Advances in adult asthma diagnosis and treatment in 2014

Andrea J. Apter, MD, MSc, MA *Philadelphia, Pa*

In 2014, new biologic therapies are emerging for severe asthma based on identification of relevant phenotypes. The exploration of nutritional supplements to treat asthma has been less successful. (J Allergy Clin Immunol 2015;135:46-53.)

Key words: *Asthma, adults, inhaled corticosteroids, asthma management*

Journal of Allergy and Clinical Immunology articles published in 2013 on adult asthma focused on its phenotypes, both their definitions and causes.[1,2] In 2014, this interest continued, leading to important potential applications for new therapies for severe asthma. Key advances in 2014 are summarized in Table I.[3-18]

Abbreviations used

AERD: Aspirin-exacerbated respiratory disease
CLCA1: Calcium-activated chloride channel regulator 1
COPD: Chronic obstructive pulmonary disease
FENO: Fraction of exhaled nitric oxide
GP: General practitioner
GWAS: Genome-wide association study
ICS: Inhaled corticosteroid
ILC: Innate lymphoid cell
IRF: Inhaler reminders and feedback
LABA: Long-acting β-agonist
NSAID: Nonsteroidal anti-inflammatory drug
PAD: Personalized adherence discussion
PGE_2: Prostaglandin E_2
RDBPCT: Randomized, double-blind, placebo-controlled trial
SLIT: Sublingual immunotherapy
Treg: Regulatory T
TRPV1: Transient receptor potential vanilloid 1

MECHANISMS OF DISEASE GUIDE THERAPEUTIC INNOVATIONS

Asthma research in 2014 has emphasized the role of T_H2-like immunity. One focus has been on innate lymphoid cells (ILCs),[19] innate non-T, non-B effector cells for which animal studies have implicated a role in regulating asthma. Type 2 ILCs (ILC2s), which were previously called nuocytes, produce IL-5, IL-9, and IL-13 in response to IL-33 and IL-25 (Fig 1).[19] Extending this research to the study of human ILC2s, Bartemes et al[20] cultured PBMCs from patients with allergic asthma (n = 18), patients with allergic rhinitis (n = 16), or healthy control subjects (n = 18) with IL-25 or IL-33. Innate type 2 responses and ILC2 numbers increased in those with asthma but not in those with allergic rhinitis or control subjects, suggesting a unique role for innate immunity in patients with allergic asthma and a potential future therapeutic target.

Traister et al[21] found increased expression of ST2L, the epithelial receptor for IL-33 (itself an IL-1 family cytokine), in endobronchial brushings and biopsy specimens from asthmatic adults and association of ST2L and its gene, *IL1RL1*, with severe T_H2-like asthma. T_H2-like asthma was assessed with a composite score reflecting blood eosinophil numbers, fraction of exhaled nitric oxide (FENO) values, epithelial calcium-activated chloride channel regulator 1 (CLCA1), and eotaxin 3. The importance of IL-33, which was noted above for its role in promoting ILC2s, gains further traction from a study in mice showing that *Alternaria* species–derived serine proteases can activate IL-33 release and T_H2-like inflammation with exacerbation of allergic airway disease.[22] Extrapolating from animal studies, Kinoshita et al[23] hypothesized that the regulatory T (Treg) cell response is insufficient to overcome T_H2 inflammation in patients with allergic asthma. In their analysis of induced sputum specimens from adults with mild allergic asthma, those who experienced both an early and late response to allergen challenge had a reduced ratio of $CD4^+$ forkhead box protein 3–positive Treg cells to total $CD4^+$ cells compared with those with only an immediate response. Further study is needed to determine whether the reduced Treg cell/total $CD4^+$ cell ratio was a cause or an effect of the biphasic inflammatory response and whether this will improve insight into T_H2-like asthma mechanisms and treatment possibilities.

New findings regarding clinical presentations and pathways governing aspirin-exacerbated respiratory diseases (AERDs) and a clinical review of management appeared in the *Journal* during 2014.[24] Using latent class analysis, Bochenek et al[25] identified 4 clinical AERD subphenotypes, suggesting that AERD might involve heterogeneous mechanisms and benefit from targeted therapies. Laidlaw et al[26] found granulocytes from patients with AERD generated more leukotriene B_4 and cysteinyl leukotrienes than those of patients with aspirin-tolerant asthma or control subjects. Compared with nonasthmatic control subjects, granulocytes from patients with AERD had similar levels of E prostanoid and prostaglandin E_2 (PGE_2)–mediated cyclic AMP but were resistant to PGE_2 suppression of leukotriene generation. Impaired protein kinase A function leading to failure of suppression of

From the Division of Pulmonary, Allergy, & Critical Care Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania.

Disclosure of potential conflict of interest: A. J. Apter is employed by the University of Pennsylvania.

Received for publication October 28, 2014; accepted for publication October 30, 2014.

Corresponding author: Andrea J. Apter, MD, MSc, MA, 829 Gates Building, Hospital of the University of Pennsylvania, 3600 Spruce St, Philadelphia, PA 19104. E-mail: apter@mail.med.upenn.edu.

