European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

Assessment of Response to Anti Leukotriene Among Children with Bronchial Asthma

Naser Miftah Asmaydeh Al Shehibi[1],Khalid Mohamed Salah[2],Mohamed Mohamed Abdel Salam[3],and Rania Mohamed Mohamed Ibrahim[4]

[1]M.B.B. Ch, of Medicine and Surgery, Benghazi University, Pediatrician, Al-Marg Teaching Hospital, Libya.

[2]Professor of Pediatrics,Faculty of MedicineZagazigUniversity.

[3]Professor of Pediatrics,Faculty of Medicine Zagazig University.

[4]Lecturer of *Microbiology and Immunology*, Faculty of Medicine Zagazig University.

Correspondingauthor:Naser Miftah Asmaydeh Al Shehibi

Email:nmofath55@gmail.com

Abstract

Background:Asthma is a chronic inflammatory disease of airways in which many cells and cellular elements play a role in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. Inflammation causes recurrent series of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread and variable airflow obstruction that is often reversible either spontaneously or with treatment.The inflammatory process can lead to an associated increase in bronchial hyper- responsiveness (BHR) to a variety of stimuli (e.g., allergens, respiratory viruses and some occupational exposures). Reversibility of airflow limitation may be incomplete in some asthmatic patients.Asthma is a heterogeneous disorder, with different mechanism of disease processes. Many clusters of demographics, clinical and pathophysiological characteristics are often called "asthma phenotypes"The antibronchoconstrictor efficacy of antileukotriene drugs provided the main impetus behind their introduction as the first novel class of asthma therapy in more than 20 yr. However, clinical trials also provided surprising evidence for a hitherto unsuspected role of cysteinyl-leukotrienes in promoting persistent eosinophilia in the airway and blood of patients with asthma, and possibly influencing pathways involved in airway wall remodeling. A better understanding of these actions of antileukotriene drugs will influence their place in asthma management.

Keywords:Bronchial Asthma (BA),Anti Leukotriene.

Bronchial Asthma:

Definition:

Asthma is a chronic inflammatory disease of airways in which many cells and cellular elements play a role in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. Inflammation causes recurrent series of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread and variable airflow obstruction that is often reversible either spontaneously or with treatment ***(1)***.

The inflammatory process can lead to an associated increase in bronchial hyper- responsiveness (BHR) to a variety of stimuli (e.g., allergens, respiratory viruses and some occupational exposures). Reversibility of airflow limitation may be incomplete in some asthmatic patients ***(1)***.

Asthma is a heterogeneous disorder, with different mechanism of disease processes. Many clusters

of demodemographicsinical and pathophysiological characteristics are often called "asthma phenotypes" **(2)**.

Epidemiology of asthma

Asthma is one of the major non-communicable diseases all over the world regarding it's wide spread. It is a common disease among children ***(3)***. WHO declared that, about 235 million people are suffering from asthma ***(4)***. In December 2016 WHO estimates that, there are 383000 cases died in 2015 due to asthma. A proper management of asthma enables people to enjoy a good quality of life ***(4)***.

The prevalence of asthma among children in Egypt is 14.7%, while the prevalence regarding physician diagnosis of asthma is 9.4%. Family history of allergy and bad housing conditions are reported as risk factors associated with prevalence of asthma in Egypt ***(5)***. It is higher in early months of year (January- February) than latter months (May- June), in rural residence more than urban residence and in younger more than in older children ***(6)***.

Risk Factors for Asthma

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily genetic) and the latter are usually environmental factors. However, the mechanisms whereby they influence the development and expression of asthma are complex and interactive.

For example, genes likely interact both with other genes and with environmental factors to determine asthma susceptibility.

