

Review Article

ASTHMA : A CONCISE REVIEW

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ABSTRACT

Asthma is chronic inflammatory disease, which includes bronchial hyperactivity and bronchospasm characterized by hyper-responsiveness of tracheo-bronchial smooth muscle to variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion and mucosal edema resulting in breathlessness or dyspnoea, wheezing cough, chest congestion and anxiety about being unable to breathe. Asthma affects over 5-10% of population in industrialized countries. It afflicts approximately 53 million people across world. More than 4000 people die every year in India as a result of complications arising from serious asthmatic attacks though there are several recommendations and treatments being reported. The attempt has been made to summarize pathophysiology, available evidence and treatment and management of asthma.

Key words: Asthma, hyperactivity, pathophysiology, treatment

INTRODUCTION

Asthma is a chronic disease characterized by acute exacerbation of coughing, dyspnoea, and wheezing and chest tightness. Patients usually have reduced forced expiratory volume in one second well as reduced airflow. Other features characteristics of asthma are airway inflammation and bronchial hyper-responsiveness, which are not unique to the other diseases. Its increased prevalence, morbidity and mortality rates have recognized the growing seriousness of asthma in the general population in the past 20 years. From 1980 to 1987 the prevalence rate of asthma in the United States increased by 29 percents. Asthma is also increasing in severity and is a leading cause of mortality throughout the world (1).

Asthma can no longer be viewed simply as “reversible airway obstruction” or “irritable airway obstruction”. Asthma should be viewed primarily as “an inflammatory illness with bronchial hypersensitivity and bronchospasm”. It is a chronic inflammatory disorder of the respiratory disorder of the respiratory airway, characterized by increased mucus production and airway hyper-responsiveness resulting in decreased air flow, and marked by recurrent episodes of wheezing, coughing and shortness of breath. It is a multifactorial disease process associated with genetic, allergic, environmental, Infectious, emotional, and nutritional components (2). Asthma may be defined, as “a condition in which there is recurrent “reversible” obstruction of airways in response to stimuli which are not in themselves noxious and which do not affect non-asthmatic subjects”. The term “reversible” says that only the acute attack of dyspnoea is reversible, but the underlying pathological changes may not be reversible (3).

According to guidelines of the National Asthma Education and Prevention Program (NAEPP) of heart, lung and blood institute, the current definition of asthma is, “A chronic inflammatory disorders of airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells.”

It is an episodic disease manifested clinically by paroxysms of dyspnoea, allergic rhinitis and wheezing without cold. Upon study it is now known that bronchial asthma is a chronic inflammatory disease of airway.

Prevalence of Asthma:

An estimated 14 to 15 million persons in the United States have asthma (about 5% of the population) and 150 million worldwide. The reported prevalence has increased 75% to 54 per 1000 populations from 1980 to 1994. The prevalence of asthma has been increasing worldwide primarily in westernized urban populations. Asthma, accounts for 1.6% of all ambulatory care visits (13.7 million) according to the National Ambulatory Medical Care Survey, results in more than 4,70,000 hospitalizations per year (3). According to the 1996 estimate, children below 18 years have the highest prevalence of asthma at 68.6 per 1000 populations. The current overall prevalence in children is estimated at 6.0 – 7.5 percent, with a total of more than five million children affected. Asthma is the fourth-leading cause of disability in children, and one of the most common reasons for school absenteeism. The prevalence in adults is approximately 5%. Asthma prevalence among African-Americans is considerably higher than Caucasians or Hispanics, with Black children having a 26% greater incidence comparison with White children in 1995-1996 (4). Problem of asthma aggravates in industrial countries and still it is increasing in prevalence and severity worldwide. Some chest specialists consider that increase in morbidity in asthma is because currently available therapy may not being used optimally.

The characteristics of Asthma:

It is currently recognised that the asthma may be chronic or acute. The signs and symptoms and characteristic features of most cases of asthma are as follows,

- ◆ Airway obstruction (reversible narrowing of the airways).
- ◆ Airway inflammation with bronchial hyper activity (5).

In Chronic asthma (severe attacks):

- ◆ Breathlessness.
- ◆ Difficulty in talking.
- ◆ Tightening of neck muscle.
- ◆ Grayish or bluish coloring of lips and fingernails.

