Review Article

Recent Updates in Bronchial Asthma Treatment : Review of Guidelines and New treatment Modalities

Patel N[1]

ABSTRACT

Asthma management is conventionally based on the guidelines provided by various prominent bodies on the disease with GINA (Global Initiative For Asthma) guidelines being most popular. In spite of these guidelines a significant proportion of patients fail to achieve good control of their symptoms or prevent severe exacerbations. For this reason new therapeutic strategies need to be explored. Recently GINA has introduced the control based asthma management cycle wherein pharmacological and non-pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review leading to better asthma outcomes. There are quite a few new therapeutic option in horizon which target cytokines (anti IgE-omalizumab, anti IL-13-Lebrikizumab, anti-IL4Rá-Dupilumab), neutrophilic inflammation (CXCR2 inhibitors), PGD2 receptor (CRTH2 antagonist). Optimal use of these agents will probably require identifying particular responsive phenotype .Novel therapy in the form of Bronchial thermoplasty has been recently approved. It involves use of radio frequency thermal energy to reduce the airway smooth muscle mass. Studies have demonstrated improvements in asthma-related quality of life and a reduction in the number of exacerbations following Bronchial thermoplasty.

Introduction :

Asthma is a chronic inflammatory respiratory disease manifesting with variable airflow obstruction and symptoms of cough, wheeze, and dyspnea. The infiltration of airway tissues with increased numbers of eosinophils, a hallmark of allergic disease, is also seen in asthma.[1] Although debate continues as to the role of these inflammatory cells in mediating the expression of asthma, little doubt remains to the long-known efficacy of glucocorticoids in reducing both the blood and airway eosinophilia with consequent improvements in symptoms and lung function,[2,3] and an attenuation in its decline.[4] Most patients with asthma achieve good disease control with principal use of inhaled corticosteroids (ICS) and long-acting ß2 - adrenoceptor agonists (LABAs) that are the mainstay of asthma therapy.[5] Overall asthma management is conventionally based on the guidelines provided by various prominent bodies on the disease with GINA (Global Initiative For Asthma) guidelines being most popular. In spite of these guidelines a significant proportion of patients fail to achieve good control of their symptoms or prevent severe exacerbations. Therefore there are lots of new treatment options which are being studied and few of them are in pipeline. This review will highlight these new treatment options and outline recent updates in GINA guidelines.

[1]Chest Physician, Dept. of Respiratory Medicine Meditrina Institute of Medical Sciences, Nagpur, Maharashtra, India

Address for Correspondence -
Dr. Nainesh Patel
E-mail : drnaineshp@gmail.com

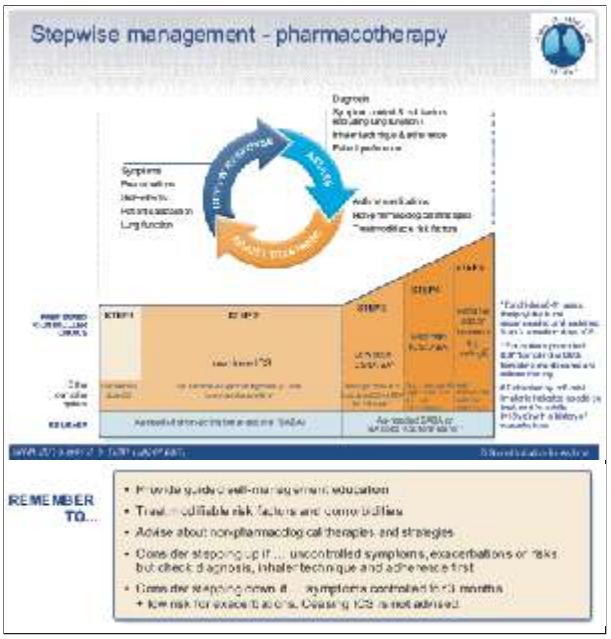
GINA updates

The control-based asthma management :

The long term goals of asthma management are to achieve good symptom control, and to minimize future risk of exacerbations, fixed airflow limitation and side effects of treatment. In this line GINA (Global Initiative For Asthma) has introduced the concept of control based asthma management in its recent update.

