EDITORIAL

In India, stratified approaches for employing biomarkers in phenotyping for severe asthma management

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ABSTRACT

Severe asthma is defined by various respiratory societies, such as the Global Initiative for Asthma (GINA), The European Respiratory Society (ERS), and the American Thoracic Society (ATS), as asthma that requires or remains uncontrolled despite treatment with systemic corticosteroids or high-dose inhaled corticosteroids plus another controller, such as a long-acting beta agonist. Due to inter-individual variability in evaluation factors, managing asthma as a separate entity is difficult. Targeted medicines for the treatment of severe asthma are becoming more common as science advances. A biomarker can be used as a substitute for phenotyping a patient or measuring the response to any medication therapy. In severe asthma, biomarkers have proved crucial in investigations of disease pathophysiology and the development of novel therapeutics. In nations with limited resources, such as India, it is critical to use biomarkers that are readily available and inexpensive. Choosing the right biomarkers is also vital when it comes to deciding on a treatment.

The cost of biologicals is significant, thus it's critical to assess the therapy's success as soon as possible, taking into account the patients' out-of-pocket expenses

Severe asthma is a disease that is both complex and heterogeneous. Severe asthma is defined by the Global Initiative for Asthma (GINA), the European Respiratory Society, and the American Thoracic Society as asthma that requires or remains uncontrolled despite treatment with systemic corticosteroids or high-dose inhaled corticosteroids combined with another controller such as a long-acting beta-agonist. To assess disease control, guidelines recommend looking at things like lung function, exacerbations, and hospitalization rates. However, due to inter-individual heterogeneity in evaluation factors, managing asthma as a separate entity is difficult.

The variability of presenting symptoms and underlying causes or triggers has been acknowledged as a factor that led to the conclusion that "one size does not fit all" with the increase in asthma research. In the assess-treat-reassess paradigm contained in the treatment protocol, GINA 2021's latest guidance recognizes the necessity of customized asthma care.

Key Words: *Anti-Immunoglobulin E (IgE) antibodies*

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With this in mind, given the availability of novel medicines to treat severe asthma, doctors and researchers are increasingly recognizing the need to further divide patients into smaller cohorts based on identifiable patient features. Phenotypes are the names given to these groups of people. The observable characteristics of an illness in an individual are referred to as phenotypes. Specific biological pathways may cause or be linked to a certain phenotype[1]. Endotypes are what they're called. Determining a patient's illness phenotype or endotype phenotype or endotype is critical, especially when choosing targeted biologic or other immunomodulatory therapies; thus, biomarkers that can differentiate between these groups are needed.

"A trait that is objectively tested and assessed as an indicator of normal biologic processes, pathogenic processes, or pharmacologic reactions to a therapeutic intervention," according to the definition of a biomarker. By definition, a biomarker can be used as a proxy to profile a patient as well as quantify the response to any therapeutic therapy. Targeted medicines for the treatment of severe asthma are becoming more common as science advances.

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Anti-Immunoglobulin E (IgE) antibodies, Anti-Interleukin (IL)-5 antibodies, and anti-IL-4 antibodies are examples of biologics that target specific inflammatory mediators in the allergic cascade. Vora et al. identified numerous phenotypes of asthma and the inflammatory mediators linked with the phenotypes in a recent review.[2] According to cohort analysis-based research, 60–70% of patients showed an early-onset allergic asthma phenotype. According to the analysis, significant biomarkers for assessing therapy responsiveness in allergic asthma patients include blood IgE, tissue eosinophilia, blood eosinophilia, periostin, and exhaled nitric oxide. With about 38 million people living with asthma, India is a country with a significant asthma burden. Because of the increasing prevalence of asthma, large public health institutions are experiencing a shortage of resources for both diagnosis and treatment. The goal of this review is to discuss the key indicators that are now accessible in India for evaluating the treatment of severe asthma in a resource-constrained situation. We'll concentrate on biomarkers associated to Th2 high asthma because biologics that target the Th2 high pathway are more readily available in India [3].

Using biomarkers to identify severe asthma phenotypes and endotypes may serve a dual goal of not only determining the best treatment strategy but also monitoring the level of responsiveness to that therapy. To properly define patients into one of these phenotypes, a combination of biomarkers may be more useful. In a resource-constrained situation, making the most use of these biomarkers can help cut hospitalization costs.

