Immunotherapy to Treat Allergies: Recent Advances and Future Prospects

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Allergen immunotherapy (AIT) has been used to treat allergic diseases, such as asthma, rhinitis, and venom-induced anaphylaxis, for more than 100 years. AIT aims to suppress immune responses established in patients sensitized to allergens, which are mediated by allergen-specific IgE and memory T cells, through the controlled administration of allergens over prolonged periods. AIT in appropriately selected patients effectively reduces the symptoms of allergic diseases. The mechanisms underlying AIT have been suggested to include the very early desensitization of mast cells and basophils; generation of regulatory T/B cell responses; regulation of IgE and IgG4; and regulation of mast cells, basophils, and eosinophils. Two types of AIT, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), are currently used in clinical practice. The main side effect of SCIT is unwanted IgE-mediated reactions. SLIT is safer than SCIT, allowing for home administration. Advances in AIT, such as alternative routes of administration, allergen standardization, modification of allergens, use of adjuvants, and combination with the anti-IgE monoclonal antibody omalizumab, have improved the safety and efficacy of AIT. Other biologics such as those targeting Th2-related pathways have been tested. This review provides a brief overview of advances and future prospects in AIT and biologics to treat allergies.

Key words: allergen immunotherapy, allergen vaccine, subcutaneous immunotherapy, sublingual immunotherapy, biologics

Abbreviations: AIT; allergen immunotherapy, FDA; United States Food and Drug Administration, SCIT; subcutaneous immunotherapy, SLIT; sublingual immunotherapy

Introduction

Allergen immunotherapy (AIT) has been used to treat allergic diseases, such as asthma, rhinitis, and venom-induced anaphylaxis, since it was first described by Noon in 1911¹⁾. AIT aims to suppress immune responses already established in patients sensitized to specific allergens, which are mediated by allergen-specific IgE and memory T cells, through the controlled administration of allergens over prolonged periods. This review provides a brief overview of advances and future prospects in AIT and biologics to treat allergies.

Allergen immunotherapy

1. Mechanisms

According to Akdis *et al.*^{2) 3)} four immunological changes occur during the course of AIT. The initial step is the very early desensitization of mast cells and basophils, which begins within hours of the use of natural allergens. The second change is the generation of allergen-specific regulatory T cells and regulatory B cells to suppress allergen-specific T cells. The third step is the regulation of allergen-specific IgE (early increase and subsequent decrease) and allergen-specific IgG4 (continuous increase). The fourth change, which occurs several months later, is decreases in the numbers and activities of tissue mast cells and eosinophils. The mechanisms underlying AIT have not yet been elucidated in detail.

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2. Routes of administration

Two types of AIT, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), are currently used in clinical practice (Table-1). The main side effect of conventional SCIT is unwanted IgE-mediated reactions, which can be local or systemic (such as anaphylaxis)³⁾. The rate of SCIT-induced systemic reactions reported in a three-year survey^{4) 5)} was approximately 0.1% of injections, the majority of which occurred within 30 minutes of the administration of SCIT. In SLIT, the allergen extract is administered as a liquid or dissolvable tablet and has to be held under the tongue for absorption with or without subsequent swallowing of the allergen extract. SLIT, a noninjection immunotherapy, is safer than SCIT. This advantage allows for the home administration of SLIT. Other routes of administration (oral, nasal, bronchial, epicutaneous, intraepithelial, or intra-lymph node routes) (Table-1), modifications to allergen vaccines, and the use of biologics, the latter of which will be described later, have been investigated for more efficacy and safety^{3) 6)-8)}.

Allergen standardization

Since the qualities of allergen vaccines/extracts

Table-1 Routes of administration in allergen immunotherapy

Injection	Non-injection
Subcutaneous (SCIT)	Sublingual (SLIT)
Intra-lymph node	Oral
	Epicutaneous
	Nasal

SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

SCIT and SLIT are currently used in clinical practice.

used in therapies and diagnoses vary depending on the production methods and manufactured lots, their standardization is necessary (Table-2)⁹⁾. Allergen standardization has contributed to improvements in the safety and efficacy of AIT.

The United States Food and Drug Administration (FDA) has regulated allergen standardization, which is based on the intradermal testing of allergic patients, and the potencies of lots are determined by surrogate *in vitro* assays based on inhibition assays of IgE binding to solid phase reference allergen extracts using pooled allergic sera or the measurement of specific allergen contents in allergen vaccines (Table-2). In Europe, products are standardized using manufacturers' in-house references and labeled in manufacturer-specific units. In Japan, the Japanese Society of Allergology standardized Japanese cedar pollen and house dust mite allergen vaccines¹⁰⁾. The *in vivo* allergenic potencies of the Japanese Society of Allergology reference extracts were determined by intradermal testing. Measurement of the contents of major allergens was selected as the surrogate *in vitro* assay to label the potencies of lots: Cry j 1 for Japanese cedar pollen and Der 1 (Der p 1 + Der f 1) for house dust mites.

Allergen modifications

1. Chemical modification

Allergoids, allergens chemically modified by a treatment with formaldehyde or glutaraldehyde, show reduced allergenicity while preserving immunogenicity (Table-3). Allergoids are used for SCIT in Europe⁶⁾.

