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Effect of Certain Comorbid Diseases on Choosing Basic Treatment of Bronchial Asthma

Key words: *bronchial asthma, leukotriene modifiers, allergic rhinitis, comorbidity, monteleukast, Singulair®.*

As is well known, for patients suffering from bronchial asthma (BA), effect of triggers (such as, tobacco smoking) or presence of comorbid diseases (such as, chronic rhinitis) may be associated with higher frequency of uncontrolled course of this disease. According to some reports, adult BA patients display nasal symptoms in 78 % of cases [9]. Equally high frequency of this nosological combination is determined by Japanese authors who informed that 44–68 % of BA patients suffered from allergic rhinitis (AR) [14].

Other studies covered correlation between allergic rhinitis and BA severity [3, 5]. It was shown, that patients suffering from BA and allergic rhinitis were admitted to hospital more often, had more frequent unscheduled visits to doctors and required higher expenses on treatment comparing to patients with BA only [16, 21]. So, aggravation of BA course in presence of AR received evidence-based explanation. According to works by E.P. de Groot et al. (2012), patients with BA in combination with AR had significantly more acute inflammatory process, than patients without allergic rhinitis. 2-fold increase in nitrogen oxide level and total IgE level was observed in patients with concurrent AR, comparing to patients without allergic rhinitis. In patients who received adequate AR treatment, asthma was controlled in the same way as in patients without AR [10]. Thus, performed studies allowed make a conclusion that removal of AR symptoms contributed to achieving control over BA. This argumentation includes an indisputable clinical fact that one of the ways of overcoming adverse reactions of a tracheobronchial tree in the form of its hyperactivity is AR treatment.

The studied correlation was also discovered in children with AR, which increased risk of BA development, in particular, in cases with manifestation of bronchial hyperactivity. Furthermore, many studies clearly demonstrate that in children suffering from AR, BA occurs three times as often in years of maturity.

According to analysis of population data of 32 research centers all over the world, AR was discovered in over 50 % of BA patients, and 35% of asthma patients turned out to be smokers [2]. On the basis of the data provided, previous versions of GINA introduced a section titled “phenotype” describing interrelation between individual genetic features and impact of environmental factors. Similar clinical and genetic differences lead to variation of response to different variants of BA basic treatment.

Relevance of this problem is determined by the fact that BA is a common, socially significant disease accompanied by AR in many patients, symptoms and pathogenesis whereof is conditioned by immediate and delayed allergic reactions. Thus, there appeared clinical understanding of necessity to eliminate AR symptoms, in order to achieve control over BA. Inhaled glucocorticosteroids (IGCS) though being a cornerstone in BA basic treatment, however, are unable to stop inflammation of upper respiratory airways with AR. At the same time, antihistamines or endonasal corticosteroids, depending on severity of rhinitis, represent the first-line treatment for patients with isolated AR. Medications of these groups successfully reduce AR symptoms, however, they do not improve asthma control.

According to GINA recommendations (2011–2013), IGCSs are acknowledged as major BA controllers. Nevertheless, in some clinical situations, leukotriene receptor antagonist (LTRA), e. g., montelukast sodium (Singulair®, MSD), became an alternative to monotherapy for some patients, e. g., in BA and AR combination [17, 23]. Moreover, addition of montelukast to IGCS basic treatment is a clinically efficient alternative to increase in IGCS dose or to addition of

long-acting beta-agonists (LABA) to the latter with patients with moderate BA severity [18]. Observational data obtained from several studies strongly indicated that montelukast addition to IGCS or IGCS + LABA basic treatment allowed control BA significantly better and improve quality of life for this group of patients [8, 11, 24, 25]. Moreover, montelukast is an effective opportunity to achieve optimal control over BA combined with AR in patients with no BA control [2].

Results of a large-scale European observational study on 5,855 patients showed efficiency of montelukast (Singulair®) for controlling BA and AR: 86,5 and 88,5 % of patients observed less severe daily and nocturnal symptoms, respectively, and a high percentage of patients (77–84 %) observed reduction in AR symptoms [24]. Also, 88.1 % of patients displayed decrease in amount of medications for AR treatment in 4 and 6 of montelukast treatment, patients evaluated their satisfaction with treatment results ("good" and "very good") in terms of symptoms and quality of life as 88,8 % for BA and 83,5 % for AR.

