REVIEW ARTICLE

When are biomarkers useful in the management of airway diseases?

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KEY WORDS

asthma, biomarkers, chronic obstructive pulmonary disease, exhaled nitric oxide, sputum eosinophils

ABSTRACT

Biomarkers are characteristics that are objectively measured and evaluated as indicators of biological or pathogenic processes, or responses to therapeutic interventions, and may provide information on the prognosis or progression of the disease and response to treatment. They are likely to be helpful in the management of airway diseases because of the heterogeneity of their pathobiology. Most biomarkers have been developed and evaluated to assess the airway inflammation (or bronchitis) associated with airway diseases. These include quantitative cell counts in sputum, fraction of nitric oxide in exhaled breath, and various metabolites in exhaled breath. This review provides a brief description of these biomarkers with a particular emphasis on how eosinophil and neutrophil counts in sputum could be used to manage airway diseases such as asthma, chronic obstructive pulmonary disease, and chronic cough.

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Introduction In medicine, "biomarker" is a term often used to refer to a measurable characteristic that reflects the severity or presence of a disease state. The study of biomarkers in airway diseases is an evolving science, and several biomarkers have been described over the past decade in an attempt to associate the disease process with pathogenic processes and therapeutic interventions. This is mainly because airway diseases such as asthma, chronic obstructive pulmonary disease (COPD), and chronic cough have been increasingly recognized as being extremely heterogeneous in nature.[1,2] Therefore, guideline-based management strategies do not work equally well in all patients. About 5% of the patients with asthma require individualized strategies for the optimum control of their disease.[3] The success of these individualized strategies depends on accurate phenotyping with the help of biomarkers. However, the role of the most available biomarkers in clinical practice has not been fully established yet.

Traditionally, the only biomarkers used to manage airway diseases have been physiological measurements of air flow, such as peak expiratory flow or forced expiratory volume in 1 second (FEV_1) and, less frequently, airway hyperresponsiveness. More recently, the biomarkers that reflect airway inflammation, an integral component of most airway diseases, have been evaluated. They include eosinophils in blood and sputum, immunoglobulin E (IgE), proteomics and gene expression markers in blood and sputum, exhaled breath nitric oxide and other volatile compounds, urine metabolites, etc. Although most of them have been described in the context of asthma,[4] it is intuitive that the same biomarkers would also be useful in COPD and chronic cough as most of these are markers for airway inflammation, which is fundamental to all airway diseases. The three important pathophysiological mechanisms are B-cell mechanisms, T-helper 2 (Th2)-driven mechanisms (predominantly eosinophil-mediated) and non-Th2 mechanisms. Currently, it is not clear whether the phenotypes identified by cluster and principal component discriminant analyses of biomarkers such as sputum cell counts[5,6] are stable over time. This is because the cellular nature of sputum seems to change with exacerbations in a significant proportion of patients.[7]

The present review will briefly describe the biomarkers that are used clinically to manage patients with airway diseases with a focus on the use of quantitative cell counts in sputum as practiced in Hamilton, Ontario, Canada, and discuss the specific situations when they are most likely to be useful.

Biomarkers in blood **Total and allergen-specific immunoglobulin E in blood** Both total and allergen-specific IgE are biomarkers for atopy[8,9] and are indicative of

a predominant B-cell mechanism as the underlying pathogenic process. However, there is a considerable overlap between atopic and nonatopic persons, which reduces its utility in identifying atopy. Despite this limitation, it is useful to identify specific allergen triggers and likely responders to anti-IgE therapy such as omalizumab in patients with severe asthma.[10] The measurement of allergen-specific IgE by the skin prick test, although widely used in the clinical setting, is considered only an emerging biomarker for research because of the variability of the test's performance.