In addition, developmental aspects such as the maturation of the immune response and the timing of infectious exposures during the first years of life are emerging as important factors modifying the risk of asthma in the genetically susceptible person ***(7).***

(1) Genetic Factors:

Genetic factors contribute importantly to asthma as known from identical twin studies ***(8).***

The severity of asthma and response to treatment have also been suggested to be dependant on genetic modulators, such as the polymorphism of the B2-receptor (found on chromosome 5), which is involved in the bronchodilator response to B-agonists ***(9).***

TIM1 (T-cell immunoglobulin mucin1) has been identified as a susceptibility gene for asthma. New research in mice now suggests that targeting TIM-1 protein might have therapeutic benefit in treating the humanized mouse model of experimental asthma, ameliorating inflammation and airway hyperresponsiveness ***(1).***

(2) Gender and Asthma

Before puberty, the prevalence is 3 times higher in boys than in girls. During adolescence, the prevalence is equal among males and females. Adult-onset asthma is more common in women than in men***(10).***

3) Bronchial hyperresponsiveness (BHR):

Wheezing during infancy has been linked to early loss of pulmonary function. There is a relation between (BHR)and progressive impairment of pulmonary function in asthmatic children***(11).***

(4) Maternal effects:

Children born from parents with asthma or atopic disorders present an increased risk of developing similar diseases.

Maternal factors, placental factors, or both may have an impact on perinatal allergic sensitization ***(12).***

Children exposed to higher maternal stress during the pre- and postnatal period were reported to

be at higher risk for wheeze. This was only true in non-atopic mothers ***(13).***

A 2012 Danish study reported an association between maternal obesity (BMI ≥35 and gestational weight gain ≥25 kg) during pregnancy with increased risk of asthma and wheezing in the offspring ***(14).***

Children who were exposed to acetaminophen prenatally were more likely to have asthma symptoms at age five.

(5) Atopic Dermatitis and Allergic Rhinitis

Atopy is the strongest identifiable predisposing factor for the development of asthma ***(15).***

Approximately 75 to 80 percent of children with asthma have significant allergies ***(16).***

(6) Residence and race

Even though slight differences in asthma prevalence between different races living in the same region have been found in some studies, these differences may be attributable to socioeconomic conditions, allergen exposures, and dietary factors rather than to racial predisposition ***(Global stategy for Asthma Management and Prevention, 2005).***

Evidence has rapidly accumulated to suggest that growing up on a farm may reduce the risk of developing atopic diseases ***(17).***

(7) Indoor and outdoor air Pollution:

Indoor factors related to incident asthma include passive exposure to environmental tobacco smoke (ETS), exposure to furred pets or other allergens, and exposure to dampness ***(18).*** Newborns whose first few months of life coincide with high pollen and mold seasons are at increased risk of developing early symptoms of asthma ***(19).***

Outdoor air pollutants including nitrogen oxide, carbon monoxide, sulfur dioxide, and parental atopy were significantly associated with physician-diagnosed asthma among children 6-15 years of age of both sexes ***(12).***

(8) Ozone (O3):

Both ozone and primary pollutants from traffic substantially increase asthma-related emergency department visits in children, especially during the warm season ***(20).***

(9) Insects and Dust mite:

There is a relation between concurrent exposure to dust mite allergen and endotoxin in early life and asthma and atopy, early exposure in infancy will increase the risk of asthma by age of 7 years old ***(21).***

(10) Effect of family pets:

There is a positive relationshipbetween cat ownership and the development of early sensitization and wheeze by developing of anti-cat IgE**(22).**

(11) Effect of passive smoking:

Smoking was significantly related to the risk of incident asthma even active or passive ***(23),*** Environmental tobacco smoke exposure will increase the expression of proinflammatory mediators in airway secretions, including IFN-gamma and IL-12, as well as IL-5 and IL-13 ***(24)***.

(12) Diet

Individuals with asthma who consumed a high-fat meal showed increased airway inflammation, the high fat meal also appeared to inhibit the response to the asthma reliever medication Ventolin **(16).**

A significant inverse relationship between serum vitamin D levels and patient IgE levels, steroid requirements, and in vitro responsiveness to corticosteroids in children has been reported ***(25).***

(13) Breast feeding:

Breast feeding might delay the onset of asthma or actively protect children less than 24 months of

ISSN 2515-8260 Volume 08, Issue 03, 2021

age against asthma. Breast feeding might reduce the prevalence of asthma in children exposed to environmental tobacco smoke *(26)*.

