Treatment of chronic cough in children with montelukast, a leukotriene receptor antagonist

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Twentytwo children (13 boys and 9 girls) with chronic cough were treated with the leukotriene receptor antagonist Montelukast (Singulair^R tbl. 5 mg) administered once daily for 4 weeks. In 14 children (68%), the cough ceased during the third week of treatment. Children responding to montelukast were found to have higher blood levels of eosinophil cationic protein (S-ECP) in the pre-treatment blood sample than children with no response (responders 14.88 ± 2.651 μg/l versus non-responders 6.62 ± 0.948 μlg/l; p < 0.01). Blood S-ECP levels remained higher also in the post-treatment blood sample in responders (10.55 ± 1.631 μg/l) compared to non-responders (6.13 ± 0.937 μg/l; p < 0.05). The difference is statistically significant. There were also differences in absolute eosinophil blood count and IgE blood levels between the two groups in the pre-treatment blood sample.
Using 24-hour pH-metry, two children not responding to therapy were subsequently diagnosed to have gastroesophageal reflux.
Judging from the results, one might deduct that patients with chronic cough who have increased levels of serum ECP and absolute eosinophil blood counts are likely to benefit from treatment with montelukast.
Key words: chronic cough in children, treatment, antileukotriene, montelukast.

LÉČBA CHRONICKÉHO KAŠLE U DĚTÍ MONTELUKASTEM – ANTAGONISTOU LEUKOTRIENOVÝCH RECEPTORŮ
U 22 dětí (13 chlapců a 9 dívek) s chronickým kašlem jsme čtyři týdny podávali antagonistu leukotrienových receptorů – montelukast (Singulair^R tbl. 5 mg) v dávce 5 mg jednou denně. U 14 dětí (68 %) tento kašel v průběhu třetího týdne odezněl. U těchto dětí s dobrým efektem léčby jsme zjistili vyšší hladinu sérového kationického proteinu (S-ECP) před léčbou než u dětí bez efektu léčby (před léčbou u dětí s efektem 14,88 ± 2,651 μg/l verzus bez léčebného efektu 6,62 ± 0,948 μg/l; p < 0,01) a i za čtyři týdny po léčbě (u dětí s efektem10,55 ± 1,631 μg/l verzus bez léčebného efektu 6,13 ± 0,937 μg/l, p < 0,05). Rozdíl mezi těmito hodnotami je statisticky významný. Mezi oběma soubory je signifikantní rozdíl (p < 0,01) v absolutním počtu eozinofilů v periferní krvi i mezi hladinami celkového IgE (S-IgE) vyšetřenými před zahájením léčby.
U dvou dětí, u kterých nebyla odpověď na léčbu, jsme následně 24hodinovou pH metrií prokázali gastroezofageální reflux.
Na základě získaných výsledků můžeme usuzovat, že u pacientů s chronickým kašlem a vyšší hladinou S-ECP, S-IgE a s vyšším absolutním počtem eozinofilů v periferní krvi je vysoká pravděpodobnost efektu léčby montelukastem.
Klíčová slova: chronický kašel u dětí, léčba antileukotrieny, montelukast.

Cough is the most frequent nonspecific manifestation of airway disease in the general practitioner's office. It has a number of forms and a very wide range of causes.

Chronic persistent cough is irritating nonproductive cough, persisting usually for more than three weeks, with a negative chest x-ray finding, with normal spirometry results, and without an obvious or documented cause[(1)]. Physiologically, it is a purposeful protective mechanism designed to maintain airway patency. Based on active forced expiratory volume, it removes from the airways not only any foreign bodies but, also, mucus and products of pathological processes in the airways and in the lungs.

Chronic cough deteriorates the child's quality of life, restricts his/her activities, results in diminishing his/her overall fitness, and in sleep disorders. Occasionally, chronic cough may be underestimated, and is a manifestation of another chronic disease.

When evaluating the intensity and duration of cough, we have to rely on anamnestic data reported primarily by parents and, partly, also by the pediatric patients themselves. For these reasons, the differential diagnosis of causes of irritating cough is often not simple.

