REVIEW ARTICLE

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Neutrophilic Bronchial Asthma – Diagnostic and Therapeutic Challenge

Robin Bhati, Sonisha Gupta**, Syed Haider Mehdi Rizvi***, Pawan Kumar****, Shubham*, Saurabh**

Abstract

Asthma is a chronic inflammatory disease, with an arrangement of cells involved in the pathogenesis of the disease. The character of neutrophils in the development of bronchial asthma is found to be complex, as they may trigger activation of immune competent cells and are a significant source of free oxygen radicals and enzymes participating in airway remodeling[1]. Approximately 3.6 - 10% of patients with asthma have severe refractory disease, which is uncontrolled on high doses of inhaled corticosteroids and long-acting β2-agonists. Some of these individuals with severe disease suffer from neutrophilic phenotype. Neutrophilic asthma is a severe and persistent disease, with frequent exacerbations and hospitalisations. Neutrophilic asthma is not responsive to high dose inhaled corticosteroids and to novel monoclonal antibody therapies. There is need for targeted precision biologics and other treatment modalities for patients with neutrophilic asthma, such as long-acting phosphodiesterase-4 inhibitors, macrolide antibiotics and bronchial thermoplasty[2].

Introduction

Asthma is a significant public health problem, affecting more than 358 million individuals globally and its prevalence has been increasing during the last 40 years[3]. It is the most common chronic respiratory disease in children in developed countries and its prevalence is steadily increasing in the developing world. Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterised by different immuno-pathological pathways, clinical presentation, severity of disease and response to treatment[4].

Phenotypes

The phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic asthma. Patients with eosinophilic asthma have an eosinophil count ≥3%, whereas patients with neutrophilic asthma have elevated sputum neutrophil count between 61% and 64%, depending on the study[5]. Mixed granulocytic phenotype is characterised by increase in both eosinophils (>3%) and neutrophils (>61% or >64%). Paucigranulocytic phenotype embraces patients with very few eosinophils (<3%) and neutrophils (<61% or <64%) in induced sputum[6]. Approximately 3.6 - 10% of patients with asthma have severe refractory disease, which is not controlled inspite of treatment with high-dose Inhaled Corticosteroids (ICS) and Long-Acting β2-Agonists (LA β2-Agonists (LABA). Neutrophilic asthma is the most common phenotype in adult patients presenting with acute severe asthma[7]. The American Thoracic Society (ATS) guidelines on the definition of severe refractory asthma lists two major and seven minor criteria for making the diagnosis of severe phenotypical asthma . The ATS criteria for established diagnosis of refractory asthma (neutrophilic) include fulfilling one, or both major criteria and at least two minor criteria[8].

Major criteria

1. Treatment with continuous or near continuous (>50% of the year) oral corticosteroids.
2. Need for treatment with high-dose inhaled corticosteroids.

Minor criteria

1. Need for additional daily treatment with controller medication (long-acting β2-agonist, leukotriene receptor antagonist, theophylline).
2. Asthma symptoms needing short-acting β2-agonists use on a daily or near daily basis.
3. Persistent airway obstruction (FEV1 <80% predicted, diurnal peak flow variability <20% predicted).
4. One or more urgent care visit for asthma.
5. Three or more oral steroid bursts per year.

**Post-Graduate Resident, **Professor, ***Senior Resident, Department of Respiratory Medicine, School of Medical Sciences and Research, Sharda University, Greater Noida - 201 306.*

*****Chest Physician, Department of Pulmonary Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*

Corresponding Author: Dr Sonisha Gupta, Professor, Department of Respiratory Medicine, School of Medical Sciences and Research, Sharda University, Greater Noida - 201 306. Tel: 8527214794, E-mail: sonishagupta@gmail.com

6. Prompt deterioration with >25% reduction in oral or inhaled corticosteroids.
7. Near fatal asthma event in the past.

Triggers

In general, any of the following factors if present, may trigger development of severe asthma[9] – Pollen, Mold, Mites, Animal dander, Perfumes and Odors, Air pollution, Laughter, Smoke, Dust. However, the factors that triggers the onset of symptoms of Neutrophilic Asthma are different[10] – Overuse of inhaled corticosteroids, Chronic infections, Obesity, Adult onset of symptoms of Asthma.

Challenges

Neutrophilic asthma is associated with more frequent visits to urgent care and hospitals, medication side-effects due to high-doses or long-term use of corticosteroids, reduced quality-of-life and increased risk of acute fatal asthma attack. If one parent has asthma, the child may be 3 - 6 times more likely to develop it than someone whose parents do not have it[11]. Some people with asthma experience most of their symptoms during the night. Over time, this can lead to serious sleep deprivation[12]. Neutrophilia in lung tissue is thought to be responsible for chronic inflammation that is thought to cause scarring of cells lining airways. This makes airway walls thicker, and the air passages narrower than normal[13]. This causes airway obstruction that allows air to get in but not out (air trapping). Because such scarring is permanent, diminished lung function and asthma symptoms are only partially reversible with treatment. This means that some shortness of breath may occur even on good asthma days[14].