Eosinophil count in blood Eosinophils in blood are nonspecific for asthma and asthmatics do not have raised blood eosinophil counts.[11,12] However, when elevated, a direct correlation exists between blood eosinophil counts and symptom scores,[13,14] while there is an inverse correlation with FEV_1 in both children and adults.[14] Mechanistically, it indicates a high Th2 phenotype and predicts responsiveness to steroids and anti-interleukin (IL) 5 therapy.[15] In patients with asthma, blood eosinophil counts start to decrease within 24 hours after intravenous administration of anti-IL-5 antibody, followed by much greater decreases several days later.[16-18] The advantage of blood eosinophils is that it is easily measured and the test is widely available. However, the sensitivity and specificity of blood eosinophil count of more than 300/μl to detect an eosinophil phenotype based on sputum eosinophil counts of more than 2% were 59% and 65%, respectively. The accuracy was 63% and the positive predictive value was 50%.[19]

Serum periostin Periostin is a systemic biomarker of airway eosinophilia in asthmatic patients and has the potential utility in patient selection for emerging asthma therapeutics targeting Th2 inflammation.[20] Recently, a clinical trial has shown that patients with higher levels of periostin respond to lebrikizumab (anti-IL-13 monoclonal antibody).[21] Serum periostin level has been reported to be a better predictor of airway eosinophilia than serum IgE levels, blood eosinophil numbers, and fractional exhaled nitric oxide (FENO) levels.[21] This biomarker has not been evaluated in COPD or other airway diseases and further evaluation is necessary before it becomes applied in routine clinical use.[22]

Sputum quantitative assay The main clinical application of sputum cell counts is in guiding treatment based on the predominant cellular nature of airway inflammation. The cell counts can accurately discriminate eosinophilic from noneosinophilic airway inflammation. The presence of eosinophilic inflammation is predictive of steroid responsiveness,[23] while noneosinophilic (neutrophilic or paucigranulocytic) inflammation is not.[24] It also helps identify impending loss of asthma control and adjust anti-inflammatory medications such as limiting the use of corticosteroids in exacerbations associated with a noneosinophilic bronchitis and increasing corticosteroid doses in exacerbations associated with an eosinophilic bronchitis. By virtue of its ability to identify patients with an eosinophil phenotype, it helps select patients for targeted therapy with anti-eosinophil agents such as anti-IL-5.[18] Sputum-cell-count-based treatment strategies help significantly reduce asthma exacerbations[25,26] and hospitalizations due to exacerbations of COPD.[27] The relation between blood and sputum eosinophils has not been reported. Sputum cell count scores over most other biomarkers because it directly measures airway inflammation and is the only available method that can identify neutrophilic and paucigranulocytic airway inflammation. Most other methods can only indicate whether or not airway inflammation exists. The only disadvantage for this method is the need for training as the test still remains to be automated as yet. This has precluded its widespread availability. The method has been validated, standardized, and well described.[28-30]

Biomarkers in exhaled breath **Exhaled nitric oxide** FENO is a simple, safe, reproducible, and most widely used biomarker in clinical practice.[31] It also has the approval of the Food and Drug Administration. However, FENO values have a wide normal range with an overlap among healthy, atopic, and asthmatic cohorts. Although the values lower than 25 ppb in symptomatic patients generally exclude airway eosinophilia, FENO cannot identify the cellular nature of airway inflammation associated with exacerbations of airway diseases. Therefore, treatment strategies that aim to reduce FENO has not consistently reduced asthma exacerbations in clinical trials,[32] and it remains unaffected by anti-IL-5 therapy.[16,33] Its role in the management of airway diseases seems to be limited to a mild airway disease,[34] patients who cannot produce sputum, such as children, and for measuring the effects of interventions (e.g., corticosteroids) on airway inflammation as a whole by observing its changes over time.

Exhaled breath condensate Exhaled breath condensate allows the measurement of several biochemical substances, many of which have not been standardized as yet.[35] Among them, exhaled breath pH is the most technically validated measurement, which focuses on biochemical disturbances common in inflammatory diseases in general.[36] A low pH represents an inflamed airway, making airway neutralization therapies a potential treatment strategy for airway inflammatory diseases. Exhaled breath condensate pH may also identify acute acid reflux.[37] However, it is not yet ready as a tool for monitoring therapy of inflammatory lung disease. Volatile substances in exhaled breath such as nitrogen oxides, hydrogen peroxide, glutathione, aldehydes, and isoprostanes can be measured by sophisticated statistical methods such as principal component analysis using a systems biology approach to recognize the patterns consistent with physiological or pathological abnormalities. Currently, it is still a research tool that has shown promise in discriminating between

eosinophilic and neutrophilic bronchitis in patients with asthma and with COPD.[38] It is currently undergoing evaluation for possible application in routine clinical practice. Temperature measurement in exhaled air is a reflection of mucosal blood flow and, therefore, it increases in the presence of airway inflammation.[39] Like FENO, it has the advantage of being easy to use and may discriminate between healthy volunteers and patients with airway diseases. This tool, however, needs further research to find a place in clinical practice.