0091-6749/$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2014.10.050

TABLE I. Key findings in the care of adults with asthma reported in 2014

- Cluster analysis is being widely used to identify distinct and clinically relevant phenotypes.[4-10,13]
- Definition of phenotype can lead to individualized treatments.[3,8,10,13,16,17]
- Distinguishing eosinophilic from noneosinophilic inflammation has led to new therapeutics.[16,17]
- Mepolizumab is associated with decreased exacerbations of eosinophilic asthma.[16,17]
- Severe childhood asthma and childhood allergic rhinitis predict asthma presence and morbidity at age 50 years.[11,12]
- Vitamin D3 supplementation in symptomatic asthmatic adults with vitamin D deficiency did not reduce the rate of first treatment failure or exacerbation.[14]
- In a small study an anti–thymic stromal lymphopoietin antibody attenuated the late decrease in FEV_1 after allergen challenge.[15]
- A postmarketing study of the safety of omalizumab found no evidence of increased risk of malignancy.[18]

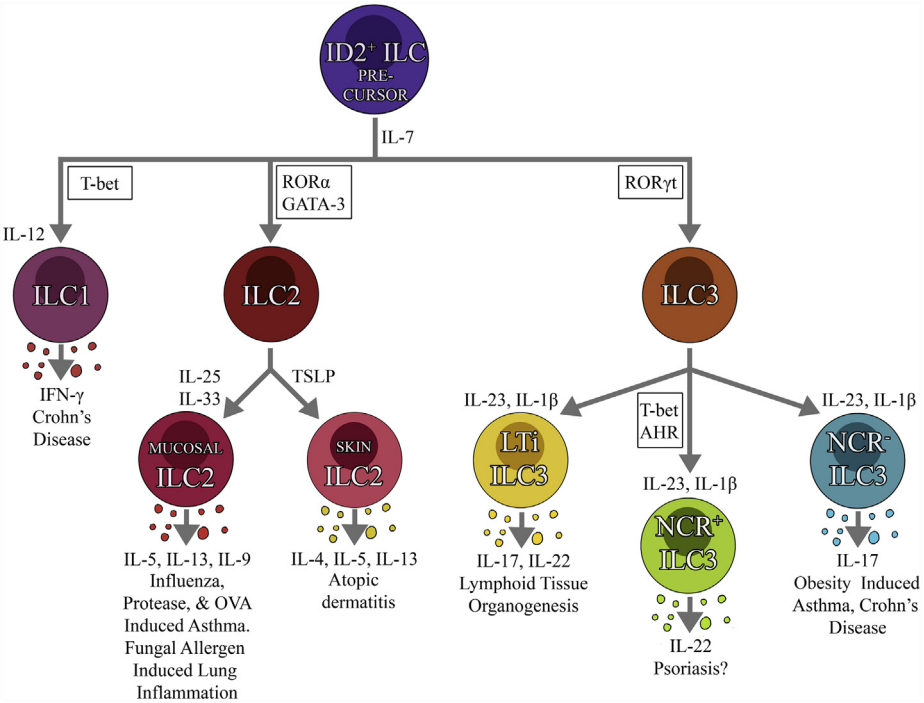

FIG 1. Development and function of ILCs. All ILCs develop from a common precursor cell characterized by expression of the transcriptional repressor inhibitor of DNA binding 2 *(ID2)*, expression of the common cytokine receptor γ chain (not shown), and dependence on IL-7 for development. ILC1s produce IFN-γ on stimulation with IL-12, depend on T-bet for their development, and are involved in the pathogenesis of Crohn disease. ILC2s depend on the transcription factors GATA-3 and retinoic acid–related orphan receptor *(ROR)* α for their development. They produce IL-5, IL-13, and IL-9, although skin ILC2s are reported to produce IL-4, IL-5, and IL-13. ILC2s are activated by stimulation with IL-33, IL-25, and IL-2 and participate in the development of some forms of asthma. Different from mucosal ILC2s, the skin ILC2 response is elicited by thymic stromal lymphopoietin *(TSLP)* and promotes atopic dermatitis. ILC3s require the transcription factor RORγt for their development and respond to IL-23 and IL-1β. ILC3s include 3 different subsets: lymphoid tissue inducer *(LTi)* ILC3s, natural cytotoxicity receptor *(NCR)*$^+$ ILC3s, and NCR$^-$ ILC3s. LTi ILC3s play an important role in lymphoid tissue organogenesis and produce IL-17 and IL-22. NCR$^-$ ILC3s express CCR6, produce IL-17 and sometimes IL-22, and are critical in the development of obesity-induced asthma and inflammatory bowel disease. NCR$^+$ ILC3s produce IL-22 and also depend on the aryl hydrocarbon receptor *(AHR)* and T-bet for their function. Some ILC3s downregulate RORγt and transform into ILC1s. NCR$^+$ ILC3s might contribute to the development of psoriasis. *OVA*, Ovalbumin. The figure and figure legend are used with permission from Yu et al.[19]

5-lipoxyenase activity by PGE_2 was a factor. These findings were corroborated in part by mouse studies.[27]

Using a mouse model to study allergic airway disease, Hatchwell et al[28] observed that salmeterol exerts anti-inflammatory effects by increasing levels of protein phosphatase 2A, which attenuates the chemotactic response to rhinovirus and subsequent exacerbation. This finding is likely to attract clinical attention.

GENETIC INFLUENCES OF POTENTIAL CLINICAL RELEVANCE

Personalized asthma management will require an understanding of genetic influences on disease and medication efficacy derived from studies of diverse populations with differing genetic variability and admixture, as well as differing environmental exposures. This is discussed by Ortega and Meyers,[29] who note the need to expand research beyond European white subjects, who

Download English Version:

https://daneshyari.com/en/article/6065514

Download Persian Version:

https://daneshyari.com/article/6065514

Daneshyari.com