On the other hand, breast feeding is associated with increased risk of asthma and recurrent wheezing beginning at the age of six years but only for atopic children with asthmatic mothers *(27)*.

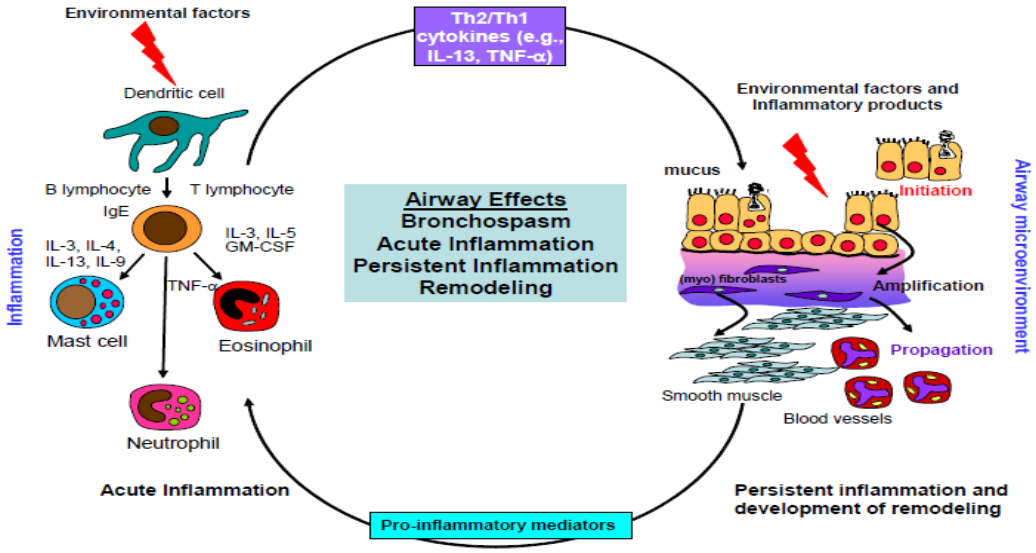

Figure (1): Factors limiting air flow in acute and persistent asthma.*(28)*

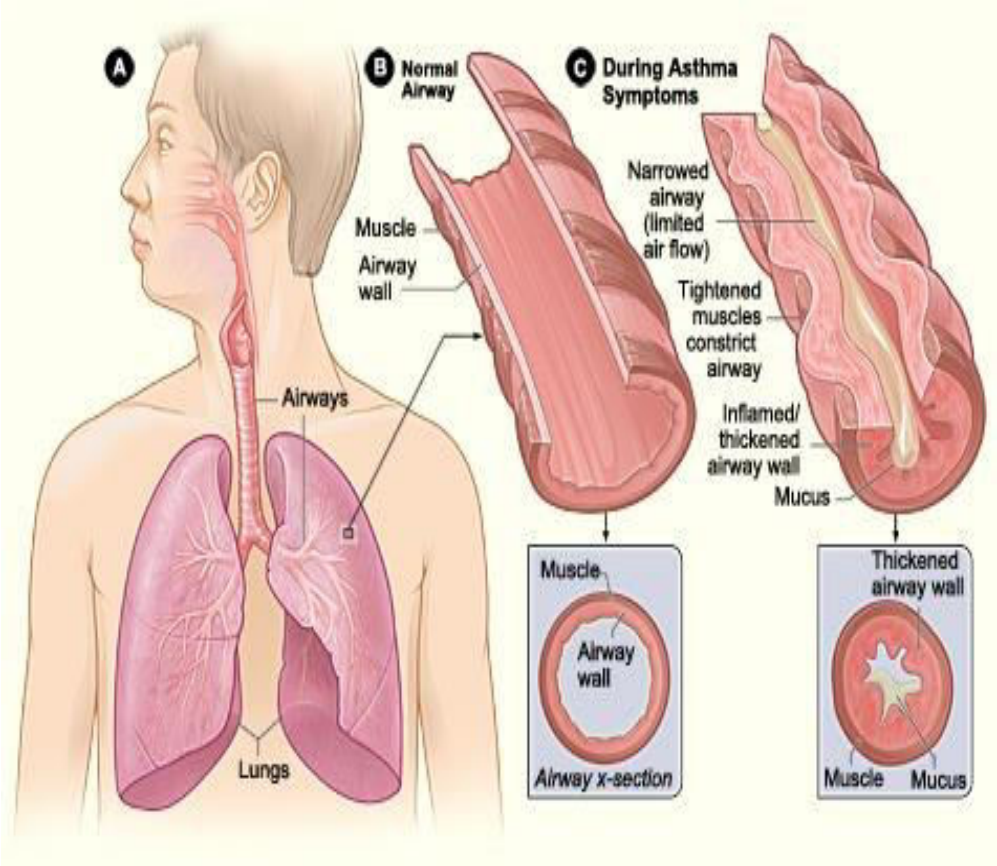

Figure (2): Changes in the airway in asthma**(29).**

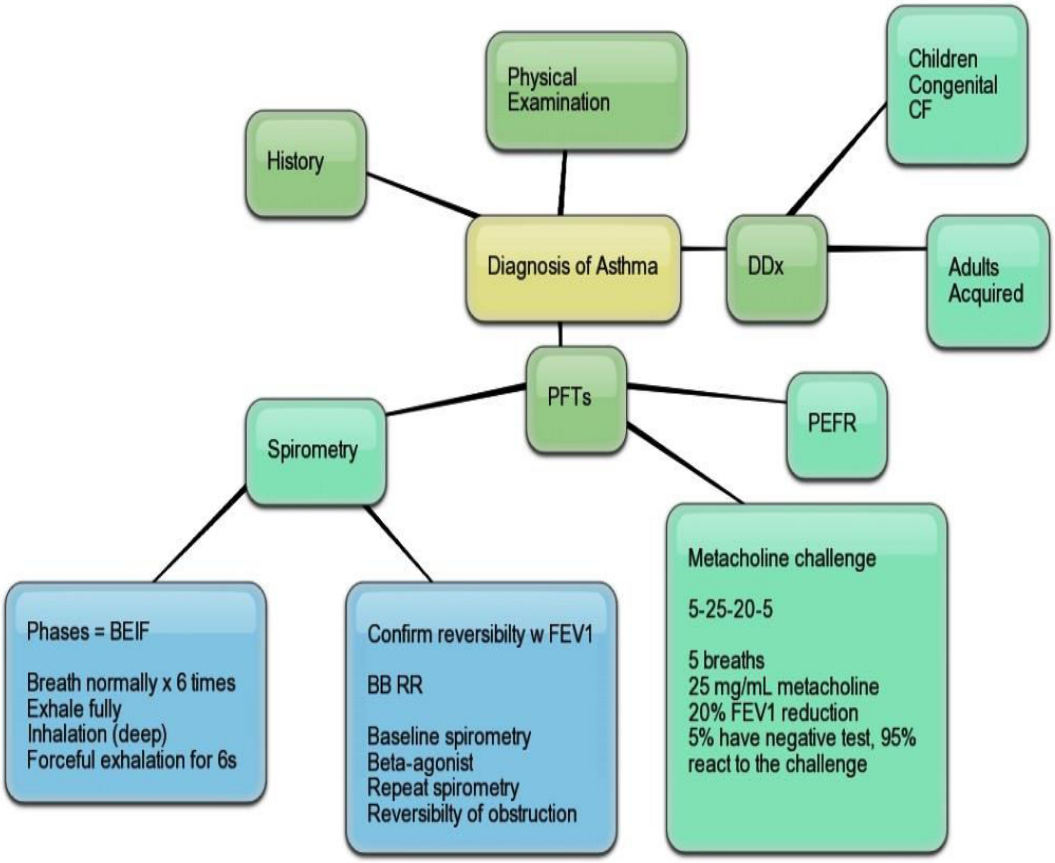

Figure (3): Diagnosis of Bronchial Asthma ***(30)***

Anti-Leukotriene Drugs

Interleukin 9 belongs to a family of cytokines that use the common IL-2Rγc for signal transduction, and similar to other family members (i.e. IL-2, IL-4, IL-7, IL-15 and IL-21), IL-9 was believed to be a T-cell growth factor and its chief function was to drive T-cell proliferation.
The antibronchoconstrictor efficacy of antileukotriene drugs provided the main impetus behind their introduction as the first novel class of asthma therapy in more than 20 yr. However, clinical trials also provided surprising evidence for a hitherto unsuspected role of cysteinyl-leukotrienes in promoting persistent eosinophilia in the airway and blood of patients with asthma, and possibly influencing pathways involved in airway wall remodeling. A better understanding of these actions of antileukotriene drugs will influence their place in asthma management ***(31).***

