Biomarkers in the assessment and management of airways diseases

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ABSTRACT

A plethora of biomarkers are becoming available in the field of respiratory medicine, but their application in clinical practice has been limited. This is changing. There is increasing scope for biomarkers to be used to define pathological as well as treatment responder phenotypes in asthma and chronic obstructive pulmonary disease. In some situations, conventional diagnostic labelling is being superseded by this approach and clinical outcomes are improved. Biomarkers are potentially very important in the development and assessment of new therapeutic agents, particularly for the treatment of severe asthma. They also have a potential role in monitoring disease activity and predicting future clinical outcomes for asthma and chronic obstructive pulmonary disease. Current evidence in relation to these issues is explored in this review.

A biomarker is a surrogate biological measurement that is used to indirectly quantify a disease process. Box 1 summarises the ideal qualities of a biomarker. Increasing attention is being given to the role of biomarkers in airways diseases, notably asthma and chronic obstructive pulmonary disease (COPD).[1–3] This has been facilitated by nearly 20 years of research, which has identified key components in the pathophysiological inflammatory pathways of airways diseases. Methods for biomarker development have included induced sputum cell and cytokine analysis, measurement of organic compounds in exhaled air (eg, exhaled nitric oxide (NO) and exhaled breath condensate), and, more recently, proteomics and gene expression microarrays. As yet, few of these techniques can be used in day-to-day clinical practice. However, neither do they belong exclusively to the realms of the ''ivory tower''.

Application of biomarkers has the potential to improve diagnosis and management of airways disease. However, their arrival will challenge some of the existing deeply rooted paradigms within which we classify and treat these conditions. In this review, we will briefly outline some of the evidence and discuss the concepts related to using biomarkers in asthma and COPD.

HOW BIOMARKERS MIGHT BE USED TO ASSESS AIRWAYS DISEASE

There are three areas where a biomarker may have a potential role in clinical practice: identifying the underlying pathological phenotype; providing an end point that is relevant to the mode of action for a specific intervention; and predicting future risk as well as usefully helping to guide treatment decisions that may modify that risk. These are described with reference to asthma in fig 1.

Firstly, a biomarker may be used diagnostically, whereby the biomarker is present/absent or increases/decreases in relation to a particular pathological process. The utility of the biomarker will depend on optimum cut-off point(s) being established in relation to optimum positive and negative predictive values either for diagnosis or for a relevant change in clinical status. For example, the fraction of exhaled NO (F_ENO) has been used to distinguish asthma from non-asthma,[4 5] with cut-off points ranging from 20 to 25 ppb determined as optimum. However, this approach somewhat naively assumes that asthma is a single disease entity. In fact, asthma is heterogeneous as to its pathology, and rather than merely establish a diagnosis of ''asthma'', the use of a biomarkers may be helpful in defining a more specific disease phenotype. Induced sputum cell counts may be used to describe the inflammatory cell phenotype.[6] Such subgroup classification is all the more useful if it can also be used to identify potential ''responders'' to a disease-modifying intervention. Indeed, treatment response may define a particular phenotype. For example, the relationship between eosinophilic airway inflammation and the response to corticosteroids has been known about for nearly 50 years.[7]

Secondly, a biomarker may also be useful in disease monitoring, in cases where the diagnosis is already established. The aim is to provide objective evidence that treatment is being optimally prescribed or administered. In asthma and COPD, there are often occasions when a patient's symptoms do not result directly from the intensity of the underlying disease process. This is especially true with severe disease and/or when there are comorbidities that give rise to similar symptoms. For example, in an obese asthmatic patient whose obesity is increasing with frequent courses of oral prednisone, the diagnosis of ''poorly controlled asthma'' may in fact be mistaken. Rather, the patient's symptoms may be due to the mechanical effects of obesity on lung function, or to worsening gastro-oesophageal reflux disease with micro-aspiration, or to the anxiety that comes of deteriorating ''asthma'', or all of the above. In such circumstances, it may be difficult to tease apart the relative importance of each of the contributors. Clearly it is inappropriate to prescribe increasing doses of anti-inflammatory treatment if airway inflammation is not the primary cause of the patient's apparently poor control. A suitable biomarker may be particularly helpful in this setting—to establish whether airway inflammation is active or inactive, and whether the proposed intervention is likely to achieve a beneficial outcome.

