Risk assessment in asthma and COPD: a potential role for biomarkers?

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ABSTRACT

There is an increasing literature on the pathological and clinical significance of "inflammatory" biomarkers in asthma and chronic obstructive pulmonary disease (COPD). Their potential role includes risk assessment, but this is somewhat different for the two conditions. In asthma the aim is to identify future risk of poor asthma control or exacerbations. Although induced sputum eosinophils and exhaled nitric oxide are the most widely investigated candidates for use in the clinical arena, there is scope for a great deal of improvement in their application and other biomarkers may prove to be better. For COPD, risk assessment is somewhat different. There is the potential to use biomarkers such as C-reactive protein, fibrinogen or interleukin 6, along with other conventional demographic and physiological measurements, to assess longer term risk of decline in lung function, hospitalisations and mortality. The well-tried model used in cardiovascular disease to assess absolute risk might possibly be adapted for use in COPD, and this should be actively explored.

A biomarker is a surrogate biological measurement used to indirectly quantify the current burden of disease activity or predict future disease-related outcomes. Ideally, a biomarker may also be used to direct an intervention so that these outcomes may be modified. Examples include viral particle count or CD4 cell count in the management of HIV/AIDS, or prostate specific antigen in the assessment of prostate cancer.

The subject of "inflammatory" biomarkers in both asthma and chronic obstructive pulmonary disease (COPD) is topical[1][2] but, as yet, their application in clinical practice—given our current state of knowledge and the limitations imposed by technology, availability and cost—has not been clearly identified. Given the differences in natural history, the particular objectives involved in measuring biomarkers differ between asthma and COPD. For asthma, a condition characterised by variability, the aim is not only to assess underlying airway inflammation but to attempt to assess the risk of future exacerbations or poor control. For COPD, the aims are somewhat different. They include predicting progressive decline in lung function, the likelihood of exacerbations and hospital admissions, and mortality.

ASTHMA

A multiplicity of biomarkers can be measured in asthma using induced sputum, exhaled air or breath condensate, or blood.[2] The most commonly cited candidates for use in the clinical arena are sputum cells[3] and exhaled nitric oxide (FeNO).[4] The use of exhaled breath condensate is still largely a research tool and it will not be considered in detail in this paper. However, it is worth noting that the pH of exhaled breath condensate appears to decrease in relation to deteriorating asthma, irrespective of the aetiology of the deterioration.[5] This non-specific characteristic may yet prove to be clinically useful in defining its role as a prognostic biomarker in asthma.

Several preconditions require to be met when using a biomarker to predict asthma deterioration (fig 1). First, the timing of the change in the biomarker must precede the change in clinical symptoms rather than occur simultaneously. Related to this is the requirement that the interval between the change in the chosen biomarker and the onset of clinical deterioration should be sufficiently long to permit an effective intervention which will abort or modify the severity of the deterioration. For example, increasing levels of biomarker X may precede an exacerbation of asthma, but the increase would need to occur within a time frame which is greater than the time required for systemic corticosteroids to act, otherwise measuring the biomarker would have limited value. Third, the magnitude of the change in the biomarker associated with a clinically significant event must be greater than the coefficient of variability (CV) for that biomarker during periods when the asthma is relatively stable. This is not necessarily the same as the CV for healthy non-asthmatic individuals (eg, FeNO[6]).

There are two ways in which a biomarker might be used to reduce future risk in asthma. First, it might be used to improve overall asthma control by optimising maintenance anti-inflammatory therapy. Both airway hyper-responsiveness (AHR), as measured by a methacholine challenge,[7] and induced sputum eosinophil counts[8][9] have been used to adjust inhaled corticosteroid (ICS) dose with considerable success. For sputum eosinophils, treatment algorithms designed to maintain a count of <3% result in a highly significant reduction in the frequency of exacerbations (even though the majority of exacerbations are non-eosinophilic), probably by improving the overall degree of asthma control.[8][9] Second, a biomarker might be used to predict individual asthma events. In this regard, the benefits of using sputum eosinophil counts to predict future loss of control are much less clearcut. In an early study, Jatakanon et al[10] investigated the changes in both sputum eosinophils and FeNO after reducing ICS therapy. The changes in sputum eosinophils correlated with subsequent negative changes in symptoms and lung function, and were a significant predictor for
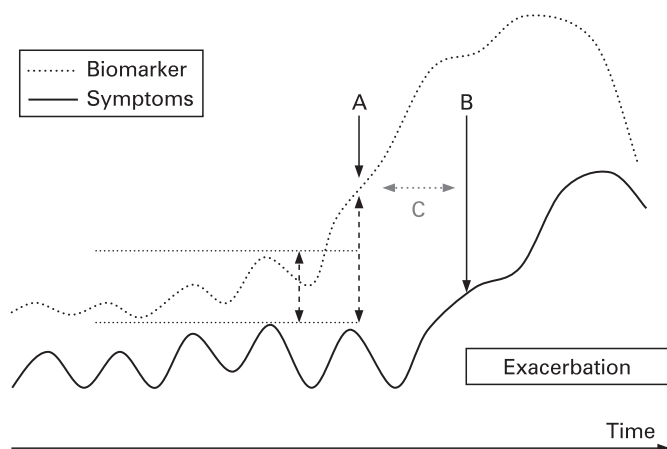
Figure 1 Using a biomarker to predict deterioration in clinical status. The lead time between the point at which the biomarker increases beyond the range of day-to-day variability (dashed arrows) and the point at which an increase in symptoms is perceived by the patient requires to be greater than the time required for an intervention to abort or modify the exacerbation. A, point at which biomarker rises beyond "normal range"; B, point at which symptoms become apparent; C, interval of time during which intervention is applied.

