Clinical utility of Asthma biomarkers w.s.r to Tamaka Śvāsa

Shilpa. S 1  R. Shylaja Kumari 2

Abstract

Tamaka Śvāsa is a stressful medical condition of today’s era well known for its episodic & chronic course and is analogous to Bronchial Asthma due to similarity in etio-pathogenesis & symptoms.

Asthma is a chronic disease characterized by airway inflammation, bronchial hyper responsiveness, and recurrent episodes of reversible airway obstruction. The disease is very heterogeneous in onset, course, and response to treatment, and seems to encompass a broad collection of heterogeneous disease subtypes with different underlying pathophysiological mechanisms.

Pulmonary function tests are most often used objectively to confirm the diagnosis. However, airflow obstruction can be variable and thus missed using spirometer. Furthermore, lung function measurements may not reflect the precise underlying pathological processes responsible for different phenotypes. There is a strong need for easily interpreted clinical biomarkers to assess the nature and severity of the disease. Currently available biomarkers for clinical practice – for example markers in bronchial lavage, bronchial biopsies, and sputum – are limited due to invasiveness or lack of specificity. The assessment of markers in peripheral blood might be a good alternative to study airway inflammation more specifically, along with FeNO, in a less invasive manner, compared to Broncho alveolar lavage, biopsies, or sputum induction.

Key words: Asthma, Bronchial hyper responsiveness, Clinical biomarkers.

1 PG Scholar, 2 Professor & HoD, Department of PG Studies in Roganidana, Govt. Ayurveda Medical College, Bengaluru, Karnataka.

CORRESPONDING AUTHOR
Dr. SHILPA S
PG Scholar, Department of PG Studies in Roganidana, Govt. Ayurveda Medical College, Bengaluru, Karnataka.
Email: drshilpa04@gmail.com
INTRODUCTION

Tamaka Svāsa is one of the stressful medical conditions of today’s era and is well known for its episodic and chronic course which afflicts the human race. It is analogous to Bronchial Asthma due to similarity in etiopathogenesis and symptoms. Though incidence of Tamaka Svāsa is increasing in day to day practice and at alarming rate but very few patients need intensive care and most of the patients can be managed effectively by Ayurveda line of treatment. Bronchial asthma is a chronic inflammatory disorder of the airway and the most common distressing disease affecting 3-5% of the total population. In 1998, the national asthma Campaign estimated the prevalence of diagnosed asthma cases in India to be 3.4 million. Current estimates suggest that 300 million people worldwide suffer from asthma and an additional 100 million may be diagnosed with asthma by 2025. Asthma is a heterogeneous respiratory disease with mixed clinical, immunological, and inflammatory characteristics and often overlapping symptoms. Biomarker identification has the potential to overcome some of the challenges in making a diagnosis and predicting responsiveness to treatment.

Asthma is a complex syndromic disorder characterized by airway inflammation, airway hyper responsiveness, and airway remodeling. The spectrum of asthma in clinical presentation is broad, and underlying pathogenic mechanisms may be quite different. In addition, responsiveness to therapies is not uniform across the asthma spectrum, nor is it necessarily consistent in individual patients over time. There is considerable variability in objective measures of asthma control, related to both known (viral infections, allergen exposures) and unknown or unrecognized triggers of asthma exacerbation. The vast majority of these worsening are associated with increased levels of airway inflammation.

Consequently, measurement of objective metrics of airway inflammation in asthma could be of significant value to clinicians who manage patients with asthma. Such measurements could inform the proper choice of therapy, provide an objective measure for adjusting asthma medication dose, and might offer objective classification of asthma for prospective clinical trials. The most direct measures of airway inflammation, however, are too invasive and have limited clinical use.

Asthma inflammation can be broadly classified as either T-helper lymphocyte 2 (Th2)-high or Th2-low. Th2-high asthma displays gene expression of interleukin (IL)-13, IL-5, and IL-4, stimulating allergic and eosinophilic inflammation in the asthmatic lung. Asthma that is Th2-high is generally responsive to treatment. Th2-low asthma is generally not atopic, less inflammatory, may be obesity related, and patients are more likely to have adult onset and respond less to corticosteroids.

