

Preface

Allergen-specific Immunotherapy—Turning the Tables on the Immune System



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Allergic disorders have emerged as a major global public health problem.¹ The initial epidemics of asthma, allergic rhinitis, followed by atopic dermatitis, food allergy, and anaphylaxis have predominantly affected the developed countries with a “western lifestyle.”^{2–4} It is estimated that up to 30% of the general population is affected by at least one allergic condition, posing a significant global socioeconomic burden.⁵ In the past decade, allergic disorders have been increasingly recognized in South America, Asia, and Africa. These countries are currently experiencing a rise in the respiratory allergic disorders; it is anticipated that food allergy and anaphylaxis will soon also become more prevalent.⁶ Among the various therapeutic options for allergic disorders, allergen-specific immunotherapy (AIT) has the unique potential to induce desensitization and long-lasting tolerance.^{7–9} The current issue of the *Immunology and Allergy Clinics of North America* is devoted to the specific immunotherapy with aeroallergens and foods. It provides a comprehensive “bench-to-bedside” review of AIT with 14 articles that explore a number of AIT topics, including mechanisms, current and future approaches, as well as practical considerations and challenges related to adherence, identifying responders, and assessing outcomes.

This issue begins with an overview of the more than 100-year history of AIT written by Passalacqua and Canonica, which also discusses recent regulatory changes and allergy diagnostic testing advances likely to impact future AIT. In 1908, Schofield reported successful oral desensitization to raw egg in a teenage boy with anaphylactic egg allergy.¹⁰ Subcutaneous allergen-specific immunotherapy (SCIT) for the treatment of hay fever was introduced by Leonard Noon in 1911.¹¹ Epicutaneous immunotherapy (EPIT) as a treatment for allergies was introduced in 1917, and the first case of successful EPIT was reported in 1921 by Vallery-Radot and Hangenau, who found that allergen administration onto scarified skin reduced systemic allergic symptoms in

patients allergic to horses.^{12,13} A decade later, intradermal allergen-specific immunotherapy was shown to be safe and highly efficacious, leading to allergic rhinitis symptom relief after administration of only three doses of pollen.^{14,15} Sublingual immunotherapy (SLIT) was introduced in the 1990s. In this issue, Nelson and colleagues compare SLIT with SCIT and conclude that SLIT has a superior safety profile, but available evidence suggests superior short-term efficacy with SCIT.

In 2008, the results of the first clinical trial of intra-lingual lymphatic immunotherapy (ILIT) were published by Senti and colleagues,¹⁶ who explore the use of this and other novel delivery routes for aeroallergen allergy in this issue. The safety and efficacy of oral immunotherapy (OIT), SLIT, and EPIT for food allergies are reviewed in two articles in this issue written by Fleisher and colleagues and Vickery and Wood.

The mechanisms of aeroallergen and food AIT are covered in articles by Mübeccel and Cezmi Akdis and Berin and Shreffler, respectively. Comparison among the different routes of AIT is presented in [Table 1](#). Probably the most important differences are the antigen uptake and processing and the total dose. Sublingual and epicutaneous routes appear to have specific advantages due to the presence of resident tolerogenic dendritic cell subsets in the sublingual mucosa and in the skin. OIT utilizes the GALT pathways that underlie physiologic responses to food antigens and oral tolerance. ILIT delivers allergens directly to the lymph nodes with minimal likelihood of systemic dissemination.

Regardless of the route of antigen delivery, successful AIT is associated with the induction of Treg cells, modulation of T- and B-cell responses, skewing of allergen specific-antibody isotype from IgE to IgG₄ predominance, early desensitization (increased threshold for activation) of mast cells and basophils, and decreased numbers and activation of eosinophils and mast cells in the tissues.^{17–22} Local induction of Treg cells in the nasal mucosa in response to AIT has been observed in allergic rhinitis patients.²³ Allergen-specific Treg cells produce IL-10 and TGF- β cytokines that suppress proliferative and cytokine responses against major allergens and their recognition sites.^{24,25} An alternative mechanism of tolerance is deletion of allergen-specific T helper 2 (Th2) cells as a consequence of repeated high-dose allergen exposure.²⁶ IL-10 promotes a noninflammatory phenotype. Serum levels of IgE decrease gradually, while allergen-specific IgG₄, referred to as blocking antibodies, increase during AIT, which is the result of class-switching of B cells from IgE to IgG₄. IgG₄ competes with Fc ϵ receptor-bound IgE for binding allergens, which limits activation and degranulation of mast cells and basophils. IgG₄ has important roles in limiting the activation of CD4⁺ T cells, by inhibition of CD23-mediated IgE-facilitated antigen presentation.^{22,27–35}

In addition to exploring different routes of allergen administration, modifications of native allergens are being actively investigated to enhance safety and efficacy of AIT. Allergenic peptides and various forms of recombinant allergens (hypoallergens, dimers, trimers, and fusion proteins) have been shown to control allergic inflammation by inducing inhibitory antibodies. These novel AIT therapies are discussed in the article by Creticos on AIT vaccine modification.

