

EDITORIAL

Monitoring airway inflammation in asthma by induced sputum

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Asthma is a disease characterized by airway inflammation, variable airflow limitation, airway hyperresponsiveness, lung function impairment and the presence of symptoms such as dyspnoea, wheezing, chest tightness and cough.

In the past, airway inflammation has been detected by the study of the cellular and biochemical composition of bronchial lavage fluid and biopsies. Owing to its invasive nature, however, bronchoscopy is not an appropriate method for repeated measurements. Therefore, a noninvasive method, such as sputum induction, is needed to understand better the role of airway inflammation in the natural course of asthma, in determining the consequences of therapeutic interventions, and in studying cellular mechanisms during exacerbation and improvement of the disease.

Sputum has been used for more than a hundred years to characterize airway diseases and in 1992 PIN *et al.* [1] proposed inducing sputum by the inhalation of hypertonic saline in those subjects and patients with airway diseases not complaining of spontaneous sputum production. Today, the method is considered to be reliable, valid, responsive and reproducible [2, 3]. Although the procedure is noninvasive, the inhalation of hypertonic saline by hyper-responsive subjects is often followed by an obstructive airway response; therefore, sputum induction should always be preceded by inhalation of bronchodilators (*e.g.* β_2 -agonist) and frequent measurements of lung function should be performed during the induction procedure to avoid significant bronchoconstriction. Experience in many laboratories has shown that when these precautions are taken into account, sputum induction with hypertonic saline is a method with acceptable side-effects [4]. In patients with more severe asthma it is even feasible to use isotonic saline and shorter inhalation periods to minimize further the risk of developing airway obstruction during the procedure. This modification has recently been proposed by PIZZICHINI *et al.* [5].

In this issue of the Journal, PIZZICHINI *et al.* [6] report the use of their modified technique of sputum induction to study eight prednisone-dependent patients with asthma during a programmed reduction of prednisone. The measurements of sputum, blood and clinical parameters were started after 1 week of high-dose prednisone treatment, during the programmed reduction, at clinical exacerbation and again after a high-dose of prednisone treatment for 1

week, and detailed data are presented for the last two time points. Although only a small number of patients were studied, the authors found that the time course of sputum eosinophilia differs from the time course of blood eosinophilia and clinical parameters and, in particular, that sputum eosinophilia precedes clinical exacerbation by several weeks. These results are in line with observations made in a similar study by the same group in which changes in sputum eosinophils, blood and clinical parameters in a group of nonprednisone-dependent asthmatics were examined after an exacerbation. Sputum eosinophils decreased later as a result of prednisone treatment compared with blood eosinophils and clinical parameters [5]. In both studies the treatment was accompanied by changes in the concentration of eosinophil cationic protein, similar to changes in eosinophil number, while the responses of fibrinogen and interleukin-5 were more pronounced in the nonprednisone-dependent asthmatics in the first study.

The results of these studies in patients with severe asthma suggest that the degree of sputum eosinophilia as a marker of airway inflammation can be used to monitor the effect of treatment more accurately than blood or clinical parameters. Clearly, this information would have substantial consequences for the understanding of the course of asthma and the timing of therapy.

Stimulated by the observations of PIZZICHINI *et al.* [5, 6], we would like to address four points: the methodological aspect, the time course of events, the target of therapy and the need for early intervention.

The methodological aspect

The modified method of sputum induction proposed by E. Pizzichini, starting with isotonic saline instead of 3% hypertonic saline, has been shown in both studies to be safe in subjects with severe asthma. According to previous observations, saline concentration should have no effect on the differential cell count [7], but it has to be kept in mind that sputum composition changes during induction, resulting in, for instance, higher proportions of neutrophils in the first sputum sample, compared with sputum produced later during the procedure [8]. As long as only the first sample that a subject produces is used for analysis, this should cause no bias; otherwise, the duration of the induction would need to be standardized. Furthermore, it was shown in two studies that the induction procedure itself is able to cause an influx of neutrophils into the airways that can be detected for at least 24 h after a sputum induction [9, 10]. This should be considered in investigations in which inductions are planned within this short period.

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PIZZICHINI *et al.* [6] showed that often <10 min is necessary to obtain safely a sufficient sputum plug from asthmatic subjects [6]. However, taking into account the time necessary for processing and performing differential cell counts, a sputum examination still takes at least 60–90 min. In addition, as sputum needs to be processed within 2 h, the number of patients that can be examined in parallel is limited. The method is, therefore, time consuming and expensive and has been used mainly in research and less in clinical practice.