As far as pharmacodynamics of montelukast sodium goes, it was proved to block first-type leukotriene receptor antagonist CysLT1 and prevent leukotrienes-dependent inflammatory effects. These receptors are predominantly located in vascular endothelium, pulmonary smooth muscle cells, and on cells playing an important role in pathogenesis of allergic inflammation, such as eosinophils, mast cells, basophils and dendritic cells. Leukotrienes when binding to leukotriene receptors cause inflammation of airways and participate in pathologic physiology both of bronchial asthma, and AR. These mediators cause bronchial spasm (1,000 times stronger than histamine), bronchial hyperactivity, edema, hypersecretion and draw inflammatory cells (eosinophils, in particular) into airways, and activate dendritic cells, which participate in allergic sensitization. With BA getting severer, aggravation of asthma, allergen challenge, number of leukotrienes in bronchoalveolar lavage fluid increases. The same occurs in nasal lavage fluid in AR patients after allergenic load. Number of leukotrienes LTE4, LTC4, LTD4 in urine increases in patients when inhaling tobacco smoke and other airborne allergens. Due to ability of montelukast sodium to block leukotriene inflammation path, the medication improves BA control and reduces AR symptoms.

So, in the course of learning the process, we not only simultaneously, but successively cover its various clinical and pharmacotherapeutic aspects. We obtain better understanding of the single function of upper and lower airways, we combine allergic inflammation into a single pathogenic process in BA and AR patients.

Implementation of post hoc analysis in the study of D. Price et al. showed effectiveness of montelukast addition to budesonide comparing to budesonide dose doubling in patients suffering from BA and AR [17]. In montelukast and budesonide group, BA and AR patients made up 216 persons, and in double budesonide dose group – 184. Patients were evaluated for improvement of morning peak expiratory flow rate (PEFR). The study results showed statistically significant difference in treatment efficiency in montelukast and budesonide group comparing to IGCS dose increase. So, after 12 weeks of treatment, increase in morning PEFR made up 9,2 % in montelukast and budesonide group, and 6 % ($p = 0,028$) in double budesonide dose group. These results confirm recommendations of Allergic Rhinitis and its Impact on Asthma (ARIA) and demonstrate advantage of montelukast (Singulair®) addition to treatment of patients suffering from BA and AR.

In another unmasked two-month trial, P. Keith et al. evaluated montelukast effectiveness for BA and AR patients, clinical course whereof was not controlled by IGCS or IGCS + LABA. In this trial, addition of montelukast(Singulair®) to the current therapy significantly improved BA and AR control ($p < 0,001$) [11]. For the major part of patients, BA control managed to be achieved both in IGCS group, and IGCS + LABA group, and quality of life related to AR presence was improved.

There is no doubt, that a design of a long-term trial on a large sample is considered for justification of pharmacological efficacy of medications. So, in an unmasked clinical trial (MONICA), which lasted for 12 months, J. C. Virchow et al. studied effectiveness of montelukast (10 mg) added to the basic IGCS or IGCS + LABA therapy [18]. This study was aimed to determine efficacy of this combination in various subgroups of patients with BA. In total 1,681 patients were included into the trial. BA control was evaluated at the baseline, during the 3rd, 6th, 9th and 12th month by means of an Asthma Control Test. Primary endpoint was evaluation of asthma control in the group of patients under study. Performed secondary post-factorial analysis allowed divide the patients under study into subgroups in terms of: age, sex, presence of comorbid AR, BA duration, and delivered IGCS or IGCS + LABA treatment. Results of the trial strongly indicated significant improvement in average BA control score in the general population group. After 6 months of monelukast treatment, percentage of patients with full BA control increased from 1,2 to 11,4 %, and that with well-controlled asthma – from 13,9 to 47,5 %. Percentage of patients with uncontrolled asthma decreased from 57,5 to 17,6 %.