Box 1: The ideal biomarker

- Indicates a key pathophysiological process in relation to the disease of interest
- May be used to distinguish a particular phenotype
- Is responsive to changes in disease activity
- Is responsive to changes in pathophysiology mediated by treatment intervention
- Is responsive within a time frame which precedes changes in clinical status and permits pre-emptive interventions
- Is easily measured
- Is minimally invasive
- Is reproducible
- Is properly validated

Thirdly, a biomarker may be used to anticipate the course and prognosis of the disease, ie, as a predictor of future disease-related events. In this regard, certain requirements regarding the performance characteristics of the biomarker require to be satisfied. Firstly, any change in the biomarker signal must precede the change in clinical status by an interval that permits pre-emptive intervention to work effectively. For example, increasing concentrations of biomarker X may precede an exacerbation of asthma, but if the increase does not occur within a time frame that is greater than the time required for an intervention, eg, oral corticosteroid, to act, then the biomarker would have limited value in this context. Secondly, the magnitude of the change in the biomarker that signals a clinically significant event must be greater than the coefficient of variability for that biomarker when the disease activity is present but well controlled. This is not necessarily the same as the coefficient of variability in healthy individuals (eg, F_ENO in stable asthma). Figure 2 illustrates these points. In practice, this model means that repeated measurements of the biomarker have to be obtained.

DEFINING A PHENOTYPE: THE PROBLEM WITH CONVENTIONAL DIAGNOSTIC LABELLING

The use of biomarkers in airways disease will challenge the accepted paradigm for airways disease classification and management.[8] "Establishing the diagnosis" is a dearly held principle of medicine. The diagnostic label (sometimes) enables the clinician to make appropriate treatment choices and to anticipate the course of the patient's disease. It crudely provides the clinician with a sense of confidence by giving something a name, and is often of importance to the patient (some will strenuously prefer to think they have "asthma" rather than "emphysema"). In airways disease, distinguishing between asthma and COPD has perplexed us for more than a generation, not least those whose task has been to provide consensus definitions. Asthma is allegedly characterised by atopy and a Th-2-dominated inflammatory pathway, giving rise to variable airflow obstruction, which is amenable to treatment with inhaled corticosteroids. COPD is allegedly characterised by neutrophilic airway inflammation, with progressive irreversible airflow obstruction in a smoker or ex-smoker and resistance to anti-inflammatory treatment. Unfortunately there is significant overlap between the two; a proportion of patients with COPD exhibit "asthmatic" features, and some patients with asthma have fixed airflow obstruction. Predicting the response to treatment cannot be judged accurately on clinical grounds,

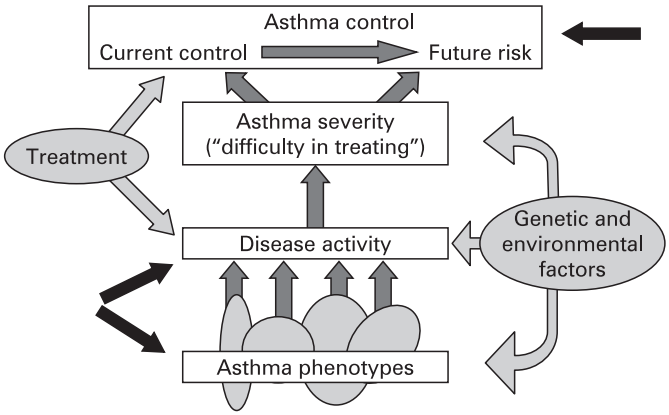

Figure 1 The black arrows indicate points at which biomarkers might be used to assess asthma. This includes establishing the phenotype of the airways disease, including possible treatment responsiveness, assessing the underlying disease activity especially when symptoms are multifactorial, and monitoring established asthma with a view to anticipating poor control or other future risk. Reproduced, with permission, from Taylor *et al*. *Eur Respir J* 2008;**32**:545–54.

and, in practice, many clinicians bypass the issue and treat the patient empirically.