2. Recombinant allergens

The identification of allergen proteins and cloning

Table-2 Allergen standardization in the United States, Europe, and Japan¹⁰⁾

Area	Institute conducting the standardization	Unit	Reference allergen extract
United States	FDA	AU/BAU	FDA
Europe	Each of the manufacturers	Manufacturer-specific unit	Manufacturer-specific in-house reference
Japan	JSA	JAU	JSA

FDA: Food and Drug Administration; JSA: Japanese Society of Allergology; AU: Allergy Unit; BAU: Bioequivalent Allergy Unit; JAU: Japanese Allergy Unit

of their cDNAs have enabled the production of their recombinant forms with well-defined molecular, immunological, and biological characteristics on a large scale (Table-3)⁷⁾. Correctly folded recombinant allergens with wild-type sequences may represent alternatives to natural allergens because of equivalencies in structures and immunogenicities. Recombinant allergens may be engineered to be hypoallergenic through the introduction of mutations, which cause conformational changes in their IgE epitopes while preserving T cell epitopes^{7) 11)}. Hypoallergenic mutant allergens and allergen fragments with reduced allergenicity are considered to not only be safer, but also more effective because their administration at higher doses may be possible. Some recombinant allergens have been tested in human clinical studies⁶⁾.

3. Peptides

AIT using peptides containing allergen T-cell epitopes have been suggested to have the following advantages such as the effective induction of regulatory T cells, better safety because the small peptides do not crosslink IgE on mast cells, and greater stability in storage as lyophilized products (Table-3)^{6) 8)}.

Adjuvants

The efficacy of AIT may be improved by the use of adjuvants. Aluminum hydroxide (alum) is a conventional adjuvant that is used in SCIT in Europe. The proposed mechanisms of alum-based immunotherapy involve slower allergen release from the injection site and stimulation of innate immune sensors, leading to increases in the duration of antigen presentation and the effective activation of antigen-presenting cells, respectively. The addition of other adjuvants such as agonists for toll-like receptors to allergens or their use by themselves without allergens have been investigated and shown to have some benefits (Table-3)^{3) 6) 8)}.

Omalizumab

Therapy using an anti-IgE monoclonal antibody (omalizumab) alone may lead to a gradual reduction in the expression of FcεRI by mast cells, basophils, and cutaneous dendritic cells (Table-4). The use of omalizumab has been shown to improve the safety and efficacy of AIT prior to its administration⁶⁾. Systemic allergic reactions to SCIT may be reduced by a pretreatment with omalizumab.

Table-3 Modifications to allergen vaccines for safe and effective allergen immunotherapy

Allergen	Modifications	Allergenicity	Immunogenicity
Natural allergen extract	None	Natural	Natural
Allergoid	Chemically modified	Reduced	Modified
Recombinant (folded)	Genetically engineered	Natural	Natural
Recombinant (unfolded/fragment)	Genetically engineered	Reduced	Modified
Recombinant (mutation)	Genetically engineered	Reduced	Modified
Short peptides	Synthesized	Reduced	Modified
Allergen + Adjuvant	Co-administration/ Covalently linked	Natural/ Reduced	Increased

Table-4 Target molecules of biologics currently available or tested for use in allergic and urticarial pathologies¹²⁾

Classification	Target
IgE	IgE*
Th2-type and Th2-promoting cytokines	IL-4, IL-5, IL-9, IL-13, IL-31, TSLP
Proinflammatory cytokines	IL-1β, IL-12, IL-17A, IL-17F, IL-23, TNF-α
Chemokine receptor	CCR4
Cell surface molecules	CD2, CD11a, CD20, CD25, CD52, OX40L

*The target molecules discussed in the text are indicated in bold.

Biologics

Biologic agents other than omalizumab such as those targeting Th2-related pathways have been tested for the treatment of allergic diseases¹²⁾. Allergic diseases are complex syndromes comprising several endotypes. The discovery of disease biomarkers for defining endotypes is desired. For example, patients with high levels of serum periostin showed better responses to IL-13-targeting therapy¹³⁾; patients with nasal polyps and higher nasal IL-5 levels are more likely to respond to IL-5-targeting therapy¹⁴⁾; and eosinophilia or polymorphisms in *IL4Ra* may be markers for responsiveness to IL-4 α -targeting therapy¹⁵⁾. The effects of a monoclonal antibody against thymic stromal lymphopoietin (TSLP)¹⁶⁾ to inhibit allergen-induced asthma attacks were very recently reported¹⁷⁾. Some of the biologics targeting IgE, Th2-type and Th2-promoting cytokines (such as IL-4, IL-5, IL-13, and TSLP), proinflammatory cytokines, chemokine receptors, and cell surface molecules may be effective in the treatment of allergic diseases in appropriately selected patients (Table-4)¹²⁾. Similar to omalizumab, the safety and efficacy of AIT may be improved by the use of biologics prior to the initiation of, during, or after AIT.

Conclusions

AIT represents an effective therapy for allergic diseases in appropriately selected patients. SCIT and SLIT are currently used in clinical practice. SLIT is safer than SCIT. Advances in AIT such as the routes of administration, allergen standardization, modification of allergens, use of adjuvants, and combination with the anti-IgE monoclonal antibody omalizumab have improved the safety and efficacy of AIT. Other biologics such as those targeting Th2-related pathways have been tested. The mechanisms underlying AIT have not yet been elucidated in detail and new forms of immunotherapy to treat allergies will further improve current allergen-specific or nonspecific immunotherapy.

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