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EDITORIAL

Fixed obstruction in severe asthma: not just a matter of time

M. Gaga

Over the last 20 yrs, extensive investigation of the pathogenetic mechanisms of asthma has led to a better understanding of the disease and to a more cognitive approach to its therapies. Controlled studies show that most asthmatic patients can achieve asthma control and lead normal lives with moderate doses of medication [1, 2], but surveys show that a substantial number of patients still face symptoms and limitations, probably due to inadequate management [3]. This is a matter of concern for both the medical community and health authorities, as control of asthma can and should be achieved in the majority of patients. Nevertheless, there still remain some asthmatics who have persistent symptoms and frequent exacerbations despite specialist care and continuous, intensive, high-dose treatment [4–6]. These severe and difficult-to-treat asthma patients have impaired health status and account for over half of the cost of the disease and probably all of its mortality [7]. Risk factors and mechanisms involved in this situation are not clear, and the clinical presentation is not homogeneous. Recent series have shown that severe and uncontrolled asthma may be associated with psychopathology, nonadherence to therapy, poor socioeconomic status, continuous exposure to inducing factors, severe upper airways disease, gastro-oesophageal reflux and viral or *Chlamydia pneumoniae* infection [4–6, 8–10]. Several patterns may be observed, including sudden-onset fatal and near-fatal, brittle, aspirin-induced, steroid-dependent/steroid-resistant, severe occupational and pre-menstrual asthma. These clinical symptoms and characteristics can probably be attributed to three underlying mechanisms: 1) airways inflammation; 2) bronchial hyper-responsiveness (BHR), which may or may not be associated with inflammation and/or bronchial smooth muscle hyper-reactivity [11]; and 3) fixed airways obstruction.

In this issue of the *European Respiratory Journal*, BUMBACEA *et al.* [12] present their findings from a study examining clinical characteristics and risk factors associated with fixed airways obstruction in severe asthma. They have compared two spirometrically distinct subgroups from the cohort of difficult-to-treat asthmatics studied at the Royal Brompton Hospital [10]: one with near normal lung function (forced expiratory volume in one second (FEV1) >80%) and one with severe obstruction (FEV1 <50%). They assessed duration of asthma, lung function, atopic status, smoking history, peripheral blood eosinophilia, nitric oxide measurement in exhaled air, quality-of-life scores and high-resolution computerised tomography (HRCT), and found that patients with fixed airflow obstruction have longer disease duration, evidence of greater inflammation and more HRCT abnormalities. Eosinophilia and bronchial thickening assessed by HRCT were the only parameters significantly and independently associated with irreversible obstructive defects in severe asthma. Patients with FEV1 between 50 and 80% predicted were not included, therefore, associations between the severity of obstruction and various markers are drawn from the ends of the curve.

Unlike chronic obstructive pulmonary disease (COPD), asthma is not a disease normally associated with a rapid decline in FEV1. However, 16–23% of asthmatics do exhibit a rapid rate of decline and progress to clinically important lung function impairment [13–14]. The factors and mechanisms associated with rapid decline in lung function are not understood. Some of the current hypotheses regarding such mechanisms will be discussed in the following paragraphs.

Eosinophilia in the bronchial tissue is a hallmark of asthma, and peripheral blood eosinophilia is also quite common. Eosinophils release potent mediators, which may cause destruction of the bronchial epithelium, and trigger repair and remodelling changes, and, *in vivo*, a reduction of eosinophils is associated with reduction in markers indicative of remodelling [15]. In this sense, one would expect to find an association between persistent, therapy-resistant eosinophilia and marked remodelling and fibrotic changes, which may lead to reduced lung function. Clinically, however, eosinophilia is not necessarily associated with more severe disease: studies using anti-interleukin-5 treatment showed moderate reduction in bronchial tissue eosinophils [15], and substantial reduction in blood and sputum eosinophil numbers [16], however, this effect did not lead to a reduction in markers of disease severity, such as BHR or the magnitude of the late-phase reaction [16]. Futhermore patients in clinical remission of asthma display bronchial eosinophilia but no clinical evidence of disease [17]. Moreover, eosinophilia is not universally present in severe asthma: in a recent study examining bronchial biopsies as well as lung function tests, two distinct groups of severe asthma were described, one exhibiting eosinophilia and the other a lack of eosinophils [18]. Severe asthma patients with bronchial eosinophilia had significantly more inflammation and thicker basement membrane but better FEV1 values than patients without eosinophils. Lastly, many patients have continuous symptoms, suffer exacerbations and have evidence of bronchial inflammation without any significant effect on lung function [4, 13–14]. In the current study by BUMBACEA *et al.* [12], the authors report indirect evidence of a link between eosinophilia, inflammation and impaired lung function. Considering, however, all the evidence, it seems that although eosinophilic inflammation may be associated with decline in lung function, the eosinophilic-remodelling hypothesis is not the only explanation.