The National Institute of Health defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”.

The ability to diagnose or treat a disease by measuring a biological molecule from a noninvasive source, such as blood, urine, or exhaled breath, has a great advantage over traditional pathological techniques because direct access to diseased tissue is not required. Levels of the marker should be low and stable in normal individuals and measurably higher in patients with disease, a difference which should be consistent between individuals with disease. Biomarker identification has the potential to overcome some of the challenges in making a diagnosis and predicting responsiveness to treatment. Lastly, the technique required to measure the biomarker should be rapid, straightforward, and relatively inexpensive.

The value of a biomarker, or surrogate marker, is maximized when the surrogate is cheaper, less invasive, technically simpler, or is more broadly available than a ‘gold standard’. An ideal biomarker is cheaper, less invasive, technically simpler, and is more broadly available than the ‘gold standard’ and clinical validity. For purposes of this review, we will consider the ‘gold standard’ of assessing airway inflammation to be bronchial biopsy.

Bronchial biopsy is expensive, invasive, technically complex, and not widely available to physicians and researchers who treat and study asthma. There is also considerable variability due to sampling locale and technical factors and hence there would be great utility in identifying and validating a surrogate marker for airway inflammation.

The purpose of review is to summarize the existing base of knowledge in the field of biomarkers in asthma, highlight key strengths and limitations of each approach, review recent contributions to the field, analyze their clinical implications, and suggest directions for future research.
Important factors in samprāpti of Tamaka Śvāsa

1. Agnimāndya / Āma
2. Kapha dusti
3. Pratiloma gati of dūśita Prāna vāyu

Due to Apathya Ahara sevana

Agnimāndyatā
Āma utpatti
Kapha Vikruti / Sāma Kapha

Sthana samśraya at URAS

Prānavaha Srotā víkṛtṛi = SANGHA
Obstruction to normal flow of PRĀNA VĀTYA

Vimarga gamana of Prāna vāyu (dūśita)
Śvāsa urdhvagamita

TAMAKA ŚVĀSA

Thus, from the general samprāpti given by Acharya Charaka it is clear that there is agnimāndya (loss of digestive fire) producing āma, obstructs channels by kapha dusti vitiating vāta doṣa in Prāna vāyu Srotas and causes Śvāsa roga.

The concept of biomarkers in Tamaka Śvāsa may be understood in a very gross sense. Here Dūśita Prāna vāyu along with Kapha dusti occurred mainly by Āma causes Śvāsa. Āma causing dūśana of prāna vāyu & kapha grossly indicates the mediators (eosinophils, neutrophils, and cytokines) responsible for airway hyperactivity, inflammation & remodeling. Hence pratiloma prāna vāyu and kapha samudirāna may be considered as biomarkers.

Invasive Biomarkers in Asthma

Biomarkers such as neutrophils, eosinophils, or other cytokines can be obtained through invasive techniques such as induced sputum, bronchoscopy/biopsy, and provide reliable and detailed information about the pathology of airway inflammation and remodeling. These techniques have been useful in the research environment but are not yet usable in clinical practice. Induced sputum provides more reliable results than spontaneously produced sputum but is more invasive, requires skilled personnel, is time-consuming, and may provide results that are difficult to reproduce. Although biopsy and induced sputum are not currently useful tools in clinical practice, the results of these tests may provide reference comparisons for more easily obtained biomarkers.

Table 1: Mediators & Proposed Biomarkers

<table>
<thead>
<tr>
<th>ASTHMA</th>
<th>MEDIATORS</th>
<th>Proposed biological BIOMARKERS</th>
<th>BIOMARKERS in TAMAKA ŚVĀSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils, mast cells, IgE, Neutrophils, macrophages</td>
<td>FeNO*</td>
<td>Pratiloma gati of dūśita Prāna vāyu</td>
<td></td>
</tr>
<tr>
<td>Th 2 related: IL-4, IL-5, IL-9, IL-13</td>
<td>Eosinophilia, sputum eosinophils*</td>
<td>Urasthaha Kapha dusti</td>
<td></td>
</tr>
<tr>
<td>Airway hyperactivity</td>
<td>Urine leukotriene E4</td>
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<tr>
<td>Airway inflammation</td>
<td>IgE</td>
<td>Serum periostin</td>
<td></td>
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<tr>
<td>Airway remodelling</td>
<td>Urine leukotriene E4</td>
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*Biomarkers most easily utilized in the clinical setting