In Acute asthma (status asthmatics) moderate and mild attacks:

- ◆ Frequent coughing (recurrent night cough, as asthma worsen in night).
- ◆ Coughing after physical activity.
- ◆ Dyspnoea (difficult or labored breathing).
- ◆ Chest tightness and/or shortness of breath, which leads to unexplained irritability.
- ◆ Feeling frightened exhaustion.

Pathophysiology:

Asthma symptoms are produced by reversible narrowing of the airway, which increases resistance to airflow and consequently reduces the efficiency of movement of air to and from the alveoli. In addition to airway obstruction, cardinal features of asthma include inflammation and hyperactivity of the airway. In contrast to chronic obstructive pulmonary disease (emphysema and chronic bronchitis), the airway obstruction associated with asthma is generally reversible. However, severe long lasting asthma changes the architecture of the airway, which includes smooth muscle hypertrophy and bronchofibrosis. This can lead to an irreversible decrement in pulmonary function. The changes are limited to the airways but lung parenchyma is generally spared(5).

Etiology:

Table 1.1: List of agents responsible as triggers in asthma

List of agents	Events triggering asthma
Respiratory infection	Respiratory syncytial virus (RSV), Rhinovirus, Influenza, Para-influenza, Mycoplasma pneumonia
Allergens	Airborne pollens (grass, trees, weeds), house-dust, mites, animal dander, cockroaches, fungal spores
Environment	Cold air, fog, ozone, sulfur dioxide, nitrogen, tobacco smoke, wood smoke
Emotions	Anxiety, stress, laughter
Exercise	Particularly in cold, dry climate
Drugs/preservation	Aspirin, NSAIDs, Sulfites, Benzalkonium chloride, β blocker
Occupational stimuli	Bakers (flour dust), farmers (hay mold), spice and enzyme workers, printers (Arabic gum), chemical workers (azodyes, anthraquinone, ethylenediamine, toluene, diisocyanates, PVC), plastics, rubber and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)

Broad classification:

There are two broad etiologic types of asthma based upon the stimuli initiating extrinsic (allergic/ atopic) and intrinsic (idiosyncratic/non-atopic) (6).

A. Extrinsic (allergic/atopic) asthma:

It is the most common of asthma. It usually begins in childhood or in early adult life. Mostly, patient is having personal and/or family history of allergic disease such as rhinitis, urticaria or eczema. Hypersensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases.

B. Intrinsic asthma:

It develops in adults having no personal and family history of allergy. There is negative skin test and normal serum levels of IgE. Most of these patients develop typical symptom-complex after an upper respiratory tract infection by viruses. Chronic bronchitis is also present. No recognizable allergen but 10% of patients becomes hypersensitive to drugs, specifically (aspirin-sensitive asthma).

Table 1.2: Contracting features of Extrinsic and Intrinsic asthma:

Feature	Extrinsic	Intrinsic
Age of onset	In child hood	In adult
Personal/ family history	Present	Absent
Preceding allergic illness	Present (e.g. Rhinitis, urticaria, eczema)	Absent
Allergens	Present (e.g. dust, pollens danders)	Absent
Drug hypersensitivity	None	Present (Aspirin)
Serum IgE	Increased	Normal
Associated chronic bronchitis	Absent	Present
Emphysema	Unusual	Common

Upon exposure to allergen or triggers, inflammatory process starts. Allergens are taken up by cells called antigen-presenting cells (APC) in the airways. APC binds to the antibody and forms a complex. The complex then attaches to cells such as mast cells that trigger the release of many chemicals from these cells. These released chemicals can stimulate the production of excess amounts of mucus and fluid in the airway, which plug the airway, and create changes in the airway structure.

Another inflammatory pathway contributes to the process by releasing others types of chemicals called leukotriene. Leukotrienes are responsible for mucus secretion, edema formation, and airway muscle contraction.

