

Comparison of Glucocorticoid (Budesonide) and Antileukotriene (Montelukast) Effect in Patients with Bronchial Asthma Determined with Body Plethysmography

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ABSTRACT

Objective: Effect of glucocorticoids-budesonide and antileukotriene-montelukast in patients with bronchial asthma and bronchial increased reactivity was studied in this work. **Methods:** Parameters of the lung function are determined with Body plethysmography. Raw and ITGV were registered and specific resistance (SRaw) was also calculated. **Results:** Results of this research, in patients with bronchial asthma, indicate that glucocorticoids – budesonide (Pulmicort; 2 x 2 mg inh) has significant action ($p < 0.01$) on reduction of the specific resistance (SRaw) of airways, applied to the same patients 3 days after administration of montelukast, at home (2 x 10 mg). Three days after administration of the montelukast, antileukotriene medicine, at home, on the fourth day same patients administered a capsule of montelukast, 10 mg dose per os, and significantly ($p < 0.05$) reduced the increased bronchomotor tonus; and the effect of the control with salbutamol (beta₂-adrenergic agonist) is effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), ($p < 0.01$). **Conclusion:** This suggests that the bronchodilator effect of glucocorticoids is more powerful than of the leukotriene, because glucocorticoids terminate the early stage of chemical mediator release (prostaglandins PgD₂, SRS, and leukotriene LTC₄, LTD₄, LTE₄ and Cytokinins also etc.) as powerful bronchoconstriction substances, whilst antileukotriene substances does not have this feature.

Key words: Respiratory system, budesonide, montelukast.

1. INTRODUCTION

Bronchial asthma is an obstructive disease of the airways caused by the smooth bronchial muscles contraction, obstruction of which has diffuse nature and improves spontaneously or after the medical treatment. In the core of this process lies the fact of mastocytes degranulation and release of active substances (such Histamine, LTD-4, LTC-4, SRS etc.) in the bronchial micro environment under the effect of antigen.

First of all, during the development of allergic asthma comes to the activation of the immune response, which includes T helper (Th) cells of the type 2.

Sensibility commences when genetically predisposed people are exposed to allergens such: pollen or protein of the house dust, including contribution of the environment, such atmospheric pollution. These allergens come in the contact with dendritic cells and Th helper lymphocytes, which fur-

ther causes development of lymphocyte Th2 forms that:

Create and release the cytokinins, and induces B cells/plasma cells to start generate IgE.

Creation of cytokinins such e.g. Interleukin-5 (IL-5), which starts differentiation and activation of eosinophils,

Creation of other cytokinins (e.g. IL-4 and IL-13), which induce the expression of IgE receptors, mainly in mastocytes, but also in eosinophils; IL-4 also induces the expression of receptors in the endothelium where specifically binds eosinophils.

System is activated in this way, and another repeated exposure to respective allergens would cause attack of the bronchial asthma.

In the early stage of allergic asthma (namely initial response to the provocation with allergen) appears vehemently and most often provokes the spasm of the smooth musculature of the bronchial tree. Allergens react with IgE an-

tibodies fixed to the mastocytes, which cause release of many spasmogen substances from cells such: histamine, cystein-leukotrienes (LTC-4 and LTD-4) and prostaglandins D-2 (PgD-2) (1,2).

From other mediator released are also IL-4, IL-5, IL-13, inflammatory macrophage protein – 1 alpha and necrotizing alpha tumor factor (TNF-alpha).

Obviously, asthma caused from the physical load causes the manifestation of the above described phenomenon.

Second, later stage or postponed response begins after a period of the exposure to certain inducers, thus, it can manifest also by the night. Essentially, this stage is a progressive inflammatory reaction, which starts in the first period of the attack, since Th2 lymphocytes are of critical importance. Manifested inflammatory reaction is different from the reaction that appears for example in the bronchitis. Specifics of this reaction is manifestation of ordinary infiltrates of the inflammatory process supplemented with the activation of the infiltrate of Th2 lymphocytes released by cytokinins, and with the activation of the eosinophils. Th2 lymphocytes and eosinophils have the protection role against any microorganism. In asthma, these cells activated inadequately, where released are cysteinyl-leukotriene, cytokinins IL-3 and IL-5, chemokines IL-8 and toxic protein, cationic eosinophil protein, major basic protein and eosinophil neurotoxin. All of these substances play an important role in the later stage of asthma in development of toxic protein, which damage and destroy the epithelium (3).

