REVIEW ARTICLE

Antileukotriene drugs in the treatment of asthma

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KEY WORDS

allergic rhinitis, antileukotriene drugs, asthma, leukotrienes

ABSTRACT

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. 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.

Leukotrienes as mediators of asthma Leukotrienes are biologically active 5-lipoxygenase (5-LO) lipid mediators of arachidonic acid (FIGURE). They include 2 classes: an unstable leukotriene A_4 (LTA_4), which is further converted into leukotriene B_4 (LTB_4), and a separate category of leukotrienes that contain cysteine and are termed collectively as cys-LTs – leukotriene C_4 (LTC_4), D_4 (LTD_4), and E_4 (LTE_4). 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 LTC_4 synthase and can therefore participate in leukotriene production via a transcellular mechanism. Eosinophils and mast cells produce mainly LTC_4, while neutrophils – LTB_4. Cys-LTs, which cause bronchoconstriction in asthma patients and are a potent chemoattractant for leukocytes (LTB_4), 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.[1,2]

Growing evidence suggests that leukotrienes play an important role in the pathogenesis of bronchial asthma and allergic rhinitis. They cause smooth muscle contraction, impair mucociliary clearance, enhance mucus secretion, attract eosinophils to the airways, and increase vascular permeability producing edema.[1,2] Moreover, in patients with asthma, the airways are 100 to 1000 times more sensitive to inhaled LTD_4 and LTE_4 than the airways of normal subjects. Furthermore, inhaled LTC_4 and LTD_4 increase bronchial reactivity to methacholine or histamine.[3,4] Such response to exogenous leukotrienes indicates the biological role of these compounds in asthma. In addition, leukotrienes have been identified in urine, plasma, nasal secretions, induced sputum, and bronchoalveolar lavage fluid from patients with asthma. Urinary LTE_4 measurements can be used to monitor systemic production of cys-LTs. During spontaneous exacerbations of bronchial asthma,[5] following exercise,[6,7] allergen,[8] and aspirin challenge,[9] urinary LTE_4 excretion increases.

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.[10,11] These drugs inhibit not only the early but also the late phases of allergic response, which implicates an anti-inflammatory component of such treatment.

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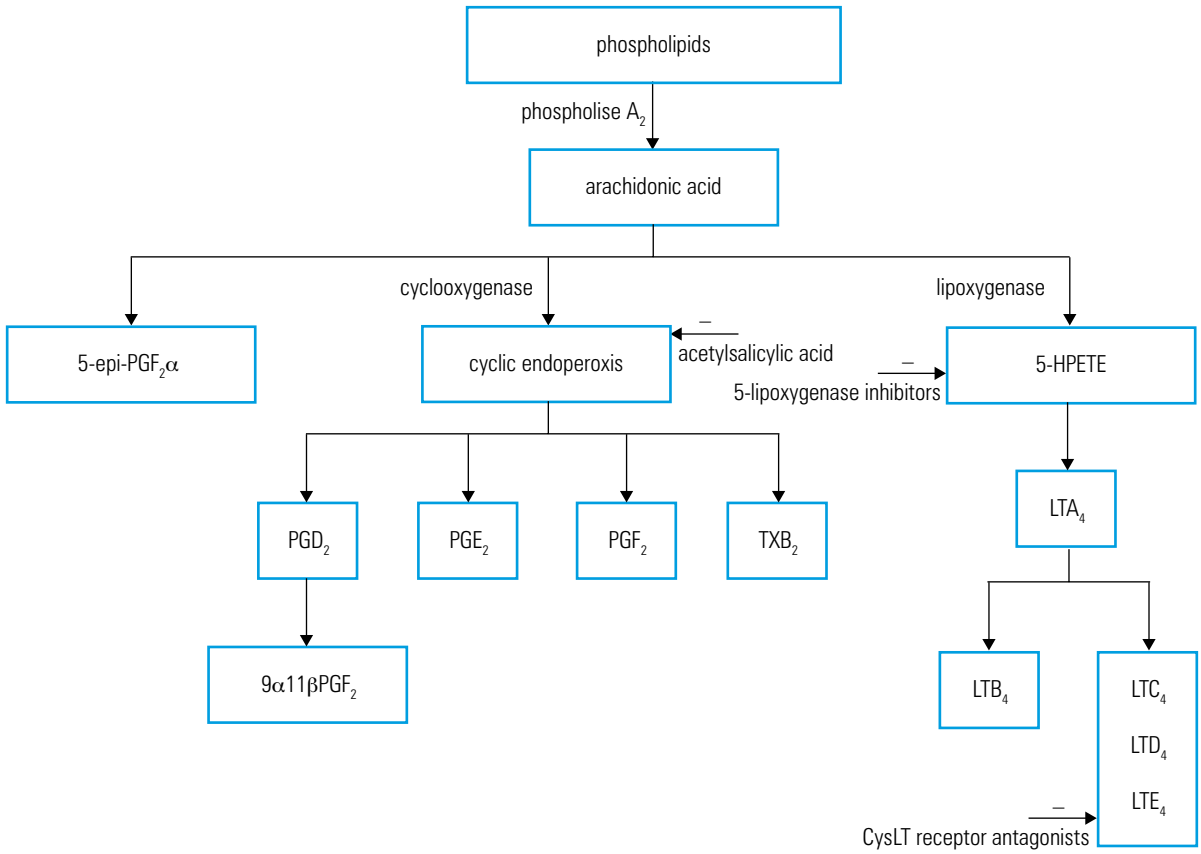

