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## Effect of antileukotriene (zileuton) in patients with bronchial asthma (emphasized reactors, moderate reactors, and non-reactors).

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### ABSTRACT

Effect of antileukotriene – Zileuton in patients with bronchial asthma with increased, and moderate reactivity or non-reacting. Parameters of the lung function are determined with Body plethysmography. Raw and ITGV were registered and specific resistance (SRaw) was calculated. Zileuton, tabl. 600 mg was used in the research. 2 days after administration of the antileukotriene medicine – Zileuton (4 x 1 tabl.) at home, on the third day to patients measured initial values by administering orally one more tablet of Zileuton in a dose of 600 mg, and again measured Raw and ITGV after 60, 90 and 120 min. and calculated was SRaw. In emphasized reactors, we have significant decrease of the airways bronchomotor tonus ( $p < 0.01$ ). In moderate reactors, there was also a significant decrease of the specific resistance of airways ( $p < 0.05$ ). There were no significant changes of the airways bronchomotor tonus in non-reactors ( $p > 0.1$ ). Effect of the corticosteroids (Berotec) in the control group is also effective in removal of the increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), ( $p < 0.01$ ). This suggests that the bronchodilation effect of Zileuton at patients with emphasized reactivity is more powerful than at the patients with moderate reactivity and non-reactors, which means that antileukotriene – Zileuton interferes the early stage of the release of chemical mediators (prostaglandins  $PgD_2$ , SRS, and leukotriene  $LTC_4$ ,  $LTD_4$ ,  $LTE_4$  and Cytokinin's etc.) as powerful broncho constriction substances. Effect of antileukotriene (Zileuton) is not immediate after oral administration, but strong effect of Zileuton seen only after two days of cys-LT's inhibition, and inhibition of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and A<sub>4</sub> (LTA<sub>4</sub>) at patients with increased reactivity.

**Keywords:** Respiratory system (emphasized reactors, moderate reactors and non-reactors), Zileuton.

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## INTRODUCTION

Progress in the molecular biology has revealed the complexity of the interaction in between a certain number of inflammatory cells and their mediators, including leukotriene.

Their reduction has paved the path for development of antagonists as new opportunity in treatment of asthma especially in severe cases or particular cases of this illness, such aspirin or physical load caused in asthma.

Antileukotriene – Zileuton as inhibitor of the biosynthesis of leukotriene is new form of anti-inflammatory medicines. Antileukotrienes (antagonists of the leukotriene receptor) are newest form of anti-inflammatory medicine. Contact antigen-antibody results in degranulation of mastocyte and release of mediator substances: LTC-4, LTD-4 and LTE-4, which cause manifestation of the bronchoconstriction in asthma [1]. From the power of their effect, major and clinical manifestation of asthma depends. Some of antileukotrienes called also modifiers of leukotriene. Antileukotriene blocks the effect of the component, which manifest contraction of smooth muscles, and block the accumulation of the inflammatory cells, oedema, and mucous secretion. They reduce the number of tissues and eosinophil cells [2]. Latest research show that antileukotriene is effective in the therapy of asthma and easily administered orally. Therapeutic effect of these medicines lies in the treatment of slight and moderate forms of bronchial asthma, including other indication (e.g. asthma from the aspirin and reduction of the corticosteroids dosage) [3]. Bronchial asthma is closely related with the inflammation and hyperactivity of airways and acute bronchoconstriction.

Pharmacologic effects of **cys-LTs'** occur not only as a consequence of the activation of **cys-LT1** receptor. For example, **cys-LTs'** which trigger the vascular smooth muscle contraction [4] and stimulate expression of the P-selectin generated by endothelial cells via receptor LT2 [5]. This provides another advantage of **zileuton** against zafirlukast and montelukast because inhibitors of 5-lipoxygenase will inhibit effects of **cys-LTs'** regardless subtypes of the receptor. In despite of the theory advantages, practically various studies showed that **zileuton** has no higher efficiency rather than antagonists of the receptor **cys-LT1** in asthma treatment [6].

