Severe refractory asthma: An asthma phenotype with multiple phenotypes?

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Asthma is a one of the most common diseases, affecting patients of both sexes and all age groups. Tremendous progress has been made in the diagnosis, management and pharmacological treatment of patients with asthma during the last three decades. This progress can be attributed to the better understanding of the pathophysiology of the disease, to the use of inhaled steroids (ICS), and finally to the quality of medical services available for the patient with asthma. For the majority of patients with asthma who have access to healthcare services the disease can be controlled with the current treatment regimes. A small percentage of patients, however, ranging between 5% and 10% in different population groups, continue to be symptomatic and experience asthma exacerbations despite the initiation of appropriate treatment, even with higher doses of ICS than those recommended by the guidelines[1].

Many approaches have been tried with regard to the definition of severe refractory asthma (SRA). It is important to differentiate the term SRA from the term "difficult to treat" asthma[2], which is used to describe patients whose asthma remains uncontrolled due to factors other than the asthma itself. These factors include persistent exposure to environmental factors, poor adherence to treatment and the presence of co-morbidities which influence asthma control both clinically and functionally, as well as the possible misdiagnosis of asthma in the case of disease entities with similar clinical presentation. We believe that the term SRA should be reserved for those patients whose symptoms persist and are difficult to control despite an extensive re-evaluation of the diagnosis, identification and avoidance of confounding environmental factors and appropriate management of aggravating co-morbidities, with all above criteria being applicable after observation for at least 6 months by an asthma expert[3]. A recently published international consensus provides evidence using an algorithm based approach for the evaluation of patients with symptoms and signs compatible with SRA[2]. This algorithmic approach must be used in all specialized centres in order to define effectively this special group of patients with asthma.

It is currently accepted that the term SRA, in terms of both the clinical presentation and the inflammatory process, is not homogenous. It is important to point out that some of the clinical phenotypes are related to the inflammatory phenotypes, indicating a complex mechanism in the field of sub-phenotypes in SRA[4]. The main clinical phenotypes are related to the

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exacerbation rate, the use of systemic steroids to achieve control and to persistent and irreversible airway obstruction. The main inflammatory phenotypes are based on the presence or absence of eosinophils[5]. These particular phenotypes are considered to be important, since they can predict the response to target-specific forms of treatment, including the recent paradigm of anti-IL-5 treatment for SRA with persistent eosinophilia[6]. Two major issues need to be addressed. The first is related to the different regulatory process of the Th1/Th2 paradigm and the second is the additive effect of other mechanisms which mediate SRA inflammation. It is also crucial to emphasize that it is possible that the whole process of SRA might be influenced by interactions between genetic and environmental factors. Genome studies have focussed on responsible genes which could identify both patients at risk and possible target therapies.

Since airway inflammation is considered a key component of SRA, an important step will be the identification of specific inflammatory patterns, not only for research purposes but also for the selection of the optimal treatment regimes. The use of fiberoptic bronchoscopy, and in particular the histopathological evaluation of bronchial biopsies, have helped us not only to identify and characterize the inflammatory cells and mediators, but also to correlate levels of individual cell types, cytokines and mediators with specific patterns of airway remodelling. Since the invasive procedures are not always acceptable for the patient, the field of non-invasive evaluation of airway inflammation has evolved in an attempt to overcome the difficulties posed by invasive techniques. A wide range of sampling procedures with their respective biomarkers is currently available. According to the published evidence, examination of induced sputum is of clinical importance for the differentiation between the eosinophilic and non-eosinophilic patterns of the disease[7]. Regarding the value of the fraction of exhaled nitric oxide (FeNO) it appears that high levels are highly predictable for the identification of eosinophilic inflammation, but low levels cannot exclude it, particularly when there is an upregulation of neutrophils[8,9].