loss of control (LOC). In a later study, Leuppi et al[11] reported that, at a cut-off point of 6.3%, sputum eosinophils had a sensitivity of 90% and a specificity of 63% for LOC with stepwise steroid reduction. Jones et al reported a sensitivity of only 59% and a specificity of 60% for LOC following complete steroid withdrawal using a cut-off point of 4%.[12] These results can only be regarded as modestly successful. But even if they were much better than they are, it is doubtful if induced sputum cell counts could be widely used for prognostic purposes because of the practical difficulties of obtaining and processing samples on a repeated or regular basis.

FeNO is a surrogate marker for eosinophilic airway inflammation, and similar studies have been conducted to evaluate the role of FeNO measurements, both to reduce asthma exacerbations (by optimising ICS treatment) and to predict the risk of poor asthma control. To date, none has been undertaken with a view to predicting asthma exacerbations per se. The interpretation of FeNO is more complex than for sputum eosinophils. Whereas a sputum eosinophil count of greater than zero is abnormal, this is not the case for FeNO where healthy individuals always have measurable levels (ie, constitutional as well as pathological factors affect FeNO levels). This is probably why, in contrast to sputum eosinophils, the results of first-generation studies designed to use FeNO to guide ICS therapy have been somewhat disappointing.[13] [14] As far as predicting poor asthma control is concerned, the data are somewhat more promising. Jones et al reported that, using weekly FeNO measurements in patients from whom ICS therapy had been withdrawn, the predictive value of a single measurement of FeNO was no better than symptoms, serial peak flows or spirometry.[12] However, a change in FeNO of ≥60% between baseline (steroid withdrawal) and the visit immediately prior to LOC had a positive predictive value (PPV) for LOC of 83% (sensitivity 50%, specificity 65%). More recently, Michils et al have similarly reported that changes in FeNO in relation to asthma control, as measured by the Asthma Control Questionnaire (ACQ),[15] are prognostically helpful. A 40% decrease in FeNO had a high PPV (83%) and similarly high negative predictive value (79%) for a clinically significant reduction in ACQ score (ie, improved asthma control). Perhaps the advent of portable nitric oxide analysers, permitting FeNO measurements to be made with greater frequency and ease, will facilitate new studies in which this approach is developed further. The ideal biomarker in asthma would be one which is easily measured, whose CV is low when asthma is stable, which changes significantly *prior* to deterioration, and which accurately predicts future loss of control. These features would be useful in patients with difficult or brittle asthma, especially where there is discordance between symptom severity and underlying airway inflammation. FeNO is not the last word.

COPD

In COPD, particular attention has been given to C-reactive protein (CRP),[16] [17] plasma fibrinogen,[18] interleukin 6 (IL6) and other cytokines,[19] co-peptin,[20] sputum cells[1] [21] and FeNO.[1] [4] More recently, using proteomics, Celli's group have explored an even wider range of "inflammatory" biomarkers.[22] However, despite this growing body of evidence, their application in clinical practice remains limited. There are a number of reasons for this.

First, most studies to date have been cross-sectional, providing evidence only of associations (reported as odds ratios or likelihood ratios) between the biomarker and particular pathophysiological or clinical features of the disease. Far fewer studies have been conducted longitudinally—which is the prerequisite for obtaining predictive power, reported as positive and negative predictive values. However, this picture is changing. Data from a number of investigations with large numbers of subjects,[18] [23–26] including both healthy and affected individuals, and with a substantial follow-up interval ranging from 3 to 10 years[18] [19] [23–26] have the potential to provide a platform upon which it may become feasible to use an "inflammatory" biomarker much more readily.