A number of studies have shown that severe asthma is associated with a reduction in diffusion capacity [4] and HRCT changes compatible with emphysema [19], suggesting that perhaps these patients suffer parenchymal destruction with loss of peribronchial support, which hence affects their lung function. This theory ties in nicely with the fact that severe asthma is characterised by neutrophilic inflammation [4, 18] and neutrophils are associated with destruction of the lung parenchyma. Elastase levels have also been reported to be higher in asthma [20]. However, neither in the 10-yr study

Correspondence: M. Gaga, Respiratory Medicine Dept, Athens University, Sotiria Hospital, 152 Mesogion Ave, Athens 11527, Greece. Fax: 30 2107770423. E-mail: mgaga@med.uoa.gr

by ULRIK and BACKER [14] nor in the current study was evidence of emphysema found. The presence of neutrophils in severe asthma is intriguing. Neutrophils are initially recruited in bronchial tissue in asthma after allergen provocation and are followed by eosinophils. Significant bronchial neutrophilia has been reported in asthma deaths that occurred within 2 h of a sudden asthma attack [21]. In contrast, neutrophil numbers were reduced and eosinophils increased when death occurred after a longer duration of the attack, implicating a time-response. In severe persistent asthma, neutrophilia may represent a continuous influx of cells from the bloodstream due to continuous antigenic stimulation of the bronchi. It may, conversely, be influenced by the high levels of steroid treatment.

The epithelium may play an important role and the concept of activation of the epithelial-mesenchymal trophic unit is a very interesting one that may explain many of the responses and remodelling changes in asthma [22]. At present, more research is needed to elucidate the role of the epithelial-mesenchymal interactions in severe asthma and the development of irreversible obstruction.

Given the wide range of clinical presentations in severe asthma, it is possible that there may be many different mechanisms that lead to the varied clinical, radiological, pathological and physiological changes. There may also be primary defects or protective mechanisms at different steps of the immune reaction, and a pathogenetic process in asthma with some patients "over" recognising various antigenic stimuli and mounting an intense inflammatory or bronchoconstrictive response, which either persists or is switched off promptly; others mounting an excessive repair reaction leading to marked remodelling and fibrosis even in the absence of persistent inflammation; and some perhaps having excessive apoptotic mechanisms leading to structural cell destruction and emphysema [23].

Comorbity factors may influence the rate of decline. Smoking is associated with decline in pulmonary function and is a strong risk factor for COPD. However, fixed-obstruction asthma is not necessarily associated with smoking. In the study in this issue of the journal, although the proportion of smokers was slightly higher in the fixed-obstruction group, this did not reach statistical significance [12]. In a 26-yr follow-up asthma study, smoking was associated with a reduced transfer coefficient but not irreversible obstruction [13]. It seems that although fixed-obstruction severe asthma and COPD share some characteristics, they are distinct entities. Bronchial pathology differs with respect to eosinophils, neutrophils, the CD4/CD8 ratio and basement membrane thickening. Clinical characteristics differ with respect to diffusing capacity, HRCT emphysema score, and reversibility to bronchodilators and steroids [24].

In the current study by BUMBACEA *et al.* [12], the rate of atopy is very high in both severe asthma groups and this is intriguing. Atopy is a risk factor for asthma and continuous allergen exposure may cause severe disease. Conversely, there are studies showing that adult-onset non-allergic asthma progresses more rapidly to severe remodelling [19] and the ENFUMOSA study results showed that severe asthma is associated with lower prevalence of atopy, as well as family history of asthma, than mild disease [4]. Nevertheless, these are not epidemiological studies and therefore no safe conclusions about atopy prevalence can be drawn.

A striking feature in this study by BUMBACEA *et al.* [12] is the extremely high dose of inhaled steroids (ICS). The mean dose of ICS was 3,400 μg and 25% of patients used doses >3,800 μg. There is no doubt that ICS are the most potent anti-inflammatory drugs available and, in severe asthma, high doses of inhaled steroids are indeed recommended. However, in most studies published so far, a mean dose of usually <2,000 μg is used. As summarised in a recent review [25], many studies show that the dose-response curve of ICS plateaus. The response varies and may be flatter with regards to peak expiratory flow, while steeper curves are found for markers such as symptom control or the use of β-agonists. Nevertheless, most published dose-response studies use low doses, and few examine doses of 1,500–2,000 μg. There may be a benefit from the daily use of 3,500 μg of ICS but this has not really been tested. As the dose response for systematic effects of ICS does not plateau and side-effects are more pronounced with increasing doses, the use of ICS needs to be rationalised, especially above 2,000 μg, and it needs to be ascertained whether there is indeed a benefit from their use. The importance of testing what is believed to be true and embraced in clinical practice was recently highlighted in a placebo-controlled, double-blind study that tested the effect of doubling the dose of inhaled steroids for exacerbation prevention [26]. This is common practice and most of us urge our patients to double their ICS dose at signs of an exacerbation. The *Lancet* study, however, showed that the addition of the higher ICS dose at first signs of an exacerbation is not different from placebo in the prevention of exacerbations [26].

The issue of severe asthma and fixed obstruction is still open. The study by BUMBACEA *et al.* [12] used well-defined patient groups and examined various factors associated with irreversible obstruction. The results support a link between inflammation, remodelling and irreversible obstruction. They could have examined correlations across the spectrum of severity in their cohort but their approach gives a clearer first impression. However, the study has the limitations of a cross-sectional study. In order to untangle the mechanisms, predict disease outcome and design better therapeutic strategies, large, prospective, long-term studies are needed, with well characterised patients and control groups, and which include clinical, pathological, physiological and genetic measurements. In the mean time, the assessment and management of patients with severe refractory asthma should ideally be undertaken in an asthma centre with extensive expertise in evaluating and treating these patients. The majority of patients will benefit from a systematic evaluation, treatment of aggravating factors and meticulous tailoring of medication to their individual requirements. Nevertheless, the efficacy of all strategies needs to be constantly tested and the long-term outcome is still uncertain, in particular with respect to airway remodelling and decline in lung function.

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