Effects of **cys-LT's**, related with the bronchial asthma, are not limited only in the contraction of smooth muscles. **Cys-LT's** can increase the microvascular blood circulation, increase generation of mucous, and appearance of eosinophils and basophils in the airways [7]. It is yet unknown how much this inhibition of leukotriene production contributes in the therapeutic effect of these medicines. Maybe, it is worth to mention that zafirlukast inhibits substantially also the appearance of basophils and lymphocytes in airways after experimental exposure of asthmatic people to an allergen [8].

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

## MATERIAL AND METHODS

Examination performed in **33** patients with bronchial asthma and increased bronchial reactivity (emphasized, moderate reactors, and non-reactors). 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  $9 \pm 6$  years (from 5-20 years). Average of their age was  $25 \pm 5$  years (from 20 – 65 years), whereas average of relative weight was  $70 \pm 4\%$  (from 65 – 70%). 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:

$$SRaw = Raw \times ITGV$$

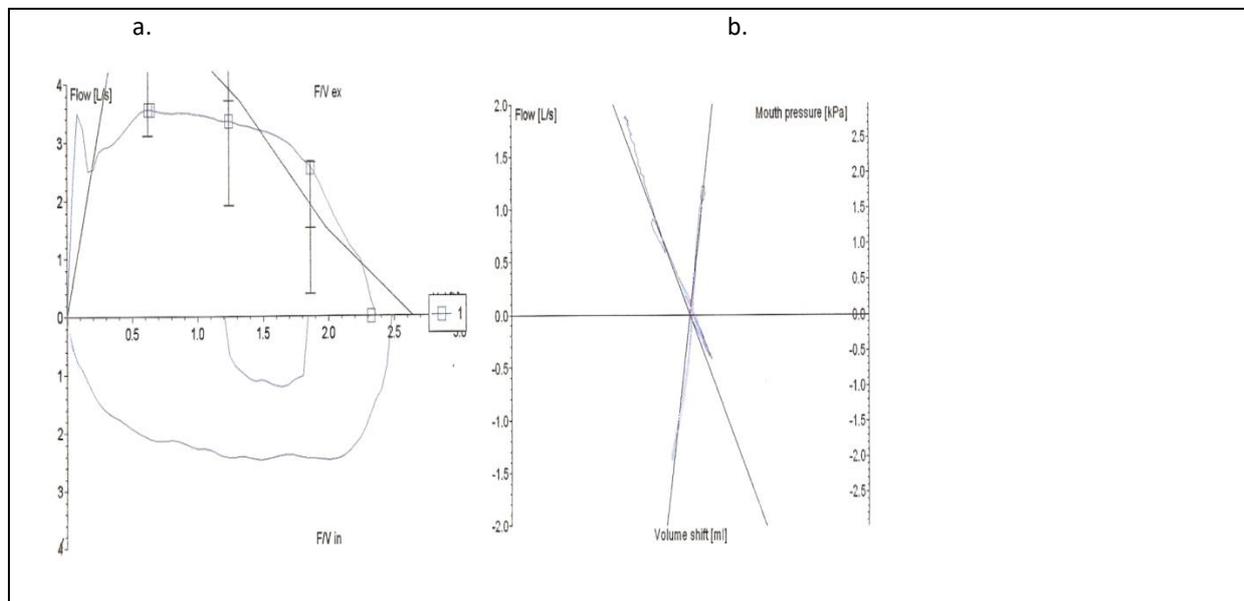
Raw and the SRaw were taken for analyses. Research of the bronchial response to different substances was done with the measurement of Raw and the SRaw as very sensitive indicators.

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)
33	55± 1,50	178.12 ± 1.25	75.81±0.5	3.55±3.5	3.05±2.46	0.22±0.01	3.55±2.05

**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.

Zileuton, as antagonist of leukotriene receptor (600 mg, tablets) administered orally 2 days in row at home (4 times 1 tabl.) and reported at the ambulance after 2 days and measured initial values, tablet administered orally at the ambulance, and afterwards, measured Raw and ITGV after 60, 90 and 120 min. At the end, as control, applied corticosteroid - Berotec in the form of aerosol and in a dose of (2 inh. x 0,2 mg). Again, were measured Raw and ITGV values 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.

