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EDITORIAL

Is sputum eosinophilia a good or poor predictor of benefit from inhaled corticosteroid therapy in asthma?

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Sputum eosinophilia was first described as a feature of asthma by GOLLASCH [1] more than a century ago. Thirty-years later, eosinophils were found to be a part of the pathological process that characterises asthma [2]. Since then, much work has been undertaken to understand the precise role of eosinophils in mediating airway inflammation, tissue damage and repair in asthma pathogenesis. There is now strong evidence supporting the association of airway eosinophilic inflammation and symptomatic asthma. Although central, sputum eosinophils and their pro-inflammatory mediators are only a part of the heterogeneous inflammatory response that distinguishes asthma from other airway diseases. There is now increasing evidence that other inflammatory mechanisms may be involved in producing the two prominent clinical features of asthma: increased bronchial responsiveness and reversible airflow limitation [3].

In fact, several recent cross-sectional studies using the examination of bronchial biopsies tissue from bronchial biopsies, bronchoalveolar lavage fluid or samples of induced sputum [4–12] have demonstrated the presence of noneosinophilic inflammation in patients with symptomatic asthma. The prevalence of noneosinophilic inflammation in asthma is variable and this may be due, in part, to differences in subject characteristics such as the severity [5–7, 11] and control [4–6] of asthma, smoking [13], dose of corticosteroid treatment [6, 7], concurrent infection [9] and recent exposure to aggravating environmental allergens [14] or pollutants [15, 16]. Nevertheless, these studies highlighted the heterogeneity of airway inflammation in asthma and this cannot always be anticipated from clinical parameters [17].

Therefore, it seems reasonable to assume that knowing the characteristics of airway inflammation of symptomatic or uncontrolled asthmatics would be of interest in accessing the effects of different asthma treatments. This is particularly relevant in relation to corticosteroid treatment, as not all asthmatics respond similarly to these drugs [18, 19]. The article by GODON *et al.* [20] in this issue of the *European Respiratory Journal* addresses this matter. This study looks at the proportion of noneosinophilic *versus* eosinophilic sputum obtained from 51 steroid-naive symptomatic adults with asthma. Their objective was to investigate the predictive value of the underlying airway inflammatory profile in determining responses to inhaled steroid treatment (fluticasone propionate 250 μg *b.i.d.*). The end-points were improvement in symptom score, use of rescue short-acting bronchodilators, prebronchodilator forced expiratory volume in one second (FEV_1), airway hyperresponsiveness and asthma quality-of-life questionnaire. These measurements were taken before and after 1 month of treatment. Their results indicate that 29% of subjects had noneosinophilic inflammation (⩽1%) on sputum analysis. In line with previous reports, clinical parameters before treatment did not differ between subjects with or without sputum eosinophilia. However, contrary to other publications, the treatment response did not differ between the two groups. The authors conclude that the absence of sputum eosinophils did not seem to predict a poor response to inhaled steroid. The results and the conclusion of this study are provocative since they challenge some of the current views regarding the relevance of eosinophilic airway inflammation in asthma pathophysiology.

The use of sputum cell counts to predict benefit of steroid treatment is not new, although only a few studies have investigated this issue. BROWN [21], in 1958, using a cruder method to examine cells in spontaneous sputum in subjects with chronic "wheezy" bronchitis (n=90), observed that 30% of the subjects did not have sputum eosinophilia. Additionally, only those with eosinophils detected on sputum responded to prednisolone. More recently, a small open study by PAVORD *et al.* [10] looked at 23 steroid-naive asthmatics with sputum eosinophilia (⩾3%) or without sputum eosinophilia. They showed that treatment with an inhaled corticosteroid (budesonide 400 μg *b.i.d.*) for 8 weeks was of greater benefit to subjects with sputum eosinophilia. Another study from LITTLE *et al.* [22] demonstrated that sputum eosinophilia (>3%) predicted improvement in FEV_1 in asthmatic subjects already on inhaled steroids (median dose equivalent to 800 μg of inhaled beclomethasone) after treatment with oral prednisolone (30 $mg \cdot day^{-1}$) for 2 weeks with a sensitivity of 54% and specificity of 76%. Subsequently, MEIJER *et al.* [23] examined the value of clinical parameters (FEV_1, the provocative concentration of methacholine causing a 20% fall in the FEV_1 (PC_{20}) and asthma quality-of-life questionnaire), and inflammatory markers in blood and sputum (eosinophils and eosinophil cationic protein

