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Effect of Monteleukast and Inhaled Corticosteroids in Asthma Disease: A Systemic Review

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Abstract
Asthma is a chronic inflammatory disorder of the airways characterized by recurrent symptoms associated with airflow limitation and by bronchial hyper responsiveness. Inhaled corticosteroids, which suppress airway inflammation, are efficient in reducing symptoms and exacerbations, and often normalize lung function. The most commonly used drugs like monteleukast and budesonide (inhaled corticosteroids) are given for the treatment of Asthma. The diagnosis is confirmed with the spirometry, chest x-Ray, FEV1 (forced expiratory volume in one second). Patients have been carefully assessed and characterized in terms of diagnosis, severity of asthma, aggravating factors and associated diseases. Inhaled rapid-acting β_2- agonists are the preferred reliever medications for the treatment of acute symptoms, and should be prescribed to all patients with asthma. ICSs are the most effective anti-inflammatory medications available for the treatment of asthma and represent the mainstay of therapy for most patients with the disease. Antileukotrienes are a new class of anti-inflammatory agents which either interfere with the leukotriene receptors or leukotriene production.

Keywords: Antileukotrienes, FEV1, Spirometry, Inhaled Corticosteroids, Asthma.

1. Introduction
The optimal treatment for mild asthma is uncertain. We showed the effects of adding monteleukast to an inhaled corticosteroid, budesonide, in subjects with mild asthma. in corticosteroid-free patients, low dose inhaled budesonide alone reduced severe exacerbations and improved asthma control, and in patients already receiving inhaled corticosteroid, adding monteleukast was more effective than doubling the corticosteroid dose [1]. As a consequence, inhaled corticosteroids are a first-line therapy in the control of symptoms and the prevention of long-term airway remodeling. This rationale has led to increased use of inhalers Patients with mild-to-moderate persistent asthma using fixed combinations of corticosteroids and long-acting β_2-agonists (LABAs) [2]. Inhaled corticosteroids (ICS) affect many inflammatory pathways in asthma but have little impact on cyteinyl leukotrienes. This may partly explain persistent airway inflammation during chronic ICS treatment and failure to achieve adequate asthma control in some patients. ICS represents a gold standard in anti-inflammatory treatment. Research into the pathogenesis of asthma has led to the development of specific anti-inflammatory treatments, including montelukast, which blocks the interaction of cysteinyl leukotrienes with their receptor and resulting downstream events. Since montelukast attenuates leukotriene mediated effects, combination therapy with montelukast and ICS represents a theoretical alternative to increasing the ICS dose in patients inadequately controlled on ICS alone [3]. Leukotriene modifiers, including leukotriene receptor antagonists (LTRA), are a relatively new class of antiasthmatic drugs. Evidence exists that LTRA, by blocking the leukotriene receptors of the smooth airway muscles, reduce airway eosinophilic inflammation and alleviate symptoms of airway obstruction [4].

Inhaled corticosteroids
Inhaled corticosteroids are taken using an inhaler (or pump).Those brands that come in a metered dose inhaler should be used with a spacer. A spacer is a plastic tube or bag you attach to your pump to help get the medicine to your airways. The few brands that come in a dry powder inhaler do not require a spacer. There is also one brand that can be used with a nebulizer machine. Inhaled medicines go right to the lungs and cause fewer side effects than medicine taken by mouth, like pills or liquid [5]. Inhaled corticosteroids play an important

role in the management of obstructive airway disease. In asthma, strong clinical evidence supports the use of inhaled corticosteroids in mild, moderate, and severe persistent asthma to improve lung function, reduce exacerbations and prevent death [6].

- Beclomethasone propionate HFA
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone furoate
- Fluticasone propionate
- Mometasone
- Triamcinolone Acetonide
- Budesonide with formetrol

Budesonide
Brand name: Budecort Inhaler
Manufacturer: Cipla Pharmaceuticals
Generic name: Budesonide
Indication: Bronchial asthma, COPD
Dose: Adults
- 200 mcg 2 oral inhalations twice daily, in the morning and in the evening.
- During periods of severe asthma the daily dosage can be increased up to 1600 micrograms.
- In patients whose asthma is well controlled, the daily dose may be reduced below 400 micrograms but should not go below 200 micrograms.

