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## Effect Antileukotriene Substances (Montelukast) In Patients With Changed Bronchial Reactivity (Non-Reactors, Moderate Reactors And Emphasized Reactors).

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### ABSTRACT

Effect of antileukotriene substances – Montelukast in the treatment of patients with bronchial asthma (non-reactors, moderate reactivity and emphasized reactivity), and of the salbutamol as agonist of the beta<sub>2</sub> adrenergic receptor studied in this work. Parameters of the lung function are determined with Body plethysmography. Raw and ITGV were registered and specific resistance (S<sub>Raw</sub>) was calculated. Montelukast (Monolast, tabl. 10 mg), was used in the research. Results of this research indicate that antileukotriene substances – Montelukast- 2 days after administration of the medicine at home, and admitting at the ambulance on the third day, administered was one tablet of Montelukast to the same patient orally in a dose of 10 mg. Afterwards, initial values measured: measured was Raw and ITGV after 30, 60, 90 and 120 min., and calculated was S<sub>Raw</sub>. There were no significant changes ( $p > 0.1$ ) of the airways bronchomotor tonus in non-reactors. In moderate reactors, there was a significant decrease of the specific resistance ( $p < 0.05$ ). Whereas, as a result of the blockage of leukotriene receptor, significantly decrease the increased bronchomotor tonus ( $p < 0.001$ ) in emphasized reactors. Treatment of the control group with Salbutamol (beta<sub>2</sub>-adrenergic agonist), which is efficient in the removal of the increased bronchomotor tonus, caused significant decrease of the resistance (Raw), respectively of the specific resistance (S<sub>Raw</sub>), ( $p < 0.05$ ). Modified medicines of leukotriene act as competitive antagonists of receptor, of leukotriene. Receptor in charge for the bronchoconstriction effect of leukotriene is sys-LT<sub>1</sub> receptor. Even though any of the cys-LTs' is an agonist to this receptor, LTE<sub>4</sub> is less powerful than LTC<sub>4</sub> or LTD<sub>4</sub>. Montelukast is selective competitive antagonist with high affinity to the receptor cys-LT<sub>1</sub>. Our results indicate that montelukast inhibits significantly connection of leukotriene to the receptor ( $p < 0.001$ ).

**Keywords:** Bronchial asthma, montelukast, salbutamol.

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## INTRODUCTION

Term bronchial hyperactivity mainly represents the bronchospastic reaction to non-specific inducers (cold air, physical load, pollution, etc.), in comparison to a bronchoconstrictor reaction seen after exposure to specific inducers (allergens, agents at the working place). Usually, the concept of bronchial hyperactivity is related with asthma but it can be met also at other condition and diseases, such e.g. patients with chronic bronchitis, allergy on the pollen, allergic alveolitis, sarcoidosis, viral infection, patients with allergic rhinoconjunctivitis, exposure to respiratory system with other irritants.

Bronchial hyperactivity can appear even transitory to healthy people after sufficient exposure to ozone, Sulphur dioxide, or after viral infection, but in these cases bronchial hyperactivity is much lower than in asthmatics with severe symptoms [1].

Large number of cells and mediator participate in the development of pathoanatomic and functional changes in the lungs of patients. After numerous studies and debate, it is generally accepted that all of these cells and mediators may participate in the process of inflammation, interact with each other in the development of airways hyperreactivity. They have bronchoconstriction and proinflammatory activity, such as: histamine, bradykinin, leukotriene (LT), prostaglandins, thromboxane, and thrombocitary activating factor. Inflammation appears under their effect or directly (through mast cells and granulated eosinophilic proteins) or indirectly, by acting to other cells (through cytokinin's and endophilins) [2].

It is clear that the appearance of inflammation is very complex and only inhibitor of the mechanism, which is not always effective in treatment of asthma at each patient.

Leukotriene are generated from the metabolism of arachidonic acid, which is found in the phospholipid layer of every cell membrane, and inflammatory cells that play an important role in development of asthma. Various inducers (activation of receptors IgE, presence of allergens and antigen-antibody interaction, presence of microorganisms and other), release arachidonic acid in the lungs. [3, 4].

