Advances in rhinitis and rhinosinusitis in 2015

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The last year has seen great progress in the understanding of upper airway disease and in its management. For allergic rhinitis, authors focused on the prediction of and effect on the natural course of disease. New evidence was published for the disease-modifying effect of allergen immunotherapy in terms of avoidance of new sensitizations and prevention of asthma in either randomized or real-life studies. Specifically, for patients with house dust mite allergies, which are often underestimated and difficult to diagnose, the efficacy of SQ house dust mite sublingual immunotherapy tablets has been demonstrated in patients with allergic rhinitis and asthma. For the first time, allergen immunotherapy significantly reduced asthma exacerbations. In patients with chronic rhinosinusitis, a novel endotyping approach purely based on T helper cell biomarkers has been developed and has shown clinical relevance through associations with asthma comorbidity and recurrence after surgery. Severe nasal polyposis with high risk for asthma comorbidity and disease recurrence is characterized by type 2 inflammatory patterns, including IgE antibodies to staphylococcal superantigens; several studies using biologic agents have targeted exactly this spectrum of mediators. This goes in parallel with new knowledge on even more type 2 mediators derived from epithelial cells, which will expand the number of possible candidates for innovative intervention. (J Allergy Clin Immunol 2016;138:1277-83.)

Key words: *Allergic rhinitis, allergen components, allergen-specific immunotherapy, house dust mite, chronic rhinosinusitis, endotype, type 2 cytokines*

In the past year, exciting new knowledge was achieved, increasing our understanding in allergic rhinitis (AR), including its causal management approach immunotherapy, and chronic rhinosinusitis related to endotypig and disease pathomechanisms. We here summarize (Table I) these findings and discuss their impact on the field.

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
AFRS:	Allergic fungal rhinosinusitis
AIT:	Allergen-specific immunotherapy
AR:	Allergic rhinitis
BAMSE:	Swedish abbreviation for "Children, Allergy, Milieu, Stockholm, Epidemiology"
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
EXCELS:	Epidemiologic Study of Xolair: Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma
GR:	Glucocorticoid receptor
HDM:	House dust mite
ICS:	Inhaled corticosteroid
MUC1-CT:	Cytoplasmic tail of mucin 1
OSM:	Oncostatin M
PGD_2:	Prostaglandin D_2
Siglec:	Sialic acid–binding protein
SLIT:	Sublingual immunotherapy
TSLP:	Thymic stromal lymphopoietin

ALLERGIC RHINOCONJUNCTIVITIS

After a substantial increase in the prevalence of atopic dermatitis, asthma, and allergy in Europe for 2 decades,[1] a recent study in Denmark and Sweden[2] using national registers demonstrated a stable incidence rate for atopic dermatitis; an increase in asthma incidence until 2006 that then stabilized, at least in Denmark; and a decrease in allergic rhinoconjunctivitis incidence in both countries. One third of all 5-year-old children were affected with at least 1 of the conditions, but there was evidence that this number would not further increase. This situation might be different from what we see in developing countries in which allergies still are on the increase.[3]

Prediction of allergic disease

Great interest goes to the prediction of allergic disease and IgE formation in children. Allergen components can be differentiated into protein families; by using an allergen chip in a population-based birth cohort, 112 component-specific IgE responses were related to asthma, eczema, and hay fever.[4] About half of the allergens clustered into 3 component groups, consisting of components from plants, mites, animals, and fungi: component group 1 (27 components from 8 plants) was associated with AR, component group 2 (7 components from mites) was associated with rhinitis and asthma, and component group 3 (27 components from plants, animal, and fungal origin) was associated with asthma and low lung function parameters (FEV_1). No association

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TABLE I. Key advances in allergic rhinitis and chronic rhinosinusitis

- Component-resolved diagnosis might improve the prediction of future allergy in young children.
- There is little possibility to interfere with the natural course of disease through early-life environment or lifestyle changes.
- For the first time, evidence for the reduction of asthma risk by using AIT was achieved in adults in a real-life setting.
- High-dose HDM extract in infants less than 1 year of age at high risk of atopy significantly reduced sensitization to any common allergen.
- General claims for AIT should be replaced by product-specific evaluations.
- Efficacy of HDM (SQ HDM) allergy tablets was demonstrated in a challenge chamber and a double-blind, placebo-controlled randomized phase III trial in adults with moderate-to-severe HDM-induced AR.
- SQ HDM tablet treatment in adults with HDM allergy–related asthma improved time to first asthma exacerbation in a period of ICS reduction.
- A 5-grass-pollen tablet demonstrated efficacy for up to 2 years after treatment in a double-blind, placebo-controlled, randomized phase III trial.
- CRS consists of multiple groups of biological endotypes, which are defined by distinct pathophysiologic mechanisms.
- Endotypes can demonstrate differences in the natural course of disease, prognosis of recurrence, risk of comorbid asthma, and responsiveness to different treatments.
- Type 2 inflammation is associated with recurrence of disease after surgery in patients with CRSwNP.
- Biologics, such as omalizumab and dupilumab, have demonstrated efficacy in proof-of-concept studies in patients with CRSwNP.
- The epithelium-derived cytokines TSLP, IL-25, and IL-33 play an important role in innate type 2 reactions.
- T_H2 cytokines, and IL-13 more specifically, influence mucociliary clearance through induction of epithelial ion transport proteins.
- Eosinophils gain attention as central effector cells in both the innate and adaptive immune systems.