Antileukotriene medications that have been implemented into clinical practice of bronchial asthma and allergic rhinitis include specific leukotriene receptor antagonists (montelukast, zafirlukast, pranlukast) and leukotriene biosynthesis inhibitors (zileuton). The current GINA (Global Initiative for Asthma) guidelines, the PRACTALL (Practicing Allergology) report on asthma treatment in children, and ARIA (Allergic Rhinitis and its Impact on Asthma) recommendations classify antileukotriene therapeutic agents as a group of drugs controlling the course of the disease. However, inhaled glucocorticosteroids still remain the first-line treatment in chronic asthma ***(32).***

According to current guidelines, antileukotriene drugs are recommended as alternative treatment to low-dose inhaled glucocorticosteroids in the second level of asthma severity and as

complementary treatment to inhaled and/or oral glucocorticosteroids, starting from the third level of asthma severity. Recently, clinical efficacy of antileukotriene drugs has been suggested in the treatment of isolated allergic rhinitis, chronic cough in the course of asthma, as a sole symptom of the disease, and as the therapy for episodes of wheezing caused by viral infections ***(32).***

Leukotrienes are biologically active 5-lipoxygenase (5-LO) lipid mediators of arachidonic acid They include 2 classes: an unstable leukotriene A4 (LTA4), which is further converted into leukotriene B4 (LTB4), and a separate category of leukotrienes that contain cysteine and are termed collectively as cys-LTs – leukotriene C4 (LTC4), D4 (LTD4), and E4 (LTE4). Cys-LTs can be produced via 5-LO pathway by a variety of inflammatory cells such as eosinophils, basophils, alveolar macrophages, monocytes, and mast cells. Endothelial cells do not express 5-LO but contain LTC4 synthase and can therefore participate in leukotriene production via a transcellular mechanism. Eosinophils and mast cells produce mainly LTC4, while neutrophils–LTB4. Cys-LTs, which cause bronchoconstriction in asthma patients and are a potent chemoattractant for leukocytes (LTB4), exert their biological actions through interactions of specific receptors. There are 2 separate receptors for cys-LTs called CysLT1 and CysLT2. Bronchoconstriction induced by cys-LTs appears to be caused by selective activation of the CysLT1 receptors ***(33).***

