THE INFLUENCE OF BACKGROUND THERAPY WITH LEUKOTRIENE INHIBITORS ON CLINICAL SPIROMETRIC PARAMETERS AND ON EXHALED NITRIC OXIDE IN THE CHILDREN WITH ASTHMA

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Abstract: *The installation of bronchial remodelling process within the chronic inflammatory process in asthma has a significant result on both: the severity of the clinical signs and also on the response to the treatment. A key argument for the support of diagnosis and asthma severity is the demonstration of the presence of bronchial obstruction in terms of spirometry and, more recently, through the demonstration of eosinophilic inflammation with the help of values of nitric oxide in exhaled air. Both methods explore the inflammatory process of the airways. The pathogenesis of asthma is increasingly well understood, but increasingly dynamic. Therefore, there are being developed new classes of drugs. Numerous studies attempt to demonstrate the effectiveness of different classes of drugs, and chronic side effects of these therapies in children with asthma. A great progress is being made in the study of two major classes of drugs currently used to treat asthma: inhaled corticosteroids (CSI) and leukotriene inhibitors (ILT), recommended as a treatment medication in early stages of the disease. The effect of this therapy in the inflammatory process correlates with the levels of nitric oxide in exhaled air and with the values of the parameters determined by spirometry. One objective of this study is precisely to evaluate the role of anti-inflammatory treatment with leukotriene inhibitors (ILT) associated with inhaled corticosteroid (CSI) in maintaining asthma control. Another objective of the study is to determine the role of exhaled nitric oxide (NO) in monitoring the development of asthma/ recurrent wheezing in correlation with spirometry (old method established).*

INTRODUCTION

The term "asthma" derives from the Greek word "ASTMA", which means difficulty in breathing, and it was introduced in the medical language by Hippocrates, Areteu, Galen etc.

According to the Report of the Committee of Experts – "The Expert Panel Report 3" (EPR) ("Guidelines for Diagnosis and Management of Asthma 2007"), asthma is defined as a chronic inflammatory disease of the airways, a complex disorder characterized by recurrent symptoms (expiratory dyspnea, wheezing, spastic cough, chest tightness, symptoms that occur predominantly during night or early in the morning).(1,3,4) These symptoms appear because of the persistent inflammation in the walls of the lower airways and airflow obstruction at this level. The symptoms are reversible either spontaneously or with treatment for the majority of patients. For some patients, however, persistent chronic inflammatory process causes changes in airway wall structure. These persistent changes reunite as "bronchial remodelling" and consist of the underlying fibrosis, mucus hypersecretion, smooth muscle hypertrophy, angiogenesis and epithelial cells injury.(14,15)

The installation of bronchial remodelling process has a significant result on both: the severity of the clinical signs and also on the response to the treatment. In most cases, these changes occur because of the errors of the treatment, meaning the delay of introduction of the inflammatory treatment early in disease (due to physician's reserves about corticosteroids) and / or patient non-compliance to this treatment, and also because of the lack in continuous monitoring of the disease and treatment.

Classification of asthma by severity is made clinically by day time and night time symptoms, daily activities and sleep impairment, by the frequency of exacerbations and the need to use "attack" medication, that is bronchodilators, but also with the help of laboratory parameters determined during spirometry. There are four main categories of asthma: intermittent asthma, mild persistent asthma, moderate persistent asthma and severe persistent asthma.(1,3,4,9)

Establishing a diagnosis of asthma, supported only on clinical criteria, is very difficult. In older children, a key argument to support the diagnosis of asthma is held by demonstrating the presence of bronchial obstruction by spirometry (FEV1 = forced expiratory volume per second which is expressed as a percentage), and more recently, the diagnosis of asthma is held by determining the amount of exhaled nitric oxide in the presence of eosinophilic inflammation (dosing of the fraction of nitric oxide in exhaled air (FENO) appreciates the inflammatory process in the airways, in direct proportion to the degree of inflammation and it is expressed in parts per billion = ppb).(9,10,20) Both methods explore the inflammatory process of the airways. FEV decreases in the inflammatory process of the airways and bronchospasm by thickening of the lining. FENO increases in the inflammatory process of the airways due to increased activity of NO synthase, the enzyme activated by pro-inflammatory cytokines secreted by various cells involved in this inflammatory process. It is necessary to correlate the determination of FENO (method under investigation) with FEV1, because spirometry is already a proven method that is correlated with true inflammatory bronchial obstruction in the asthma.(16,17)