Pathophysiological mechanism and development of bronchial hyperreactivity is very complex, and it is logic to seek many therapeutically accesses for better control of the illness in particular those correlating with the treatment and longterm prevention of medicines.

Main longterm experimental studies, and those clinical also, in large series, in duration of two decades, undoubtedly tells us about effectiveness of antileukotriene medicines.

These medicines are well tolerated from the organism, and have no emphasized side effects, which is positive for their therapeutical effect. Their discovery and clinical usage, nonetheless has not reduced effectiveness, nor changed the attitude regarding application of corticosteroid inhaling medicines in long-term preventive treatment of the diseased. Having in mind the abovementioned facts, there are some real chances that these medicines in the future find a proper place in medication of bronchial asthma.

Work studied the effect of antileukotriene – Montelukast administered orally (10 mg) in people with bronchial hyperreactivity and asthma (non-reactors, moderate reactors, and emphasized reactors). After administration of the medicine, measured are Raw and ITGV and calculated SRaw.

## MATERIAL AND METHODS

49 patients with bronchial asthma and increased bronchial reactivity were subject to examination. Study included 49 patients. At least 48 hours' prior research of bronchial reactivity response, patients has not administered any of the bronchodilator substances. Examined were informed regarding method of the functional pulmonary tests. Patients were suffering from asthma, with or without associated bronchitis. Average of the disease period was  $5 \pm 6$  years (**from 10-20 years**). Average of their age was  $35 \pm 7$  years (**from 20 – 45 years**), whereas average of relative weight was  $78 \pm 7\%$  (**from 65 – 75%**). The aim of the examination was explained to each of the patients in advance. Pulmonary function, composed of measurement of vital capacity (VC), forced expiratory volume in the first second (FEV<sub>1</sub>), resistance in the airways (Raw) and intrathoracic gas volume (ITGV), was defined at the rest.

Overall quantity of the intrathoracic gas volume (ITGV) was measured with the plethysmography method, including not ventilated closed gas. If the residual functional capacity is taken from the ITGV, obtained by the plethysmography method, we will gain information regarding quantity of closed gas due to a severe obstruction, cystic lungs, or pneumothorax. In healthy people with a normal pulmonary function, volume of the intrathoracic gas is equal to the residual functional capacity. From the beta and alpha angles, assisted by tables, values of the airways resistance and volume of the intrathoracic gas are calculated. From gained values, specific resistance was calculated:

$$SRaw = Raw \times ITGV$$

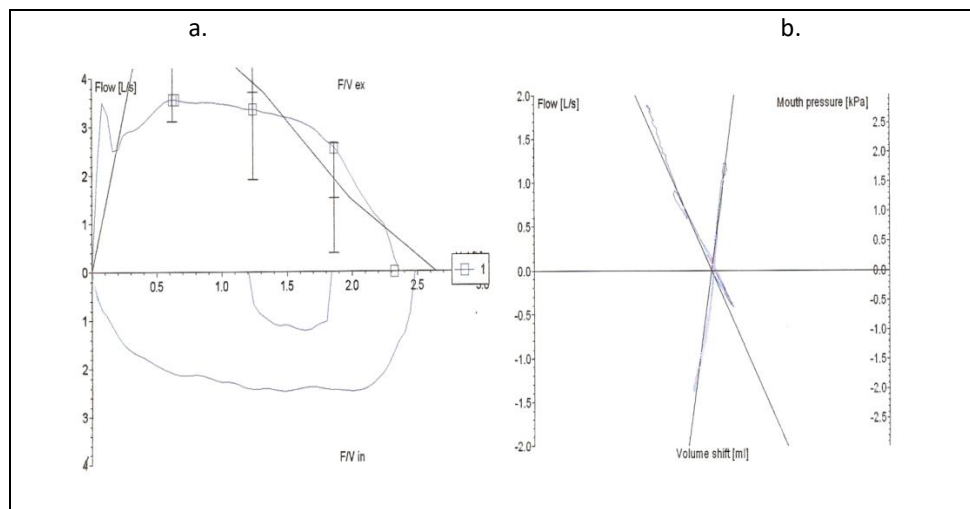
Raw and the SRaw were taken for analyses. Research of the bronchial response to different substances was done with the measurement of Raw and the SRaw as very sensitive indicators.