In the above trial, patients with comorbid AR at the age of 30 had better quantitative indexes than those without comorbid AR. More significant achievement of BA control was informed in patients with less than 5 years duration of disease and in patients receiving IGCS monotherapy without LABA. As a rule, addition of montelukast displayed significant reduction in BA symptoms and improvement in pulmonary function for all patients under examination, including patients with comorbid AR.

There is another group of patients for whom approach to a basic treatment is not sufficiently customized in recommendation documents on BA treatment. It involves patients with long-term smoking history. Indeed, recommendations on BA treatment consider IGCSs as a standard for BA treatment based on data concerning their effectiveness in symptom reduction, enhancement of pulmonary function and inflammation decrease. However, these recommendations are based on data obtained from clinical trials which excluded smoking patients, and this category comprises a significant part of asthma patient population [20, 22]. Available data show that BA is less controlled in this group of patients comparing to non-smokers, as both total control and individual control

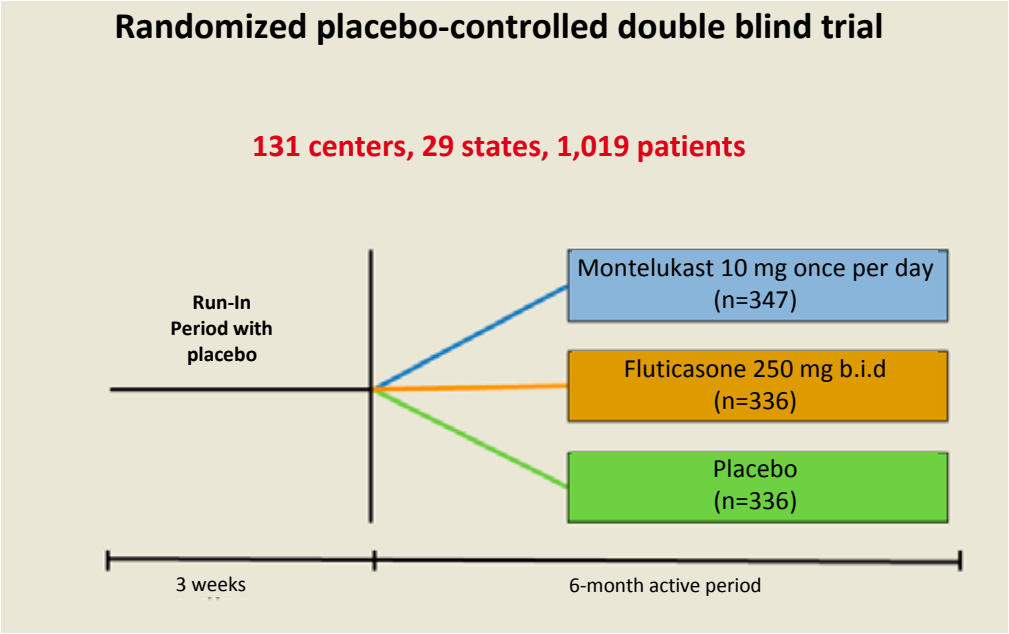

Figure 1. **Trial design**

parameters deteriorate. Number of awakenings at night, daytime symptoms, and implementation of first-aid means significantly increases. Smoking patients display more apparent limitation of physical activity, higher frequency of aggravations, increase in bronchial hyperactivity, decrease in FEV_1 and progressive decline in pulmonary function, which is to a great extent associated with smoking. Taking into account, that level of smoking among BA patients is the same as with general population and makes up from 30 to 50 % according to various authors, relevance of this problem is high.

For deeper understanding of this problem, it should be mentioned that knowledge on efficacy of corticosteroids for smoking BA patients is currently not sufficient. Data available to us show only that efficacy of corticosteroids for smoking patients and those who have long-term smoking history is lower [12, 15]. In these trials, corticosteroid therapy in active smokers suffering from BA didn't improve pulmonary function comparing to non-smoking patients. R. Chaudhuri et al. found that smoking impaired response to corticosteroid therapy. A group of actively smoking patients, and a group of patients who quitted smoking displayed no significant improvement in pulmonary function and BA control in response to prednisolone administration, according to asthma-control questionnaire. Only a group of non-smoking BA patients displayed improvement of these parameters [7].