Efficacy and safety of AIT can be also enhanced by the use of the adjuvants that skew the immune response toward T helper 1, which downregulates the allergic Th2 inflammation. Various adjuvants have been studied, including alum, toll-like receptor agonists, probiotics, and nanoparticles.^{36–40} Current and novel AIT adjuvants are reviewed in the article by Schmidt-Weber and Chesné.

Following the AIT studies focusing on the aeroallergens and venom, in the past decade, food allergy has become a prime target for immunomodulation. OIT, SLIT, and EPIT are being currently investigated in clinical trials for milk, egg, and peanut allergy.⁴¹ Pretreatment with anti-IgE antibody (omalizumab) has been shown to

Table 1
Comparison of different routes of allergen-specific immunotherapy

	SCIT	SLIT	OIT	EPIT	ILIT
Allergens	Aeroallergens, venom	Aeroallergens, food, latex	Foods	Aeroallergens: grass pollen, dust mites, cat dander Foods: milk, peanut	Grass pollen, MHC class II-targeting cat dander (MAT-Fel d 1)
Dose	Micrograms	Micrograms (aeroallergens) - miligrams (foods)	Grams	Micrograms	Micrograms (1000-fold less than in SCIT)
Up dosing	Initial dose escalation can be rush or gradual every 1–2 wk	No	Initial rapid dose escalation over 1 day, followed by up-dosing every 2 wk	No	No
Dosing interval	Variable, usually maintenance every 4 wk	Daily	Daily	Daily	3 injections every 4 wk are equivalent to 3 y of SCIT
Allergen uptake	Subcutaneous dendritic cells	Oral mucosal uptake by Langerhans cells	Intestinal mucosal uptake by dendritic cells	Allergens are captured within the superficial layers of intact stratum corneum by Langerhans cells subpopulation of dendritic cells expressing the langerin-specific surface marker cytotoxic T lymphocyte-associated antigen 4	Antigen-presenting cells in the inguinal lymph nodes
Safety/side effects	Most commonly local reactions (induration, erythema) at the site of injection, uncommonly anaphylaxis	Local, mild oropharyngeal	Most commonly mild oropharyngeal and gastrointestinal; systemic reactions may occur in the setting of fever, infection, exercise, or asthma flare	Local skin irritation, eczema, hives, and gastrointestinal (diarrhea)	Infrequent mild urticaria and angioedema

increase safety of the up-dosing during OIT.⁴² Multifood OIT has been shown to have a comparable safety profile to a single-food OIT, opening a new venue for patients with multiple food allergies.⁴¹ As an alternative to AIT, diets containing extensively heated (baked) cow's milk and hen's egg are well-tolerated by the majority of the milk and egg-allergic children, and they appear to accelerate development of tolerance to unheated milk and egg, and have already changed the paradigm of strict dietary avoidance for cow milk and hen's egg allergy management.⁴³ Leonard and Nowak-Węgrzyn discuss this approach.

Practical aspects of AIT are also covered in the issue:

- Identifying biomarkers to predict and monitor response (Moingeon)
- Outcome measures for assessing AIT efficacy, the magnitude of improvement that is clinically significant, and unmet needs (Demoly, Bousquet)
- Use of component-resolved diagnosis to guide AIT prescription (Kleine-Tebbe, Matricardi)
- Adherence challenges and strategies for improvement (Bender, Lockey)

Considering the unique disease-modifying potential of AIT, it will remain an attractive therapeutic approach to allergic disorders. Currently, SCIT and SLIT are approved for clinical use, whereas OIT, EPIT, and ILIT remain in the sphere of clinical research. The improvements increasing efficacy, safety, and treatment adherence in AIT are needed to take the full advantage of the beneficial immunomodulation afforded by AIT. This issue of *Immunology and Allergy Clinics of North America* provides a wide-ranging review of the “art and science” of current AIT practice and a preview into possible future approaches.

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