Dose: Children
-200–800 mcg daily, in divided doses.
-The dose should be reduced to the minimum needed to maintain good asthma control

Route of administration: Oral inhaler
Contraindication:
-History of hypersensitivity to budesonide or any of the excipients, Status asthmaticus or acute episodes of asthma or COPD, Primary treatment

Side effects
-Gastrointestinal: Oral candidiasis, stomach ache, vomiting
-Musculoskeletal: Back ache
-Neurological: Headache
-Respiratory Nasal congestion, Nasopharyngitis, Pain in throat, sinusitis.

Drug interaction
-Acebutol, Atenolol, Isocarboxazid, Metoprolol, seligiline, Timolol

Storage: 20-25 ^{0}c, avoid to exposure of light (up to date, NFI).

Monteleukast
Brand name: Monatair, Montek.

Manufacturer: Montair (Cipla Pharmaceuticals), Montek (Silom medical)

Generic name: Monteleukast.

Indication: Bronchial asthma, Exercise induced Asthma, Prophylaxis, seasonal allergic rhinitis, perennial allergic rhinitis.
Dose: **Adult:** Asthma: One 10mg orally in evening
-Exercise induced asthma, Prophylaxis: 10mg orally 2 hr before exercise.

Dose: Pediatrics
-12-23 months 4mg granules orally.
-Age 2-5 yr one 4mg chewable or granules in the evening
-6-14yr 5mg orally in the evening

Route of Administration: Oral Granules, coated tablets and chewable tablet.

Contraindication: Hyper sensitivity to any component of the product, pregnancy and lactation.

Side effects: Headache, Cholestatic hepatitis, Altered behavior, aggressive behavior

Drug interaction: Gemfibrozil, Prednisone

Storage: Store between 59^{o} and 86^{o}, protect from moisture and light (up to date, NFI)

Asthma
Asthma is a chronic inflammatory condition of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing [7]. When a person with asthma is exposed to an asthma trigger, the airway lining becomes inflamed and begins to swell, making it difficult to breathe. The disease can vary in severity from one person to another and for each individual over time. A person having an asthma "attack" will often feel short of breath, tight-chestness and may cough or wheeze [8].
Asthma is clinically characterized by followimg:
- Airway inflammation: The airway lining becomes red, swollen, and narrow.
- Airway obstruction: The muscles encircling the airway tighten causing the airway to narrow making it difficult to get air in and out of the lungs.
- Airway hyper-responsiveness: The muscles encircling the airway respond more quickly and vigorously to small amounts of allergens and irritants.

Epidemiology
Approximately 22.5 million Americans had asthma in 2005, conferring an estimated financial burden of $19.7 billion in annual health care costs [9]. In 2005, nearly 1.8 million patients with asthma were treated in emergency departments (EDs). The ED was the portal of admission for 50.2 percent of all non-obstetric admissions in the United States in 2006, an increase from 36.0 percent in 1996 [10]. Approximately 2% to 20% of admissions to intensive care units (ICUs) are attributed to severe asthma, with intubation and mechanical ventilation deemed necessary in up to one third in the ICU and mortality rates in patients receiving intubation from 10% to 20% in this patient population [11]. According to the reality of Asthma Control (TRAC) in Canada suggests over 50% of Canadians with asthma have uncontrolled disease [12].

Etiology
Factors that influencing the risk of asthma can be divided into those that cause the development of asthma and that

trigger symptoms (Table no.1). The former include host factor (genetic) and the latter are usually environmental factor [13].

Pathophysiology

- **Bronchoconstriction.** In asthma, the dominant physiological event interference with airflow which causes airway narrowing [14]. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle [15]. Aspirin and other nonsteroidal anti-inflammatory drugs can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells [16]. In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines. [17]
- **Airway edema.** Bronchospasms, edema, excessive mucus and epithelial and muscle damage can lead to bronchoconstriction with bronchospasm. Defined as sharp contractions of bronchial smooth muscle, bronchospasm causes the airways to narrow; edema from micro vascular leakage contributes to airway narrowing. Airway capillaries may dilate and leak, increasing secretions, which in turn causes edema and impairs mucus clearance [18].
- **Airway hyper responsiveness**. Airway hyper responsiveness—an exaggerated bronchoconstrictor response to a wide variety of stimuli—is a major, but not necessarily unique, feature of asthma. Seasonal variations in the house dust mite allergen load and air pollution are paralleled by fluctuations in BHR, with higher house dust mite and air pollution levels being associated with increased responsiveness. Treatment directed toward reducing inflammation can reduce airway hyper responsiveness and improve asthma control [19, 20].