Metabolomics in urine Metabolites in urine can be analysed in random urine samples by nuclear magnetic resonance spectroscopy.[40] Such analysis can discriminate between healthy people and patients with stable asthma in an outpatient clinic or unstable asthma in the emergency department.[41] It has also been shown to discriminate between children with asthma and other obstructive airway diseases, including infective bronchitis and pneumonia.[42] Thus, it has the potential to become a useful noninvasive diagnostic technique for clinicians managing asthma, especially for those who cannot produce samples (sputum or exhaled breath) such as in children. However, it is a matter of further research to see whether this technology can differentiate eosinophilic from noneosinophilic airway inflammation.

Clinical application of sputum cell counts in airway diseases The biomarker that has been most successful in its clinical application is sputum cell counts. Strategies using sputum cell counts to guide therapy are beneficial in both asthma and COPD and superior to guideline-based strategies.[43] The main reason for this is its ability to identify the actual cellular nature of the underlying airway inflammation, which is not possible with the majority of other biomarkers that have been used in clinical trials so far.

Sputum, either spontaneous or induced with hypertonic saline,[44] is collected from patients (with chronic cough, COPD, asthma, bronchiectasis) at the time of initial assessment and at the time of every exacerbation. The induction of sputum with hypertonic saline is safe even in patients with FEV_1 as low as 0.9 liters.[45] FEV_1 is measured after each concentration (7 minutes of each of 3%, 4%, and 5%) is inhaled using a low-output ultrasonic nebulizer. If the FEV_1 drops by 15%, salbutamol is administered and the procedure abandoned.[46] This method is successful in almost all patients with smoker's bronchitis and COPD, in 80% of the patients with asthma, and in 60% of the patients with dry chronic cough.[2] Sputum is then processed and cell counts obtained by following a standardized procedure.[28] The procedure has recently been simplified by the introduction of a sputum filtration device (Accufilter™) and a kit.[47]

Bronchitis can be classified into eosinophilic (normal total cell count, eosinophils >3%), neutrophilic (total cell count usually greater than 10 million cells/g, neutrophils >65%), and paucigranulocytic (normal total count and differential).[48] Noneosinophilic inflammation is unlikely to respond to an increase in steroid therapy, and absent eosinophils suggest that the dose of steroids is excessive and can be reduced without a recurrence of an eosinophilic exacerbation. When eosinophils are in the upper normal range, a recurrence of sputum eosinophilia is likely if corticosteroid is reduced (FIGURE 1). Serial measurements associated with adjustments to therapy can guide identification of the minimum corticosteroid dose required to maintain control of the eosinophilic inflammation and reduce

