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Chapter

Current Developments in Allergen-Specific Immunotherapy: A Brief Review

Mariana Giarola Benedito Bartholazzi, Tatiana de Morais Lodi and Olga Lima Tavares Machado

Abstract

Immunotherapy is a treatment for patients with type I-mediated allergic diseases. Molecular forms of allergen-specific immunotherapy (AIT), based on inducing immunological tolerance characterized by increased IL-10, TGF-β, and IgG4 levels, and Treg cell are continuously emerging to improve the efficacy of the treatment, shorten the duration of protocols, and prevent any side effects. This review covers the recent progress in AIT and routes of antigen administration. Classical immunotherapy uses allergen extracts obtained from natural sources. Limitations of the uses of these extracts, such as sensitizations with nonspecific agents, can be avoided using purified components, hypoallergenic recombinant proteins, and vaccines based on peptides (epitopes). However, these molecules have low immunogenicity requiring new carriers or more effective adjuvants. Vaccines based on carrier-bound B-cell epitope-containing peptides and the constructions of allergens coupled to virus-like particles (VLPs) are under evaluation. The possibility of vaccinating with DNA encoding the allergen to obtain an allergen-specific Th1 and IgG response is in development and the success of messenger ribonucleic acid (mRNA) vaccines against severe acute respiratory syndrome Coronavirus 2 must encourage as well the re-exploration of mRNA vaccine platform for innovative AIT.

Keywords: allergen-specific immunotherapy, vaccine, allergen, routes of administration, safety of immunotherapies

1. Introduction

Epigenetic factors and changes in the population's lifestyle are some of the factors that have contributed to the increase in IgE-mediated allergies worldwide. Data from the World Health Organization reveal that about 30% of the world population suffers from allergies in all age groups. Due to this increase and the effect that allergic diseases have on people's quality of life, a treatment, or even a cure, has been a priority among researchers, doctors, and society [1, 2]. Allergic reaction episodes are usually controlled with medication; however, the only treatment that acts on the

immunological cause of the disease is allergen-specific immunotherapy (AIT) [2]. AIT is used to treat various forms of allergic diseases involving type I hypersensitivity, as it can modify TH2-driven immune responses by reducing symptoms after exposure to the allergen [3, 4].

Upon receiving a dose of immunotherapy containing the allergen, a shift from the allergenic TH2 inflammatory profile to the TH1 inflammatory profile and the generation of regulatory immune cells occurs. Decreased levels of mast cells, basophils, and eosinophils are seen in the mucosa and an increase in the production of allergen-specific regulatory T and B cells (Treg/Breg) occurs [5].

The generation of regulatory T cells (Treg) is the key event for the development of immune tolerance. Immune tolerance occurs in a peripheral and specific way, where the first is initiated by the secretion of IL-10 and TGF-β by allergen-specific Treg cells during continuous exposure and the second is associated with the increase in cells that present CD3+, CD25+ markers, and FOXP3+ in the nasal mucosa [6].

Essential features of AIT suggest that it has many advantages for the treatment of allergy because it works on a specific type of allergen and thus leads the individual's immune system to establish an immune response against the one who caused the disease [7, 8]. Furthermore, allergy vaccines can be produced relatively quickly and inexpensively compared to treatments with biological agents. Another advantage is that, unlike treatments with an anti-inflammatory profile, AIT can stop the progression of both mild allergy (rhinitis) and more severe forms such as asthma, modifying the natural course of the disease [9–11]. However, some aspects need to be considered for the success of immunotherapy. The first is that AIT is in the group of precision medicine treatments, where the allergens causing the disease need to be identified so that the correct vaccine is administered. The second aspect is the need to produce effective and safe vaccines against different allergens to be co-administered, thus causing polysensitization. Furthermore, thirdly, the administration of AIT can cause side effects in patients [12, 13].

