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A Review of the Pathogenesis of Pediatric Asthma and the Effect of Leukotriene Modifiers in Pediatric Asthma Management

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ABSTRACT

Background: Asthma is the most common chronic illness that affects children**.** It is described by chronic airway inflammation, remodeling of the airway wall, and airway hyper-responsiveness to non-specific spasms in response to stimuli causing a reversible airflow obstruction. Leukotrienes are one of the primary chemical mediators of inflammation in asthmatic airway, therefore leukotriene modifiers are an important class of drug for treating asthma. **Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1981, through February 2017. The following search terms were used: *asthma pathophysiology, chemokines, leukotriene, leukotriene modifiers, Montelukast in asthma management* **Aim:** our aim was to understand in depth the pathophysiology of pediatric asthma, and to study the effect of leukotriene modifiers in asthma management. **Conclusion:** For management of pediatric asthma, the leukotriene modifiers play a key role. New studies have shown that they could help in reducing dose and dependency on inhaled corticosteroid for maintenance, and decrease the need of systemic steroids in exacerbation. Leukotriene modifiers can have a positive impact on future asthma management and requires more studies to be done in this subject**.**

Keywords: pediatric asthma, asthma pathophysiology, leukotriene modifiers for asthma management

INTRODUCTION

Pediatric asthma is a disorder in children characterized by recurrent airway obstruction, airway inflammation, and bronchial hyper-responsiveness. Asthma is the most common chronic illness that affects children, which roughly is seen in 8.5% of children in the United States. Asthma is more prevalent in males in early years of life, but more commonly seen in females in adolescence. The global death rate from asthma is around 0.7 per 100 000 children[1].It is also one of the most common causes of a large number of school absences, thus impairing a child's academic and social achievement. Asthma can be classified as allergic (extrinsic) or non-allergic (intrinsic) based on the type of trigger.

Common triggers that cause extrinsic asthma are plant pollen, fur, dust mites, cigarettes smoke both active and passive, food substances, certain chemicals, perfumes, and fumes. Triggers that may induce an intrinsic asthma are released from within the body mostly due to viral or bacterial infection. Physical or emotional stress can also cause one to have asthma symptoms[2]. Coughing and wheezing are the most common symptoms children present with. Other symptoms are sudden shortness of breath during asthma attacks, chest tightness, and dyspnea after physical activity. The symptoms happen episodically, and may occur at night too. Asthma is diagnosed with the presence of symptoms and pulmonary function test. Demonstration of airways obstruction and its reversibility (which is indicated by increase of more than 12% and 200 ml increase in FEV1) after inhaling a bronchodilator is recommended to confirm the clinical diagnosis[3].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1981, through February 2017. The following search terms were used:

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.The study was done after approval of ethical board of King Abdulaziz University.

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Pathophysiology of Asthma

Asthma is described by chronic airway inflammation, remodeling of the airway wall, and airway hyper-responsiveness to non-specific spasms in response to stimuli causing a reversible airflow obstruction. Allergic illnesses, comprising allergic rhinitis and asthma, are chronic inflammatory disorders with a fundamental Th2 immune response. Inhalation of allergens causes bronchial hyper-reactivity and enrollment of eosinophils, lymphocyte, and mast cells in the upper and lower airways, activating the inflammatory cascade and producing local and systemic inflammatory reactions[4]. The inflammatory process is mostly limited to the conducting airways but as the disease converts to severe and chronic forms, the inflammatory infiltrate ranges both proximately and distally to comprise the small airways and adjacent alveoli. The inflammatory response in the small airways seems to be mainly external to the airway smooth muscle, although in the big airways inflammation of the submucosa takes over. Many factors are important to the pathogenesis of asthma and its subsequent airflow obstruction[5].

Sensitization and T cell response

Asthma begins from childhood with respect to sensitization to various inhaled allergens, such as house dust mites, fungi, pollen, cockroaches, and animal dander. These inhaled allergens trigger T helper type 2 (Th2) cell proliferation, consequently Th2 cytokines, interleukin (IL)-4, IL-13 and IL-5 production and release in blood. A fundamental character of allergen sensitization is the processing of inhaled allergens by dendritic cells located in the airway epithelium and submucosa. Allergen uptake is improved by IgE bound to high-affinity receptors on those dendritic cells that enable allergen internalization[6].

The capability of dendritic cells to produceIL-12 defines the balance among Th1 and Th2 responses. Nonetheless, while IL-12 is able to neutralize Th2 sensitization, it is also able to add to utmost expression of allergic airway disease after sensitization. After sensitization occurs, T cells migrate back to the airways to the site of dendritic cells under the influence of the chemokines[7].They also turn into potent producers of a various types of cytokines, such as IL-3, IL-4, IL-5, IL-6, IL-9, IL-13 and granulocyte–macrophage colony-stimulating factor. IL-1β is produced by macrophages, dendritic cells, monocytes, smooth muscle and epithelial cells in huge amounts, while IL-2 produced by T cells additionally boosts antigen-induced T-cell proliferation and maturation[8].

