

Allergy immunotherapy: A continually evolving set of therapeutic procedures

This first issue of the New Year's *Proceedings* features a diversity of topics with a special focus on five articles directed to allergy immunotherapy (AIT), including subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), oral immunotherapy (OIT), and epicutaneous immunotherapy (EPIT), for both respiratory and food allergies. The historical aspects of AIT were described in a previous editorial.¹ The first AIT procedure, SCIT, was introduced into clinical practice in 1911 by Noon and Freeman, two microbiologists working at Saint Mary's Hospital in London, who based their procedure on the mistaken notion that the existence of a toxin component of pollen was the causative agent of hay fever. They believed, therefore, that protection conferred by injection treatment for allergic disease was due to the development of pollen antitoxin in a manner similar to the protective immunity achieved after the use of vaccines for the prevention of infectious diseases. Despite its relative success over the past century, SCIT has faced several challenges, including worldwide standardization, limitations in efficacy, sometimes severe adverse effects, low patient adherence, and high costs due to the long duration (3 to 5 years) required for treatment. Subsequently, various alternative approaches were pursued to address these challenges that were directed to the introduction of mucosal (*i.e.*, SLIT and OIT) and cutaneous (*i.e.*, EPIT) forms of AIT, which are described in this issue.

In the first of two review articles written by Nelson,² he critically assesses the literature for optimal practices to minimize adverse reactions associated with SCIT and SLIT. He provides a review of the evidence that supports the need for care in the preparation of allergy extracts for treatment, the use of modified extracts, the location for administration of SCIT and SLIT, risk factors for systemic reactions, the use of AIT in patients receiving adrenergic blocking agents or angiotensin-converting enzyme inhibitors, the use of premedication, the need for a prescription of epinephrine autoinjectors, dose adjustments for pollen seasons, interruptions in treatment, current guidelines for local and systemic reactions, and the safety in patients with autoimmune diseases and

during pregnancy.² In his second review article, Nelson³ critically appraises the literature for optimal practices to enhance the efficacy of AIT. Evidence is presented that supports optimal dosing for SCIT, a discussion of dosing with liquid SLIT, the management of the patient who is polyallergic, considerations in mixing allergen extracts, advantages and disadvantages of different up-dosing regimens with SCIT, the optimal duration of AIT, the comparative efficacy of SCIT and SLIT, and improving adherence to AIT. Nelson³ also reviews two potential future AIT approaches, the use of adjuvants and alternative routes of administration of currently available extracts.

To expand on issues related to AIT safety are two original articles, the first explored the use of expired extracts, the second evaluated the efficacy of epinephrine and diphenhydramine syringe rinses in conjunction with SCIT administration. With regard to the use of expired extracts, Stein *et al.*⁴ examined the *in vivo* efficacy and bioavailability of outdated allergen extracts for a diagnosis of allergic sensitizations. These investigators analyzed skin-prick test results in 39 patients and compared 356 prick tests with expired extracts with 111 prick tests with unexpired extracts. The results showed that outdated extracts produced positive wheal reactions that were not significantly different from the unexpired allergens. In addition, none of the extracts were found to have bacterial or fungal contamination. The authors concluded that outdated allergen extracts are safe and do not seem to differ in potency and bioavailability from unexpired extracts for the detection of allergen sensitization by skin-prick testing.⁴ This may have implications for their duration of clinical use beyond the expiration date. With regard to the utility of epinephrine and diphenhydramine rinses in decreasing local reactions to conventional doses of SCIT, Mustafa *et al.*⁵ performed a prospective, single-blinded, randomized controlled trial that compared pre-rinsing SCIT syringes with diphenhydramine, epinephrine, or placebo in patients who were receiving aeroallergen SCIT and who experienced local reactions despite pretreatment with an antihistamine. In analyzing the data from 490 patients who received aeroallergen SCIT per a conventional dosing schedule, the authors found that an epinephrine rinse significantly decreased local

reactions.⁵ The authors concluded that, in patients already premedicating with an oral antihistamine, adding an epinephrine syringe rinse is a safe and effective strategy to decrease local reactions to aeroallergen SCIT.⁵

In expanding the realm from AIT for respiratory allergens to AIT for food allergens is a review article by Wang.⁶ This is a timely topic because the prevalence of food allergy has been rising and is now estimated to occur in 8% of children and 10.8% of adults in the United States.⁷ In particular, peanut allergy is among the most common food allergies, affecting 1% to 4.5% of children and resulting in a significant personal, family, community, and societal burden.⁸ In this context, Wang⁶ provides a review of the available data for OIT and EPIT for peanut allergy. With regard to efficacy, she reports demonstrable evidence that peanut AIT can raise the threshold of peanut allergen necessary to induce allergic reactions for many patients, thereby potentially reducing the risk for allergic reactions and decreasing the burden of peanut allergy.⁶ However, with regard to safety, adverse reactions, ranging from mild to severe, are possible. Although OIT and EPIT will offer patients and families more options for managing peanut allergies, she emphasizes that shared decision-making will be important to help each individual and his or her family determine the best approach for peanut allergy management. Because of the importance of this article and its clinically useful implications, it was chosen for this issue's "For the Patient" section. This segment, found in the final pages of the print version of this issue and also available online, consists of a one-page article synopsis, written in a readily comprehensible fashion to help patients better understand the content of the full article.

