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

Iwona Stelmach^{a,*}, Agata Ożarek-Hanc^a, Magdalena Zaczeniuk^a,
Włodzimierz Stelmach^b, Katarzyna Smejda^a, Paweł Majak^a, Joanna Jerzyńska^a,
Janas Anna^{b,c}

^a Department of Pediatrics and Allergy, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland

^b Department of Social and Preventive Medicine, Medical University of Lodz, Lodz, Poland

^c Institute of Dental Surgery, Faculty of Medicine and Dentistry, Medical University of Lodz, Poland

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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 FEV₁ 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.

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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 hyperactivity; PEF, peak expiratory flow.

* Corresponding author. Department of Pediatrics and Allergy, N Copernicus Hospital, 62 Pabianicka Street, 93-513 Lodz, Poland. Tel.: +48 42 689 59 72; fax: +48 42 689 59 73.

E-mail address: alergol@kopernik.lodz.pl (I. Stelmach).

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, FEV₁, asthma control test (ACT) score, the change from baseline in FEV₁ 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/night-time asthma symptoms, lung function, and the frequency of short-acting β_2 -agonist inhaler use. At visit 1, all patients were administered 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 μ g). The percentage change from baseline in FEV₁, pre-bronchodilatory FEV₁ 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.

2.9. Standardized exercise treadmill challenge (ETC)

Exercise-induced bronchoconstriction was tested by the use of a motor-driven treadmill (Kettler, Ense-Parsit, Germany) according to ATS/ERS guidelines [14]. FEV₁ was measured before the running exercise, immediately afterwards, and 3, 6, 10, 15, 20 and 30 min after running. The maximum percentage fall in FEV₁ parameter was calculated using the following formula: [(pre-exercise value – lowest post-exercise value)/pre-exercise value] x 100. The cutoff ≥10% fall in FEV₁ during ETC was used for a positive EIB challenge.

2.10. Methacholine bronchial provocation test (MBPT)

Methacholine bronchial provocation testing was performed using the dosimeter technique and APS Pro (Erich Jaeger GmbH-Hochberg, Germany), with controlled tidal breathing. After the pulverization physiological diluent, methacholine was delivered in four cumulative doses: 0.015 mg, 0.045 mg, 0.18 mg, and 0.72 mg. A negative MBPT was defined as a PD₂₀ > 0.72 mg. MBPT was continued with 2 min intervals between the inhalations until a fall in the forced expiratory volume over 1 s (FEV₁) of ≥20% was obtained. PD₂₀ was calculated by linear interpolation on a log-dose–response curve [12].

2.11. Asthma exacerbation

Asthma exacerbation was defined as episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness or some combination of these symptoms which required introduction of systemic glucocorticosteroids. Exacerbation was calculated as a cumulative amount per group between visits as well as for the whole trial.

2.12. Statistical methods

Minimal sample size was calculated as 35 children per group in the analyzes. Sample size was calculated on the following assumptions: i) at least 20% greater reduction in ICS dose in montelukast group compared to placebo group, ii) expected power of conclusion- 85%, iii) 20% of drop-out rate. Within and between-groups differences were assessed with analysis of variance for repeated measurements (ANOVA) or with Friedman and Mann–Whitney tests. To assess correlation between continuous

Table 1
Baseline characteristics.

	Placebo N = 37	Montelukast N = 39
Age [years], mean ± SD	10.5 ± 2.8	10.9 ± 2.5
Male gender, n (%)	26 (70.3)	28 (71.8)
Asthma control test [points], median (interquartile range)	24 (23–26)	25 (23–26)
FEV ₁ [% pred.], mean ± SD	101.6 ± 10.1	102.2 ± 15.5
FEV ₁ /FVC [% pred.], mean ± SD	101.5 ± 7.7	103.2 ± 10.6
FeNO [ppb], median (interquartile range)	21.7 (11.6–37.3)	29.3 (17.2–45.8)
ICS ^a dose [mcg/day], mean ± SEM, (min–max),	218.3 ± 16.8 (200–600)	218.6 ± 17.2 (200–600)

^a Budesonide or equivalent during the high exposure season preceding the study.

variables, Spearman's test was used. Associations between nominal or categorized variables were verified by chi-square or Fisher exact tests. All statistical analyses were performed using StatSoft Statistica for Windows, release 8.0 (StatSoft, Inc., Tulsa, USA). *P* < 0.05 was used as the definition of statistical significance.

