Assessing airway inflammation

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In the first paragraph of most reviews we are reminded that 'asthma is an inflammatory disease characterised by ...'. This perspective has been influenced by—and, in turn, has driven—a great deal of respiratory research over the last 20 years. In the clinical sphere, studies based on factor analysis inform us that airway inflammation is an independent domain of the asthma syndrome, distinct from airways hyper-responsiveness, abnormal lung function and symptoms.^{1–2} Established treatments (notably inhaled corticosteroids and antileukotrienes) as well as potential new therapies are directed towards modifying the underlying inflammatory process rather than just providing symptom relief. For all of these reasons, actually measuring airway inflammation ought to be a regular feature in the management of asthma. In that regard, the renowned passion of Professor Freddie Hargreave and colleagues for using induced sputum analysis in the routine assessment of airways disease is entirely logical and is to be applauded.³ The strength of induced sputum analysis is that inflammatory cell characteristics (eosinophil predominance or not) may be used to interpret the aetiology of a patient's symptoms, anticipate the short to medium-term prognosis and, most importantly, the likelihood of response to treatment with corticosteroid.^{4–6} Unfortunately, 15 years on, for pragmatic reasons, the approach he encouraged is not routine except in a few centres.

Against this background, the measurement of nitric oxide as the fraction in exhaled air (FeNO) came on the scene and interest in its clinical applications has grown.⁷ Chief among these, for reasons we have referred to, has been its role as a surrogate measurement of eosinophilic airway inflammation. This appeared to be very convenient, given the desirability of measuring airway inflammation by a less time-consuming and well-validated method.⁸ The relationship between FeNO and eosinophils is based on studies

reporting correlations between the two parameters in both mucosal biopsies and induced sputum.^{9–16}

But how does FeNO actually measure up as a true surrogate for eosinophilic airway inflammation? At best, the relationship between NO and eosinophilic airway inflammation is indirect.¹⁷ The magnitude of correlations varies widely and they are not necessarily significant (ranging from $r=0.30^{15}$ to $r=0.78^{10}$). For this reason, doubts have been expressed about the clinical utility of FeNO measurements,¹⁸ particularly given that, in contrast to using sputum eosinophils,^{19–20} the outcomes of studies using FeNO as a guide to asthma management have been much less successful.²¹

In this issue of *Thorax*, Schleich *et al* provide further data on the relationship between FeNO and sputum eosinophils in a large population of patients with asthma ($n=295$) (see page 1039).²² They confirm a significant but modest correlation between FeNO and sputum eosinophils ($r=0.54$, $p<0.0001$) and provide information on the optimum cut-off points for FeNO which predict clinically significant sputum eosinophilia ($>3\%$). Overall, this was 41 ppb, which is remarkably close to the threshold of clinical significance in other studies. More importantly, Schleich *et al* provide a further series of predictive cut-off points, together with positive and negative predictive values (PPV and NPV), in relation to common factors that influence FeNO levels de novo (eg, sex, smoking and atopy). Finally, they anchor these data to recently published predicted values,²³ enabling the clinician to get a feel for where 'pathological' FeNO levels lie in relation to so-called 'normal' values.

How do these new data help us, if at all? The authors themselves describe the predictive utility of FeNO for sputum eosinophils as having 'excellent accuracy'. This is perhaps rather exaggerated. To the doubters they offer a cup which is half empty: the need to take so many variables into account, such as dose of inhaled corticosteroid and smoking, will be seen as a disincentive to using FeNO. However, to believers they offer a cup which is somewhat more than half full. The message is that the pathological relevance (in relation to sputum eosinophils) of even a modestly

raised FeNO can now be more accurately interpreted.

However, in our view this is probably only a modest gain. It is based on the underlying assumption that FeNO should be thought of primarily as a surrogate for eosinophilic airway inflammation. But is this how we ought to think? Should sputum eosinophilia be regarded as the 'gold standard' against which to judge the value of FeNO measurements? Whereas sputum eosinophilia is almost always pathological, the same is not true for exhaled NO which is measurable in healthy asymptomatic individuals and is subject to a range of modifying factors.²⁴ Reasons for the concordance/discordance between FeNO and sputum eosinophilia are pathologically complex. This means that correlations between the two will at best be limited, as the data from Schleich *et al* confirm.²² It also means that, whereas the PPVs for a clinical end point such as asthma exacerbations are high for a high value of sputum eosinophils, the same cannot be so for a high value of FeNO. Rather, the NPVs associated with low FeNO values are much greater. The data provided by Schleich *et al* confirm this to be true (see table 3): low FeNO is a reliable marker of what is *not there* in terms of inflammatory cells.

This does not negate the usefulness of FeNO measurements.²² The clinical utility of other well-established biomarkers such as pro-BNP and D-dimer is greatest when values are normal/low, and they are used to rule out—rather than rule in—left ventricular failure or thromboembolism, respectively. Ruling out active airway inflammation is important in the interpretation of symptoms in patients, for example, with chronic cough or poorly controlled asthma in the presence of comorbidities such as obesity and anxiety-hyperventilation. A low FeNO (ruling out) in these settings enables the clinician to widen the diagnostic focus and/or avoid unnecessary steroid treatment.

Predicting whether or not the patient is likely to respond to the introduction of or a change in the dose of inhaled steroid therapy in patients with airways disease is the key clinical issue when using FeNO. Predicting sputum eosinophilia may be helpful but can only be considered as an intermediate goal. The former is a more important 'performance indicator' by which the value or otherwise of FeNO should be measured, independently of sputum eosinophilia. Although this question has been studied in randomised trials, their focus has been narrow.²¹ The issue is

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not 'How much?' but 'Yes or no?'.²⁵ Interestingly, in the study by Schleich *et al*,²² FeNO levels were progressively lower in patients who were taking low, moderate or high daily doses of inhaled steroid, in contrast to the sputum eosinophil counts which did not change substantially across these groups. This indicates that, in the presence of anti-inflammatory treatment, the two parameters are even more dissociated.

Let us say something more about the relationship between FeNO and steroid response—that is, the available clinical improvement if steroid therapy is to be commenced or increased.²⁶ Recently, Cowan *et al* compared the predictive values of FeNO for steroid responsiveness in eosinophilic (EA) versus non-eosinophilic asthma (NEA),²⁷ as measured by the reduction in airway hyper-responsiveness to AMP following treatment with fluticasone. For EA the optimum FeNO cut-off point predicting steroid responsiveness was 39 ppb, yielding a PPV of 91%, NPV of 67% and overall accuracy of 84%. However, for NEA the outcomes were unexpectedly very similar, with a lower optimum cut-off point of 33 ppb and PPV, NPV and accuracy values of 82%, 82% and 82%, respectively. These results suggest that FeNO has a role where sputum eosinophils may be lacking. Thus, the relevant question is not: what does FeNO tell me about underlying eosinophilic airway inflammation, but what does it tell me about the potential for benefit from commencing or increasing the dose of inhaled corticosteroid treatment? A paradigm in which FeNO is uncoupled from airway eosinophilia (or from achieving a diagnostic label⁶) and is more strongly linked to the concept of the 'available treatment response' is, for a variety of reasons, the way to go.

In conclusion, the study by Schleich *et al*²² provides data which clarify the strength of the relationship between FeNO and sputum eosinophils, notably in

patients who are smokers or already taking regular corticosteroids, but knowing this information is an intermediate objective. The usefulness of FeNO is greatest when values are low and the absence of sputum eosinophilia but, more importantly, the likelihood of steroid responsiveness can be predicted.

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