Review Article

Stratified approaches for using biomarkers in phenotyping for the management of severe asthma in India

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ABSTRACT

Various respiratory societies including the Global Initiative for Asthma (GINA), European Respiratory Society (ERS) and American Thoracic Society (ATS) define severe asthma as asthma that requires or remains uncontrolled despite treatment with systemic corticosteroids or high-dose inhaled corticosteroids plus another controller such as long acting beta agonist. The management of asthma as an entity is not straightforward due to inter-individual variability in assessment parameters. With the advent of science, targeted therapies are on the emergence for management of severe asthma. A biomarker can be used as a surrogate to phenotype a patient as well as to measure the response to therapy with any drug. Biomarkers have been critical for studies of disease pathogenesis and the development of new therapies in severe asthma. From a resource constraint perspective like countries in India, it is imperative to use biomarkers that are easily available are affordable cost. Choosing an ideal biomarkers is also important from a perspective of choosing a particular therapy. The cost associated with the biologicals is high and it is imperative to gauge the treatment effectiveness with the therapy at the earliest considering the out of pocket spends of the patients.

KEY WORDS: Asthma management, biologics, biomarkers, severe asthma, stratified approaches

INTRODUCTION

Severe asthma is a complex, heterogeneous set of disease. Various respiratory societies including the Global Initiative for Asthma (GINA), the European Respiratory Society , and the American Thoracic Society define severe asthma as asthma that requires or remains uncontrolled despite treatment with systemic corticosteroids or high-dose inhaled corticosteroids plus another controller such as long-acting beta-agonist. Guidelines suggest the assessment of parameters such as lung function, exacerbations, and hospitalization rates to assess disease control. However, the management of asthma as an entity is not straightforward due to inter-individual variability in assessment parameters.[1,2]

With the increase in research on asthma, the heterogeneity of presenting symptoms and underlying causes or triggers have been recognized as a factor that led to the conclusion that "one size does not fit all". The latest guidance

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provided by GINA 2021 acknowledges the importance of individualized management of asthma in the assess-treat-reassess paradigm incorporated in the treatment protocol.[2,3] With this in mind and with the availability of newer therapies to treat severe asthma, clinicians and researchers increasingly acknowledge the importance to further classify patients basis identifiable patient characteristics into smaller cohorts.[4-8] These cohorts are called phenotypes. A phenotype refers to the observable characteristics of the disease in an individual. Specific biological mechanisms may lead to or are associated with a given phenotype. They are termed endotypes. Determining a patient's disease phenotype or endotype becomes crucial, particularly when selecting targeted biologic or other immunomodulatory therapeutics; hence, the need for biomarkers that will help to distinguish among these groups.[5,6,9]

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." A biomarker, by definition, can be used as a surrogate to phenotype a patient as well as to measure the response to therapy with any drug. With the advent of science, targeted therapies are on the emergence for the management of severe asthma. These biologics target specific inflammatory mediators in the allergic cascade, for example., anti-Immunoglobulin E (IgE) antibodies, anti-Interleukin (IL)-5 antibodies, and anti-IL-4 antibodies. A recent review by Vora *et al*. has enumerated various phenotypes of asthma and the inflammatory mediators associated with the phenotypes. According to cohort analysis-based studies, 60%–70% of patients had a phenotype of early-onset allergic asthma As per the review, blood IgE, tissue eosinophilia, blood eosinophilia, periostin, and exhaled nitric oxide were identified as important biomarkers for the assessment of treatment response in allergic asthma patients.[5]

India is a country with a high asthma burden with close to 38 million people living with asthma.[10] Due to such a high burden of asthma, there is a state of resource constraint in major public care centers for diagnosis as well as treatment. The intent of this review is to describe the important biomarkers available in India to assess the treatment of severe asthma in a limited resources setting. We will be focusing on the biomarkers related to Th2 high asthma, as they are more relevant from an Indian context due to the availability of biologics that target the Th2 high pathway.