FIGURE Arachidonic acid metabolism via cyclooxygenase and 5-lipoxygenase pathways (Mastalerz L, Kania A. Pneumonol Alergol Pol. 2010; 78: 474-478). Abbreviations: LTA_4 – leukotriene A_4, LTB_4 – leukotriene B_4, LTC_4 – leukotriene C_4, LTD_4 – leukotriene D_4, LTE_4 – leukotriene E_4, PGD_2 – prostaglandin D_2, PGE_2 – prostaglandin E_2, PGF_2 – prostaglandin F_2, TXB_2 – thromboxane B_2, 5-HPETE – 5-hydro -peroxyeicosatetraenoic acid, 5-epi-$PGF_2\alpha$ – 5-epi-prostaglandin$F_2\alpha$, $9\alpha11\beta PGF_2$ – $9\alpha11\beta$prostaglandinF_2

Clinical division of antileukotriene drugs used in asthma and rhinitis Antileukotriene drugs used in asthma and rhinitis include:

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.

Long-term treatment of bronchial asthma and rhinitis vs. antileukotriene drugs The current GINA (Global Initiative for Asthma) guidelines,[12] the PRACTALL (Practicing Allergology) report on asthma treatment in children,[13] and ARIA (Allergic Rhinitis and its Impact on Asthma) recommendations[14] classify antileukotriene therapeutic agents as a group of drugs controlling the course of the disease.

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 β_2-agonist, lung function (peak expiratory flow/forced expiratory volume in 1 second [PEF/FEV_1]), 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 β_2-agonist may be used as needed:

step 1
– short-acting β_2-agonist as needed
step 2
– low-dose inhaled glucocorticosteroid or
– antileukotriene
step 3
– low-dose inhaled glucocorticosteroid plus long acting β_2-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 β_2-agonist plus antileukotriene or
– medium- or high-dose inhaled glucocorticosteroid plus long acting β_2-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.

Cysteinyl receptor antagonists in the long-term treatment of asthma Numerous studies have been published that supply evidence for the positive effect of antileukotriene agents in persistent asthma. Cloud et al.[15] have been one of the first to prove the beneficial effect of cysteinyl receptor antagonists in the management of chronic asthma. This double-blind placebo-controlled study was conducted on 136 asthma patients, who received an antileukotriene for 6 weeks. A significant decrease in the intensity of day and night symptoms was observed in comparison with placebo. However, the frequency of clinical symptoms did not reduce. At 6 week, there was an increase in the mean FEV_1 value, but it was not reflected in the daily PEF rate values. Spector et al.[16] provided more evidence for the efficacy of the studied medication group in the long-term management of asthma. Compared with placebo, the investigators noticed a decrease in day and night asthma symptoms (72% of the studied patients), less frequent use of short-acting β_2-agonist on demand, and higher values of evening lung function parameters (FEV_1 and PEF rate). The multicenter study conducted by Barnes et al.[17] seems to be particularly interesting. They assessed the efficacy of therapy with cysteinyl receptor inhibitor in comparison with placebo in terms of the frequency of asthma exacerbations. At 13 week, there were significantly fewer asthma exacerbations that required medical intervention.[17] In a study published in the 1990s, Reiss et al.[18] examined the efficacy of montelukast in comparison with placebo, administered for 3 months to 681 asthma patients. The authors observed an improvement in the evening parameters of lung function and a decrease in the number of days with asthma exacerbation as compared with placebo. Moreover, the number of days without clinical symptoms of asthma increased.

5-lipoxygenase inhibitors in long-term asthma treatment Zileuton, which belongs to this group of drugs, blocks the synthesis of leukotrienes. Its efficacy in chronic asthma compared with placebo was assessed in several clinical trials.[19,20] During treatment, an increase in a FEV_1 value and a smaller risk of asthma exacerbations requiring oral glucocorticosteroids were observed.

