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Inflammatory markers as exacerbation risk factors after asthma therapy switch from inhaled steroids to montelukast

Janusz Ciółkowski [a], Henryk Mazurek [b, *], Paweł Hydzik [c], Barbara Stasiowska [a]

[a] The Regional Public Hospital, 38-600 Lesko, ul.Kochanowskiego 2, Poland
[b] Department of Pneumonology and Cystic Fibrosis, Institute of Tuberculosis and Lung Disorders, ul.Prof.Rudnika 3b, 34-700 Rabka – Zdrój, Poland
[c] Department of Quantitative Methods, Rzeszów University of Technology, al.Powstańców Warszawy 8, 35-959 Rzeszów, Poland

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ABSTRACT

Background: Asthma guidelines allow anti-leukotriene medications to be used as an alternative to inhaled corticosteroids (ICS) in second-step intensity therapy. The aim of the study was to analyze the risk factors of exacerbations, particularly inflammatory markers, during the 12-month period following therapy reduction from an ICS to montelukast in young patients with mild asthma.

Methods: A total of 84 patients (aged 7–18 years old) with mild asthma controlled by low-dose ICS, had their treatment switched to montelukast. Exhaled nitric oxide (eNO), sputum eosinophils (sEos), and bronchial hyperreactivity (BHR) were assessed at the beginning and then every three months throughout the one-year period. The patients with asthma exacerbations (first severe or third mild) were discontinued from the study.

Results: Over the study period, 22 patients (26%) discontinued montelukast due to asthma exacerbations. An increased risk of exacerbations was noted among patients with initial sEos above 2.5% (relative risk, RR 36.6; 95% CI: 7.1–189.3; $p < 0.001$), as well as those with augmented BHR (RR 9.5; 2.8–31.6; $p < 0.001$), or eNO greater than 20 ppb (RR 3.7; 95% CI: 1.3–10.7; $p = 0.013$). An increase in BHR and eNO was observed during the last visit before exclusion.

Conclusions: After switching treatment from a low-dose ICS, montelukast maintained control of asthma symptoms in 75% of patients. High sEos before the treatment change was the strongest exacerbation risk factor. In patients with asthma controlled by low-dose ICS and low inflammatory markers, treatment could be safely switched to montelukast.

1. Introduction

GINA 2006 and subsequent updates allow the use of montelukast as an alternative drug in the second step of asthma management [1]. According to the last GINA edition, montelukast is suitable for patients not willing or unable to use ICS, experienced important side-effects, or have concomitant allergic rhinitis [1]. Authors of the guidelines base their recommendations on studies comparing the anti-inflammatory potency of the LTRA and low-dose ICS. However, consensus PRACTALL and Australian guidelines recommend anti-leukotrienes as a good equivalent to low-dose inhaled corticosteroids [2,3]. In particular, some reports suggest a comparable efficacy with both drugs [4,5]. Moreover, GINA experts emphasize the necessity to find lowest ICS dose to maintain control of symptoms, but tapering ICS may increase the risk of uncontrolled asthma symptoms. In recent GINA Guidelines, sputum eosinophilia and airway hyperresponsiveness are mentioned as increasing the risk of future exacerbations, even if asthma is well controlled by current treatment. In patients with persistent eosinophilic inflammation this risk may occur during the reduction of treatment, or after exposure to triggers as allergens or smoking. Other important risk factors are low FEV1, comorbidities and exposure to smoking or allergens. Additionally, complete cessation of ICS therapy is associated with increased risk of exacerbations.

However, only few step-down studies have been performed in children. Moreover, none of the current guidelines formulate specific recommendations for the switch from ICS to LTRA as a possible strategy for inflammatory treatment reduction, and there is a lack

* Corresponding author.
E-mail addresses: janusz_ciolkowski@op.pl (J. Ciółkowski), hmazurek@igrabka.edu.pl (H. Mazurek), phydzik@prz.edu.pl (P. Hydzik), bstasiowska@o2.pl (B. Stasiowska).

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of data on the possible risk of such modification. Montelukast provides a good control of symptoms in the majority of mild asthma cases [6,7]. However, the data on the control of eosinophilic inflammation by montelukast is scarce and applies mainly to adults [8,9]. In *in vitro* studies, montelukast has a beneficial effect on eosinophilic inflammation in the context of chemotaxis and apoptosis [10,11], but clinical studies have demonstrated only an attenuation of inflammation [8,12,13]. Therefore, is unknown how subclinical eosinophilic inflammation translates into early and late sequelae of asthma, especially exacerbations. Additionally, there is a lack of data assessing the disease progression in the context of risk (or success) factors of exacerbations following treatment reduction in asthmatic children.

The aim of the study was to determine the risk factors of asthma exacerbations after replacing ICS treatment with LTRA in children with mild asthma. In particular, we investigated various inflammatory markers and control of airway hyperresponsiveness during the year-long follow-up period.