But is this appropriate any longer? Perhaps it is because the conventional approach to securing a diagnostic label has been driven, at least in part, by the only available and relatively inadequate technology. Of necessity, physiological tests have been the principal means of objective support for a clinical diagnosis. Serial peak flow measurements and spirometry to identify "variable airflow obstruction" and "reversibility" to bronchodilator have been the mainstays of investigation. In the 1980s, tests for airway hyper-responsiveness (AHR) were added. But these largely define the functional impact of the underlying airways pathology, and not the pathology itself. Further, the tests are neither sensitive nor specific.[9] In asthma, evidence for "reversible" or variable airflow obstruction will be sought, but may be absent if the disease is mild. In COPD, the diagnostic label may be applied if the airflow obstruction is largely irreversible. However, some patients with COPD may exhibit an "asthmatic" component, and "irreversibility" also occurs in a proportion of patients with asthma.[10] Clearly, the aetiological factors in the two diseases are different, but differences in the natural history and treatment responsiveness are much less distinct. Given this picture, the value of diagnostic labelling based on physiological measurements may be confusing or even misleading.

DEFINING A PHENOTYPE USING BIOMARKERS: THE ALTERNATIVE TO DIAGNOSTIC LABELLING

The alternative to disease-oriented diagnostic labelling is to define the phenotype in relation to potential treatment responsiveness. Given that corticosteroids are the most potentially successful treatment for airways inflammation, this approach is already used empirically in the management of individual patients, usually as a "trial of steroid". The assumption is that a short-term response to steroid is closely related to the potential for beneficial long-term use. This is potentially flawed. Firstly, there are false positives. Conditions that mimic asthma, such as post-viral bronchial hyper-responsiveness, anxiety–hyperventilation syndrome and vocal cord dysfunction, may improve spontaneously with time, leading to the mistaken belief that inhaled corticosteroid (ICS) treatment

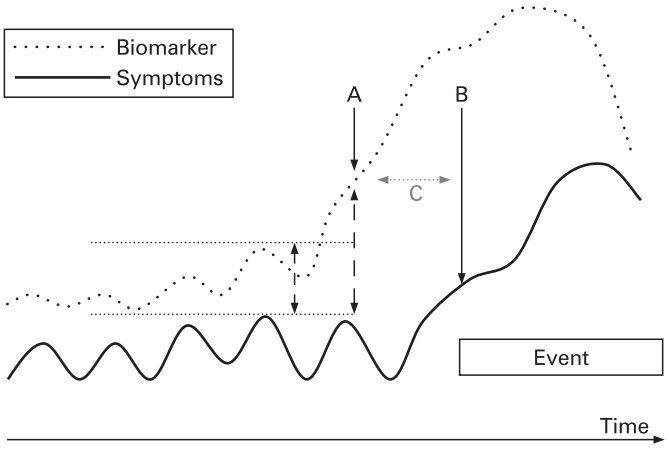

Figure 2 Using a biomarker to predict future clinical event or status. A, Point at which biomarker rises beyond "normal range" and the signal is meaningful. B, Point at which symptoms become apparent. C, Interval of time during which intervention may be applied. This needs to be greater than the time required for an intervention to abort or modify the exacerbation. The time interval may be days or years depending on the disease (eg, asthma or chronic obstructive pulmonary disease), the event or outcome (eg, exacerbation or chronic respiratory failure).

has been beneficial. Secondly, there are false negatives. This is likely where change in spirometric values, ie, peak flows or forced expiratory volume in 1 s (FEV_1), is being used to measure response. There may be minimal response in patients with fixed airflow obstruction (either asthma or COPD) despite a potentially steroid-responsive pathology being present.[11] Finally, expectation bias, observer bias and poor compliance with prescribed treatment may also influence results. All of these problems, together with the natural tendency of clinicians to err on the side of caution in difficult cases, increase the likelihood that patients may be inappropriately committed to corticosteroid treatment, with the associated cost and potential toxicity.