An important role in irritating cough is played by an increase in bronchial hyperresponsiveness. Children with wheezing and chronic cough due to viral infection, have been shown to have increased levels of IFN-gamma and leukotrienes in sputum[(2)]. Leukotrienes produce edema, increased mucus formation in the airways and bronchoconstriction. Chronic irritating cough is thus a consequence (a condition after an infectious disease), or a symptom (in a patients with asthma bronchiale). A diagnosis of asthma bronchiale in pre-school children is difficult to establish. The most frequent symptoms are difficulty breathing and cough symptoms deteriorating at night. Lung function examination in this particular age group is complicated and depending on the child's cooperation limited by age[(2)]. Chronic cough as the first symptom of bronchial asthma continues to be underestimated. Cough persisting for more than 2 to 3 weeks is often exhausting for the child and interferes with the life of the entire family; it is often a cause of dissatisfaction of parents with the treatment of their children and a loss of confidence into the physician's competence. In our study, 22 children with protracted cough, referred to our department by district physicians and allergologists, received the antileukotriene agent montelukast, a competitive specific antagonist of CysTL1 receptors for leukotrienes LTC4, LTD4 a LTE4 was given (Singulair^R tbl. at a dose

of 5 mg once daily) and the effect of four-week therapy was assessed.

Group of patients and methods

In our study, a group of 22 children (13 boys and 9 girls) aged 4–8 (median 5) years with non productive, predominantly night-time cough persisting for more than three weeks, had a detailed analysis of their personal history; in addition, absolute eosinophil blood count (EoA), blood levels of IgE and blood levels of eosinophil cationic protein (S-ECP) were performed. Excluded from the study were children with congenital airway anomalies, documented airway infection within the past two months, or severe respiratory tract disease (e.g. cystic fibrosis). None of the children had been previously treated with inhaled corticosteroids.

In an attempt to break the vicious circle as well as a therapeutic trial, (parents signed informed consent), we started to administer montelukast, a leukotriene receptor antagonist for a period of four weeks (montelukast tablets at a dose of 5 mg once daily).

A second serum ECP level was determined at an interval 4 weeks from the first collection. Based on data from parents and children themselves on the cough resolution or non-resolution, children were divided after 4 weeks into two groups:

a) a subgroup with cough resolution
b) a subgroup without a therapeutic effect

Blood eosinophils were examined using automatic GenS™ System 2 device by Coulter, USA and Sysmex™ device by Sysmex Corporation, USA.

Nephelometry was used for total S-IgE determination. S-IgE values > 150 IU/ml IgE were defined as significant for allergy.

Serum ECP was determined using fluorescent enzyme imunno assay (FEIA) CAP System by Pharmacia, Sweden. Blood for ECP was collected into Vaccutainer test tubes with activator (Beckton-Dickinson, England). Samples were incubated for 60–120 minutes at room temperature, subsequently centrifuged and the aspired serum was frozen prior to complete processing. S-ECP < 15 μg/l was defined as physiological.

The results obtained were analyzed statistically using the paired and unpaired t-tests with group normality determination.

When taking the history, we found, in the group with good effect of montelukast therapy, a positive family history of atopy in three children; two children had atopic eczema within the first year while another three had manifest atopic eczema on the limbs. At other visits, parents of four children admitted their children had pet animals (dogs, cats) which could have been the cause for recurrent problems in these children following therapy discontinuation (Table 1).

Tab 1. Characteristic groups of children with and without an effect of montelukast therapy

	with an effect (n = 14 %)	without an effect (n = 8 %)
positive FH	3 (21.4 %)	0
history of atopic eczema	2 (14.3 %)	1 (12.5 %)
present atopic eczema	3 (21.4 %)	0
pets (dog, cat)	4 (28.6%)	0
GER	0	2 (25 %)

FH – family history; GER – gastroesophageal reflux

Results

Fourteen children (68 %; 8 boys and 6 girls) showed, within 72 hours of instituting montelukast therapy, a decrease in the frequency and severity of night-time cough with improved sleep. The cough completely disappeared within week 3 of therapy.

Children responding to montelukast therapy were found to have higher blood levels of eosinophil cationic protein (S-ECP) in the pretreatment blood sample than children with no response (responders 14.88 ± 2.651 μg/l versus non-responders 6.62 ± 0.948 μg/l; $p < 0.01$). The S-ECP blood levels also remained higher in the post-treatment blood sample in responders (10.55 ± 1.631 μg/l) compared to non-responders (6.13 ± 0,937 μg/l, $p < 0.05$). The difference is significant in responders.

The difference between these values in the group with an effect of montelukast therapy is significant, while ECP did not change in the group without an effect (Figure 1). Only in the group with a therapeutic effect did we demonstrate S-ECP higher than 18 μg/l prior to therapy institution in four children.

In 11 children of the group with an effect, we demonstrated peripheral eosinophil counts over 350×10^6/l prior to therapy initiation. A significant difference was observed between both groups also in baseline absolute peripheral blood eosinophil counts before therapy initiation (Figure 2).