Antileukotriene drugs in isolated rhinitis and rhinitis with coexistent asthma Bronchial asthma is usually accompanied by rhinitis. Furthermore, isolated allergic rhinitis increases the risk of developing asthma. The ARIA 2007 report recommends the use of antileukotriene drugs in isolated allergic rhinitis as well as rhinitis accompanied by asthma.[14] In mild allergic rhinitis, these drugs may be used as monotherapy. For example, montelukast alone (10 mg/day for a 4-week treatment) effectively reduced day and night nasal symptoms and improved rhinoconjunctivitis quality of life in patients with allergic rhinitis.[21] However, there is clinical evidence that simultaneous use of a cysteinyl leukotriene receptor antagonist with H_1-receptor antagonist provided effective treatment for allergic rhinitis compared with placebo and each drug alone.[22]

Aspirin-induced asthma and antileukotriene drugs Bronchial asthma with hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (aspirin-induced asthma) is a particular phenotype of asthma[23,24] characterized by an increased production of cysteinyl leukotrienes. Moreover, the systemic production of cys-LTs increases in these patients after spontaneous intake of aspirin or other nonsteroidal anti-inflammatory drugs as well as after aspirin provocation tests. The principle of pharmacotherapy in this phenotype of asthma is based on glucocorticosteroids, and antileukotrienes are a valuable complement. So far, there have been no research or clinical evidence that would indicate the beneficial effect of cysteinyl receptor antagonists in aspirin-induced asthma compared with asthma patients that tolerate aspirin well.[7,25] However, a certain genotype of patients with a polymorphism of a region promoting the leukotriene C_4 synthase (characterized by a "mutated" allele C of the LTC_4 synthase) predisposes to a better response to montelukast treatment.[25] Treatment with a 5-LO inhibitor demonstrated a moderate clinical improvement in aspirin-induced asthma, especially a reduction in nasal symptoms.[26] This might be related to the genetic polymorphism of the 5-LO promoting gene.

Side effects of antileukotriene drugs Antileukotriene agents are generally well tolerated by patients. In the 1990s, soon after the introduction of cysteinyl receptor antagonists to the market, their association with Churg-Strauss syndrome was reported.[27-31] It could, however, be a result of a reduction in the dose of systemic glucocorticosteroids during antileukotriene treatment of asthma in the course of a not yet diagnosed Churg-Strauss syndrome.

Zileuton has a hepatotoxic effect. Prior to drug administration, liver enzymes in serum have to be examined and their activity during treatment monitored. Drug interactions have been reported involving zileuton and several other drugs (e.g., terfenadine, warfarin, and theophylline). There

are data showing that co-administration of zileuton and warfarin considerably prolongs prothrombin time related to reduced warfarin clearance and increased serum warfarin concentration.

Summary According to current guidelines, antileukotriene agents are recommended in the long-term treatment of asthma. Antileukotriene drugs reduce the clinical symptoms of asthma, including cough,[32] improve lung function by slight, variable bronchial dilatation, reduce inflammation of the bronchial mucosa, and thus decrease the frequency of asthma exacerbations.[33,34] In combination with inhaled glucocorticosteroids, they may allow to reduce the dose of steroids used and to control the disease in patients with moderate and severe asthma.[35-39]

Nonetheless, the use of antileukotrienes in adult asthma patients as a single asthma controller is usually less effective than inhaled glucocorticosteroids,[40-41] although they are an alternative to glucocorticosteroids in the second stage of the disease. Moreover, they are usually less effective than long acting β_2-agonists in combined therapy.[42-45]

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ARTYKUŁ POGLĄDOWY

Leki przeciwleukotrienowe w leczeniu astmy

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STRESZCZENIE

Do leków przeciwleukotrienowych, które znalazły zastosowanie w praktyce klinicznej leczenia astmy oskrzelowej i nieżytu nosa zaliczamy antagonistów receptorów leukotrienów cysteinylowych (montelukast, zafirlukast, pranlukast) i leki hamujące biosyntezę leukotrienów (zileuton). Aktualne wytyczne GINA (Global Initiative for Asthma), raport PRACTALL (Practicing Allergology) dotyczący leczenia astmy u dzieci i zalecenia ARIA (Allergic Rhinitis and its Impact on Asthma) klasyfikują leki przeciwleukotrienowe do grupy leków kontrolujących przebieg choroby. Jednak glikokortykosteroidy wziewne pozostają nadal lekami pierwszego rzutu w astmie przewlekłej. Według aktualnych wytycznych leki przeciwleukotrienowe zalecane są jako leczenie alternatywne do niskich dawek glikokortykosteroidów wziewnych w 2. stopniu ciężkości astmy oraz, od 3. stopnia, jako leczenie uzupełniające do glikokortykosteroidów wziewnych i (lub) systemowych. Ostatnio sugeruje się również dużą skuteczność leków przeciwleukotrienowych w leczeniu izolowanego alergicznego nieżytu nosa, przewlekłego kaszlu w przebiegu astmy, który może być jedynym objawem choroby oraz epizodów świszczącego oddechu wywołanego infekcjami wirusowymi.

SŁOWA KLUCZOWE

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