2. Material and methods

2.1. Subjects

The study group consisted of children and adolescents diagnosed with mild asthma for at least two years. In that period (i.e. at least one year prior to enrollment to the study), the disease activity was confirmed by the measurement of nonspecific bronchial hyperresponsiveness by a challenge with hypertonic saline after a four-week break in ICS treatment. There were no asthma exacerbation during this short ICS withdrawal. Eligible patients: maintained control of asthma for at least one year using a low dose of inhaled corticosteroid (budesonide 100 mcg or equivalent once a day); had an FEV1 greater than 80% of predicted; no exacerbation requiring systemic steroids within the last year; and no symptoms of respiratory tract infection for one month. They were selected from a pool of 133 patients with mild asthma from the Allergy Clinic of The Regional Public Hospital in Lesko (Poland). There were 14 patients that were not included due to changes in asthma symptom intensity; 7 did not receive ICS; 14 were non-compliant; and 12 refused to participate in the study.

The study was approved by the Bioethics Committee of National Institute of Tuberculosis and Lung Disorders (the approval number KE-3/2009). Parents or guardians of all patients, and patients over the age of 15 provided written consent to participate in the study prior to its commencement.

2.2. Study design and assessment of inflammation

The study consisted of an initial two-week period of clinical observation of the current treatment by low-dose ICS (running in) and 12-month clinical follow-up after the change of treatment (proper period of the study).

During the initial 2-week phase, patients continued their low-dose ICS and kept a diary of daily and nocturnal symptoms, including the use of beta-agonists, medical intervention, and measured PEFR (Personal Best) twice a day.

At the end of the initial period, patients' asthma control on low −dose ICS therapy was evaluated by the physician according to the GINA criteria and using the ACT test (version for adults and older children). Only patients with good asthma control and an ACT result of 20 points or greater were included in the switch to LTRA, and baseline values of monitored parameters were calculated.

The fraction of nitric oxide in exhaled air (eNO) was measured using an electrochemical-based Medisoft HypAir FE (NO) device (Medisoft SA, Belgium). The measurements were performed at an expiratory flow rate of 50 mL/s and the duration of exhalation was at least 6 s to ensure a stable eNO level. Three measurements were obtained for all subjects, and the mean value was recorded as the level of eNO [14].

Next, spirometry was performed (Easy One - Medizin Technik Schweiz) according to the ATS/ERS guidelines [15], with at least three correct forced exhalations. FEV1 (forced expiratory volume in 1 s), FVC (forced vital capacity), and MMEF (maximal mid-expiratory flow) were retained for analysis.

Next, the induction of sputum and measurement of airway hyperresponsiveness to hypertonic saline was performed at a single stage using the combined method [16]. The test consisted of 8 cycles of inhalation of 4.5% sodium chloride: 30 s, 30 s, 1 min, 2 min, and then four times for 4 min. FEV1 was measured at 1 min after each cycle and sputum expectoration was attempted. The procedure was terminated after the last inhalation or earlier if the FEV1 fell by more than 15%.

The induced sputum was processed according to the method described by the Polish recommendations in Ref. [17]. The sputum was initially assessed macroscopically for plugs at the time of collection. Total cell counts were determined, and cytospin slides were prepared. An adequate specimen was defined as one producing countable cytospin slides for an estimation via differential cell count, with minimal squamous contamination (<50%) and pulmonary macrophages present. A differential cell count was obtained from 200 cells on May-Grunwald-Giemsa stained slides.

The dose-response slope (DRS) was calculated as the ratio of reduction of FEV1 (% of initial value) by volume of the sodium chloride inhaled (mL) [18].

Upon the completion and analysis of these tests, the anti-inflammatory treatment was changed in all patients from 100 mcg/day of budesonide to a montelukast dose of either 5 mg (children under 15) or 10 mg (children over 15).

Patients kept a diary of daily observations of asthma symptoms, use of beta-agonists and PEFR measurements performed during the 12-month follow-up period for the first three months, and then continuously for four weeks straight prior to further testing at 6, 9, and 12 months. Moreover, patients reported to their primary physician every four weeks during the first 12 weeks of the study for the evaluation of asthma control according to the GINA guidelines [1] and the ACT tests. Measurement of nitric oxide in exhaled air and spirometry were performed during these visits.

Further visits conducted every three months included a spirometry measurement, determination of nitric oxide levels, bronchial hyperresponsiveness, and induced sputum collection. During these visits, a question regarding compliance was always asked, and physicians insisted that the patient take all prescribed doses. Monthly phone interviews were also carried out with the patients' parent or guardian to inquire about the child's well-being, results of observations, and compliance.

2.3. Definitions of an exacerbation

Participation of the patient in the study was terminated upon an occurrence of the first severe exacerbation or third mild exacerbation [19]. A severe exacerbation was diagnosed in patients if there was a decreased PEFR of more than 30% of baseline during two consecutive days or need for systemic steroids (oral prednisone 1 mg/kg for seven days) prescribed by a physician in addition to beta-agonists. Patients were diagnosed with a mild exacerbations if their PEFR decrease was in between 20% and 30% of the average baseline for two consecutive days, if they needed to use more than three additional inhaled SABA doses per day, or there was an occurrence of nighttime awakenings (or early in the morning) due to asthma symptoms. Therefore, beta-agonists were given ad-hoc