Study Title:

Inflammatory Indices in Predicting the Failure of Inhaled Corticosteroids Reduction in Young Participants With Asthma

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Objective:

Evaluation of the Usefulness of Induced Sputum Eosinophilia, eNO (exhaled nitric oxide) and Bronchial Hyperresponsiveness in Predicting the Failure of Inhaled Corticosteroids Dose Reduction in Children and Adolescents With Stable Asthma

Trial design:

A prospective, observational, interventional, single-blind study (blinded for a clinician in the field of inflammatory parameters).

Abstract:

In participants with a stable course of the asthma (confirmed in the run -in period), every 3 months the dose of ICS is halved, according to GINA (Global Initiative for Asthma) guidelines, until the control is lost or the lowest daily ICS dose is reached (200 mcg, calculated as budesonide equivalent). Throughout the treatment reduction period, the participants run an observation card (clinical symptoms) and PEFR (peak expiratory flow rate) measurements. Clinical evaluation is performed every month, with spirometry, exhaled NO and exhaled breath temperature measurements. Before the reduction and then one month after the change of treatment, the hyperresponsiveness measurement is carried out with the sputum induction (combined method using hypertonic saline), and 2 months after the change of treatment with the exercise challenge test.
In the case of loss of asthma control, beta-mimetic will be administered (temporarily) and return to dose of ICS (inhaled corticosteroid) before reduction or further increase of treatment is planned. In severe asthma exacerbations, oral steroids will be considered.
The study is observational: treatment is modified according to GINA guidelines based on clinical data as part of routine medical care. Only difference compared do standard care is supplementary inflammation evaluation (exhaled NO, sputum eosinophilia, bronchial hyperreactivity).

Introduction:

Guidelines for asthma treatment recommend using the smallest dose of ICS, which allows to maintain control of the symptoms of the disease. The GINA 2006 guidelines proposed (and later editions it upheld) that in the case of symptom control by monotherapy with ICS, to reduce their dose every 3 months, up to the lowest dose administered once a day, which should be used for one year before taking possible decision to stop it.
There are no clear of simple and sensitive indicators that would allow detection of a threatening loss of control before the clinical symptoms worsen.
The aim of the study is the evaluation of the usefulness of induced sputum eosinophilia and other inflammatory indices [exhaled nitric oxide (NO), exhaled breath temperature (EBT), bronchial hyperresponsiveness] in predicting the failure of treatment reduction with inhaled corticosteroids in stable asthma in children and adolescents.

Methods:

This is a prospective, observational, single-blind study (blinded for a clinician in the field of inflammatory parameters). The clinician makes a decision about reducing the ICS dose based on clinical data only and is not aware of the results of the inflammatory parameters measurement.

Participants:

Participants aged 12-18 years with stable asthma (mild or moderate), treated in the Allergy Clinic of the Hospital in Lesko with medium doses in ICS. The severity of asthma was initially determined in accordance with the GINA criteria and verified during several years of observation by the assessment of clinical symptoms, functional examinations and the dose of inhaled steroids controlling the disease.

Eligibility Criteria:

Inclusion criteria:

- mild or moderate asthma with a stable course of at least 3 months:
- symptoms less than 4x per week,
- use of SABA below 3x a week,
- night awakening below 1x per week,
- FEV1 (forced expiratory volume at one second) > 80% of predicted
- no dose change in ICS or use of systemic steroids from 3 months
- good adherence to treatment

Exclusion Criteria:

- infection or exacerbation of asthma requiring the use of systemic steroids (or changes in the dose of inhaled steroids) in the last 3 months before the study
- other chronic lung diseases or general diseases affecting the respiratory system
- tobacco smoking
- FEV1 below 80% of the predicted value

Interventions:

First period (run-in):

A four-week run-in period in which clinical symptoms and the use of short-acting beta2 agonists (SABA) and PEFR are monitored. At the end of this period, in participants with stable disease, the following parameters are measured: eNO, EBT, spirometry, and sputum induction with hyperosmolar saline in combination with hyperresponsiveness. An exercise challenge test is also performed before the reduction of treatment on another day.

The criteria for the stability of asthma in the run-in period are:

- symptoms no more than 3 times a week
- SABA is used less than 3 times a week
- no night awakening due to asthma
- PEFR variability below 20%
- FEV1 above 80% of predicted

Second period of the study - reduction of anti-inflammatory therapy.

