ARCHIVOS DE
Bronconeumología

Editorial

Novel Biomarkers in Severe Asthma[☆]

Nuevos biomarcadores del asma grave

Eleftherios Zervas, Konstantinos Samitas, Mina Gaga[*]

7th Respiratory Medicine Dept. and Asthma Center, Athens Chest Hospital «Sotiria», Atenas, Greece

Severe asthma is increasingly associated with many different specific phenotypes and endotypes as well as increased morbidity. Asthma-related healthcare costs are rising, accompanied by a pressing need for effective therapy.[1] Although there are no definitive epidemiologic data on the prevalence of severe asthma, approximately 5%–10% of patients are probably affected by severe asthma, and 1%–2% of these, with significant geographic variations, have severe treatment-resistant/refractory asthma.[1,2]

The concept of asthma severity has evolved substantially over the years. According to the latest joint ERS/ATS Taskforce, severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy.[2] It is, however, increasingly recognized that severe asthma is not a single disease, as evidenced by the variety of clinical presentations, pathophysiological characteristics and outcomes. Studies of severe asthma cohorts, such as the ENFUMOSA/BIOAIR studies, the TENOR/SARP studies, the Belgium Severe Asthma study and, more recently, the U-BIOPRED study, also show that severe asthma is an extremely heterogeneous disease in terms of clinical presentation and pathophysiologic mechanisms. Asthma is usually characterized as a T2-high disease, associated with atopy and/or eosinophilic airway inflammation. However, inflammation in severe asthma is not necessarily characterized by eosinophilia and Th2 type cytokines, but may in many cases be T2-low, either neutrophilic or pauci-granulocytic.[3]

The T2-high asthmatic endotypes are associated with increased epithelial expression of Th2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13. Although heterogeneous in nature, the designation of the Th2-high endotype has primarily been based on the presence of eosinophilic airway inflammation, with sputum and/or blood eosinophils used as relevant biomarkers.[4] Other well studied and established biomarkers for T2-high asthma are exhaled NO, total IgE and serum periostin. In a recent study by Busse et al., the cut points used to define a high level of T2 immune activation were IgE $\geq$100 IU/mL, eosinophil count $\geq$300/mL and F_{ENO} $\geq$30 parts per billion.[5] Total IgE and blood eosinophils are currently biomarkers of disease and also key-elements in the management algorithm for a specific subgroup of severe asthmatics eligible for anti-IgE (omalizumab), anti-IL-5 (mepolizumab) and anti-IL-4Ra (dupilumab) treatment. Moreover, periostin-high severe asthmatics have been found to be more responsive to anti-IL-13 treatment with lebrikizumab. The usefulness of combining biomarkers for T2-high severe asthmatic disease was also shown in a study by Hanania et al., which demonstrated that severe atopic asthmatics with high IgE levels and high T2 markers, i.e., elevated blood eosinophils, FeNO, and periostin, were better responders when treated with omalizumab.[6] Novel research on T2-high biomarkers also includes angiopoietins-1, osteopontin, GM-CSF and IL-13.

T2-low disease was initially considered to be a rather rare entity in the context of severe asthma. However, recent data indicate that it may affect up to one third of severe asthmatics.[7] Although T2-high asthma with atopy and/or eosinophilia is easy to distinguish, there is no widely-accepted definition of T2-low disease. In most cases, the T2-low endotype is defined by the absence of markers of Th2-mediated inflammation, and is usually characterized by neutrophilic or, less commonly, pauci-granulocytic infiltration in the airways. However, there is no consensus regarding the percentage of sputum neutrophils required to define the neutrophilic asthma phenotype, and different cut-off values, ranging from 40% to 76%, have been used in the literature.[3] Besides sputum differential cell counts, other specific biomarkers to discriminate T2-low from T2-high asthma are under investigation, but are not yet used in clinical practice.[8] IL-8, a cytokine related to neutrophilic chemotaxis and degranulation, is elevated in the sputum of patients with treatment-resistant severe asthma, and is associated with airway colonization with potentially pathogenic micro-organisms and neutrophilic airway inflammation.[9] Moreover, receptors for IL-8, such as CXCR1 and CXCR2, are increased in the sputum of patients with neutrophilic asthma. Myeloperoxidase (MPO) and neutrophil elastase (NE) are 2 other biomarkers under investigation for neutrophilic asthma, mainly assessed in the sputum of severe asthmatics.[10] TNF-α started as a promising biomarker and target for treatment in neutrophilic severe asthma, however initial clinical studies were rather disappointing. Recently, IL-17, a biomarker of Th17 pathway activation leading to non-type 2 inflammation, has also been the subject of evaluation as a biomarker and a strong correlation between IL-17 and both IL-8 and neutrophils has been proven in induced sputum and blood of

severe asthmatics.[11] All possible biomarkers discussed above concern neutrophilic T2-low asthmatic endotype; in the subgroup of patients with pauci-granulocytic asthma there is a lack of characteristic biomarkers. As this patient population lacks a predominant inflammatory type, it is possible that other markers of cardinal features of severe asthma, such as airway remodelling (i.e., osteopontin or angiopoetins), may serve as relevant biomarkers.

In conclusion, current strategies in the management of severe asthma involve the use of biomarkers in phenotyping and the treatment decision-making process. We currently have a number of well-studied and established biomarkers for T2-high severe asthma, however there is a clear need for biomarkers in severe T2-low disease. Currently, the most logical approach to identify T2-low asthma in everyday clinical practice is to consider the absence of markers of atopic and/or eosinophilic asthma. Understanding the pathogenetic mechanisms behind the T2-low endotype is a necessary step in identifying future biomarkers.

References

1. Gaga M, Zervas E, Samitas K, Bel EH. Severe asthma in adults: an orphan disease? Clin Chest Med. 2012;33:571–83.
2. 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.
3. Samitas K, Zervas E, Gaga M. T2-low asthma: current approach to diagnosis and therapy. Curr Opin Pulm Med. 2017;23:48–55.
4. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4:549–56.
5. Busse WW, Holgate ST, Wenzel SW, Klekotka P, Chon Y, Feng J, et al. Biomarker profiles in asthma with high vs low airway reversibility and poor disease control. Chest. 2015;148:1489–96.
6. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187:804–11.
7. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med. 2014;108:1723–32.
8. Schleich F, Sophie D, Renaud L. Biomarkers in the management of difficult asthma. Curr Top Med Chem. 2016;16:1561–73.
9. Green BJ, Wiriyachaiporn S, Grainge C, Rogers GB, Kehagia V, Lau L, et al. Potentially pathogenic airway bacteria and neutrophilic inflammation in treatment resistant severe asthma. PLOS ONE. 2014;9:e100645.
10. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. Chest. 2012;142:86–93.
11. Agache I, Ciobanu C, Agache C, Anghel M. Increased serum IL-17 is an independent risk factor for severe asthma. Respir Med. 2010;104:1131–7.