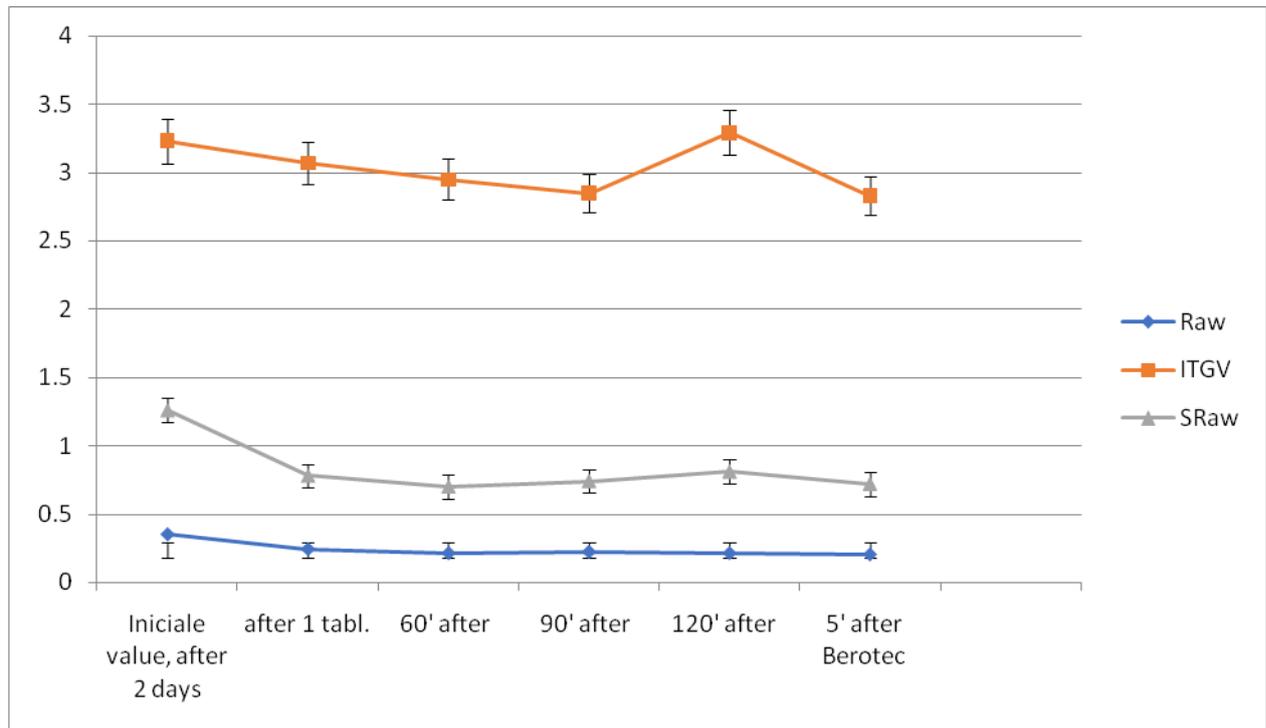
Gained results grouped and analyzed. Statistic data processing included determination of the average values (X), standard deviation (SD), standard mistake (SEM), and testing of significance of changes in between groups of patients treated with antileukotrienes.

Gained results tested with a t-test in order to ascertain significant changes in between examined groups. For data processing, used was the statistics software GraphPad InStat III.

