BRIEF CLINICAL UPDATE

Understanding Different Phenotypes of Asthma and Treatment Strategies: A Brief Clinic Review

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Definition

Asthma is a chronic inflammatory disease affecting the large and small airways, associated with variable airway obstruction and bronchial hyperresponsiveness. It is typically manifested by intermittent episodes of wheezing, chest tightness, cough, and difficulty breathing.

Pathophysiology

Our understanding of the pathophysiology of asthma has evolved over the last several years. Until recently, it was thought that the chronic inflammation in every patient with asthma was caused by activation of T helper 2 (Th2) lymphocytes in response to an inhaled antigen. Th2 cells are important for stimulating eosinophilic infiltration into the airways, mediated by cytokines IL4, IL5, and IL13. While IL-5 is vital for the maturation, survival, and accumulation of eosinophils into the tissues,[1] IL4 and IL-13 also play a very crucial role in migration of eosinophils into the tissue sites.[2-3] Additionally, in patients with allergic asthma, IL 4 and IL 13 causes activation of B cells, which releases IgE immunoglobulins.

However, new evidence suggests that there is also a neutrophilic driven pathway causing inflammation in a subset of patients with asthma. It involves an IL-8 mediated activation of neutrophils, acting as a stimulus to increased airway responsiveness.[4] Environmental exposures to bacterial endotoxin, particulate air pollution and ozone, as well as viral infections, also play an important role as triggers of neutrophilic airway inflammation in asthma.

The importance of these findings is that asthma can now be broadly classified into two distinct subgroups: eosinophilic asthma and non-eosinophilic asthma.

Eosinophilic asthma

Current management of eosinophilic asthma begins with standard guideline-based therapy, including inhaled corticosteroids and bronchodilators. Generally, the presence of eosinophils has been associated with responsiveness to corticosteroids. Now, more targeted therapies are available for patients who failed standard therapy or remain steroid dependent.

IgE

Majority of eosinophilic-driven asthmatic patients are also allergic. IgE, involved in the pathophysiology of allergic asthma, has been one target of therapy. Omalizumab, a monoclonal antibody, directed against IgE, acts to prevent its binding to other cells, such as mast cells, basophils, and dendritic cells. It is the first biologic agent, approved in 2003, to be used in treatment of asthma. Numerous clinical trials and meta-analysis have confirmed that Omalizumab, when used as an add-on therapy, reduces asthma exacerbations, improves overall quality of life and decreases the dose of inhaled corticosteroids (CCS) needed to control asthma.[5] It was approved to treat patients who have with moderate to severe asthma, who have a positive skin or blood test to environmental allergens, whose symptoms are not well controlled on inhaled CSS, and who have an elevated IgE levels. It is considered to be relatively safe with few side effects noted in the clinical trials. However, FDA has a black box warning for Omalizumab induced anaphylaxis, although it is very rare.

Modulation of cytokines

IL4 and IL 13

Cytokines, produced by Th-2 lymphocytes, play a key role in mechanisms causing inflammation in eosinophilic asthma. Both IL-4 and IL-13 are important in eosinophil accumulation and are vital factors in IgE synthesis by B cells.

A randomized, multicenter study of the anti-IL-13 biologic lebrikizumab (Genentech/Chugai Pharmaceutical) has recently demonstrated that it significantly improved lung function in patients with inadequately controlled asthma, but only in a subgroup who had a higher exhaled nitric oxide values (a proinflammatory marker).[6]

Similarly, Tralokinumab, an injectable anti-IL-13 biologic, was found to be well-tolerated and safe in phase 1 studies, when used in adult patients with moderate to severe uncontrolled asthma, who maintained their existing controller therapy. However, it did not significantly reduce asthma exacerbation rates in phase 2b study.[7] A phase 3 trial is in process. Clinical trials looking at interrupting the actions of IL-4 have been ineffective so far, but additional studies are underway.

IL-5

It is well-established that IL-5 plays a crucial role in the development and release of eosinophils from bone marrow. IL-5 is therefore a rational target to prevent or blunt eosinophils mediated inflammation in asthma.

Reslizumab, a humanized IL-5 monoclonal antibody, was recently approved by FDA for patients with severe asthma, aged 18 years and older, with asthma exacerbations despite treatment with other medications. Based on two separate post hoc analyses, presented at the annual meeting of American Academy of Allergy, Asthma and Immunology in 2016, Reslizumab was found to be particularly effective in patients with severe eosinophilic asthma accompanied by chronic sinusitis and nasal polyps.[8]

Mepolizumab, another IL-5 Ab, has also been found to be safe and effective in patients with eosinophilic asthma. Recent post hoc analysis from two randomized placebo controlled trials, (MENSA[9] and DREAM[10]) showed significant reduction in the frequency of asthma exacerbations in patients with blood eosinophilic count of 150 cells per uL or more at baseline. This study provided further evidence that blood eosinophils are robust markers for selecting patients who could benefit from such treatments.[11]

Tumor Necrosis Factor-alpha

Tumor necrosis factor (TNF) alpha is a pro-inflammatory cytokine that has been implicated in many aspects of the airway inflammation in asthma. Early studies with anti-TNF showed encouraging results; however, the results of a recent double-blind, placebo controlled study by Wenzel and coworkers were disappointing. This study[12] evaluated golimumab, an anti-TNF-α monoclonal antibody, in 309 people with asthma, and it was terminated early due to severe adverse effects, including pneumonia, sepsis, increased rate of malignancy, and one death.

Non-eosinophilic asthma

Non-eosinophilic asthma or neutrophilic asthma is a distinct phenotype affecting a substantial subgroup of patients with asthma. It is usually associated with increased asthma severity, increased airflow limitations and air trapping,[13-14] lower response to bronchodilators, and anti-inflammatory treatments. It is more common in smokers. Environmental exposure to bacterial endotoxins, particulate air pollution and ozone, as well as viral infections, may play an important role as triggers of neutrophilic airway inflammation in asthma.[13-14]

Most targeted therapies and prevention strategies are almost entirely focused on allergic/eosinophilic asthma. As of yet, there are no successful trials of targeted therapies in asthmatic patients without evidence for Th2 mediated inflammation (Non-eosinophilic asthma).

Macrolides

There is evidence that macrolides may specifically target neutrophilic airway inflammation. For example, a study of 45 patients with refractory asthma found that 8 weeks of treatment with clarithromycin (500 mg twice daily) significantly reduced levels of sputum IL-8, reduced airway neutrophil numbers, and improved quality-of-life scores compared with placebo, particularly in the subgroup of patients with neutrophilic asthma.[15]

Bronchial Thermoplasty (BT)

While most therapies target underlying inflammatory process, BT is the only therapy that targets the airway smooth muscles. This therapy involves delivery of thermal energy to the airway walls in a series of three bronchoscopies that takes place 3 weeks apart. This reduced airway smooth muscle mass and decrease bronchoconstriction.[16]

Several clinical trials have shown that it is safe and effective in improving quality of life and reducing exacerbations in patients with severe asthma. The exact mechanisms that underlie the improvements seen with BT remain poorly understood but are under intense study. Identifying the patients most likely to respond to this therapy is a critical next step and will be instrumental in determining the precise role of BT in the management of severe asthma.[17]

Understanding the two different phenotypes of asthma will help stratify patients to deliver more personalized treatment for those with severe asthma.

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