Newer Strategies in the Management of Asthma

PS Shankar

Introduction

Bronchial asthma is a complex and heterogeneous syndrome characterised by episodic intrathoracic airways obstruction, airway hyper-responsiveness and airways inflammation resulting in episodic occurrence of dyspnoea and wheezing, which varies widely over time either spontaneously or in response to treatment. Multifactorial stimuli are responsible for airway hyperreactivity leading to obstruction which varies widely over time either spontaneously or in response to treatment. There is marked heterogeneity in the clinical course and in the response to standard treatment. The symptoms of bronchial asthma are controlled in majority of patients by the administration of bronchodilators and corticosteroids. However the symptoms persist and frequently exacerbate in some patients.

Allergen Immunotherapy

If the causal allergen is pollen or house dust mite and it is supported by clinical history, it can be successfully treated by hypo-sensitisation.

Subcutaneous Immunotherapy

Specific immunotherapy is undertaken via the subcutaneous route (SCIT). It takes about three years and involves the injection of increasing doses of allergen extracts to induce both immunological and clinical tolerance. It is possible to stimulate the production of antibodies belonging to the IgE class by hypo-sensitization. These will compete with IgG as blocking antibodies, and bind the allergen and eliminate it without causing any symptoms of allergy. The amount of histamine liberated with IgG is 500 times less than that of IgE.

The hypo-sensitisation is carried out pre-seasonally and can be repeated in the next season. It is done with the use of aqueous solution containing pollen extract and is injected subcutaneously in gradually increasing doses of allergen extracts over weeks. The duration of therapy takes about three years. The slow releasing depot preparations like alum-precipitated extracts have shown to be useful. The analysis of SCIT trials in atopic asthma has shown that it reduces asthma symptoms and medication and improvement in bronchial hyperreactivity. However, the results are not consistent.

Sublingual Immunotherapy

Sublingual (SLIT) administration using allergen extracts is being tried instead of SCIT. It has a better safety profile and greater convenience. It is self-administered at home. It has fewer systemic side effects. Use of multiple allergen extracts may cause anaphylaxis reaction. It appears to be effective in the treatment of grass pollen allergy.

Anti-IgE Therapy: Omalizumab

Omalizumab is a recombinant, DNA-derived, humanised monoclonal anti IgE-antibody. It binds to the portion of IgE that recognises its high affinity receptors on the surface of mast cells, basophils, monocytes and dendritic cells considered as immune modulating cells. It inhibits the binding of IgE to the receptors thus preventing the activation and subsequent release of their inflammatory mediators.

Omalizumab is available as a sterile, white, lyophilised powder and it has to be reconstituted with water. It is to be administered subcutaneously over 30 seconds in the deltoid region or in the thigh. The dose is determined using a specified dosing table, on the basis of the patient’s weight and blood IgE level. It is absorbed slowly and its clearance is slow. It is administered every 2 or 4 weeks. It should be continued in those patients who respond for as long as they continue to benefit from this treatment.
Occasionally systemic allergic reactions in the form of anaphylaxis may occur. Such reaction may occur within 2 hours following administration of the first few doses.

Omalizumab is well tolerated. The adverse events may occur in the form of upper respiratory tract infection, headache, nasopharyngitis and sinusitis. These manifestations are of mild-to-moderate severity and of short duration. The drug is expensive. Its long-term effectiveness and side effects are not known.

Omalizumab is recommended in the treatment of moderate and severe persistent asthma, especially allergic (IgE-mediated) variety that is non-responsive to inhaled corticosteroids, long-acting beta-agonists and leukotriene modifiers. The aim is to reduce free IgE levels in IgE-mediated allergic asthma. It is indicated as add-on therapy to achieve improvement in asthma control in patients 12 years of age and above with severe persistent allergic asthma provided they demonstrate a positive skin test to a perennial allergen, forced expiratory volume in one second (FEV1) of less than 80%, frequent day-time symptoms or night-time awakenings, multiple documented severe asthma exacerbations, and treatment with daily high doses of inhaled corticosteroids (ICS) long acting beta-2 agonists (LABA).