Basic and pulmonary function features of researched are provided in table 1.

**Table 1: Basic airways characteristics**

n	Age (v)	Height (cm)	Weight (kg)	VC (%)	FEV <sub>1</sub> (%)	Raw (kPa L/s)	ITGV (L)
49	35 ± 1,30	173.19 ± 1.17	78.81±0.78	3.19±3.2	2.55±3.46	0.29±0.01	3.66±0.14

**Figure 1: Measurement with Body plethysmography:**



- a. Measurement of parameters of the gas volume in the sternum (ITGV); registration of flux-volume curve (inspiratory flux and expiratory flux - L/min);
- b. Resistance of airways (Raw - L/sec.) expressed in kPa.

**Montelukast**, as antagonist of leukotriene receptor (10 mg, tablet) administered orally 2 days in row at home (1 x 1 tabl.) and reported at the ambulance on the 3<sup>rd</sup> day and measured initial values, and one more tablet administered orally at the ambulance, and afterwards, measured Raw and ITGV after 30, 60, 90 and 120 min. At the end, as control, applied salbutamol (beta<sub>2</sub>-adrenergic agonist) in the form of aerosol and in a dose of (2 inh. x 0.2 mg); Raw and ITGV values were measured again and SRaw was calculated.

Used was the hypothesis that changes in the respiratory system are not important, not related to the development of bronchial asthma or other obstructive diseases, and not related to allergic manifestation. Gained results grouped and analyzed. Statistic data processing included determination of the average values (X), standard deviation (SD), standard mistake (SEM), and testing of significance of changes in between groups of patients treated with antileukotrienes.

Gained results tested with a t-test. In order to compare groups, utilized was statistic test ANOVA. Potential mistakes with t – test avoided with ANOVA used as a method of statistic test.

**RESULTS**

Applied antileukotriene substance **Montelukast** (1 x 10 mg), administered orally 2 days in row at home (1 x 1 tabl.). On the 3<sup>rd</sup> day, same patient reported at the ambulance and administered one capsule of montelukast orally in a dose of 10 mg, and afterwards measured initial values at the ambulance; measured Raw and ITGV after 30, 60, 90 and 120 min, and calculated the SRaw.