Molecular allergy diagnostics (MA) is currently the most helpful patient selection method for prescribing allergen-specific immunotherapy (AIT). Component-resolved diagnosis (CRD) was established in 1980 as a new concept in allergy diagnosis. The CRD identifies a specific IgE toward natural or recombinant allergens rather than raw allergen extracts to determine a patient's sensitization at the molecular level [14]. More than 130 allergen molecules are commercialized. For more precise identification of the allergen, assays such as singleplex-ImmunoCAP, ImmuLite, and HyTech or many allergens per sample depot in microarrays (multiplex platform-ImmunoCAP ISAC-ThermoFisher Scientific/Phadia) can be employed [15, 16]. On the other hand, allergy Immunoproteomics can be an excellent ally for identifying unknown allergens. Proteomics has become critical to identify and structurally characterize allergens, including in vitro diagnostics, allergen discovery, and the analysis of biologicals proposed for AIT [11, 17].

Concerns about patient safety and treatment efficacy are the main reasons for the search for new approaches to AIT, so we have brought together several strategies that have been proposed to improve the effectiveness and safety of immunotherapies.

1.1 Technologies in the development of AIT—Molecular Approaches to AIT

The first to work with allergen-specific immunotherapy (AIT) was Noon [18], injecting grass pollen extracts into allergic patients. In this study, Noon was able to

observe a reduction in symptoms and greater allergen tolerance for almost 1 year. Later, in 1935, Cooke and his team [19], after successful clinical trials, demonstrated that AIT induces allergen protection through specific IgG antibodies that can suppress allergen-induced skin inflammation.

Allergen-specific immunotherapies (AIT) use allergen extracts obtained from natural sources. Characteristically, the active products in AIT are a combination of allergens with other proteins extracted from biological sources (egg, pollen, and mites), used without alteration or treated with aldehydes, and then formulated with or without an adjuvant [5]. The new proposals to produce AIT rely on recombinant, synthetic proteins, or DNA, instead of using natural extracts of allergens in their formulation. After identifying the genomic sequence of interest or the allergen itself, these are extensively tested through in vitro assays and animal models to obtain information about their allergenicity and immunogenicity [20].

The molecular era of AIT employs native recombinants, hypoallergenic recombinants, peptides containing short, and nonreactive IgE T-cell epitopes, followed by hypoallergenic recombinant peptides, as AITs needed to improve immediately in two aspects: specificity and safety [21].

A summary of each of the molecular approaches currently used for AIT will be presented below.

1.1.1 Native recombinants

The use of native recombinants offers advantages over natural allergen extracts as they are well defined and contain relevant epitopes. Although, native recombinants cause immediate and late-phase side effects like natural allergens because of preserved IgE reactivity and T-cell epitopes. Thus, the preparation of AIT with these recombinants requires the maintenance of dosing schedules and multiple maintenance injections. However, the high quality of the vaccine (low cost and reproducibility) is the main advantage over natural extracts [22].

After producing the first recombinant allergens, it was demonstrated through in vitro experiments that the characteristics and the high proportion of epitopes resembled the allergen extracts [23]. Two other critical AIT studies also demonstrate this: in the survey by Jutel et al. [24], a mixture of 5 recombinant grass pollen demonstrated that a recombinant allergen vaccine can be an effective and safe treatment to improve the symptoms of allergic rhinitis. Clinical benefit is associated with modification of the specific immune response with IgG4 production and reduction of IgE antibodies consistent with the induction of IL-10-producing regulatory T cells. And the study by Pauli et al. [25] showed the efficacy of an AIT with native recombinants for the treatment of birch allergic rhinoconjunctivitis, concluding that the vaccine was safe and effective in the treatment of birch pollen allergy and induced a highly specific immune response.

1.1.2 Hypoallergenic recombinants

Recombinant hypoallergenic derivatives are characterized by having a reduced reactivity to IgE. Several techniques have been developed to reduce IgE reactivity, including fragmentation, oligomerization, mutation, and sequence reassembly [26]. Hypoallergens do not cause immediate side effects. However, after immunization, they induce specific IgG antibodies. Allergen-specific T-cell epitopes remain preserved in these molecules and may lead to late-phase T-cell mediated side effects [21].

In this sense, a clinical study with patients not allergic to birch pollen was carried out for 2 years. Three injections were administered subcutaneously with a monthly interval of a vaccine containing hypoallergenic recombinants obtained from the mentioned allergen. Vaccine administration also took place before the period of the first birch pollen season, with a booster dose later given before the next birch pollen season, thus allowing better monitoring of vaccination in the face of seasonal exposure to the allergen. It was observed that most patients immunized with the hypoallergenic recombinant vaccine induced levels of IgG antibodies against the allergen Bet v 1, which suggests that these antibodies act by blocking the IgE interaction with the allergen Bet v 1 [27].