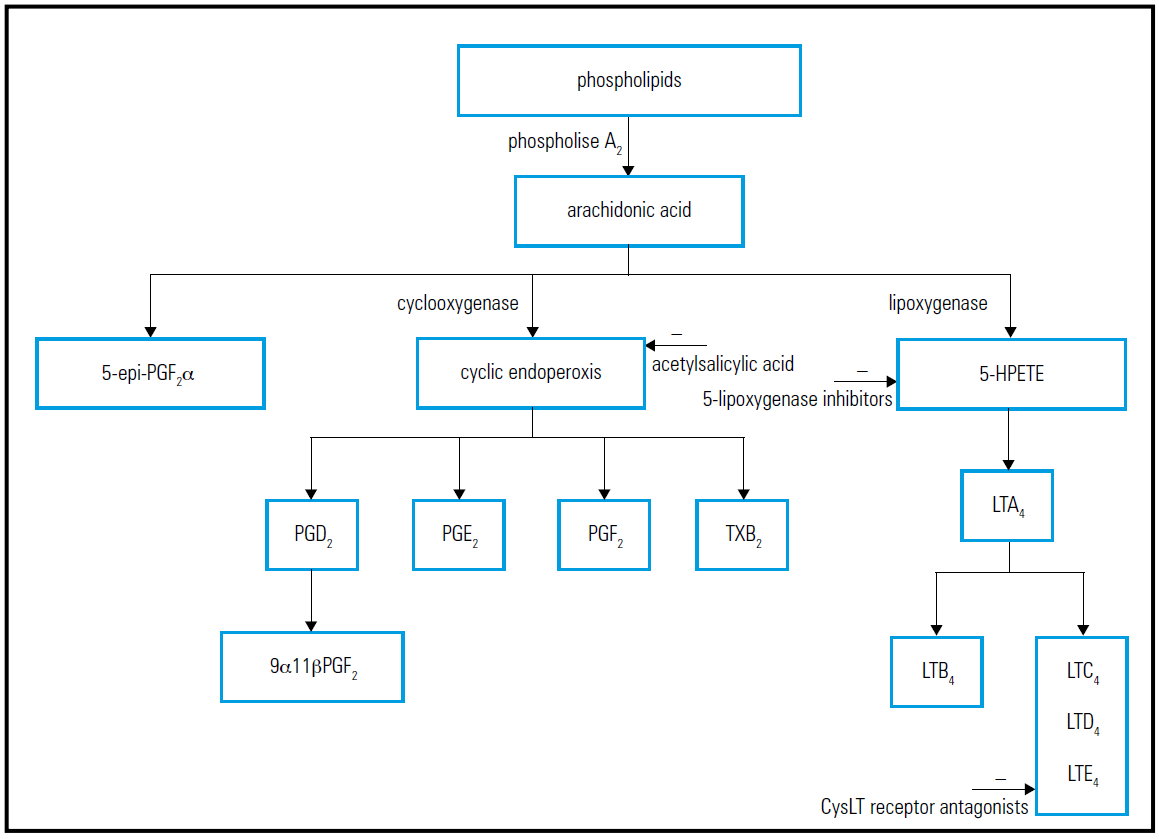

Figure (4): The effects of leukotriene biosynthesis inhibitors ***(28)***

The effects of leukotriene biosynthesis inhibitors (inhibitors of 5-LO) or specific leukotriene receptor antagonists in patients with asthma have suggested that interventions in the 5-LO pathway may be of therapeutic use in the treatment of asthma and rhinitis. These drugs inhibit not

only the early but also the late phases of allergic response, which implicates an anti-inflammatory component of such treatment.

Antileukotriene drugs used in asthma:

1. inhibitors of 5-LO, which inhibit leukotriene biosynthesis: zileuton (Zyflo), used mainly in the USA
2. CysLT1 antagonists: montelukast (Singulair), zafirlukast (Accolate), and pranlukast (Ono), which is used mainly in Japan.

Still investigated (not yet in clinical practice) are the so called FLAP inhibitors that inhibit the 5-LO-activating proteins ***(3).***

The choice of medication used in long-term asthma management depends on the level of disease control. From a clinical point of view, the most significant problem concerns the possibility of applying antileukotriene drugs in the long-term treatment of asthma. Depending on life activity limitation, day and night symptoms, need for use of a short-acting β2-agonist, lung function (peak expiratory flow/forced expiratory volume in 1 second [PEF/FEV1]), and the number of exacerbations requiring treatment intensification, asthma can be divided into:

1. controlled
2. partly controlled
3. uncontrolled, which may cause exacerbation of the disease.

