



Contents lists available at ScienceDirect

Allergy International

journal homepage: <http://www.elsevier.com/locate/alit>

Editorial

What we know, do not know, and should know about severe asthma

In *Allergy International* (AI) vol. 68, Issue 2, we feature a set of review articles entitled “What We Know, Do Not Know, and Should Know about Severe Asthma” as well as original articles and letters to the editor. We believe that this issue will greatly contribute to our readers’ understanding of the phenotyping of severe asthma and of strategies for its treatment.

Although classifying asthma is useful to understand its pathophysiology, for the management of mild to moderate asthma in clinical practice, standard therapies have been generally effective, regardless of the disease subtype. In contrast, treatment strategies for severe asthma, which cannot be controlled with high-dose inhaled corticosteroids and long-acting bronchodilators, need to be tailored to the individual case, based on phenotypes and biomarkers. For example, an anti-IL-5 antibody, mepolizumab, is useful only in patients with severe eosinophilic asthma.¹

Since Halder reported four distinct phenotypes in 2008,² phenotyping of severe asthma using cluster analysis has attracted the attention of researchers. Based on large cohort studies such as ENFUMOSA and U-BIOPRED in Europe, SARP in the US, and others, age at onset (early-onset vs. later-onset) and co-morbidities such as obesity and underlying immunological mechanisms (type 2 vs. non-type 2) are considered to be essential factors in defining the phenotypes of severe asthma.³ The ERS/ATS international guidelines published in 2014 state that there are at least three major phenotypes of severe asthma: early-onset allergic, later-onset obese, and later-onset eosinophilic.⁴

This review series include five articles written by distinguished international researchers on various aspects of severe asthma. Tashiro and Shore describe the epidemiology and clinical characteristics of obesity-related severe asthma.⁵ This phenotype is of the later-onset type, more common in women, and dominated by neutrophils in the sputum. Vitamin D deficiency, systemic inflammation induced by IL-6 and IL-1 β , and dysbiosis of the gut microbiome are all possible mechanisms behind this phenotype, as discussed by the authors.

Type 2 and non-type 2 inflammation are both important in the pathophysiology of severe asthma. Type 2 inflammation is characterized by airway eosinophilia along with Th2 cytokines released from Th2 cells and group 2 innate lymphoid cells.⁶ In contrast, the mechanisms of neutrophilic, non-type 2, inflammation are less well characterized. Duvall, Krishnamoorthy, and Levy demonstrate

the role of dysregulated release of pro-resolving lipid mediators such as lipoxin A4 and decreased numbers of NK cells in the key mechanisms of non-type 2 inflammation.⁷ They also explore the roles of neutrophilic extracellular traps (NETs) and enucleated neutrophil cytoplasts, showing that cytoplasts can induce antigen-specific, IL-17–producing cells.

Two phenotypes of severe asthma are related to type 2 immunological mechanisms: early-onset allergic and later-onset eosinophilic. Pediatric asthma is mostly atopic and presents as the early-onset allergic phenotype. Haktanir-Abul and Phipatanakul comprehensively review this type of severe asthma, from diagnosis to treatment.⁸

Several biologics—such as anti-IgE antibody, anti-IL-5 antibody, and anti-IL-5 receptor antibody—are already on the market for the treatment of type 2 severe asthma. New drugs, such as anti-IL-4 receptor α chain antibody, will be available soon. Since these antibodies are effective only when applied to the appropriate cases, a detailed knowledge of the modes of action of these drugs and of biomarkers to identify the target phenotypes, as described by Busse, will be helpful for clinicians.⁹

Japanese researchers involved in cohort studies such as KiHAC in Western Japan, KEIO-SARP in Eastern Japan, and HiCARAT in Northern Japan have made substantial contributions in the field of severe asthma research. A review by Nagase thoroughly covers the research outcomes from Japan.¹⁰

There has been substantial progress in the research and clinical management of severe asthma during the last decade. Clinicians and researchers who read this review series will be able to understand what has been clarified so far and what are still unmet needs.

In addition, several interesting clinical and basic research papers are published as original articles in this issue of AI.

The prevalence of non-IgE-mediated food gastrointestinal food allergies (non-IgE-GI-FAs)—including food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), and food protein-induced enteropathy (FPE)—has recently been increasing worldwide in both neonates and infants. The classification of non-IgE-GI-FAs by severity is a prerequisite for appropriate treatment of these diseases. Yagi and her colleagues propose a severity grading system based on concomitant extra-gastrointestinal symptoms such as poor weight gain, fever, and shock.¹¹ They report that the degree of severity evaluated by this

system is associated with laboratory and pathological findings, response to treatment, and prognosis. This severity grading system should be useful in the clinical setting to select appropriate treatment and to predict prognosis.