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FEV1 is the forced expiratory volume per second, it is the maximum volume of air exhaled in the first second of forced exhalation, preceded by a maximal inspiration. Normal values of FEV are above 80%. Values between 70-80% mean airway obstruction at a lower level, 50-70% means moderate obstruction and values below 50% mean a severe bronchiolar obstruction.(9,10,20)

FENO is the fraction of nitric oxide in exhaled air. Normal values of this inflammatory marker are below 20 ppb. FENO values above 35 ppb mean eosinophilic inflammation present in the airways. Values between 20-35 ppb must be interpreted according to the Asthma Control Test (ACT), a questionnaire that assesses clinical manifestations (e.g. presence/absence of cough and/or dyspnea and/or wheezing in different circumstances - diurnal and/or nocturnal and/or during effort). FENO level rises by 20% compared to the previous determination in patients with initial FENO > 35 ppb (or an increase with 10 ppb in patients with initial FENO < 20 ppb) means incomplete response to background therapy. FENO levels that have declined by 20% over the previous determination in patients with initial FENO > 35 ppb (decrease with 10 ppb in patients with initial FENO < 20 ppb) means good response to background therapy.(10,16,17) The pathogenesis of asthma is increasingly well understood, but increasingly dynamic. Therefore, there are being developed new classes of drugs. Numerous studies attempt to demonstrate the effectiveness of different classes of drugs, and chronic side effects of these therapies in children with asthma.

A great progress is being made in the study of two major classes of drugs currently used to treat asthma: inhaled corticosteroids (CSI) and leukotriene inhibitors (ILT), recommended as a treatment medication in early stages of the disease. There are studies showing that the symptoms and the frequency of nocturnal attacks decrease in both cases (inhaled corticosteroids and leukotriene inhibitors).(9,22) However, there are conflicting data regarding the action of montelukast on FEV1 or data supporting the higher effectiveness of inhaled corticosteroid (most of the literature). (NPC study "Montelukast Sodium Oral Inhaled Fluticasone Propionate versus Mild Persistent Asthma", 2008).

PURPOSE

One objective of this study is precisely to evaluate the role of anti-inflammatory treatment with leukotriene inhibitors (ILT) associated to inhaled corticosteroid (CSI) in maintaining asthma control ("Combined treatment with CIS and ILT with/without antihistamine in the early stages is an advantage, that provides a better control of the inflammatory process, equivalent with decreased FENO and increased FEV1?) Another objective of the study is to determine the role of exhaled nitric oxide (NO) in monitoring the development of asthma / recurrent wheezing in correlation with spirometry (old method established) ("Could we use the determination of NO in exhaled air to evaluate the control of the inflammatory process in asthma / in recurrent wheezing with the background therapy instituted (CSI or CSI in combination with ILT) and possibly of modelling background therapy with the help of this method?").

MATERIALS AND METHODS

The study was performed on 83 patients with asthma/recurrent wheezing, who are in the evidence of the "Laboratory, Clinical and Paraclinical Pediatric Research Centre in Respiratory Medicine" (Pediatric Hospital Sibiu) between 2013 and 2014. This was a "case-control" study: a group of children with inhaled corticosteroids as background therapy and other group with inhaled corticosteroids associated with leukotriene inhibitors as background therapy. Both groups were evaluated after 3 months of background therapy (simple, with one class of drug or combined, two classes of drugs) the clinical parameters (cough, dyspnea and wheezing, diurnal, nocturnal and during effort), spirometry (FEV1) and the value of exhaled nitric oxide (FENO). There were included in the study children previously diagnosed with asthma (various severity degrees) or recurrent wheezing, aged up to 3 years and under 18 years, non-smoking, inhaled corticosteroid as basic therapy or corticosteroid with leukotriene inhibitors as basic therapy (with or without antihistamine treatment), with the basic therapy established for at least 3 months, with correct technique of inhaled corticosteroid administration, patients during the stable stage of the disease, capable of forced expiratory manoeuvres.