3. Results

3.1. Subjects

The patient flow is shown in Fig. 1. A total of 80 children were approached to participate in the study. Of those, 3 refused, in the majority of cases because they were too busy with school, and 1 child could not be randomized after run in. Finally, 76 children were included in the study, 39 in the montelukast group and 37 in the placebo group. Due to loss of follow-up, 5 patients were excluded (Fig. 1). The groups were well matched for age, sex, lung function tests, and initial ICS dose (Table 1). Patient's baseline characteristic, revealed FeNO baseline values much higher in montelukast group, when compared to placebo group (Table 1). According to data taken from medical records all patients (from both groups) had negative ETC before the study (mean ± SEM of maximum % fall in FEV₁ was 4.5 ± 0.27 and 4.6 ± 0.25 in montelukast and placebo group respectively).

3.2. Asthma control test (ACT)

Analysis of variance showed an increasing linear trend in ACT scores in the montelukast group (*p* = 0.013). There was no

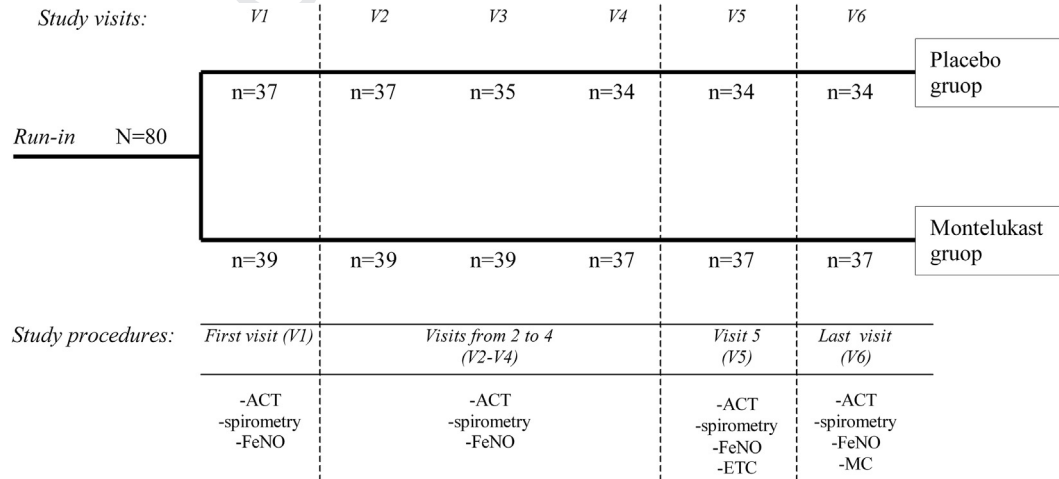


Fig. 1. Flow chart of the study.

significant change in ACT scores in the placebo group. There were no significant differences in ACT scores between the study groups ($p = 0.419$) (Table 2, Fig. 2).

3.3. FeNO

There were no significant changes in FeNO levels within either study group. Additionally, there was no significant difference in FeNO levels between study groups ($p = 0.477$) (Table 2).

However, when compared between groups, significant difference in reduction in FeNO level (FeNO from visit 6 – FeNO from visit 1) has been shown (mean reduction for montelukast group = 10.9 ppb vs mean reduction for placebo group = 0 ppb; $p = 0.0252$) (Fig. 3A). Based on the ROC curve analysis, we showed the association between baseline FeNO measurement and FeNO reduction, after treatment with montelukast. What is more, using ROC curve analysis, we have calculated cut-off level of baseline FeNO, with the highest sensitivity and specificity for prediction of more or equal 10.9 ppb reduction after treatment (Fig. 3C). This prediction value of baseline FeNO is 31 ppb.

3.4. Steroid doses

Overall, the mean (SEM) cumulative ICS doses (sum of doses of Visits 1–6) did not differ between groups: 1376 (112) mcg for the montelukast group and 1458 (124) mcg for the placebo group ($p = 0.714$). In both groups, the mean daily ICS dose incrementally increased until visits 3–4 and subsequently gradually decreased. The Friedman test showed that the ICS dose significantly changed throughout the observation period in both groups ($p < 0.001$). The maximal difference in the montelukast group (between Visits 1 and 3) was 44 mcg ($p = 0.072$), while the maximal difference in the

Table 2

Asthma symptoms score, FEV₁, FeNO and inhaled corticosteroid dose (ICS dose) at following visits of the study in both placebo and montelukast group.

