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Do children with stable asthma benefit from addition of montelukast to inhaled corticosteroids: Randomized, placebo controlled trial

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ABSTRACT

Background: To determine the effects of montelukast added to maintenance inhaled steroids (ICS) therapy during the school year in children with stable asthma on the ICS use, frequency of exacerbations, lung function, asthma symptoms, fractional exhaled nitric oxide (FeNO) level and exercise-induced bronchoconstriction (EIB).

Methods: Seventy six asthmatic children aged 6–14 years, allergic to house dust mites were randomized to a double-blinded trial comparing montelukast therapy to a matching placebo. We studied following end-points: the reduction in the ICS dose, the frequency of exacerbations, lung function, asthma control test score, and the change from baseline in FEV_1 during a standardized exercise treadmill challenge. ICS dose was adjusted in a stepwise fashion to determine the lowest dose necessary to control asthma symptoms.

Results: We showed that children with baseline value of FeNO above 31 ppb and well controlled asthma symptoms on low doses of ICS, benefit the most from additive therapy with montelukast; their cumulative ICS dose is lower than in children treated with ICS only. Also, the addition of montelukast to regular treatment in asthmatic children resulted in a significant reduction in the frequency of exacerbations and EIB protection.

Conclusion: It is reasonable to add montelukast to ICS therapy in asthmatic children during the school year, to lower cumulative ICS dose in children with well controlled asthma symptoms, as well as to reduce number of exacerbations, and to achieve better control of EIB.

Trial registration: NCT01266772.

1. Introduction

Leukotriene modifiers are recommended as an add-on therapy to inhaled corticosteroids (ICS) treatment for the management of patients with moderate-to-severe asthma [1–3]. However, the use of leukotriene inhibitors has not consistently been shown to have an inhaled-steroid-sparing effect, or a reduction in the need for systemic steroid treatment [4]. Regular anti-asthma treatment with ICS and leukotriene modifiers alleviates exercise-induced bronchoconstriction (EIB) in children [5]. It is unknown whether the addition of montelukast to ICS therapy can reduce the frequency of exacerbations in children [6]. Fractional exhaled nitric oxide (FeNO) has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, or airway hyperresponsiveness [7,8].

We aimed to indicate if children, allergic to house dust mites, with well controlled asthma on inhaled steroids can achieve the reduction in steroids via addition of montelukast. Secondly, we studied the effects of montelukast on the frequency of

List of Abbreviations: ICS, inhaled glucocorticosteroids; EIB, exercise-induced bronchoconstriction; FeNO, fractional exhaled nitric oxide; ACT, asthma control test; ETC, exercise treadmill challenge; BHR, bronchial hyperreactivity; PEF, peak expiratory flow.

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exacerbations, lung function, asthma symptoms, FeNO level, EIB and methacholine challenge in above children during the school year.

2. Methods

2.1. Patients

Eighty children aged 6–14 years with IgE-dependent asthma allergic only to house dust mites (HDM; *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* or both) were randomly selected (using a computer-generated allocation schedule) from the outpatient population at our Allergy Clinic Center.

2.2. Inclusion criteria

Patients with regular asthma symptoms requiring long-term daily treatment with inhaled corticosteroids (between 200 and 600 mcg of budesonide) to control asthma symptoms during the high exposure season (September–March) preceding the study were included. During the time outside of the exposure season (April–August), patients did not require medication and their asthma was well control. All patients had to have exercise treadmill challenge (ETC) test done previously, during diagnostic evaluation of asthma.

2.3. Exclusion criteria

Exclusion criteria included loss of asthma control (which usually require use of higher doses of ICS for short period of time) during the summer season; immunotherapy; active smoking; and diagnosis of acute or chronic lung diseases.