The leading candidate at present is CRP. As well as acting as a biomarker, this acute phase protein has a pathogenic role and is strongly linked to IL6 which, in turn, is intimately related to airway inflammation. CRP is easily measured. It is raised in COPD independently of other factors, notably current cigarette smoking and other comorbidities.[16] Some studies report that baseline levels are associated with subsequent decline in lung function,[25] although this is not a consistent finding.[24] However, *increases* in CRP over time are associated with *decreases* in forced expiratory volume in 1 s (FEV$_1$ % predicted).[26] The same is true for IL6.[19] Increased baseline CRP is also associated with subsequent risk of hospitalisation and mortality.[23] Similar results have been obtained for plasma fibrinogen.[18] [19] As a surrogate marker for eosinophilic airway inflammation, FeNO may have a role in identifying asthma/COPD overlap syndromes[27] or potential steroid responsiveness,[28] but it has no clear prognostic utility.

Second, in the analysis of these studies, authors have rarely included a calculation of the predictive power of the biomarker or of optimum cut-off points in relation to a particular end point. This makes it difficult to judge whether or not the biomarker is potentially clinically useful. In the study by Dahl et al the PPV 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%.[18] On the face of it, this is a very discouraging outcome. However, such data only provide information regarding the potential use of the test in isolation. What improvements might be achieved if an iterative approach was adopted and the predictive power for a biomarker *combined with* other clinical and physiological data was calculated? This is a largely unexplored but potentially fruitful issue. An optimised "nest"

of relevant measured features might be used prognostically. In the Copenhagen Heart Study, the lowest 10-year risk for hospitalisation with COPD was 5.7% in subjects who were aged <70 years *and* were non-smokers *and* whose FEV_1 % predicted was ⩾80%. 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.[23] Although PPVs and NPVs were not reported, these data suggest that the performance characteristics of *combined* data are likely to be enhanced and are potentially more clinically applicable than using a single biomarker alone.

This approach is not new. It was adopted and applied in relation to risk assessment for cardiovascular disease many years ago. Whereas managing individual risk factors such as hypertension and diabetes was earlier based on separate guidelines designed to reduce the *relative* risk, the methodology changed during the 1990s. The calculation of *absolute* risk based on combining a hierarchy of known risk factors became the basis for a paradigm shift away from emphasising a single risk factor.[29] Risk charts providing the probability of a significant cardiovascular event (percentage risk within 5 years) were developed, incorporating age, sex, smoking status, diabetes, hypertension and blood cholesterol.[30 31] Jackson has highlighted that such a strategy, with the calculation of absolute risk followed by appropriate intervention strategies, is the basis for reducing long-term morbidity and mortality from cardiovascular disease.[32]

Can a similar approach be adopted for respiratory disease? This is a relatively unexplored question, but may be helpful in the development of risk assessment for COPD during the next few years. Cardiovascular risk analyses were derived from data from the Framingham study, comprising 5000 subjects monitored over an interval of 10 years.[33] A comparable resource is potentially available for COPD using databases from studies such as the Lung Heath Study and the Copenhagen City Heart Study, which have included biomarkers among the measured parameters. Of course it might be argued that, since the only intervention likely to alter the course and prognosis for COPD is smoking cessation, the availability of a more elaborate risk profile in COPD is unlikely to be helpful. However, although the scope for preventive strategies is perhaps more limited in respiratory disease than in cardiovascular disease, this is no reason to be nihilist. The studies cited above provide evidence of the prognostic importance of ''inflammatory'' biomarkers in COPD, and a more dynamic and inclusive approach would appear timely. The incorporation of one or more biomarker candidates (eg, CRP or fibrinogen) for which robust performance characteristics have been established, along with age, sex,[34] a history of childhood asthma, smoking history[35] and current lung function (and/or others) as the basis for developing a composite risk chart for COPD should now be actively explored.

The aim would be to improve risk assessment when dealing with individual patients. For example, faced with a 38-year-old woman with a history of childhood asthma who is currently smoking 10 cigarettes/day (20 pack-years), whose FEV_1 is 81% predicted, FEV_1/vital capacity (VC) ratio is 79% with a CRP level of 3.5 mg/ml (high), what is the risk of her developing COPD? Or what is the risk of a hospital admission within 5 years in a 62-year-old man with diagnosed COPD who stopped smoking 5 years ago (40 pack-years), whose FEV_1 is 45% predicted and whose plasma fibrinogen is 3.8 g/l (high)? At present, when faced with these questions, we cannot offer a clear answer. The *individual* data points for these two patients may have prognostic significance, but it is difficult to quantify the overall risk. What would be the added value if they were taken together and used quantitatively to predict future risk? The work of Fletcher and Peto led to the development of a now iconic illustration of lung function decline in smokers.[35] Perhaps the time is now right to take Fletcher and Peto a step further and follow in the footsteps of our colleagues in cardiovascular medicine.