Similar criteria are applied to assess the efficacy of treatment (including antileukotriene agents) in the long-term management of asthma. According to the GINA guidelines,12 5 steps in the intensity of asthma management can be distinguished depending on the severity level of asthma and its control. In all steps a short acting β2-agonist may be used as needed:

Step 1: Short-acting β2-agonist as needed

step 2: low-dose inhaled glucocorticosteroid or antileukotriene

step 3

- low-dose inhaled glucocorticosteroid plus long acting β2-agonist or
- medium- or high-dose inhaled glucocorticosteroids

or

- low-dose inhaled glucocorticosteroid plus antileukotriene

or

- low-dose inhaled glucocorticosteroid plus sustained release theophylline

Step 4:

- medium- or high-dose inhaled glucocorticosteroid plus long-acting β2-agonist plus antileukotriene

or

- medium- or high-dose inhaled glucocorticosteroid plus long acting β2-agonist plus sustained release theophylline

step 5

- same as step 4 and additionally oral glucocorticosteroid (lowest dose) and/or anti-immunoglobulin E antibodies.

Antileukotrienes are classified according to standing guidelines as a group of drugs controlling the course of asthma. However, inhaled glucocorticosteroids still remain the first-line treatment in chronic asthma. Antileukotriene agents are recommended as alternative treatment to low-dose inhaled glucocorticosteroids in the second level of asthma, or as complementary treatment to glucocorticosteroids, starting from the third level of asthma ***(3).***

Numerous studies have been published that supply evidence for the positive effect of

antileukotriene agents in persistent asthma.

However, a certain genotype of patients with a polymorphism of a region promoting the leukotriene C4 synthase (characterized by a "mutated" allele C of the LTC4 synthase) predisposes to a better response to montelukast treatment. Treatment with a 5-LO inhibitor demonstrated a moderate clinical improvement in aspirin-induced asthma, especially a reduction in nasal symptoms. This might be related to the genetic polymorphism of the 5-LO promoting gene ***(16)***.

ConflictofInterest: Noconflictofinterest.

References

1. **SanchaitaSriwal Sonar, Yen-Ming Hsu, Melanie Lynn, et al. (2010):** Antagonism of TIM-1 blocks the development of disease in a humanized mouse model of allergic asthma. J Clin Invest.; 120(8): 2767–2781.
2. **Walia M, Lodha R and Kapra SK (2006):** Montelukast in pediatric asthma management.Indian J.pediatr.;73:275-282.
3. **GINA (2007): Global Initiative for Asthma:** Global strategy for asthma management and prevention. Global initiative for Asthma web site.
4. **World Health Organization (WHO) (2014):** Prevalence of asthma. ISBN 97892 4 156381 9.
5. **Akinbami LJ, Moorman JE and Liu X (2011):** Asthma prevalence, health care use, and mortality. Natl Health Stat Report; 32:1–14.
6. **Abd El-Khalek KA, Deraz TE and Rafik M (2001):** Assessment of urinary leukotriene E4 and pulmonary function tests before and after leukotriene antagonist. Modifying agents in asthmatic children. Egyptian J Pediatr., 7(4):31-54.
7. **Ober C (2005):** Perspectives on the past decade of asthma genetics. J Allergy Clin Immunol ;116(2):274-278.
8. **Koeppen-Schomerus G, Stevenson J, plomin R (2001):** Genes and environment in asthma: a study for 4-year-old twins. Arch. Dis. Child., 85: 398-400.
9. **Liggett S (2000):** The pharmacogenetics of beta 2 –adrenergic receptors: relevance to asthma. J. Allergy Clin. Immunol., 105: 487-492.
10. **Girish Sharma, Thomas Scanlin, Mary L Windle, et al. (2006):** Asthma.
11. **DelacourtC, Benoist MR, Le Bourgeois M et al. (2007):** Relationship between bronchial hyperresponsiveness and impaired lung function after infantile asthma. PLoS ONE. 14; 2(11):1179-1180.
12. **Arroda K, Sole D and Baena-Cagnani CE (2006):** Risk factors for asthma and atopy current opinion. Allerg. Clin. Immunol., 5: 153-159.
13. **Mathilda Chiu YH, Coull BA, Cohen S, et al. (2012):** Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization. Am J Respir Crit Care;186(2):147-154.
14. **Harpsøe MC, Basit S, Bager P, Wohlfahrt J, et al. (2012):** Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: A study within the Danish National Birth Cohort. J Allergy Clin Immunol. J Allergy Clin Immunol. 2013 Apr; 131(4):1033-1040.
15. **Lemanske R and Busse W (2003):** Asthma. J. Allergy Clin.Immunol. 2003; 111(2): S502-519.
16. **American Lung Association (ALA) (2014):** Asthma &Allergy: Chilhood asthma overview. Available at web site: http//www.lungusa.org/site/pp.asp

