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Review

Advances in rhinitis—models and mechanisms

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ABSTRACT

Objective: To summarize studies highlighting recent advances in rhinitis-related research in the past 2 years.
Data Sources: Original research articles were procured and examined from the Rhinitis and Upper Airway Disease section of the 2015 to 2017 *Annals of Allergy, Asthma & Immunology* issues. Additional original research articles were identified from PubMed and Google Scholar using the following search terms: *allergic rhinitis, rhinitis, chronic rhinosinusitis, environmental exposure unit,* and *nasal allergen challenge.* Only research articles published in the past 2 years were procured.
Study Selections: Articles conducting research in allergic rhinitis (AR) or chronic rhinosinusitis or using controlled allergen challenge facilities or the nasal allergen challenge model were selected.
Results: Studies in the past 2 years have focused on using skin prick tests and early-life phenotyping to predict AR development in children. They also have elucidated the role of a subset of $CD4^+$ T cells, basophils, and mast cells in non-eosinophilic chronic rhinosinusitis with nasal polyps, a relatively new chronic rhinosinusitis subtype in the Asian population. Several advances have been made in understanding the role of several cytokines and peripheral cell mitochondrial function in AR using controlled allergen challenge facilities and direct nasal allergen challenges.
Conclusion: Findings from the recent literature highlight the utility of early-life predictors of AR in possibly targeting high-risk groups for prophylactic interventions. Studies also emphasize the use of controlled allergen challenge facilities and the nasal allergen challenge model as robust experimental models to study AR pathogenesis.

Introduction

During the past 2 years, the *Annals* has published several key studies that have advanced our understanding of allergic rhinitis (AR), chronic rhinosinusitis (CRS), and the experimental models used to study them. This article summarizes the main findings and highlights those with clinical significance.

Recent Advances in AR

Allergic rhinitis is an upper airway inflammatory disorder characterized by immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa. In recent years, the prevalence of AR has rapidly increased, with the disease affecting 10% to 40% of the global population, and is one of the most common medical conditions in children.[1,2] Current research has focused on identifying early-life predictors of AR development.

Codispoti et al[3] evaluated the predictive value of skin prick test wheal areas during the first 3 years of life for the development of allergic eosinophilic rhinitis at 4 years of age using the Cincinnati Childhood Allergy and Air Pollution Study cohort. This prospective birth cohort followed high-risk infants born to aeroallergen-sensitized and symptomatic parents since birth. Physical examinations, parental interviews, and skin prick tests to common aeroallergens were conducted annually, and nasal epithelial smears were collected at 4 years of age to determine allergic eosinophilic rhinitis. Codispoti et al found a significant association of 3-year skin prick test wheal areas to *Penicillium* species (adjusted odds ratio [aOR] 1.18) and maple (aOR 1.07) and a borderline association for elm (aOR 1.06) with the development of allergic eosinophilic rhinitis at 4 years of age.[3] Another study sought to identify rhinitis phenotypes for the prognosis of asthma development in children enrolled in the Children's Health and Environmental Research cohort with current rhinitis. This prospective cohort conducted follow-up tests and surveys at the time of enrollment and at 2 and 4 years

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of age. Using latent cluster analysis, Lee et al[4] identified 4 rhinitis phenotypes in this population: cluster 1 (24.8%) with a very small atopic burden (presence of specific IgE to aeroallergens) and low socioeconomic status; cluster 2 (36.3%) with high atopic burden and normal lung function; cluster 3 (21.9%) with high atopic burden and impaired lung function; and cluster 4 (17.0%) with small atopic burden and high socioeconomic status. Of the phenotypes, children belonging to cluster 3 demonstrated the largest percentage of blood eosinophils and total serum IgE levels at enrollment and the highest incidence of asthma and bronchial hyperresponsiveness cases at follow-up.[4] Overall, the studies highlight the utility of skin testing for specific allergens and early-life phenotyping in identifying children at risk of developing asthma.

Gelardi et al[5] detailed the use of nasal cytology as a low-cost and effective diagnostic procedure for assessing AR. By performing a nasal scraping, May-Grunwald-Giemsa staining, and optical microscopy, it is possible to identify inflammatory cells and predominant cell types. This leads to a fast and accurate diagnosis of non-AR, AR, and viral infections. A detailed assessment of disease, which can be gained through the use of nasal cytology, leads to an increase in knowledge and efficiency in research, diagnosis, and therapy.

Recent Advances in CRS

Chronic rhinosinusitis is an inflammatory disorder of the nasal and sinus passages and is defined as having active symptoms (eg, nasal obstruction, postnasal drip, facial pressure) lasting at least 12 weeks without complete resolution.[6] CRS affects 1% to 9% of the general population and exhibits 2 traditional clinical phenotypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP is characterized by T-helper cell type 2–skewed inflammation, whereas CRSsNP exhibits a T-helper cell type 1–mediated inflammatory response.[6] However, these classifications are continually evolving because of the increasing complexity and appearance of different CRS endotypes defined by unique pathophysiologic mechanisms.