	Placebo	Montelukast	p
Asthma symptoms score [points], mean $\pm$ SD			
V1	24.2 $\pm$ 1.7	24.6 $\pm$ 2.0	0.306
V2	23.8 $\pm$ 1.8	24.4 $\pm$ 2.1	0.161
V3	24.2 $\pm$ 1.8	24.2 $\pm$ 2.0	0.874
V4	23.7 $\pm$ 2.1	24.4 $\pm$ 1.9	0.208
V5	25.0 $\pm$ 1.6	24.8 $\pm$ 1.6	0.677
V6	24.5 $\pm$ 2.1	25.2 $\pm$ 1.9	0.106
FEV ₁ [% pred.], mean $\pm$ SD			
V1	101.6 $\pm$ 10.1	102.2 $\pm$ 15.5	0.979
V2	99.7 $\pm$ 11.0	99 $\pm$ 14.9	0.751
V3	101.3 $\pm$ 10.2	100.5 $\pm$ 11.7	0.888
V4	97.3 $\pm$ 9.7	101.8 $\pm$ 11.8	0.106
V5	103.1 $\pm$ 11.2	102.8 $\pm$ 10.4	0.877
V6	99.9 $\pm$ 9.6	102.4 $\pm$ 9.7	0.229
FeNO [ppb], median (quartile range)			
V1	21.7 (11.6–37.3)	29.3 (17.2–45.8)	0.214
V2	20.9 (11.4–31.4)	26.7 (15.3–38.6)	0.385
V3	21.2 (9.4–30.5)	24.8 (12.1–33.9)	0.420
V4	19.85 (15.8–30.9)	25.2 (15.1–37.9)	0.796
V5	19.75 (15.65–33.95)	24.4 (15.3–35.8)	0.645
V6	21.1 (13.1–31.8)	21.6 (15.4–31.6)	0.827
ICS ^a dose [mcg/day], mean $\pm$ SEM			
V1 ^b	218.1 $\pm$ 15.2	218.6 $\pm$ 17.2	0.884
V2	253.4 $\pm$ 18.5	248.0 $\pm$ 26.7	0.588
V3	252.1 $\pm$ 27.4	258.8 $\pm$ 26.9	0.730
V4	280.1 $\pm$ 40.0	237.8 $\pm$ 19.4	0.924
V5	230.9 $\pm$ 29.9	225.0 $\pm$ 17.2	0.433
V6	210.6 $\pm$ 21.0	191.4 $\pm$ 21.2	0.648

^a Budesonide.

^b At visit 1, all patients were administrated budesonide in daily dose which controlled their asthma symptoms during the high exposure season preceding the study.

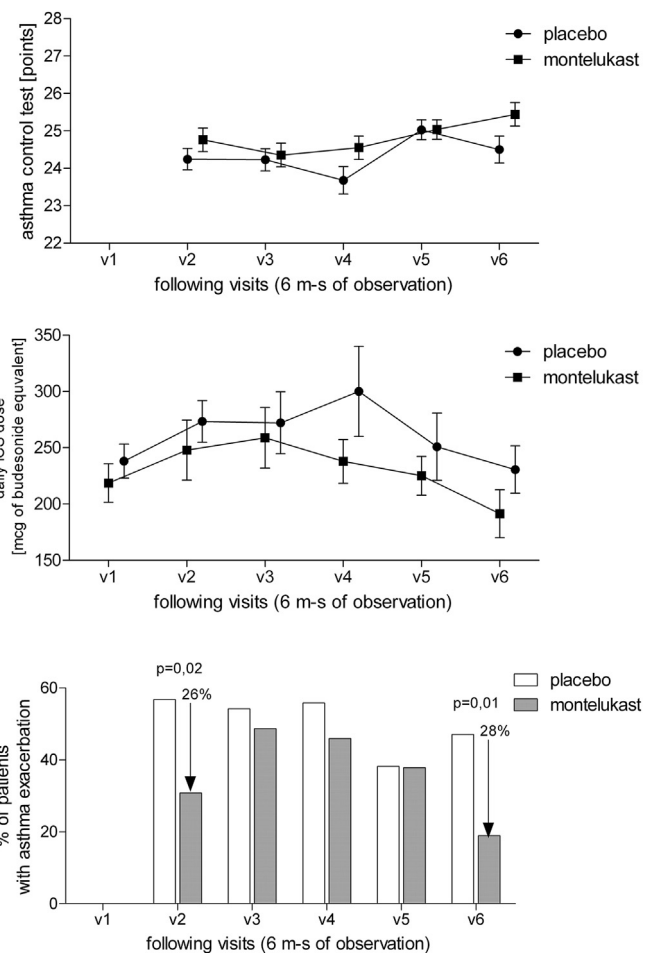


Fig. 2. Asthma control test score (mean $\pm$ SEM), daily ICS dose [mcg of budesonide] (mean $\pm$ SEM), percentage of patients with asthma exacerbations in both placebo and montelukast groups at visits 1 to 6 (V1–V6).