Acute inflammation and associated symptoms:

Sudden attack of asthma is caused by exposure to allergens, viruses, or indoor and outdoor pollutants (7). Inhaled allergen challenge in allergic patients' leads to an early phase allergic reaction that may be followed by a late phase reaction. Activation of cells bearing allergen-specific IgE initiates the early phase reaction leading to activation of airway mast cells and macrophages. The activated cells release pro-inflammatory mediators such histamine, eicosanoids, and Reactive Oxygen Species causing contraction of airway smooth muscle, mucus secretion and vasodilatation (8). Inflammatory mediators induce microvascular leakage with exudation of plasma in the airway (9). Acute plasma protein leakage induces thicker, engorged and edematous airway wall and narrowing of the airway lumen. Plasma exudation leads to reduced mucus clearance (10).

The late-phase inflammatory reaction occurs 6-9 hours after allergen provocation and involves the recruitment and activation of eosinophils, CD4+ T cells, basophils, neutrophils and macrophages (7). The activation of T cells after allergen challenge leads to the release of T-helper cell type 2-like cytokines that may be a key mechanism of the late-phase response (11). The release of performed cytokines by mast cells is the likely initial trigger for the early recruitment of cells.

Chronic inflammation site and cell survival:

Eosinophilic apoptosis limits inflammatory tissue injury and promotes resolution rather than progression of inflammation (11). Reduction in apoptosis leads to a chronic and self-perpetuating inflammatory cell survival and accumulation. Chronic inflammation may be due to reduction of cell apoptosis leading to a chronic and self-perpetuating inflammatory cell survival and accumulation. There is increased expression of adhesion molecule on epithelial cells. Cytokines and chemokines that are over expressed in asthmatic airway may promote cell survival; these include granulocyte-macrophages-colony stimulating factor, IL-3, IL-5, and IL-8 (12). Antiasthmatic agents may resolve inflammation by causing apoptosis.

Characteristics of chronic inflammation:

In asthma, all cells of the airways are involved and become activated. Included are eosinophils, T cells, mast cells, macrophages, epithelial cells, fibroblasts and bronchial smooth muscle cells. These cells also regulate airway inflammation and initiate the process of remodeling by the release of cytokines and growth factors.(12).

A. Epithelial cells:

Epithelial cells participate in inflammation by release of eicosanoids, peptidases, matrix proteins, cytokines and NO. IgE dependent mechanism, viruses, pollutants and histamines can activate epithelial cells. Epithelial shedding includes increased airway responsiveness, altered

permeability of the airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzyme responsible for degrading proinflammatory neuropeptides (7).

B. Eosinophils:

Eosinophils release proinflammatory mediators, cytotoxic mediators and cytokines. Eosinophils migrate to the airways by cell rolling, through interaction with selectin and eventually adhere to the endothelium through the binding of integrins to adhesion proteins {vascular cell adhesion molecule 1 and intercellular adhesion molecule 1} Eosinophil survival is prolonged by IL-5 and GM-CSF. On activation, eosinophils release inflammatory mediators such as leukotriene and granule proteins to injure airway tissue (7,12).

In the late phase, especially in the development of allergic asthma, eosinophils plays role as an inflammatory cells, as it secretes mediators such as eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDNT), granulocyte macrophage colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), and Prostaglandin (PG), which results in epithelial shedding, bronchoconstriction and promotion of inflammation in respiratory tract (13).

In histopathological samples of patients with asthma, eosinophils can be found clustered around the vagal nerve ganglia in the lung. Eosinophils have been shown to bind to parasympathetic nerve endings in the intracellular molecule receptor. However, the increased presence of eosinophils alone is not the key factor of asthma (7).

C. Lymphocytes

There are two types of T-helper CD4⁺ cells. Th1 produce IL-2 and IFN- γ , both essentials for cellular defense mechanism. Th2 produce IL-4, IL-5, IL-6, IL-9, and IL-13, that mediates allergic inflammation. Mucosal-biopsy specimens obtained from patients during an episode of asthma after the inhalation of allergen contain lymphocytes, many of which express surface markers of activation. In mice, there are two types of helper CD4⁺ T cells. In simple terms, type1 helper T (Th1) cells produce interleukin-2 and interferon- that are essential for cellular defense mechanisms. In contrast, type 2 helper T (Th2) cells produce cytokines (interleukin-4, 5, 6, 9, and 13) that mediate allergic inflammation. Furthermore, there is reciprocal inhibition, in that Th1-type cytokines inhibit the production of Th2-type cytokines and vice versa. CD8⁺ T cells may also be classified in a similar fashion according to their cytokines profiles (Tc1 and Tc2). Allergic asthmatic inflammation results from Th2 mediated mechanism. Thus Th1/ Th2 imbalance is a cause of asthma (12).