There were excluded from the study patients with acute or chronic respiratory pathology in addition to asthma, asthma attack patients, patients unable to perform spirometry correctly or expired NO measurement (who do not meet the criteria for acceptability and reproducibility). Spirometry was performed with the spirometer of Pediatrics Clinic of Sibiu. Spirometric curves were considered invalid in the following situations: the child coughs during the measurement, presents improper breathing (rapid/slow), the child does not reach maximum expiratory pressure, tightness improper mouthpiece, curve flat or round, without showing a peak, the peak of the curve to the right or the presence of two peaks. As regards the determination NO (with portable device NObreath®) the technique was considered inappropriate if: it shows improper breathing (rapid/slow), cannot maintain for an appropriate period of time the indicator between the two lines, improper sealing of the mouthpiece.

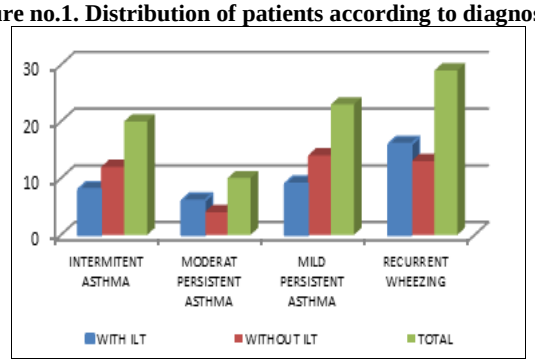
For statistical analysis we used SPSS software. Patients were divided into two groups: experimental group with treatment with inhaled corticosteroids and leukotriene inhibitors associated with the control group background therapy with inhaled corticosteroids. The distribution of the groups according to the basis of diagnosis is shown in table no. 1, figure no. 1.

In both groups, there were evaluated, after approximatively 3 months of the background treatment initiation (only simple therapy or combination therapy), clinical parameters (cough, dyspnea and diurnal, nocturnal and during effort wheezing - using a questionnaire "Asthma Control Test"-ACT), spirometry (FEV1) and the amount of exhaled nitric oxide (FENO).

Table no. 1. Distribution of groups according to diagnosis

Diagnosis	Group		Total	p
	With ILT	Without ILT		Likelihood ratio
Intermittent Asthma	8	12	20	0.448
	40.0%	60.0%	100.0%	
Moderate Persistent Asthma	6	4	10	
	60.0%	40.0%	100.0%	
Mild Persistent Asthma	9	14	23	
	39.1%	60.9%	100.0%	
Recurrent Wheezing	16	13	29	
	55.2%	44.8%	100.0%	
Total	39	44	83	

Figure no.1. Distribution of patients according to diagnosis



RESULTS

We considered the development of asthma symptoms (dyspnea, cough, wheezing), occurring under different circumstances (day time and /or night time and /or effort), spirometric parameters (FEV1) and, in particular, exhaled nitric oxide fraction (FENO), in patients with known asthma (intermittent, mild to moderate persistent) or recurrent wheezing in either treatment with inhaled corticosteroids or inhaled corticosteroids in combination with inhibitors of leukotriene (with /or without antihistamines) (table no. 2, figure no. 2, figure no. 4).

Table no. 2. Clinical parameters depending on the group

Parameter		Group		p Likelihood ratio
		With ILT	Without ILT	
Cough	Diurnal, nocturnal, during effort	10.3%	4.5%	0.736
	Diurnal, effort	2.6%		
	Nocturnal, effort	7.7%	11.4%	
	Diurnal	15.4%	11.4%	
	Nocturnal	2.6%	4.5%	
	Effort	23.1%	29.5%	
	Without cough	38.5%	38.6%	
Dyspnea	Diurnal, nocturnal, during effort	5.1%	9.1%	0.899
	Nocturnal, effort	2.6%	2.3%	
	Nocturnal	2.6%	2.3%	
	Effort	25.6%	31.8%	
	Without dyspnea	64.1%	54.5%	
Wheezing	Diurnal, nocturnal, during effort		2.3%	0.358
	Nocturnal		2.3%	
	Effort	15.4%	9.1%	
	Without wheezing	84.6%	86.4%	
FEV1		93.414±11.7691	92.98±15.80	0.887
FENO		21.00±38.59	19.21±28.05	0.811