In participants with the previously stable course of asthma (confirmed in the run-in period), asthma control is monitored regularly throughout the observation period. All participants run an observation card (clinical symptoms) and PEFR measurements. Monthly spirometry, exhaled NO and exhaled breath temperature measurements are performed. Every 3 months and one month after the change of treatment (i.e in months 0, 1, 3, 4, 6 and 7), the hyperresponsiveness measurement is carried out with the sputum induction (combined method, [7]). Two months after the dose change (months 2, 5, 8) the exercise challenge test is carried out.

Every three months, the control of the asthma symptoms is evaluated based on the clinical data, and a possible change of ICS dose is considered. The results of bronchial reactivity measurements and sputum cytology are not known to the clinician who decides on a possible ICS dose change—he is blinded to the results of tests, and the therapeutic decision is based solely on clinical evaluation.

In participants with a stable course of the disease over the past 3 months, the dose of ICS is halved, following GINA guidelines. In the case of loss of asthma control, appropriate treatment modifications are administered, and the patient is withdrawn from the study.

If control of symptoms is maintained (evaluation based on clinical symptoms solely), every 3 months the dose of ICS is halved according to GINA guidelines, until the control is lost or the lowest daily dose is reached (200 mcg, calculated as budesonide equivalent) without losing asthma control at the next visit.

In the case of loss of asthma control, beta-mimetic will be administered (temporarily) and return to the chronic administration of the previous, twice higher dose of ICS is restored (or further increase of treatment). In severe exacerbations, oral steroids will be considered.

Measurements

1. Daily clinical evaluation by the patient:
    - Symptoms score according to the Santanello` questionnaire
    - PEFR measurement
2. Every month
    - Asthma Control Test
    - Spirometry: forced expiratory flow in 1st second (FEV1), forced vital capacity (FVC), FEF25-75 (forced expiratory flow between 25% and 75% of FVC), eNO measurement
    - exhaled breath temperature measurement (EBT)
3. every 3 months
    - quality of life test (QoL, Polish version of the questionnaire), i.e. months 3, 6, 9
    - cytological evaluation of induced sputum (i.e. months 0, 1, 3, 4, 6, 7)
    - Assessment of bronchial hyperresponsiveness:
        - one month after the ICS dose reduction and then before each subsequent dose reduction in ICS ((i.e. months 0, 1, 3, 4, 6, 7) - during the sputum induction with hyperosmolar salt (combined method)
        - 2 months after each treatment reduction (i.e. months 2, 5, 8): exercise challenge test (6-minute free-running test monitored by pulse)

Criteria for loss of control [1, 6] - any of the following:

- use of bronchodilators> 5 times a week
- the need for treatment with oral corticosteroids
- PEFR decreased above 20% for two consecutive days, compared to the average run-in period. In the case of loss of asthma control, beta-mimetic will be administered (temporarily), and return to the chronic administration of the previous, twice higher dose of ICS will be restored (or further increase of treatment). In severe exacerbations, oral steroids will be considered.

Criteria for discontinuation of participation in the study

1. Loss of asthma control (treatment strategy: beta-mimetic temporarily, return to a dose of ICS before reduction or further increase of treatment; in severe exacerbations, oral steroids).
2. Lack of adherence to the recommendations or failure to report.

The centre staff has experience in obtaining induced sputum in patients with asthma

The test will be performed in conditions ensuring patient safety, with an anaesthesiologist and anti-shock kit available.

Outcomes:

Primary Outcome Measures :

The percentage of patients with loss of asthma control [Time Frame: at 9 months]

Criteria for loss of control (any of the following):

- use of bronchodilators > 5 times a week
- the need for treatment with oral corticosteroids
- PEFR decrease >20% for 2 consecutive days, compared to the average run-in period

Secondary Outcome Measures :

Change in sputum eosinophilia [Time Frame: at 1, 3, 4, 6 and 7 month]

eosinophil percentage in induced sputum compared to baseline

Other Outcome Measures:

Change in airway hyperresponsiveness to hypertonic saline [Time Frame: at 1, 3, 4, 6 and 7 month]

Airway hyperresponsiveness to hypertonic saline measured using combined method (together with sputum induction) and compared to baseline

Change in airway hyperresponsiveness (exercise) [Time Frame: at 2, 5 and 8 month]

Airway hyperresponsiveness assessed using an exercise challenge test and compared to baseline

Change in exhaled NO [Time Frame: months 1 - 8] measured monthly and compared to baseline

Change in exhaled breath temperature (EBT) [Time Frame: months 1 - 8] measured monthly and compared to baseline

Change in FEV1 [Time Frame: months 1 - 8] measured monthly and compared to baseline

Change in FVC [Time Frame: months 1 - 8] measured monthly and compared to baseline

Change in FEF25-75 [Time Frame: months 1 - 8] measured monthly and compared to baseline

Other: ICS dose reduction