Asthma is related with the inflammation and hyperactivity in airways and acute bronchoconstriction. Glucocorticoids do not relax directly smooth muscles of the airways, thus, have little effect on the acute bronchoconstriction. On the other side, these agents, even alone, are efficient in the inhibition of the airways inflammation. Only a small number of inflammation mechanism avoided inhibitory effect of these medicines (4). Anti-inflammatory effects of glucocorticoids in asthma include modulating of the cytokines and chemokines; inhibition of synthesis of eicosanoids; inhibition of the basophils, eosinophils and other leukocytes accumulation in the lung tissues and decrease of the vascular penetration (4).

Asthmatic patients treated with inhaled glucocorticoids show improvement of symptoms and decrease of the needs for use of β_2 agonists (3).

Antileukotrienes (antagonists of leukotriene receptor) are newest form of anti-inflammatory medicine. Contact antigen-antibody results in degranulation of mastocytes and release of mediator substances: LTC-4, LTD-4 and LTE-4, which cause appearance of the bronchoconstriction in asthma. From the power of their effect, major and clinical manifestation of asthma depends. There are two types of leukotriene: antagonists of the receptor and inhibitors of the synthesis. Some of antileukotriene 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, edema, and mucous secretion. They reduce the number of tissues and eosinophil cells. Latest research show that antileukotriene is effective in the therapy of asthma and easily administered per os. Therapeutic effect of these medicines lies in the medication of slight and moderate forms of bronchial asthma, including other in-

dications (e.g. asthma from the aspirin and reduction of the corticosteroids dosage) (5).

Effect of the corticosteroids–budesonide (Pulmicort) applied through inhalation and of antileukotriene – montelukast applied per os at people with bronchial asthma and increased bronchial reactivity was studied in this work. Afterwards, respectively in the end, salbutamol (beta₂-adrenergic agonist) administered via inhalation as the control and after all application, measurement of Raw and ITGV conducted, and SRaw calculated.

2. MATERIAL AND METHODS

Our sample of 12 patients with bronchial asthma and increased bronchial reactivity were subject to examination. Study included 12 diseased. At least 48 hours prior research of bronchial reactivity response, patients has not administered any of the bronchodilator substances. Examined were informed regarding manner of the functional pulmonary tests. Patients were suffering from asthma, with or without associated bronchitis. Average of the disease period was 8 ± 6 years (from 4-20 years). Average of their age was 35 ± 7 years (from 29 – 45 years), whereas average of relative weight was $78 \pm 7\%$ (from 65 – 72%). 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 (FEV₁), resistance in the airways (Raw) and intrathoracic gas volume (ITGV), was defined at the rest.

Overall quantity of the volume of the intrathoracic gas (ITGV) was measured with the plethysmography method, including closed gas that do not ventilate. 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 persons 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 in-

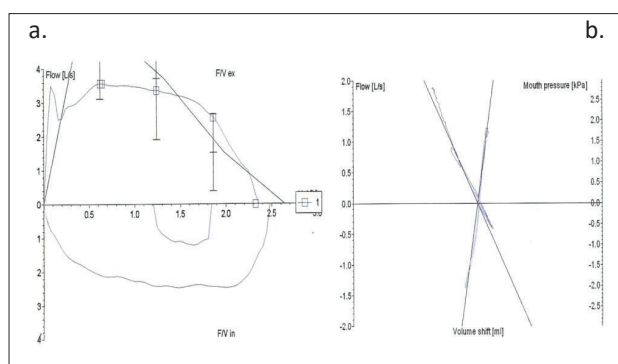


Figure 1. Measurement with Body plethysmography: a. Measurement of parameters of the gas volume in the sternum (ITGV); registration of flux-volume curve (inspiratory flux and expiratory flux–L/min); b. Resistance of airways (Raw–L/sec.) expressed in kPa.

n	Age(v)	Height (cm)	Weight (kg)	VC (%)	FEV1 (%)	Raw (kPa L/s)	ITGV (L)
12	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

Table 1. Basic airways characteristics

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

In persons with bronchial asthma and increased bronchial reactivity (n=12), glucocorticoid–budesonide (Pulmicort) was applied through inhalation. After measurement of initial values, applied (2 inh x 0.2 mg) and measured Raw and ITGV after 5, 30, 90 and 120 min., and in the end, in terms of control, applied salbutamol (beta₂-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.

