



CODEN [USA]: IAJPB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.7569158>Available online at: <http://www.iajps.com>

Review Article

BIOMARKERS OF BRONCHIAL ASTHMAVinuth Chikkamath¹, J. S. Venkatesh², Varsha K^{*3}, Vamshi D^{*4}, Jahangir Alom^{*5}¹Lecturer, S C S College of Pharmacy, Harapanahalli.²Professor, S C S College of Pharmacy, Harapanahalli.³⁻⁵Pharm D Interns, S C S College of Pharmacy, Harapanahalli.**Article Received:** November 2022 **Accepted:** December 2022 **Published:** January 2023**Abstract:**

Asthma is a complex disease with a variable course. Biomarker research has expanded greatly with the advancement of molecular research techniques. A biomarker should be suitable to identify the disease as well the specific endotype/phenotype, useful in the monitoring of the disease and to determine the prognosis, easily to obtain with minimum discomfort or risk to the patient. An ideal biomarker should be suitable to identify the disease as well the specific endotype/phenotype, useful in the monitoring of the disease and to determine the prognosis, easily to obtain with minimum discomfort or risk to the patient - exhaled breath analysis, blood cells and serum biomarkers, sputum cells and mediators and urine metabolites could be potential biomarkers of asthma bronchiale. Presently an ideal biomarker doesn't exist and the overlap between the biomarkers is a reality.

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Please cite this article in press **Vinuth Chikkamath et al, Biomarkers Of Bronchial Asthma., Indo Am. J. P. Sci, 2023; 10 (01).**

INTRODUCTION:

Asthma is a complex disease with more than one Phenotypes¹. With the increasing Incidence of bronchial asthma, the continuous loss of Novel treatment plans and inefficient disease prevention, the need for predictive biomarkers for allergic rhinitis and Asthma is steadily growing. By following the present Clinical suggestions, it's important to identify allergen Sensitization patterns and lung function parameters.

Except genetic predisposition, Immunological changes within the airways may also give Essential information for allergic disease endotypes. Biomarker research has elevated substantially with the Development of molecular research techniques. For discovering or conformation of disease particular biomarkers are needed². This study is basely concern on fundamental review of biomarkers in asthma.

Exhaled breath analysis

Exhaled breath condensate [EBC] analysis is a recent, noninvasive method of detecting biomarkers, mainly coming from the lower respiratory tract. The Chemicals used in EBC consist of nitric oxide merchandise, hydrogen peroxide, Leukotrienes, and cytokines. Several additives correlate with the bronchial asthma analysis, others with asthma severity. EBC reflects changes in the respiratory fluid that lines the airways and is an inexpensive, non-invasive tool that has potential for scientific research.³ Exhaled air contains traces of fractional nitric oxide (FeNO) gives information about the inflammatory state of the airways^{4, 5, and 6}. During the conversion of the amino acid L-arginine to L-citrulline, nitric oxide formation takes place in the lungs. Nitric oxide plays an important role in lung physiology as bronchodilator and inflammatory mediator. During this allergic inflammation, airway epithelium produces nitric oxide as a result of inducible nitric oxide synthase activation takes place; hence the biomarker FeNO is originated from nitric oxide.^{2,7} Single, stand-alone FeNO can be used as a biomarker only if it is combined with comprehensive panel.² In The present guidelines, the use of FeNO is not recommended as a routine for the management of adults and children with asthma.⁸ The estimation of exhaled volatile organic compounds by gas chromatography coupled with mass spectrometry can predict the risk for exacerbation in asthmatic children.⁹

Blood cells and serum biomarkers

Asthmatic patients with type 2 inflammation, Blood eosinophil can serve as a prognostic biomarker and it

can also predict several therapeutic responses.¹⁰ presently, blood neutrophils count is not used as a biomarker for the diagnosis of asthma (GINA).

During the eosinophil degranulation, Eosinophil cationic protein (ECP) is found in the primary matrix of the eosinophil and is released. In previous data of adults and children with atopic asthma, the serum ECP is increased, associated with airway resistance and bronchospasm.¹¹ In the children where biomarkers are less feasible, ECP assessment could be useful for the initiation and dose titration of inhaled corticosteroids². but other methods are required for monitoring this strategy.¹²

Lipoxins have anti-inflammatory action and play a major role in chemotaxis and related signal transduction. Periostin, an extracellular matrix protein secreted by airway epithelial cells in response to IL-13 that regulates epithelial-mesenchymal interactions.² has been associated with T2-high eosinophilic asthma.¹³ Periostin expression is increased in the asthmatic airway.¹⁴ In adults with asthma (without seasonal effect) the stability of serum periostin over disease progression supports its use as a biomarker for type 2-high asthma.¹⁵

IgE is an immunoglobulin which mediates type 1 hypersensitivity reactions and plays a major role in the pathological process of allergic asthma. IgE binds to igE receptors on mast cells and basophils, produces cytokines that mediate T2 responses.³ Serum igE plays important role in the making of the asthma condition worsen.