Another model of recombinant hypoallergens is peptides containing transporter-linked B cell epitopes, where the presence of allergen-specific T cell epitopes is reduced to decrease allergen activity further, thus increasing safety. The use of carrier molecules on these peptides facilitates their production and increases their immunogenicity and ability to induce blocking IgG antibody responses [21, 28].

1.1.3 Carrier-bound B-cell epitope-containing peptides

A complement to hypoallergenic recombinants is the construction of peptides containing B cell epitopes linked to a transporter [28]. Vaccines containing B cell epitopes are composed of small peptides that cannot react with IgE, being obtained from allergens, specifically from the sites where the interaction with this antibody occurs. With the transporter, they offer patients a good IgG response that works by blocking the binding of the allergen to IgE [8].

These vaccines are produced from the fusion of recombinant proteins by expression in a bacterial system, using *Escherichia coli*, where the fused proteins are delivered in large quantities and quality [29]. Another essential characteristic of vaccines obtained from B cell epitopes is the reduction of their allergenic potential, since small fragments are used, which allows for the administration of higher doses, as well as their immunogenic potential, which makes it possible to administration of approximately three doses throughout the year, thus contributing to patient adherence to the treatment of allergic diseases [8].

BM32 is a B-cell epitope-based vaccine built to treat grass pollen allergy that has already been evaluated in several clinical trials and is the most advanced vaccine [30].

An important allergen from peanuts is Ara h 2. A fusion protein of the S-layer protein, SIpB from *Lactobacillus buchneri* CD034, and the Ara h 2-derived peptide AH3a42 was produced. This peptide comprised immunodominant B-cell epitopes as well as one T-cell epitope [31].

A study was carried out with Der p 1, a potent mite allergen responsible for causing respiratory allergies, for obtaining a fusion protein of a tetanus toxoid molecule with two copies of a peptide with hypoallergenic characteristics, previously identified through bioinformatics tools. After getting the protein DpTTDp, mice were immunized to assess the allergenic potential and production of IgG antibodies. It was observed in this study that the protein DpTTDp induced relevant levels of IgG antibodies, which act by inhibiting the interaction with IgE of patients allergic to mites, making it a candidate for a vaccine based on B cell epitope for the treatment of allergies to mites [32].

Another similar study was carried out with Salsola kali pollen, an allergen that triggers allergic rhinitis in dry and desert areas worldwide. A hypoallergenic vaccine based on B-cell epitopes was designed and called Sal k 1-KLH, composed of a peptide

derived from the allergen Sal k 1 conjugated to the keyhole limpet hemocyanin transporter molecule. This study showed that the vaccine produced high IgG levels in immunized mice that block IgE interaction but did not show a T cell lymphocyte response compared to the extract and the recombinant [33].

1.1.4 Peptides containing T cell epitopes

Peptide-based immunotherapy (PIP) has been considered a safe strategy for epitope-based vaccines. Peptides must contain T cell epitopes. Peptides cannot bind IgE but bind to major histocompatibility complexes. Successful trials involve Japanese cedar pollen, grass pollens, ragweed, cat allergen Fel d 1 [34], honeybee venom, and house dust mite [35]. The role of innate immune cells in allergen immunotherapy that confers immune tolerance to the sensitizing allergen is unclear. The efficacy of immunotherapy is underscored by the induction of tolerance (T helper cell type 2 anergy Treg cell upregulation of immune deviation) and modification of innate and adaptive immune responses. It is speculated that they can induce. [36].

Through epitope mapping studies, it is possible to identify which protein sequence is related to the induction of immunological tolerance and which does not participate in the inflammatory process triggered by the allergen. This is because peptides based on allergen epitopes have essential characteristics used in the clinical field to bind to a variety of class II HLA molecules [37].

