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Approaches to the use of anti-inflammatory medications in the treatment of bronchial asthma

Key words: *asthma, control, inflammation.*

Over the past few decades, the frequency of bronchial asthma (BA) cases shows a sharp growth. At present about 300 million people worldwide suffer from this disease particularly in highly industrialized countries, Ukraine in particular. Asthma is associated with higher mortality, disability and economic costs.

Asthma is a chronic disease manifested by recurrent episodes of wheezing, coughing, shortness of breath, feeling of tightness in the chest usually associated with variable airway obstruction and bronchial hyper reactivity. Chronic airway inflammation has been recognized as the basis of the pathogenesis of asthma. This chronic inflammatory process is characterized by extensive infiltration of the airway mucosa and lumen by increased numbers of activated eosinophils, mast cells, macrophages and T- lymphocytes. Immune cells, in turn, release inflammatory mediators, including histamine, prostaglandins and leukotrienes. These mediators play a crucial role in the initiation of inflammation and bronchoconstriction. Taking into account that inflammatory cells and mediators circulate in the systemic circulation, asthma can be regarded as a systemic disease that requires a broader approach to treatment in terms of inflammation including the peripheral small airways (15).

On the basis of the pathogenic characteristics of the disease, it is easy to answer the question why it is so important and possible to get inflammation in asthma under control. Control of inflammation in asthma leads to controlled symptoms and to reduction of the severe exacerbations (4) risk. Besides, chronic eosinophilic inflammation in the lower respiratory tract may contribute to their remodeling (13, 14, 20). Remodeling is expressed in

- increasing the number of goblet cells - hypersecretion
- hypertrophy of smooth muscle cells - increased bronchoconstriction activity

- increasing the number of vessels and the capacity for rapid and pronounced edema.

- in severe long-term course of asthma collagen deposition beneath the basement membrane is also observed (Fig. 1).

Standards of treatment

Currently, the main goal of asthma treatment is recognized as achieving optimal disease control. It is important to prevent future risks, including exacerbations and side effects of the applied therapy. There is a considerable interest in controlling not only the clinical manifestations of asthma, but also inflammation and fundamental process in the pathogenesis of asthma. Nowadays, it is established that reduction of inflammation allows to achieve effective control and reduce clinical exacerbations. However, due to cost and/or the unavailability of tests for determination of sputum eosinophils and nitric oxide in exhaled air, invasiveness of bronchial biopsy on existing recommendations purpose is to control the symptoms.

Considering that asthma is an inflammatory disease the basic therapy includes drugs having an anti-inflammatory activity. The most versatile anti-inflammatory effects have inhaled corticosteroids (ICS).

Short-acting b-2 agonists (SABA) on an as-needed basis should be provided for symptom relief

or rescue. Verifying ICS therapy should be administered if necessary 3 or more times a week using SABA. Leukotriene receptor antagonists (LTRA) are recommended as a second line monotherapy in patients with a poor adherence to inhaled corticosteroids at low doses or in patients with concomitant AR. Lack of response to inhaled corticosteroids as monotherapy may require the addition of other groups of drugs. There are several options to make a choice: adding a leukotriene receptor antagonist (LTRA) in combination of

biomarkers of inflammation as these groups differ significantly in "point of application". Some biomarkers of inflammation mainly react to the impact of inhaled corticosteroids such as nitric oxide which is reduced under the influence of corticosteroids and poorly responsive to the impact of LTRA. Another predominantly reduced one under the influence of LTRA is cysteine leukotrienes. The third significantly reduced under the impact of LTRA and under the influence of inhaled corticosteroids is a number of eosinophils in induced sputum. However LTRA group and low dose steroids to reduce the swelling, hypersecretion and bronchoconstriction are sufficiently easy to control asthma. Thus these two groups of preparations are effective in a successful asthma control in children by reducing the activity of inflammation. In adults the preferred first step of monotherapy is ICS and LTRA are recommended as a second-line monotherapy in patients with poor adherence to ICS, low-dose ICS requirements or in those who also have concurrent AR.

The mechanism of anti-inflammatory activity of inhaled corticosteroids is associated with suppression of inflammatory mediator release cascade, decrease the synthesis and release of IL-1, IL-5, IL-6 and TNF- α ; TH2 cytokine production inhibitor, IL-4 and IL-5 CD4+ T-cells. Inhaled corticosteroids reduce airway reactivity both early and late phase of allergic response to inhaled allergens, diminish the attraction of inflammatory cells.