Fractional Exhaled Nitric oxide (Feno) in Asthma

FeNO has been described by the American Thoracic Society (ATS) as a marker of eosinophilic airway inflammation. To date, fractional exhaled nitric oxide (FeNO) is the most widely used exhaled biomarker of airway inflammation in asthma. Levels of nitric oxide in exhaled breath can be measured relatively quickly in the clinic, although the gas analyzers required are expensive. FeNO is derived from the action of inducible nitric oxide synthase expressed by the airway epithelium. FeNO has been shown to be feasible and easy to use in adults and children in the primary care setting and in asthma patients.

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clinics. FeNO has also been used in primary care to differentiate asthma from COPD. The ATS and European Respiratory Society have provided recommendations for standardized procedure. FeNO levels in exhaled breath can be obtained through use of a hand-held analyzer in the clinic, as illustrated in Figure, which shows a typical use of a hand-held FeNO analyzer.

Asthma biomarkers obtainable in the clinic

Figure: 1 hand-held feno analyzer

Peripheral Blood Eosinophils in Asthma

Th2-driven inflammation is thought to be highly eosinophilic and has been studied as a biomarker to measure therapeutic effect in severe allergic asthma patients. IL-13 mediates eosinophil infiltration and mucus hypersecretion and is being studied as a therapeutic target in asthma. IL-5, another important cytokine involved in the inflammation of Th2-high asthma, promotes eosinophil differentiation, proliferation, and activation.

Serum periostin in Asthma

Periostin is a matricellular protein that is secreted by bronchial epithelial cells in response to cytokines IL-13 and IL-4. Serum periostin shown to be a useful biomarker for Th2-induced eosinophilic airway inflammation in patients with severe asthma.

Urine Leukotriene metabolites in Asthma

Leukotriene E4 is produced by various inflammatory cells, and leukotrienes have been implicated in asthma. Urinary leukotriene E4 is a validated marker of cysteinyl leukotriene activity and can be measured in urine samples; however, it is only modestly associated with lung function. Although urinary leukotriene has been measured in clinical anti-leukotriene studies, its measurement is complex and not useful for the clinical practice setting.

Total and allergen-specific IgE

- Measurement of allergen-specific IgE by skin prick test, although widely used in the clinical setting, is considered an emerging biomarker for research because of the variability of the test’s performance.

- Total serum IgE has been associated with asthma and is considered a supplemental measure for study population characterization, as well as an outcome for intervention and observational studies.

The quantity of total IgE and presence of allergen-specific IgE antibody in serum are both important biomarkers for defining the phenotype of a patient who presents with asthma symptoms. The titers of allergen-specific IgE in serum also may be useful in predicting persistent wheeze and in targeting allergen specificities for allergen avoidance management.

Total serum IgE has been associated with asthma. Serum IgE levels are highly age-dependent: Atopic infants have an earlier and steeper rise in serum IgE levels than age-matched non-atopic controls. Total serum IgE reaches adult levels by age 10 to 15 years and gradually declines from the second decade of life. However, a bigger problem is the considerable overlap in IgE levels between atopic and non-atopic populations, which reduces its utility in identifying atopy.

Allergen-specific IgE defines an individual as having atopic asthma. It confirms sensitization in support of a clinical history-based diagnosis and aids in identifying allergen triggers. The probability of wheeze and reduced lung function increases with increasing specific IgE levels in serum.