Omalizumab has been included in Global Initiative for Asthma (GINA) 2007 guidelines at step 5 as an add-on therapy to high doses of ICS plus LABA. It is also indicated when these drugs have produced intolerable adverse effects. It is to be administered to those patients exhibiting a blood IgE levels varying from 30 to 700 IU per ml, exhibiting sensitisation to a perennial allergen such as dust mites, animal dander, mould or cockroaches. Omalizumab has shown to reduce the frequency of asthmatic exacerbations. It is able to bring down the dose of inhaled corticosteroids when used together.

**Anti-interleukin-13 Therapy**

On many occasions, asthma remains as an uncontrolled disease despite administration of inhaled corticosteroids. In this heterogeneous disorder, many factors come into play in the development of clinical manifestations. Of them the expression of interleukin (IL)-13 is responsible for airway abnormality in some cases. IL-13 is a cytokine of type 2 helper T (Th2) cells and plays an important role in the development of asthma. This group of patients has been recognised as a separate subphenotype associated with an ‘interleukin-13 signature surrogate’ or a high type 2 helper-T-cell (having an IgE level >100 ng/ml and > 0.14 X 10⁹ eosinophils/L in the peripheral blood) phenotype. Such patients may benefit following administration of anti-interleukin-13.

Among many effects inhaled glucocorticoids exhibit an inhibitory effect on the production of IL-13. However some patients exhibiting uncontrolled asthma exhibit an elevated level of IL-13 in the sputum and bronchial biopsy specimens.

IL-13 shares a receptor with IL-4, and it is critical in the expression of the TH2 phenotype, responsible for the formation of IgE antibody. IL-13 is seen in the airways of asthmatics and appears to mediate airway hyperresponsiveness, inflammation, mucus hypersecretion, and subepithelial fibrosis. It must be noted that IL-13 is one of the pathways that can lead to expression of an asthma phenotype.

Interleukin-13 induces bronchial epithelial cells to secrete periostin. Periostin is a matricellular protein. It is secreted in large amounts by the activated epithelial cell function and paracrine effects on fibroblasts.

Lebrikizumab, an IgG4 humanised monoclonal antibody to interleukin-13. It specifically binds to interleukin-13 and inhibits its action.

A randomised, double-blind, placebo-controlled study has been carried out to determine the usefulness of lebrikizumab in the control of asthma. The study group consisted 219 adult asthmatics who had been controlled inadequately despite inhaled glucocorticoid therapy. These patients were taking 580 micrograms of inhaled fluticasone propionate daily through a dry-powder inhaler and 80% of them were also taking a long-acting beta-agonist. Lebrikizumab (N=107) was given at a dose of 250 mg subcutaneously once a month for a total of 6 months. The placebo group (N=112) received sterile water.

At week 12, there was a mean increase in FEV1 of 5.5 percentage points higher in the lebrikizumab group compared to placebo group. Among those exhibiting a high-periostin level, the increase from baseline FEV1 was 8.2 percentage points higher in the lebrikizumab group than in the placebo group. Those patients showing a low-periostin content, the increase from baseline FEV1 was 1.6 percentage points higher in the lebrikizumab group than in the placebo group. The patients receiving lebrikizumab exhibited musculoskeletal side effects.

Administration of Lebrikizumab in uncontrolled asthma shows an improvement in lung function. There is a greater improvement in lung function in those exhibiting high pretreatment levels of serum periostin than those with low periostin levels. High-Th2 phenotype is associated with an increase in circulating periostin. Serum periostin can be used to identify patients with asthma who may have an increased response to lebrikizumab treatment. This observation needs replication through a larger study.
in different phenotypes. This, according to Monica Kraft will move us closer to personalised medicine in the treatment of asthma.18

**Airway Hyper-responsiveness**

In the normal airways, smooth muscle is likely to provide structural support, help in regulation of gas exchange and contribute to mucus clearance, defense mechanism and cough.19 In asthma airway smooth muscle mediates acute bronchoconstriction and participates in airway hyperresponsiveness. It is likely to be involved in the pathogenesis of airway inflammation by secreting cytokines, modifying tissue matrix, binding migrating inflammatory cells in the bronchial tree, and remodelling, and interact with bronchial epithelium and nerves.