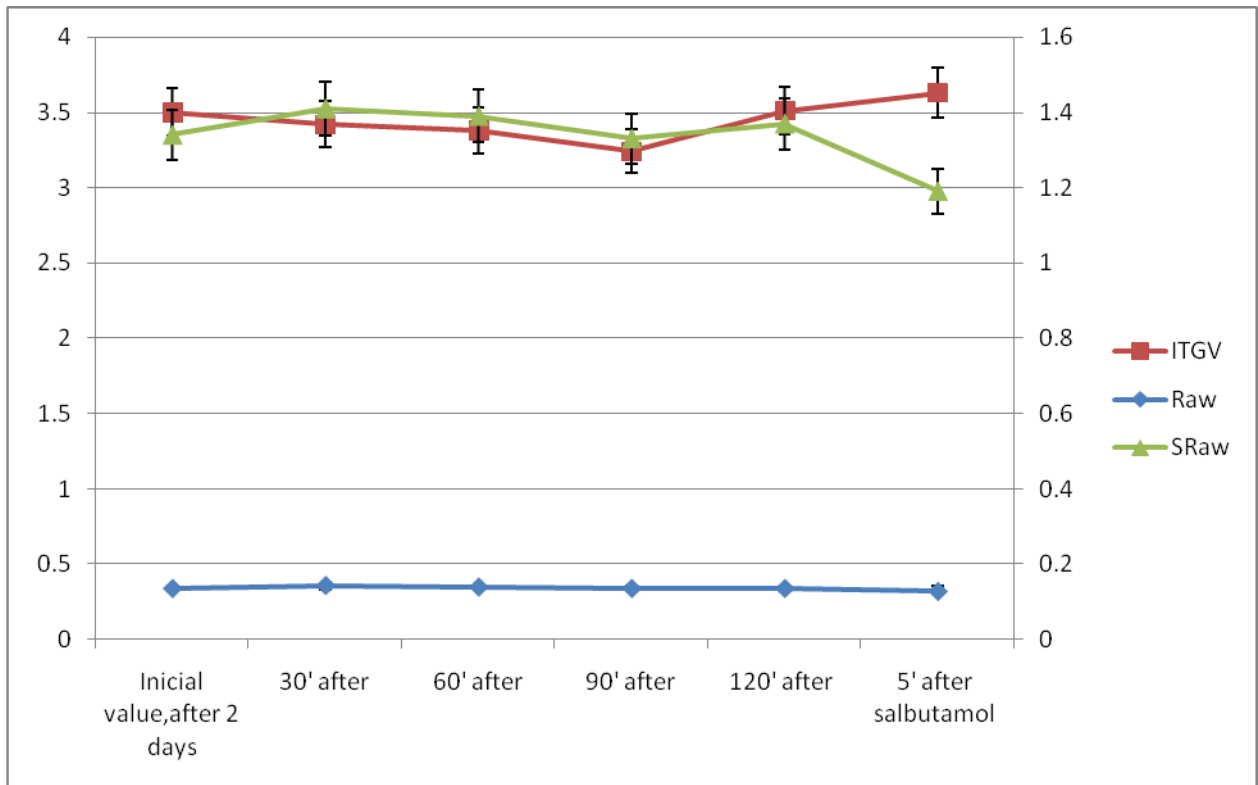
There were no significant changes of the specific resistance in patient with decreased bronchial reactivity of the tracheobronchial system (non-reactors) (SRaw) ( $p > 0.1$ ). Mainly, these are patients with pulmonary chronic obstructive changes and severe bronchial asthma.

In patient with moderate bronchial reactivity of the airways (**moderate reactors**), appeared significant decrease of the specific resistance of airways ( $p < 0.05$ ). We have to deal here mainly with patients with moderate to severe type of asthma.

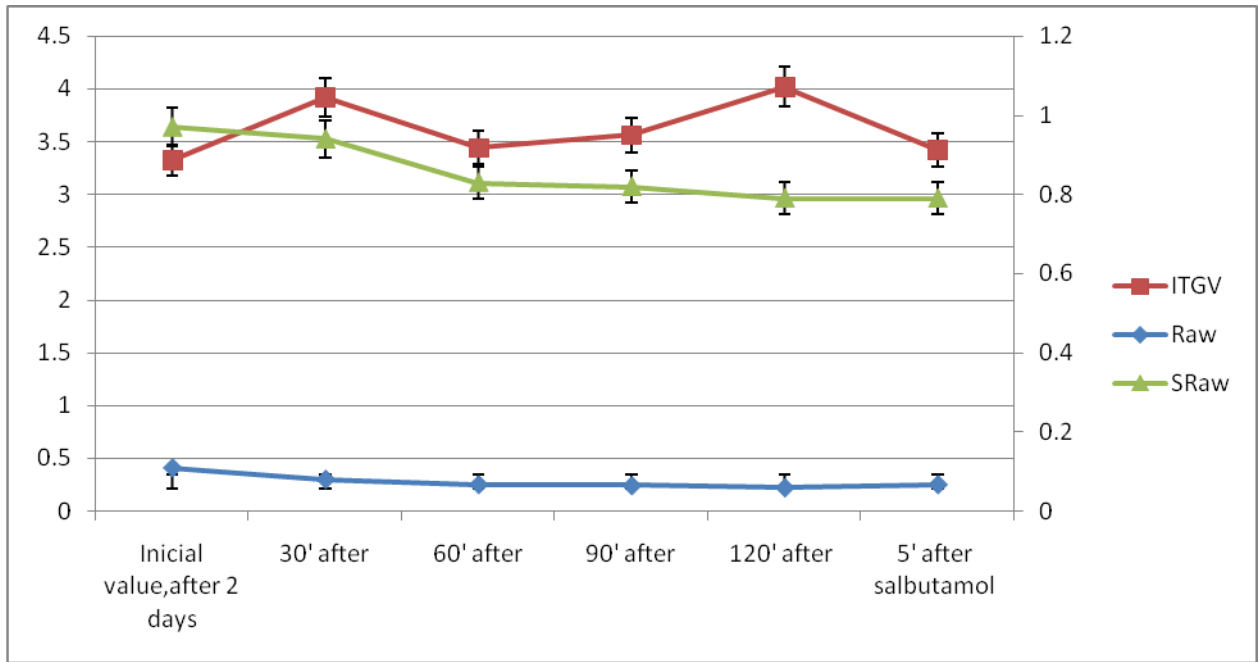
Whereas, as a result of blockage of leukotriene receptor, decreases significantly increased bronchomotor tonus ( $p < 0.001$ ) in patient with emphasized reactivity (**emphasized reactors**). Here included are patients with reversible changes of emphasized bronchial reactivity.