The phenotype for treatment responsiveness is inevitably based on the effect of treatment on the underlying pathology. Studies have shown that biomarkers such as induced sputum eosinophils and exhaled NO measurements may be used to predict steroid-responsive airways disease (box 2). This term can be used to define a disease phenotype. It is entirely logical that both the indications for and the outcomes of anti-inflammatory treatment should be related to the presence of airway inflammation rather than its physiological effects. Heterogeneity in steroid responsiveness is found in patients with the diagnostic label of both asthma[12] and COPD,[13] highlighting the weaknesses of labelling based on physiological measurements. There is now consistent evidence that eosinophilic airway inflammation is the most reliable predictor of response to corticosteroids in patients with airways disease. In COPD, the response to a 2-week course of oral prednisone 30 mg daily was significantly greater in patients with raised pretreatment sputum eosinophilia (>4.5%).[14] In asthma, the same picture emerges. Meijer *et al*[15] reported that the spirometric improvement with a 14-day trial of either oral prednisolone or inhaled fluticasone in 120 children with asthma was related to the baseline sputum eosinophil count (fig 3). In contrast, if sputum eosinophils are low (<3%[16]) or absent,[17] steroid responsiveness is highly unlikely.

Sputum induction and analysis is technically demanding, and results are not immediately available. Exhaled breath condensate has attracted interest as a potential non-invasive means for assessing airway inflammation, but it is at an early stage of development and there are several unresolved methodological issues.[18] Whether markers of inflammation measured in exhaled air can provide important information that is clinically useful is currently unclear. In contrast, measuring the F_ENO, provides an easily performed, reproducible, on-line clinical tool. Smaller less expensive analysers are now available, and this opens the way for F_ENO to be used more widely in clinical as well as research settings.[19]

The exact relationship between F_ENO and underlying airway inflammation is complex, but it is increasingly used as a surrogate marker for eosinophilic airway inflammation with which levels correlate.[20] There is a dose–response relationship between F_ENO levels and ICS dose in asthma,[21] and, just as for sputum eosinophils, a high F_ENO level is a reliable indicator of a positive response to corticosteroids in patients with non-specific symptoms.[22] Importantly, this finding is independent of the clinical diagnosis at presentation, in particular the label of asthma (fig 4). In the study by Smith *et al*,[22] at a cut-off point of 47 ppb (normal range up to 15–35 ppb in adults), there was a positive predictive value of 47% and a negative predictive value of 89% for an increase in FEV_1 of >12%. These values increased to 82% and 91% for a significant decrease in AHR (decrease in response to inhaled AMP of two doubling doses or more). The practical value of F_ENO measurements in this context has been highlighted in two further studies. After withdrawal of inhaled steroids, the advent of high F_ENO levels (>49 ppb) over the following 4 weeks predicts subsequent relapse in asthma symptoms,[23] whereas the persistence of low levels predicts successful withdrawal.[24]

Box 2: Steroid-responsive airways disease

- Is associated with clinically relevant improvements in symptoms, lung function and airways hyper-responsiveness during long-term treatment with inhaled corticosteroids
- Occurs in moderately large (up to 80%) and in usually low (10–15%) proportions of patients with asthma and COPD, respectively, independently of the diagnostic label
- Is poorly identified using physiological measurements such as spirometry
- May be inaccurately identified using a short-term "trial of steroid"
- Is characterised and predicted by the presence of underlying eosinophilic airway inflammation, measured by induced sputum analysis or exhaled NO