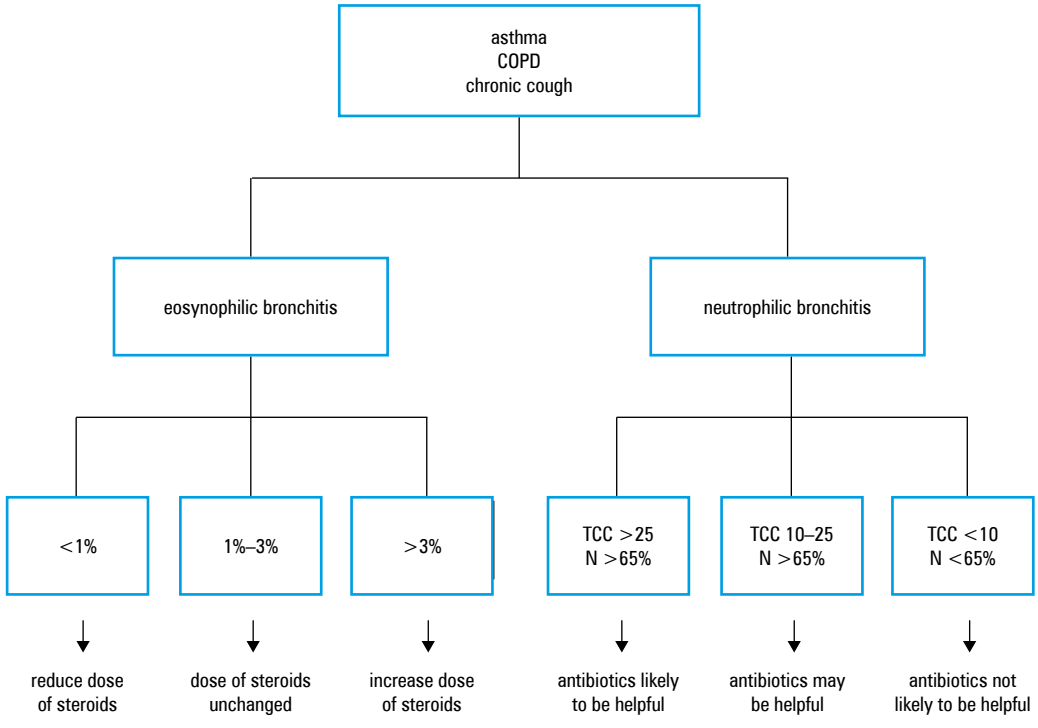

FIGURE 1 Management strategy based on sputum cell count; patients with asthma, chronic obstructive pulmonary disease or chronic cough may have an eosinophilic or a neutrophilic bronchitis; dose of corticosteroids and the decision to use antibiotics can be guided by the intensity of eosinophilic and neutrophilic bronchitis, respectively
Abbreviations: COPD – chronic obstructive pulmonary disease, N – neutrophils, TCC – total cell count × 10^6/g of sputum

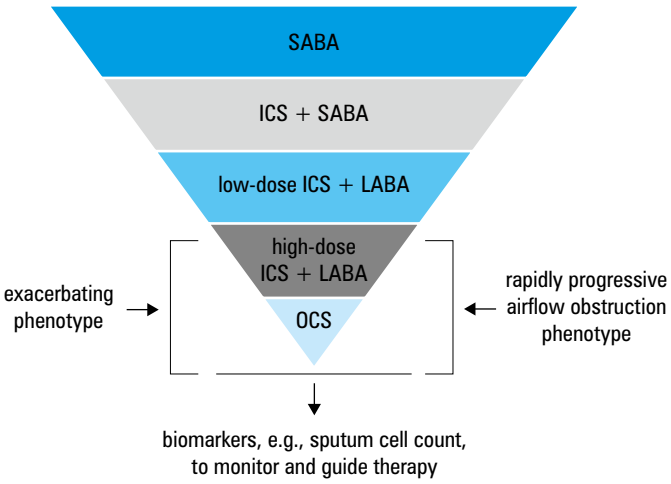

FIGURE 2 Selection of patients for biomarker-targeted therapy for asthma; the majority of patients (depicted in this hierarchical pyramidal depiction) can be adequately controlled with modest doses of inhaled corticosteroid (ICS) or ICS plus long-acting bronchodilator. Biomarkers are probably only required for patients who are not controlled on high doses of ICS or those who require oral corticosteroid
Abbreviations: LABA – long-acting β-agonist, OCS – oral corticosteroid, SABA – short-acting β-agonist

exacerbations. A noneosinophilic neutrophilic bronchitis with a raised total cell count and neutrophils of more than 80% is suggestive of bacterial infection and should benefit from appropriate antibiotic therapy (FIGURE 1). It would make intuitive sense to add a long-acting bronchodilator (LABA) to inhaled corticosteroid after controlling bronchitis as LABA do not have proven additive anti-inflammatory effect.[49] In addition to characterizing bronchitis, inclusions within the macrophages of hemosiderin or lipids help identify left ventricular dysfunction[50] and oropharyngeal reflux with microaspiration,[51] respectively, both of which may contribute to dyspnea in patients with chronic respiratory disease.