Mast Cells

On activation, mast cells release already-made granule which contains substances such as histamine, tryptase, heparin and cytokines, along with newly formed eicosanoids that comprise platelet derived growth factor (PGD2), thromboxane A2, and the cysteinyl leukotriene (CysLT) specially LTC4 and LTD4. These mediators are strong smooth muscle contractile mediators and also upsurge microvascular permeability[9].Both PGD2 and LTD4 cooperate with cell-surface receptors on eosinophils, macrophages, mast cells, and basophils where they function as chemo-attractant and priming agents. Therefore, CysLT antagonists such as montelukast and pranlukast block the acute effects of leukotrienes on the airway, and further, show some anti-inflammatory effect[10].

Stimulation of mast cells, predominantly by the high-affinity IgE receptor, leads to the release of some cytokines that are formed within mast cell granules, namely tumor necrosis factor α, IL-4 and IL-5. These cytokines and chemokines certainly contribute to the continuing inflammatory response in asthma. They may be somewhat accountable for the allergen-induced late-phase inflammatory response typical of allergen trigger[11].

In chronic asthma, mast cells are noticeably amplified along the airway smooth muscle in large and small airways. Mast cells at this location not only work on with airway smooth muscle by the action of autacoid mediators such as LTD4, prostaglandin PGD2 and histamine, but also contribute to fibrogenesis and increase proliferation of smooth muscle which is known as remodeling response[10].

Eosinophils

A very noticeable cell in the inflammation of allergic asthma is the eosinophils. They are present in the airway wall and found in huge amount in the sputum and bronchoalveolar lavage of patients with uncontrolled asthma. These cells are initially produced from the bone marrow as CD34 precursors. The maturing eosinophils then travel from the circulation through the microvascular compartment toward the airway wall[12].Eosinophils are a source of granule basic proteins, which include major basic protein, eosinophil peroxidase, and eosinophil cationic protein. They have the ability to produce eicosanoids like prostacyclin (PGI2) and cysteinyl leukotriene and release theoretically tissue-damaging

superoxide and a lot of cytokines and chemokines. On treatment of asthma with inhaled or oral corticosteroids, there is significant decrease in sputum and tissue eosinophils. That is associated with clinical progress and has led to the impression that eosinophils are important to airway dysfunction in asthma, therefore are the chief target in management[13].

Monocytes and Macrophages

Monocytes are capable of differentiating into macrophages and dendritic cells. Dendritic cells require IL-4. In chronic asthma both monocytes and macrophages are noticeable cells in the airway mucosa and play a central role in disease pathogenesis. While these cells are a significant source of cysLT, reactive oxygen and a range of lysosomal enzymes, but their role in facilitating tissue damage and to the overall airway pathology of asthma is mainly not known. In corticosteroid-refractory asthma, monocytes and macrophages are believed to play an ever more vital role and may be responsible for the continuing chronic inflammation[14].

Airway Epithelium

The airway epithelium is now identified to be central to asthma pathogenesis. Bronchial biopsies show areas of epithelial metaplasia and damage, increased myofibroblast, thickening of the subepithelial basal lamina, and other indication of airway remodeling like hypertrophy and hyperplasia of airway smooth muscle, angiogenesis and an altered deposition and composition of extracellular matrix proteins, and mucous gland hyperplasia[15].One imperative characteristic of the epithelium is its ability to defend itself in contradiction of oxidant injury, a characteristic that might partially explain why asthmatic patients are so sensitive to oxidant pollutants such tobacco smoke[16].

Airway Remodeling

Variations in the formed elements of the airway add significantly to the pathophysiology of asthma. Presence of chronic inflammation might change the homeostasis of lung tissue, causing to airway remodeling. Tissue remodeling comprises epithelial changes, amplified matrix deposition, matrix degradation and buildup of plasma proteins. Genetic effects, intra-uterine exposures and early life happenings, and chronic uncontrolled inflammation could all add to airway remodeling[17].The most noticeable alteration is in the airway smooth muscle. This increases in quantity due to hypertrophy and hyperplasia, and spreads across the airways. In chronic asthma the airways change and become thickened as a result of the laying down of matrix proteins such as collagen fibers, proliferated of microvessels, and deposited proteoglycans[18].