To control symptoms while taking inhaled corticosteroids alone is often insufficient. Such situations arise even if ICS are administered in high dose. This is not surprising, since corticosteroids have no direct impact on the reduction of leukotriene synthesis by cells (monocytes, T-lymphocytes, eosinophils), does not reduce the number and activity of CysLT1 receptors and can only indirectly reduce the amount of RNA required for the synthesis of leukotriene (14). Mondino and others have shown that taking 200 mcg of fluticasone propionate for 4 weeks caused a reduction of LTE4 in exhaled air by only 18% (17). Gylfors P. et al studied 13 patients with mild asthma a few days prior to treatment and 2 weeks after the LTD4 level measured in the urine, as a marker of leukotriene biosynthesis. They also performed methacholine challenge test and measured levels of nitric oxide in exhaled air as a marker of response to corticosteroids. Patients were treated with 1000 mcg of fluticasone propionate. This was a double-blind, placebo-controlled crossover design with 2 weeks in each period and a three-week washout period in between. The results showed that fluticasone propionate significantly reduced methacholinic hyper-reactivity and nitric oxide in exhaled air, but the level of LTD4 in urine from the same patients did not decrease (18). These data suggest that inhaled corticosteroids do not prevent bronchospasm, edema and hypersecretion caused by leukotrienes. Thus, the factors that cause the lack of efficacy of inhaled corticosteroids in adults and children over 12 years include poor inhalation technique, continued exposure to allergens, smoking, poor adherence to therapy and insufficient suppression of leukotriene mechanisms of the inflammatory response.

So, with little effect of inhaled corticosteroids it is recommended to move to step 3. The doctor has the choice between the following variations within the same therapeutic steps:

increasing the dose of inhaled corticosteroids to high, to add LTRA or LABA. Three of these combinations have comparable efficacy to control the clinical manifestations. Regarding the ability to affect the activity of the inflammation, the first two variants have greater anti-inflammatory therapy potential compared to a fixed combination. And in making "informed" therapeutic decisions are likely to take into consideration the comparative effectiveness of these three combinations in controlling asthma symptoms and the ability to control disease activity. Below are details of two large meta-analyses comparing the effectiveness of each of the steps in asthma control.

Adding LTRA to inhaled steroids

In 2012 meta-analysis data were published which included prior studies of August 2011. Of potentially relevant studies inclusively 13 studies criteria for inclusion in the meta-analysis (n = 2774) has been taken. In total, the meta-analysis included 1217 patients. The researchers concluded that low-dose inhaled corticosteroids in combination with SINGULAIR[®] as effective in improving FEV1 and reduces the severity of eosinophilic inflammation as a high dose of inhaled corticosteroids. Inhaled corticosteroids in combination with SINGULAIR[®] more effectively reduces multiple use of short-acting agonists in comparison with high-dose inhaled corticosteroids (12).

Montelukast, compared with LABA when added to ICS

In case where no clinical control on low-dose inhaled corticosteroids is achieved, we can switch to a fixed combination of ICS and LABA, add LTRA or increase dose of inhaled corticosteroids. There are a number of studies that compared the efficacy of LABA and LTRA when added to inhaled corticosteroids. In 2011, Ducharme FM et al published a meta-analysis which included 17 studies carried out before 2010. The researchers concluded that the difference in the effectiveness of adding LTRA and LABA to low-dose inhaled corticosteroids is statistically significant in favor of LABA but very small with the addition of LABA and is associated with the risk of serious adverse events occurred in 1.3 times higher (3).

LABA safety is problematic especially when used without inhaled corticosteroids. In 2010 the Committee of FDA (U.S. Food Safety Committee and drugs) taking into account data of studies, concluded that the benefit of LABA continue outweigh the risks when used properly. However, given the serious risk, FDA recommends administration of LABA to patients whose control cannot be achieved with the help of drugs asthma controllers. Some studies have shown that the use of LABA in conjunction with inhaled corticosteroids reduces the risk, other studies have not confirmed these findings, and therefore FDA insists that long-term use of LABA should be limited to those cases in which patients do need them (2).