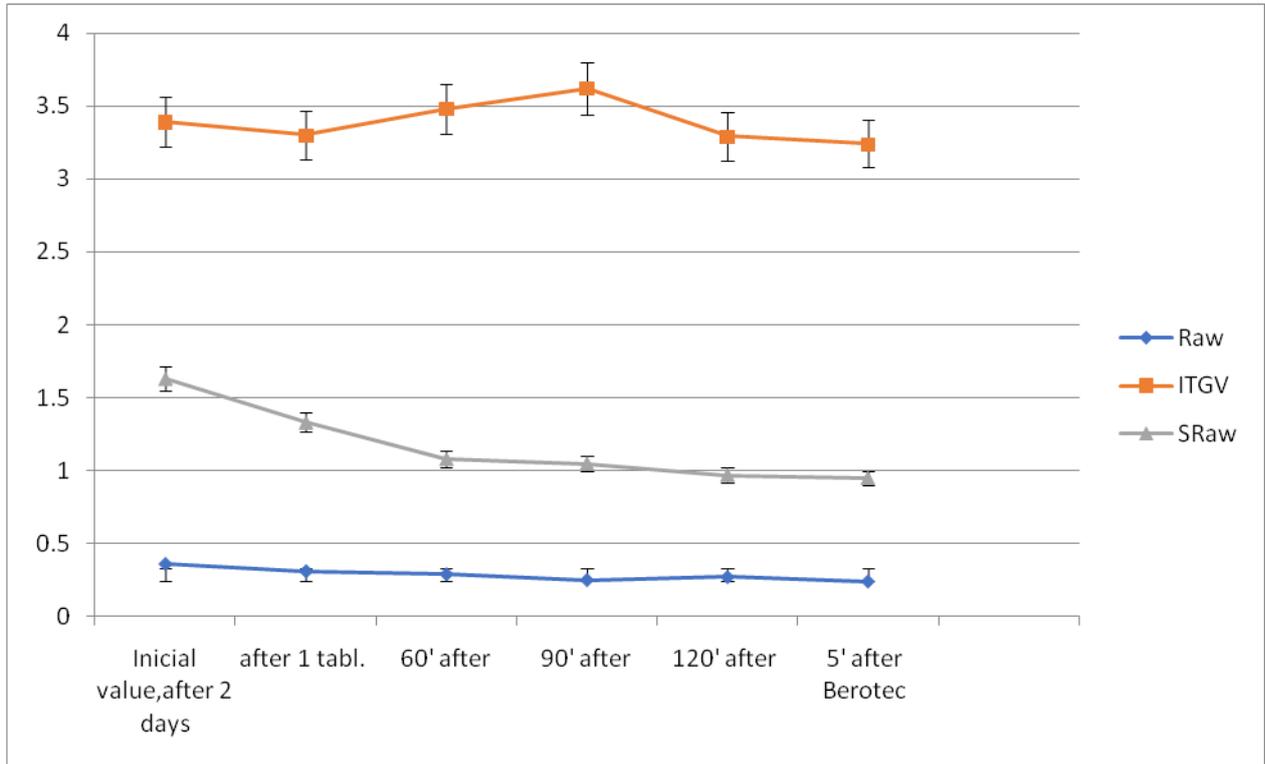
**RESULTS**

Results of this research, in patients with bronchial asthma, indicate that patients with **emphasized bronchial reactivity** two days after administration of Zileuton at home, in a dose of 600 mg orally, as a result of inhibition of leukotriene biosynthesis significantly ( $p < 0.05$ ) decreased was increased bronchomotor tonus; whilst this action was not met at **moderate reactors and non-reactors** ( $p > 0.1$ ). Berotec administered at the control group is very effective in removal of the increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively of the specific resistance of airways (SRaw), ( $p < 0,01$ ). See fig. 2, 3, 4.