placebo group (between Visits 1 and 4) was 65 mcg ($p = 0.230$). There was no difference between groups (Table 2, Fig. 2).

In the next step, in each study group (montelukast and placebo), we compared cumulative ICS doses between two groups of children: with FeNO reduction < 10.9 ppb and with FeNO reduction > 10.9 ppb (10.9 ppb = mean reduction in FeNO level for montelukast group). Significantly lower cumulative ICS doses were observed among children with FeNO reduction more than 10.9 ppb when compared to those with less FeNO reduction in montelukast group; no difference in placebo group has been shown (Fig. 3B).

3.5. Asthma exacerbation

We observed a significant difference between groups with regards to the percentage of patients with asthma exacerbations at the first and the last study visit (Fig. 2). In the montelukast group, compared to the placebo group, we observed a lower frequency of asthma exacerbations at the second study visit (between-groups difference: 26%; OR = 0.34, 95%CI: 0.13–0.87; $p = 0.02$) and at the last study visit (between-groups difference: 28%; OR = 0.26, 95%CI: 0.09–0.76; $p = 0.01$). We also observed a significant difference between groups with regards to the total number of asthma exacerbations during the study (entire school season) (median value: 4.5 in placebo group vs. 3 in montelukast group, $p = 0.004$); the difference between groups for each individual visit did not reach the level of significance (Fig. 2).