D. Mast cells:

Mast cells degranulation is important in the initiation of immediate responses following exposure to allergens (7). Almost 3-5 times increase in mast cells in-patient of asthma. Once binding of allergen to cell-bound IgE occurs, mediators such as histamine, eosinophils, neutrophils, chemotactic factor LTC₄, LTD₄, and LTE₄, PG, and PAF etc. are released from mast cells. Mast cell degranulation is believed to be an integral cause of exercise-induced bronchospasm following either drying or cooling of the airways (16).

E. Alveolar macrophages:

They act as scavenger' engulfing and digesting bacteria and other foreign material. PAF, LTB₄, LTC₄, LTD₄ are produced by macrophage and produce inflammation. Additionally, alveolar macrophages are able to produce neutrophils chemotactic factor and eosinophil chemotactic factor, which in turn further the inflammatory process(9).

F. Neutrophils:

High numbers of neutrophils have been reported to be present in the airways of patients who died from sudden-onset fatal asthma. This suggests that neutrophils may play a pivotal role

in the disease process. Neutrophils are source for a variety of mediators' viz. PAF, PGs, TXs, LTs causing Bronchial Hyper Responsiveness and airway inflammation (17).

G. Inflammatory mediators:

Mast cell degranulation releases interleukins, proteases and other enzymes. Several classes of important mediators, including arachidonic acid and its metabolites are derived from cell membrane phospholipids. Once AA is released, it can be broken down by Cox, to form prostaglandin. PGD₂ is potent bronchoconstricting agent. PGD₂ and PGD₂α are important inflammatory mediators. TXA₂ is produced by alveolar macrophages, fibroblast, epithelial cells, neutrophils, and platelets within the lung. TXA₂ have effects, including bronchoconstriction, involvement in the late asthmatic response, and involvement in the development of airway inflammation and BHR. 5-lipoxygenase pathway of arachidonic acid breakdown is responsible for production of cysteinylleukotrienes (LTC₄, LTD₄, and LTE₄) that constitute the slow-reacting substance of anaphylaxis. When stimulated, they produce bronchospasm, mucus secretion, microvascular permeability and airway edema (7).

H. Adhesion molecules:

Adhesion molecules are important to promote adhesion of various cells to each other and tissue matrix to facilitate infiltration and migration of these cells to the site of inflammation. Those important in inflammatory process are integrins, Ig supergene family, selections and carbohydrate ligand including ICAM-1 and VCAM-1. Various inflammatory mediators activate adhesion molecules. Upon complex interaction, mediators affect expression of adhesion molecules and adhesion molecules produce mediators. A major role of adhesion molecules is in the recruitment of leukocytes from the vascular lumen to tissue. The initial step involved in this leukocyte-endothelial cell adhesion cascade is transient and reversible binding of the adhesion molecule to specific ligands on endothelial cells. (12).

Clinical consequences of chronic inflammation:

A. Remodeling of the airways:

Acute inflammation is a beneficial, nonspecific response of tissues to injury and generally leads to repair and restoration of the normal structure and function. In contrast, asthma represents a chronic inflammatory process of the airways followed by healing. The end result may be an altered structure referred to as a remodeling of the airways (14). Repair involves replacement of injured tissue by parenchyma cells of the same type and replacement by connective tissue and its maturation into scar tissue. In asthma, the repair process can be followed by complete or altered restitution of airways structure and function, presenting as fibrosis and an increase in smooth muscle and mucus gland mass.

B. Mucus production:

The mucosiliary system is the lung's primary defense mechanism against irritants and infectious agent. Bronchial epithelial glands and goblet cells produce mucus, composed of 95% water 5% glycoprotein. Mucus either too viscous or too watery will not be transported optimally. The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucosiliary transport. The bronchial glands are increased in size and the goblet cells are increased in size and number in asthma. Expectorated mucus from patients with asthma tends to have a high viscosity (14).