In transitioning from immunoglobulin E (IgE) mediated to non-IgE-mediated food allergic disorders, Cetinkaya *et al.*⁹ examined the predictors for late tolerance development in food protein-induced allergic proctocolitis (FPIAP). This condition is a non-IgE inflammatory disorder of the distal colon that typically presents with blood-mixed mucoid stools of variable frequency. Treatment consists of complete dietary elimination of the suspected antigen (most commonly cow's milk). The objective of this study was to identify predictors that affect the timing of the development of tolerance to the causative food in infants with FPAIP. Based on their analysis of 185 infants with FPIAP, this study showed that early introduction of complementary feeding was associated with earlier tolerance development.⁹ The authors suggest that conservative avoidance measures and an earlier introduction of complementary feeding may be beneficial in infants with FPIAP.⁹

Two articles in this issue turn our focus toward asthma. In the first article, Rajagopal *et al.*¹⁰ seek to determine the prevalence of *Aspergillus* sensitization in patients with bronchial asthma and its clinical

significance. In a prospective cross-sectional study of 57 patients, the authors reported finding that the proportion of patients with uncontrolled symptoms was higher among patients sensitized to *Aspergillus* (45%) compared with patients not sensitized (18.9%) and that *Aspergillus* sensitization is significantly associated with bronchiectasis.¹⁰ In the second article, Zhu *et al.*¹¹ reported on the effectiveness of the Chinese Children's Asthma Action Plan in the management of children with asthma. Perhaps due to the short assessment period (3 months) and/or inadequate powering, use of the Chinese Children's Asthma Action Plan did not have a significant effect on asthma outcomes in children compared with usual asthma care.

Children with asthma frequently exhibit the comorbidity atopic dermatitis, a disease state addressed in previous issues of the *Proceedings*¹²⁻²² as well as in the current issue, in which Byeon *et al.*²³ reported their measurement of serum cytokine levels, including interleukin (IL) 31, IL-4, and IL-12 in 38 children with atopic dermatitis. These investigators found that serum IL-31 levels were significantly elevated in pediatric patients with atopic dermatitis in comparison with healthy children and correlated well with disease severity.²³

Another topic frequently addressed in previous issues of the *Proceedings* as well as in the current issue is hereditary angioedema, a condition that manifests as episodic swelling, which most often results from deficiency of C1-inhibitor and is associated with dysregulation of the contact activation system. Deficient C1-inhibitor permits activation of plasma kallikrein, which leads to the production of the vasoactive peptide bradykinin. Although therapies directed at inhibiting kallikrein have been shown to be effective in reducing attacks of angioedema, the potential negative effects of kallikrein inhibition are unknown. To provide greater insight, Girolami *et al.*²⁴ authored a review article on hereditary prekallikrein (Fletcher factor) deficiency. They identified 45 publications (representing 53 patients with prekallikrein deficiency) that report a spectrum of health outcomes from asymptomatic to infrequent reports of cardiovascular, bleeding, and autoimmune comorbidities.²⁴ Reassuringly, the majority of reports did not indicate any association between prekallikrein deficiency and comorbidities; however, additional observation will be required to confirm the long-term safety of plasma kallikrein inhibition.

In this issue's final review article, Bonilla²⁵ addressed personalized treatment options for common variable immunodeficiency (CVID). Immune globulin therapy has been the standard of care for patients with CVID for >50 years. However, with further advances in the understanding of the pathophysiology of CVID together with ongoing development of biologics and small molecule immune modulators, additional target therapies are expected to emerge.

Combining the multiple issues that affect allergic diseases described in this issue, Bobrowska-Korzeniowska *et al.*²⁶ reported on the role of antioxidants and 25-hydroxyvitamin D during pregnancy in the development of allergic diseases in early-school-age children. These investigators assessed the associations between cord blood concentrations of zinc, copper, selenium, β -carotene, and vitamins A, E, and D, and the occurrence of atopic dermatitis, food allergy, allergic rhinitis, and asthma in 211 early-school-age children from the Polish Mother and Child Cohort Study.²⁶ Their results suggest that an imbalance in antioxidant defense identified in cord blood may lead to the occurrence of childhood allergic diseases and that maternal diet may play a modifying role.

Rounding out this issue are two *Patient-Oriented Problem Solving "POPS"* case presentations, the first of which explored the differential diagnosis of lymphopenia that complicated the clinical course of a 71-year-old man with pulmonary mycobacterial avium complex infection. The second case addressed the differential diagnosis in a 72-year-old woman with new-onset periorbital swelling. The *POPS* case presentation is a recurring feature of the *Proceedings*, which, as per tradition, is written by an allergy/immunology fellow-in-training from one of the U.S. allergy/immunology training programs. In this issue's *POPS*, Al-Shaikhly *et al.*,²⁷ from the University of Washington, and West *et al.*,²⁸ from the University of Pittsburgh Medical Center, lead the reader through this learning process and illustrate the complexity of the differential diagnostic process and the importance of a detailed history, physical examination, and appropriate laboratory assessment in arriving at a correct diagnosis.

In summary, the collection of articles found within the pages of this issue provides further insight into the intersecting crossroads of genetics and the environment that impact the allergic, cutaneous, and respiratory disorders that afflict patients whom the allergist/immunologist serves. In particular, they exemplify how the complexities of food allergy, asthma, allergic rhinitis, atopic dermatitis, hereditary angioedema, and immunodeficiency continue to challenge the allergist/immunologist. In keeping with the overall mission of the *Proceedings*, which is to distribute timely information with regard to advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients, it is our hope that the articles found within this issue will help foster enhanced patient management and outcomes. On behalf of the Editorial Board, we hope that you are able to make practical use of the diversity of literature offered in this issue of the *Proceedings*.

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