, 30]. A decrease in the level and activity of Th2 cells during AIT results in the deviation from Th2 to Th1 immune response.

Another example of modulatory effect of AIT is suppressing T follicular helper cells (Tfh), which induce proliferation and maturation of B cells in germinal centres of secondary lymphoid organs. Together with the circulatory counterpart of Tfh present in peripheral blood, germinal Tfh secrete IL-4, a cytokine involved in IgE production [28].

Regulatory B cells exhibit immunomodulatory effect by releasing IL-10, IL-35 and TGF-β. Their role in generating and maintaining immune tolerance relies on suppressing Th2 immune response, inducing Treg lymphocytes and suppressing the maturation of dendritic cells. Moreover, Breg cells can produce specific IgG4, antibodies with blocking activity, which compete with IgE for the allergen [27, 28].

As shown above, AIT influences both cellular and humoral response. In the initial phase of AIT, an increase in the level of IgE can be observed, which declines in the course of therapy. Simultaneously, allergen-specific IgG, mainly IgG4, are produced. These antibodies have allergen-neutralising capacity and block the formation of allergen-IgE complexes. In this situation the allergen is not able to bind to FcεRI receptors localised on mast cells and basophils, hence the degranulation of effector cells is inhibited, and to low-affinity FcεRII receptors on B cells, which prevents IgE-facilitated antigen presentation to T cells [28]. The aim of all of these changes is to control the allergic inflammation and to induce tolerance to a specific allergen.

Allergen immunotherapy is recommended by EAACI and AAAAI (American Academy of Allergy, Asthma and Immunology) experts for use in patients with inhaled allergies and Hymenoptera venom allergy with anaphylaxis. For patients with inhaled allergies, subcutaneous (SCIT) and sublingual (SLIT) allergen extracts can be offered. Importantly, sublingual allergen extracts can be administered by patients at home. Allergen vaccines used in Hymenoptera venom allergy can be applied only subcutaneously [27, 31–34]. We expect that recommendations regarding oral allergen immunotherapy (OIT) in food allergies (cow's milk and peanut allergy) will be developed in the near future.

Local (swelling, pruritus at the injection site) and systemic (angioedema, dyspnoea due to bronchospasm, cardiovascular symptoms) adverse reactions can occur in course of AIT. However, the latter are rare [6].

Prophylactic vaccines administration in patients undergoing allergen immunotherapy

As both anti-infectious vaccines and allergen immunotherapy influence the immune system, combining these two procedures in patients may raise concerns regarding safety and effectiveness.

This problem relates to older children, teenagers and adults, as AIT is offered mainly to patients starting from 5 years of age [30]. This is why it might seem that combining prophylactic vaccinations and AIT should not cause any problems, as the majority of anti-infectious vaccines are administered in the youngest children. However, according to vaccination schedules of many countries, there are vaccines recommended for adults, for instance annual influenza vaccine, tetanus booster doses every 10 years or vaccinations recommended due to older age (pneumococcal vaccine), particular residence (tick-borne encephalitis vaccine), practised profession (measles, mumps, rubella vaccine; varicella vaccine, meningococcal vaccine) and vaccines related to travel medicine [35–38]. A possibility of administration of prophylactic vaccines and AIT during one appointment with a doctor would simplify performing vaccinations in allergic patients, reduce the waiting time for medical visits, and as a result of applied prophylaxis it would decrease the costs connected with treatment of infectious diseases and their complications. Current guidelines recommend keeping a one week interval between subcutaneous allergen vaccines and anti-infectious vaccines [31]. On the other hand, there are single studies showing that shorter intervals may also be safe [39, 40].