S-IgE levels higher than 150 IU/ml were seen in ten children of the group with an effect of therapy, and in one child of the group without an effect. After excluding an individual with high S-IgE levels (692 IU/ml) in the group of children without an effect, who was subsequently shown to have gastroesophageal reflux, a significant difference was observed between both groups also in S-IgE levels.

Using 24-hour pHmetry, two children (9 %) not responding to therapy were subsequently diagnosed to have gastroesophageal reflux.

Discussion

Chronic persistent cough is dry/irritating nonproductive cough or productive cough with expectoration persisting usually for more than three to six weeks, with a negative chest x-ray finding, with normal spirometry results, and without an obvious or documented cause[1].

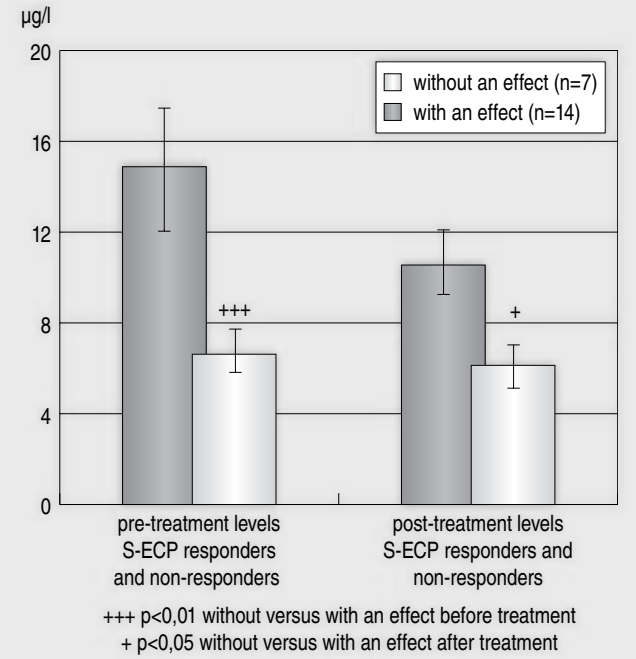
Asthma bronchiale (AB) is a syndrome characterized by airway obstruction, varying both spontaneously and as a result of therapy. At present, it is defined as a chronic inflammatory airway disease with recurrent bronchospasms to stimuli not causing airway narrowing in most individuals. The main pathogenic mechanism of asthma bronchiale is a special form of chronic inflammation–chronic eosinophil-based inflammation of the bronchial mucosa increases airway hyperactivity to a wide range of stimuli resulting in marked narrowing of the bronchi. The narrowing of the airway lumen is usually reversible, either spontaneously or as a result of therapy;

however, in some patients with chronic asthma is may imply permanent, irreversible obstruction. The main cells involved in the development of chronic allergic inflammation are eosinophil granulocytes and mast cells, with minimal activity of neutrophil and basophil granulocytes[3].

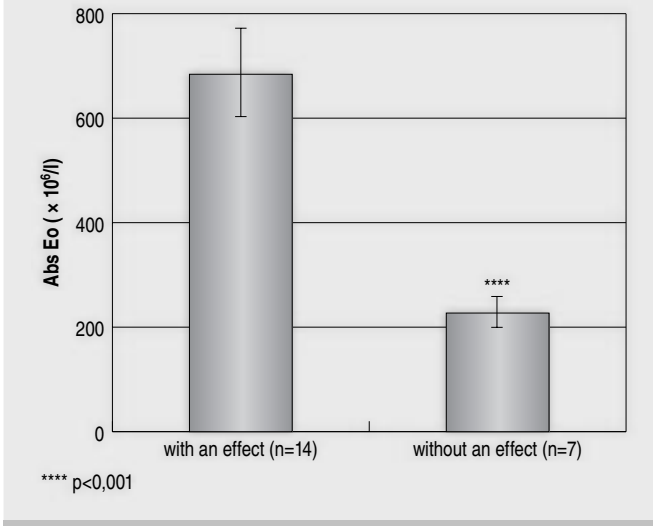
The most frequent symptoms of AB in children is wheezing while about 60 % of children present with chronic cough.