Diagnosis

- Adult onset, most cases after 20 years of age.
- Less atopic compared with eosinophilic asthma
- Less severe exacerbations compared with eosinophilic asthma
- Less subepithelial fibrosis as compared to eosinophlic asthma
- Sputum neutrophil count, 40% - 64%;
- Sputum Eosinophils <2% - 3%
- Low FeNO <30 ppb
- Fixed airflow limitation (low FEV1)
- High hydrogen sulfide levels
- Less responsiveness to methacholine challenge tests
- Corticosteroid unresponsiveness

Neutrophilic asthma is characterised by a high neutrophil count in induced sputum ranging from 40% to 76% of sputum cells, or a neutrophil count of 500×10^4/mL. Additionally, patients with neutrophilic asthma have less sputum eosinophil count which has been quoted to be between less than 1.9% and 3% by various authors. Increased neutrophils in sputum has been associated with severe persistent asthma , fixed airway obstruction, with very low Forced Expired Volume in 1 second (FEV1) and post-brochodilator FEV1[15]. Shaw and colleagues, have reported that both patients with eosinophilic asthma and neutrophilic asthma had low pre-bronchodilator FEV1, but only patients with neutrophilic asthma had lowest post-bronchodilator FEV1, indicating persistent airflow limitation[16]. Furthermore, patients with neutrophilic asthma are less atopic and have less responsiveness to methacholine challenges compared with patients with eosinophilic asthma[17]. Patients with neutrophilic asthma are unresponsive to LABA and high-dose ICS and the newly introduced targeted biologics. Furthermore, neutrophilic asthma is typically associated with a worse quality-of-life and has a poor prognosis[18].

Treatment

Treatment of neutrophilic asthma requires novel anti-inflammatory agents and therapeutic strategies targeted against airway smooth muscle hypertrophy and airway remodeling, such as phosphodiesterase-4 inhibitors, macrolide antibiotics and bronchial thermoplasty[19].

Phosphodiesterase-4 inhibitors are appropriate as add-on therapy for patients with neutrophilic asthma, because they suppress immune cell trafficking, activation and degranulation. They also suppress the release of cytokines, chemokines and growth factors which promote subepithelial membrane fibrosis, Airway smooth muscle cell proliferation, airway smooth muscle hypertrophy and airway remodeling . Long-acting selective PDE4-inhibitors, such as roflumilast have been shown to significantly reduce airway hyper responsiveness, which is a key feature of neutrophic asthma. Oral roflumilast 500 mg morning or evening has been shown be beneficial as add-on treatment for fixed airflow limitation[20].

Macrolide Antibiotics-Azithromycin (250 mg daily three times per week) as add-on treatment in patients with nonesonophilic asthma, defined by normal blood eosinophil counts and normal FeNO, resulted in significantly fewer severe exacerbations during 26-week period compared with controls. Azithromycin significantly reduced severe exacerbations and lower respiratory tract infection in non-eosinophilic asthma phenotype by approximately 67% compared to 38% in placebo group. Clarithromycin in

patients severe refractory asthma reduced neutrophil count and sputum IL-8 levels, Neutrophilic asthma is nonresponsive to corticosteroids. Corticosteroid-resistance is associated with airway hyperresposniveness and decreased Histone Deactylase 2 (HDAC2) activity and expression . HDAC2 has been shown to inhibit inflammatory protein coding genes such as granulocyte macrophage colony stimulating factor or cyclooxygenase 2, promoted by IL-1β, TNF-α and NFκB kinase. Macrolides reverse corticosteroid insensitivity by restoring the HDAC activity, via inhibiting Phosphoinositol 3 Kinase (PI3K) pathway and by attenuating TNF-α and IL-17 immune responses[21] .

Bronchial Thermoplasty (BT) is a bronchoscopic treatment for subjects aged 18 years and above with severe persistent asthma not responding to high-dose ICS and LABA. Selection and preparation of patients for BT is very important and the procedure should be performed by experienced pulmonologists or bronchoscopists. Bronchial thermoplasty has a long-term safety profile and may be considered for patients with predominant chronic airflow obstruction and patients who do not respond to anti-IgE, anti-interleukin biologics, or macrolides. Patients with neutrophilic phenotype of asthma are suitable candidates for bronchial thermoplasty because they have excessive airway smooth muscle hypertrophy, hyperplasia and hyper-responsiveness. They are also unresponsive to treatment with high-dose ICS, LABA, LTRA and interleukin antagonists targeted against eosinophilic asthma[22].

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