FUTURE ASTHMA TREATMENTS AND THE NEED FOR BIOMARKERS

The relationship between sputum eosinophils/F_ENO and steroid responsiveness provides a model for the biomarker–phenotype relationship that not only circumvents the need for diagnostic labelling but ought to be applied in the assessment of all future drug treatments. A biomarker that reflects underlying pathology and which changes with a specific intervention should be used to define other treatment-specific phenotypes. Intensive efforts are being made to develop targeted drug treatments that will be of particular benefit to patients with severe asthma. However, patients with "severe asthma" comprise a very heterogeneous group, defined either by their need for high doses of corticosteroid to maintain control or by the fact that

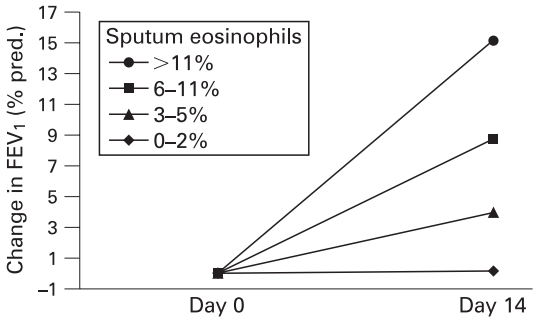

Figure 3 Changes in forced expiratory volume in 1 s (FEV_1) % predicted (pred.) from baseline to 14 days after the start of treatment with either inhaled fluticasone or oral prednisone (results for treatment groups pooled) in 120 patients with asthma whose inhaled steroid treatment was withdrawn for 3 weeks before randomisation. The results have been stratified by baseline induced sputum eosinophil count (%). Reproduced, with permission, from Meijer *et al*.[15]

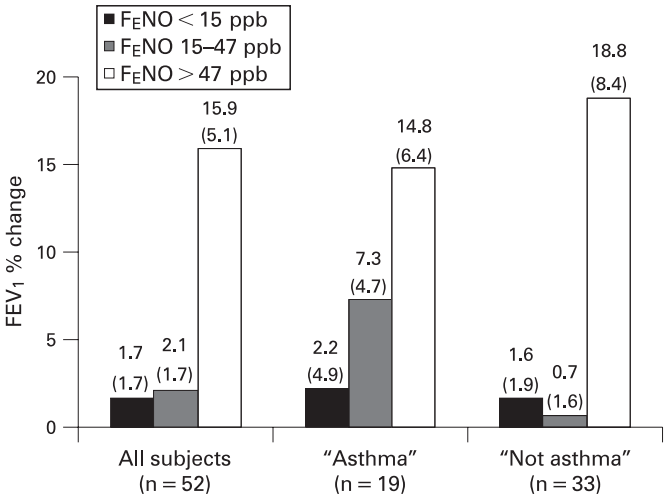

Figure 4 Mean (SEM) changes in forced expiratory volume in 1 s (FEV_1) after a 4-week trial of inhaled fluticasone in 52 steroid-naïve patients who presented with a 6-week history of previously undiagnosed chronic respiratory symptoms. The group is further classified as having or not having asthma, where the diagnosis was based on the presence of variable symptoms plus either a positive bronchodilator response test (>12% increase in FEV_1 with salbutamol) or a positive methacholine challenge (PD_{20} (ie, the dose of methacholine producing a 20% fall in FEV_1) <8 μmol). Steroid responsiveness was greatest in the group with the highest tertile for F_ENO (>47 ppb). The relationship between F_ENO and steroid response is independent of the diagnostic label. The data are modified from Smith *et al*.[22]

control remains poor despite these high doses.[25] The reasons for this definition are understandable, but again the label has practical limitations in relation to intervention studies. Perhaps the mixed outcomes with treatments such as anti-IgE or anti-(tumour necrosis factor α) would be improved if patients were selected on the basis of their "responder" phenotype—measured using a biologically plausible, validated marker. Although this may not be easy, in the absence of the parallel development of a relevant biomarker alongside a new asthma treatment, the value of the novel therapy may be lost if clinical trials include "all comers".