LABA have another effect that is not dependent on whether the patient receives LABA inhaler or different inhaler devices. It should be born in mind that the regular use of LABA in the control of symptoms and lung function has no effect on inflammation in the airways. McIvor and others have shown in their study that the dose of corticosteroids may be reduced by 87% with the addition of LABA while there will be no symptoms and the level of eosinophilic inflammation

will be quite high. Thus LABA may mask increasing inflammation and lead to severe exacerbations (10). A meta-analysis in 2006 showed that regular use of LABA, despite taking inhaled corticosteroids can cause an increased risk of severe exacerbations (14). These data were confirmed by two Cochrane reviews that assessed the risk of severe exacerbations requiring hospitalization of patients who received LABA with ICS. It was concluded that LABA should be considered as adjunctive therapy to standard therapy with inhaled corticosteroids. If it is necessary to add a LABA to ICS, we must switch the patient to a fixed dose combination. While the benefits of LABA greatly exaggerated, and the potential risks are high, LTRA are comparable choice as an addition to inhaled corticosteroids.

Effectiveness of montelukast in real clinical practice

It is important to note that the data on the comparative efficacy of montelukast to inhaled corticosteroids as monotherapy and addition to ICS compared with LABA is taken from randomized controlled trials that have strict inclusion and exclusion criteria. These restrictions do not allow you to transfer data from randomized trials to clinical practice. The difference between the results of randomized trials and clinical practice is often revealed. This may partly explain the inadequate broadcasting the results to clinical practice. Interestingly, only 5.4 % of patients with asthma of the total cohort can take part in the study, due to the fact that the majority of patients did not meet the strict criteria for inclusion in randomized trials (7). In order to use the results of the effectiveness of montelukast, studies have focused on observational of “real-world clinical practice.”

In 2005, Dupont conducted a study of 313 patients aged 15 and older with persistent asthma which inadequately controlled ICS and LABA (4). Montelukast significantly improved asthma control and impact on quality of life according to ACQ test (4). In 2009 the same open, prospective, multicenter, observational study was published that evaluated the role of montelukast as a second controller. Korn and other authors evaluated the addition of montelukast 10 mg and 4.5 to ICS or ICS and LABA in 5700 patients, many of whom were children aged 4 years and older. It was noted significant improvement in quality of life, measured by ACQ test and reducing the symptoms of asthma (9). In 2009, a study SAS, and in 2010 in the STAR study and MONICA study it was shown that the addition of montelukast to current therapy with inhaled corticosteroids or inhaled corticosteroids and LABA improves asthma control, quality of life of patients with asthma and lung function (6, 17, 18). Thus, the data from clinical practice confirm the efficacy of montelukast in asthma control as shown in randomized studies. The necessity of adding montelukast to improve asthma control due to the ability to control the development of leukotriene's pathway inflammation, which cannot be eliminated with corticosteroids. Thus, when there is insufficient control of asthma with inhaled corticosteroids alone with preserved lung function values within 80% and more it would be more appropriate, in our opinion, to strengthen anti-inflammatory therapy with LTRA. This combination is particularly suitable in the presence of allergic rhinitis as LTRA affect systemic aller-

gic inflammation as opposed to an inhaled corticosteroids and especially LABA, which do not have an anti-inflammatory action.

Conclusions

Asthma is a chronic inflammatory disease. A balanced approach to anti-inflammatory therapy may be useful to control symptoms, reduce the volume of therapy in the future, prevent bronchial remodeling, and reduce the risk of exacerbations. The background for the basic therapy is drugs having an anti-inflammatory activity. Inhaled corticosteroids are the cornerstone of asthma therapy; LTRA are an important component of the basic treatment of asthma, which act differently from the mechanisms of inhaled corticosteroids, which eliminate the inflammation in the airways. For better control of inflammation it is necessary to use a combination of anti-inflammatory agents (ICS with LTRA).

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ПІДХОДИ ДО ЛІКУВАННЯ БРОНХІАЛЬНОЇ АСТМИ ПРОТИЗАПАЛЬНИМИ ЗАСОБАМИ

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Вступ. Бронхіальна астма являє собою комплекс процесів, результатом яких є запалення дихальних шляхів, що проявляється бронхоспазмом. Слизова оболонка дихальних шляхів інфільтрується активними запальними клітинами, відбувається масове вивільнення медіаторів запалення. Такі медіатори, як лейкотрієни, відіграють важливу роль у цьому процесі. Нині інгаляційні кортикостероїди (ІКС) є наріжним каменем у контролі астми. Проте контроль над астмою може залишитися нижче оптимального внаслідок недотримання режиму прийому ІКС, неправильної техніки виконання інгаляцій, побоювань відносно побічних ефектів кортикостероїдів, тобто часто необхідні додаткові можливості щоб контролювати симптоми бронхіальної астми. Антагоністи лейкотрієнових рецепторів (ЛТРА), а саме монтелукаст, є другим ефективним і добре переносимим проти-запальним компонентом базисного лікування. Існує особлива перевага для пацієнтів з астмою і супутнім алергічним ринітом.