C. Neural control / Neurogenic inflammation:

The airway is innervated by parasympathetic, sympathetic and noradrenergic inhibitory nerves.

The normal resting tone of human airway smooth muscle is maintained by vagal efferent activity. The nonmyelinated C fibers of the afferent system lie immediately beneath the tight junction between epithelial cells lining the airway lumen. These endings probably represent the irritant receptors of the airways. Stimulation of these irritant receptors produces reflex bronchoconstriction.

The airway smooth muscle contains β_2 adrenergic receptors that produce bronchodilation. Major resistance airways contain α - adrenergic receptors whose stimulation produces bronchoconstriction that is enhanced by pretreatment with histamine. One theory on the pathogenesis of BHR is that asthma represents a relative β - adrenergic blockade.

The nonadrenergic, noncholinergic nervous system has been described in the trachea and bronchi. Substance P, neurokinin A, neurokinin B, Vasoactive Intestinal Peptide is the best-characterized neurotransmitters in the NANC nervous system. VIP is an inhibitory neurotransmitter. Inflammatory cells in the asthma can release peptidases that can degrade VIP, producing exaggerated reflex cholinergic bronchoconstriction. The NAVC system may play an important role in amplifying inflammation in asthma by releasing NO (14).

Further identification of various types of asthma:**A. Chronic asthma:**

Asthma has a widely variable presentation from chronic daily symptoms to only intermittent symptoms. The interval between the symptoms could be weeks, months or years. It is a disease characterized by recurrent exacerbations and remissions (7).

B. Acute severe asthma:

Uncontrolled asthma, with its inherent variability, can progress to an acute state where inflammation, airways edema, excessive accumulation of mucus and severe bronchospasm result in a profound airways narrowing that is poorly responsive to usual bronchodilator therapy (18). Hyper acute attacks are associated with neutrophilic as opposed to eosinophilic infiltration and resolve rapidly with bronchodilator therapy, suggesting that smooth muscle spasm is the major pathogenic mechanism (19). Underutilization of anti-inflammatory drugs and excessive reliance on short acting inhaled β agonists are the major risk factors for severe exacerbation.

Table 1.3: Severity of asthma according to the symptoms

	Symptoms	Lung function
Step 1	Day time ≤ 2 times/ week	FEV1 or PEF ≥ 80 %
Mild intermittent	Asymptomatic	PEF variability < 20 %
	Brief exacerbation	
	Nocturnal ≤ 2 times/month	
Step 2	Day time > 2 times/week,	FEV1 or PEF $\geq 80\%$
Mild persistent	$< once a day$	PEF variability 20-30%
	Asymptomatic	
	Brief exacerbation	
	Nocturnal > 2 times/month	
Step 3	Daily symptoms	FEV1 or PEF 60-80%
Moderate persistent	Asymptomatic	PEF variability $> 30\%$

	Exacerbation ≥ 2 times/ week	
	Exacerbation affect activity	
	Nocturnal > once a week	
Step 4	Continual symptoms	FEV1 or PEF $\leq 60\%$
Severe persistent	Limited physical activity	PEF variability >30%
	Frequent exacerbation	
	Nocturnal frequent	

C. Allergic asthma:

When allergic asthmatics are given an inhalational challenge with an allergen to which they are sensitized, the patients demonstrate an early-phase asthmatic reaction, characterized by a drop in pulmonary function. Many Subject experience a late phase asthmatic reaction that begins 4 hours after the challenge, reaches maximum intensity in 6-9 hours and is often more severe than the EAR, and may last as long as 24 hours. The late asthmatic reaction may be the pathogenic mechanism for inducing and maintaining BHR in atopic asthmatics (7).

D. Exercise-Induced bronchospasm:

Some patients developed wheeze that regularly follows within a few minutes of exercise. A similar response occurs following the inhalation of cold air since the common mechanism appears to be airway drying. During vigorous exercise, pulmonary function in asthmatic patients increases during the first few minutes but then begins to decrease after 6-8 minutes. EIB is defined as a drop in FEV1 of greater than 15%-16% of baseline. 70-90% asthmatics experience EIB. Heat loss and/or water loss from the central airways to play an important role. EIB is more easily provoked in cold, dry air (16).