MONITORING AIRWAYS DISEASE: ASSESSING AND MODIFYING FUTURE RISK

Asthma

Several studies have explored whether a biomarker might be used to reduce the frequency of exacerbations by optimising anti-inflammatory treatment on the basis of a biomarker with predetermined, clinically relevant cut-off points. The first proof-of-concept study was by Sont *et al*.[26] Using measurements of AHR to guide ICS treatment, these investigators showed that the frequency of asthma exacerbations could be reduced. However, more recently, Nuijsink *et al*[27] failed to confirm this, although they showed that decline in lung function could be attenuated.

Evidence that blood eosinophils, sputum eosinophilic cationic protein, exhaled breath condensate pH or cytokines may be used in asthma monitoring is lacking. However, using sputum eosinophil counts has been shown to provide significant benefits. Steroid-withdrawal studies indicate that unstable asthma is associated with counts of >10%. In stable asthma, the count is below 1.9%, and there is a consensus that clinically significant change is an increase or decrease of 50% or more.[28] On the basis of these data, two studies have investigated whether the frequency of exacerbations can be reduced when ICS dose is adjusted so that the sputum eosinophil count is kept within the "normal" range. Significant reductions were achieved, notably in patients with moderate or severe asthma.[29 30] These studies provide a model for how a biomarker ought to be used in day-to-day practice. However, the major limitation is the availability and cost of the sputum induction and analysis.

The possibility that F_ENO measurements might be used as a simpler alternative to sputum eosinophil counts has also been explored. Unfortunately, the outcomes have been less convincing. Certainly, a significant reduction in ICS dose requirements can be achieved without compromising clinical outcomes.[31] However, the overall reduction in exacerbations in the studies that have investigated this issue, at ~25%, was non-significant.[31–33] These data do not mean that F_ENO cannot be used reliably as a biomarker, but rather that it cannot be used reliably for this particular indication.[34]

Evidence that single biomarker measurements may be used to predict impending loss of asthma control has been sought usually in the somewhat artificial setting of steroid-reduction studies. The results are not clear cut. Leuppi *et al*[35] reported that, at a cut-off point of 6.3%, sputum eosinophils had a sensitivity of 90% and a specificity of 63% for loss of control after stepwise reduction of inhaled steroid dose. Using a cut-off point of 4%, Jones *et al*[36] reported a sensitivity of only 59% and a specificity of 60% for loss of control after complete steroid withdrawal. These results can only be regarded as modestly successful. For F_ENO, however, the data are somewhat more promising. Jones *et al*[36] reported that a 60% increase in F_ENO between two visits provided a positive predictive value of 83%. More recently, Michils *et al*[37] reported that changes in F_ENO in relation to asthma control (as measured by the Asthma Control Questionnaire) are prognostically helpful. A single F_ENO measurement of >45 ppb excluded well-controlled asthma with a negative predictive value of 89%. On the basis of repeated measurements, a 40% decrease in F_ENO had a high positive predictive value (83%) and similar negative predictive value (79%) for a clinically relevant reduction in Asthma Control Questionnaire score, ie, improved asthma control. F_ENO consistently <30 ppb was associated with a low likelihood of exacerbation within 3 months. Finally, van Veen *et al*[38] reported that, in "difficult asthma", F_ENO is a predictor of accelerated

decline in lung function when levels remain high. These data suggest rather than confirm the exact role for F_ENO monitoring in asthma, and it is likely that the indications will become clearer with the advent of portable analysers and studies that include more frequent measurements.

COPD

In COPD, the natural history of the disease dictates that biomarkers will potentially serve a somewhat different role in predicting clinical course and future risk compared with asthma. The aims in COPD may also vary depending on whether the patient is "at risk" or has established disease. The most important end point for the former group is the future development of COPD itself, for which decline in lung function may not always be a marker. For the latter, it is decline in lung function, the advent of respiratory failure, hospital admissions and mortality.