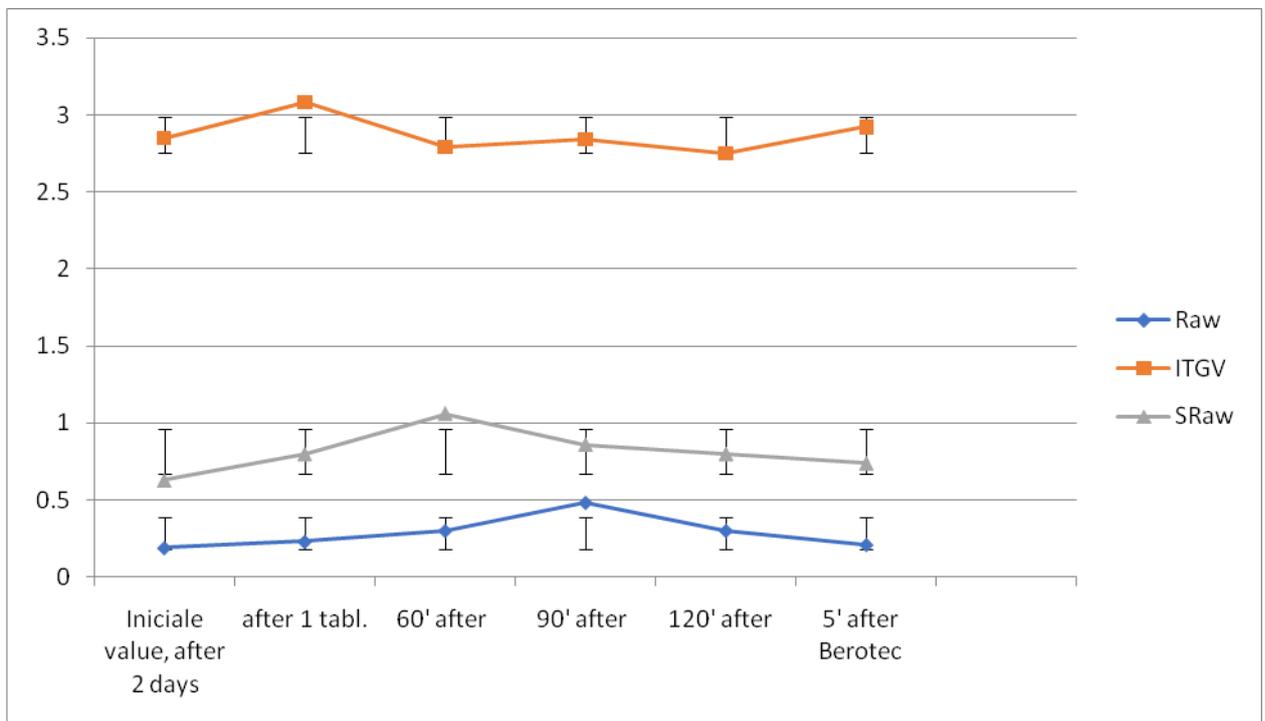
Antagonists of leukotriene in doses administered 2 days after taking of Zileuton at home, to the same patients caused decrease of the systolic and diastolic arterial pressure (AP) ( $p > 0.1$ ). See fig. 5, 6.