An in silico study was carried out with the aeroallergen Zea M 1, a corn pollen allergen responsible for causing allergic reactions. The study aimed to evaluate the epitopes that had the potential to compose a vaccine based on the combination of B and T cell epitopes. After identifying B and T cell epitopes through prediction analyses, it was observed that the T cell epitope (AEWKPMPSW) presented an ideal and stable fit to the binding groove of the MHC I complex from B cells. The epitope KVPPPGPNITTNY remained conserved among homologous allergens and showed more significant potential for the vaccine [38]. The vaccine strategy based on T-cell epitopes is also being investigated for food allergies. First, the peptides were synthesized, and the T cell epitopes were mapped through assays of the proliferation of T cell responses in allergen-sensitized mice. Subsequently, the animals were treated with synthetic peptides and evaluated for antibody and cytokine levels. It was found in animals a reduction in symptoms and levels of cytokines and antibodies manifested in the allergic process, as well as a shift in response to a Th1 pattern and the production of IgG2a antibodies, which are characterized as adequate immunotherapy to treat allergy to shrimp [36, 39].

1.1.5 Allergens coupled to immunomodulatory compounds

Vaccines proposed a 100 years ago, and still used today, employ crude extracts and attenuated viruses. After identification of the allergens structures, AIT began to use recombinant proteins and epitope-peptides. However, highly refined antigens and derived peptides present low immunogenicity and often lead to the stimulation of weak and short-lived immunity, not activating all facets of the immune response, requiring adjustment of new immunostimulatory adjuvants to enhance immune responses induced by poorly immunogenic antigens. There are only a few adjuvants approved for human use. Alum, various aluminum salts, and the first and most commonly used adjuvant were the only human vaccine adjuvant for more than nine decades until 2009 [40]. Alum is not compatible with mucosal vaccines

and is unsuitable for aluminum intolerant individuals. In 2009, the Food and Drug Administration (FDA) approved AS04, a combination of alum and monophosphoryl lipid A (MPLA), for human use [41]. From 2016 to 2018, the FDA approved three more adjuvants (i.e., MF59/AS03, CpG 1018, and AS01b). The first, MF59/AS03 is a squalene-based oil-in-water emulsion used in influenza vaccines [42]. The adjuvant CpG 1018 is a short synthetic oligonucleotide, agonist of TLR9 that is being used in a vaccine against hepatitis B. moreover, AS01b is a combined adjuvant containing MPLA and saponin QS-21 in a liposomal formulation that induces strong humoral immune responses and cellular and has been approved by the FDA for use in Shingrix® against herpes zoster and by the European Medicines Agency (EMA) for use in Mosquirix® against malaria [40].

Studies have found that CpG oligodeoxynucleotides are helpful as adjuvants in inducing Th1-type immune responses, demonstrating their immunomodulatory activity in a murine model of asthma, as they improve the function of antigen-presenting cells and increase the generation of vaccine-specific humoral and cellular immune responses [43]. Based on this technology, a randomized, double-blind, placebo-controlled, phase 2 trial of a vaccine based on ragweed pollen antigen (Amb 1), conjugated to an immunostimulatory DNA phosphorothioate oligodeoxyribonucleotide (AIC), was done in 25 adults allergic to the pollen of this plant. In this work, the vaccine (with a regimen of 6 weeks) offered long-term clinical efficacy in treating ragweed allergic rhinitis [44].

A powerful strategy for safe development of AIT is the covalent conjugation of allergens to toll-like receptor (TLR) agonists. Méndez et al. [45], synthesized two families of ligands, an 8-oxoadenine derivative as a ligand for TLR7 and a pyrimido[5,4-b]indole as a ligand for TLR4, both conjugated to a T-cell peptide from Pru p 3, one of major allergen from Prunus persica (Peach). These conjugates interacted with dendritic cells, inducing their specific maturation, T cell proliferation, and cytokine production in peach-allergic patients. In addition, they increased the frequencies of Treg cells in these patients and could induce IL-10 production [45].

1.1.6 Virus-like particle-coupled allergens

The construction of allergens coupled to virus-like particles (VLPs) started from a similar principle to that described for allergens coupled to immunomodulatory sequences. In this technique, the allergen molecules are chemically coupled or specific binding systems to virus-like particles through recombinant expression [46]. This technology has shown reduced allergenic activity in vaccines and good immunogenicity. The impediment to its use, on the other hand, is the difficulty in producing the vaccines in a replicable way due to the uncontrollable coupling process [21]. A sophisticated approach to engineering virus-like nanoparticles (VNPs) has been demonstrated by Kueng et al. [47],. This work showed that the cDNA encoding the allergen was coupled to the DNA encoding the virus.