As in asthma, sputum cells[1 39] and F_ENO[1 40] may have a role as biomarkers in COPD. Around 30% of patients with COPD have induced sputum evidence of eosinophilic airway inflammation,[14] and again, as in asthma, this is associated with a good response to corticosteroid therapy.[14 41] Titration of treatment to suppress the sputum eosinophil count below 3% is associated with a significant reduction in severe exacerbations.[42] Unfortunately, data pertaining to the use of F_ENO to predict steroid responsiveness in smoking-related fixed airflow obstruction are limited; in only one small study has the relationship between baseline F_ENO and change in FEV_1 with inhaled budesonide been investigated.[43] There may be added value in measuring alveolar as well as airway NO concentrations. This potentially reflects more peripherally distributed lung inflammation in COPD.[44]

In addition to sputum cells and F_ENO, the list of biomarkers relevant to COPD is more extensive. A leading candidate is C-reactive protein (CRP).[45] Others include plasma fibrinogen,[46] interleukin 6 and other cytokines,[47] and co-peptin.[48] More recently, using proteomics, Celli's group have explored an even wider range of "inflammatory" biomarkers.[49] CRP is raised in COPD independently of other factors, notably current cigarette smoking and other comorbidities.[45] Some studies report that baseline concentrations are associated with subsequent decline in lung function,[50] although this is not a consistent finding.[51] However, increases in CRP over time are associated with decreases in FEV_1 % predicted.[52] Increased baseline CRP is also associated with subsequent risk of hospitalisation and mortality.[53] Similar results have been obtained for plasma fibrinogen.[46 47]

At present, the evidence for using biomarkers prognostically in COPD is limited. But, as has been argued elsewhere,[54] perhaps more than one marker used in combination may provide prognostic accuracy where none of the individual candidates seems to offer benefit when used singly. For example, in the study by Dahl *et al*,[46] the positive predictive value of a high baseline fibrinogen (>2.7 mg/ml) for a hospital admission due to COPD during the 6-year follow-up was only 4%! However, in the Copenhagen Heart Study, the lowest 10-year risk for hospitalisation with COPD was 5.7% in subjects who were aged less than 70 years, *and* were non-smokers, *and* whose FEV_1 % predicted was 80% or greater. In contrast, the risk increased significantly to 54% among those aged >70 years and who were smokers and whose FEV_1 at baseline was <50% predicted.[53] Unfortunately, positive and negative predictive values were not reported, but the data suggest that an optimised "nest" that combines several relevant objective measures might be better.

This approach has been used in relation to risk assessment for cardiovascular disease. Whereas managing individual risk factors such as hypertension and diabetes was earlier based on separate guidelines designed to reduce relative risk, the approach changed during the 1990s. Absolute risk based on combining a hierarchy of known risk factors became the basis for a paradigm shift away from emphasising a single factor.[55] Risk charts providing the probability of a significant cardiovascular event (% risk within 5 years) were developed, incorporating age, sex, smoking status, diabetes, hypertension and blood cholesterol.[56 57] Such a strategy, in which the calculation of absolute risk is followed by a raft of intervention strategies, is the basis for reducing long-term morbidity and mortality from cardiovascular disease.[58] Can a similar approach be adopted for respiratory disease? This is a relatively unexplored question, but may be important in predicting future risk for COPD and may provide scope for clinically relevant use of biomarkers.

Key learning points

- Biomarkers may be used to identify the pathological phenotype in patients with airways disease.
- The pathological rather than the physiological phenotype is more likely to be relevant when choosing drug therapy.
- Induced sputum eosinophilia (>2%) and raised exhaled NO concentrations (>50 ppb) are associated with steroid responsiveness irrespective of the clinical diagnosis.
- In selected settings, biomarkers can be used to assess underlying disease activity, and this may be helpful when the manifestations of disease are difficult to interpret.
- Biomarkers are important in the assessment of targeted therapeutic agents particularly when symptoms and abnormal lung function are multifactorial in origin.
- Systemic biomarkers, eg, C-reactive protein, also have the potential to be used to define a phenotype as well as the likely prognosis in chronic obstructive pulmonary disease.