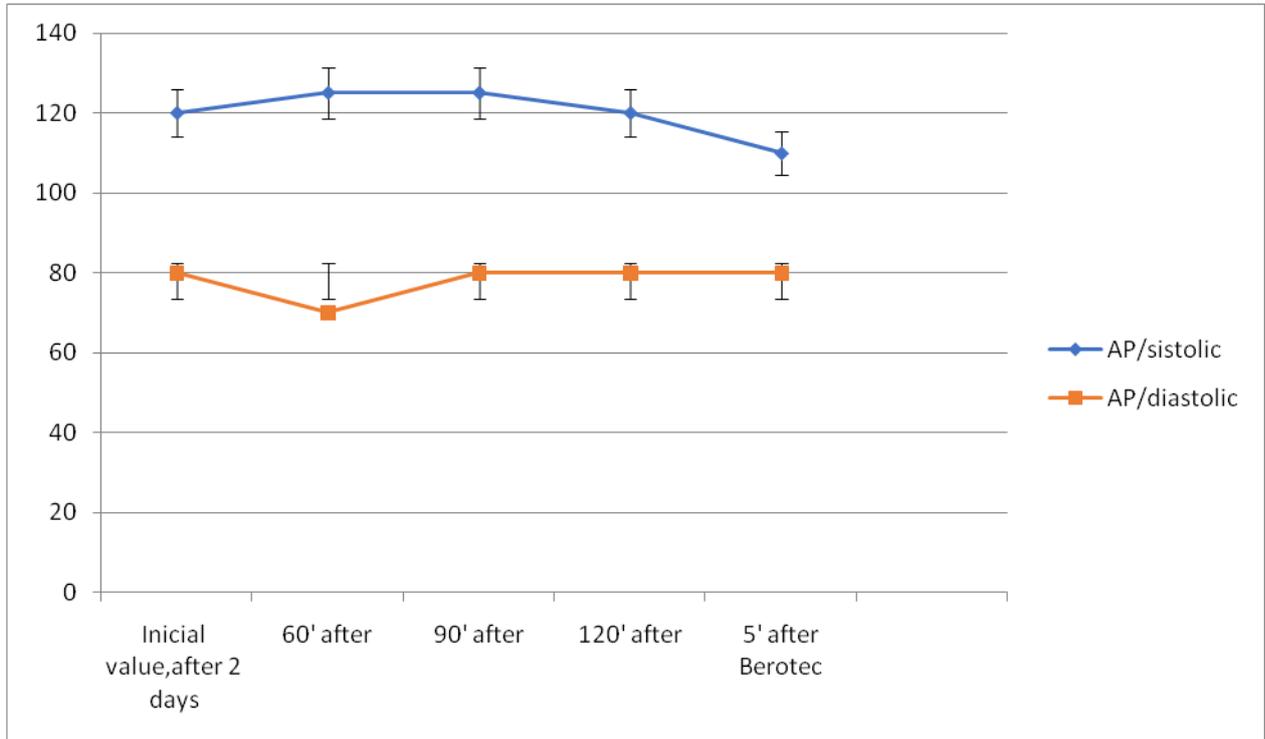
**Fig 2: Effect of Zileuton (600 mg tablet – per os), and Berotec (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 2 days after administration of Zileuton at home (4 x 600 mg); (emphasized reactors) (n = 8; X ± SEM).**



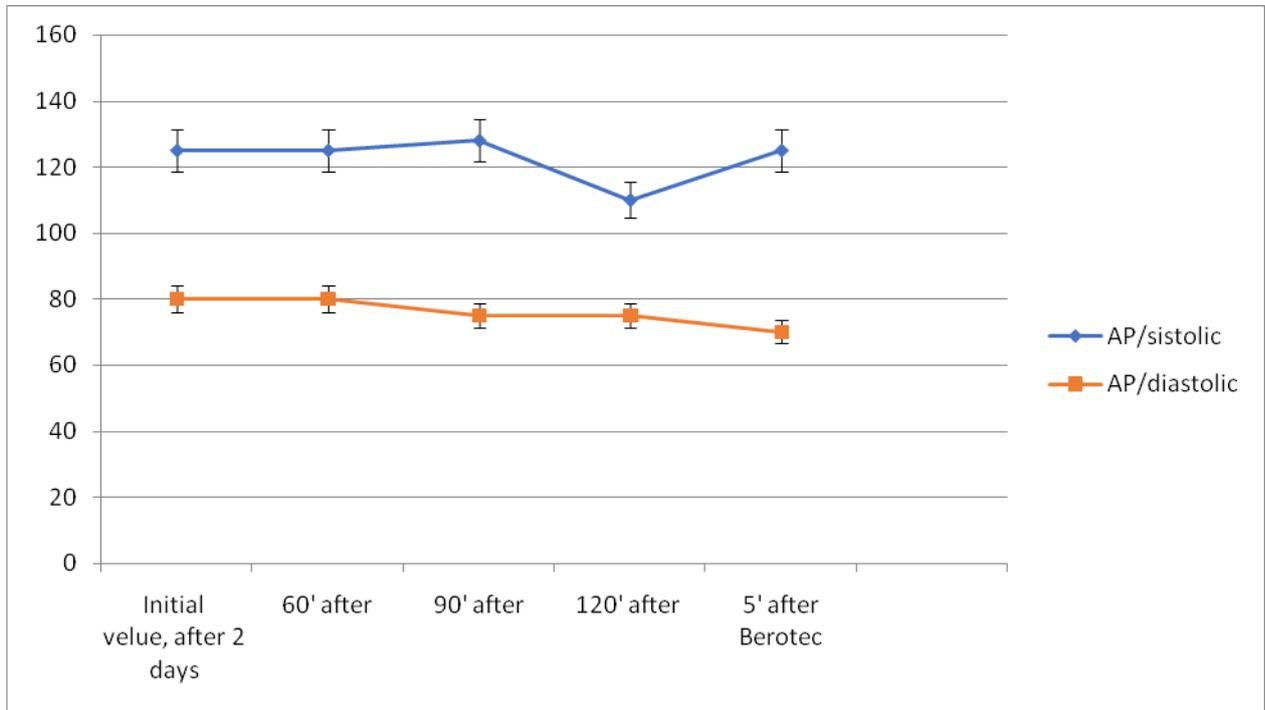
**Fig 3: Effect of Zileuton (600 mg tablet – per os), and Berotec (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 2 days after administration of Zileuton at home (4 x 600 mg); (moderate reactors) (n = 14; X ± SEM).**