Treatment of the control group with Salbutamol (beta<sub>2</sub>-adrenergic agonist), which is efficient in the removal of the increased bronchomotor tonus, causes significant decrease of the resistance (Raw), respectively of the specific resistance, ( $p < 0.05$ ). See fig. 2, 3, 4.

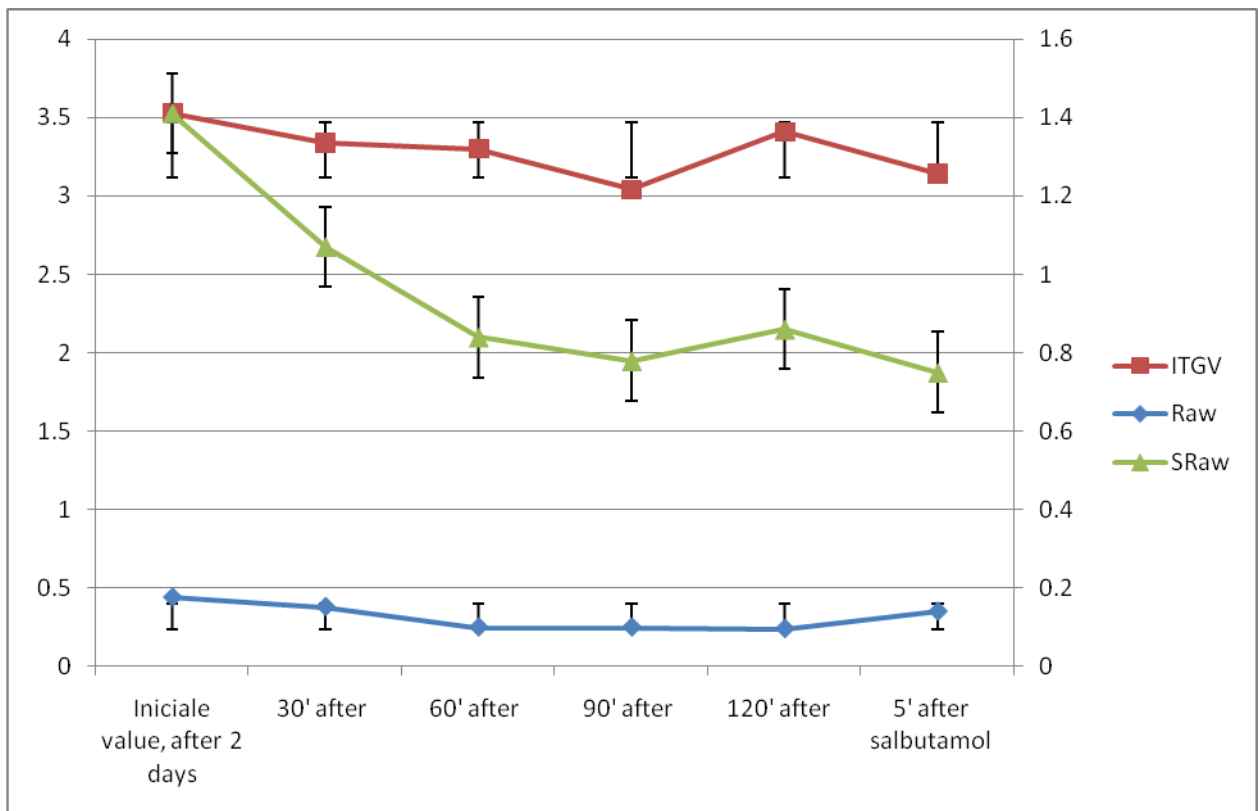
**Montelukast**, antagonist of leukotriene, administered in doses of 10 mg, has not caused significant decrease of the systolic and diastolic arterial pressure (AP) ( $p > 0.1$ ). See fig. 5.