Treating SRA is still the main problem of this specific phenotype, since it is characterized by partial resistance to the currently available forms of treatment. High doses of ICS plus the use of systemic steroids at the lowest possible dose needed to maintain asthma control are the main treatment options in SRA. Omalizumab, a monoclonal antibody against IgE, has been established as a treatment step in SRA patients with atopy[10]. Bronchial thermoplasty has been shown to be associated with some benefits, but its overall value is considered limited[11]. Looking into the future, we believe that the targeted inhibition of inflammatory mediators provides some promising research results, but is still far from application in clinical practice. What we need are studies involving large numbers of patients with SRA in order to examine strictly the treatment options for them and to define the relevant phenotypes which will be sensitive to effective targeted therapy.

The aim of the series on SRA presented in the current and following issues of the "Pneumon" journal is to present a detailed overview of this particular asthma phenotype. In collaboration with our Greek colleagues, we have invited a distinguished faculty of international experts in the field to provide a comprehensive overview of the genetics, the pathophysiology, the inflammatory process, the diagnostic challenges, the non-invasive assessment and the management options of SRA[12-16]. Sometimes it is quite difficult not only to treat these patients but even to identify them, and particularly to sub-phenotype them according to the underlying inflammatory process and/or the clinical presentation. The greatest efforts must be focussed on the diagnostic procedure, and particularly on the area of overlap with other diseases that present with similar clinical signs and symptoms. The international perspective on the diagnostic criteria of severe asthma and the proposed algorithm used for the identification of patients at risk are the cornerstones for the management of SRA. Looking to the future, we strongly believe that phenotypic characterization of severe asthma in its multiplicity is the crucial step for creating target specific therapies.

REFERENCES

1. Global strategy for asthma management and prevention. National Institutes of Health. National Heart, Lung and Blood Institute. NIH Publication, 2010 updated.
2. Bel EH, Sousa A, Fleming L, et al; on behalf of the members of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011 May 27. [Epub ahead of print]
3. American Thoracic Society. Proceedings of the ATS Workshop on Refractory Asthma. Current understanding, Recommendation, and Unanswered Questions. Am J Respir Critical Care Med 2000; 162:2341-2351.
4. Kaminska M, Foley S, Maghni K, et al. Airway remodeling in subjects with severe asthma with or without chronic persistent

airflow obstruction. J Allergy Clin Immunol 2009; 124:45-51.
5. Lemiere C, Ernst P, Olivenstein R, et al. Airway inflammation assessed by invasive and noninvasive means in severe asthma: Eosinophilic and noneosinophilic phenotypes. J Allergy Clin Immunol 2006; 118:1033-1039.
6. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973-84.
7. Brightling CE. Clinical applications of induced sputum. Chest 2006; 129:1344-1348.
8. Silkoff PE, Lent AM, Busacker AA, et al. Exhaled nitric oxide identifies the persistent eosinophilic phenotype in severe refractory asthma. J Allergy Clin Immunol 2005; 116:1249-55.
9. Tseliou E, Bessa V, Hillas G, et al. Exhaled nitric oxide and exhaled breath condensate pH in severe refractory asthma. Chest 2010; 138:107-13.
10. Gruenberg D, Busse W. Biologic therapies for asthma. Curr Opin Pulm Med 2010; 16:19-24.
11. Gildea TR, Khatri SB, Castro M. Bronchial thermoplasty: A new treatment for severe refractory asthma. Cleve Clin J Med2011; 78:477-85.
12. Rovina N, Baraldo S, Saetta M. Severe asthma: Inflammation. Pneumon 2011, 24:201-208.
13. Steiropoulos P, Ito K. Genes and Severe asthma. Pneumon 2011, 24:202-209.
14. Tzortzaki EG, Papi A, Siafakas NM. Severe Asthma: Diagnostic Criteria & Diagnostic Problems. Pneumon 2011, in press.
15. Katsaounou P, Asimakos A, Barnes PJ. Non invasive assessment of Severe asthma. Pneumon 2011, in press.
16. Zervas E, Brightling C, Gaga M. Severe asthma - current and future treatments. Pneumon 2011, in press.