**Fig 4: Effect of Zileuton (600 mg tablet – per os), and Berotec (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 2 days after administration of Zileuton at home (4 x 600 mg); (non-reactors) (n = 11; X ± SEM).**



**Fig 5: Effect of antileukotriene – Zileuton (600 mg per os) and Berotec (2 inh. x 0.2 mg); to the arterial pressure (AP/systolic/diastolic); in patients: Emphasized reactors (n = 33; X ± SEM).**



**Fig 6: Effect of antileukotriene – Zileuton (600 mg per os) and Berotec (2 inh. x 0.2 mg); to the arterial pressure (AP/systolic/diastolic); in patients: Moderate reactors and non-reactors (n = 33; X ± SEM).**

**DISCUSSION**

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” on it. For patients responding to the treatment with antileukotriene, pulmonology institution has recognized these medicines as alternative to inhaled steroids, in small doses, in order to maintain slight chronic asthma under the control.

Formation of leukotrienes depends on the lipoxygenation of the arachidonic acid by 5-lipoxygenase.

**Zileuton** is an active and powerful inhibitor of the activity of 5-lipoxygenase and as such inhibits generation of its products. Consequently, besides inhibition of cys-LTs’, zileuton also inhibits the creation of leukotriene B<sub>4</sub> (LTB<sub>4</sub>), which is a powerful chemotactic of other eicosanoids too, which depend on the synthesis of leukotriene A<sub>4</sub> (LTA<sub>4</sub>). Theoretically, therapeutic effects of 5-lipoxygenase should include all those seen at the antagonist cys-LT<sub>1</sub>, but also other effects which include inhibition of the LTB<sub>4</sub> and other products of 5-lipoxygenase. It is deemed that LTB<sub>4</sub> acts through receptor LT<sub>1</sub> and LT<sub>2</sub>, by causing accumulation of neutrophils, but their role remains yet unclear [9, 10].

**Zileuton** is absorbed immediately after oral administration and extensively metabolized by CYP and UDP glucuronosyltransferase. Even in this case, initial medicine is responsible for the therapeutic effect. Zileuton is a medicine with short effect and a half-life of approximately 2.5 hours and also very much bound to the proteins (93%).

When **Zileuton and montelukast** compared with the low dose therapy of inhaled glucocorticoids, and in the reduction of the needsto administer the therapy with  $\beta_2$  adrenergic agonists, response was better at patients treated with inhaled glucocorticoids. More studies are needed 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 [11]. If so, this can be quite important, especially in children suffering from a more severe asthma.

Work studied the effect of antileukotriene – Zileuton in the treatment of patients with bronchial asthma and increased bronchialreactivity,comparing itwith control group treated with salbutamol (beta<sub>2</sub> adrenergic receptor agonist) applied via inhalation.