The role of Leukotriene in Asthma Pathophysiology

Leukotriene were formerly identified as slow-reacting substance of anaphylaxis (SRS-A). They were named as such due to the fact that parent molecule was initially isolated from leukocytes. Leukotrienes are one of the primary chemical mediators of inflammation in asthmatic airway. They are made from arachidonic acid. Leukotrienes are secreted by eosinophils, neutrophils, mast cells, basophils, lymphocytes, and macrophages [19]. Many of the effects of the cysteinyl leukotriene are intervened by the CysLT1 receptor. That leads to performing certain actions, such as contracting airway smooth muscle, increasing vascular permeability, and chemotaxis. Leukotriene C4 and leukotriene D4 have the same ability to stimulate smooth-muscle contraction by performing on CysLT1 receptors in the human lung tissue. On the other hand, the strength of leukotriene E4 is lower than C4 and D4 by a factor of 10. Many chemically different, precise, and selective antagonist medications that do not permit the binding of leukotriene to CysLT1 receptors have been recognized. This family of molecules is now referred with the generic suffix –lukast[20].

CysLTs are the most powerful bronchoconstrictor agents yet known, about a thousand times more powerful compared to histamine. They increase airway hyper-responsiveness, decrease ciliary activity, and intensify microvascular permeability. They have also been reported to induce proliferation of airway smooth muscle[8].They may have a role in airway remodeling in case of chronic asthma. LTC4 and LTD4 are very strong airway secretagogues. These LT display a direct chemotactic activity for eosinophils. Bronchial epithelial cells are triggered by cysteinyl LT for example LTD4, with the help extracellular signal-regulated kinase (ERK) activation, and also with help of the signal transducer and activator of transcription (STAT)-1. Eventually this leads to increasing their adhesiveness to eosinophils [21].The above mentioned factors propose that CysLT display a central biological part in pathogenesis of asthma. LTB4 role yet is not well understood, but is noticed to have a strong chemotactic ability for neutrophils. This property can

be linked with the high neutrophil count seen in acute severe asthma, as well as in late response to allergen challenge[22].

Leukotriene Modifiers

Leukotriene modifiers characterize the first class of mediator, among other asthma drugs as a specific therapeutic option for treatment and control, in the light of understanding pathophysiology of asthma. They comprise two groups of medications: leukotriene receptor antagonist (LTRA) and leukotriene biosynthesis inhibitor. Zileuton is the only sold medication from the group of Leukotriene synthesis inhibitor. It works by inhibiting 5-LO enzyme. Due to this property, it has the ability to prevent synthesis of CysLTs and also LTB4 [23]. Some studies have found zileuton to be more advantageous than leukotriene-receptor antagonists in relations of both controlling asthma as well as shrinking nasal polyps as seen in asthma triad which is asthma, aspirin sensitivity, and nasal polyposis. The disadvantage of Zileutonn is lack of strength. Its half-life of two hours and duration of action is short so it requires a dose four times a day. Additionally, adverse effect of zileuton is its possible hepatic toxicity. This chemical hepatitis is reversible in 2 to 4% of patients, requires routine liver enzyme testing[24].

Some of the CysLT receptor antagonists approved in various markets are Pranlukast, Zafirlukast and Montelukast. LTRAs are selective blocker of the binding of CysLTs to the CysLT1 receptor, which has been recognized as the receptor by which many of their actions are facilitated. These actions comprise constriction of bronchus, hypersecretion of mucus, increased vascular permeability, and migration of eosinophil. In studies across various patient subgroups, montelukast, pranlukast, and zafirlukast are beneficial when given per oral. They improve control of symptom and function of airway in patients with chronic persistent asthma. They also help in decreasing the frequency of asthma exacerbations there by decrease the requirement of oral corticosteroids[25].The LTRAs create bronchodilator effects which work additive along with β-agonists and have also shown to decrease requirement for consumption of these drugs. Bronchodilation happens shortly within hours of the first dose, and its maximum effect is evident within the first few days once administered. The amount of eosinophils circulating in blood decreases in response to treatment with LTRA[26].

New studies show, montelukast has revealed similar activity like that of an inhaled corticosteroid for managing asthma in adults, and further, on condition that additional control in patients to some extent controlled on an inhaled corticosteroid. Furthermore, the dose of inhaled corticosteroid might be lessened while continuing control of asthma for adult patients getting oral montelukast once daily, or pranlukast given twice daily[25]. This is possibly because of corresponding anti-inflammatory properties, as corticosteroids do not inhibits the creation of cystLT in asthma. Along with their additive properties with β-agonists and inhaled corticosteroids, the LTRAs could also yield an additive effect with H1 receptor antihistamines leading to inhibiting allergen-induced airway obstruction during the early and late phase in asthmatics. In the double-blind, placebo-controlled pediatric trial for eight weeks, management with montelukast produced significant reduction (P=0.02) in peripheral blood eosinophil counts in contrast with placebo for the duration of the active treatment period [27]. This suggests that montelukast may have clinically significant effects on inflammation of asthma. In a current study among adult patients who suffer from chronic asthma, montelukast showed a decrease in blood eosinophil levels that was comparable to that caused by inhaled corticosteroid. In additional adult studies, eosinophilic inflammation along the airways of patients known for asthma was decreased by management with montelukast or pranlukast[28].