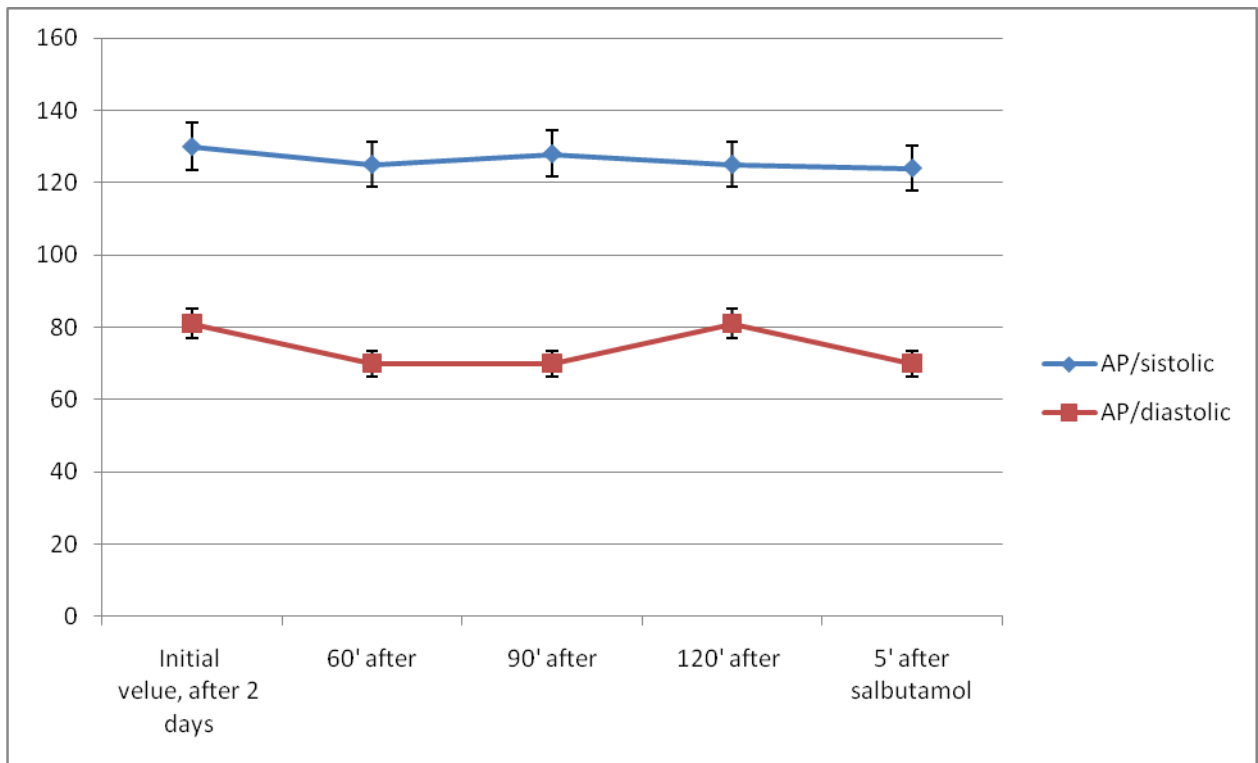
**Fig 2: Effect of Montelukast (tablet 1 x 10 mg) and Salbutamol (2 inh. x 0.2 mg) on Raw, ITGV and SRaw. Non-reactor patients; (n = 22; X ± SEM).**