17. **Von Hertzen LC and Haahtela T (2004):** Asthma and atopy – the price of affluence? Allergy, 59: 124-137.
18. **King M E, Mannino D M and Holguin F (2004):** Risk factors for asthma incidence. Panminerva Med., 46(2): 97-110.
19. **Kim G. Harley, Janet M Macher, Michael Lipsett, PaureneDuramad, et al., (2009):** Fungi and pollen exposure in the first months of life and risk of early childhood wheezing.
20. **Strickland MJ, LA Darrow, M Klein et al. (2010):** Short-term Associations between Ambient Air Pollutants and Pediatric Asthma Emergency Department Visits. American Journal of Respir. and Crit Care Med., 182(3): 307-3016.
21. **Celedón JC, Milton DK, Ramsey CD, et al. (2007):** Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J Allergy Clin Immunol. 120(1):144-149.
22. **Perzanowski MS, Chew GL, Divjan A,et al. (2008):** Cat ownership is a risk factor for the development of anti-cat IgE but not current wheeze at age 5 years in an inner-city cohort. J Allergy Clin Immunol.;121(4):1047-52.
23. **Patricia C, Chuladaph D, Samuel J, et al. (2003):** Breastfeeding and the prevalence of asthma and wheezing inchildren. J. Allergy Clin. Immunol.
24. **Feleszko W, Zawadzka-Krajewska A, Matysiak K, et al. (2006):** Parental tobacco smoking is associated with augmented IL-13 secretion in children with allergic asthma. J Allergy Clin Immunol. 117(1):97-102.
25. **Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY (2012):** Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. J Allergy Clin Immunol. J Allergy Clin Immunol. May; 129(5):1243-1251.
26. **Patricia C, Chuladaph D, Samuel J, et al. (2003):** Breastfeeding and the prevalence of asthma and wheezing inchildren. J. Allergy Clin. Immunol.; 111: 328-336.
27. **Wright AL (2001):** Factors influencing the relation of infantfeeding to asthma and recurrent wheeze in childhood.Thorax.
28. **Holgate ST and Polosa R (2006):** The mechanisms, diagnosis, and management of severe asthma. Lancet; 368 (9537): 780–793.
29. **National Heart Lung and Blood institute (NHLBI) (2007):** National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Updated 2007. NIH Publication No. 07-4051.
30. **Dimov V and S Randhawa (2008):**Advances in basic and clinical immunology in 2007. Journal of Allergy and Clinical Immunology - Volume 122, Issue 1.
31. **Haldar P and Pavord ID (2008):** Noneosinophilic asthma: a distinct clinical and pathologic phenotype. J Allergy Clin Immunol.; 119(5): 1043-52; quiz 1053-4.
32. **Atkins D and Leung DY (2004):** diagnosis of allergic diseases. In "Nelson Textbook of Pediatrics" (EDS). Bahrman RE, Kliegmen RM, and Jenson HB, 17th edition, Philadelphia, 747-751.
33. **Liu AH, Spahn JD and Leung DY (2004)**: Childhood asthma. In: "Nelson Textbook of pediatrics" (Eds). Behrman RE, Kleigmen RM, and Jenson HB, 17th edition, Philadelphia, 760-774.