Охоплені питання. Монтелукаст (Сингуляр) вивчений у ході добре спланованих рандомізованих клінічних досліджень. У цій публікації представлений ретельно проведений аналіз літератури, метою якого була оцінка доказової бази, що підтверджує необхідність використання ЛТРА. Цей огляд присвячений ролі Монтелукасту в якості монотерапії, додаткової терапії до ІКС в популяції дорослих пацієнтів з бронхіальною астмою, у тому числі із супутнім алергічним ринітом. Крім того, часто можуть виявлятися деякі розбіжності між фактичними даними, отриманими у ході рандомізованих досліджень з набраними «ідеалізованими» хворими на астму, від результатів в умовах реальної клінічної практики. Включення даних, отриманих в реальних умовах у широкого кола пацієнтів, з великим набором кінцевих точок, повинне допомогти клініцистам приймати більш обґрунтовані терапевтичні рішення. Такі дослідження можуть виступати орієнтирами у веденні більшості пацієнтів, забезпечуючи ширший погляд на проблему коморбідності, сприяючи прихильності до лікування.

Думка експертів: Зважений підхід до проти-запальної терапії може бути корисним для контролю симптомів, успішного зменшення об'єму терапії надалі, попередження ремоделювання бронхів, зниження ризику загострень. Основою базисної терапії є препарати, що мають проти-запальну активність. ІКС залишаються наріжним каменем в терапії БА; ЛТРА є важливим компонентом базисної терапії БА, які відмінними від ІКС механізмами усувають запалення в дихальних шляхах.

Для кращого контролю запалення необхідно використовувати проти-запальні комбінації (ІКС у сполученні з ЛТРА).

Ключові слова: бронхіальна астма, контроль, запалення.

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ANTI-INFLAMMATORY BASIC THERAPY OF BRONCHIAL ASTHMA

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Introduction: Asthma is a complex processes that results from airway inflammation and manifests as bronchoconstriction. Infiltration of the airway mucosa and lumen by activated inflammatory cells, along with release of mediators, can occur extensively. Chemical mediators known as leukotrienes are believed to play a major role in this process. At present, inhaled corticosteroids (ICS) are the pharmacologic cornerstone of asthma management. However, asthma control may remain suboptimal when relying on ICS because of problems with compliance, poor inhaler technique and concerns about the side effects of steroids; additional agents are often required to control symptoms. Leukotriene receptor antagonists (LTRA), namely montelukast, provide a safe and effective additional anti-inflammatory treatment option. There is particular benefit for patients with asthma and concomitant allergic rhinitis.

Areas covered: Montelukast has been well studied through rigorous clinical trials. A thorough review of the literature has been undertaken to assess the evidence supporting the use of LTRAs. This review focuses on the role of montelukast not only as monotherapy but also as add-on therapy to ICS in the adult asthma population, as well as adult asthmatics with concomitant allergic rhinitis. In addition, there is often some discrepancy between the evidence generated in the idealized asthma patients recruited into randomized clinical trials and results obtained in the real-life setting. This review assesses recent clinical trials evaluating the real-life evaluation of montelukast, achieved mainly through open-label observational studies.

Expert opinion: Oral LTRA bring remarkable ease of anti-inflammatory treatment administration and symptom improvement with minimal side effects to the management of adult asthma. Balanced approach to anti-inflammatory therapy may be useful for controlling symptoms, successful magnitude of treatment reduction, prevent bronchial remodeling, reducing the risk of exacerbations. The mainstays of therapy are drugs having an anti-inflammatory activity. Inhaled corticosteroids are the cornerstone of asthma therapy; LTRA is an important component of basic therapy of asthma, which reduces inflammation by mechanisms other than corticosteroids. For better control of inflammation is necessary to use an anti-inflammatory combination (ICS with LTRA).

Key words: asthma, control, inflammation.

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