SUMMARY

The use of biomarkers in the assessment and management of airways disease is in its infancy, but the future is promising. Biomarkers may be used to define a particular phenotype, including treatment response, assess underlying disease activity, and predict future clinically relevant events. Just as mobile phones may obviate the need for land lines, so the advent of biomarker technology provides the incentive to move away from traditional diagnostic labelling of asthma and COPD based on physiological measurements. Defining "steroid-responsive airways disease" is helpful irrespective of the background physiology. Identifying a "responder" phenotype using a biomarker is likely to be even more important in the development of new targeted drugs for asthma, particularly if it is severe. In day-to-day practice, the use of induced sputum is usually not possible, but it represents the current "gold standard" as a biomarker for monitoring asthma. F_ENO measurements are a practical but less reliable alternative, the application of which is best suited to determining the need to start or withdraw ICS treatment and interpreting the aetiology of respiratory symptoms in complex asthma, where these are likely to be multifactorial. In COPD, there is a need to investigate how biomarkers might be used in combination with other measurements to assess the risks of future adverse long-term outcomes.

Research issues and questions

- The development of new targeted therapies for severe asthma requires the parallel validation of an appropriate biomarker that can be used to select likely responders and monitor underlying disease activity.
- Does F_ENO-guided management result in better outcomes in severe asthma?
- Can corticosteroid therapy be safely withheld in patients with airway disease and a normal sputum eosinophil count and/or a low FE_{NO}?
- Can assessment of airway inflammation using exhaled breath condensate be used to assess underlying disease activity and/or response to treatment?
- What is the best biomarker or combination of biomarkers for predicting decline in lung function in patients with airways disease?

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCE)

1. A good biomarker:

(A) Is sensitive rather than specific

(B) Is characterised by statistically significant changes which coincide with significant changes in the clinical status of the patient

(C) Should be more responsive to treatment intervention than a clinical marker

(D) Should have a low coefficient of variation for repeated measurements

2. The distinction between asthma and chronic obstructive pulmonary disease (COPD):

(A) Is best made by defining the reversibility of airflow obstruction to a bronchodilator

(B) Is important in anticipating the likely future clinical history in a patient with chronic respiratory symptoms

(C) Is less important than the distinction between ''responders'' and ''non-responders'' to anti-inflammatory therapy

(D) Is confounded in patients whose asthma is characterised by fixed airflow obstruction

3. In relation to induced sputum cell counts:

(A) An eosinophil count of greater than 2% is associated with stable asthma

(B) Eosinophils are never present in patients with COPD

(C) Tailoring inhaled corticosteroid treatment against sputum eosinophil counts has been shown to improve asthma control

(D) The absence of sputum eosinophilia precludes a diagnosis of asthma

4. C-reactive protein:

(A) May be used as a predictor for decline in lung function in patients with mild COPD

(B) Is raised in patients with COPD independently of current cigarette smoking

(C) Is associated with progressive decline in lung function in subjects with increasing levels over time

(D) Is associated with increased long-term mortality in patients with COPD

5. Regarding exhaled nitric oxide (F_ENO) measurement:

(A) It is a good predictor of steroid-responsiveness when levels are high i.e. >50 ppb

(B) It is a good diagnostic test for asthma

(C) Tailoring inhaled corticosteroid treatment against F_ENO has been shown to improve asthma control

(D) It may be used to distinguish the aetiology of non-specific symptoms in difficult asthma

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ANSWERS

1. A (F); B (F); C (T); D (T)
2. A (F); B (T); C (T); D (T)
3. A (F); B (F); C (T); D (F)
4. A (F); B (T); C (T); D (T)
5. A (T); B (F); C (F); D (T)

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Notes