Asthma: still a promising future?

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The pathobiology of asthma is better understood but most of the treatments are still symptom-driven controllers http://ow.ly/CUxjy

To date, asthma remains one of the most frequent chronic diseases in children and adults worldwide [1, 2]. Despite our increased knowledge of the mechanisms and treatments of asthma, we need to better understand the natural history of this lifelong disease. In mild asthma, compliance and adherence to existing and efficient therapies are the main problem whereas in severe asthma, innovative treatments are the new challenges to better control the disease [3–5]. A new series on asthma is, therefore, very welcome in the *European Respiratory Review* in order to focus on specific areas discussed in recent findings. These series articles, written by expert opinion leaders, can be used to stimulate new ideas as well as provide new forms of management and treatment [6]. The articles deal with hot topics requiring balanced expertise and opinion. The experts will discuss new views on those important questions for researchers and physicians.

The continuing increase in asthma prevalence (more than 400 million cases by 2020) points to a potential role of risk factors. Genetic background is obvious but multiple genes are involved and have been shown to be influenced by environmental factors (epigenetics), even during the gestation period. Lifestyle and environmental exposures are the most commonly studied risk factors. Their role in the inception of asthma is still a matter of debate and despite much research between allergy and asthma the causality between the two has yet to be demonstrated. The hygiene hypothesis is an elegant way to bring together the development of a switch of the immune system and contact with a specific microbial environment. A specific link with nurture is suspected in children with some specific genetic polymorphisms, but again allergy and asthma are not completely discriminated in most studies. The geolocalisation of the subjects (using personal GPS) and the precise environmental exposure to pollutants, allergens and microbes may help to define a more personalised risk to developing the disease [1].

The characteristic mechanisms of asthma include bronchial hyperreactivity, airway inflammation and structural changes of the airways. These different pathways may explain many of the clinical phenotypes, symptoms and exacerbations, and perhaps natural history, of the disease. Eosinophils are key players as the major granulocytes that are recruited, activated and survive within the airway wall, and also migrate to the epithelium lumen [1]. Asthmatic inflammation is associated with an eosinophilic T-helper (Th)2-driven mechanism based on the release of cytokines, such as interleukin (IL)-5, IL-4 and IL-13. This well-established inflammation model is based on various allergic responses requiring an adaptive immune pathway. More recently, it was found that bronchial epithelial cells can communicate with immune cells, such as dendritic cells and innate lymphocytes, though the release of mediators such as thymic stromal lymphopoietin (TSLP), IL-25 or IL-33. This cooperation leads to airway inflammation without a constant need for adaptive immune cell commitment. The respective roles of innate and adaptive immunity requires further clarification, but the role of innate cells in control of eosinophil recruitment is being investigated.

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Interestingly, both immunity pathways may collaborate to amplify the phenomenon. Bronchial epithelial cells are key in sensing deleterious agents like viruses, allergens or pollutants through specific or nonspecific receptors, such as pathogen-associated molecular patterns, NOD2 or the family of Toll-like receptors. Dendritic cells and innate lymphocytes possess receptors for TSLP. IL-33 and IL-25 can mature and be activated by these pathways leading to the release of cytokines previously considered as Th2 related. Natural killer and type-2 innate lymphoid cells are activated in severe asthma, and have been linked to eosinophilia and the promotion of cytokine release. Lipoxin A4, a mediator derived from the arachidonic metabolism, has been shown to promote the resolution of inflammation linked to innate immunity by inhibiting the *in vitro* release of IL-13 by type-2 innate lymphoid cells and promoting the apoptosis of eosinophils induced by natural killer cells. Because of the potential defect of lipoxin and other pro-resolution mediators released in severe asthma, hyperactivation of innate immunity may participate in the perpetuation of airway inflammation in these patients, despite current pharmacological treatments [3, 7, 8].

Corticosteroids are still the cornerstone treatment for asthma. In the concordant phenotype, characterised by early onset, usual allergic trigger and eosinophilic bronchial inflammation, low doses of inhaled corticosteroid are usually efficient and safely control the disease. However, if the level of evidence in the literature is high enough to sustain their use as stated in the guidelines, the overall response at a group level is heterogeneous and will depend on the outcomes being studied. The concept of variable corticoresponsiveness is more interesting to investigate than complete corticoresistance, which is rare.

New interventions are currently under development for severe asthma [7, 9–11]. The anti-IL-5 strategy is the most advanced. Findings from proof-of-concept studies in severe asthma with a persistent eosinophilic phenotype, despite high dose of inhaled corticosteroids and long-acting β-agonists therapies, were confirmed in larger multicentre studies. Exacerbation rate and time to first exacerbation were significantly lower in the treated arm compared with the placebo arm in two large studies of mepolizumab [10]. New treatments are emerging for severe asthma, including new anti-IgE therapies and biotherapies against ''Th2-high'' well-phenotyped patients (anti-IL-13, anti-IL4R/IL-13). Original molecules against epithelium-derived cytokines, such as TSLP and IL-33 or IL-25, are at an early stage but may find their place. Anti-allergic therapies using tablets have been developed to demonstrate efficiency in allergy-driven asthma. We are at the start of a new period when we need to find an organised strategy for the use and combination of these new treatments. Perhaps in the future several lines of biologics will be used subsequently or concomitantly to achieve an optimal control. The major issue remains the cost and the need for the health authorities to compare drugs and evaluate long-term efficacy and safety.

Bronchial thermoplasty is a technique that is available worldwide to treat asthma, and has been approved by several health agencies including the European Medicines Agency and the US Food and Drug Administration [12–14]. It is a new, yet promising treatment for severe asthma. The benefit of long-term asthma control outweighs the short-term risk of deterioration and hospitalisation in the days following treatment according to current literature. However, many questions remain concerning the mechanisms of action of this treatment and many studies are ongoing to find out the optimal responders to bronchial thermoplasty.

Overall, the future for asthma is promising. We are on our way to discovering the roots of the disease with potential for early intervention. New mechanisms have emerged that can provide new biomarkers and focused targets for intervention. It is an important time with drugs that can impact on the natural history of the disease, possibly cure mild asthma, and considerably improve the control and quality of life of the most severe patients. We hope this series in the *European Respiratory Review* will contribute to reporting this knowledge and provide up-to-date information on this ''new deal period'' in asthma.

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