In control based asthma management, pharmacological and non pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review ***(Fig-1).*** Asthma outcomes have been shown to improve after the introduction of control based guidelines.[6]

Fig. 1 : **The control-based asthma management cycle**[6]



ICS = Inhaled corticosteroids, LABA = Long acting Beta agonist, LTRA = Leukotriene receptor antagonists, SABA = Short acting beta 2 agonists

Fig. 2 : **Stepwise asthma management plan.**[6]

Updates in Stepwise asthma management plan :

Anti-inflammatory therapy in the form of **inhaled corticosteroids** remains the cornerstone for asthma management. However there has been update with regards to add on therapy.

Tiotropium :

Add-on Tiotropium (long acting muscuranic antagonist) by soft-mist inhaler is a **new 'other controller option'** for Steps 4 and 5, in patients ≥18 years with history of exacerbations. ***(Fig. 2)*** (*Tiotropium was previously described in GINA as an add-on option on the basis of clinical trial evidence).[6]

Studies have shown that addition of **Tiotropium significantly increased the Time to the first severe exacerbation** and provided modest sustained bronchodilation and hence the recommendation.[7]

Budesonide / Formoterol combination :

Budesonide / Formoterol combination is recommended as a Single maintenance and reliever therapy (SMART). Inherent in persistent asthma is the periodic need for reliever medication for symptoms that may invite over reliance on short-acting ß2 - agonists at the expense of reduced adherence to inhaled corticosteroid therapy (ICS).[5] Formoterol, an LABA, uniquely offers both immediate (within 13 min.) and sustained bronchodilation[8] equivalent to salbutamol, allowing its use in combination preparations to be used in single maintenance and reliever therapy (SMART). This has been now recommended by GINA as well as other international guidelines ***(Fig. 2).*** Although short-acting bronchodilators provide rapid relief of symptoms such as dyspnea associated with allergen-induced bronchoconstriction, they fail to address the accompanying eosinophilic inflammation known to precede exacerbations in asthma.[9] One potential advantage of the SMART strategy is that patients will simultaneously receive additional doses of inhaled corticosteroids alongside a bronchodilator when they use their combined inhaler for symptom relief. This may target anti-inflammatory treatment to periods of poor control when it is most needed. Apart from this it allows patients a reduction in inhalers, which may play a helpful role in improving adherence,[10] particularly in those who are poorly adherent to ICS.[11]

Other GINA updates .....

GINA has recognised the subset of patients with overlapping clinical features of both asthma and COPD in its recent update with description and chapter on it. It has been named as **Asthma-COPD overlap syndrome (ACOS).**[6]

The aims of the chapter are mainly to assist clinicians in primary care and non-pulmonary specialties in diagnosing asthma and COPD as well as ACOS, and to assist in choosing initial treatment for efficacy and safety. A specific definition has not be provided for ACOS at present, because of the limited populations in which it has been studied. ACOS is not considered to represent a single disease; it is expected that further research will identify several different underlying mechanisms.

Concerns regarding **over-usage of SABA**

Recent studies have indicated that High usage of SABA is a risk factor for **exacerbations**[12] and Very high usage (e.g. > 200 doses / month) is a risk factor for **asthma-related death.**[13]

As regards to **Beta-blockers and acute coronary events** GINA states that if **cardioselective beta-blockers** are indicated for acute coronary events, asthma is **not an absolute** contra-indication. These medications should only be used under close medical supervision by a specialist, with consideration of the risks for and against their use.[6]

Newer treatment options and concept of phenotypic approach.

There are quite a few new therapeutic option in horizon which target **cytokines (antiIg E-omalizumab, anti IL-13-Lebrikizumab, anti-IL4Rα-Dupilumab), neutrophilic inflammation (CXCR2 inhibitors), PGD2 receptor (CRTH2 antagonist)** apart from already existing anti inflammatory therapy with inhaled corticosteroids. To get the best out of these medicines there is a need to find out the subset of patients who are likely to benefit most from these agents. This can be done by phenotyping i.e. classifying patients with similar characteristics into groups.