Figure no. 2. Distribution of groups according to cough

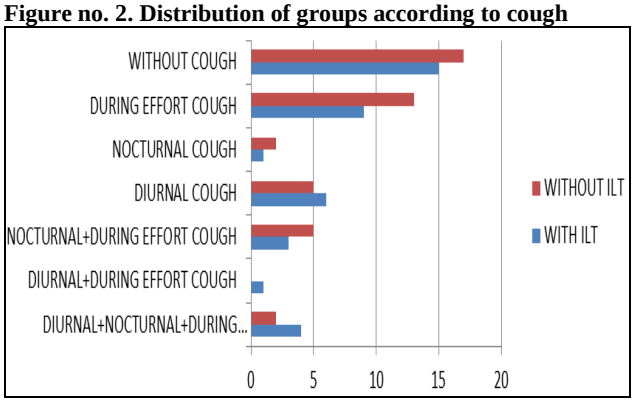


Figure no. 3. Distribution of groups according to dyspnea

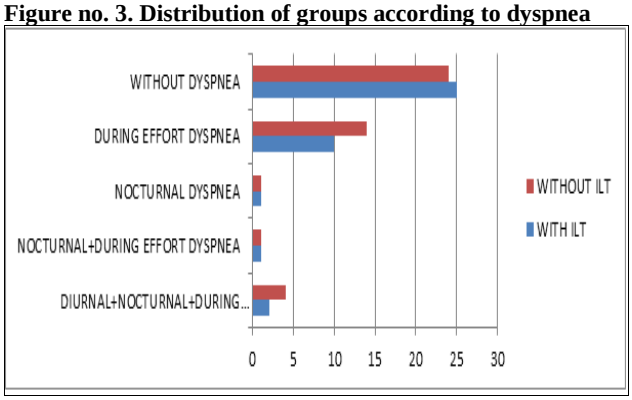
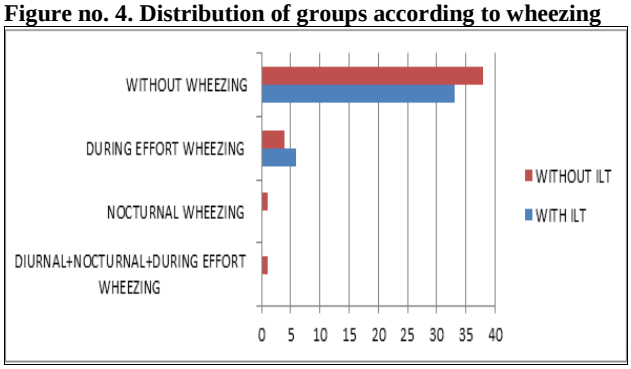


Figure no. 4. Distribution of groups according to wheezing



DISCUSSIONS

The estimated results according to literature consider that there is a moderate inverse correlation between FEV values and those of FENO, while, in association with clinical parameters (measured by means of ACT) and FENO, the literature shows that there is a significant inverse correlation between ACT and FENO value, mean FENO was significantly higher in the patients presenting ACT < 20 compared with patients with ACT > 20.

Statistical analysis shows that there is no an association between the study group and the clinical parameters, but it can be said that both cough during effort (see table no. 2, figure no. 2) and dyspnea (see table no. 2, figure no. 3) are less common in those without Singular and that wheezing during effort is more common in those with Singulair (see table no. 2, figure no. 4).

CONCLUSIONS

Early introduction of background therapy for asthma patient with leukotriene inhibitor leads to a slight improvement in symptoms in particular for dyspnoea and cough, but it does not significantly improves wheezing.

Regarding FEV1 or FENO, there is no increase or decrease in their values, which means that the process of eosinophilic inflammation in the airways is not well controlled in the patients treated with leukotriene inhibitor in addition to the corticosteroid inhalation, at least not after only 3 months of treatment.

In terms of the usefulness of the dosage of nitric oxide in exhaled air, it appears that it correlates well with the degree of eosinophilic inflammation, as well as FEV1 determined by spirometry, the old method dedicated to the diagnosis of asthma.

Exhaled nitric oxide indicates eosinophilic airway inflammation, airway response to inhaled corticosteroids and/or with leukotriene inhibitors, allows the adjustment of the dose inhaled corticosteroids, possibly the supplementation of the

background therapy with other classes of drugs; it detects the non-responsive patients to corticosteroid therapy and it is a viable, noninvasive marker of airway inflammation, which allows the analysis and monitoring of the disease and also monitoring the treatment to be secure, fast and simple.

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