E. Nocturnal asthma:

Worsening of asthma during sleep is referred to as nocturnal asthma. Patients with nocturnal asthma exhibit significant falls in pulmonary function between bedtime and awakening. It has been associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine.

F. Drug induced asthma:

Several pharmacological agents provoke asthma. Aspirin- sensitive asthma is an uncommon, yet fascinating type, occurring in patients with recurrent rhinitis and nasal polyps. These individuals are very sensitive to small doses of aspirin, and they experience not only asthmatic attacks, but also urticaria. It is probable that aspirin triggers asthma in these patients by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thus tipping the balance towards elaboration of the bronchoconstrictor leukotriene.

Current status of treatment of asthma:

As outlined by the National Asthma Education Program's Guidelines for the Diagnosis and Management of Asthma, the treatment should have the following goals (7).

1. Maintain normal activity levels, including exercise.
2. Maintain normal or near normal pulmonary function.
3. Prevent chronic and troublesome symptoms.
4. Prevent recurrent exacerbation.
5. Avoid adverse effects from medications.

1. β -Adrenergic receptor agonist:

The β 2-agonists are the most effective bronchodilators available and first treatment of choice for acute severe asthma. It causes direct relaxation of airway smooth muscle causing bronchodilation. Bronchial smooth muscle contains large no. of β 2-adrenergic receptors. β 2-agonists provide symptomatic relief only. Albuterol, levalbuterol, metaproterenol, terbutalin, bitolterol, pirbuterol, formoterol, salmeterol are the classical examples of selective β 2 adrenergic agonists (20).

2. Methylxanthines:

Methylxanthines inhibit cyclic nucleotide phosphodiesterase (PDE), thereby producing bronchodilation. PDE catalyze breakdown of cAMP and cGMP. Inhibition of PDE leads to accumulation of cAMP and cGMP that leads to increased signal transduction. Theophylline, aminophylline are examples of this class (21,22,23).

3. Anticholinergics:

Anticholinergics are competitive inhibitors of muscarinic receptors. They produce bronchodilation in cholinergic mediated bronchoconstriction; they are not the functional antagonists. Ipratropium bromide, tiotropium, oxitropium, revatropate, darifenacin are examples of this class. (24).

4. Corticosteroids:

The corticosteroids are the most effective anti-inflammatories available to treat asthma. Hydrocortisone, prednisone, methyl prednisone, dexamethasone, fluticasone, beclomethasone dipropionate, budesonide, flunisolide, triamcinolone acetonide are the examples of this class.

5. Cromolyn sodium and Nedocromil sodium:

They are available for the prophylactic treatment. They are mast cell stabilizer and itself have no direct bronchodilator action. Nedocromil is more potent. (25,26).

6. Phosphodiesterase inhibitors:

Considerable interest has been generated in the potential utility of isoenzyme-selective inhibitors of cyclic nucleotide phosphodiesterase (PDE) in the treatment of asthma and other inflammatory disorders. Most of the work now is focused on selectively targeting PDE4, primarily because inhibitors of this isoenzyme family have a notably appealing therapeutic profile: broad spectrum anti-inflammatory activity coupled with additional bronchodilatory and neuromodulatory action, Rolipram, LAS-31025, RP-73401 and denbufylline are selective PDE4 inhibitors. SB 207499, V11294A, CP-220 and Roflumilast are PDE4 inhibitors with less gastrointestinal side effects (27,28).

7. Leukotriene modifiers:

Formation of leukotrienes from arachidonic acid results from cell stimulation, such as an inflammatory stimulus. This could occur due to an antigen-antibody interaction or an altered ionic environment that would cause phospholipase A2 to cleave arachidonic acid from the membrane. 5-lipoxygenase translocates from the euchromatin of the nucleus to the nuclear membrane, where it interacts with 5-LO activating protein (FLAP). The arachidonic acid is then oxygenated and subsequently, dehydrated to form LTA4. This is then metabolized to LTC4, LTD4, and subsequently to LTE4. Leukotriene modifiers are drugs that modify the response of these mediators of inflammation by one of the four ways (29,30,31).