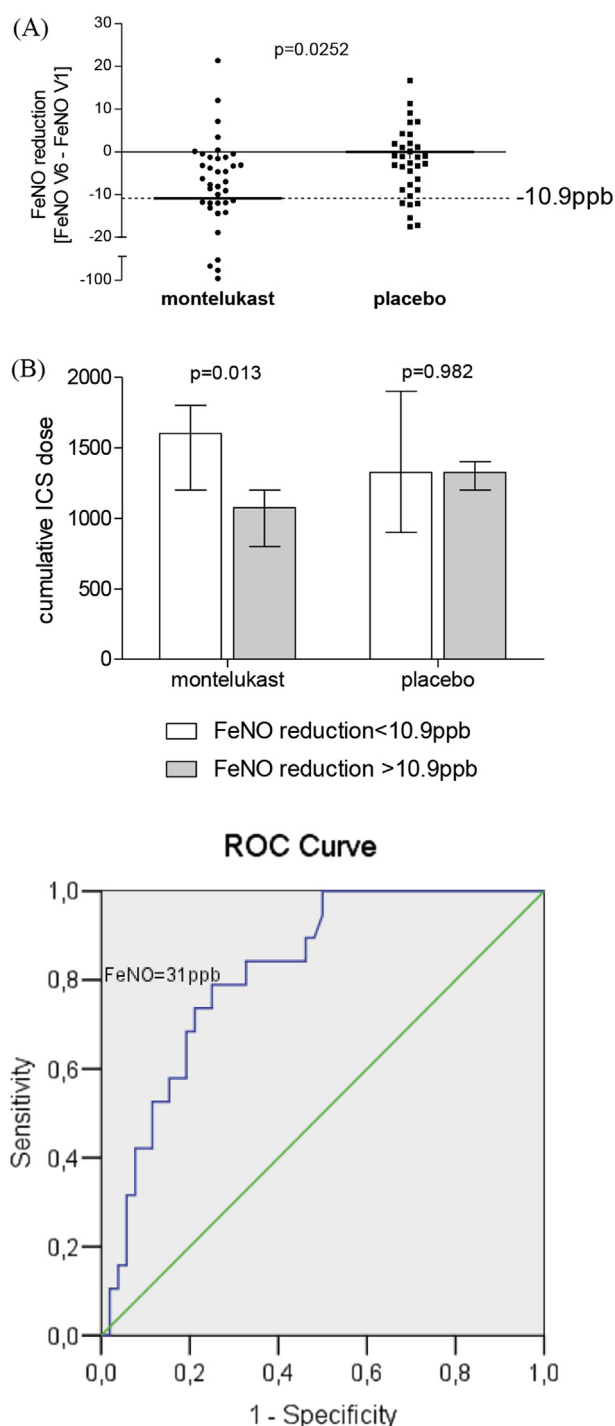


Fig. 3. FeNO reduction (FeNO level from visit 6 – FeNO level from visit 1) [ppb] in montelukast and placebo groups. Mean FeNO reduction in montelukast group is given (A). Cumulative ICS dose (sum of doses of Visits 1–6) in montelukast and placebo groups according to FeNO reduction (B). Roc curve analysis of baseline FeNO from visit 1 with FeNO reduction > 10.9 ppb as state variable. Cut-off level of baseline FeNO with the highest sensitivity and specificity for prediction of more or equal 10.9 ppb reduction after treatment is given.

3.6. Lung function

Analysis of variance did not show significant linear or non-linear trends in FEV₁ within either study groups; observed changes within groups were below 5% of predicted value. There was no significant difference in FEV₁ measurements between the study groups

($p = 0.318$) (Table 2). No improvement of the small airway's parameters, such as FEV_{25–75} was found (data not shown).

3.7. EIB and bronchial provocation tests

We found a higher frequency of positive exercise treadmill challenge test results in the placebo group (17.6%) compared to the montelukast group (0%) at the completion of the study.

There was no difference between groups with regards to the frequency of positive methacholine provocation test results (5.9% in the placebo group vs. 5.4% in the montelukast group; $p = 0.93$).

4. Discussion

Trials of add-on therapy of montelukast have been reported, but this study is rigorous and our findings are of clinical significance. 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. In this study, the addition of montelukast to regular treatment with an ICS for management of asthmatic children during the school season resulted in a significant reduction in the frequency of exacerbations and EIB protection, with no effect on asthma control, and lung function.

The PREVIA study clearly showed that montelukast effectively reduced viral-induced asthma exacerbations in patients between 2 and 5 years old with intermittent asthma over 12 months of treatment [15]. Recently, Simons et al. [16] showed that montelukast added to ICS therapy in asthmatic children significantly improved asthma control with a clinically relevant reduction in exacerbation days. This effect could be explained by the significant reduction in leukotriene-induced airway inflammation observed during viral infections. Although our study did not reveal an improvement in ACT scores after montelukast compared to placebo therapy, it demonstrated a significant reduction in the frequency of asthma exacerbations concurrent with frequent viral infections. In our study, we treated asthmatic children during the school season, a time period correlated with an increased risk of infections and higher exposure to house dust mites (heating season). Natural seasonal variation of symptoms requiring ICS dose adjustment in our patients explains the lower dosage of ICS at the beginning and at the end of school season. The significant effect of montelukast was observed mainly at the beginning and at the end of the school season (when the ICS doses were lower) than in the middle of the season. However, in the context of the available data, our results encourage the addition of montelukast to ICS therapy for the entire school season, as no individual symptom is predictive of an asthma exacerbation and as a single dose of montelukast is not effective for the treatment of asthma exacerbation [17,18].

The results of our study did not show a steroid-sparing effect of montelukast, likely due to the insufficient anti-inflammatory properties of montelukast in treatment of chronic allergic asthma. Lemanske et al. in their study characterized the effect of addition of montelukast to ICS on exacerbation in a very rigorous way with a large sample size (although not compared directly with placebo) [2]. They showed that long-acting beta-agonist step-up was significantly more likely to provide the best response than either ICS or LTRA step-up. Evidence for the relatively weak anti-inflammatory action of montelukast is comparable to the placebo effect of montelukast on FeNO and on methacholine challenge results in our study. Many studies have demonstrated a reduction in FeNO in asthmatic children treated with montelukast regardless of concomitant treatment with ICS [5,6], but only few studies have specifically addressed the effect of additive montelukast therapy to

ICS and the effect of successive withdrawal [19,20]. Evidence of airway inflammation can be found even in asthmatic subjects with mild or well-controlled symptoms [21]. Although in our study, no significant changes in FeNO levels were observed in the montelukast group when compared to ICS group, 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 was lower than in children treated with ICS only. Our findings are consistent with those obtained by Bisgaard et al. [22].