Chitinases are hydrolases characterized by their affinity to cleave chitin that are thought to play a role in remodeling and regulation of the extracellular matrix.² The chitinase-like protein YKL-40 (human cartilage glycoprotein 39) same to be an interesting biomarker for distinguishing asthma from chronic obstructive pulmonary disease (COPD) and healthy controls. More studies are needed to prove how useful YKL-40 is in the finding of future asthma outcomes and risk .¹²

Recent data showed that airway mucosal expression of CCL26 (the most differentially expressed gene) is the best discriminator for type 2 inflammation.¹⁶ serum urokinase plasminogen activated receptor is elevated in adult patients with severe, non-atopic asthma.¹⁷ and the expression of ten selected microrna (HS_108.1,112,182.1,240,261.1,3,55.1,91.1, has-mir-604, and has-mir-638) is higher in children with severe asthma.¹⁸ Serum high-sensitive C-reactive protein (hs-CRP) is increased in asthmatic patients

than in healthy control, in poorly controlled vs well controlled, and may represent a useful biomarker of airway inflammation in non-smoking asthmatic patients without complications, such as heart disease, hypertension, hyperlipidaemia, chronic obstructive pulmonary disease, or infection.¹⁹ Evaluation of inflammatory markers interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) in serum showed higher levels in asthmatic patients vs controls and were associated with more severe asthma.²⁰ A high serum level of IL-8 could discriminate COPD from asthma patients.²¹ Although all advantages of serum biomarkers, it is important to remember that peripheral blood studies often do not reflect airway biology, and therefore peripheral blood biomarkers might not represent physiologic mechanisms in the airways.¹³

Sputum cells and mediators

In asthmatic patients induced sputum is a non-invasive method which allows quantifying the inflammatory cell pattern in airways. To obtain samples for sputum analysis, patients nebulize 3 % saline for 20 min and the sputum expectorated over this period is centrifuged, stained, and analyzed by quantifying the number of different cell types.³

Sputum quantitative cell count is the reference standard to reflect the airway inflammation in asthmatic patients. The main advantage of sputum differential cell counts is that this method is feasible even on frozen samples.¹⁰ Four inflammatory phenotypes are identified in the Severe Asthma Research Program (SARP) cohort – eosinophilic (≥ 2 % eosinophils in induced sputum), neutrophilic (≥ 40 % neutrophils), mixed granulocytic and paucigranulocytic.²² The presence of sputum neutrophilia is one predictive biomarker for non-T2 asthma.³ Difference in sputum eosinophil count over time shows change in clinical asthma control.²³ The high level of the innate lymphoid cell (Group 2 ILC) in the sputum is correlated with severe asthma suggesting these cells could be a potential novel biomarker.²⁴ Unfortunately, despite its use as a biomarker in many clinical trials, the use of sputum cells count in daily practice has limitation. This method requires specialized training, equipment, and laboratory for processing, patient coaching and cooperation, emergency protocols and equipment, is difficult to collect (impossible in young children), not easily repeatable, and had several contraindications.²

Several sputum mediators could be the efficient biomarkers. For the diagnostic of inflammatory pattern, sputum eosinophil peroxidase is correlated

with sputum eosinophilia.²⁵ Particular micrnas helps in differentiating neutrophilic from eosinophilic asthma.²⁶ neutrophil myeloperoxidase has the potential to differentiate asthma COPD overlap syndrome from asthma.²⁷ As a prognostic biomarker, sputum expression of human tumour necrosis factor-like weak inducer of apoptosis correlates with higher severity, poor asthma control and decreased lung function in children with non-eosinophilic asthma.

Urine metabolites

Bromotyrosine is formed from post-translational modification of tyrosine protein residues by hypobromous acid produced by activated eosinophils in the process of a respiratory burst. It have more benefits as a biomarker given its stability and non-invasive detection in the urine. The utility of bromotyrosine in the clinical setting would probably be best when appraised as a part of a larger panel of inflammatory biomarkers.²

Leukotriene E4 is a stable and product of cysteinyl leukotriene metabolism possible to be measured non-invasively in urine samples. Urinary leukotriene E4 (ulte4) concentrations are increased in children with allergic asthma and adults with aspirin-exacerbated respiratory disease,² Several studies suggest that ulte4 might be an potent biomarker in the selection of asthma therapy.¹²

DISCUSSION:

In asthma, and particularly in severe asthma, many biomarkers have been investigated but only a few of them can be easily used in clinical practice so far.²⁸ An ideal biomarker should be suitable to identify the disease as well the specific endotype/phenotype, useful in the monitoring of the disease and to finding the prognosis, easily to obtain with minimum discomfort or risk to the patient.¹⁰ Unfortunately, an ideal biomarker doesn't exist and the overlap between the biomarkers is a reality at the moment. Using panels of biomarkers could probably improve the identification of asthma endotypes in the era of precision medicine.¹²

CONCLUSION:

In conclusion, upcoming research and validation of emerging biomarkers are needed to define the molecular phenotype of asthma. Viewing the heterogeneity of asthma, the development of composite biomarkers from blood, urine and exhaled breath seems to be a more appropriate solution in practice to predict therapeutic response.

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