with eczema was observed. Similarly, component-resolved diagnosis might improve the prediction of future allergy in young children, as was shown using the BAMSE birth cohort.[5] IgE reactivity to the pathogenesis-related class 10 protein family, including Bet v 1 and other proteins, at 4 years of age was associated with AR to birch pollen and its severity at 16 years of age.

The longitudinal development of IgE patterns was also the subject of a study investigating the evolution of IgE responses to allergenic components of timothy grass and dust mites during childhood.[6] For grass pollen, there were 3 sensitization patterns: no/low sensitization, early-onset sensitization, or late-onset sensitization. The early-onset pattern was associated with asthma and diminished lung function, whereas the late-onset pattern was associated with rhinitis. For house dust mite (HDM) sensitization, it was important to note which allergens were included: no/low sensitization and sensitization to group 1 allergens, group 2 allergens, and both. Children with sensitization to both group 1 and 2 allergens had the highest odds ratios for asthma (odds ratio, 7.15; 95% CI, 3.80-13.44) and were the only group significantly associated with comorbid asthma, rhinitis, and eczema (odds ratio, 5.91; 95% CI, 2.01-17.37). Among children with wheezing, those with this pattern only had a significantly higher risk of severe exacerbations. Thus the analysis of allergen components might help predict the natural course of allergic airway diseases in the future.

Can we change the natural course of disease?

The question then arises whether we can also prevent those patterns by changing the early-life environment or lifestyle. Using the Multicenter Allergy Study cohort, risk factors for allergic rhin(oconjunctiv)itis up to age 20 years were analyzed.[7] The risk of AR was higher with a parental history of AR, early allergic sensitization, eczema within the first 3 years of life, male sex, and birthday in summer or autumn were independent predictors of AR up to age 20 years. However, none of the socioeconomic, environmental, lifestyle, pregnancy, or birth-related factors were associated with AR at age 20 years. This study indicated little possibility to interfere with the natural course of disease by early-life environment or lifestyle changes.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (AIT) is considered the only treatment option for allergic airway diseases, specifically for AR but increasingly also for asthma. AIT has been demonstrated to have a disease-modifying effect, which translates into long-term clinical improvements even after AIT is discontinued.[8] Allergen immunotherapy also has the potential to prevent the onset, progression, or both of asthma and reduce or slow down neosensitizations to other allergens.[9,10] In a prospective, randomized, double-blind, placebo-controlled proof-of-concept study involving 111 infants less than 1 year of age at high risk of atopy (≥2 first-degree relatives with allergic disease) but with negative skin prick test responses to common allergens, a high-dose HDM extract and appropriate placebo solution were administered orally twice daily for 12 months. The study showed a significant reduction in sensitization to any common allergen in the active (9%) compared with placebo (25%) treatment groups.[9]

For the first time, evidence for the reduction of asthma risk was also achieved in adults in a "real-life setting"[10]: using routine health care data from German National Health Insurance beneficiaries retrospectively, a consecutive cohort of 118,754 patients with AR but without asthma who had not received AIT in 2005 was identified. Two percent of those patients received AIT for about 3 years in 2006; asthma was newly diagnosed in 1.4% of all the patients from 2007-2012. The risk of incident asthma was significantly lower in patients exposed to AIT compared with those receiving no AIT in 2006 (risk reduction of 40%). Preventive effects were demonstrated for subcutaneous immunotherapy and native (nonallergoid) aqueous allergens; AIT tablets were not used in enough patients to test their preventive effects.

The recent year has seen excellent studies to support disease-modifying claims for AIT, which will be discussed here. At the same time, we moved away from the undifferentiated use of claims for every allergen preparation marketed that has never demonstrated evidence for efficacy and tolerability to product-specific evaluations.[11] The broad use of the abovementioned claims for all AIT products available is unjustified and should be replaced by a per-product appreciation of available evidence; this includes efficacy for the first year or 3 years of treatment or