Montelukast, as antagonist of leukotriene receptor (10 mg, tablet) administered 3 days in row at home per os (2 x 1 tab.) and after 3 days reported at the ambulance and measured initial values, tablet administered per os at the ambulance, and measured Raw and ITGV after 60 and 120 min. At the end, as control, administered salbutamol (beta₂-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 patient treated with corticosteroids and leukotrienes.

Gained results tested with a test (t-test) in order to ascertain significant changes in between examined groups. Records processed by using the computer statistic software GraphPad InStat III.

3. RESULTS

Results of this research, in patients with bronchial asthma, indicate that glucocorticoids – budesonide (Pulmicort; 2 x 2 mg inh.) has significant effect (p< 0.01) on reduction of the specific resistance (SRaw) of airways, applied to same patients 3 days after administration of montelukast at home (2 x 10 mg).

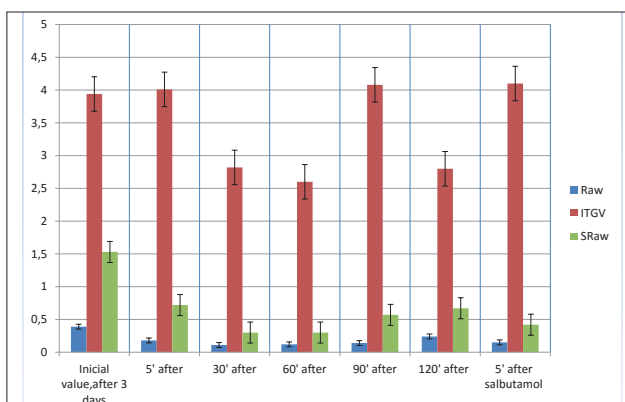


Figure 2. Effect of glucocorticoids – budesonide (2 inh x 2 mg), and Salbutamol (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 3 days after administration at home (2 x 10 mg); (n = 6; X ± SEM).

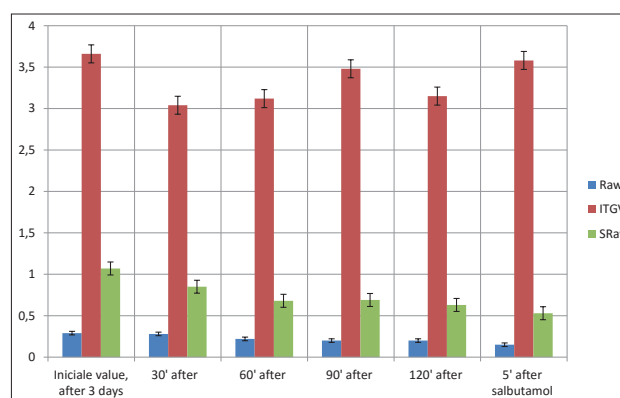


Figure 3. Effect of montelukast (10 mg tablet – per os), and Salbutamol (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 3 days after administration of montelukast at home; (n = 6; X ± SEM).

Three days after administration of montelukast at home, on the fourth day administered was a capsule to the same patients, and as a result of the blockage of leukotriene receptor (in a dosage of 10 mg per os) significantly (p < 0.05) reduced the increased bronchomotor tonus; same as the effect of the control with Salbutamol (beta₂-adrenergic agonist), which is very effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), (p < 0,01). See fig. 2 and 3.

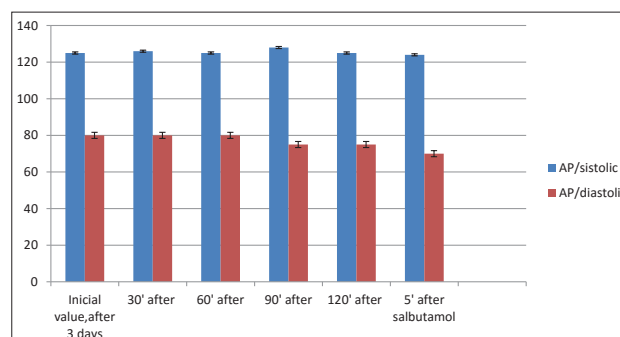


Figure 4. Effect of glucocorticoids – budesonide (2 inh x 2 mg), and Salbutamol to the arterial pressure (AP/systolic/diastolic); 3 days after administration of montelukast at home (2 x 10 mg); (n = 6; X ± SEM).