Late-phase reactions (LPRs) are characterized by eosinophil-rich inflammation, which contributes to the augmented symptoms of allergic conjunctivitis as well as of asthma and of atopic dermatitis. It is known that periostin, an extracellular protein, is highly expressed in the inflamed regions of allergic conjunctivitis.¹² Asada and his colleagues show that in ragweed-induced experimental allergic conjunctivitis (RW-EAC) in mice, periostin is critical to establish LPRs, but not sensitization or acute-phase reactions.¹³ The number of eosinophils in the conjunctival tissue of RW-EAC decreased by about 90% in periostin-deficient mice compared with wild-type mice, in association with significant reduction of CCL5/RANTES expression in the tissue. Thus, periostin may have a unique role in the development of LPRs in allergic conjunctivitis.

Obesity is a well-known risk factor for asthma. However, most of the evidence is based on studies from Western countries, often involving a cross-sectional design. Tomita and his colleagues clarify that in women, but not in men, overweight (BMI ≥ 25 kg/m²), obesity (≥ 30 kg/m²), or waist circumference ≥ 90 cm are associated with an increased risk of new-onset asthma by analyzing data extracted from a longitudinal database of health insurance claims.¹⁴ Although obesity is closely linked with metabolic disorders, metabolic syndrome was unrelated to the incidence of asthma. This study highlights the impact of obesity on adult-onset asthma in middle-aged Japanese women.

It is known that aspirin exacerbates food allergy symptoms in patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) and that one of the underlying mechanisms is to promote absorption of ingested allergens, such as wheat gliadin proteins. Yokooji and his colleagues demonstrate that in rats, aspirin promotes absorption of not only pepsin-digested gliadin but also of undigested gliadin into the blood, maintaining allergenicity, possibly via the paracellular intestinal transport pathway.¹⁵ Although this study used naive rats, it sheds new light on the pathophysiological mechanisms underlying food allergies including WDEIA.

We offer our appreciation to all the authors for their contributions to the present issue of *Allergy International*.

Koichiro Asano^a, Kenji Izuhara^{b,*}

^a Division of Pulmonary Medicine, Department of Medicine, Tokai University, School of Medicine, Kanagawa, Japan

^b Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan

* Corresponding author. Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, 5-1-1 Nabeshima, Saga 849-8501, Japan.

E-mail address: kizuhara@cc.saga-u.ac.jp (K. Izuhara).

References

- Ortega H, Li H, Suruki R, Albers F, Gordon D, Yancey S. Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. *Ann Am Thorac Soc* 2014;**11**:1011–7.
- Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–24.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;**181**:315–23.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;**43**:343–73.
- Tashiro H, Shore SA. Obesity and severe asthma. *Allergol Int* 2019;**68**:135–42.
- Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;**16**:45–56.
- Duvall MG, Krishnamoorthy N, Levy BD. Non-type 2 inflammation in severe asthma is propelled by neutrophil cytoplasts and maintained by defective resolution. *Allergol Int* 2019;**68**:143–9.
- Haktanir Abul M, Phipatanakul W. Severe asthma in children: evaluation and management. *Allergol Int* 2019;**68**:150–7.
- Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int* 2019;**68**:158–66.
- Nagase H. Severe asthma in Japan. *Allergol Int* 2019;**68**:167–71.
- Yagi H, Takizawa T, Sato K, Inoue T, Nishida Y, Ishige T, et al. Severity scales of non-IgE-mediated gastrointestinal food allergies in neonates and infants. *Allergol Int* 2019;**68**:178–84.
- Fujishima H, Okada N, Matsumoto K, Fukagawa K, Igarashi A, Matsuda A, et al. The usefulness of measuring tear periostin for the diagnosis and management of ocular allergic diseases. *J Allergy Clin Immunol* 2016;**138**:459–67.
- Asada Y, Okano M, Ishida W, Iwamoto S, Fukuda K, Hirakata T, et al. Periostin deletion suppresses late-phase response in mouse experimental allergic conjunctivitis. *Allergol Int* 2019;**68**:233–9.
- Tomita Y, Fukutomi Y, Irie M, Azekawa K, Hayashi H, Kamide Y, et al. Obesity, but not metabolic syndrome, as a risk factor for late-onset asthma in Japanese women. *Allergol Int* 2019;**68**:240–6.
- Yokooji T, Fukushima T, Hamura K, Ninomiya N, Ohashi R, Taogoshi T, et al. Intestinal absorption of the wheat allergen gliadin in rats. *Allergol Int* 2019;**68**:247–53.

Conflict of interest

The authors have no conflict of interest to declare.

Received 19 February 2019