## PHENOTYPES OF ASTHMA AND BIOMARKER BASED APPROACH TO IDENTIFY THEM

The term "clinical observable characteristic" that is the basis of phenotype definition might partially explain the multifactorial pattern of asthma. Parameters such as age, atopy, lung function tests, symptoms, exacerbations, and some special conditions such as aspirin use, or pregnancy

are used to divide asthma patients into subgroups. Researchers have identified biomarkers specific to phenotypes based on the presence or absence of allergic inflammation. Most of them are based on the predominant type of cells or cytokines or inflammatory mediators in different biological fluids [Table 1].[5,11,12]

Table 1: Hypothesis based phenotypes in asthma and their associated inflammatory markers[5,11-13]

Phenotype	Associated inflammatory markers
Th2 high	
Allergic asthma	IgE
	IL-5
	Sputum/Blood eosinophilia
	IL-4/IL-13
	NO
AERD	IL-33
	TSLP
	Urine (LTE4)
Hyper responsive and variable obstruction	Not specific
Th2 low	
Nonallergic eosinophilic asthma	Sputum eosinophilia
	Blood eosinophilia
Paucigranulocytic (noninflammatory) asthma	Polymorphonuclear neutrophils in sputum
Obesity-related asthma	IL-6
	TNF-α
	VEGF
Exercise-induced asthma	Blood eosinophils
	NO
	8-isoprostane
Mixed	
Mixed eosinophilic and neutrophilic asthma	Overlapping biomarkers
Neutrophilic asthma	
Late-onset asthma	
Variable obstruction/fixed obstruction	

Th2: T helper type 2 lymphocytes, IgE: Immunoglobulin E, IL: Interleukin, TNF α: Tumor necrosis factor α, VEGF: Vascular endothelial growth factor, NO: Nitric oxide, AERD: Aspirin-exacerbated respiratory disease, TSLP: Thymic stromal lymphopoietin, LTE4: leukotriene E4
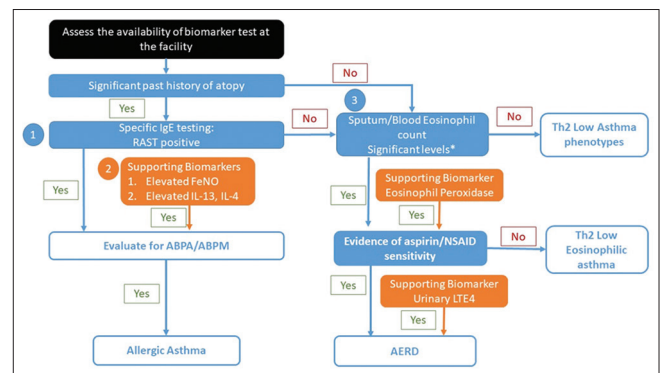
Figure 1: Biomarker bases assessment of phenotypes.[13] IgE: Immunoglobulin E, RAST: Radioakllergosorbant Test, FeNO: Fractional Exhaled Nitric Oxide, IL: Interleukin, ABPA: Allergic Bronchopulmonary Aspergillosis, ABPM: Allergic Bronchopulmonary Mycosis, Th2: T helper type 2 lymphocytes, LTE4: Leukotriene E4, AERD: Aspirin Exacerbated Respiratory Disease, NSAID: Nonsteroidal Anti-inflammatory Drugs

Applying biomarkers to identify phenotypes and endotypes of severe asthma may serve a dual purpose of not only choosing the ideal treatment strategy but also assessing the level of responses with a particular therapy. Combinations of biomarkers may be more helpful to fully characterize patients into one of these phenotypes. In a resource constraint setting, the optimal use of these biomarkers can help reduce the cost of hospitalization. Figure 1 is an algorithm that helps to phenotype a severe asthma patient regarding the presence of specific biomarkers.

Since, allergic asthma is the most common phenotype in India, the discussion on biomarkers for Th2 low asthma is out of scope of this review. Moreover, biologics for the management of severe asthma in India cater to only the allergic phenotypes.