Exhaled breath condensate

Exhaled breath condensate (EBC) analysis is a noninvasive method to evaluate airway inflammation through various inflammatory mediators and markers, which helps in the understanding of the pathophysiology of asthma. EBC is obtained by collecting warm breath in a cold condensing tube. The condensate is rich in volatile and non-volatile inflammatory mediators and allows simultaneous analysis through high output methods. EBC reflects changes in the airway lining fluid.
EBC collection is easy and can be used in children and in office settings without much training. EBC collection procedures are not standardized and to date remains a research tool. EBC parameters are influenced by smoking, alcohol consumption, equipment, exercise, mode and rate of breathing, nasal and salivary contamination, environmental temperature and humidity, and assays used leading to undesirable variability. The influence of age, sex, circadian rhythm, and infection remain unknown.

Recent findings

Increasing attention is given to biomarkers in exhaled breath, both gaseous (exhaled nitric oxide) and higher molecular weight moieties [in exhaled breath condensate (EBC)]. Current research in EBC analysis has focused on validation, standardization, and technical considerations, whereas research on exhaled nitric oxide (ENO) has moved to testing its predictive value in clinical situations. The use of advanced biostatistical techniques, and combinatorial analyses has led to additional advances in the utility of biomarkers.

Future for Biomarkers in Asthma

In recent years, it has become increasingly accepted that pulmonary function testing has its limitations. Spirometry can identify a broad spectrum of asthmatics, but it is incapable of discerning the various subtypes of disease and therefore which individuals will respond to normal treatment regimes. Tissue biopsies and inflammatory cell counting in induced sputum are accepted measures of determining airway inflammation, but both techniques are invasive, expensive, and difficult to standardize, making them unsuitable for routine clinical use. Biomarkers hold the promise of being able to diagnose and monitor various subtypes of asthma rapidly and specifically in a noninvasive manner.

Before considering biomarkers for use in the clinic, we must appreciate that asthma is a heterogeneous disease. Expecting a single biomarker to improve the treatment of all asthematics regardless of their underlying disease phenotype is unrealistic. The most well developed biomarker in current use is FeNO. However, as previously discussed, its utility is lost when it is applied to all asthmatics because of the underlying heterogeneity of the phenotypes. In practice, a panel of biomarkers is needed to indicate the various different underlying disease pathologies, thus enabling the definitive and objective categorization of asthmatics into distinct sub phenotypes. Standardization of protocols is vital when designing a panel of asthma biomarkers for clinical use. FeNO is a promising biomarker, but at present there is disagreement about what is a normal or abnormal FeNO level. Defining appropriate cutoff points is crucial to guide the appropriate clinical response.

Exhaled breath condensate is a potentially rich source of airway biomarkers, but again standard collection protocols are required before use in the clinic is even considered. In contrast, protocols for biofluid (serum and urine) collection and processing are well developed, and indeed several studies have shown that monitoring systemic or secreted metabolites may be the best way to define multiple biomarkers for the diagnosis and design of treatment regimens for asthma.

To date, the majority of asthma biomarkers have reflected airways inflammation, but inflammation is not the only pathological component of the disease. Airways remodeling plays a major role in asthma pathology, and so markers designed to indicate structural changes, such as epithelial damage, mucous hyperplasia, myofibroblast proliferation, and smooth muscle growth, may also prove useful to define a disease phenotype accurately. Regardless of the complexity or completeness of a future panel of asthma biomarkers, it is highly unlikely that they will completely replace pulmonary function testing in the clinic. Indeed, biomarker testing will be designed to complement rather than replace existing methods of clinical diagnosis and disease monitoring.

CONCLUSION

Till date, the best validated, and best performing biomarkers for clinical asthma appear to be measures of inflammation in peripheral blood (allergy biomarker), and measures of ENO. Some trials using ENO appear particularly promising for early clinical use. EBC metrics are at present too inchoate for clinical purposes. However, not all important clinical and research questions can be addressed with sputum, EBC, or ENO metrics, leaving an important place for BAL (Bronchoalveolar lavage), bronchial biopsy, and perhaps EBC measurements in the research arena. FENO with Peripheral blood biomarkers may be utilized in Ayurvedic field as a diagnostic tool and to assess the causative factors along with treatment outcomes in Ģavaka Śvāsa.
REFERENCES


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