It may be possible to develop a standardized, short protocol that allows faster measurement of sputum eosinophilia. Owing to the requirements of safety and reproducibility, however, it seems to be unlikely that a sputum examination can be performed more quickly than the measurement of hyperresponsiveness, but the advantage of measuring the degree of inflammation directly would seem to be worth the extra time spent.

The time course of events

It is known from previous studies that the changes of symptoms, lung function and hyperresponsiveness during reduction of treatment follow different time courses [11–14]. The studies of PIZZICHINI *et al.* [5, 6] and of FAUL *et al.* [15] demonstrated that the change in airway inflammation as, for example, detected by sputum eosinophilia, also follows its own specific time course. The sequence of events during reduction of medication seems to start with early increases in the proportion of sputum eosinophils and continues later with changes in blood inflammatory markers and a worsening of symptoms and lung function. In contrast, the treatment of an exacerbation with inhaled or systemic steroids results in early improvement of lung function, symptoms and blood parameters, while hyperresponsiveness and sputum eosinophilia need a longer treatment period to reverse [6, 13]. Correlations found between hyperresponsiveness and sputum eosinophils [16, 17], as well as the similar time course, suggest that these two parameters are closely related to each other and the measurement of hyperresponsiveness in studies performed in the past can probably be considered as an indicator for the degree of inflammation within the airways.

The target of therapy

According to the present guidelines, the targets of asthma treatment are symptoms and lung function; however, owing to the results presented by PIZZICHINI *et al.* [5, 6] there is now further evidence that targeting inflammation could be more beneficial. The idea that this different strategy might indeed be more successful has been investigated by Sterk and coworkers [18, 19] and the data were presented at the European Respiratory Society meeting 1997 in Berlin. In their study, two protocols were compared: strategy A aimed at reducing symptoms, forced expiratory volume in one second and peak expiratory flow (PEF), while strategy B aimed also at reducing airway hyperresponsiveness. In strategy B, the reduction of both mast cells in biopsies and reticular layer thickness was more pronounced. At the same time, strategy B resulted in improvements in PEF and lung function, a lower exacerbation rate and lower airflow variability. Therefore, it

would be interesting to know whether targeting the degree of inflammation as monitored by sputum examinations could be even more beneficial.

The need for early intervention

Targeting inflammation instead of symptoms has also been suggested by those who favour a first-line treatment with corticosteroids when asthma is diagnosed [20]. Corticosteroids are known to be the most effective drug against airway inflammation and the early treatment of inflammation with low doses has been shown to be beneficial in the management of even mild forms of the disease. A dose as low as 400 $\mu\text{g}\cdot\text{day}^{-1}$ of budesonide was able to reduce the number of patients with daily symptoms, improve peak flow rates and avoid exacerbations and emergency-room visits [20]. Furthermore, the early use of corticosteroids has been shown to slow down the decline in lung function more effectively than the first-line treatment of symptoms with β_2 -agonists [21]. The benefit in asthma treatment was greater when treatment with steroids was started early after diagnosis compared with later steroid treatment following other treatment regimens to control asthma symptoms [22]. This has been shown to be true in adults as well as children [23]. Finally, it has been shown that early treatment is cost-beneficial, owing to fewer hospital admissions or physician visits [20].

Taking all of these points together, there is overwhelming proof that airway inflammation is an important feature of asthma. Furthermore, there is increasing evidence that early knowledge of the state of airway inflammation can be beneficial for diagnosis and treatment. The most appropriate way to detect and follow the course of inflammation seems to be the analysis of induced sputum, as it can be performed repeatedly. Therefore, this method is now used increasingly and some case reports indicate that patients in clinical practice can benefit from monitoring the cellular composition of their airways [24, 25]. In our hospital we also see patients with cough of unknown origin, normal lung function and without airway hyperresponsiveness. A sputum examination often reveals a high proportion of eosinophils and treatment with steroids improves their symptoms and the inflammation. A similar group of patients was described in 1989 [26]. These patients clearly benefited from the sputum examination and the additional time taken for the analysis seemed to be well invested. It would be interesting to know whether these patients would have developed airway hyperresponsiveness had the eosinophilia not been treated. In future studies addressing this question, the use of sputum induction will be extremely helpful as a tool to monitor airway inflammation.

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