ECP is a cytotoxic product of eosinophil leukocytes and monitoring of its serum levels can be used for quantitative evaluation of these inflammatory processes. Serum ECP levels reflect actual serum eosinophil activity, i. e., their ability to release granular proteins during activation during an inflammatory response. Eosinophil activity can also be documented by the presence of ECP in bronchial tissue, in the form of EG2+ cells using monoclonal antibody. Serum ECP determination has become, over the approximately 15 years of use of this method worldwide, another adjunct technique for diagnosing and, particularly, monitoring of treatment of anti-inflammatory inhaled agents in children and adults with AB[4].

Graf 1. Blood levels of eosinophil cationic protein in the pre-treatment blood sample and in the post-treatment blood sample of responders and non-responders to montelukast



Graf 2. Absolute peripheral blood eosinophil counts before therapy with montelukast in responders and non-responders



Leukotrienes are lipid mediators, generated de novo frommembrane-associated arachidonic acid founded in all cells.

Arachidonic acid is further converted via three pathways:

1. Cyclooxygenase – whose products are prostaglandins (PGE2, PGD2, PGF2), prostacyclin (PGI2) and thromboxane (TXA2)
2. 5-lipo-oxygenase – progressively giving rise to hydroperoxyeicosatetraene acids (nPETE), which are further metabolized to hydroxyeicosatetraene acids (HETE, main products of 12- and 15-lipooxygenase), leukotrienes (main products of 5-lipooxygenase) and lipoxins (formed by the simultaneous action of 5- and 15-lipooxygenase)
3. Oxygenation in the presence of the cytochrome P 450.

Leukotrienes, when combined with other factors, produce:

1. an increase in vascular wall permeability and development of edema
2. Mucus secretion
3. Bronchoconstriction
4. Cellular infiltration (5).

The leukotriene receptors, $CysLT_1$, occur on the surface of mast cells, macrophages, smooth muscle cells, monocytes, B-lymphocytes as well as eosinophils. An interesting finding was that interleukin 5 increases $CysLT_1$ receptor expression, which significantly interferes with the development of allergic inflammation[2]. Leukotriene LTD_4 binding is followed by Ca ion release, actin polymerization, and an increase in cell chemotaxis.

Early allergic reaction, after two IgE molecules have been coupled with the antigen on the surface of mast cells, is associated with release of mediators, followed by release of leukotrienes, which subsequently bind to the $CysLT_1$ receptor (autocrine process) on the mast cell surface. This is followed by the release of Ca^{2+} affecting the allergic inflammatory response. In turn, this autocrine signal again leads to increased generation of leukotrienes and their release resulting in the „cysteinyl-based mast cell vicious circle" as part of the allergic reaction thereby controlling the function of mast cells and, partly, also smooth muscle cells by leukotrienes released by paracrine mechanisms (Fig. 1). Another relationship affecting the dynamics of the allergic response is the interrelation between histamine and leukotrienes. Histamine-activated macrophages are associated with increased leukotriene (LTD_4) formation; contrarywise, leukotrienes may promote the release of inflammatory mediators in the airways, with the implication being that the effects of these mediators in the early and late phases of allergic inflammation are enhanced[5].

Graf 3. Serum levels of Immunoglobulin E before therapy with montelukast in responders and non-responders

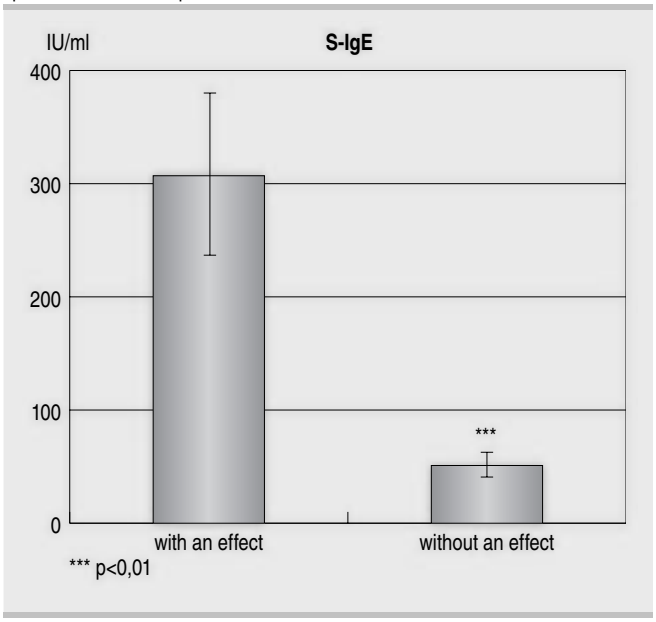
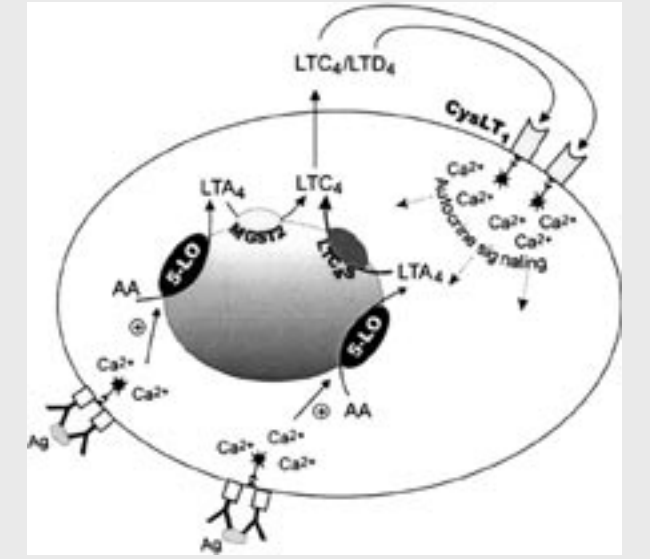