BIOMARKERS OF TH2 HIGH INFLAMMATION

Immunoglobulin E
IgE is the most important inflammatory mediator in the allergic cascade probably due to its role in the origin of all the other inflammatory mediators of Th2 high asthma. After aeroallergen sensitization, B cells are primed to the allergen through the Th2 Pathway and with the subsequent exposure release IgE. The free IgE then binds to the FCeRI and FCeRII receptors on mast cells and basophils to release the inflammatory mediators such as IL-5, IL-13, and IL-4. Hence, IgE is a relevant biomarker to all the allergic phenotypes of severe asthma.[5,13-15]

Two isoforms of IgE can be measured, i.e., total, and specific IgE. The IgE levels are independent of the specific aeroallergen exposure. Raised total IgE levels are a predictive biomarker for asthma, however, this should be augmented with specific aeroallergen and the presence of allergic symptoms on exposure to such allergens. The role of a healthcare professional is critical here in the diagnosis part of severe allergic asthma as it requires clinical correlation with the IgE levels.[5,13-15]

In India, the anti-IgE antibody omalizumab is the specific biologic available for the management of moderate-to-severe asthma. IgE levels are a basic requirement to start omalizumab therapy. A patient with a total IgE value range of 30–1500 IU/ml and the presence of documented allergy is eligible for treatment with omalizumab.[16] Total IgE, unfortunately, cannot be used as a predictor of response to treatment in severe asthma patients as the levels remain high up to 1 year of treatment with omalizumab.

Eosinophils
Eosinophils are tissue leucocytes and a marker of airway inflammation in the local tissue. IL-5 is the cytokine responsible for the production and maintenance of tissue eosinophils. Eosinophils are present in multiple compartments of the human body. From a biomarker point of view in the diagnosis and management of asthma, clinicians consider sputum eosinophils and blood eosinophils of value. Eosinophils are the endpoint of the inflammatory cascade and responsible for local remodeling of the airway and have a direct co-relation with symptom control and exacerbation rate. Eosinophils are primarily a tissue inflammatory mediator and its correlation with the blood levels for establishing atopy in asthma may not be adequate. Approximately half of the asthma patients exhibit the phenomenon of airway eosinophilia. As per studies, peripheral blood eosinophil counts had a sensitivity of 71% and specificity of 77% for detecting sputum eosinophils of >3%.[14,17]

Anti-IL-5 antibody mepolizumab is approved in India for the management of severe asthma with the eosinophilic phenotype.[16] Reference values for sputum eosinophil percentages have been determined through epidemiologic studies of healthy patients. In general, a sputum eosinophil level of >2%–3% and blood eosinophil counts of >300 per microliter (mL) defines eosinophilia.[13] However, it is imperative to rule out the presence of other allergic conditions as blood eosinophils are raised and cannot be used to associate with atopy related to asthma.[7,8,13,18]

Eosinophil level has a diagnostic as well as predictive value in the management of severe asthma.[7,13] Correlating the blood or airway eosinophils sputum and airway gene expression IL-4, IL-5, and IL-13 and increased expression of the gene encoding for the eosinophil's CharcotLeyden crystal protein can identify the eosinophilic inflammatory phenotype. Furthermore, eosinophil peroxidase, released during activation of eosinophils, can be used as a

Table 2: Biomarkers for assessing severe allergic asthma[13]

Biomarker	Surrogate cytokine	Diagnostic	Predictive
Specific IgE	IgE	+	−
Sputum eosinophil	IL-5	+	+
Blood eosinophils	IL-5	+	+
FENO	IL-13 and IL-4	−	+
Urinary (LTE4)	IL-5	+	+

IgE: Immunoglobulin E, IL: Interleukin, LTE4: Leukotriene E4,
FENO: Functional exhaled nitric oxide, + = has value, - = has no value

Table 3: Phenotypes and preferred treatment option[19]