The first of the mentioned studies retrospectively analysed data regarding 875 patients from one German otolaryngological medical practice. Among this group, 444 individuals received vaccine against infectious disease, 336 allergic patients received a subcutaneous allergen extract and 95 individuals received prophylactic vaccination and subcutaneous immunotherapy in a time shorter than that recommended in the guidelines. All patients were in the maintenance phase of SCIT and the majority of them were undergoing subcutaneous immunotherapy due to early-blooming trees and grasses or mite allergy. Most patients received an influenza vaccine. No systemic allergic reactions were observed among patients who received both allergen immunotherapy and prophylactic vaccine [39]. In a prospective

study conducted among patients treated in Clinical Department of Internal Medicine, Pneumology and Allergology in Wroclaw, the safety of administering influenza vaccine after 30 minutes of subcutaneous allergen extract injection was evaluated. 44 patients (14 individuals were vaccinated during two consecutive influenza seasons) who were in the maintenance phase of AIT because of Hymenoptera venom allergy took part in the study. None of the patients reported allergic adverse reactions. Moreover, there were no differences in frequency and type of side effects typical for influenza vaccine in comparison with the control group (57 patients vaccinated only against influenza) [40].

An opinion on the lack of negative interference between vaccinations and AIT is declared by 95% of AIT experts who took part in an international survey. The majority of physicians did not observe any alarming AIT (98%) or prophylactic vaccines (87%) adverse effects while combining these two procedures, and the only reported unfavourable reactions were local and mild [41].

What is more, there is data suggesting that booster prophylactic vaccines during AIT are effective in providing optimal specific antibodies response against pathogens [42]. Such conclusions result from a clinical study conducted in Austria. Patients were divided into three groups: allergic patients receiving symptomatic treatment (49 individuals), allergic patients undergoing the maintenance phase of allergen immunotherapy (21 individuals) and healthy volunteers (21 individuals). All patients received a booster dose of tick-borne encephalitis vaccine. Humoral and cellular response of all patients was evaluated after a week, a month, and six months. The level and kinetics of neutralising antibodies specific for tick-borne encephalitis did not differ significantly in all groups. What is more, in AIT patients an increase in Treg cells and lack of TBE-specific IL-5 was demonstrated, which probably reflects the immunomodulatory effect of this form of allergy treatment [42].

The limited experience regarding safety and effectiveness of prophylactic vaccinations in patients undergoing allergen immunotherapy proved significant in the context of the COVID-19 pandemic. Mass vaccination implementation due to the possibility of generating herd immunity gave hope of stopping the pandemic. Although we lack global data, it appears that the initial interest of COVID-19 vaccines among Polish AIT patients was similar to COVID-19 vaccine uptake in the whole Polish population after a year of availability of these vaccines in Poland [43]. The mechanism of action of allergen immunotherapy and COVID-19 vaccines, as well as assessment of potential immunological interaction of both procedures is described in recent EAACI recommendations regarding COVID-19 vaccinations in patients receiving AIT or biologicals. This position paper indicates that COVID-19 vaccinations induce T1 polarisation, what may have additive effect to AIT. On the other hand, induction of Treg cells because of AIT may increase the risk of early inflammatory adverse reactions if these two interventions are separated by a short time interval [44]. Recommendations of Polish Society of Allergology published in 2021 enable administration of COVID-19 vaccines in patients undergoing allergen immunotherapy with a two-week interval [45]. EAACI recommends administering COVID-19 vaccines at the interval of 7 days from the subcutaneous allergen immunotherapy. Sublingual daily dose of allergen extract should be stopped 3 days before and restarted 7 days after the administration of COVID-19 vaccine. These time intervals should guarantee a possibility to distinguish adverse reactions of AIT and COVID-19 vaccine [44].

Summarising, limited clinical experience regarding combining prophylactic vaccinations and AIT is consistent with current knowledge concerning immunology. Immune responses triggered by prophylactic vaccines and AIT do not seem to interfere negatively, as both procedures interact by different immunologic mechanisms. Conservative recommendations of maintaining time intervals between these two interventions result from technical issues of monitoring adverse reactions of vaccines and allergen extracts rather than the possibility of negative interactions.

Conclusions

There is not enough clinical data evaluating the impact of combining prophylactic vaccines and allergen immunotherapy in one patient. However, this procedure appears to be safe and effective, as from the immunological point of view, the responses to pathogens and allergens involve distinct immune cells and result in different outcomes.

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