In a preclinical trial of allergy to mugwort pollen (also known as a queen of grass, field chamomile, or fireweed), these particles were used successfully for prophylactic vaccination [48]. Virus-like particles (VLPs) are safe platforms for inducing protective antibodies, and several VLP-based vaccines are commercially available, including cat allergens. In a previous study, a vaccine composed of Qβ-derived VLPs coupled to the cat allergen Fel d 1 was highly immunogenic and capable of inducing IgG

antibodies in mice. Immunization of Fel d 1 sensitized mice with protected Qβ-Fel d 1 against anaphylaxis after challenge with Fel d 1 allergen [49]. A recent study showed that the allergens displayed in Qβ-VLP are immunogenic but not reactogenic and do not activate human mast cells. VLP could constitute a platform to deliver allergens to allergic patients immunogenically and effectively but safely. [50] tested peanut allergy vaccine candidates based on the immunologically optimized VLP derived from cucumber mosaic virus (CuMVtt). They demonstrated that the inactivated, VLP-coupled allergen reduced systemic and local allergic symptoms after challenge with the whole allergen extract (composed of about 12 allergenic proteins), demonstrating that immunization against a single allergen protected against a mixture of allergens could be a hope for patients allergic to many components of an extract from a single source [50].

1.1.7 Nucleic acids encoding allergens

Publications from three decades ago showed that nucleic acid constructs (plasmid DNA or mRNA) could be injected into mice, resulting in the encoded protein made in situ. An initial study demonstrated that plasmid DNA encoding virus antigens could result in the generation of immune responses, so efforts were directed toward the use of plasmid DNA in vaccines [51].

Nucleotide vaccines are vectors that encode antigens and retain adjuvant-like activity by stimulating innate immune responses that contribute to adaptive responses [52]. Some questions were raised on whether a DNA vaccine could initiate an autoimmune disease since anti-DNA antibodies are a hallmark of autoimmune diseases. The results demonstrate that there is safety in using these vaccines and that this incorporation does not occur [51].

DNA vaccination presents the ability to rapidly induce strong CD4 and CD8 T cell and antibody responses. Several animal models for allergic diseases have demonstrated that DNA vaccination can induce a Th1 type immune response, which could counterbalance the Th2 response. Immunomic Therapeutics, Inc.'s research group developed novel allergy immunotherapy based on LAMP technology to treat pollen-induced allergies. Lysosomal Associated Membrane Protein 1 (LAMP-1 or LAMP) is a lysosomal residential protein. It has been shown that the inclusion of LAMP in the DNA plasmids significantly enhanced both cellular and humoral responses in vaccinated animals. The LAMP-Vax platform utilizes an up-to-date targeting approach, which should avoid therapy-induced side effects caused by high amounts of free allergen. Alternatively, the synthesized allergen-LAMP fusion protein is directly shuttled into the lysosomal compartment, circumventing the patient's exposure to the native allergen. Instead of inducing tolerance, this therapy is designed to reverse the allergenic IgE/TH2 response toward an IgG/TH1 response [53].

Cry j 1 and Cry j 2 proteins are the 2 major allergenic components in Japanese red cedar (JRC) pollen and cause pollinosis (JCP) in 30–35% of the Japanese population. Su et al. [54] demonstrated that DNA plasmids encoding LAMP fused with Cry j 1 and Cry j 2 proteins elicited a strong Th1 response in mice. After repeated allergen exposure, vaccinated mice were well protected, as indicated by a minimal level of allergen-specific IgE production. The safety and immunological effects of an investigational DNA vaccine encoding CryJ2-LAMP were evaluated by Phase IA and IB clinical trials. Results indicated that CryJ2-LAMP DNA vaccine is safe

and has the potential therapeutic potential for JRC and/or Mountain Cedar (MC) sensitive subjects.