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(ECP)) or exhaled nitric oxide to predict benefit from corticosteroid treatment. In this double-blind, double-dummy, parallel-group study, 120 subjects with uncontrolled asthma were randomised to receiving a 2-week treatment with either prednisolone 30 mg·day^{-1}, fluticasone propionate 1,000 μg *b.i.d.* or fluticasone propionate 500 μg *b.i.d.* after their treatment with inhaled steroids had been gradually reduced or withdrawn. The results of this study demonstrated that baseline values of the clinical parameters (FEV_1 and PC_{20}) were the major predictors of clinical response to corticosteroid treatment. They also showed that eosinophils, both in blood and in sputum, provided additional information, whereas measurements of ECP or exhaled nitric oxide did not. Taken together, these studies indicate that the presence of sputum eosinophilia seems to predict benefit from corticosteroid treatment in asthma.

The results of various studies using sputum cell counts to predict the benefit of steroid treatment and the one by GODON *et al.* [20] and the various studies using sputum cell counts to predict benefit of steroid treatment, do not provide clear evidence as to whether sputum eosinophilia predicts benefit from corticosteroid treatment in asthma because of a number of methodological issues. These issues are acknowledged in part by GODON *et al.* [20] and include: small sample size, lack of a placebo control group, the short-term duration of the corticosteroid treatment and the choice of outcome measurements. These are relevant issues because it is still not known whether the absence of sputum eosinophils in these patients is a transient or a persistent feature. In this respect a placebo group would help to exclude spontaneous fluctuations in sputum cell counts and regression towards the mean. Although sputum cell counts are very reproducible within a week in stable subjects [6], no study has evaluated the spontaneous variability of airway inflammatory indices in longer periods or in uncontrolled asthmatics.

Also, to answer this question the role of measuring symptoms, physiological abnormalities and airway inflammation in the management of asthma must be viewed from distinct perspectives. First, from the perspective of patients, the most important parameters are symptoms, activity limitation and emotional impairment. This is clearly shown in recent studies using validated specific health- related quality-of-life questionnaires [24, 25]. These studies have also shown that quality of life, as measured by a disease-specific questionnaire, has a good correlation with clinical control of asthma but not with FEV_1. It is not known whether or not it correlates with objective measurements of airway inflammation. Second, from the perspective of efficacy of asthma treatment, the assessment of symptoms and physiological abnormalities only may not be enough. Potent bronchodilator drugs may reverse or prevent airway constriction and improve symptoms, airflow limitation and airway hyperresponsiveness without affecting airway inflammation [26–29]. On the other hand, anti-inflammatory drugs without bronchodilator effects may have no effect on asthma symptoms and airflow limitation if airway inflammation is not present to begin with. In addition, as mentioned previously, different causes of airway inflammation, such as viral or bacterial infections and exposure to allergens, cause different types of airway inflammatory responses which may not be identified by clinical and physiological parameters alone [17]. Different causes of airway inflammation may respond differently to a particular treatment. Moreover, it is critical to keep in mind that airway inflammation in asthma consists not only of airway infiltration with activated eosinophils, lymphocytes and mast cells, secretion of proinflammatory cell products and cytokines but also of increased microvascular permeability with exudation of plasma, mucus secretion and structural changes including patchy desquamation of the airway epithelium, thickening of the basement membrane and airway smooth muscle hypertrophy. This is relevant because, an anti-inflammatory drug may act on different aspects of airway inflammation such as vascular leakage and this may not be directly sampled when measuring sputum eosinophils only.

Finally, from the perspective of long-term benefit of a particular asthma treatment, the degree of control of asthma achieved, as measured by frequency of exacerbations, the minimum dose of inhaled corticosteroid required to maintain control and perhaps, the magnitude of airway remodelling are additional important end-points. This can be exemplified by a recent study from GREEN *et al.* [28]. In a 12-month controlled study the authors randomised 74 asthmatic subjects to be managed either according to British Thoracic Society Guidelines or using an algorithm targeting the normalisation of sputum eosinophils. The results of this long-term study demonstrated that treatment directed at normalising the induced sputum eosinophils count reduced the number of asthma exacerbations without the need for additional anti-inflammatory therapy. Therefore, this study strengthens the view that there is a role for sputum cell counts in asthma management. However, the question whether sputum eosinophilia predicts long- or short-term benefit from corticosteroid treatment remains unanswered. As stated by GODON *et al.* [20] this will only be properly addressed in a long-term large double-blind placebo-controlled study.

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