The possible effect of montelukast on lung function warrants commentary. We previously observed a significant improvement in different parameters of lung function (including FEV₁) after 4-week montelukast treatment [23]. Other available data show significant improvement in lung function and quality of life in patients treated with anti-leukotrienes [24]. Nevertheless, more than a 7.5% increase in FEV₁, defined as a clinically significant effect in treatment of asthma, was very rarely observed after montelukast treatment [25]. Although, improvement of lung functions and bronchial hyperresponsiveness were not significant in our study, the small airway's parameters were interesting to look at, however no improvement of FEV_{25–75} was found.

Lack of reduction in asthma symptoms, or FeNO levels and lack of clinically significant improvement in lung function in the study participants treated with montelukast could be a result of the variability of steroid adjustment during the study and the relatively short period of observation: the relatively short time intervals between study visits (6 weeks) and the small increments/decrements in the ICS dose (100 mcg) that were permitted by the protocol. Another limitation could be the level of compliance in completion of the ACT diary data by the subjects in both groups.

The protection effect of combined therapy with montelukast and budesonide on EIB has been previously described [26]. Studies revealed that montelukast alone reduced the immediate and late phase of bronchoconstriction after exercise [27–30]. In our study, we observed that montelukast in combination therapy with budesonide provided protection against EIB. Despite the outcome favoring improved EIB with montelukast, we showed that neither group had baseline significant fall in FEV₁ during exercise challenge, and that they both had a mean fall around 4.5% in FEV₁. So, in relation to these data, the outcome above seems to imply that the montelukast group had no change in EIB, and the placebo group had a slight worsening of EIB. Vidal et al., in a crossover study, observed better protection against EIB with budesonide therapy than with montelukast therapy, showing striking individual variation in responses to both therapies [30]. There are few available data regarding the effect of montelukast on bronchial hyperactivity (BHR) in children. Dempsey et al. showed additive broncho-protective effects with montelukast therapy in patients with asthma who were receiving inhaled corticosteroids [31]. In our previous study, we found that BHR decreased after treatment with montelukast, but we did not observe a significant difference compared to a placebo [32]. In the current study, we did not observe an effect of montelukast on non-specific bronchial hyperactivity. Because a baseline MCH challenge was not conducted at the first study visit nor at the time of loss of control of asthma symptoms, it is very difficult to assess the significance of these study findings. Therefore, due to ethical reasons, methacholine challenge testing was performed only after 6 months of therapy. A potential bias of our study could be a group of subjects selected for HDM sensitivity only; that was done to obtain the homogeneity of the group.

What is the clinical significance of our findings? Primarily, these data indicate that adding montelukast to regular ICS therapy during the school season in children with persistent asthma facilitates safe

titration of steroid therapy and reduces the risk of asthma exacerbation. In our opinion, this is the most important, interesting and truly significant finding of this manuscript. Secondly, montelukast demonstrates protection against EIB by reducing the maximal fall in FEV₁ during the exercise treadmill challenge, which could partially be due to the specific anti-leukotriene effect. Thirdly, in our study, treatment with montelukast was beneficial for children with well controlled asthma symptoms on low dose ICS and FeNO above 31 ppb; cumulative ICS dose in those children is lower than in children treated with ICS only. Although, recent Cochrane review did not show any significant advantage of montelukast together with ICS in comparison to ICS alone [33], our results point out to asthmatic children who may benefit from montelukast in add-on therapy. It is reasonable to add montelukast to ICS therapy to achieve better control of EIB, to reduce number of exacerbations as well as to lower cumulative ICS dose in children with well controlled asthma and baseline FeNO above 31 ppb. Overall, this study has the potential to demonstrate beneficial effect of montelukast added to ICS in selected children with stable asthma allergic to house dust mites during the school season.

Author contribution

Iwona Stelmach: concept of the study, analysis and interpretation of data, manuscript preparation.

Agata Ożarek-Hanc: acquisition of data, analysis and interpretation of data, manuscript preparation.

Joanna Jerzynska: concept of the study, analysis and interpretation of data, manuscript preparation.

Magdalena Zaczeniuk: acquisition of data, analysis and interpretation of data, manuscript preparation.

Włodzimierz Stelmach: concept of the study, analysis and interpretation of data, manuscript preparation.

Katarzyna Smejda: concept of the study, analysis and interpretation of data, manuscript preparation.

Paweł Majak: concept of the study, analysis and interpretation of data, manuscript preparation.

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