Due to its function in the formation of all other inflammatory mediators of Th2 high asthma, IgE is the most critical inflammatory mediator in the allergic cascade. Following aeroallergen sensitization, B cells are primed to the allergen via the Th2 Pathway and release IgE as a result of exposure. The free IgE binds to the FCeRI and FCeRII receptors on mast cells and basophils, causing inflammatory mediators like IL-5, IL-13, and IL-4 to be released. As a result, IgE is a biomarker for all allergic phenotypes of severe asthma.

The anti-IgE antibody omalizumab is the only specific biologic for the treatment of moderate-to-severe asthma in India. IgE levels must be below a certain threshold before starting omalizumab therapy. Patients who have a total IgE value of 30–1500 IU/ml and a verified allergy are candidates for omalizumab treatment. Total IgE levels remain high even after a year of treatment with omalizumab, so it can't be used to predict treatment response in severe asthma patients. 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.[4]

Eosinophils are tissue leucocytes and a local tissue marker of airway inflammation. The cytokine IL-5 is responsible for tissue eosinophil generation and maintenance. Eosinophils can be found in many parts of the human body. Clinicians regard sputum eosinophils and blood eosinophils to be useful biomarkers in the diagnosis and management of asthma. The inflammatory cascade's endpoint, eosinophils, is responsible for local airway remodeling and has a direct link to symptom control and exacerbation rate.

Eosinophils are predominantly a tissue inflammatory mediator, and the link between blood levels and atopy in asthma may be insufficient. Airway eosinophilia is a condition that affects about half of asthma sufferers.

In India, the anti-IL-5 antibody mepolizumab has been authorized for the treatment of severe asthma with eosinophilic phenotype. Epidemiologic studies of healthy people were used to establish reference values for sputum eosinophil percentages. Eosinophilia is defined as a sputum eosinophil count of more than 2–3% and a blood eosinophil count of more than 300 per microliter (mL). However, because blood eosinophils are elevated and cannot be used to associate with atopy associated to asthma, it is critical to rule out the presence of other allergic diseases.

Nitric oxide (NO) is a consequence of the inflammatory cascade, which is heavily influenced by IL-4 and IL-13. A test termed Functional Exhaled NO is used to measure NO in the breath of severe asthma patients (FeNO). Elevated FeNO is a typical feature in asthma sufferers; however, the marker is also elevated in smokers, those at extremes of age, people with other atopic disorders, and healthy people. FeNO can be utilised as a marker for response to biologics and medicines that target these locations because IL-4 and IL-13 are higher in the inflammatory cascade and have an influence on IL-5 production. FeNO can be used as a biomarker for assessing therapy success in biologics like mepolizumab and dupilumab.

Aspirin-Exacerbated Respiratory Disease (AERD) is a phenotype characterized by substantial atopy in terms of the symptoms it causes. Aspirin is a nonselective Cyclooxygenase (COX) inhibitor that reduces prostaglandins by acting on the arachidonic acid pathway (PGs). This results in a decrease in PGE2, a bronco protective PG. The arachidonic acid metabolites are available to the lipoxygenase enzymes since the COX route is blocked, resulting in an increase in leukotrienes. LTE4 in the urine is a diagnostic biomarker for AERD patients.

In severe asthma, biomarkers have proved crucial in investigations of disease pathophysiology and the development of novel therapeutics. In nations with limited resources, such as India, it is critical to use biomarkers that are readily available and inexpensive. Choosing the right biomarkers is also vital when it comes to selecting a treatment. The cost of biologicals is significant, thus it's critical to assess the therapy's success as soon as possible, taking into account the patients' out-of-pocket expenses.

The current indication for omalizumab in atopic asthma is an allergic background to a perennial allergen with an elevated total IgE level (>30 kUL 1), with accompanying eosinophilic inflammation increasing the likelihood of a response. Although the importance of (local) IgE in atopic asthma is undisputed, its role in nonatopic asthma requires further investigation, although eosinophilia unambiguously predicts anti-IL-5 response. Th-2-low phenotypes, on the other hand, lack specific medicines but may benefit from developing therapeutic possibilities.

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