a) Cysteinyl LT receptor inhibitors: -

They antagonize or inhibit leukotriene predominantly LTD4. These agents inhibit phospholipids, prostaglandins, leukotrienes, and IL-1 synthesis. Probenzocaine and Irabekast belong to this class

(29,32,33). LTs increase microvascular leakage, increase mucus production and increase eosinophils and basophiles influx in airways.

b) 5-lipoxygenase inhibitors:-

They prevent the formation of leukotrienes by blocking a pathway in their synthesis. Zileuton, ZD-2138, Abt-761 belongs to this class (34).

c) 5-lipoxygenase activating protein (FLAP) inhibitors:-

MK-0591, BAY x 1005, MK-886.

d) Leukotrienes receptors antagonists:-

Montelukast, Zafirlukast, Pranlukast are selective and high-affinity LT1 antagonists. Antileukotrienes improve lung function and diminish symptoms, exacerbation rate and the need for rescue bronchodilator. These agents are drugs of choice in treatment of specific disease subtype, like aspirin induced asthma in which patients have LTE4 levels in urine and even higher after taking aspirin (35).

8. Endothelin modulators:

ET-1 is a 21-amino acid peptide isolated from cultured endothelial cells. The diverse biological effects of ET-1 are mediated via two receptors, designated as ETA and ETB, which belongs to the super family of G-protein coupled receptors. There are two approaches for ET-1 directed therapeutics – (1) Inhibitors of endothelin-converting enzyme (ECE), which mediates the synthesis of ET-1 from its precursor. (2) Receptor antagonists of the effects at the end-organ level. These agents reverse and/or prevent the increase in pulmonary artery pressure and vascular remodeling elicited by acute or chronic hypoxia. Examples are BQ-123, SB217242 and bosentan(36).

9. PAF inhibitors:

Platelet activating factor is a mediator of inflammation and bronchoconstriction that, in addition, increases mucus secretion and recruits platelets and eosinophils from the extracellular space into the lungs (36).

10. TXA2 inhibitors:

TXA2 is potent bronchoconstriction, mucus producer and blood and vessel permeability inducer and causes airway hyper responsiveness. Serabenas, domitroban and ozagrel are the examples (37).

11. Tachykinin receptor antagonists:

The effects of the tachykinins induced by activation of neurokinin-1 receptors in the lung include mucus secretion, microvascular permeability and inflammatory cell recruitment and activation. CP-96, 345 is a potent nk-1 receptors antagonist. SR 48968, GR159897 and SR 142190 are selective nonpeptide NK-2 receptor antagonists. SR 142801 and SB 223412 is selective NK-3 receptor antagonist. The most prominent effect of NK-2 receptor activation in the lung is bronchospasm, in addition to activation of alveolar macrophages, neurogenic inflammation and potentiation of nerve-induced responses (38).

12. Trypsin inhibitors:

They inhibit both early and late reactions. APC-366 and BAY-17 are examples of this class.

13. Vary Late Antigen inhibitors:

VLA-4 is integrin receptor on eosinophils, basophils and lymphocytes but not on neutrophils. This specificity makes it a more selective agent for the allergic response. VLA-4 inhibitors are effective in inhibiting allergic inflammation in the late reaction (39).

CONCLUSION:

Asthma no longer can be viewed simply as reversible airway obstruction but should be viewed primarily as an inflammatory illness that has bronchial hyper activity and bronchospasm as result. This recognition has been based on studies in human beings, i.e., increased number of inflammatory cells like eosinophil, macrophages and lymphocytes found in bronchoalveolar lavage fluid from asthmatic patient (with and without asthma exacerbation and normal baseline lung function) as compared to that from normal individual. It is true for both allergic and non-allergic asthmatic subjects. In these patients, exposure to allergens is partially or substantially responsible for their asthmatic inflammation via immediate hypersensitivity-type reactions.. Inflammation is a major cause for chronic asthma. Inflammation of the airway may be related to immunomodulatory process. Since there are growing evidences for extensive communication between neurons and immunomodulatory cells, the mechanism of this neuro-immune cross talk in lungs and airway of asthmatic patient are becoming the focus of asthma research.

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