Figure 1. Model of double stimulation of leukotriene formation by mast cells: 1. Early allergic reaction, after two IgE molecules have been coupled with the antigen (Ag) on the surface of mast cells, is associated with release of mediators. 2. After binding of released leukotrienes to CysLT1 receptors on the mast cell surface, and autocrine stimulation of leukotriene formation by released Ca2+ ions. (Adapted by Sjöstroma M, Biochim Biophys Acta 2002, 1853, 53 – 62); AA – arachidonic acid, LTC4S - LTC4 syntetase, 5 – LO – 5-lipo-oxygenase, LTA4, LTC4, LTD4 - leukotrienes



The anti-inflammatory response in viral infection is associated with increased generation of IFN γ by Th1 lymphocytes in the airways. Even in individuals without asthma, viral infection may result in increased airway reactivity and cough persisting for weeks to months. The exact mechanism by which viruses interfere with smooth muscle function is not known. IFN γ has been shown to increase $CysLT_1$ expression in the airways and enhance the response to LTD_4. IFN γ seems likely to affect the degree of bronchial hyperactivity during viral infection and, also, allergic reactions.

Attacks of dry, irritating cough, mainly at night, occasionally with expiratory wheezing, without typical asthmatic dyspnea, with normalization after bronchodilators, have been termed, in the relevant literature, asthma equivalents or, alternatively, „cough variant asthma". Antitussive agents are absolutely ineffective in these cases! These patients are often shown blood and sputum eosinophilia and airway hyperresponsiveness[10].

Montelukast is a competitive specific CysLT1 receptor antagonist. After administration, a bronchodilator effect becomes evident within 2 hours; it inhibits bronchoconstriction produced by leukotriene LTD4 inhalation and modulates the early and late phases of response to an allergen.

Based on the above facts we instituted, in children with chronic cough, referred to the Immuno-Allergology Outpatient Unit of Dept. of Pediatrics for examination by a consultant, and in whom treatment with antitussants, antihistamines or antibiotics had failed, therapy with montelukast, an antileukotriene. Information, which came to us as a surprise yet, on the other hand, information confirming the declared therapeutic effect of antileukotrienes by suppressing the activity of released leukotrienes, was the fact that children in the group with a therapeutic effect did not experience attacks of cough as early as the third night following therapy initiation. Evaluation of the results of examinations suggested that most children with a therapeutic effect of montelukast showed significantly increased levels of total S-IgE, S-ECP but, also, absolute peripheral eosinophil count compared with children without a therapeutic effect. Based on the data obtained and clinical experience, we can recommend to consider, in children with chronic cough and increased absolute peripheral eosinophil count as well as increases in S-IgE or S-ECP, after ruling out another pathology, initiation of therapy with montelukast as a therapeutic and differential diagnostic step in children with recurrent obstructive bronchitides.

Chronic cough is a relatively frequent clinical symptom unjustly underestimated by physicians. A knowledgeable pathophysiological analysis may significantly aid in pinpointing the underlying cause of cough. Early and rational treatment of cough results in remission of the bothersome symptom. Montelukast therapy in the exhausting form of chronic cough could possibly reduce the severity of problems experienced by a proportion of patients, speed up remission of inflammation, or even beneficially affect the immunopathological mechanisms of allergy. A benefit not to be dismissed is a reduction in the discomfort experienced by the child, and concern on the part of the child's parents about its health condition.

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