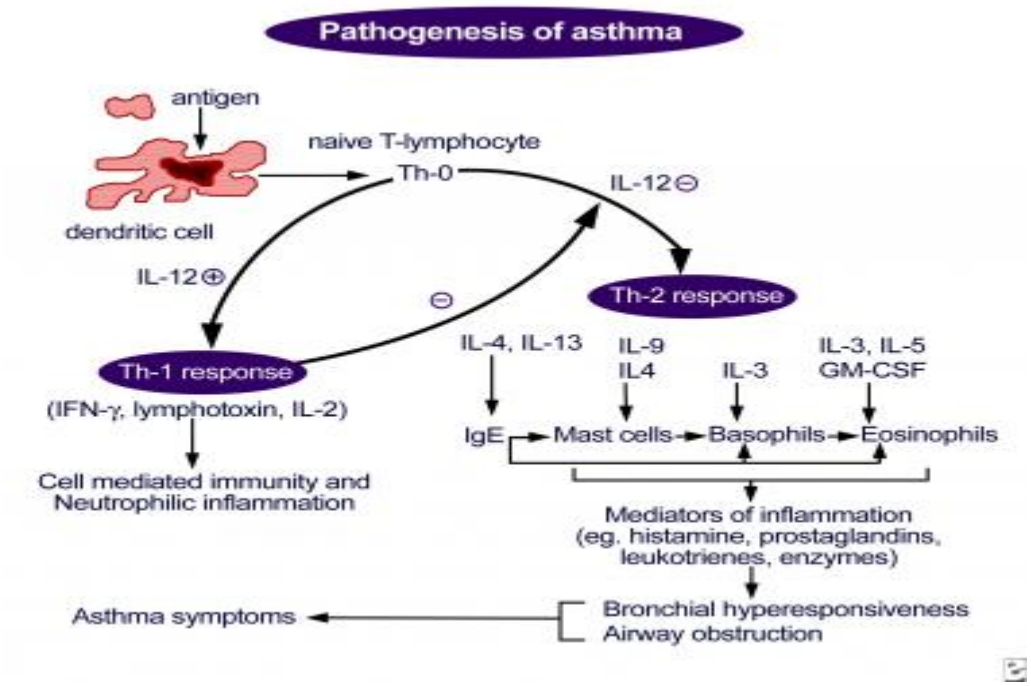

Fig 1: Pathogenesis of Asthma

- **Airway remodeling**. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy. These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion. Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response [20].

Common signs and symptoms of an acute asthma episode include:

- Coughing
- Wheezing - may be absent
- Breathlessness - while walking or while at rest
- Respiratory rate increased
- Chest tightness
- Chest or abdominal pain
- Fatigue, feeling out of breath
- Agitation
- Increased pulse rate
- Inability to participate in sports

Diagnosis

Lung Function

- Spirometry (FEV1) – preferred, FEV1 /FVC preferred in children
- Pulse oximetry

Physical Exam

- Vital signs: Temperature, blood pressure, pulse rate, respiratory rate, pulsus paradoxus
- Alertness
- Ability to talk
- Use of accessory muscles
- Auscultation of chest
- Color

Laboratory Studies: Treatment with bronchodilators should not be delayed for laboratory studies. Tests which may be useful include:

- Arterial blood gases (ABG's)
- Chest x-ray (CXR)
- Complete blood count (CBC)
- Electrocardiogram (EKG) Electrolytes
- Theophylline level (if appropriate)

Treatment

There are two categories of antiasthma drugs: bronchodilators and anti-inflammatory agents. Bronchodilators reverse the Bronchospasms of the immediate phase; anti-inflammatory agents inhibit or prevent the inflammatory components of both phases [21].

Specific five therapeutic steps for adults and children with chronic asthma

Step 1: Very mild disease may be controlled with short-acting bronchodilator alone.

Step 2: If patients need this more than once a day a regular inhaled corticosteroid should be added.

Step 3: If the asthma remains uncontrolled, the next step is to add a long-acting bronchodilator (salmeterol or formoterol); this minimises the need for increased doses of inhaled corticosteroid.

Step 4: For patients with more severe asthma who remain symptomatic and/or the dose of inhaled corticosteroid increased to the maximum recommended that patient needs Theophylline and leukotriene antagonists, such as montelukast, also exert a corticosteroid-sparing effect, but this is less reliable so one or other is added.