Studies in Phase 1 trials to evaluate the safety, tolerability, and immune response in adolescents or adults allergic to peanut allergens employing multivalent peanut-LAMP-1 DNA vaccine, including Ara h 1, Ara h 2, and Ara h 3, are promising [55].

1.1.8 IgG blocking antibodies specific to recombinant allergens

To obtain vaccines defined for passive immunization, specific blocking antibodies for human allergens are necessary. The first published studies where these allergen-specific antibodies were reported appeared more than two decades ago [21]. A combinatorial library to obtain IgE was constructed from peripheral blood mononuclear cells of an allergic patient to grass pollen where, for the first time, the Fabs regions of IgE specific for human allergens were isolated [56]. An IgE Fab specific for the major grass pollen allergen (Phl p 2) was converted into recombinant human IgG, and this blocked the Phl p 2 induced basophil degranulation, thus demonstrating its therapeutic potential [57].

Bi-specific antibodies were created so that an IgG-specific recombinant allergen could block the entry of allergens through the respiratory epithelium. It was possible to demonstrate the immobilization of allergen-specific IgG blocking antibodies using IgG specific for ICAM1 in respiratory epithelial cells, thus preventing the entry of allergens and opening up possibilities for topical treatment using blocking antibodies [58]. The idea of passive immunization from allergen-specific recombinant IgG antibodies is exciting and is undoubtedly a possible approach for allergen sources that contain mainly a significant allergen that can be blocked with one or a few monoclonal antibodies. This approach will be beneficial for seasonal allergies, as a preseasonal immunization can effectively protect the patient during seasonal exposure to the allergen [21].

1.1.9 Cell-based therapy

This technology for formulating a safer immunotherapy is based on the classic studies of hematopoietic stem cell transfer from one mouse strain to another strain with different MHC origins early in life [21]. From that study, Baranyi et al., [59] demonstrated that rats received such cells that express the allergen could not be sensitized against the corresponding allergen. Furthermore, even using a sensitization protocol with aluminum hydroxide adsorbed allergens, it was not possible to induce allergen-specific T cells, antibodies (of any isotype, including IgE), or allergic immune responses, indicating that a robust lifetime tolerance was achieved, which depend on mechanisms of central tolerance rather than peripheral regulation.

This technique has an immunomodulatory treatment, uses a protocol for cell transduction – which can be dangerous – and needs to be applied early in life, probably immediately after birth. However, a cell-based treatment shows that a robust, lifelong, allergen-specific immune tolerance is achievable [21].

The cell-based allergen-specific prevention approach is highly experimental, warranting further investigation in clinical trials, as major safety hurdles can be overcome [21].

2. Routes of administration

Other approaches are being sought to try to reduce the risks of side effects and have a safer AIT and with that alternative routes of administration have been studied.

Subcutaneous immunotherapy (SCIT) is the route of administration with the most well-established underlying mechanisms and has been in use since 1911. Already the Sublingual immunotherapy (SLIT) has been considered due to its ease of use and reduced side effects [21].

The appropriate candidates for AIT are mainly children with allergic asthma. The use of molecular diagnosis techniques [component-resolved diagnostics (CRD)] increases the effectiveness of AIT since it allows physicians to identify better whether children with allergic respiratory symptoms are sensitized to major allergens or cross-reactive molecules [60].

A review by Tsaburi [61] and colleagues gives us an understanding of the use of SCIT and SLIT in the treatment of children with allergic asthma. Studies have shown a significant decrease in asthma symptoms and also a preventive effect at the onset of the disease. And while SLIT safety profile appears better, some results suggest that SCIT efficacy is better with an earlier onset than SLIT in children with allergic asthma. Furthermore, there is no effective SLIT for significant allergens such as food and aeroallergens [62, 63].

Another approach to improving AIT is oral immunotherapy (OIT). This pathway has been tested primarily for allergens from food sources that are resistant to digestion, such as milk, egg, peanuts, and wheat, while not being used for other allergen sources [21].

Clinical studies show that the advantages of OIT are associated with the induction of specific IgG antibodies, which can block the IgE-allergen interaction as well as in SCIT. It was also described that oral immunotherapy induced changes in cellular immune responses, which could lead to clinical oral tolerance [64].