Thus in asthma subset of patients with recognizable clusters of demographic, clinical and/or pathophysiological characteristics are labeled as 'asthma phenotypes' ***(Fig. 3).***[14]

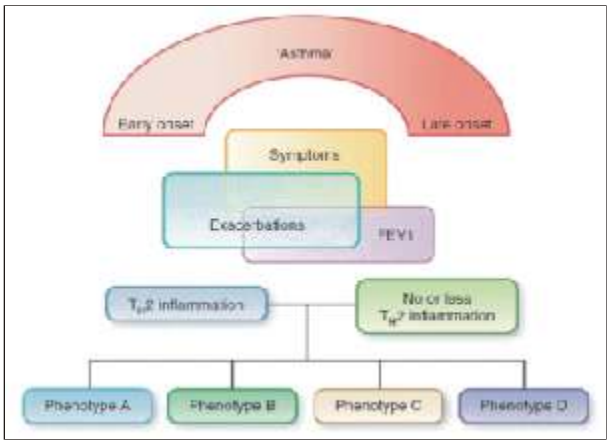


Fig. 3 : **Asthma phenotypes-schematic representation.**[14]

So one can have

1. **Clinical phenotypes by** grouping patients based on clinical characteristics like **Age of onset, exacerbation frequencies, Triggers, Obesity, Smoking, Lung function** etc.
2. **Inflammatory phenotypes** based on whether inflammation is **eosinophilic or neutrophilic.**
3. **Immunopheno types** with either **TH2 response or absent/less TH2 response.**

To phenotype patients in the above mention categories, measurable **clinical parameters or markers** are needed. Examples are as follows

Eosinophilic inflammation Th2 response[15]

Sputum eosinophilia	**Periostin gene (serum periostin level can be measured)**
Feno (Fracational expired nitrous oxide levels)	**CLCA1 gene**
Serum IgE Levels	**Serpin B2 gene**
Positive skin test	

So if patient has high sputum eosinophilia and FENo is increased then patient is likely to respond to Inhaled corticosteroids.

High IgE levels predict response to Omalizumab.

Similarly high level of periostin predicts response to therapies targeting TH2 response like Lebrikizumab.[15]

Thus phenotypic approach may guide treatment in future especially in patients not responding to conventional guideline based treatments.

Bronchial thermoplasty

Bronchial thermoplasty (BT) is a novel therapy for patients with severe asthma. Using **radio frequency thermal energy,** it aims to reduce the airway smooth muscle mass.

A full course of bronchial thermoplasty treatment includes three separate bronchoscopic procedures: one for the each lower lobe of the lung and another for both upper lobes. Each outpatient procedure is performed approximately three weeks apart.

Under sedation, a catheter inside a bronchoscope delivers thermal energy into the airways. The catheter delivers a series of 10-second temperature controlled bursts of radio frequency energy which heat the bronchial mucosa to 65 degrees Celsius ***(Fig. 4).*** It is this heat that destroys some of the muscle tissue which constricts during an asthma attack, reducing the number and severity of exacerbations.[16]

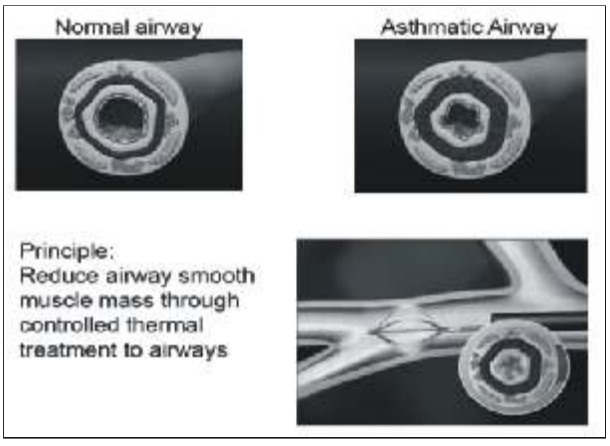


Fig. 4 : **Bronchial thermoplasty.**[16]

Several clinical trials have demonstrated improvements in asthma-related quality of life and a reduction in the number of exacerbations following treatment with BT. In addition, recent data has demonstrated the long-term safety of the procedure as well as sustained improvements in rates of asthma exacerbations, reduction in health care utilization, and improved quality of life.[17,18]

Summary

There is rapid evolution in Treatments for asthma with the development of both novel pharmacological therapies and the establishment of new management strategies. Correspondingly frequent updates in guidelines are expected in near future. Although novel biological therapies helpful for those patients who are unresponsive to conventional treatment, the varied responses to these agents emphasize the need for careful patient selection highlighting the vital importance of accurate phenotyping of the asthma population. It may ensure that each individual patient receives the most appropriate therapy.

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Conflict of interest

There are no conflicts of interest

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