Phenotype	Is serum total (IgE >30 k U/L)	Is eosinophils (blood EOS >300 cells/µL) and sputum eosinophils (>3%)?	Preferred treatment
Th2 low asthma	No	No	Bronchial thermoplasty
Atopic asthma	Yes	No	Anti IgE antibody (omalizumab)
Atopic asthma with eosinophilia	Yes	Yes	Anti IgE antibody and anti-IL-5 antibody
Nonatopic asthma	No	Yes	Anti-IL-5 antibody (mepolizumab and benralizumab)

EOS: Eosinoplil, IgE: Immunoglobulin E, IL: Interleukin, Th2: T helper type 2

predictive marker for response to therapy.[13] However, due to complexities involved in gene expression studies, blood eosinophils are preferred biomarker currently due to the ease of measurement considering the resource constraints in India.

Fractional exhaled nitric oxide

Nitric oxide (NO) is a byproduct of the inflammatory cascade that involves IL-4 and IL-13 to a high extent. NO is measured in the breath of the severe asthma patient by a measure called Functional Exhaled NO (FeNO). Elevated FeNO is a common attribute in asthma patients; however, the marker is confounded by its elevation in smokers, extremes of age, other atopic conditions, and normal healthy individuals. Since IL-4 and IL-13 are higher in the inflammatory cascade and have an influence of IL-5 production, FeNO can be used as a marker for response to biologics and drugs targeting these sites. Mepolizumab and dupilumab are the biologics that can make use of FeNO as the biomarker for assessment of treatment effectiveness. FeNO can also be used as a marker for treatment adherence with inhaled corticosteroids and studies have shown a reduction in FeNO in patients with good adherence to treatment.[13]

Urinary biomarkers

Aspirin-exacerbated respiratory disease (AERD) is a phenotype which involves significant atopy with respect to the symptoms associated with it. Aspirin is a nonselective cyclooxygenase (COX) inhibitor and acts on the arachidonic acid pathway to reduce prostaglandins (PGs). This in turn leads in reduction of PGE2, a bronco-protective PG. Since the COX pathway is blocked, the arachidonic acid metabolites are available to the lipoxygenase enzymes and this leads to increase in the leukotrienes. Urinary LTE4 is a diagnostic biomarker for patients with AERD.

SUMMARY

Biomarkers have been critical for studies of disease pathogenesis and the development of new therapies in severe asthma. From a resource constraint perspective such as countries in India, it is imperative to use biomarkers that are easily available are affordable cost. Choosing an ideal biomarkers is also important from the perspective of choosing a particular therapy. The cost associated with the biologicals is high and it is imperative to gauge the treatment effectiveness with the therapy at the earliest considering the out-of-pocket spends of the patients. Table 2 enumerates the important biomarkers that may be of diagnostic and predictive value in the management of severe allergic asthma while Table 3 gives an account of phenotypes and the preferred treatment option.[19]

The current indication of omalizumab in atopic asthma includes the allergic background to perennial allergen with increased total IgE level (>30 kU·L − 1), whereas concomitant eosinophilic inflammation increases the chance of response. The role of (local) IgE in atopic asthma

is undebated, however, its role in nonatopic asthma needs further exploration, whereas eosinophilia clearly predicts response to anti-IL-5. In contrast, Th-2-low phenotypes have no targeted therapies but might benefit from emerging therapeutic options.

The path to understanding the disease of asthma is far from complete. With new research, new targets emerge on a regular basis. With new targets, newer biomarkers will also be developed. Hence, much research is the need of the hour to develop an ideal biomarker that has a diagnostic as well as predictive value and is easy to quantify at affordable costs.

Conflicts of interest

Dr. Deepak Talwar has received payments for educational activities from Novartis, GSK and Astra Zenica and has served on advisory boards and/or served as speaker and/or participated in education arranged by arranged by Novartis, GSK and Astra Zenica in the past. Brig. Dr. Sarvinder Singh is not having any conflict of Interest. Col. Dr. Vikas Marwah is not having any conflict of Interest. Dr. Ketan Asawale is an employee of Novartis Healthcare Pvt. Ltd. Bharat Bhushan is an employee of Novartis Healthcare Pvt. Ltd.

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