Intralymphatic Immunotherapy (ILIT) is a new application approach that has been developed within subcutaneous immunotherapy (SCIT). The proposal for this route of administration is the large amount of immune system cells that lymph nodes present, and a direct exposure of the allergen to these cells will induce a protective IgG response and faster immunomodulation [65].

A recent review by Senti et al. [66] provides an excellent overview about intralymphatic AIT, ultrasound-guided injection of allergen extracts into lymph nodes. However, there are no studies comparing the immunological and clinical responses of ILIT and SCIT using vaccines of the same allergen, making it difficult to confirm whether intralymphatic immunotherapy induces faster and stronger responses than subcutaneous.

ILIT has an acceptable safety profile, but its disadvantage is the need to use an ultrasound device for vaccine application in lymph nodes. Furthermore, few studies have been carried out so far when compared to other routes [67].

Epicutaneous immunotherapy (EPIT) assumed that applying allergens through the non-vascularized epidermis would induce fewer systemic side effects [21].

Another critical point is that EPIT does not use a needle, being considered especially suitable for children. Furthermore, this type of immunotherapy uses high doses of allergen and, despite showing some improvement in seasonal symptoms, it does not show considerable benefit in terms of local side effects when compared to subcutaneous immunotherapy (SCIT) [68].

Routes for administration	Advantages	Disadvantage	References
SCIT—subcutaneous injection	Best mechanisms documented applicable for most allergen sources	Severe side effects rares but possible; Injection needed	[18, 61, 63]
SLIT—sublingual application in form of drops or tablets under the tongue by self-administration	Clinical efficacy demonstrated in studies	Less effective than SCIT Mechanisms are less well defined than for SCIT cumbersome treatment with low compliance applicable / available only for few allergen sources	[61, 62]
OIT—Oral administration and swallowing	Effective for food allergey	High rate of side effects	[64]
ILIT—Ultrasound-guided injection into subcutaneous lymphnodes	Experimental AIT form Clinical efficacy partly shown	Ultrasound-guided injection needed Advantage over SCIT not demonstrated	[65–67]
EPIT—epicutaneous administration on stripped skin	Experimental AIT form	Clinical efficacy not demonstrated	[68]

Table 1.
Routes for administration of AIT, showing the advantages and disadvantages of each route.

Table 1 brings together all the proposed administration routes, showing the advantages and disadvantages that each one presents.

3. Conclusion

Allergen-specific immunotherapy has been applied for over a 100 years. This review emphasized the fundamental importance of accurately identifying the structure of allergens and their dominant epitopes, as well as choosing adjuvants. For the market establishment or acceptance new molecular AIT preparations would be the demonstration of clear added value, e.g., shortened therapy duration and superior effectiveness or tolerability. Despite the development of new approaches to allergen-specific immunotherapy, licensing any vaccine for the clinic proved complicated. Currently, allergen-specific immunotherapy with extracts of natural allergens is the only universally approved treatment for allergic patients. Isolated treatments are made with purified allergens to avoid adverse effects caused by the allergenicity of natural extracts. The latest generation of allergy vaccines based on T-cell epitopes and B-cell epitopes linked to carriers has the potential to transform AIT as it can prevent side effects, allowing the administration of doses to induce strong allergen-specific IgG responses and provide patients with sensitized with lasting effects.

AIT, like other therapies, has advantages and disadvantages in its use, but with new technologies and molecular strategies much has been sought so that safer AIT is developed and better routes of administration are developed, revolution-izing traditional immunotherapy-based in natural allergenic strata. Since success

of COVID-19 vaccine allergen DNA and mRNA vaccination has been gaining prominence.

We hope that more people will benefit from this preventive way of controlling allergic diseases.

Abbreviations

AIT	Allergen-specific immunotherapy
CRD	Component-resolved diagnosis
EPIT	Epicutaneous immunotherapy
FDA	Food and Drug Administration
ILIT	Intralymphatic Immunotherapy
LAMP	Lysosomal Associated Membrane Protein
LTP	Transfer protein of lipids
MA	Molecular allergy diagnostics
MPLA	Monophosphoryl lipid A
OIT	Oral immunotherapy
PIP	Peptide-based immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
TLR	Toll-like receptor
VLPs	Virus-like particles

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