Several studies have described a new subtype of CRSwNP in East Asia, characterized by T-helper cell type 1–mediated non-eosinophilic inflammation in nasal polyps (NPs) and a different comorbidity rate of asthma compared with classic CRSwNP.[7–9] Denoted as non-eosinophilic CRS (NECRS), Iinuma et al[10] characterized tissue $CD4^+$ T cells collected from NP samples from patients with CRSwNP classified as having NECRS or eosinophilic CRS (ECRS; akin to classic CRSwNP). They noted increased levels of interleukin (IL)-25 from NPs and increased IL-5, IL-9, and IL-17RB mRNA expression in NP $CD4^+$ T cells from patients with ECRS vs patients with NECRS. Increased IL-5 and IL-9 production from NP mononuclear cells after IL-25 and T-cell receptor stimulation also was observed only from patients with ECRS and not those with NECRS.[10] In another study assessing the pathologic differences between ECRS and NECRS, Kagoya et al[11] reported a significant increase in basophils in NPs from patients with ECRS vs patients with NECRS. Furthermore, NP basophil counts were positively correlated with the Lund-Mackey composite score (self-reported assessment of CRSwNP symptom severity) only in patients with ECRS.[11] A study published in this year's *Annals* evaluated the role and phenotypes of NP mast cells in patients with ECRS and those with NECRS. Baba et al[12] found a significant increase in NP mast cells in patients with ECRS and those with NECRS compared with controls, with mast cell infiltration primarily localized to the epithelium and glands of ECRS polyps and the submucosa of NECRS polyps. Infiltrating mast cells to these regions were primarily positive for tryptase and doubly positive for tryptase and chymase in ECRS and NECRS polyps, respectively. ECRS polyps also exhibited a significant increase in IgE^+ mast cells, with few detected in NECRS polyps.[12] Together, these studies illustrate the pathologic differences between the 2 subtypes of CRSwNP; subpopulations of $CD4^+$ T cells, basophils, and IgE^+ mast cells could contribute to the eosinophilic infiltration and overall pathogenesis of ECRS.

Chronic rhinosinusitis is often accompanied by comorbid asthma in children and adults. In 2 recent studies, 47% of children had evidence of rhinosinusitis after endoscopic examination and 50% of adults with CRS had concomitant asthma.[13,14] Medical and surgical management of CRS have been shown to alleviate asthma symptoms and improve lung function.[15–17] Owing to the association between the 2 diseases, Anfuso et al[18] evaluated the impact of comorbid asthma on the upper airway inflammatory response in children with CRS refractory to medical management. Sinus and adenoid tissue samples were collected from children with CRS with and without asthma and analyzed for mucosal expression of 40 inflammatory cytokines. Inflammatory profiles in sinus and adenoid tissues were more severe in children with CRS and asthma compared with children with CRS without asthma. Significant increases were observed for sinus levels of tumor necrosis factor-β and adenoid levels of platelet-derived growth factor-AA, eotaxin, epidermal growth factor, growth-related oncogene, and fibroblast growth factor-2.[18] In a cross-sectional study involving adults with CRS and asthma, Phillips et al[19] evaluated the association between CRS symptom severity and asthma control. Severity of CRS symptoms and degree of asthma control were measured using the 22-item Sinonasal Outcome Test and the Asthma Control Test, respectively. After controlling for age, sex, presence of nasal polyps, at least 1 aeroallergen sensitivity, use of asthma controller inhaler, and smoking status, Phillips et al observed a negative association between CRS symptom severity and degree of asthma control ($P = .02$). CRS severity also was significantly associated with poor asthma control (defined as Asthma Control Test score ≤ 19; aOR 1.06).[19]

Controlled Allergen Challenge Facilities

Controlled allergen challenge facilities (CACFs) are clinically validated experimental models of AR that have been used to evaluate new therapeutics for AR.[20,21] They allow large groups of participants to be exposed to a controlled quantity of aeroallergen under regulated conditions. Confounding factors such as temperature, humidity, and allergen concentration (present in traditional natural exposure studies) can be controlled for, creating a standardized environment within the facility.[20,22] Recent studies published in the *Annals* have used CACFs to phenotype individuals with AR and study AR pathophysiology.

Using the Environmental Exposure Unit, Soliman and Ellis[23] phenotyped participants with ragweed-induced AR based on late-onset nasal symptoms after a 3-hour ragweed pollen challenge in the unit. Participants recorded their total nasal symptom scores (TNSS; composite of nasal congestion, nasal itching, sneezing, and rhinorrhea) and peak nasal inspiratory flow (PNIF) at baseline, 30-minute intervals for the first 3 hours, and hourly until 12 hours after the challenge. Soliman and Ellis identified 3 AR phenotypes based on their pattern of late-onset TNSS (symptoms at hours 6–12) after an initial peak in TNSS at 3 hours. These 3 phenotypes were (1) early-phase responders (EPRs) who demonstrated at least a 50% decrease in TNSS by hours 6 to 7 compared with their peak at 3 hours and returned to baseline by hour 12, (2) protracted EPRs who did not exhibit at least a 50% decrease in TNSS by hour 6 to 7 compared with their peak at 3 hours and did not return to baseline by hour 12, and (3) dual-phase responders who demonstrated at least a 50% decrease in TNSS at hour 6 to 7 compared with their peak at 3 hours, maintained at least 2 hours of decreased symptom severity, followed by a sustained increase in symptom severity by hour 12. Using these criteria, 14 participants were EPRs, 21 were protracted EPRs, and 8 were dual-phase responders. Significant differences in late-onset TNSS profiles also were observed among all 3 phenotypes.[23]