**Thromboxane A2 Receptor Antagonist**

Thromboxane A2 (TXA2) is a bronchoconstrictor prostanoid. TXA2 is a cyclooxygenase product of arachidonic acid involved in the pathogenesis of asthma, and takes part in its acute and chronic inflammatory processes.20

Seratrodust, a thromboxane A2 (TXA2) receptor antagonist has found a place in the treatment of asthma. It is a quinone derivative. It has no action on blood coagulation cascade such as thrombus formation, prothrombin time and activated partial thromboplastin time. It inhibits bronchoconstriction induced by TXA2. It causes airway smooth muscle and vascular dilatation, and decreases airway hyperresponsiveness. It exerts its anti-inflammatory effect by acting as an antagonist of TXA2 receptors. On oral administration seratrodust is absorbed rapidly and is slowly cleared by hepatic biotransformation. It is administered in a dose of 80 mg once a day orally, and the dose can be increased up to 320 mg a day. Lower dose is advocated in elderly. It is generally well-tolerated. It is contraindicated in individuals exhibiting hypersensitivity to seratrodust, and in patients with impaired hepatic functions. Seratrodust has shown to exhibit better control on asthma than that of cysteinyl leukotriene receptor antagonists in the management of asthma. Global initiative for Asthma (GINA) guidelines has recommended seratrodust as a controller of asthma in step1 for long term management.21 This drug has been in use as a controller therapy in the management of asthma since 15 years in Japan.

**Long-acting Beta-2 Adrenoceptor Agonist**

Inhaled beta-2 adrenoceptor agonists are most effective bronchodilators for management of bronchial asthma. Currently available long acting bronchodilators (LABAs) have duration of action of 12 hours at recommended doses. There is a need to administer the drugs twice daily to get an optimal clinical effect. The availability of a once daily dosing beta-2 agonist could be of great help in the management of asthma as it can be administered with greater convenience and obtain sustained bronchodilation.

Indacaterol is an ultra-long acting beta-2 adrenoceptor agonist.22 It is considered a full beta-2 agonist with a high intrinsic efficacy. It is delivered as an aerosol formulation through a dry powder inhaler at once daily dosing in patients with asthma.23 The drug is rapidly absorbed and it has a fast onset of action showing its effect within 5 minutes. The effect is sustained for 24 hours on once daily dosing. In a dose of 200-800 microgram, it has a favourable therapeutic index.24 It provides sustained 24-hour bronchodilation. It is to be noted that it has a mean effective half-life of more than 30 hours.25 It is well tolerated without side-effects. However it is not to be used to treat acute episodes of bronchospasm as it may cause paradoxical bronchospasm.24 The convenience of once daily dosing could lead to a better compliance and it may be useful either to take during day time or night.

**Phosphodiesterase-4 Inhibitors**

Phosphodiesterases(PDEs) are intracellular enzymes that inactivate cyclic adenosine monophosphate (cAMP). Methyl xanthines are non-selective phosphodiesterase inhibitors. PDE-4 sub type is the predominant isoenzyme found in inflammatory cells and it specifically targets cAMP.

Roflumilast acts as a selective, long-acting inhibitor of the enzyme PDE-4 to exhibit anti-inflammatory effects seen in asthma and COPD. It is developed as an orally administered drug.26 Each tablet contains 500 mcg of roflumilast. It is administered once daily. It is well tolerated. It may cause nausea, loss of appetite, headache, backache, and insomnia as side effects.27 Roflumilast controls chronic inflammation of airways. It improves FEV1 and peak expiratory flow rate. It attenuates allergy-induced inflammation in mild asthma.28 Roflumilast as a PDE-4 inhibitor increases intracellular cAMP leading to regulation of inflammatory cell function. Roflumilast has a protective effect on allergen induced airway inflammation which is not well controlled by corticosteroids.29

**Bronchial thermoplasty**

Bronchial thermoplasty (BT) has been tried to reduce the potential for smooth muscle-mediated
broncho-constriction by reducing smooth muscle mass in the walls of conducting airways. Cox et al tried radiofrequency ablation of airway smooth muscle mass to reduce smooth muscle-mediated broncho-constriction.30 Bronchial thermoplasty is a novel intervention in which controlled radiofrequency energy is delivered to the intra-parenchymal airways distal to the main stem bronchi down to airways 3 mm in diameter during a series of bronchoscopies resulting in a prolonged reduction of airway smooth muscle mass. Danek et al had tried to heat the airway in a controlled manner by radiofrequency energy in dogs and it had resulted in reduction in airway hyper-responsiveness to methacholine challenge.31