Pharmacokinetics

Montelukast is quickly absorbed subsequent to oral administration. For the ten milligram film-coated tablet dose, the mean peak plasma concentration (Cmax,) is attained 3 hours (Tmax) when administered in adults in the fasting state. The average oral bioavailability is found to be 66%.The oral bioavailability and Cmax are not prejudiced by a regular meal. For the five milligram chewable tablet, the Cmax is achieved in 2 hours after administration in the fasting state among adults[27].The average oral bioavailability is 73% and is reduced to 63% by a regular meal. Subsequent to administration of the four milligram chewable tablet during fasting state to pediatric patients of age two to five, Cmax is achieved two hours after administration. More than 99% of Montelukast is bound to plasma proteins. The steady-state volume of distribution of montelukast is around 8-11 per litres[2]. Studies that were done in rats

with radiolabeled montelukast show negligible distribution through the blood-brain barrier. Furthermore, concentrations of radiolabelled material 24 hours after the dose was given were insignificant in all other tissues [29]. Montelukast is comprehensively metabolized. Studies that were done with therapeutic doses of montelukast, plasma concentrations of the metabolites were undetectable at steady state in adults as well as children. More studies done in vitro showed that cytochromes P450 3A4, 2A6 and 2C9 play a role in the metabolism of montelukast in human liver microsomes[30].

The plasma clearance of montelukast is roughly 45 ml/ min in adults with no other complication. Montelukast and its metabolites are excreted nearly entirely with the help of the bile. Nevertheless, no dosage modification is essential for the elderly or those patients with mild to moderate hepatic insufficiency. Since montelukast and its metabolites are removed by the biliary course, no dose modification is projected to be required in patients with renal impairment[31].

Adverse Effects

Pediatric studies on montelukast discovered that it was well tolerated by patients. The preponderance of the reported side effects was mild. They comprised headache, nausea, ear infection, pharyngitis, and abdominal pain. In clinical trials, interestingly, the occurrence of these side effects was not greater than with placebo. In several patients receiving oral corticosteroids and Zafirlukast, cutbacks in steroid dose have been connected with Churg-Strauss syndrome[31].This phenomenon is thought to be due to decreased steroid dosage, but not causally connected to Zafirkast. Similar phenomenon has not been described with montelukast. No dose adjustment with montelukast is required for patients with renal impairment, and mild-moderate hepatic impairment. It goes through the placenta and is secreted in breast milk; therefore , Montelukast must not to be prescribed to pregnant and lactating women, due to lack of controlled trials[32].

When to use Leukotriene Modifiers?

Even though it is essential to identify that the use of inhaled corticosteroids is currently the suggested first-line, primary long-term management for children with asthma, studies recommend that montelukast delivers effective disease control to several children suffering from mild asthma. Additionally, an oral, age-appropriate, once-daily prescription may have benefits for younger children in terms of comfort of use. This, eventually, may be connected with better compliance and may contribute positively to more consistent medication delivery and asthma control[33]. The current evidence shows that first-line monotherapy with anti-leukotrienes is not normally suggested in asthma sufferers, with perhaps the omission of those who suffer from aspirin-intolerant asthma and exercise-induced asthma. Generally, inhaled corticosteroids deliver better asthma control compared to leukotriene modifiers. Consequently, an inhaled corticosteroid is the suggested drug of first choice in the management of patients with persistent asthma, together with children of all ages[28].LRTAs are an alternative management for mild persistent asthma. For patients of any age in whom good asthma control is not attained with the help of a leukotriene modifier, shifting to an inhaled corticosteroid is directed. For patients with further severe asthma, the addition of a LRTA to a low dose of an inhaled corticosteroid may advance asthma control, but other treatment arrangements (specially, an inhaled corticosteroid with long-acting β-agonist) are more beneficial[33]. Nevertheless, by virtue of their great systemic bioavailability, anti-leukotrienes may be appreciated in those asthmatic patients who find it challenging to use inhaled medications. In conclusion, Cys-LTRAs have proved moderately effective in asthmatic children, an effect which gives the impression to be complementary to current corticosteroid management[34].

CONCLUSION

In this review, we have summarized the pathophysiology in detail regarding the various factors involved in such as T cells, mast cells, eosinophils, the airway epithelium itself, and chemokines and leukotrienes. Therefore, for management of pediatric asthma, the leukotriene modifiers play a key role. New studies have shown that they could help in reducing dose and dependency on inhaled corticosteroid for maintenance, and decrease the need of systemic steroids in exacerbations. Leukotriene modifiers can have a positive impact on future asthma management and requires more studies to be done on this subject.

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