CONCLUSION

The potential for using biomarkers in risk assessment for asthma and COPD is growing, but differs between the two conditions because of differences in their natural history and the clinical outcomes of interest. Identifying future risk is increasingly important in the management of asthma, and selecting a biomarker which will improve the effectiveness with which we do so is a current challenge. Although induced sputum eosinophils and FeNO have been investigated, there is scope for a great deal more to be done to define their role as well as explore other biomarkers. This is likely to be technology-dependent. For COPD there is the potential to use biomarkers such as CRP, fibrinogen or IL6, along with other conventional demographic and physiological measurements to improve the long-term risk assessment in patients particularly with early COPD. The possibility that the risk assessment model used in cardiovascular disease might be adapted for use in COPD should be actively explored.

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Pulmonary puzzle

ANSWER

From the question on page 210

This case describes an extremely rare condition of extramedullary plasmacytoma (EMP) hidden in the middle media-stinum, giving no systemic signs but causing severe central airway narrowing detectable by the pattern of the flow-volume loop. The constant expiratory and inspiratory flow limitation is consistent with severe fixed narrowing of the central airway.[1] Accurate analysis of the flow-volume curve pattern at the onset of symptoms would have given rise to a suspicion of tracheal compression several months earlier.

Fixed intrathoracic airway obstruction is usually due to intramural infiltration (post-endotracheal intubation, recurrent polychondritis, primitive tracheobronchial neoplasia and amyloidosis) or to extrinsic compression (intrathoracic goitre, thymoma, lymphoma).[2] Mediastinal localisation of plasma-cytoma is very uncommon, usually presenting as a large mass visible on the chest radiograph.[3] In this case, EMP was hidden in the middle mediastinum and could only be detected on the chest CT scan.

Transbronchial biopsy was consistent with IgG lambda plasmacytoma. Multiple Russell bodies on PAS staining were indicative of cytoplasmic inclusions of immunoglobulins. The results of immunohistochemical staining are shown in fig 1.
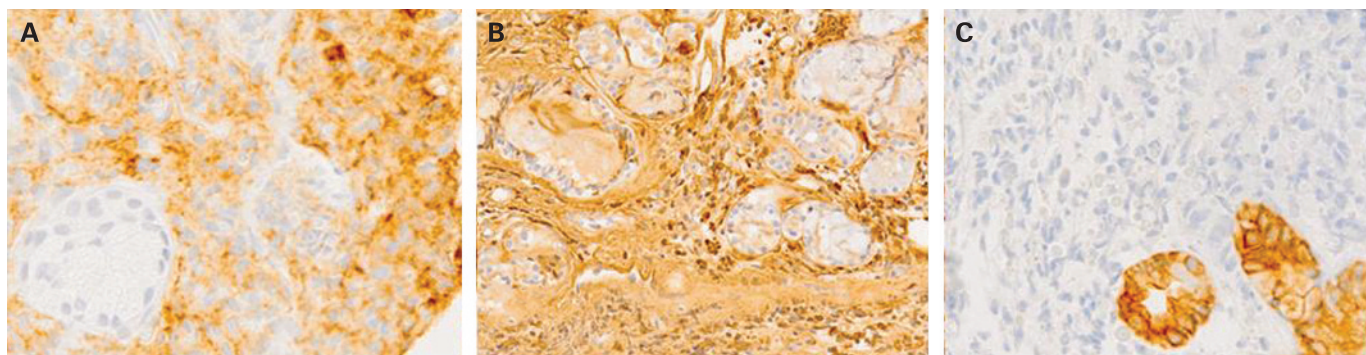
EMP is a plasma cell neoplasm of soft tissue without bone marrow involvement or other systemic characteristics of multiple myeloma, representing about 3% of all plasma cell neoplasms.[4] It can be differentiated from reactive plasmacytoma and plasma cell granuloma or lymphoma (MALT, marginal and immunoblastic) by the expression of specific cell surface markers.[5]

This case suggests that the pattern of the flow-volume loop may give a hint of central airways narrowing caused by hidden masses not visible by traditional procedures.

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Figure 1 Immunohistochemical analysis of the proliferating cells phenotypically characterised to be (A) CD138+, CD79a+, (B) cIgG lambda+ (weak), (C) cIgG kappa- and cytokeratin AE1/3−. Staining for cIgM, cIgD, cIgA, cIgE, CD3 and CD45RO were all negative. Since there were very few non-neoplastic (cIg-kappa+) plasma cells and small lymphocytes, these findings were suggestive of IgG lambda plasmacytoma.