When are biomarkers useful in the management of airway diseases? For the majority of patients with asthma, acceptable clinical control can be achieved using a combination of inhaled corticosteroids and long-acting β-agonists or leukotriene antagonists. Currently, there are no studies of any biomarkers to identify which of the two add-on therapies would be better for an individual patient. Studies of urinary leukotriene levels or single-nucleotide polymorphisms of the enzymes involved in the leukotriene synthetic pathways have been disappointing. It remains to be seen whether airway responsiveness to cysteinyl leukotriene or mannitol provocation would be useful to identify patients that may respond better to leukotriene antagonists. For the small proportion of patients who remain uncontrolled and are atopic, the total serum IgE level is useful to select anti-IgE monoclonal antibody as add-on therapy. There are no biomarkers that would be useful to identify patients who may respond to bronchial thermoplasty although it may appear intuitive that patients with more severe airway hyperresponsiveness are likely to benefit from this therapy. The most useful discriminative test is to try and identify an eosinophil phenotype that would be an indicator of response to therapies directed at attenuating Th2 pathways. Although the combinations of FENO levels, blood eosinophils, and serum periostin or IgE may be useful,[52] they are not as accurate as sputum eosinophils in identifying an eosinophil phenotype to guide anti-eosinophil therapy. Identifying a neutrophil phenotype is even more problematic. However, biomarker-guided therapy, for example, using FENO, is not superior to usual management strategies guided by clinical history and spirometry for the majority of patients with mild asthma,[53] suggesting that biomarkers are only useful and necessary in patients with more severe asthma who have frequent exacerbations requiring high maintenance doses of corticosteroids. We have a very simple recommendation. For the large majority of patients with asthma or COPD, initiate a step-up therapy according to the major international guidelines (FIGURE 2). Sputum cell counts are probably not necessary to make a significant impact on treatment outcomes in most patients with mild airway diseases who can be controlled on low to moderate doses of inhaled corticosteroids.[25,53] Sputum examination is essential to optimize treatment for patients who require high doses of inhaled corticosteroids (for example, greater than 1000 mcg/d equivalent of fluticasone) or frequent courses of prednisone (more than 2 a year) or maintenance prednisone, or who experience frequent exacerbations (more than 2 a year), or those patients who lose their lung function rapidly (unexplained loss of FEV_1). This helps identify appropriate treatment, recognize infective bronchitis, and select patients for targeted therapy of bronchitis with small molecule antagonists and monoclonal antibodies. The examination of sputum is also particularly helpful in the evaluation of patients with a refractory chronic cough and normal chest imaging who do not seem to improve despite adequate treatment of reflux, postnasal symptoms, and a reasonable course of inhaled corticosteroids or antibiotics. However, the cell count is much more variable in children[54] and is reported to be less beneficial in titrating therapy to reduce exacerbations.[55]

Conclusion Several biomarkers are available for airway diseases that help individualize treatment particularly in situations when disease is severe and nonresponsive to usual treatment. Currently, their value in predicting prognosis or natural history of asthma or COPD is not established.[56] Sputum cell counts are currently the most useful method to guide treatment to decrease exacerbations. A point-of-care test in sputum to identify eosinophils and infections would be extremely useful for primary care management of airway diseases. Urine and exhaled breath metabolomics seem to be promising and may find clinical application in the future.

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ARTYKUŁ POGLĄDOWY

Przydatność markerów biologicznych w postępowaniu w chorobach dróg oddechowych

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astma oskrzelowa, eozynofile w plwocinie, markery biologiczne, przewlekła obturacyjna choroba płuc, tlenek azotu w wydychanym powietrzu

STRESZCZENIE

Markery biologiczne to cechy charakterystyczne obiektywnie mierzone i oceniane jako wskaźniki procesów fizjologicznych bądź patologicznych, jak również odpowiedzi na interwencję terapeutyczną. Mogą więc one dostarczyć informacji na temat rokowania, postępu choroby czy wreszcie odpowiedzi na zastosowane leczenie. Istnieje duże prawdopodobieństwo, że markery biologiczne będą użyteczne w postępowaniu w chorobach dróg oddechowych ze względu na dużą różnorodność procesów patobiologicznych przez nie opisywanych. Większość tych wskaźników opracowano i oceniono w celu oceny miejscowych procesów zapalnych (lub zapalenia oskrzeli) związanych z chorobami dróg oddechowych. Zaliczyć do nich można ilościową ocenę komórek w plwocinie oraz zawartość tlenku azotu i innych metabolitów w wydychanym powietrzu. Obecna praca przeglądowa skrótowo opisuje te markery biologiczne, kładąc szczególny nacisk na rolę liczby eozynofili i neutrofili w plwocinie i na to, w jaki sposób ta informacja przekłada się na konkretne postępowanie terapeutyczne w takich chorobach jak astma oskrzelowa, przewlekła obturacyjna choroba płuc oraz przewlekły kaszel

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