2.4. Study design

This was a randomized, double-blinded trial comparing montelukast (Montessan, Apotex, Canada) therapy given once daily at bedtime to a matching placebo. At the time of asthma diagnosis, anti-dust measures were recommended for all patients. We studied following end-points: the reduction in the ICS dose necessary to control asthma symptoms, the frequency of exacerbations, FEV_1, asthma control test (ACT) score, the change from baseline in FEV_1 during a standardized ETC and methacholine provocation test. ICS dose was adjusted in a stepwise fashion to determine the lowest dose necessary to control asthma symptoms. The mean (SEM) cumulative ICS doses (sum of doses reported at visits 1–6) were also calculated.

Both montelukast and placebo were prepared and blinded by the pharmacy. Children received 5 mg oral tablets. The study was performed during one season; there were 7 study visits: one prior to the study and six study visits at the clinic. During the screening visit (June 2012), all participants were informed of the purpose of the study and were instructed in the scoring of asthma symptoms at home using the ACT. Lung function tests and FeNO measurements were also performed. During the first visit (September–October 2012), conducted at the time of reasonably well asthma control (patients were off ICS for summer season in order to get to visit 1), all patients underwent baseline spirometry, and FeNO measurements. Control of asthma was defined according to published guidelines [1] based on the presence of daytime/nighttime asthma symptoms, lung function, and the frequency of short-acting β_2-agonist inhaler use. At visit 1, all patients were administrated budesonide in daily dose which controlled their asthma symptoms during the high exposure season preceding the study, including between 200 and 600 mcg of budesonide (Pulmicort Turbuhaler, AstraZeneca, UK) and a β_2-agonist (Ventolin, GlaxoSmithKline, Philadelphia, PA, USA) as needed for symptomatic relief purposes. Next, the subjects were randomized according to a computer-generated allocation schedule to either additional treatment with montelukast (*montelukast group; montelukast*) or placebo (*control group; placebo*).

At visits 2 to 6, every six weeks, during the heating season (maximum natural exposure to HDM: Sept–March) [9], baseline spirometry and FeNO measurements were performed.

Additionally, at visit 5, a standardized exercise treadmill challenge was performed, and at visit 6, a methacholine challenge test was performed.

At visits 2 through 6, the ICS dose adjustment was determined based on reported symptoms. For children reporting good control of asthma symptoms, the daily ICS dose was decreased by 100 mcg budesonide; for children with poorly controlled asthma symptoms, the daily ICS dose was increased by 100 mcg budesonide.

Visits were scheduled so that lung function testing in individual patients would always take place on the same day of the week and at the same time. Prior to lung function testing, short-acting β_2-agonists were withheld for 12 h. During the entire study period, patients completed daily diary entries to assess symptom scores. Every morning and evening, they assigned themselves a score that expressed their well-being as an asthmatic patient; the diaries were filled out by patients and checked by doctors on each visit. ACT score was evaluated at visits 1 to 6. Compliance with asthma medication was checked; the patients were asked to bring all used and unused medication to each follow-up visit. Also, children had to demonstrate the inhalation technique and taken of a Turbuhaler competence was checked on each visit.

2.5. Ethics

The study was approved by a Medical University of Lodz Ethics Committee. Written consent from the patients and their parents was obtained.

2.6. Asthma control test

Described in details elsewhere [10,11].

2.7. Lung function tests

Pulmonary function testing was performed using a Master Screen unit (Erich Jaeger Gmbh-Hochberg, Germany). Predicted values for all lung function variables were based on a previous study of healthy controls, the results of which were provided by the manufacturer of the lung function test equipment [12]. Flow-volume curves were performed according to American Thoracic Society standards [12]. The highest of 3 successful measurements was recorded. The results were expressed as percentages of the predicted values. Reversibility testing was performed after administration of salbutamol (200 μg). The percentage change from baseline in FEV_1, pre-bronchodilatory FEV_1 and peak expiratory flow (PEF) were included in the analysis.

2.8. Nitric oxide measurement

The NO measurements were performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations [13], with a chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO, USA) and defined in parts per billion.