Mechanisms of resistance to corticosteroid therapy determined by smoking are unclear. Supposedly, it is associated with enhanced IGCS excretion due to increased sputum production in smoking patients, decline in histone deacetylase activity, worse penetration of inhaled medications through inflamed tissues [6, 26]. And what is extremely important, trial results confirm the fact that smokers display increased cysteinyl leukotrienes production causing expected aggravation of BA symptoms.

That is why, smoking BA patients may benefit from LTRA therapy. These data were confirmed in trial of D. Price et al. published in 2013. The authors studied efficiency of Montelukast, 10 mg daily, and Fluticasone propionate, 250 mg b.i.d., comparing to placebo in active smokers with BA who could not quit smoking. The trial included patients of 18–55 with at least one year BA duration, with FEV_1 from 60 to 90 % of proper parameters, over 12 % bronchodilator reversibility, and smoking volume made up from 0,5 to 2 packs per day. After 3 weeks of run-in period with placebo, patients were randomized into a placebo-controlled double blind trial by 3 parallel groups for 6 months (*figure 1*).

The trial studied a percentage of days with BA control in all patients, and a percentage of days with BA control in subgroups of patients with various periods of smoking. The both treatment methods both in montelukast group, and fluticasone group, were more effective than placebo. There was no significant difference between active treatment groups ($p = 0{,}140$). However, higher efficiency was displayed by IGCS in patients with history of smoking less than 11 packs/years, and montelukast was more effective in patients with smoking history of over 11 packs/years. Thus, with regard to decline in IGCS effectiveness for BA in patients with long-term smoking history, montelukast is an effective alternative to increase in dose of glucocorticosteroids in absence of BA control within the current therapy.

Conclusions

The described trials of different duration (between 2 and 12 months), which included patients at the age of 15–80 with varied BA duration, and with comorbid AR or a long-term smoking history, proved clinical efficiency of montelukast as monotherapy or as addition to IGCS or to IGCS+LABA. Administration of montelukast significantly reduced need in «first-aid» bronchial spasmolytics, improved clinical control and quality of life in BA and AR patients. Montelukast (Singulair®) improved external respiration and decreased bronchial hyperactivity, which had crucial importance for BA patients. In view of the above facts, montelukast is an integral component of BA basic therapy in patients with comorbid AR and long-term smoking history.

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ВПЛИВ ДЕЯКИХ КОМОРБІДНИХ ЗАХВОРЮВАНЬ НА ВИБІР БАЗИСНОЇ ТЕРАПІЇ БРОНХІАЛЬНОЇ АСТМИ

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Резюме. *У статті розглядається роль алергічного риніту (АР) та інших специфічних факторів чи коморбідних станів (тютюнопаління), що часто поєднуються з неконтрольованою бронхіальною астмою (БА). Ці стани погіршують перебіг БА через посилення лейкотрієнового механізму запалення. Автори проаналізували дані багатоцентрових досліджень, в яких доведена терапевтична ефективність монелукасту (Сингуляру®) при поєднанні БА з АР та іншими коморбідними станами. Показано, що базисне лікування монелукастом має оптимальне клінічне обгрунтування у хворих з астмою, що поєднується з АР або курінням.*

Ключові слова: *бронхіальна астма, модифікатори лейкотрієнів, алергічний риніт, коморбідність, монелукаст, Сингуляр®.*

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IMPACT OF SOME COMORBIDITIES ON THE CHOOSE OF BASIC ASTHMA MANAGEMENT

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Abstract. *This article examines the role of allergic rhinitis (AR) and other specific factors or comorbidities (smoking), which are often combined with uncontrolled asthma. These conditions can impair the progress of asthma by enhancing leukotriene-associated inflammation. We have analysed data from multicenter trials that demonstrated the clinical efficacy of montelukast (Singulair®) in patients with combination of asthma and AR or other comorbidities. It is shown that basic treatment with montelukast in patients with asthma and concomitant AR or smoking has good clinical evidence.*

Key words: *asthma, leukotriene modifiers, allergic rhinitis, comorbidity, montelukast, singulair®*

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