**Fig 3: Effect of Montelukast (1 x 10 mg.), and Salbutamol (2 inh. x 0.2 mg) on Raw, ITGV and SRaw; Moderate reactor patients; (n = 13; X ± SEM).**



**Fig 4: Effect of Montelukast (tablet 1 x 10 mg – per os), and Salbutamol (2 inh. x 0.2 mg) on Raw, ITGV and SRaw. Emphasized reactor patients;(n = 14; X ± SEM).**



**Fig 5: Effect of antileukotriene - Montelukast (2 x 10 mg) and Salbutamol (2 inh. x 0.2 mg) to the arterial pressure (AP/systolic/diastolic); non-reactor, moderate, and emphasized reactor patients (n = 49; X ± SEM).**

### DISCUSSION

Even though leukotriene inhibitors are efficient in the prophylactic treatment of slight asthma; their role in the asthma therapy is not clearly defined. Most of the clinical trials with these medicines studied at the patients with slight asthma, who do not administer glucocorticoids. In general, studies show a modest, but important improvement to the pulmonary function and a decrease of symptoms and asthma exacerbations. Chronic presence of the increase of LT concentration in the airways causes hyperplasia of goblet cells, of the cells of smooth musculature, proliferation of endothelial cells, fibrosation of the sub-epithelium and its remodeling [5].

Antagonists of leukotriene receptors have powerful anti-inflammatory activity, which is based on the blockade of CysLTR1 where caused powerful bronchodilation, reduction of inflammation and obstruction of remodeling. It is interesting to mention that neutrophil leukocytes are extremely sensitive in usage of these medicines [6].

According to the newest data, anti-inflammatory effect can be reached also with inhibition of 5-LO where achieved inhibition of CysLT and LTB<sub>4</sub>, and also nonspecific inhibition of nucleotide cyclic phosphodiesterase, which causes increase of 3-AMPC and 5-AMPC, which are key regulators of the proinflammatory activity of born immunity [7,8].

**In our study, Montelukast** administered 2 days at home at a dose of (1 x 10 mg). On the 3<sup>rd</sup> day, to the same patient administered one capsule of montelukast and afterwards conducted measurement with body plethysmography (Raw, ITGV and calculated SRaw); as a result of blockage of leukotriene receptor, decreases significantly increased bronchomotor tonus (**p < 0.001**); same as the treatment of the control group with salbutamol (beta<sub>2</sub>-adrenergic agonist), which is effective in removal of the increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), namely specific resistance of the airways (SRaw), (**p < 0,05**).

In clinical trials with zafirlukast, all of the studies indicated some decrease in the number of asthma exacerbations, with average of reduction to 50% [9]. When zafirlukast [10] and montelukast [11] compared with the low dose therapy of inhaled glucocorticoids, improvement in pulmonary function and in the need to reduce the administration of therapy with  $\beta_2$  adrenergic agonists was higher at patients treated with glucocorticoids. Nonetheless, there was little difference in between subjects treated with steroids and those treated with montelukast in decrease of the number of asthma exacerbations. Clinical trials with antileukotriene medicines were quite heterogeneous in response to the therapy, with patients that can be classified in two groups, those “responding” on the treatment and those “not responding” to it. For patients responding to the treatment with antileukotriene, pulmonology and hematology institution have recognized these medicines as alternative to inhaled steroids, in small doses, in order to maintain slight chronic asthma under the control.

More studies are necessary to define the role of these medicines in moderate and severe asthma. Some clinical trials indicated that leukotriene antagonists have ability to reduce the dose of inhaled steroids necessary to control asthma exacerbations [12]. If so, this can be quite important, especially in children suffering from a more severe asthma. This class of medicines is not indicated for fast bronchodilation; thus, patients are advised to maintain agonists of the  $\beta$  adrenergic receptor with short effect as rescue medicines. Montelukast and zafirlukast are efficient when administered respectively one or two times a day. Whilst, zileuton is administered four times a day. Hepatic enzymes should be monitored in patients that have just entered the treatment with zileuton, in order to be protected from a potential toxicity of the liver. In hospital admitted patients, often used short courses of systemic steroids. Other new agents are aiming to effect on specific mechanisms, which are important in the beginning and progression of asthma. These include antagonists of leukotriene receptor and therapy with anti-IgE, omalizumab.