**Radiofrequency energy:** It is thought that the major source of resistance to airflow is in the central airways and any attempt to reduce obstruction in the central airways will result in reduction of overall resistance to airflow and decrease the symptoms.32 Bronchial thermoplasty involves application of radiofrequency energy in a controlled manner using the Alair system, directly to intra-parenchymal airways of the lungs through a bronchoscope. The treatment is confined to the wall of airways and to the immediate peri-bronchial region. The thermal energy heats the tissue up to about 65ºC. It will be able to reduce smooth muscle mass avoiding tissue damage.31

**Procedure:** Under general or local anaesthesia in a patient who had received systemic steroids a day prior and during the procedure, to minimise potential side-effects of bronchoscopy, such as oedema and inflammation, a catheter containing an expansile basket is passed through the working channel of bronchoscope, and activated after positioning in small-to-medium sized airways moving from distal to proximal under direct vision. The treatment is carried out in 3 sessions approximately 3 weeks apart. Initially the treatment is carried out in each of the lower lobes separately, and in subsequent session the accessible airways in both upper lobes.

Cox et al has carried out bronchial thermoplasty in 16 subjects with mild-to-moderate asthma. The study has shown a statistically and clinically significant improvement in airway hyper-responsiveness after bronchial thermoplasty, which persisted for at least 2 years after treatment. There was a significant improvement in the percentage of symptom free days, and peak expiratory flow at 12 weeks interval.33

In a randomised, controlled trial conducted at 11 centers in four countries, 112 subjects who had moderate or severe persistent asthma receiving inhaled corticosteroids and long-acting beta-2 adrenergic agonists (LABA) were studied by Cox et al.34 In them LABA were withdrawn and either underwent bronchial thermoplasty or treated as a control group. The effect of bronchial thermoplasty was evident in 3 months after the procedure. The results showed reduction in frequency of mild exacerbations of asthma in bronchial thermoplasty group. At 12-months, there was significantly greater improvement in the bronchial thermoplasty group than the control group in the morning peak expiratory flow. There was an increased percentage of symptom-free days and they required fewer puffs of rescue medication. It improved the quality of life. There was no significant different in the values for airway responsiveness and forced expiratory volume in 1 second between the two groups.

Generally the treatment is well-tolerated. The frequently reported side-effects of the device and/ or procedure-related are related to airway irritation manifesting in cough, dyspnoea, wheeze, and bronchospasm within a week of bronchial thermoplasty.7 In a post-treatment of 6 weeks to 12 months, the adverse respiratory events were dyspnoea, cough, nasal congestion, wheezing and productive cough.34

**Contraindications:** The treatment is not advocated when there is a history of respiratory tract infection in preceding 6 weeks, a history of two or more infections of the lower respiratory tract per year -requiring antibiotic treatment and the use of more than four puffs in a 24-hour period of a short-acting beta 2-adrenergic agonist.33

**Clinical benefit:** Bronchial thermoplasty is likely to provide clinical benefit by reducing the contractile function of airway smooth muscle and exacerbation of asthma. By modifying the structure and elements of the airway wall, BT can bring about changes in airway hyper-responsiveness. The airway with a decreased muscle mass is likely to contract less in response to stimulation.

This procedure has a potential to become a therapeutic option in patients with chronic asthma who are not satisfactorily controlled with pharmacotherapy.35 However in long term, the procedure is likely to lead to permanent widening of large airways, bronchiectasis and increased collapsibility of the airway wall. The thermoplasty procedure is not having access to the peripheral airways which might be a primary cause of refractory asthma.

BT is totally a new approach to treat asthma. 2-year follow up has not shown any deterioration in respiratory health status. Patients who have undergone BT have expressed satisfaction with the procedure in a survey undertaken 1-year following the procedure.36 It has been envisaged that BT might become a real breakthrough for the treatment of refractory asthma due to severe airway hyper-responsiveness, associated
with marked smooth muscle hyperplasia in the airway. It has the potential usefulness of targeting airway smooth muscle in the treatment of asthma. However it must be noted that the treatment helps in ablation of airway myocytes situated only in the bronchi 3 mm or larger in diameter. Moreover the treatment involves three bronchoscopic procedures to bring about reduction in the airway smooth muscle mass. It also causes epithelial damage. The procedure needs further refinements for its wider practical applications.

References
21. Global initiative for asthma Global strategy for asthma management and prevention NIH Publication no. 02:3659 (updated 2004), National Institute of Health/National Heart. Lung and Blood Institute, 2004