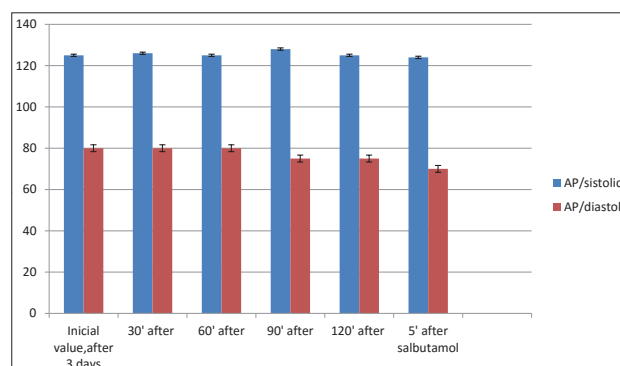


Figure 5. Effect of montelukast (2 inh x 2 mg), and Salbutamol to the arterial pressure (AP/systolic/diastolic); 3 days after administration of montelukast at home (2 x 10 mg); (n = 6; X ± SEM).

4. DISCUSSION

Systemic glucocorticoids are administered for a long time in treatment of severe chronic asthma or severe acute exacerbations of asthma. Production of forms with aerosol has significantly improved the safety of the treatment with glucocorticoids enabling thus its usage in moderate asthma. Asthmatic patients, in the need for inhalation of β_2 adrenergic agonists four or more times per week, are candidates for inhaled glucocorticoids (6). Although glucocorticoids are very effective in the control of asthma, treatment with systemic glucocorticoids causes considerable side effects. Development of inhaled glucocorticoids, which forward the medicine directly to the inflamed area, is a step ahead in the asthma therapy. These forms increase significantly the therapeutic index of medicine, by lowering very much the number and level of side effects without endangering clinical benefits. Although they change a lot in terms of the affinity to glucocorticoids receptor, namely fluticasone and budesonide have a higher affinity than beclomethasone, these medicine, in proper dosage, are all efficient to control the asthma. Some studies have defined the therapeutic index of various forms of inhaled steroids in treatment of asthma, but in so far data indicate that none of them has any higher therapeutic index (7).

Glucocorticoids acts passively in the nerve system by entering to cells, and inducing creation of lipocortin. This protein plays a key role in the inflammatory processes, because it inhibits the phospholipase A2, an enzyme in charge for creation of arachidonic acid—precursor of inflammation mediator (prostaglandin, leukotriene). Mainly administered medicines in asthma are as follows: Pulmicort, Fluticasone, and Budesonide. Corticosteroids (oral, parenteral, or inhalator) reduce the amount of synthesized prostaglandin and leukotriene. Corticosteroids increase the number of beta-adrenergic receptor in leukocyte and increase the response of beta-receptor in the smooth musculature of airways. During the treatment of pneumocystic pneumonia, destroyed organisms release antigens, which cause lung's inflammatory response, which damages the pulmonary function. Corticosteroids administered orally or intravenously are useful as adjuvant therapy in treatment of severe pneumocystic pneumonia. Concise mechanism of these effects is unknown, but corticosteroids can decrease the subglottic edema by reducing the permeability and capillary dilation. Corticosteroids administered nasally have local anti-inflammatory effect and minimal systemic effects. Immediate termination of budesonide is generally associated with increase of the bronchial hyperactivity and exacerbations of symptoms, though at 1/3 of patients the symptoms have not aggravated. Patients with a very well controlled disease should undergo a test for termination of inhaled glucocorticoids (4).

In 1990, three new medicines produced, which are used in asthma treatment: Antagonists of leukotriene receptor zafirlukast (8), montelukast (9), and inhibitor of the leukotriene synthesis such zileuton (10).

LTD4 is approximately 1000 times more powerful than histamine in bronchoconstriction. Receptor responsible for the bronchoconstriction effect of leukotriene is sys-LTI receptor. Although each of cys-LT is agonist to this receptor, LTE4 is less powerful than LTC4 or LTD4. Zafirlukast and montelukast are selective competitive antagonists with high

affinity for the receptor cys-LT1 (9).

Pranlukast is another antagonist of the receptor cys-LT1 administered in some countries in treatment of asthma. Inhibition of cys-LT, which induces the contact of smooth bronchial muscles, included in the therapeutic effects of administration of these agents for relief of asthma symptoms. Effects of cys-LT, born with the bronchial asthma, are not limited only in the contraction of smooth muscles. Cys-LT can increase the micro vascular blood circulation, increase generation of mucous, and appearance of eosinophils and basophils in the airways (11). 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 manifestation of basophils and lymphocytes in airways after experimental exposure of asthmatic people to an allergen (12).

