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Review Article

Refractory asthma – An old disorder: Novel approaches for effective control

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ARTICLE INFO

Article history:
Received 6 January 2016
Accepted 25 April 2016
Available online 24 June 2016

Keywords:
Refractory asthma
Triggers
Phenotypes
Therapeutic options
Targeted therapy

ABSTRACT

Bronchial asthma is an inflammatory disorder of airways characterized by hyper-responsiveness to a wide range of triggers and is associated with variable airflow obstruction that remits spontaneously or with the treatment. Several phenotype of asthma not responding to the currently acceptable standard therapy of high dose inhaled gluco-corticosteroids along with along acting β2 agonists come under the purview of refractory asthma. This condition is a heterogeneous and complex disease that requires a multi-disciplinary approach to identify accurately various sub-phenotypes to enable improved understanding of the pathogenesis and development of effective management strategies including use of novel methods and targeted therapy.

Bronchial asthma is an inflammatory disorder of airways characterized by hyper-responsiveness to a wide range of triggers and is associated with variable airflow obstruction that remits spontaneously or with the treatment. It is a common condition affecting both sexes and all age groups, more often children and young adults with an approximate prevalence of 300 million globally. It is a heterogeneous condition wherein both environmental and genetic factors have been implicated as causative factors. Being an anti-inflammatory condition of airways, inhaled corticosteroid therapy has been established as a standard along with β2-agonists for symptomatic relief of airway obstruction.[1]

Refractory asthma

Even maximal inhaled therapy does not ensure adequate control in approximately 5% of asthmatics, which encompass a variety of sub-phenotypes of asthma not responding to the currently acceptable standard therapy of high-dose inhaled gluco-corticosteroids along with long-acting β2-agonists.[2] These cases, variously called as difficult-to-treat asthma, corticosteroid-dependent asthma, ''problematic'' asthma, ''poorly controlled'' asthma and refractory asthma, need to be differentiated, investigated and corrected for any mechanism that may be aggravating asthma.[3,4]

Triggers

Significant number of cases labelled as severe or difficult-to-control asthma do not suffer from severe refractory asthma since control is possible by addressing the triggering factors that include poor compliance to treatment, inappropriate inhalation techniques and continued exposure to environmental triggers. Presence of co-morbidities, such as obesity,

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http://dx.doi.org/10.1016/j.mjafi.2016.04.006

rhinosinusitis, allergic bronchopulmonary aspergillosis (ABPA), gastroesophageal reflux and chronic infection, should be evaluated and treated. The role of hormonal abnormalities, especially in females, should be investigated and treated if considered to be a precipitating factor. Infection due to mycoplasma pneumoniae or chlamydophilia can trigger asthma and appropriate antibiotic therapy helps in improving asthma control. Intake of common drugs like aspirin and beta blockers[5,6] can make asthma control worse and should be omitted. In the Indian context, underlying ABPA is observed to be present in 39% of acute severe asthma cases admitted to intensive care units.[7] In tuberculosis (TB) endemic areas, ABPA is often misdiagnosed as TB. Early recognition of this condition in asthma is extremely important for initiating appropriate therapy and to prevent progression of the disease to irreversible bronchiectasis and lung fibrosis. Aspergillus hypersensitivity is the first step in the pathogenesis of ABPA and has a very high (51%) prevalence in acute asthma cases. Thus, routine screening, for all patients of asthma, by Aspergillus skin testing is required for detection of hypersensitivity.[7]

Phenotypes – newer insights

It is important to identify phenotypes of true refractory asthma. Three distinct phenotypes of severe refractory asthma with different clinical and physiological features have been identified by unsupervised cluster analysis, as shown in Table 1.[8–13] Further, based on sputum eosinophilia, severe asthma has been categorized under three sub-types: early onset severe atopic asthma with eosinophilia, late onset asthma among males with severe persistent eosinophilic airway inflammation and late onset asthma in female obese cases without eosinophilia. Bronchial biopsy has given more insight in to heterogeneous nature of the condition with some showing eosinophilic inflammation while others having neutrophilic airway inflammation. Antibiotic therapy with macrolides may help in those with neutrophilic asthma. Unpredictable and chaotic lung functions have been observed in some asthmatics who are labelled as cases of brittle asthma, which is a rare form of severe asthma with a wide variation of peak expiratory flow (PEF) despite heavy dose of steroids, and these patients are prone to very serious and often, life-threatening attacks.

Some of these cases have almost normal lung function with intermittent severe exacerbations due to swift and unpredictable fall in lung functions, with a high risk of mortality. These cases categorized as Type 2 Brittle Asthma often do not respond well to steroids and are treated effectively by sub-cutaneous epinephrine. On the other hand, Type 1 Brittle Asthma has frenzied variations in lung functions in spite of appropriate therapy. These cases may require OCS and continuous infusion of β2-agonists.

A pan European study, using an innovative systems biology approach, is being conducted for finger printing refractory asthma phenotypes by integration of patient-reported outcomes, non-invasive (exhaled air, sputum and blood), and invasive (bronchial biopsies) data, in an effort to target the pathway of asthma pathogenesis.[3]

Table 1 – Phenotypes of refractory asthma.

1	Early onset severe allergic asthma with very low forced expiratory volume in 1st second (FEV1).
2	Late onset non-atopic steroid-dependent eosinophilic asthma with fixed airways obstruction, aspirin sensitivity and rhinosinusitis.
3	Older obese females with late onset asthma and reduced lung function.

Therapeutic options

As per current guidelines (Global Initiative for Asthma, National Asthma Education and Prevention Programme and the British Thoracic Society), the treatment of patients with severe asthma comprises high-dose inhaled corticosteroids combined with long-acting β2-agonists (LABAs) and/or additional controller medications.[1,14] Most of the cases of refractory asthma are corticosteroid-dependent requiring maintenance treatment with oral corticosteroids. Some cases of refractory asthma showing poor response to 40 mg corticosteroid administered daily for 2 weeks need to be

Table 2 – Treatment approaches for the spectrum of refractory asthma.

S. No	Approaches
1	**Optimizing bronchodilatation** Tiotropium and salmeterol are comparable and both are superior to doubling ICS dose for improving lung function and asthma control. Tiotropium is superior to salmeterol in improving evening PEF and pre-bronchodilator FEV1. The currently recommended treatment approach is addition of tiotropium to ICS/LABA treatment for significant improvement in lung function, as measured by FEV1 over 24 h.
2	**Reducing airway smooth muscle** Bronchial thermoplasty, a therapeutic procedure to heat the airways by using radio frequency energy (65 °C), reduces the volume of airway smooth muscle in the treated airways. Three bronchoscopies, spaced several weeks apart, are required for a complete treatment.
3	**Reducing airway inflammatory cell number and/or activity (use of biological agents)** Anti-IgE therapy; omalizumab; targeting Th2 response; anti-IL5 (mepolizumab and reslizumab); anti-IL13 (lebrikizumab); anti-IL4 (dupilumab).
4	**Macrolide prophylaxis** Immunomodulatory and anti-inflammatory effects along with antibacterial effects of macrolides are well known. Maintenance treatment with macrolides, such as azithromycin, has been proven to be effective.
Treatment approaches: summary	
Optimizing bronchodilatation, reducing airway smooth muscle, reducing airway inflammatory cell number and/or, activity, use of macrolide antibiotics.	