Modifying medicines of the leukotriene are taken orally. Montelukast is absorbed immediately with about 60-70% bio-efficiency. In therapeutic concentration, it is highly bound to the proteins. It is found the increase of the LTE4 level in urine during early asthmatic reaction at most of the patients [13]. It is metabolized extensively by CYP3A4-a and CYP2C9-a. Half-life of montelukast is between 3 to 6 hours.

There are a small number of side effects directly related to the inhibition of the synthesis or function of leukotriene. This may appear as a consequence of the fact that generation of leukotriene is mainly limited in the place where inflammation occurs.

In numerous clinical trials, summary of side effects gained because of these medicines was similar to those seen in treatment with placebo. Rarely, patients administering these medicines develop a systemic eosinophilia and a vasculitis with similar features to Chung-Strauss syndrome. This problem, often related with the increase of glucocorticoids, may represent a discovery of a disease that used to be present. Zafirlukast, but not montelukast, may interact with the warfarin and increase the prothrombin time, which should be monitored in patient subject to this interaction. Zafirlukast and montelukast are selective competitive antagonists with high affinity for the receptor cys-LT1 [14].

Pranlukast is another antagonist of the cys-LT1 receptor administered in some countries in treatment of asthma, but not approved for administration in USA. Inhibition of cys-LTs', which induces the contact of smooth bronchial muscles, included in the therapeutic effects of administration of these agents for relief of asthma symptoms.

Key principles of the asthma therapy have remained unchanged since many decades. Bronchodilation medicines such beta<sub>2</sub> agonists of adrenergic receptor with short time of effect are administered immediately to improve the bronchospasm during an asthmatic attack. Anti-inflammatory medicines such inhaled glucocorticoids are administered in relief of the bronchial inflammation aiming reduction of severity and frequency of asthmatic attacks. In hospital admitted patients, often used short courses of systemic steroids.

Once often used, today the methylxanthines are less used because of the modest effects and narrow therapeutic window.

We hereby declare: that the manuscript is original and the work has not been published elsewhere. The authors have no conflicts of interest that are directly relevant to the content of this article.



## CONCLUSION

- ❖ Antileukotriene substance - Montelukast administered for 2 consecutive days per os at a dose of 10 mg in **non-reactor patients** has not caused significant decrease of the specific resistance of airways (SRaw) ( $p > 0.1$ ).
- ❖ Antileukotriene - Montelukast administered for 2 consecutive days orally, in a dose of 10 mg (1 time a day 1 tabl.), in **patients with moderate reactivity** has caused significant decrease of the specific resistance of airways (SRaw) ( $p < 0.05$ ).
- ❖ Antileukotriene - Montelukast administered for 2 consecutive days orally, in a dose of 10 mg (1 time a day 1 tabl.), in **patients with emphasized reactivity** has caused significant decrease of the specific resistance of airways (SRaw) ( $p < 0.001$ ).
- ❖ Treatment of the control group with salbutamol (beta<sub>2</sub>-adrenergic receptor agonist) is effective in removal of the increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), namely specific resistance (SRaw), ( $p < 0.05$ ).
- ❖ Receptor responsible for the bronchoconstriction effect of leukotriene is sys-LTI receptor. Although each of cys-LTs' is agonist to this receptor, LTE<sub>4</sub> is less powerful than LTC<sub>4</sub> or LTD<sub>4</sub>. Montelukast is selective competitive antagonist with high affinity for the receptor cys-LT<sub>1</sub>. Our results indicate that montelukast in patient with increased reactivity significantly causes decrease of the airways specific resistance by inhibiting binding of leukotriene to the receptor and their effect ( $p < 0.001$ ).

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