Two days after administration of leukotriene antagonists - **Zileuton** at home, administered was also one another tablet to the same patients on the third day, and as result of blockage of leukotriene receptors (at a dose of 600 mg orally) significantly ( $p < 0.01$ ) decreases the bronchomotor increased tonus with emphasized reactivity; this was not ascertained in patients with moderate reactivity and non-reactors; effect of corticosteroids – Berotec is very efficient in removal of increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively specific resistance (SRaw), ( $p < 0,01$ ).

Antagonists of leukotriene in doses administered 2 days after home administration of Zileuton, at the same patients, cause decrease of the arterial systolic and diastolic pressure (AP) but not significantly ( $p > 0.1$ ). Side effects of the patients administering zileuton are similar to those of patients administering placebo. In estimated 4 to 5% of the patients administering zileuton there is an increase of liver enzymes respectively within 2 first months of treatment. Zileuton reduces the elimination of the theophylline, by increasing significantly plasma concentration. Zileuton also decreases the elimination of the warfarin. Due to many of the pharmacokinetic features, related to the safety, this medicine is not administered anymore in the USA. 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.

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.

More studies are needed to define the role of these medicines in moderate and severe asthma. Some clinical trials indicated that antagonists of leukotriene have an affinity in reduction of 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  $\beta_2$  adrenergic receptor with short effect as rescue

medicines. Montelukast and zafirlukast are efficient when administered respectively one or two 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.

Leukotriene are 100 to 10.000 times more powerful constrictor of smooth musculature in comparison to histamine or methacholine. [13].

These are newest antiasthmatic medicines, which are used successfully worldwide in the clinical practice, in about two decades. Their administration leads towards improvement of symptoms, parameters of lung function, reduction in usage of medicines, less obstructed breathing during the night, namely improvement of all parameters which serve in the process of illness control. They are used also in combination with other antiasthmatic medicines, such: corticosteroids and agonists of beta<sub>2</sub>-adrenergic receptors, with which they have synergic and additive effect [14, 15]. Compared with cromoglycate, comparison studies showed better efficiency.

Most of the authors agree that by applying these facts in practice, we come to a conclusion that antileukotriene medicines are the first line of asthma therapy, as an efficient alternative for reduction of inhaling doses of corticosteroids [16].

Medicines are not recommended for people younger than 12 years. Medicine is also not recommended to pregnant and breastfeeding women because until now no studies conducted in this direction.

We have to stress out that their discovery and clinical use has not reduced the efficiency, nor changed the attitude towards administration of inhaling corticosteroid medicines in long-term prevention of diseased. Having in mind aforementioned facts, there are real chances that these medicines in the future find a proper place in medication of bronchial asthma.

## CONCLUSION

Based on results gained, it can be concluded that:

- ❖ In patients with emphasized bronchial reactivity, orally administered antileukotriene – Zileuton, causes significant decrease of the specific resistance (SRaw) of airways ( $p < 0.01$ ).
- ❖ In patients with moderate bronchial reactivity, orally administered antileukotriene – Zileuton, does not cause significant decrease of the specific resistance (SRaw) of airways ( $p < 0.05$ ).
- ❖ In non-reactor patients, orally administered antileukotriene – Zileuton, does not cause significant decrease of the specific resistance (SRaw) of airways ( $p > 0.1$ ).
- ❖ Corticosteroids (Berotec) in terms of the control – applied through inhalation in patients with bronchial asthma and increased bronchial reactivity has caused significant decrease of the specific resistance (SRaw) of airways ( $p < 0.01$ ).

Effect of antileukotriene (Zileuton) in reactor patients is not immediate after oral administration, but the powerful effect of Zileuton seen only after two days of intake by causing inhibition of cys-LT's, and inhibition of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and A<sub>4</sub> (LTA<sub>4</sub>). Whilst, in moderate reactors and non-reactors, this effect of Zileuton was not seen.

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