In clinical trials with zafirlukast, all studies indicated some decrease in the number of asthma exacerbations, with average of reduction to 50% (13). When zafirlukast (14) and montelukast (15) compared with the low dose therapy of inhaled glucocorticoids, improvement in pulmonary function and in the need to reduce the administration of therapy with β_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" on it. For patients responding to the treatment with antileukotriene, heart, lungs, and blood 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 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, which are necessary to control asthma exacerbations (16). If so, this can be quite important, especially in children suffering from a more severe asthma. Currently, it is impossible to forecast who would benefit more from a provided treatment. This forecast on response generally reflects our limited knowledge on the physiopathology of asthma. Moreover, some components of these changes are possible to explain by many pharmacogenetics factors (17).

Three important mutations found in the promoter region in the gene, which codes 5-lypoxygenases. These mutations bring a small reduction of the promoter activity and synthesis of leukotriene. Around 35% of the population has at least one of these mutations in at least one of the alleles. In clinical trials with placebo seen that individuals with mutation in both alleles responded less to treatment with inhibitors of 5-lypoxygenases than those with two alleles of "wild" type (18).

Zafirlukast and montelukast, antagonists of leukotriene receptor, today are administered in treatment of bronchial asthma. First as addition to other antihistamines, whereas second in prevention of asthmatic attacks. Zileuton is in use, but not found a final place in the therapy. Iralukast is in the stage of preclinical research.

Results of this research in diseased with bronchial asthma,

indicate that glucocorticoid – budesonide (Pulmicort) has significant effect ($p < 0.01$) in reduction of the specific resistance (Sraw) of airways, applied to same patients 3 days after administration of montelukast at home (2×10 mg).

Three days after administration of leukotriene antagonist–montelukast at home, on the fourth day administered was a capsule to the same patients. As a result of the blockage of leukotriene receptor (10 mg per os dose) significantly ($p < 0.05$) reduced the increased bronchomotor tonus; same as the effect of the control with Salbutamol (β_2 -adrenergic agonist), which is very effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), ($p < 0.01$). Effect of glucocorticoids is more powerful in the obstruction of the creation of the arachidonic acid, of which afterwards released leukotriene with the process of lipoxigenase, and prostaglandin, prostacyclin, and other local chemical mediator, also with very powerful bronchoconstriction effect, are released by cyclooxygenase. Glucocorticoids – budesonide and antagonists of leukotriene in administered doses 3 days after home administration of montelukast at same patients cause decrease of the arterial systolic and diastolic pressure (AP) but not significantly ($p > 0.1$).

Results of this research in diseased with bronchial asthma, indicate that glucocorticoid – budesonide (Pulmicort) has significant effect ($p < 0.01$) in reduction of the specific resistance (Sraw) of airways, applied 3 days after administration of montelukast at home in same patients (2×10 mg).

Key principles of the asthma therapy have remained unchanged since many decades. Bronchodilator medicines such β_2 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.

In patients yet with symptoms, although administered the therapy with inhaled glucocorticoids, to steroid regime can be added agonists of the β_2 -adrenergic receptor, for a long period and good results. Once often used, today the methylxanthines are less administered because of the modest effects and small therapeutic window. Selective inhibitors of PDE4, which may have the same efficiency but with less side effects, are being assessed in the clinical trials. 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. As a conclusion, anticholinergic agents such tiotropium approved lately in treatment of the chronic obstructive pulmonary disease.

5. CONCLUSION

Based on gained results, it can be concluded as follows:

Glucocorticoids – budesonide applied via inhalation are more effective in patients with bronchial asthma and increased bronchial reactivity, cause decrease of specific resistance (SRaw) of airways ($p < 0.1$). Antileukotriene – montelukast administered per os also causes significant decrease of specific resistance (SRaw) of airways ($p < 0.05$). As control

– salbutamol, as agonist of β_2 -adrenergic receptor applied via inhalation in patients with bronchial asthma and increased bronchial reactivity, cause also significant decrease of specific resistance (SRaw) of airways ($p < 0.01$). This suggests that the bronchodilator effect of glucocorticoids is more powerful than the one of antileukotriene, because corticosteroids terminate the early stage of the chemical mediator release (prostaglandin Pgd_2 , SRS, and leukotriene LTC_4 , LTD_4 , LTE_4 and cytokinin, etc.) as powerful bronchoconstriction substances, whilst antileukotriene substances have not this feature.

CONFLICT OF INTEREST: NONE DECLARED.

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