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EDITORIAL

An eye to the future: exhaled nitric oxide as a predictor of clinical outcomes in asthma

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Recent guidelines for the management of asthma now emphasise the importance of anticipating what lies ahead. The concept of ''future risk'' has been introduced into our clinical terminology [1]. While it may be argued that clinicians have always intuitively paid attention to ideas of future risk as well as future benefit, it is only recently that these have been articulated. Future risk refers to the risk of adverse outcomes such as exacerbations, poor asthma control, accelerated decline in lung function or side-effects of treatment in the near or distant future [2]. Similarly, although anticipating future benefit may seem easy, it is not: the response to most asthma treatments is heterogeneous, and predicting those who are likely to benefit from a therapeutic intervention is possible in only a proportion of patients. This is particularly true for anti-inflammatory treatment [3, 4], and many clinicians prescribe empirically.

In asthma studies, the effect of an intervention on some future risks (*e.g.* exacerbations) may be measured directly, or inferences may be drawn from measuring physiological variables or biomarkers. The latter are of increasing importance because the future benefits and risks associated with treatment intervention may be related to control of the underlying disease process, as reflected in biomarker levels. For asthma exacerbations, we can assess future risk in three ways. Firstly, we can identify epidemiological factors that characterise the ''at risk'' patient, *e.g.* male sex, ethnicity, smoking history [5]. Second, there is the patient's individual history. The past is a good predictor of the future. Previous exacerbations and/or consistently poor asthma control are strongly predictive of future exacerbations [6–8]. This may seem self-evident, but may not be the case in patients who are poor perceivers or in patients taking long-acting β_2-agonists (LABAs) [9]. Third, there are pathophysiological parameters which may be used prognostically: prebronchodilator forced expiratory volume in 1 s (FEV_1, as % predicted) is an independent predictor of asthma exacerbations [10, 11]. Similarly, but less available, measurements of airway hyperresponsiveness (AHR) may be used to predict loss of control [12] and, in the longer term, the development of irreversible airflow obstruction [13].

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What about biomarkers? Here the potential advantages are greatest because of their relationship to the underlying disease activity and, in some cases because of this, to treatment responsiveness. This is relevant to both future risk and future benefit. Sadly, in this regard, few candidate biomarkers have managed to go from bench to bedside. Eosinophils in induced sputum reflect underlying disease activity in allergic asthma and are associated with an increased risk of exacerbations [14] as well as a greater likelihood that patients will respond to corticosteroid therapy [15]. Unfortunately, this biomarker is not readily available except in major centres. As an alternative, (the fraction of) exhaled nitric oxide ($F_{E}NO$) is increasingly being used. The relationship between $F_{E}NO$ and underlying inflammation in asthma is indirect and complex. $F_{E}NO$ correlates only modestly with sputum eosinophils [16]. In complex asthma, its value lies in the high negative predictive value of a low $F_{E}NO$ level ($\leqslant$25 ppb in adults). In the study by SHAW *et al.* [17], the correlation between $F_{E}NO$ and sputum eosinophils was 0.67 ($p<0.001$), and at a cut-point of <26 ppb, the likelihood that patients had a sputum eosinophil count of <3% (the clinically relevant cut-point) was 85%. Negative prediction is particularly relevant when assessing the potential for steroid response in patients whose respiratory symptoms are multifactorial, *e.g.* due to anxiety, obesity and asthma.

Several studies have been conducted to explore the role of $F_{E}NO$ in assessing future risk. Changes in $F_{E}NO$ provide acceptably high predictive values for loss of asthma control [18, 19]. For example, PAPAIOANNOU *et al.* [18] reported that an increase in $F_{E}NO$ of >30% is highly predictive of loss of control (positive predictive value 89%), while an increase of <20% was unlikely to be associated with loss of control (negative predictive value of 81%). PIJNENBURG *et al.* [20] and ZACHARASIEWICZ *et al.* [21] have highlighted that loss of asthma control, or not, following inhaled corticosteroid (ICS) dose reduction can be predicted using follow-up $F_{E}NO$ measurements. Persistently low values (<25 ppb in adults, <20 ppb in children) are reassuring. GELB *et al.* [22] have reported that, among 44 asthmatics followed for 3 yrs, the positive and negative predictive values of $F_{E}NO$ >28 ppb for a future exacerbation were 77% and 87% respectively. Finally, VAN VEEN *et al.* [23] followed 98 asthma patients for 5 yrs and found that excess decline in lung function was significantly related to an elevated baseline $F_{E}NO$ (>20 ppb), notably in patients with normal spirometry.

$F_{E}NO$ is also marker of potential future benefit, notably in relation to steroid responsiveness. In the study by SMITH *et al.* [24], clinical

improvements resulting from ICS therapy were greatest in patients with high F_{ENO} (>47 ppb), and at a cut-point of <35 ppb there was a negative predictive value of 93% for a reduction in airway responsiveness with inhaled fluticasone. The relationship between increased F_{ENO} and steroid response also appears to hold true in patients with noneosinophilic asthma [25].

In the current issue of the *European Respiratory Journal*, PEREZ DE LLANO *et al.* [26] report the results of a study in which these observations have been applied in a ''real-life'' setting. Recognising that high dose ICS/LABA treatment is only selectively beneficial [3], these authors sought to identify patients with suboptimal asthma control who would benefit from increased anti-inflammatory treatment (*i.e.* achieve an Asthma Control Test (ACT) score $\geqslant$20). 102 patients were treated openly with maximum doses of inhaled fluticasone/salmeterol in combination for 1 month (phase 1) and then oral corticosteroid was added for a further month if asthma was still poorly controlled (phase 2). The authors evaluated the prognostic role of a single baseline F_{ENO} measurement. Using receiver operator characteristic analysis, the area under the curve for F_{ENO} as a predictor of improved asthma control (*i.e.* achieving an ACT score $\geqslant$20) was 0.925, which is highly significant. At a cut-point of 30 ppb, the positive predictive value was 87.5% and the negative predictive value was 90.6%. At lower cut points, the negative predictive values were even higher. Importantly, only 37 of the 102 patients achieved control at 1 month, and only a further 16 gained control after using oral steroid. Thus 48% were ''nonresponders'' for whatever reason.

Notwithstanding the significant weaknesses in this study, including the short duration of phase 1 and the failure to assess adherence, these data provide important messages. Chief among them is that a significant proportion of patients with poorly controlled asthma do not necessarily respond to guidelines-directed step-wise increases in corticosteroid-based therapy. Second, nonresponders can be anticipated using an objective, easily obtained measurement (F_{ENO}). Consistent with the results of other studies, low F_{ENO} levels at baseline (<25–30 ppb in adults) provided a robust indicator that a response to increased treatment was unlikely to occur. These findings are generalisable: only in a small minority will there be true steroid resistance characterised by high F_{ENO} and treatment unresponsiveness.

The study by PEREZ DE LLANO *et al.* [26] points us to the future, and the future for patients with difficult asthma will invariably be better if the potential benefits of increasing their treatment can be identified, and the potential risks (steroid-related adverse effects and unnecessary drug costs) can be minimised. Any tool that improves our ability to judge what lies ahead is worth having, and F_{ENO} appears to have a role.

STATEMENT OF INTEREST

A statement of interest for D.R. Taylor can be found at www.erj.ersjournals.com/misc/statements.dtl

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