Step 5: If the patient's condition is still poorly controlled, it may be necessary to add a regular oral corticosteroid e.g: Prednisolone.

Bronchodilator Therapies

1. **Inhaled β_2-agonists:** Inhaled short-acting b2-agonists (salbutamol, fenoterol and terbutaline) are the most effective bronchodilators for patients with asthma, regardless of age. Their main therapeutic action is represented by a rapid (within 10 min) bronchial smooth muscle relaxation that persists over 4–6 h [22].
2. **Anticholinergics:** Anticholinergic antimuscarinic compounds, including atropine, had been used in the treatment of asthma for long; though their use was accompanied by the frequent occurrence of side effects, including decreased urinary flow rate and increased intraocular pressure, that represented an important limitation to their use particularly in the elderly population where the prevalence of prostatic diseases and glaucoma is high [23].
3. **Methylxanthines:** The three important methylxanthines are theophylline, the obromine, and caffeine. Their major source is beverages (tea, cocoa, and coffee, respectively). The importance of theophylline as a therapeutic agent in the treatment of asthma has waned as the greater effectiveness of inhaled adrenoceptor agents for acute asthma and of inhaled anti-inflammatory agents for chronic asthma has been established, but theophylline's very low cost is an important advantage for economically disadvantaged patients in societies where health care resources are limited [24].

Controller Therapies

1. **Inhaled corticosteroids:** ICS are the most effective controllers of asthma. They suppress inflammation mainly by switching off multiple activated inflammatory genes through reversing histone acetylation via the recruitment of histone deacetylase 2 (HDAC2). Through suppression of airway inflammation ICS reduce airway hyperresponsiveness and control asthma symptoms. ICS are now first-line therapy for all patients with persistent asthma, controlling asthma symptoms and preventing exacerbations. Inhaled long-acting β2-agonists added to ICS further improve asthma control and are commonly given as combination inhalers, which improve compliance and control asthma at lower doses of corticosteroids. By contrast, ICS provide much less clinical benefit in COPD and the inflammation is resistant to the action of corticosteroids. This appears to be due to a reduction in HDAC2 activity and expression as a result of oxidative stress. ICS are added to bronchodilators in patients with severe COPD to reduce exacerbations. ICS, which are absorbed from the lungs into the systemic circulation, have negligible systemic side effects at the doses most patients require, although the high doses used in COPD has some systemic side effects and increases the risk of developing pneumonia [25].
2. **Systemic Corticosteroids:** Corticosteroids are used intravenously (hydrocortisone or methylprednisolone) for the treatment of acute severe asthma. A course of oral corticosteroids (usually prednisone or Prednisolone 30-45 mg/day, for 5-10 days) is used to treat acute exacerbations of asthma; no tapering of the dose is needed.
3. **Antileukotrienes:** cold dry air challenge (CACh) is hypothesized to stimulate the release of inflammatory mediators. Suggestive evidence indicates that the cysteinyl leukotrienes (cys-LT) may be involved in the constrictor response to CACh, since inhibition of a precursor enzyme (5-lipoxygenase [5-LO]) was associated with an increased tolerance to cold, dry air in adult asthmatic individuals. The specific leukotriene receptor antagonist (LTRA) montelukast on the

bronconstrictor response to CACh in 3- to 5-yrold asthmatic children [26].

4. **Chromones:** Cromolyn sodium and nedocromil sodium are asthma controller drugs that appear to inhibit mast cell and sensory nerve activation, and are therefore effective in blocking trigger-induced asthma, such as EIA, and allergen- and sulfur dioxide–induced symptoms [27].

5. **Omalizumab** is a blocking antibody that neutralizes circulating IgE without binding to cell-bound IgE; it thus inhibits IgE-mediated reactions. Omalizumab is usually given as a subcutaneous injection every 2-4 weeks and appears not to have significant side effects [28].

Table 1: Etiology of Asthma

Endogenous factor	Environment factor	Trigger factor
• Genetic predisposition • Atopy • Airway hyper responsiveness • Gender	• Indoor allergens • Outdoor allergens • Occupational sensitizers • Passive smoking • Respiratory infections	• Allergens • Upper respiratory tract viral infections • Exercise and hyperventilation • Cold air • Sulphur dioxide, drugs(Aspirin, □□blockers) • Irritants(paints, fumes, sprays)

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